From more sustainable isocyanide-based multicomponent reactions to spiro-heterocyclic compound syntheses

By

Sodeeq Aderotimi Salami

THESIS

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

(PhD)

in the

Department of Chemistry

Rhodes University

September 2022

Supervisor: Prof. R.W.M Krause

Co-supervisor: Dr V. Smith

Acknowledgement

This thesis was carried out in the Krause (F22) and Smith (F2) Laboratories, in the Chemistry Department at Rhodes University, under the supervision of Prof. Rui Krause and Dr. Vincent Smith.

First and foremost, I would like to express my deepest gratitude to the Almighty God for His Grace, Help, Strength, and Wisdom to conclude my PhD work. I want to thank my PhD supervisors Prof. Rui Krause and Dr. Vincent Smith for welcoming me into their groups and allowing me to work as part of their research teams and for being there whenever I needed them during my doctoral programme. This would not have been possible without their unquantifiable support and contributions. I owe both much more than I can express, from the willingness to accept me as a PhD student to the readiness to offer guidance and motivation whenever I confronted challenging problems emanating from my research. I am grateful to both. They have been very understanding, they have the interest of their students at heart, and they take the time to get to know their students as individuals and for that I am sincerely grateful. I thank both from the bottom of my heart for their keen guidance and the efforts they have put into me in the scientific training field especially in the area of sustainable chemistry.

Profound appreciation goes to Dr. Kathrine Kaschula at Stellenbosch University for being instrumental in the scholarship that gave birth to this PhD.

I am grateful to Dr. Siwe-Noundou Xavier for his meaningful contribution to the success of my PhD. program. Indeed, frequent fruitful discussions with him contributed greatly to the success of this program. Also, I appreciate the contributions of Dr. Meloddy Manyeruke for his guidance through the structure elucidation of some compounds in this thesis.

I wish to appreciate the team spirit of the members of my research group (F22 and F2): I would like to personally thank Dr Douglas, Dr Lydia, Dr Baa, Mum Bertha and my brother Dr Olamide Daramola for their unmatchable support. To my colleagues in the lab, Bafokeng, Safari, Grady, Siya, Elizabeth, Obakeng, Francis, Paula, Thienry, and Dr Sakthikumar their selflessness beats my imagination, and I cannot thank them enough for their sincere companionship that gave me the needed stability to fully concentrate on the program.

I wish to express my sincere gratitude to Prof. G.A. Olatunji for his great investment in me during my M.Sc. Programme. Appreciation goes to Dr Olubunmi Tolani, Dr Funmi Ajayi, Dr Fadeji Laolu, Dr Victor Ogundele for their valuable encouragement during this programme. I am also grateful to Prof. Cosmos, for his trust in me and his encouragement all the time. My sincere appreciation to those who ministered to my needs in my days of hopelessness including Mr Remember Patrick, Dr Fagbemi, Elder Bola Ogunkola, and Eng Kayode Hamzat.

To my family, Prof I.S Ogundiya, and Prof. Jimoh Olaiya Amzat, thanks for the fatherly roles you have played over the years. I can't thank you enough. I appreciate my mother Deac, Flourence Atunni for

her constant prayers and the unflinching support of my sibling Mrs Peju Salami and Mrs Ibidun Ganiyu towards the success of my PhD programme.

Finally, a hearty appreciation goes to my lovelies: my darling wife Tolulope Ruth Aderotimi and my beautiful daughter (Favour Aderotimi Erimide) for their love, patience, endurance and understanding in bearing my absence. They are the strength that keeps me going even at difficult moments. I am indeed grateful to everyone who I have not mentioned but who has been instrumental to my success.

Abstract

The global pharmaceutical industry has undergone profound transformations in the past two decades in the search for new drugs. For this reason, most pharmaceutical companies made significant investments not only in the development of new drugs but new methodologies. Modern drug development is confronted with the challenge of developing chemical reactions that are highly capable of providing most of the elements of structural complexity and diversity with the fewest possible synthetic steps for the specific target with the most intriguing properties. The discovery of more sustainable, environmentally friendly reactions capable of forming multiple bonds in a single step has been a challenge in organic synthesis over the years. Many organic chemists have recently started focusing on creative ways of reducing environmental pollution. The use of hazardous solvents has been reduced or eliminated in research to limit harm to both people and the environment. The pursuit of this goal has drawn many organic chemists to the study of various sustainable synthetic techniques including catalysis, aqueous organic reactions and mechanochemistry. The scope of this thesis was to apply sustainable techniques to design multicomponent synthetic protocols for the Passerini reaction and further apply these new protocols to construct spiro-heterocyclic compounds, all based on green chemistry principles. There is a need to develop rapid, efficient, and versatile strategies for the synthesis of bioactive molecules via multicomponent reactions. This project tried to avoid some of the pitfalls of traditional approaches, such as toxicity, low yield, long reaction times, harsh conditions, experimental complexity, and limited functionalization scope. This was achieved by focussing on the use of isonitriles and isothiocyanates as key reactive intermediates, and making extensive use of aqueous reaction conditions, mechanochemistry and microwave activation.

The work described in this thesis is divided into six chapters:

Chapter one contains an overview of the literature surrounding the project, focusing on green and sustainable chemistry, synthesis, and application of isocyanide (isonitriles) and isothiocyanate in multicomponent reactions and spiro-heterocyclic compound formation. After a brief introduction on green and sustainable isocyanide syntheses and their applications in multicomponent reaction such as the Passerini reaction, a more sustainable method for synthesizing isocyanides from *N*-substituted formamides is presented here.

Chapter two describes efforts towards developing a simple, efficient, and sustainable method for the synthesis of isocyanides (isonitriles). First, an efficient procedure for the *N*-formylation of various amines with triethyl orthoformate in the presence of the immobilized sulfuric acid on silica gel as promoter system was developed. The product formamides were obtained in excellent yields with no requirement for purification. In addition to this approach, a more sustainable amine-catalysed isocyanide synthesis from *N*-substituted formamides using phosphorus oxychloride under solvent-free conditions was also developed. Having realized that the aqueous workup is the major problem in

isocyanide synthesis since it is associated with yield losses. As a result, it was necessary to develop a non-aqueous workup procedure for the purification of the isocyanides mixture.

In chapter three, a group of medicinally valuable compounds was synthesised via a 3-component Passerini reaction under aqueous and mechanochemical conditions. The results of the investigation revealed the advantages of water in organic reaction and mechanochemistry over the conventional approaches. Under these conditions, a 3-component Passerini reaction was used to synthesise a novel-compounds library of functionalized α-acyloxycarboxamide derivatives employing *N*-formamides as the carbonyl precursor.

Chapter four, the synthesis of isothiocyanates from isocyanides using Lawesson's reagent as a sulfurization agent under aqua microwave irradiation and its application in the synthesis of spiro-heterocyclic compounds have been developed. The direct thionation of isocyanides using Lawesson's reagent is reported here for the first time.

This chapter also uncovered some remarkable benefits in the synthesis of spirocyclic compounds under aqueous and mechanochemical conditions. Spiro[indole-pyrrolidine] was readily synthesized in 85-94 % and 90-98% yields by the Michael condensation of 3-dicyanomethylene-2*H*-indol-2-ones with various isothiocyanate derivatives, using piperidine as a catalyst under aqueous and mechanochemical reaction conditions, respectively.

Chapter five provides information on research design, equipment, materials, procedures, and characterization of the synthesized compounds.

Chapter six: Summary and Conclusion

Abbreviations

General

EI	Electron ionization
ES	Electrospray
FTIR	Fourier-transform infra-red
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
J	Coupling constant
MW	Microwave irradiation
MCR	Multicomponent reaction
NMR	Nuclear magnetic resonance
TLC	Thin layer chromatography
^{13}C NMR	(C-13) Nuclear magnetic resonance spectroscopy
^{1}H NMR	Proton (H-1) nuclear magnetic resonance spectroscopy
Ac	Acetate
EtOH	Ethanol
MeOH	Methanol
aq	Aqueous
br	Broad
c	Concentration
cc	Column chromatography
CD_3OD	Deuterated methanol
$CDCl_3$	Deuterated chloroform
DMSO-d6	Deuterated dimethyl sulfoxide
D_2O	Deuterated water
COSY	Correlated spectroscopy

d	Doublet
dd	Double of doublets
DABCO	1,4-diazabicyclo[2.2.2]octane
TEA	Triethylamine
DEPT	Distortionless enhancement by polarization transfer
EIMS	Electron impact mass spectroscopy
HMBC	Heteronuclear multiple bond coherence
HPLC	High-pressure liquid chromatography
HREIMS	High-resolution electron impact mass spectroscopy
HSQC	Heteronuclear single quantum coherence
IR	Infrared
m	Multiplet
Me	Methyl
Mp	Melting point
MS	Mass spectroscopy

Table of Contents

List of Schemes.

List of Figures.

List of Tables.

Declaration

This thesis in its entirety or part has not been submitted to this or any other institution in support of an application for the award of a degree. It represents the author's work and where the work of others has been used, proper reference has been made.

Sodeeq Aderotimi Salami

……

Contributions from the thesis

Published articles from the thesis

Salami, S.A.; Smith, V.J.; Krause, R.W.M. Aqua/Mechanochemical Mediated Synthesis of Novel Spiro [Indole–Pyrrolidine] Derivatives. *Int. J. Mol. Sci.* 2023, *24*, 2307. https://doi.org/10.3390/ijms24032307

Salami, S.A.; Vincent, Smith, J.; Krause, R.W.M. The *N*-Formamide as carbonyl precursor in the catalytic synthesis of Passerini adducts under aqua and mechanochemical conditions, *RSC Adv.*, 2023, 13, 4019, doi: 10.1039/d2ra06189a.

Salami, S.A., Smith, V. J., Krause, R. W. M., Water-Assisted Passerini Reactions under Mechanochemical Activation: A Simple and Straightforward Access to Oxindole Derivatives, Salami, S. A., Smith, V. J., Krause, R. W. M., *ChemistrySelect* 2023, 8, e202204325.

Salami, S.A.; Vincent, Smith, J.; Krause, R.W.M., Aqueous microwave assisted novel synthesis of isothiocyanates by amine catalyzed thionation of isocyanides with Lawesson's reagent. *Journal of Sulfur Chemistry*, 2023, pp.1-13. doi: 10.1080/17415993.2022.2164196

Salami, S.A.; Siwe-Noundou, X.; Krause, R.W.M. A More Sustainable Isocyanide Synthesis from N-Substituted Formamides Using Phosphorus Oxychloride in the Presence of Triethylamine as Solvent. *Molecules* 2022, 27, 6850. https://doi.org/ 10.3390/molecules27206850

Salami, S.A.; Manyeruke, M.; Siwe-Noundou, X.; Krause, R.W.M. Immobilized Sulfuric Acid on Silica Gel as Highly Efficient and Heterogeneous Catalyst for the One-Pot Synthesis of Novel α-Acyloxycarboxamides in Aqueous Media. *Int. J. Mol. Sci.* 2022, 23, 9529. https://doi.org/10.3390/ijms23179529

Salami, S.A.; Siwe-Noundou, X.; Krause, R.W. Catalytic Performance of Immobilized Sulfuric Acid on Silica Gel for N-Formylation of Amines with Triethyl Orthoformate. *Molecules,* 2022, 27, 4213. https://doi.org/ 10.3390/molecules27134213

My role in all the publications mentioned above included carrying out all the experimental work and writing the publications. My supervisor guided me and assisted me with writing the results for publication. The other co-authors contribution was mainly in the structure elucidation and checking whether the results were correctly interpreted.

Chapter 1

This chapter forms the basis for the publication in Molecules, see details above or visit https://doi.org/10.3390/molecules27134213, https://doi.org/10.3390/molecules27206850.

Introduction

For a long time, green chemistry was a somewhat abstract concept without any underlying principles or definitions of its useful applications. The definition of "green chemistry" as it is used today is "the development, design, and use of chemical products and processes to reduce or to eliminate the use and generation of hazardous compounds for workers and customers [1, 2]. Green chemistry encompasses broader topics that can ultimately encourage sustainable development in addition to safer products, less harmful effects on the environment, and energy and water savings. The focus of environmentalists has recently switched to mitigating the negative effects (monitoring environmental contamination, lowering pollutants, recycling, etc.) because of the rapid development of new chemical technologies and the vast number of new chemical products [3, 4]. However, the reality is that the best way to lessen the adverse effects is to design and innovate in the manufacturing processes, considering energy, materials, the atom economy, the use and generation of secondary materials that are dangerous, and finally the life cycle of the products and their practical recycling into new materials [5, 6].

Recent years have seen a significant rise in the use of "green chemistry" in research and development, particularly in advanced industrial nations. The idea of green chemistry is gaining ground, as evidenced by the numerous international conferences, academic journals, countless publications, and new university courses.

1.1 The Twelve Principles of Green Chemistry

The most important objectives of green chemistry were outlined in a set of twelve principles. The number twelve has great significance and is extremely symbolic since it reflects all the essential steps we must take to achieve a variety of tasks (much like the twelve months of the year) [3]. Green Chemistry must address a wide variety of chemical and technological concerns to provide its alternative hypothesis for sustainable development. To effectively reduce or eliminate environmental pollution, green chemistry must incorporate specialized, long-term preventative measures [7]. Alternative, ecologically acceptable chemicals must be the main emphasis of green chemistry, but it must also work to speed up reactions and cool them down to conserve energy. Green chemistry pays close attention to the effectiveness of reactions, the use of less toxic solvents, reducing the hazards of feedstocks and products, and waste reduction [8].

The following set provides a comprehensive analysis of the Twelve Principles of green chemistry (GC) [9, 10, 11].

1.1.1 Prevention: It is preferable to prevent than to clean up (waste or pollution). Many chemical reactions that have been developed by scientists over the last few decades can be drastically altered by preventative intervention. Most chemical reactions and synthetic pathways result in waste and hazardous by-products. Green chemistry may reduce waste and toxic by-products by envisioning the feedstocks and chemical processes and proposing creative modifications.

1.1.2. Maximise synthetic methods, atom economy: All synthetic processes used up until this point were inefficient and had yields between 70 and 90 %. According to green chemistry, it is possible to plan synthetic processes to maximize the incorporation of all reagents employed in the chemical process into the finished product, hence avoiding the need to recycle the by-products.

1.1.3. Less hazardous chemical synthesis: Green chemistry must make every effort to create less hazardous compounds and synthesis products, as well as safer synthetic procedures whenever possible. Less toxic substances entail fewer risks for workers in manufacturing and research labs, as well as less environmental contamination.

1.1.4. Designing safer chemicals: Green chemists must make designing their primary objective if they are to achieve the required function and features of the chemical product while reducing its toxicity to both humans and the environment.

1.1.5. Safer solvents and auxiliary substances: It is necessary to replace or reduce the number of harmful compounds employed as solvents, separation agents, and auxiliary chemicals in synthetic chemistry. As a result of significant improvements brought about by green chemistry, new methods and less hazardous solvents have been used in chemical laboratories over the past ten years.

1.1.6. Design for energy efficiency: Chemists must understand that energy requirements in synthetic chemical processes have received relatively little consideration up until this point. Designing more energy-efficient processes is essential, and if it is practical, synthetic processes should be carried out at room temperature and pressure.

1.1.7. Use of renewable raw materials and feedstocks: The primary raw materials used as the basis for synthetic processes are petrochemicals and refined products. Extremely low toxicity and, if possible, renewable resources should be prioritized over depleting ones for raw materials.

1.1.8. Reduce intermediate derivatives: The use of blocking groups, protection/deprotection strategies, and transient alteration of physical and chemical processes are examples of derivatization that should be avoided in synthetic pathways, from a green chemistry point of view.

1.1.9. Catalysis, catalytic reagents: It is generally known that the use of catalysts can significantly alter both the yield of products and the efficiency of chemical reactions. Stoichiometric reagents may

not always be preferable to highly selective catalytic reagents. The future of green chemistry techniques is in the development of new catalysts and a greater focus on catalytic processes.

1.1.10. Design products which degrade easily: Most chemical products and consumer goods do not disintegrate very quickly, which results in environmental issues. Green chemistry aims to produce products that break down into harmless compounds at the end of their useful lives. A common flaw with consumer goods, like those made of plastic, is their environmental persistence. Designing products that break down quickly can change this feature.

1.1.11. Real- time analysis for pollution prevention: Further development of analytical approaches is required to provide real-time, in-process monitoring and control before the formation of hazardous compounds.

1.1.12. Inherently safer chemistry for accident prevention. Raw materials and chemical compounds employed in chemical processes should be intrinsically safe, meaning that neither their properties nor the results of their degradation should be poisonous or hazardous (e.g., explode, be combustible, create allergic reactions in people, cause skin burns, etc.).

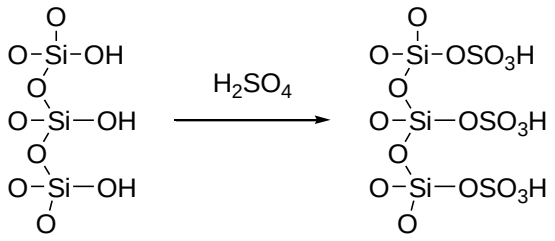
1.2. Green Chemistry and Reduction of Solvent Toxicity. Alternative Solvents or Replacement

The prevalence of poisonous organic solvents employed in chemical reactions and synthetic processes makes it difficult to practice green chemistry. One of the tenets of green chemistry is to use solvents as little as possible, to substitute less hazardous ones when appropriate, or to employ alternative methods [12]. In both organic and inorganic chemical reactions, solvents account for 80–90% of contamination. Traditional organic solvents, which are derived from oil, are hazardous and have a negative influence on safety, the environment, and human health. Consequently, the solvents that will be employed as green media for organic synthesis must be biodegradable, have low toxicity, high boiling, easily recyclable, and non-miscible with water [13, 14]. Solvents are one of the key concerns when it comes to the health and safety of employees as well as environmental degradation in the chemical industry. Many operations, including synthesis, product separation, cleaning, drying, analysis, and recycling, make use of solvents. Changing technological processes and solvents is a difficult endeavour. Alternatives abound, but some may be more costly, time-consuming, or difficult to perform when considering the established order of chemical techniques [15, 16]. The green chemistry movement has recently led to the replacement of some solvents and the adoption of methods that are less harmful to the environment. The following is a brief list of a few of these new methodologies in the synthesis of chemical compounds.

1.2.1. Catalytic selectivity. Another area of study for lowering the usage of solvents, increasing yields, and producing less waste is catalytic selectivity. Catalysis by silicated acids is a field of growing importance [17]. A silica-gel supported acid, such as silicated sulfuric acid, has attracted a lot of interest

in organic synthesis due to its distinctive qualities, including high efficiency because of its larger surface area, more thermal stability and reusability, low toxicity, greater selectivity, and ease of handling [18, 19]. A silicated sulfuric acid catalyst has reportedly been used for a variety of heterogeneous organic transformations, including Michael addition, Knoevenagel condensation, and Hantzsch condensation [20]. The silicated sulfuric acid catalyst is employed in two different forms: silica adsorbed sulphuric acid and silica sulfuric acid. For large-scale synthesis, silica-adsorbed sulfuric acid is particularly easy to utilize and is cost-effective because it can be recovered and used again for several runs without affecting the catalytic system's activity [21]. The desired transformation can be completed in a considerably shorter length of time than with other strategies that have been discussed in the literature. It has been reported in studies to be a safe, environmentally sustainable, and reusable catalyst [22]. Silica-adsorbed sulfuric acid is a great alternative to sulfuric acid or chlorosulfonic acid since it avoids drawbacks such as the destruction of acid-sensitive functional groups, the use of highly toxic solvents, and the cost of expensive reagents or solvents [20]. Silica sulfuric acid (SSA), on the other hand, is a distinct approach for accelerating chemical reactions to boost the yields as well as many other variables [23]. Fundamentally a solid acid, silica sulfuric acid (SSA) has been used as a reagent or catalyst in a variety of heterogeneous organic functional group transformations, including the nitrosation of thiols, aromatization of quinoline derivatives, stereoselective synthesis of amino ketones, formylation of alcohols, and aza-Michael addition reactions [24, 25, 26].

There are two types of functional groups on the silica surface: siloxane (Si–O–Si) and silanol (Si–OH). Thus, silica gel modification can occur through the reaction of a specific molecule with either the siloxane (nucleophilic substitution at the Si) or silanol (direct reaction with the hydroxyl group) functions, though it is widely accepted that the reaction with the silanol function is the most common modification pathway **(Scheme 1.1)** [27, 28].



Scheme 1.1 Immobilized sulfuric acid on silica gel.

1.2.2. Mechanochemistry. The use of mechanical energy to induce chemical transformations has exploded in popularity in recent years, giving chemists new tools to improve the synthetic chemical design. [29, 30]. According to IUPAC, this is one of the top 10 technologies that would change the world. Mechanochemical reactions are usually carried out by milling, grinding, shearing, or pulling reactants in the absence of organic solvents or the presence of a catalytic amount of solvent (liquid-assisted grinding, LAG) [31]. The method incorporates several green chemistry principles, including

the utilization of ambient conditions, fast reaction kinetics, significant reduction or elimination of solvent consumption, and frequently no lengthy workup step [32]. This exciting development appears to be a viable substitute for various chemical processes developed in the solution phase, often with higher yields [33]. Mechanochemistry has promising future applications not only in conventional organic synthesis or organometallics, but also in a range of contemporary domains, including the synthesis of APIs, biocatalysis, material chemistry, polymer chemistry, and supramolecular chemistry [34].

A mortar and pestle are traditional mechanochemical equipment that is still employed to efficiently carry out chemical transformations, such as the production of dyes and other organic reactions. The grinding tools come in a range of sizes and are made of porcelain, granite, or agate [35]. Modern technologies are used to perform mechanochemical milling reactions most frequently in planetary ball mills or mixer mills. In a planetary mill, the reaction jars with the grinding balls inside move in a planetary motion during milling (Figure 1); in a mixer mill, the reaction jars are rapidly shaken at a specific frequency, leading to grinding the chemical components by inducing shearing of the enclosed balls [36]. The jars and balls come in different sizes and are made of stainless steel (SS), tungsten carbide, zirconia, agate, Teflon, etc. The other typical variable is the oscillation frequency for mixer mills and the milling speed for ball mills. Single-screw (SSE) and twin-screw (TSE) extrusion are utilized for mechanochemistry in continuous mode. In TSE, two intermeshings, and counter-rotating screws drive solid reactants constantly through a barrel **(Figure 1.1).** Although neat grinding is desirable, the reaction kinetics are frequently slowed when the substrates or intermediaries become trapped inside the solid mass of the reaction mixture [35]. A straightforward remedy is the addition of a small volume of solvent to create a pasty mass and facilitate the contact of the solid substrates at the solid-liquid interface. Liquid-assisted grinding (LAG) is a method that has been used frequently to synthesize various organic compounds using common solvents including MeOH, DCM, and water. Furthermore, solid matrices can also be utilized as grinding auxiliary to speed up mechanochemical reactions (e.g., silica, alumina) [37].

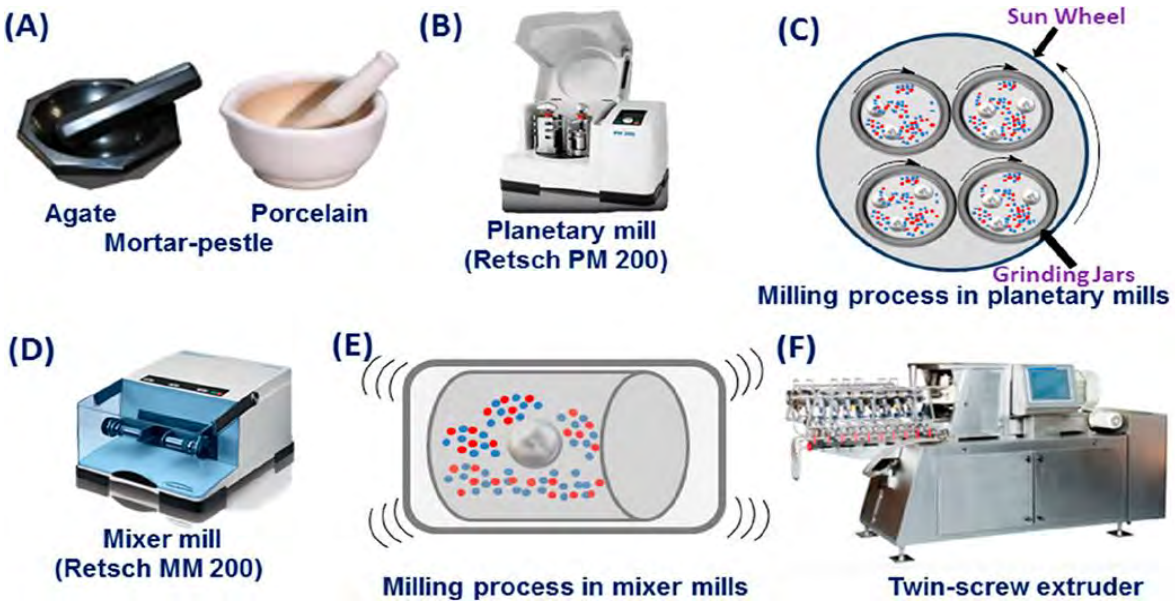


Figure 1.1: Common equipment for mechanochemistry. (Adapted from Mainak, *et al*) [31]

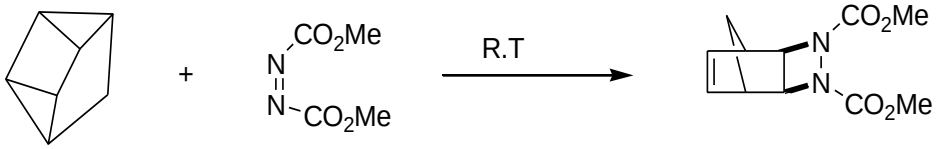
In organic chemistry many reactions including metal-catalysed transformations [7, 38], organocatalytic [10] and enzymatic processes [39], lignin [40] and cellulose depolymerizations [41, 42], multicomponent reactions [43], and many others [44, 45] have been studied using electric ball mills. Mechanosynthesis is currently used, among other things, when organic substrates are sensitive to temperature conditions, for instance in the reactions of C-C bond formation (such as Suzuki and Glaser coupling, Knoevenagel condensation, McLurry, Wittig, Gewald, Michael, Reformatsky and Grignard reactions, arylamino methylation, etc.) [37, 46]. As a result of these studies, mechanochemical activation and techniques have revealed a variety of benefits, including faster reaction milling times, higher yield, less waste formation, enhanced selectivity, and stoichiometry control, to name a few [29]. Despite the attractive and well-known benefits of ball-milling technology, many unexplored potential applications, such as multicomponent reactions, remain in the field of modern organic synthesis [31]. Mechanochemistry has been explored in these present studies for the synthesis of various Passerini adducts and spiro-heterocycles.

1.2.3. Organic synthesis in water. The usage of organic solvents is a constant source of worry since it is associated with toxicity, hazards, pollution, and waste treatment issues**.** Additionally, most of the wasted mass in a particular process or synthesis pathway is typically attributed to solvents [47]. The optimum solution to this problem from the perspective of strict green chemistry would be to conduct the reactions under neat conditions, that is, without any solvent. As a result, many efforts have been made to identify sustainable reaction media, and most recently, the use of water as a solvent has garnered a lot of attention [47]. Indeed, water has a lot of benefits because it is an affordable, easily accessible, non-toxic, and non-flammable solvent, making it very appealing from both an economic and an environmental point of view [48]. As a result of the low solubility of organic compounds in water

and the fact that it has long been regarded as a contaminant, water initially appears to be a poor solvent for chemical transformations [49]. However, it is now well known that the peculiar structure and physicochemical properties of water give rise to specific interactions including polarity, hydrogen bonding, the hydrophobic effect, and trans-phase interactions that may significantly affect the reaction's course [50]. The sustainability of a reaction is significantly impacted by its rate and selectivity since improved rates and selectivities may result in reduced reaction time, lower temperatures, lower catalytic loadings, greater yields, and easier purification [49].

Since Breslow's pioneering work in 1980, a wide range of organic reactions has been proved to occur in aqueous media, with considerable increases in reaction rates and selectivities when compared to results achieved using typical organic solvent-based systems [13, 51]. In these experiments, he found that the cycloaddition of butenone and cyclopentadiene occurred 740 times faster in water than in isooctane and that the selectivity of the reaction was higher in water (endo/exo = 21.4) than in cyclopentadiene (endo/exo = 3.85). In aqueous media, several organic processes have shown a significant increase in the rate of organic reaction, even though their origin is still a mystery [52, 14] However, heterogeneous aqueous reaction rates are frequently related to mixing speed and method, and these rates are frequently inversely proportional to reaction temperature [53]. The effects have been interpreted as a result of the aqueous media's cohesive energy density, the hydrophobicity of the reagents, increased hydrogen bonding in the transition state, or a decrease in the transition state's volume [54].

Recently, Sharpless et al. defined "on water" conditions as those in which water is used as a solvent for the reaction of reactants that are not soluble in water [55]. The interaction of quadricyclane and dimethyl azodicarboxylate was presented by his group as a particularly clear example of how the reaction rate could be accelerated "on water" (Scheme 1.2). The time to completion was measured in a wide range of solvents, and it was evident that not only did the dipolar effect and hydrogen bonding speed up the reaction (18 h in methanol compared to 36 h in DMSO, 72 h in dichloromethane, or more than 120 h in toluene), but heterogeneity also contributed significantly to large rate acceleration with only a 10 min reaction time in the water. In contrast, the reaction carried out under neat conditions takes 48 hours to complete. It is interesting to note that the reaction time increased to 45 minutes when D_2O was used as the solvent **(Table 1.1).** This might be because the hydrophobic effects were reduced and the viscosity was higher, which hinders the homogeneous mixture from mixing well.

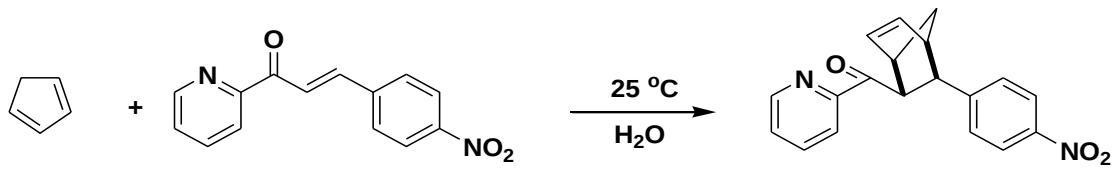


Scheme 1.2: Reaction of quadricyclane with dimethyl azodicarboxylate in various solvents.

Solvents	Time of completion
Toluene	>120 h
Ethyl acetate	>120 h
Acetonitrile	84h
Dichloromethane	72h
Methanol	18h
Neat	48h
D_2O	45 min
Water	10 min

Table 1.1. Time to completion for the cycloaddition of quadricyclane with azodicarboxylate.

Another astounding finding on the acceleration of the cycloaddition rate came from the Engberts group's study of the Diels-Alder reaction involving cyclopentadiene and 3-aryl-1-(2-pyridyl)- 2-propen-1-ones derivatives **(Scheme 1.3**) [56]. They demonstrated that the reaction in water was 287 times faster than the same reaction in acetonitrile. They also discovered that, in contrast to the reaction in acetonitrile, the reaction in water was accelerated by a factor of 1 800 000 when a Lewis acid and micellar catalysis were used. As a result, water as a reaction medium has received a lot of attention in synthetic organic chemistry and offers features that may be useful in a range of reactions [57, 58]. Application of the techniques for the present studies in various multicomponent reactions furnishes the corresponding adducts in high yields and purity within 10-15 minutes.



Scheme 1.3: Diels–Alder reaction of cyclopentadiene and (E)-3-(4-nitrophenyl)-1-(pyridin-2-yl)prop-2-en-1-one.

1.2.4. Use of microwave techniques for organic synthesis. Microwaves have been used in organic synthesis for a long time, and their effectiveness in meeting "green" synthesis requirements is widely documented. This heating technique is suitable for both organic and inorganic synthesis since it is based on conduction and dipolar polarization [59, 60]. This efficient, rapid, and clean method has reportedly been used to create several organic compounds. It is currently recognized as a standard synthetic chemistry technique and has considerably improved organic synthesis [1]. Microwave (MW) energy and other non-ionizing radiation do not affect the molecular structure of compounds. Since the MW coupling of a substance depends on its dielectric constant, *N,N*-dimethylformamide (DMF), methanol, acetone, and water are rapidly heated under MW irradiation as opposed to CCl_4, toluene, or aliphatic

hydrocarbons [61]. Compound interactions are fuelled by electromagnetic energy, which is converted into heat. The MW irradiation and reaction components interact directly, and therefore only a small amount of energy is required to heat them without extending the process to the furnace material [62]. As a result, samples heated using traditional heating techniques and MW technology have various temperature profiles (in the case of MW irradiation the interior is hotter, and the surface is cooler). Thermal conduction within the sample results in less energy being used for heat transfer because consistent volumetric heating occurs throughout the entire sample [63]. Due to the quick transfer of MW energy heat, the MW heating occurs nearly instantly and is very quick. It can be halted instantly by simply turning off the MW equipment. Additionally, MW heating is selective since different reagents have different capacities for MW heating. This enables, for example, the heating of certain active regions within a sample rather than the entire sample [64]. The following benefits of MW heating include, but are not limited to, quick process speeds, pure products, less heat loss, high heating efficiency, reduced waste, cheap operating costs, and a lower likelihood of side products [65]. To prevent quick, uncontrolled solvent heating and dramatic explosions, it is recommended to conduct MW-assisted reactions in a dry medium without the use of solvent.

There is a lot of pressure nowadays to make chemistry "green" and "sustainable." To prevent further environmental damage, this suggests that the bulk of (industrial) processes needs to be completely redesigned. The main cause of ecological contamination is the use of flammable and highly volatile solvents [15]. Water seems like a great substitute; however, most organic reagents are insoluble in water. The use of microwave irradiation can successfully address this issue and enable the rapid heating of reaction mixtures since water has a good propensity to absorb microwaves. Moreover, water behaves as a pseudo-organic solvent at higher temperatures as the dielectric constant is substantially reduced [59]. The use of water as a solvent in combination with microwave irradiation seems to have a remarkable synergistic impact. The application of this technique in the current studies offers the rapid synthesis of various isothiocyanates with high structural diversities within 10 minutes.

1.3. Medicinal Chemistry and Multicomponent Reactions

Organic synthesis has come a long way since Wohler first synthesized urea in 1828 [66]. However, today's synthetic organic chemists are just as enthusiastic as their forefathers in pursuing the difficult challenge of developing compounds with advanced capabilities and novel chemical architectures. This has fuelled the development of novel reactivity, reagents, and catalysts that have allowed synthetic chemists to build reaction sequences to access molecules of any complexity [67]. For many years, getting there has been synonymous with unquestionable achievement, but in the last 30 years, chemists have been increasingly concerned about how they will get there. Defining criteria that chemists evaluate while developing their synthetic method include phrases like "concise," "efficient," and "convergent," which are now common in the titles of (total) synthesis papers [68].

Designing and synthesizing pharmacologically active compounds is a critical field of chemistry because there are still many diseases for which there are no viable remedies [69]. New drugs continue to improve human health despite the world's rapidly growing population. Medicinal chemists can regularly discover new biological processes and the protein targets that are implicated in them, bridging the gap in drug development for unmet medical needs [70]. Medicinal chemists begin by designing agonists and antagonists for proteins and enzymes, whereas structural biologists leave off in deciphering the dynamics and crystallographic structures of vast biological structures. Small molecules, for example, can be used to influence natural processes such as pathway deactivation or activation by mimicking the structure and electrostatics of a small natural ligand [71]. Small compounds are frequently discovered and their binding affinity at receptor binding sites is optimized through diversity-focused synthesis. Structural variety is normally achieved by introducing individual moieties in the target molecule one at a time, and each structural change necessitates the repetition of a part or perhaps the entire synthesis method [72]. This divergent and sequential approach to chemical library synthesis can be time and material intensive. Assembly of a versatile scaffold and acquiring the variations in a single reaction step would be a more convenient method [73]. Divergent synthesis of very vast chemical space and size based on accessible building blocks is inevitably limited to two-component reactions. Multicomponent reactions (MCR), on the other hand, allow for simultaneous variation of three or more building units and hence cover a vast chemical space [74].

The exponential growth of chemical space is the foundation of MCR theory. MCRs, such as the Ugi 4-component reaction (U-4CR), Passerini (P-3CR), Gewald (G-3CR), Groebke-Blackburn-Bienaymé (GBB-3CR), Biginelli (B-3CR), and many other MCR named reactions, enable the introduction of various scaffold shapes via a range of MCR variations [53].

MCRs provide a versatile approach to meeting these efficiency standards. These reactions, in contrast to traditional multistep sequential synthesis, combine at least three reactants in one pot to make a product that contains the majority (ideally all) of the starting materials' atoms [75].

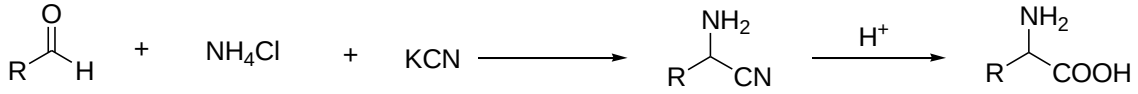
The high degree of convergence and step economy of MCRs has a substantial impact on the resource side of a chemical synthesis process (namely, the use of starting materials and time) [76]. MCRs help increase the process's sustainability by improving reaction mildness and compliance with green chemistry standards (e.g., atom economy, waste prevention, benign solvents, and less hazardous synthesis) [77]. All of this explains MCRs central role in the toolset of modern synthetic organic methods.

MCRs have been widely used in natural product synthesis [78], medicinal chemistry and drug discovery programs, [9] combinatorial chemistry, [79] agrochemistry [80], and polymer chemistry, notably in the last two decades [81]. This is owing not just to their tremendous efficiency, but also to their unrivalled capacity to swiftly build enormous collections of compound libraries, as previously stated [9]. Indeed,

utilizing several variation points in the input materials (at least three) reduces the synthetic work required to create libraries of analogues of the desired dimension substantially. MCRs involving isocyanides as one of the components (IMCRs) has seen significant progress in recent decades and are now widely explored at both the fundamental and applied levels [73].

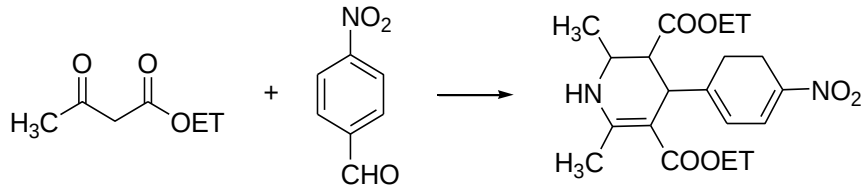
1.3.1. History of Multi-component reactions (MCRs)

MCRs have been known for more than 150 years [82]. Strecker was the first to notice a MCRs in motion. In the presence of potassium cyanide, an aldehyde is condensed with ammonium chloride to produce an α-aminonitrile, which can subsequently be hydrolysed to produce the α-aminoacid **(Scheme 1.3.1)**.



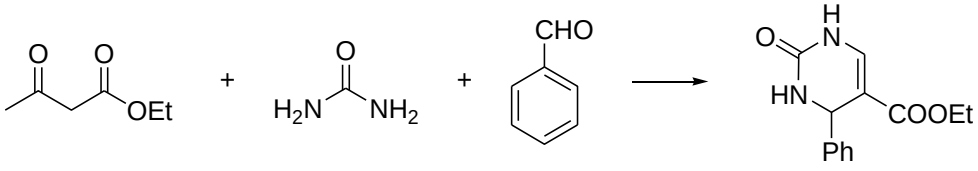
Scheme I.3.1: Strecker synthesis of α-aminoacid.

Numerous important heterocycle syntheses are MCRs in the literature. Hantzsch [83] developed the syntheses of dihydropyridine using ammonia, an aldehyde, and two equivalents of ethyl acetoacetate in 1882 **(Scheme 1.3.2)**.



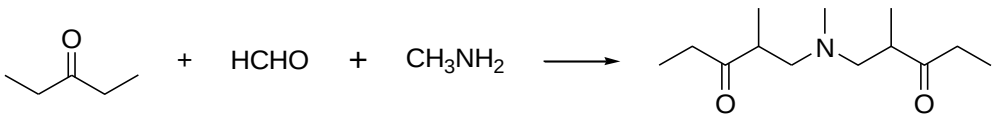
Scheme I.3.2: Hantzsch dihydropyridine synthesis.

In 1891, Biginelli [26] accomplished the synthesis of 3,4-dihydropyrimidin-2(1H)-ones from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde), and urea **(Scheme 1.3.3)**.



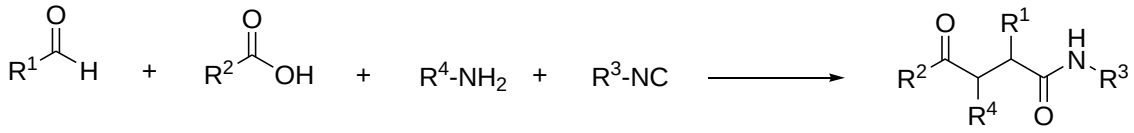
Scheme I.3.3: Biginelli 3,4-dihydropyrimidin-2(1*H*)-one synthesis.

In 1912, Mannich described a reaction [72], involving an amino alkylation of an enol with an aldehyde and an amine **(Scheme 1.3.4)**.



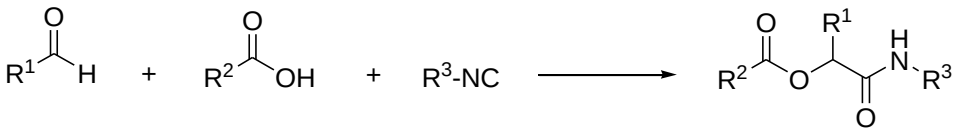
Scheme I.3.4: Mannich reaction.

The Ugi MCR [84], which was discovered in the 1960s, involves a ketone or aldehyde, an amine, an isocyanide, and a carboxylic acid to produce a bis-amide **(Scheme 1.3.5)**.



Scheme 1.3.5: Ugi reaction 4C-MCR.

The Passerini MCR (P-MCR) uses three reagents, an isocyanide, a carboxylic acid, and an aldehyde to produce an esterified α-hydroxycarboxamide, an important intermediate for chemical synthesis [85] **(Scheme 1.3.6)**.



Scheme I.3.6: Passerini Reaction 3C-MCR.

There have been numerous MCRs reported in the literature, but isocyanide-based MCRs (IMCRs) are arguably the most well-documented. The highest number of distinct scaffolds can be synthesized using IMCRs. Furthermore, because many of them are made from commercially available starting materials, one sort of reaction can access potentially vast libraries of compounds.

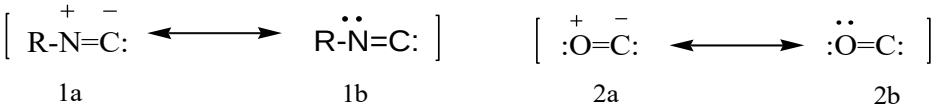
1.3.2. (Isonitriles) General aspects of the Passerini's reaction

Isonitriles, also known as isocyanides or carbylamines, are the most important reagents in IMCR chemistry. In the synthetic organic world, these compounds are distinguished by the presence of a terminal isocyano functional group, which causes the unpleasant odour of their volatile representatives [86]. They are the longest-known stable divalent carbon derivatives. In reality, the isocyanide have a unique functional group with an intriguing structure [73] and unusual chemical reactivity. They have the same cyano/nitrile functionality (CN) as their structural isomers, the more frequent nitriles, but the connection in isocyanides (also termed isonitriles) is through the nitrogen atom rather than the carbon centre. This means that the carbon atom in isocyanides is formally divalent, a structural trait found only in carbon monoxide and carbenes in organic chemistry [76]. The carbon atom of the isocyanide functionality, however, is normally sp and not sp^2-hybridized, as the structure is better defined as the

zwitterionic form with a triple bond between the carbon and nitrogen, unlike in ordinary carbenes.

1.3.2.1. Reactivity of Isocyanides

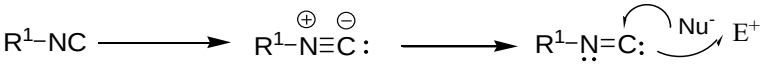
Isocyanide is a well-known example of a stable organic compound with a carbon atom that carries lone-pair electrons, as the structure indicates. Its stability can be explained using two resonance structures (1a) and (1b) **(Scheme 1.3.7)**.



Scheme 1.3.7: Resonance structure of isocyanides

Lone pair electrons on a carbon atom distinguish carbon monoxide (2a) and carbene (1a). Carbon monoxide, in particular, has a structurally similar structure (1a) with oxygen replacing the N-R of isocyanide (which is isoelectronic with isocyanide) [87].

Isocyanides have a peculiar chemistry that allows them to operate as nucleophiles, electrophiles, and even radicals [88]. This makes them an efficient and versatile synthetic reagent **(Scheme 1.3.8)**.



Scheme 1.3.8: Reactivity of Isocyanides

Isocyanides differ from other organic compounds, such as the related nitriles, in that both the electrophilic and nucleophilic centres, specifically the isocyanide carbon atom, are located at the same site in the molecule [89]. Most isocyanide reactions are expressions of this structural feature. Isocyanides react with both electrophilic and nucleophilic partners via ionic pathways, usually in this order, but concerted mechanisms are also possible [90]. Isocyanide chemistry also includes reactions involving radicals, which arise from their carbenoid nature [91]. Furthermore, the acidic behaviour of the proton(s) available at the isocyanide site has spawned a broad variety of valuable molecules [92].

Although isonitriles play an important role in a variety of chemical reactions, their popularity and significance are strongly linked to some of the most well-known multicomponent methodologies [93], such as the Ugi [76] and Passerini [94] coupling reactions. Several downsides outweigh the benefits of these functional categories. Major commercial producers have a limited supply of isonitriles. In most circumstances, they are not simple to produce.

Even though there are over 26 000 isocyanides reported and over 3000 classified as commercially available, only a small percentage of these are used in chemistry **(Figure 1.2)**. Most isocyanide research

leverage on well-known commercial isocyanides. Isocyanides are cited in over 21 000 papers, excluding patents, according to a recent bibliometric analysis using Sci-Finder. Only 9 isocyanides, on the other hand, account for almost 19 000 citations (more than 90%) of all isocyanide research papers [95]. The commercially available *tert*-butyl isocyanide, cyclohexyl isocyanide, TOSMIC, isocyanoacetic acid esters, 2,6-dimethylphenyl isocyanide, benzyl isocyanide, methyl isocyanide, and phenyl isocyanide are among the recurrent isocyanides.

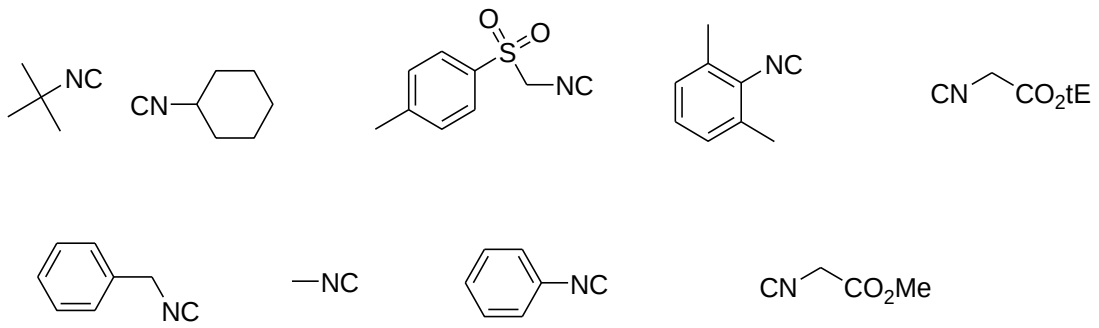


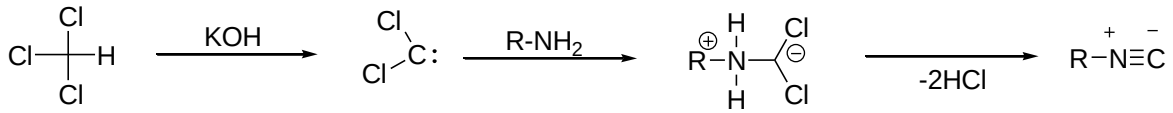
Figure 1.2: Most common isocyanides.

1.3.2.2. Synthesis of isocyanides

Isocyanides were first synthesized in 1859 by Lieke [96] by a nucleophilic substitution reaction of AgCN with alkyl halides, and he obtained a product with an unpleasant odour that vanished after prolonged heating **(Scheme 1.3.9)**.

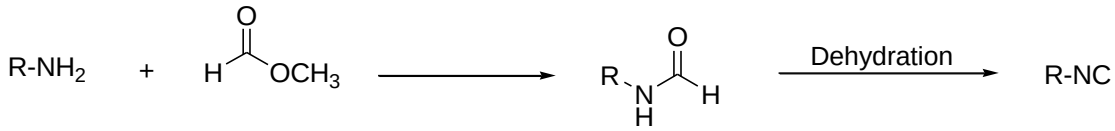
Scheme I.3.9: Lieke synthesis of an isocyanide

Shortly after, Hofmann [97] found a new approach to isocyanides synthesis via the condensation of a primary amine with a dichlorocarbene, generated in situ by heating chloroform with potassium hydroxide **(Scheme 1.4)**. However, this approach has issues with reproducibility, yield, and purification.



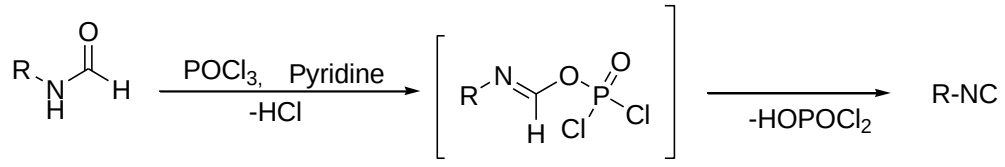
Scheme 1.4: Hoffmann synthesis of isocyanide (carbylamine method).

Ivar Ugi has made a substantial contribution to isocyanide chemistry. Ugi improved isocyanide synthesis by dehydrating *N*-monosubstituted formamides, which can be made from primary amines and methyl or ethyl formate or formic acid [98] **(Scheme 1.4.1)**.

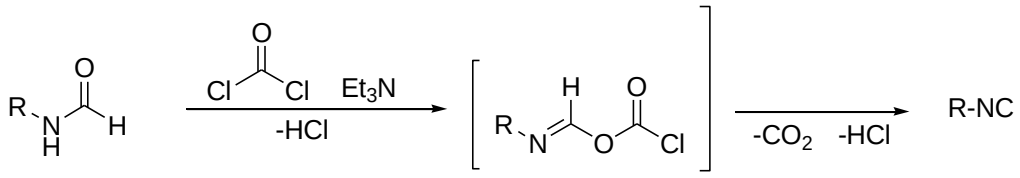


Scheme 1.4.1: Synthesis of isocyanide by dehydration of formamide

For this reaction, phosgene [99], diphosgene (trichloromethyl carbonochloridate) [78], organic chlorophosphate derivatives [100], XtalFluor-E [101], tosyl chloride [102] and phosphoryl chloride [103] have been employed as dehydrating reagents in combination with bases, most commonly tertiary amines to avoid the reduced yields of the products **(Scheme 1.4.2)**.



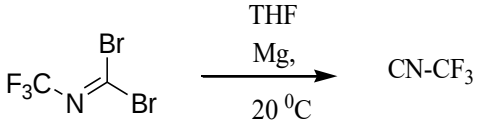
a. Using $POCl_3$ as dehydrating agent



b. Using Phosgene as dehydrating agent

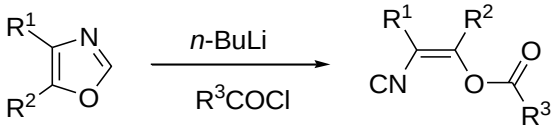
Scheme I.4.2: Synthesis of Isocyanide by dehydration of formamide.

Isocyanides can be synthesized from isocyanide *gem*-dihalide. For example, treatment of *gem*-dihalide of trifluoromethyl isocyanide with magnesium afforded the corresponding isocyanide [104] **(Scheme 1.4.3)**.



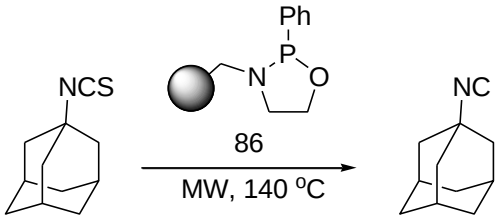
Scheme 1.4.3: Synthesis of isocyanide from *gem*-dihalo isocyanide with Mg in THF

Isocyanides can also be produced by reacting oxazoles with *N*-butylithium and quenching the resultant anion with an electrophile **(Scheme 1.4.4)** [105].



Scheme 1.4.4: Synthesis of isocyanides from oxazoles

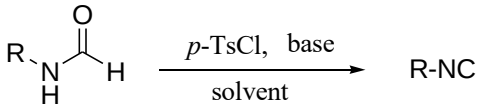
Ley *et al.* under microwave conditions used a polymer-supported reagents to reduce isothiocyanate to isocyanide [106] **(Scheme 1.4.5)**.



Scheme 1.15: Synthesis of isocyanide from isothiocyanate

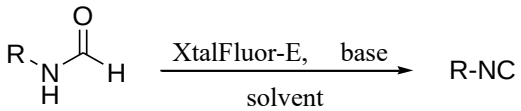
Isocyanide was synthesised in a yield of 96 %, and after removing the solid support by filtration, it was found to be analytically pure.

Waibel also investigated and optimized the synthetic protocols to convert *N*-formamides into isocyanides using three different dehydration reagents (*p*-toluenesulfonyl chloride (*p*-TsCl), phosphoryl trichloride ($POCl_3$) and the combination of triphenylphosphane (PPh3) and iodine) while considering the principles of green chemistry [107]. Among the reagents examined *p*-TsCl was the reagent of choice for non-sterically demanding aliphatic mono- or di-*N*-formamides (yields up to 98%) **(Scheme 1.4.6)**.



Scheme 1.4.6. Dehydration of formamide using *p*-TsCl and a base

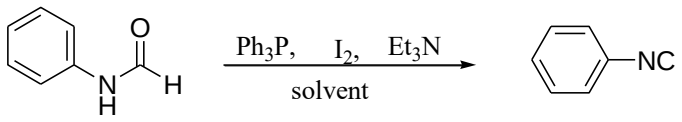
The formation of isocyanides from formamides using XtalFluor-E, $[Et_2NSF_2]BF_4$, was reported by Keita [101]. A wide range of formamides was used to produce the corresponding isocyanides in up to 99% yield **(Scheme 1.4.7)**.



Scheme 1.4.7. dehydration of formamides with XtalFluor-E

To avoid the use of expensive and toxic dehydration reagents, Wang developed a practical method for the dehydration of formamides into isocyanides that use the combination of trimethyl phosphite and

molecular iodine, in the presence of a tertiary amine, to produce high yields of the appropriate isocyanides under ambient conditions [108] **(Scheme 1.4.8)**.



Scheme 1.4.8: Dehydration of formamides promoted by trimethyl phosphite and molecular iodine.

The Ugi method is still utilized for the vast majority of isocyanide syntheses today, despite the availability of numerous additional isocyanide procedures. According to a review of isocyanides, the most practical method used phosphorus oxychloride as a dehydration agent [95].

Depending on the reactivity of the formamide, the most typical $POCl_3$ method is carried out at low temperatures up to -50 °C. To avoid isocyanide hydrolysis, the workup entails cautious hydrolysis to eliminate any excess dehydrating agent while keeping the pH in the basic range. Finally, distillation, chromatography, or recrystallization must be used to purify the crude isocyanide [95]. Due to the presence of small amounts of acidic materials, this step can also cause significant yield losses. As a result, the traditional $POCl_3$-enabled isocyanide synthesis not only necessitates meticulous reaction, workup, and purification conditions, but it is also time-consuming and exposes the chemist to the often-smelly isocyanide vapours for an extended period of time.

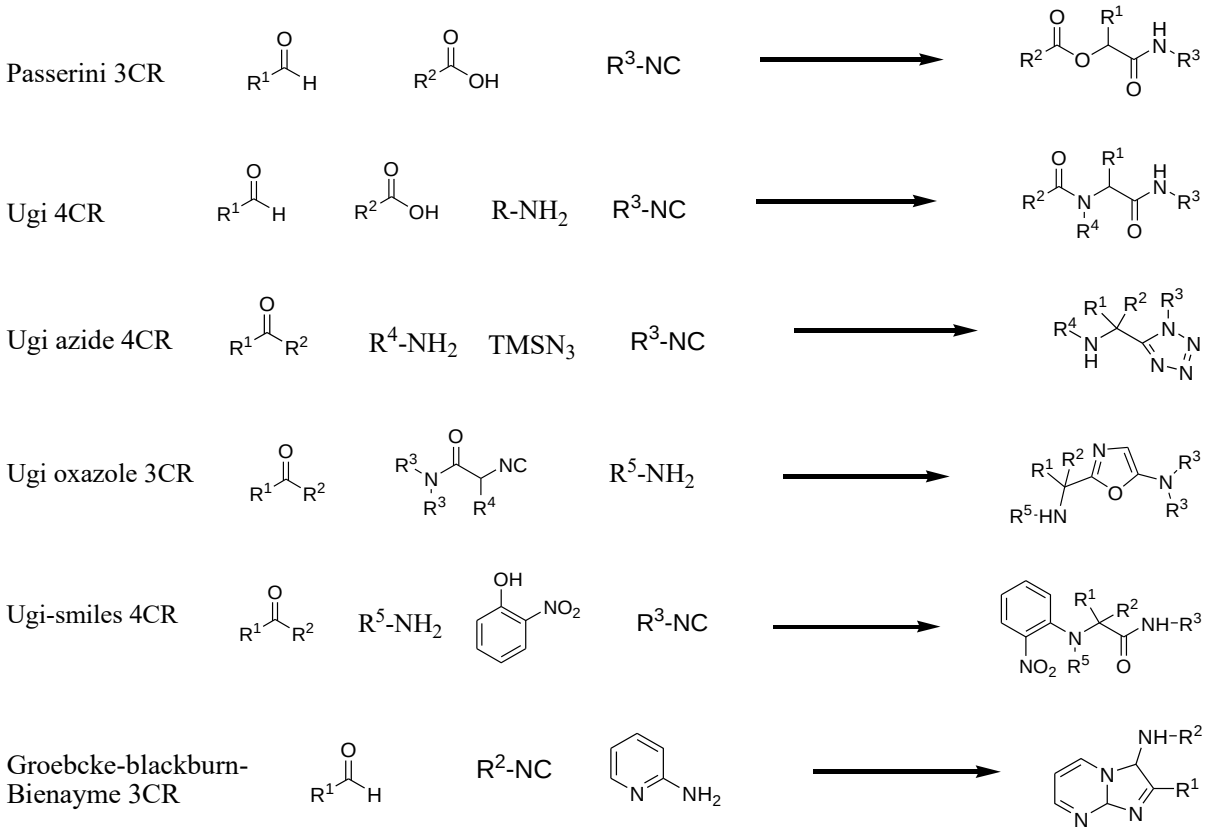
Furthermore, due to considerable volumes of waste generated during the synthesis, traditional isocyanide syntheses cannot be considered sustainable. Wang *et al*. recently developed a less toxic dehydration reagent based on PPh_3 and iodine employing dichloromethane as solvent, which produced high yields of up to 90% within 1 hr for mainly aromatic formamides [108]. Shortly after, Porcheddu *et al.* reported an improvement of the Hoffmann approach towards a more sustainable protocol using mechanochemical activation via ball-milling and significantly reducing the amount of solvent used. As a result, isocyanides with a broad range of aliphatic, benzylic, and aromatic moieties were obtained in 71% yields within 30 min [88]. These few examples demonstrate one of the major drawbacks of this system, namely the use of volatile organic solvent, unsatisfactory yield, and long reaction time. Meanwhile, when the three different dehydration reagents (i.e. *p*-toluenesulfonyl chloride (*p*-TsCl), phosphoryl trichloride ($POCl_3$) and the combination of triphenylphosphane (PPh_3) and iodine were investigated under slightly different experimental conditions for dehydration of formamides by Waibel *et al.* high yields of isocyanides were generated, but still the reactions often require constant use of volatile solvent and prolonged reaction times (2 hrs) [102].

In 2020, Patil *et al*. published a convenient synthesis protocol for isocyanides towards improving the technique for $POCl_3$-based formamide dehydration by avoiding any aqueous workup [95]. The protocol afforded a great structural diversity of isocyanides in high yields and purity within 1 hour. The protocol,

however, still relied on the use of a volatile organic solvent such as DCM which had to be avoided for the reasons discussed above. There is a need for the development of rapid, efficient, and more sustainable strategies for the synthesis of isocyanides. Given the limitations of existing methods and as part of continuous program to develop solvent-free reactions, reported herein is a fast and solventless synthesis of several functionalized isocyanides. Using this methodology, 34 functionalized isocyanides were synthesised in high yields and purity within 5 minutes and minimal waste was generated.

1.4. Isocyanides-based MCRs

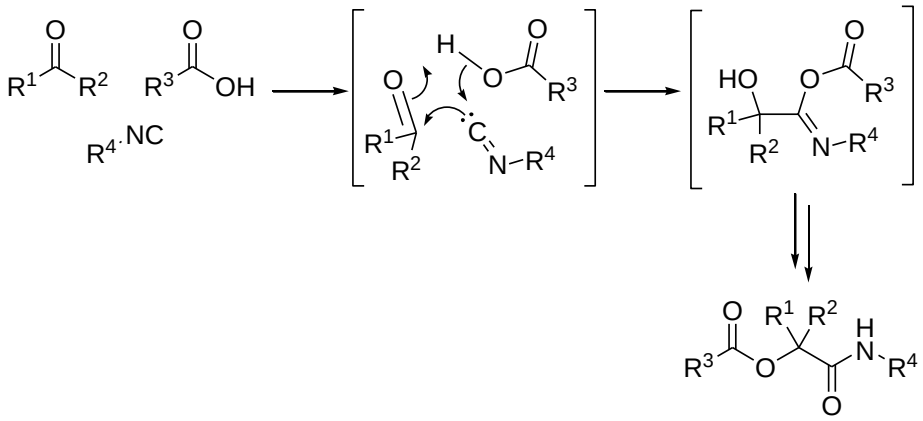
Isocyanides offer a wide range of uses in multicomponent chemistry due to their capacity to engage in many bonds formation processes. IMCR chemistry, which began in 1921 with the Passerini reaction, has produced a slew of key reactions [98]. The synthesis of extremely valuable α-acyloxyamide in a three-component condensation with carbonyl compounds (electrophiles) and carboxylic acids (nucleophiles) is a famous example of isocyanide ambident reactivity. Ugi's upgrade to a four-component reaction, which he completed forty years later by adding amines as extra reactants [109], laid the groundwork for a remarkable diversity of unique reactions that have since been produced. This field of study is continually evolving; Scheme 2 shows a few exemplary old and new IMCRs.



Scheme 1.4.9. Isocyanide-based MCR.

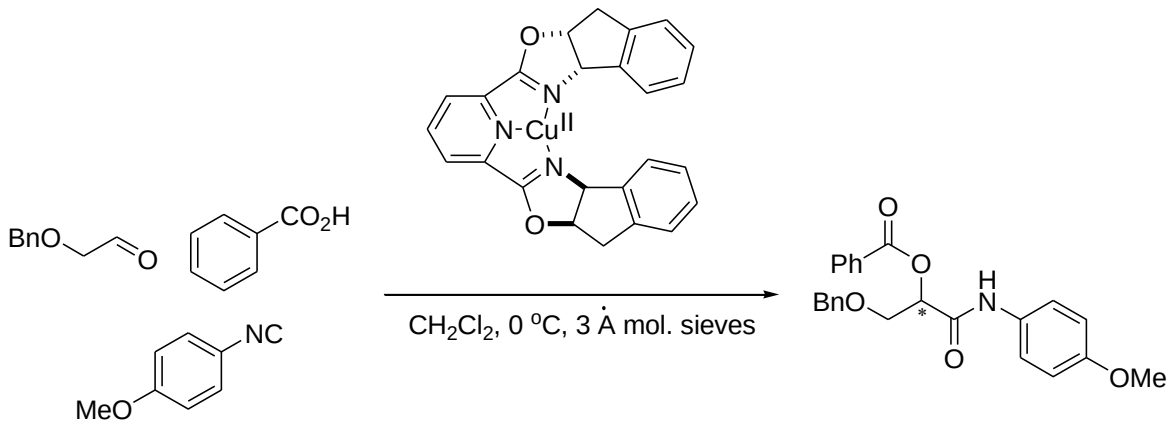
1.4.1. The Passerini reaction

The Passerini reaction combines an isocyanide with an aldehyde or ketone, followed by a carboxylic acid, to produce α-acyloxyamide [110]. The reaction offers good atom economy since each component's atom is integrated and a new stereo centre is formed. The Passerini reaction has been thoroughly investigated, and two solvent-dependent processes have been proposed. The reaction takes a non-ionic path in aprotic solvents, with the three components passing via a trimolecular reaction [111]. The isocyanide binds to the carbonyl component and the carboxylic acid in a hydrogen-bonded complex. This produces an acyl-imidate intermediate (the adduct), which then undergoes intramolecular acyl transfer (the so-called Mumm rearrangement) to provide the Passerini 3CR product. This mechanism is supported by a great deal of experimental and theoretical evidence. In non-polar aprotic solvents (dichloromethane, toluene, THF), the reaction proceeds at high molarities, whereas conversions in protic solvents like methanol are low [74]. Under ideal conditions, the formation of a hydrogen bond-associated complex is favoured, but ionic pathways using the nitrilium ion as an intermediary are unusual **(Scheme 1.5.)**. The final phase of the rearrangement has attracted less attention; however, it has been suggested recently that an extra carboxylic acid molecule could act as a catalyst in this step. Even though the nitrilium ion is not commonly thought to be a crucial intermediate for the Passerini reaction, new theoretical research suggests otherwise [112], and therefore the Passerini 3CR mechanism is a source of debate.



Scheme 1.5. Mechanism of the Passerini reaction in aprotic solvents

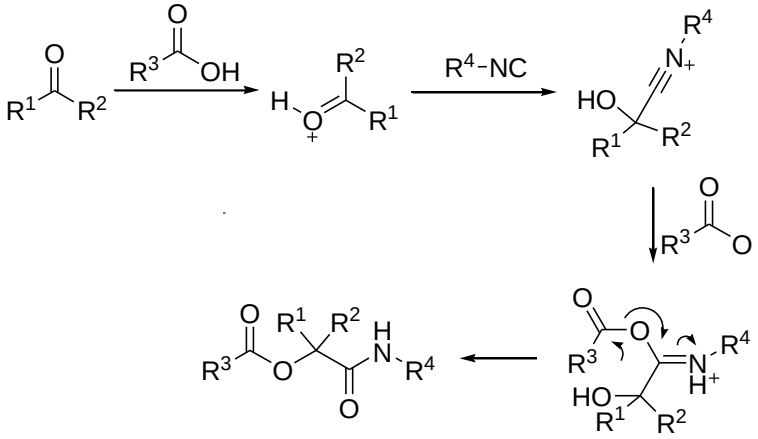
The Passerini reaction in an aprotic solvent according to Schreiber *et al.* generated enantioenriched compounds. The addition of the tridentate copper-complex afforded the α-acyloxyamide in 93 % yield with 97 % enantiomeric excess **(Scheme 1.5.1)**.



Scheme 1.5.1. Stereochemical control of the Passerini reaction

To produce a high degree of enantioselectivity, water is required to enhance the Passerini reaction via a protic pathway, strictly under anhydrous conditions.

In protic solvents, the Passerini reaction is thought to occur via an ionic process in which the carbonyl species become activated by protonation. The α-acyloxy amide is formed when this intermediate combines with the isocyanide component, followed by acyl group transfer and amide tautomerism **(Scheme 1.5.2)**.



Scheme 1.5.2. Mechanism of the Passerini reaction in protic solvents

1.5. Applications to spiro-heterocyclic synthesis

MCRs are extremely powerful synthetic tools for medicinal chemistry and the pharmaceutical industry due to the potential of the resulting scaffolds. Indeed, depending on the functional groups integrated into the MCR's various partners, post-modifications can be made. Large libraries of structurally diverse complex compounds for biological screens can be synthesized quickly and easily in this fashion [113].

The spirocyclic motif can be found in chiral ligands, natural products, and molecules that are of pharmacological importance [114]. Spiro compounds have recently become more important in the

development of pharmaceuticals due to the obvious conformational restriction imposed by the spiro atom, which allows the reduction of the entropy penalty associated with the binding to an active site of a protein target, a process that requires the adoption of a determined conformation [115]. Figure 1.3 shows some examples of spirocyclic natural products as well as spiro compounds of pharmaceutical interest, including acutumine, which is derived from the medicinal herb *Sinomenium acutum* and may have potential memory-improving properties, and vetivone, an antifungal agent produced by the fungus *Streptomyces griseus* [114, 115].

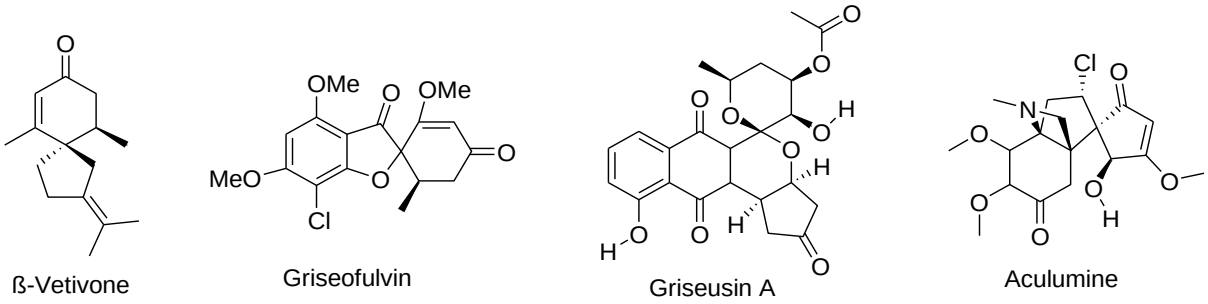


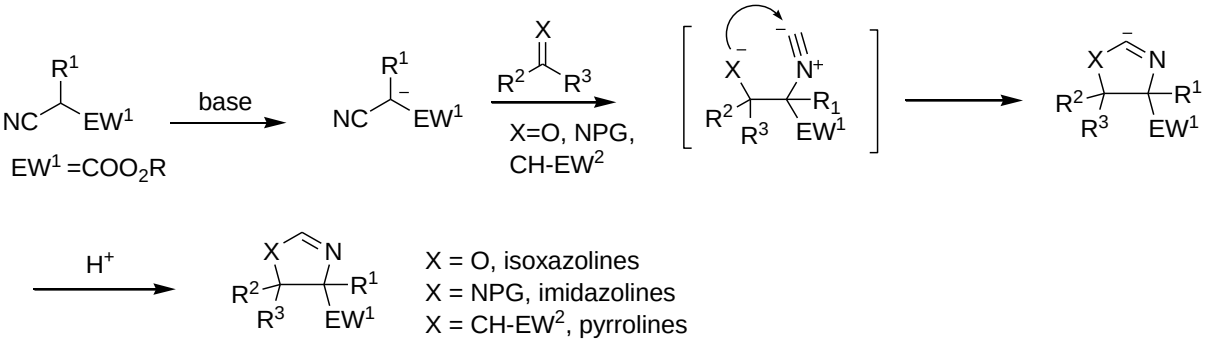
Figure 1.3. Selected examples of natural products and compounds of pharmaceutical interest which contain spiro rings.

Due to the significance of these types of molecules, interest in developing synthetic techniques for producing them, particularly in an enantioselective manner has been increasing [116]. Cycloaddition reactions using exocyclic double-bonded cyclic molecules stand out from the rest due to their ease of operation and wide range of potential reaction partners [117].

1.5.1. Isocyanide and isothiocyanate derivatives as formal 1,3-dipoles

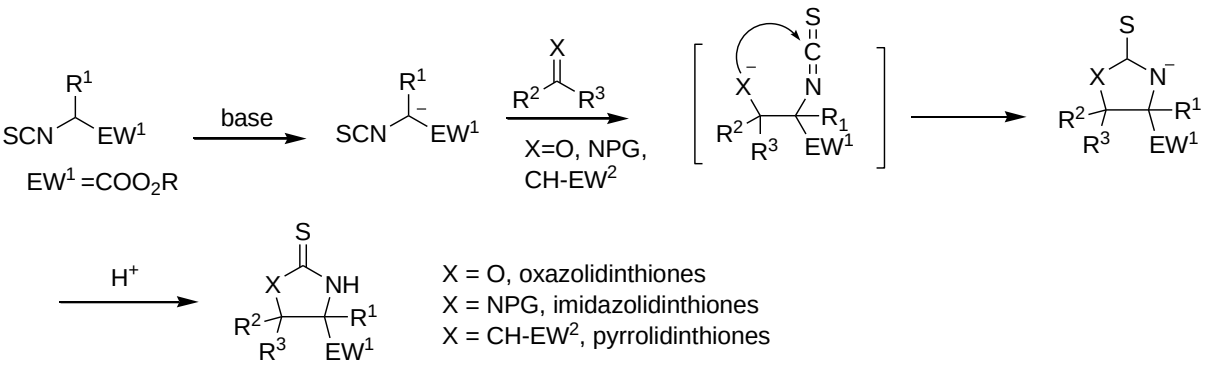
The isocyanides functional group (-NC) is associated with highly special properties that highlight its uniqueness in the field of organic chemistry [114]. Isocyanides can behave as both nucleophiles and electrophiles, which allows them to interact with a wide range of nucleophilic or electrophilic species. Isocyanides also possess a high degree of α-acidity, which can be further enhanced by adding electron-withdrawing groups to this position, such as carboxylic or phosphoric esters, nitriles, or sulfonyl groups, nucleophilic or electrophilic species as well as radicals to produce a variety of primary imine adducts[92]. A carbanion is produced when the α-position is deprotonated, and it can perform addition reactions to electrophilic double bonds such as carbonyl groups, imines, and C=C double bonds conjugated with electron-withdrawing groups. This addition produces a new anion that can intramolecularly attack the isocyanide moiety's terminal carbon atom, which has electrophilic properties [117]. This attack results in the formal divalent carbon atom being transformed into a tetravalent state, a relatively uncommon process in typical organic reactions. The overall process can be technically referred to as a [3+2] cycloaddition in which the isocyanide behaves like a 1,3-dipolar molecule

(Scheme 1.5.3). According to the reaction partner, oxazolines, imidazolines, or pyrrolines are produced [118].



Scheme 1.5.3. Generic formal [3+2] cycloaddition of isocyanides with electrophilically-activated double bonds.

Similar to this, isothiocyanates with an electron-withdrawing group in the α-position can react as formal 1,3-dipoles and produce oxazolidine, imidazolidine, or pyrrolidine thiones when they react with unsaturated bonds that have been electrophilically activated (Scheme 1b) [119, 120] **(Scheme 1.5.4)**.



Scheme 1.5.4. Generic formal [3+2] cycloaddition of isothiocyanates with electrophilically-activated double bonds.

1.5.2. Oxindoles as dipolarophiles

Spirooxindoles have come to be recognized as privileged structures that can be found in both pharmaceutically relevant drugs as well as natural alkaloids including horsfiline, which was isolated from the Malaysian tree *Horsfieldia superba* [114]. Examples include potential candidates for targeted cancer therapy, antimalarial drugs, cell growth inhibitors like spirotryprostatin A, fungicidal drugs like welwitindolinone A, and compounds that may be employed in inhibitor-based treatments for tuberculosis **(Figure 1.5)** [50]. As a result, numerous synthetic techniques that target these molecules have been developed. Many of them make use of isothiocyanates as formal dipoles [117].

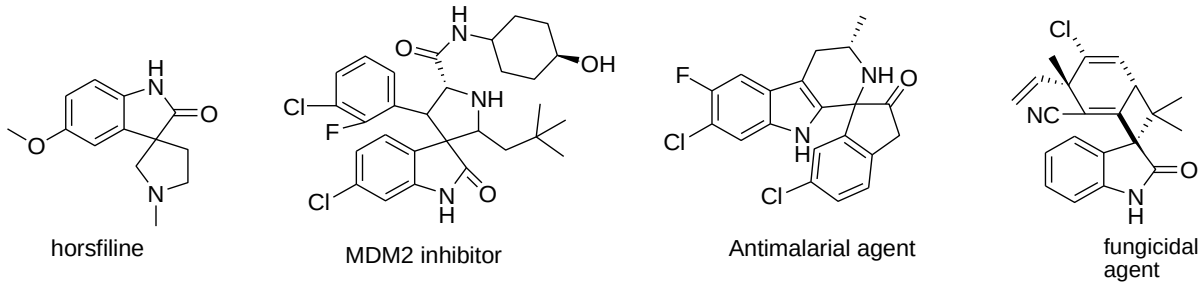
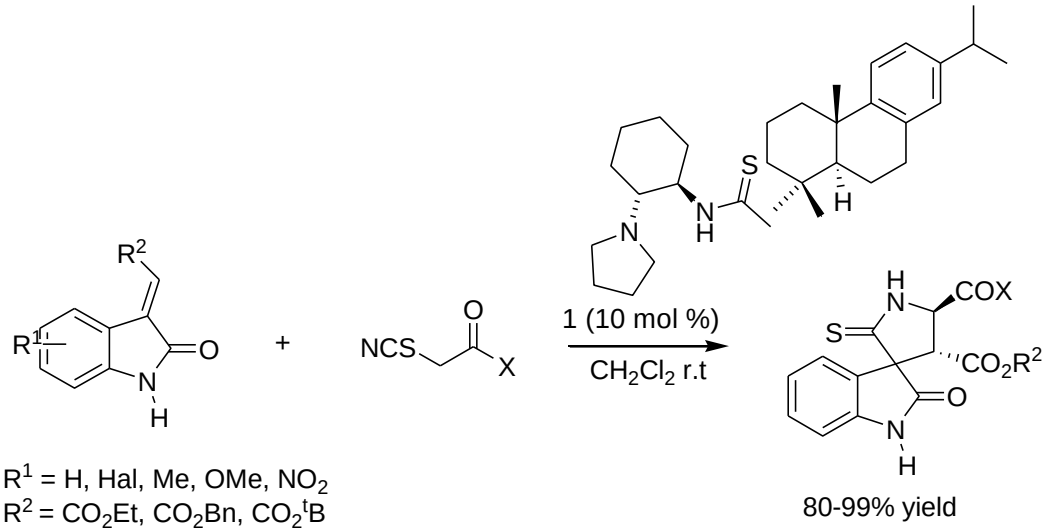


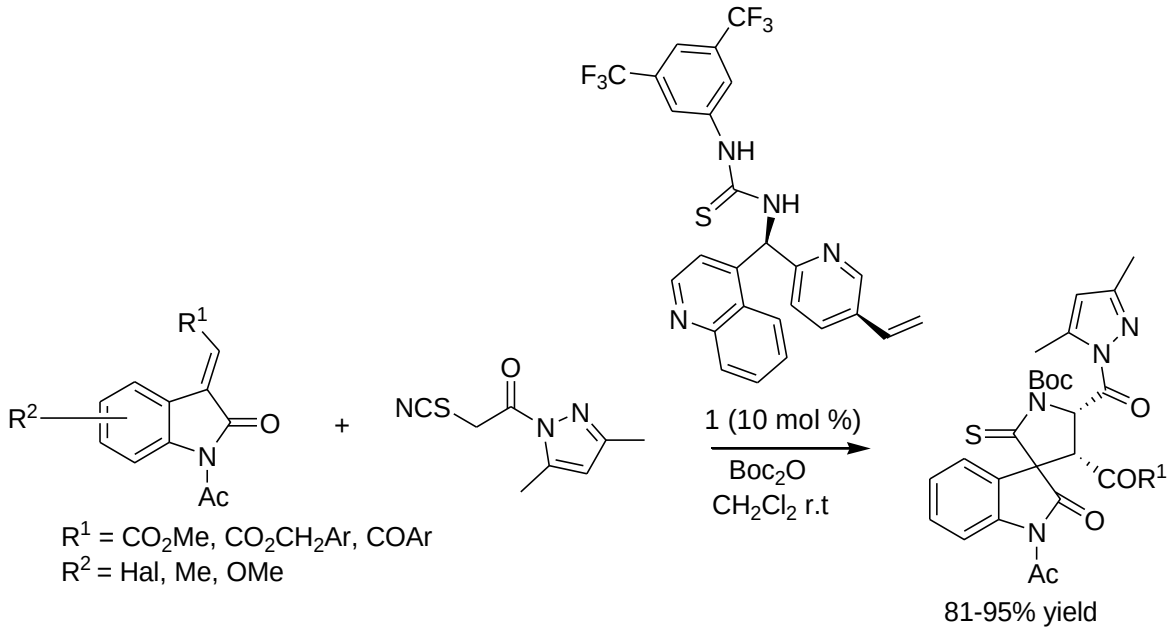
Figure 1.4. Selected natural and bioactive compounds featuring a spirooxindole motif

The Wang group reported the first asymmetric synthesis of a spiro molecule from isothiocyanates in 2011. The reaction of 3-methyleneindolin-2-ones and α-isothiocyanato imides in the presence of rosin-derived tertiary amine thiourea produced optically active spirooxindoles with good to excellent yields and good diastereo and enantioselectivities **(Scheme 1.5.5)** [121].



Scheme 1.5.5. Synthesis of 3,3'-thiopyrrolidonyl spirooxindoles catalysed by rosin-derived thiourea.

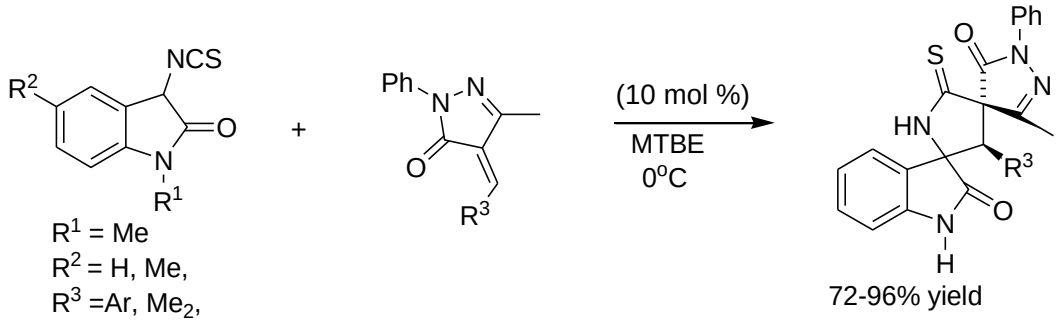
In another asymmetric synthesis performed by Barbas and Zhong in 2012, 3-methyleneindolin-2-ones were converted into 3,3'-thiopyrrolidonyl spirooxindoles. The dimethylpyrazolone moiety was used instead of the oxazolidinone moiety found in isothiocyanates because it improved diastereoselectivity **(Scheme 1.5.6)**. This modification made it possible to use a thiourea catalyst based on cinchonidine, which produced outstanding results in terms of yield, diastereo- and enantioselectivity for substituents having distinctive characteristics on the oxindole ring or the exocyclic double bond [122].



Scheme 1.5.6. Synthesis of thiopyrrolidonyl spirooxindoles from methylene oxindoles and dimethylpyrazoyl isothiocyanates.

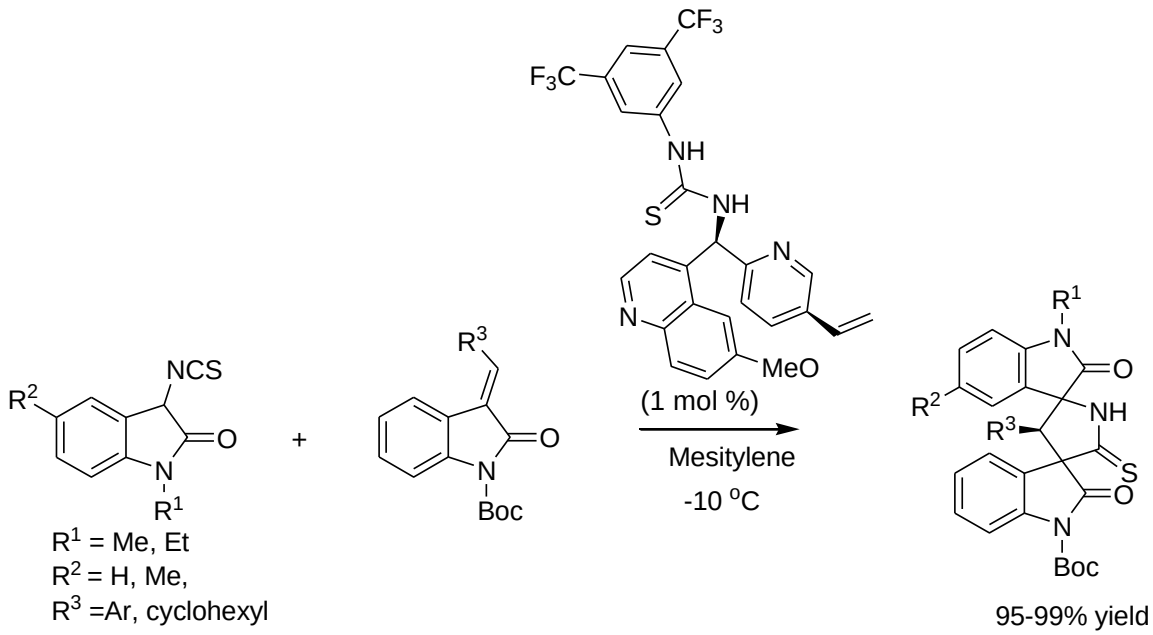
1.5.3. 3-Isothiocyanato oxindoles as formal dipoles

Oxindoles with an isothiocyanate group at position 3 have been used as formal dipoles in a variety of enantioselective processes that produce spirooxindoles. Using this technique, it is possible to produce these 3,2'-pyrrolidonyl spirooxindoles, which have a nitrogen atom close to the spiro carbon core. Rui Wang and colleagues reported on the synthesis of optically active bi-spirocycles from isothiocyanato oxindoles and alkylidene pyrazolones catalysed by their rosin-derived thiourea **(Scheme 1.5.7)** [121]. With good to excellent yields and enantiomeric excess, the reaction avoids the use of environmentally harmful halogenated solvents and produces multicyclic structures with three contiguous stereogenic centres, including two spiro quaternary centres, except for pyrazolones disubstituted at the exocyclic double bond.



Scheme 1.5.7. Synthesis of thiopyrrolidonyl spirooxindoles from methylene oxindoles and dimethylpyrazoyl isothiocyanates.

Later in 2013, a different approach to the earlier synthesis of bi-spirocycles with two oxindole units was reported by the Yuan group [123]. The usage of thiocarbamate organocatalyst, produced from quinine, in this work was innovative since it had a different hydrogen donor/acceptor unit. The process employs a small amount of catalyst and generates the desired products with outstanding diastereo- and enantioselectivities **(Scheme 1.5.8)**, despite the need for cooling to significantly lower reaction temperatures.



Scheme 1.5.8. Thiocarbamate-catalysed Michael addition/cyclization of isothiocyanato oxindoles and methylidene indolinones.

1.6. Aim and Objectives

In modern-day drug discovery, there is a drive to find greener ways to turn molecules into medicine. The shift towards more sustainable chemical processes used in the manufacture of medicines includes using greener solvents, less energy and reducing hazardous waste. As a result, our motivation is to find new reactivity, reagents, sustainable techniques, and catalysts that will allow synthetic chemists to build reaction sequences to access molecules of any complexity. The major aim and objectives of this thesis are related to the discovery of new sustainable multicomponent reactions involving an isocyanide such as Passerini reactions and further developing it to new sustainable methodologies in spiro-heterocyclic compound synthesis.

1.6.1 Diagram of project objectives

During the project, the objectives were divided into five areas of research: **(Figure 1.6)**

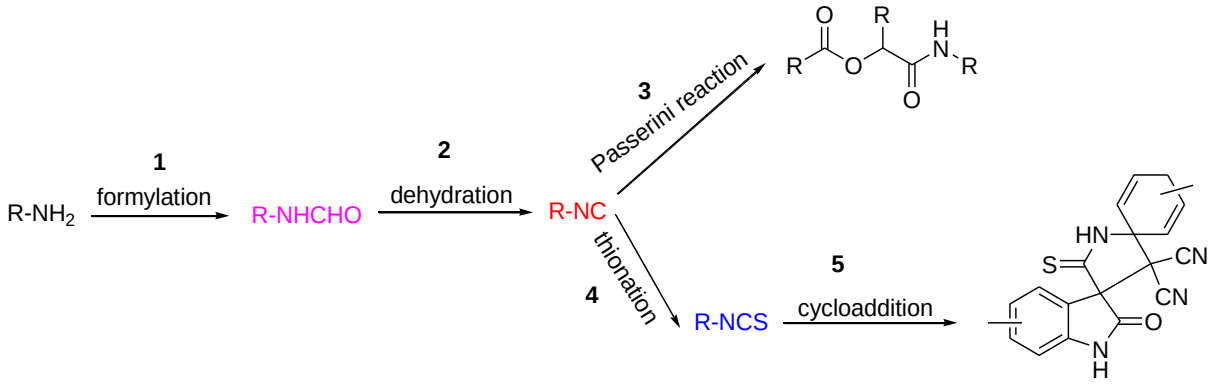


Figure 1.5: Diagram of project objectives

Initially, a two-step synthesis of isocyanides from amines was investigated and divided into two sections: amines to formamides **(1)** and formamides to isocyanides **(2)**. Additionally, the synthesis of a library of biologically important α-acyloxycarboxamides derivatives utilizing isocyanides, benzoic acid, and aldehyde/ketone was investigated under green conditions **(3)**. Furthermore, a more sustainable novel conversion of isocyanides to isothiocyanates was also studied **(4)** followed by Michael condensation/cycloaddition to furnish the corresponding spiro-heterocyclic compounds **(5)**.

Chapter 2

This chapter forms the basis for two publication in Molecules, see details above or visit https://doi.org/10.3390/molecules27134213, https://doi.org/10.3390/molecules27206850.

Isocyanides from amines

There are numerous methods for producing isocyanides from amines. According to Ugi, the most efficient method involves the formylation of the amine followed by dehydration to the isocyanide. Therefore, the initial investigations focused on designing two separate methods: firstly, to develop a procedure for formylating amines using triethyl orthoformate in the presence of the immobilized sulfuric acid on silica gel; and secondly to develop a procedure for dehydrating formamides to isocyanides using phosphorus oxychloride under solvent-free condition.

Part A.

2. Catalytic Performance of Immobilized Sulfuric Acid on Silica Gel for *N*-Formylation of Amines with Triethyl Orthoformate.

2.1. Introduction.

The formylation of amines is a crucial process in organic chemistry, owing to the widespread application of *N*-formylamine derivatives in industry and biologically active compounds, such as fluoroquinolones, substituted imidazoles, 1,2-dihydroquinolines, and nitrogen-bridged heterocycles, among others [124]. *N*-Formyl amine derivatives have also been used as reagents in Vilsmeier formylation reactions as amino acid-protecting groups and the synthesis of several other important derivatives, such as formamidines[125], isocyanates and nitriles [95].

Although there are a variety of reagents for the *N*-formylation of amines, the synthesis of formamides utilizing triethyl orthoformate as a formylating agent is still popular [126]. The reaction of ethyl orthoformate with aniline to afford *N,N* -diphenylformamidine was initially reported in 1869 by Wichelhaus [127]. Subsequently, Claisen synthesized ethyl *N*-phenylformimidate in low yields from the same reactants, but under slightly different experimental conditions [103]. Swaringen and colleagues went on to show that the reaction of *N*-alkylanilines with orthoformates in the absence of a catalyst or with hydrochloric/acetic acid produced orthoamides in low yields [128]. These few examples demonstrate one of the major drawbacks of this system, namely, the low yield. Meanwhile, when *p*-toluenesulfonic acid was employed as a catalyst, high yields of *N*-alkylformanilides and *N,N*-dialkylanilines were generated, but the reactions still often required high temperatures and prolonged reaction times. For example, Swaringen and co-workers demonstrated the synthesis of *N*-ethyl

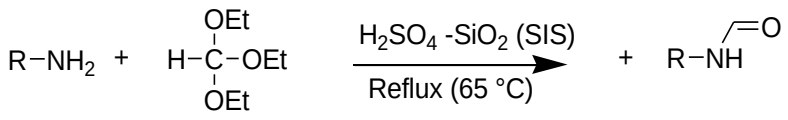
formamides from the reaction of amines with triethyl orthoformate in the presence of H_2SO_4, but under severe conditions (temperatures above 140 ºC) [128].

Various other formylating agents have been reported, including chloral [129], acetic formic anhydride [130], formic acid [131], ammonium formate [132], formate esters[133], polymer-supported formate [62], ethyl formate[134], triethyl orthoformate [135], aldehydes and methanol [136], carbon monoxide [18], and carbon dioxide [137]. However, these also tend to suffer from similar problems of long reaction times (hours to days), variable or low yields, and harsh conditions (or expensive catalyst systems). Several catalysts have been employed for the formylation of amines, including silica-supported sulfuric acid [21], H_2SO_4/$NaHSO_4$-activated charcoal [134], K-F alumina [138], amberlite IR 120 [139], natrolite zeolite [124], indium metal [140], sulfated titania [141], and sulfated tungstate [138], among others.

In the absence of a catalyst or promoter, *N*-formylation of amines is a sluggish reaction that usually requires unique reaction conditions or long-time frames for completion. However, some of these methods have quite some limitations, including harsh reaction conditions, the need for expensive metal catalysts or organocatalysts, and long reaction time frames. Thus, for organic transformations, the development of a safe, benign, environmentally friendly, high yield, quick reaction, and recyclable catalyst for the *N*-formylation of amines remains extremely desirable. In the last few years, H_2SO_4–SiO_2 has demonstrated significant promise as a cost-effective and easily retrievable solid catalyst for driving a variety of essential organic reactions in solvent-free environments [21]. H_2SO_4–SiO_2 is appealing for industrial usage because of its high catalytic activity, operational simplicity, and recyclability. The notion of employing H_2SO_4–SiO_2 as a transamidation catalyst was inspired by Rasheed *et al.* [25]. Thus, the catalyst was employed to build a generic formylation with triethyl orthoformate for the first time.

Results and Discussion

Initially, the reaction of aniline with triethyl orthoformate was chosen as the model reaction. During the optimization of reaction parameters, it was observed that aniline reacted smoothly with triethyl orthoformate, providing the desired product with a good yield (96%) within a short period of time (4 min) **(Table 2.1)**.



Scheme 2.1. *N*-Formylation of amines with triethyl orthoformate.

To generalize the protocol for the formylation of sterically hindered amines, the reaction was optimized by changing the temperature and molar ratio. The temperature was raised to 65 °C and was observed to

be quite sufficient to carry out the reaction with an optimum yield of the desired product (**Table 2.1**). It was observed that the need for an excess of triethyl orthoformate was no longer required, as a 1:3 molar ratio of amine to triethyl orthoformate was sufficient to yield the desired product **(Table 2.1, entry 3)**.

Table 2.1. Optimization of reaction parameters for *N*-formylation of amines with triethyl orthoformate (TEOF).

Entry	Reaction condition	Time	Yield
1	Aniline (1 mmol)/TEOF (1 mmol), SIS (0.2 g)	10 min	44%
2	Aniline (1 mmol)/TEOF (2 mmol), SIS (0.2 g)	6 min	66%
3	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.2 g)	4 min	96%
4	Aniline (1 mmol)/TEOF (4 mmol), SIS (0.2 g)	4 min	90%

*SIS is H_2SO_4-SiO_2

Next, we explored the impact of immobilized sulfuric acid on silica gel stoichiometry on the outcome of the reaction **(Table 2.1.1)**. We observed that excess H_2SO_4–SiO_2 was not beneficial for faster conversion. Conversely, a lower amount of H_2SO_4–SiO_2 led to substantially slower conversion. The background reaction (used as a model) was also measured in the absence of H_2SO_4–SiO_2, confirming its vital role.

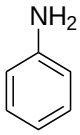
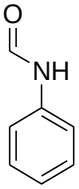
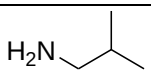
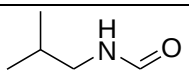
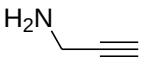
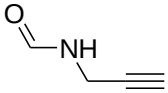
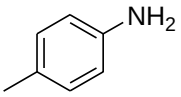
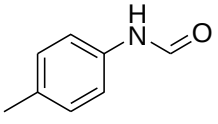
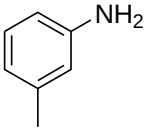
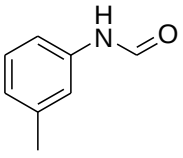
Table 2.1.1. *N*-Formylation of aniline under different catalytic conditions.

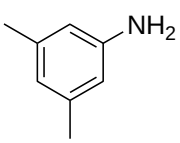
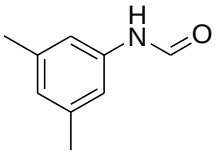
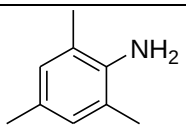
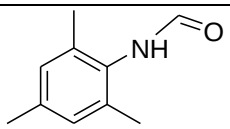
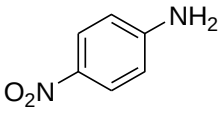
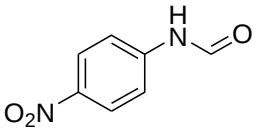
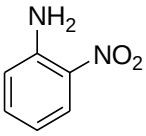
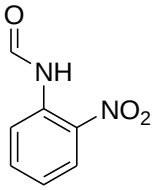
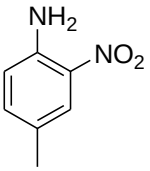
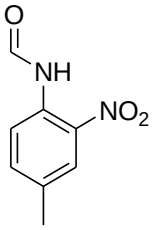
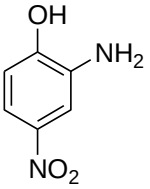
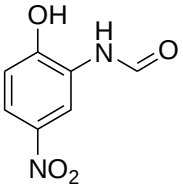
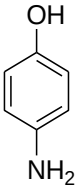
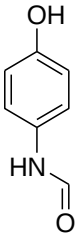
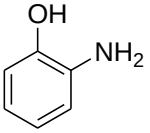
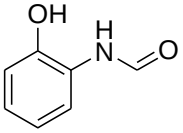
Entry	Catalytic Condition	Time	Yield
1	Aniline (1 mmol)/TEOF (3 mmol) without catalyst at 65 °C	3 h	traces
2	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.1 g), 65 °C	5 min	78%
3	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.2 g), 65 °C	4 min	96%
4	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.3 g), 65 °C	4 min	88%
5	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.4 g), 65 °C	6 min	71%
6	Aniline (1 mmol)/TEOF (3 mmol), SIS (0.5 g), 65 °C	6 min	64%

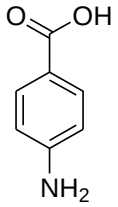
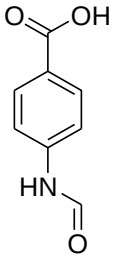
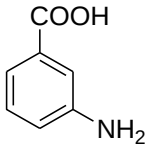
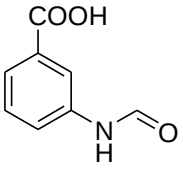
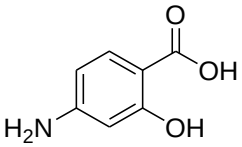
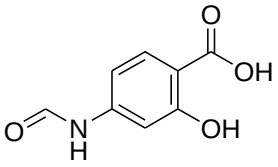
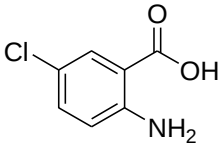
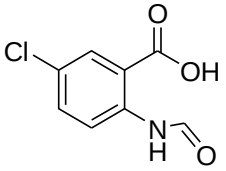
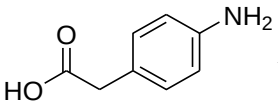
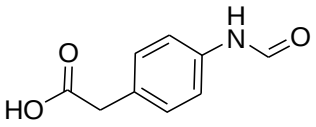
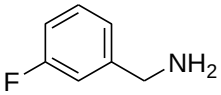
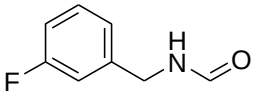
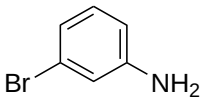
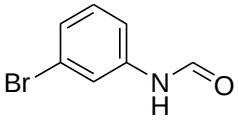
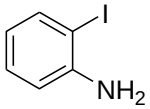
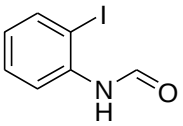
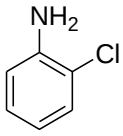
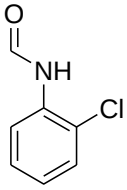
In general, the reaction proceeded efficiently, with various amines reacting with triethyl orthoformate to produce the corresponding *N*-formylated product with a good-to-excellent yield within a very short time. Aliphatic and aromatic primary amines underwent smooth *N*-formylation and gave the product in 70–96% yields (**Table 2.1.2)**.

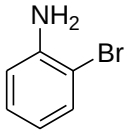
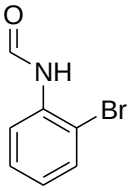
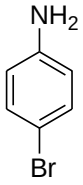
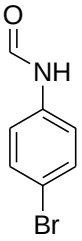
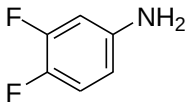
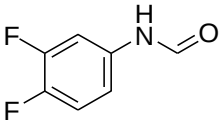
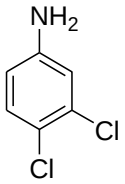
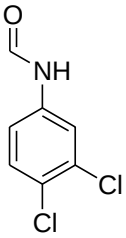
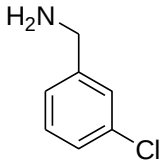
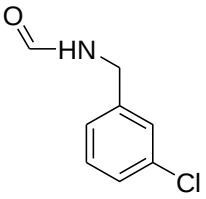
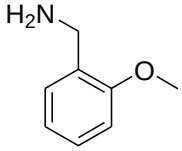
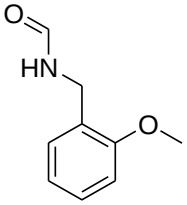
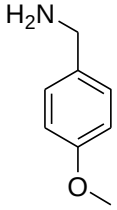
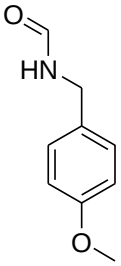
Aniline with electron-donating groups provided an excellent yield of 65–96% with triethyl orthoformate. The mono- or dihalogenated anilines (F, Cl, Br, I) provided outstanding yields, ranging from 73% to 96% of the corresponding products. Similarly, electron-withdrawing groups were found to react smoothly under the optimized reaction conditions and demonstrate excellent yields of desired products (85–96%). Generally, under these optimized reaction conditions, various functional groups were tolerated. However, finding a general method for generating amide bonds will surely benefit the drug discovery process. In general, the formylation of aryl/heteroaryl amines (electron-neutral, -rich, deficient), aliphatic, and cyclic secondary amines afforded the formylation products in excellent yields (70–96%). Interestingly, sterically hindered arylamines, such as compounds **6**, **7**, **10**, **11**, **16**, **17**, and **33–38**, were found to react smoothly under the optimized reaction conditions, demonstrating good yields of desired products. Less reactive heteroaromatics, such as **42–49**, **51**, and **56**, produced the product with a surprisingly high yield (77–90%) although these required a substantially longer reaction time (35–60 min). Still within the context of improvements, these are very modest reaction times. When secondary amines **52–54** were employed, the reaction was somehow also slow, providing a good yield of products in 1 h.

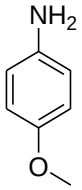
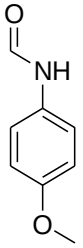
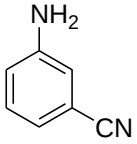
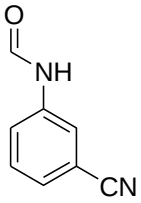
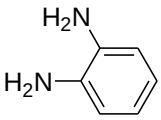
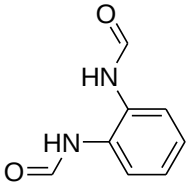
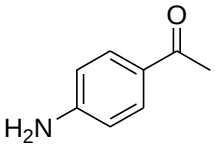
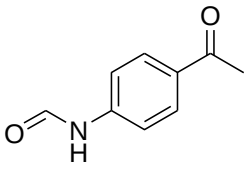
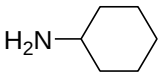
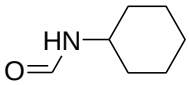
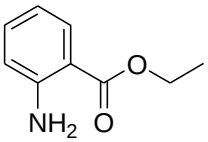
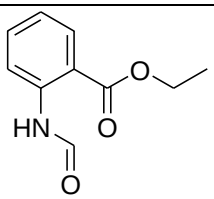
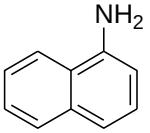
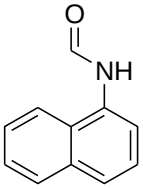
Table 2.1.2. *N*-formylation of amines using triethyl orthoformate in the presence of immobilized sulfuric acid on silica gel.

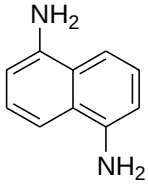
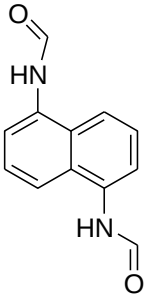
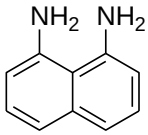
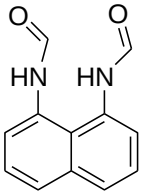
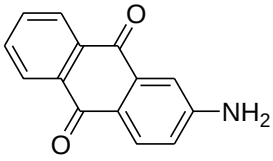
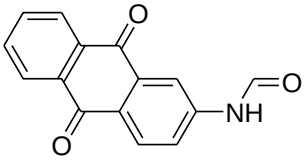
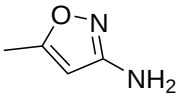
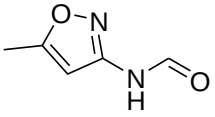
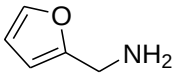
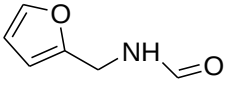
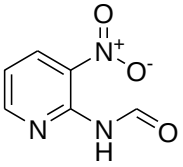
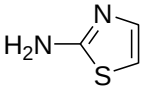
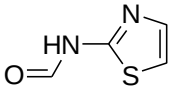
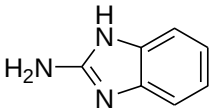
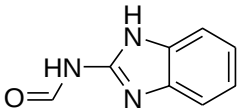
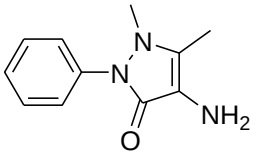
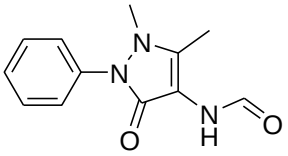
Entry	Amines	Time (min)	Product	Yield (%)
1		4		96
2		4		81
3		4		78
4		9		95
5		4		90

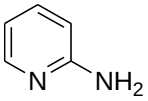
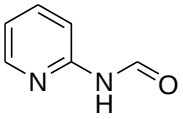
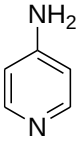
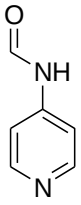
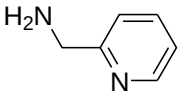
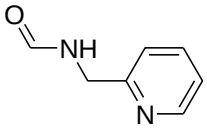
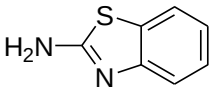
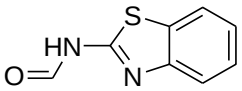
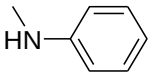
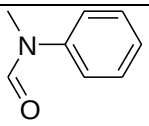
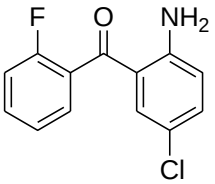
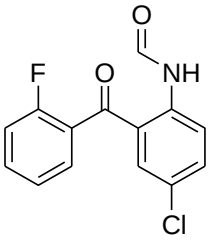
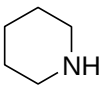
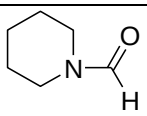
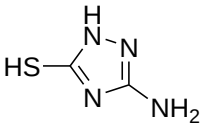
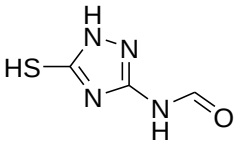
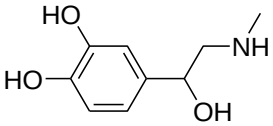
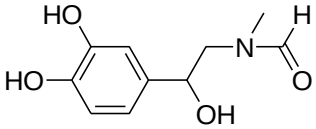
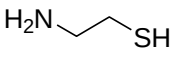
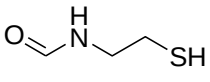
6		4		97
7		10		83
8		10		97
9		10		90
10		10		96
11		15		90
12		13		75
13		13		81

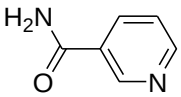
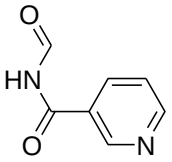
14		5		86
15		5		94
16		20		75
17		12		73
18		20		85
19		6		97
20		6		78
21		5		94
22		6		78

23		6		84
24		5		81
25		10		56
26		10		81
27		12		82
28		15		85
29		15		96

30		8		93
31		6		94
32		20		96
33		18		95
34		5		86
35		12		93
36		12		98

37		15		80
38		20		91
39		24		93
40		15		95
41		13		92
42		25		77
43		30		67
44		54		76
45		45		79

46		45		71
47		60		94
48		50		94
49		40		87
50		40		78
51		50		73
52		40		85
53		40		75
54		60		85
55		35		93

56		60		93

Reusability of Catalyst

While the catalyst is cheap and easy to prepare, we wanted to explore the reusability of the catalytic system. The catalyst was separated by simple filtration and washed with ethyl acetate after the reaction was completed, and it was reused for two consecutive cycles within the same time frame (4 min), with only a slight decrease in catalytic activity (7–13%) (Table 2.1.3.). Future work will explore the longer-term reusability in a flow system.

Table 2.1.3. The efficiency of the recycled SIS in the *N*-formylation of aniline.

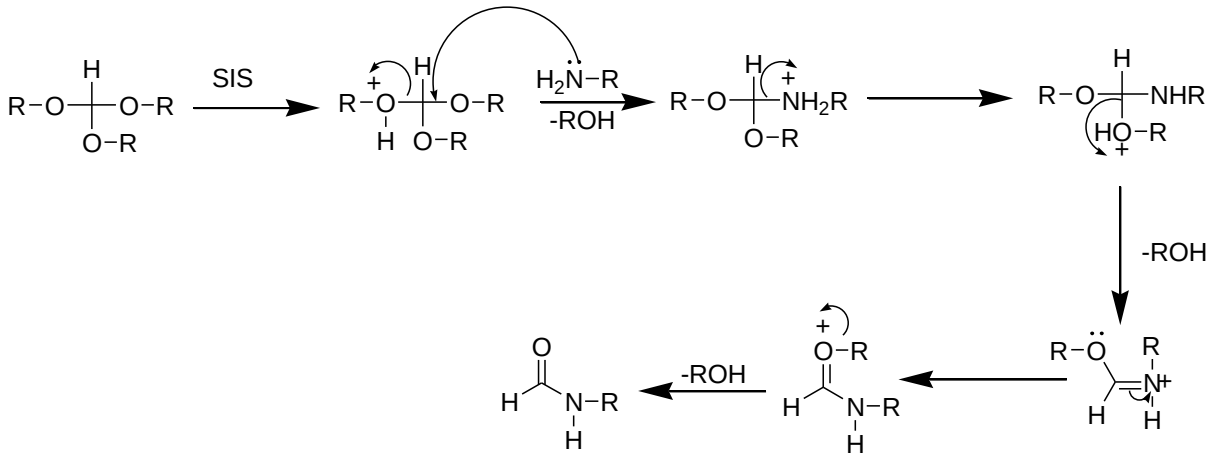
Entry	Turn	Yield %
1	1	96
2	2	89
3	3	83

To demonstrate the efficiency and versatility of the H_2SO_4–SiO_2 system, the result of *N*-formylation of aniline was compared with other protocols that have been published based on reaction times and yields **(Table 2.1.4)**. The results showed that the other approaches required longer reaction times for efficient conversion than for the present protocol. Therefore, on this basis, the present protocol is more efficient or comparable with other methodologies and is applicable in many laboratory settings.

Table 2.1.4. Comparison of efficiency of various conditions in the *N*-formylation of aniline.

Entry	Conditions	Time	Yield	References
1	Triethyl orthoformate in H_2O under ultrasound irradiation	3 h	88%	[142]
2	Solid-supported formate, DMSO, 70–80 °C	4 h	60%	[62]
3	SSA, HCOOH, 50–60 °C, solvent-free	7 min	99%	[22]
4	SA on activated charcoal, ethylformate, 54 °C	4 min	95%	[134]
5	Triethyl orthoformate in H_2O under neutral condition Microwave irradiation, 90 °C	2 h	87%	[135]
6	SIS, triethyl orthoformate, 60–65 °C, solvent-free	4 min	96%	Present protocol

Although the reaction's mechanism has not yet been established experimentally, **Scheme 2.1.1** suggests a possible explanation. The first step is the activation of the electrophilic carbon of triethyl orthoformate by the sulfonic group of H_2SO_4–SiO_2, which leads to the formation of a cationic intermediate. The cationic intermediate reacts with amine nucleophiles, which, on further elimination of ethanol, furnished the desired formylated product.



Scheme 2.1.1. Proposed mechanism for *N*-formylation of amines with triethyl orthoformate.

While 1,8-diformamido-naphthalene **(38)** and 3-formamido-1,2,4-triazole-5-thiol **(53)** are new derivatives and were characterized by one- and two-dimensional NMR analysis and high-resolution mass spectroscopy, all other products are known compounds and were identified by melting point, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The synthesis of formamides was confirmed by IR spectra, which revealed two distinct absorption bands between 3300 and 3400 cm^{-1} (secondary NH) and 1640 and 1680 cm^{-1} (*N*-formyl, C=O).

Furthermore, formamide molecules have both a conformational stereogenic axis and a configurational stereogenic centre. These molecules take on two distinct *syn* and *anti*-conformational diastereomers as a result of restricted rotation around the Ar–N bond [143]. The ^{1}H and ^{13}C NMR spectra of most of the synthesized formamides at 25 °C were consistent with the presence of two rotamers. These are not generally conformationally restricted, and we were not able to separate these chromatographically, apart from those described below, but some of this work is ongoing. Only one rotamer was observed for the compounds **8**, **14**, **27**, **45** and **46**.

During the purification of compounds **12** and **35**, two products appeared as partially separated spots on thin-layer chromatography (TLC) plates. Using normal silica gel chromatography, these compounds were identified as A and B rotamer pairs. After purifying compounds **12** and **35**, pure rotamers **12A** and **35A** were isolated **(Figure 2.1)**. Compounds **12A** and **35A** were the only pure isomers that could be isolated, while **12B** and **35B** were always contaminated to some degree by **12A** and **35A**, respectively. The fact that rotamers A and B could be isolated at room temperature and characterized using basic spectroscopic techniques astounded us. This occurrence may be viewed as a specific form of atropisomerism because atropisomers are stereoisomers with restricted rotation around a single bond where the rotational barrier is high enough to allow isolation of the isomeric species [144].

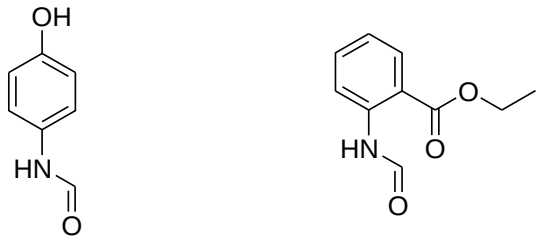


Figure 2.1. The yield of isolated conformers 12A and 35A.

Conclusions

We have developed a simple, green, and highly efficient protocol for the *N*-formylation of various amines in the presence of immobilized sulfuric acid on silica gel, with excellent yields and by means of a remarkably simple and environmentally benign process. The approach is compatible with a wide range of aromatic, heteroaromatic, aliphatic, and cyclic/acyclic primary and secondary amines. The H_2SO_4–SiO_2 catalytic system described here is a good complement to previously reported protocols due to its ease of manipulation, low cost, and benign nature. We are optimistic that, with this approach, we will be able to develop the biologically relevant heterocyclic ring system more efficiently. This protocol is generic, and it will undoubtedly offer value to this growing area of organic synthesis.

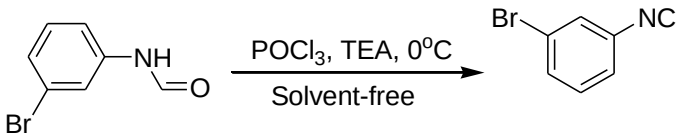
Part B.

2.2. A More Sustainable Isocyanide Synthesis from *N*-Substituted Formamides using Phosphorus Oxychloride in the Presence of Triethylamine as Solvent

With a successful method for formylating a variety of functionalized amines, our attention turned to the dehydration reaction. As mentioned in the introduction (**Chapter 1**), several reagents have been reported to successfully dehydrate *N*-formamides to isocyanides including phosphorus oxychloride, phosgene, triphosgene, cyanuric trichloride, phenylchlorothionoformate, and Burgess reagent. According to a recent review on isocyanides, the best dehydrating agent is phosphorus oxychloride. Phosphorus oxychloride ($POCl_3$) was initially chosen as the dehydrating reagent and triethylamine as the base, as these were the optimum conditions described by Ugi [73].

Result and Discussion

The dehydration of *N*-(3-bromophenyl)formamide with phosphorus oxychloride, in the presence of triethylamine (TEA) under solvent-free conditions at 0 ºC, produced 3-bromo-1-isocyanobenzene in excellent yield **(Scheme 2.2)**. The starting point for our experiments was to optimize the reaction conditions such as solvent and reaction time for the synthesis of isocyanides with wide structural diversity.



Scheme 2.2. Dehydration of *N*-(3-bromophenyl)formamide to 3-bromo-1-isocyanobenzene.

Since the phosphorus oxychloride employed for the dehydration of formamide is a highly reactive reagent, the reaction solvents must be chemically inert, which rules out alcohols, ketones, water, and amines while allowing a variety of acceptable and more sustainable solvents to be employed in the optimization study because some solvents commonly used for the dehydration of *N*-formamides are typically poisonous or not considered very green [8].

Here, our focus is directed towards the development of a more sustainable synthesis approach for isocyanides by significantly reducing the toxicological impact of the synthesis reagent employed as well as minimizing waste (E-factor), two critical factors of overall sustainability.

To achieve sustainable conditions for the above transformation, a series of experiments was carried out. First, we investigated the dehydration of *N*-(3-bromophenyl)formamide with phosphorus oxychloride, in the presence of triethylamine in various solvents, as well as under solvent-free conditions. Although

the reaction occurs in all the solvents tested, dichloromethane and tetrahydrofuran were the best among the tested solvents producing 94 and 72% yields respectively **(Table 2.2)**.

When the reaction was carried out in diethyl ether, toluene, and acetonitrile, only a small amount of the product was observed with yields of 37, 15, and 56% respectively **(Table 2.2**, **entry 1-5)**. Therefore, DCM was found to be the best organic solvent for the current reaction as it provided the desired product with a 94% yield within 15 minutes **(Table 2.2, entry 4)**. This is unsurprising given that formamides are weakly soluble in most organic solvents. Though, among the solvents examined, dichloromethane was the most effective, which is consistent with literature reports **(Table 2.2, entry 4)**. However, in the context of sustainability, attention was given to greener alternatives for commonly used solvents according to solvent selection guides. At this point, we thought of carrying out these reactions under green conditions. Interestingly, when the reaction was performed under solvent-free condition dehydration was completed in 5 minutes and the product was obtained in 98% yield **(Table 2.2, entry 5)**, thus lowering the overall environmental impact.

The best overall results were obtained under solvent-free conditions for $POCl_3$ based formamides dehydration, which further boosts the reaction's sustainability because ideally from the green chemistry point of view, a reaction should be carried out under solvent-free or aqueous conditions. Interestingly, this strategy resulted in an E-factor of 5.5 and a yield of 98%. As a result, this technique proved to be the most sustainable and practicable, and it was employed in further investigations.

Table 2.2. Solvent test for the dehydration of *N*-(3-bromophenyl)formamide with $POCl_3$ and a base.

Entry	Solvent	Yield %	E-factor	Time
1	THF	72	10.4	1 h
2	Diethyl ether	37	17.2	30 min
3	Toluene	15	20.3	40 min
4	Acetonitrile	56	46.4	1 h
5	DCM	94	8.2	25 min
6	**Solvent-free**	**98**	**5.5**	**5 min**

However, to generalise the protocol for the dehydration of various functionalized *N*-formamides, we tested various bases bearing in mind that the dehydration reaction could be accomplished with common organic bases **(Table 2.2.1**, **entries 1–4)**, but not with inorganic bases. Among the tested common organic bases, tertiary amines such as triethylamine proved to be superior **(Table 2.2.1**, **entry 2)**. Therefore, we established optimized conditions for the dehydration of formamides using phosphorus oxychloride for the synthesis of isonitriles.

Table 2.2.1. Dehydration of *N*-(3-bromophenyl)formamide under different basic conditions.

Entry	Solvent	Base	Time	Yield
1.	Solvent-free	Pyridine	20 min	76%
2.	Solvent-free	Triethylamine	5 min	98%
3.	Solvent-free	Diisopropylamine	25 min	62%
4.	Solvent-free	Diisopropyl ethylamine	30 min	59%

However, to generalise the protocol for the dehydration of *N*-formamides for a large number of functionalized isocyanides, the reaction was optimized by changing the temperature and molar ratio **(Table 2.2.2)**. The temperature was reduced to 0 °C, which was found to be sufficient for carrying out the reaction with the highest possible yield of the required product **(Table 2.2.2**, **entry 1)**. It was discovered that using an excess of phosphorus oxychloride was unnecessary because a 1:1 molar ratio of *N*-formamides to phosphorus oxychloride was adequate to produce the desired product **(Table 2.2.2**, **entry 1)**.

Table 2.2.2. Dehydration of *N*-(3-bromophenyl)formamide with $POCl_3$ under different molar and temperature conditions.

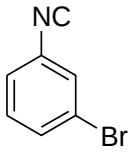
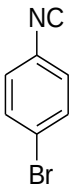
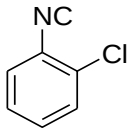
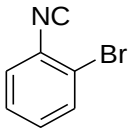
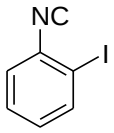
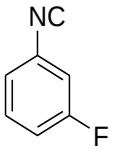
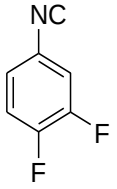
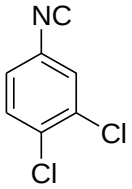
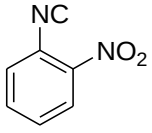
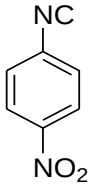
Entry	Reaction Conditions	Time	Yield
1.	*N*-formamide (1 mmol)/ $POCl_3$ (1 mmol) 0 °C	5 min	98%
2.	*N*-formamide (1 mmol)/ $POCl_3$ (1 mmol) r.t.	35 min	51%
3.	*N*-formamide (1 mmol)/ $POCl_3$ (0.5 mmol) 0 °C	20 min	67%
4.	*N*-formamide (1 mmol)/ $POCl_3$ (0.5 mmol) r.t.	35 min	28%
5.	*N*-formamide (1 mmol)/ $POCl_3$ (1.5 mmol) 0 °C	5 min	89%
6.	*N*-formamide (1 mmol)/ $POCl_3$ (1.5 mmol) r.t.	5 min	84%

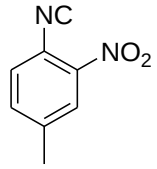
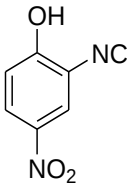
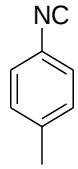
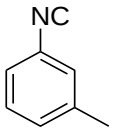
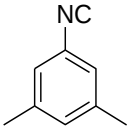
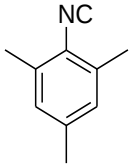
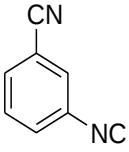
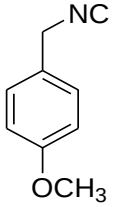
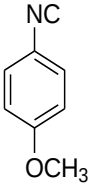
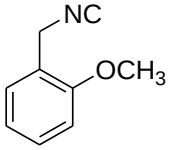
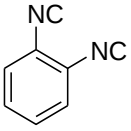
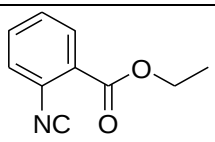
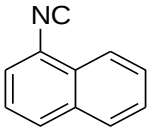
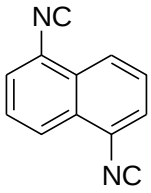
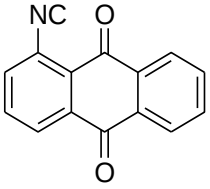
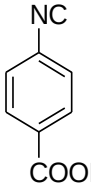
r.t. room temperature

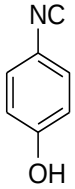
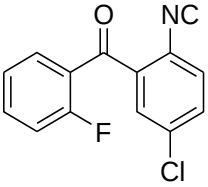
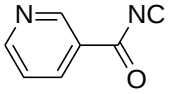
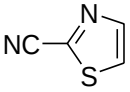
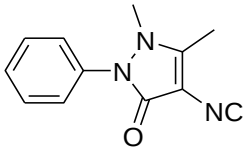
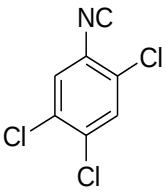
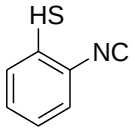
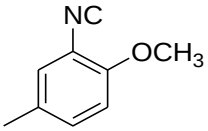
In good to excellent yields (98-45%), a wide range of *N*-aryl- and *N*-alkyl-substituted formamides were transformed swiftly into the anticipated isonitriles. Substituted *N*-aryl substrates with an electron-withdrawing or electron-donating group **(1-28)** on the benzene ring performed satisfactorily. Under these conditions, ether **(18-20)**, halo **(1-8)**, nitro **(9-12)**, ester **(22)**, hydroxyl **(12**, **27)**, and nitrile functional groups **(17)** were only slightly affected. Various mono, di, and trisubstituted *N*-phenylformamides **(1-31)** also yielded good results, indicating that steric effects did not significantly hinder the reaction progress. At room temperature, heterocyclic isocyanides, especially those with the isocyano group *ortho* to the heteroatom, are generally unstable. They tends to undergo further reactions, such as polymerization or cyclization [145]. Our approach, on the other hand, allows for the synthesis of these compounds with the use of an ice bath and isolation at ambient temperature. In good yields, 2-

isocyanothiazole (54%), 4-isocyano antipyrine (68%), and isocyano(pyridin-3-yl)methanone (45%) were isolated. In the cases of 3-isocyano-5-methylisoxazol, 2-(isocyanomethyl)furan, 2-isocyano-3-nitropyridine, 2-isocyano benzyimidazole, 2-isocyanopyridine, 4-isocyanopyridine, 2-(isocyanomethyl)pyridine, and 2-isocyanobenzothiazole, we were unable to isolate the desired product in its purest form. However, the characteristic isocyanide smell of the reaction mixture and the formation of a new spot on the TLC plate indicated their formation. Since we intened to use these compounds as *in situ* reactants in various multicomponent reactions, we were not overly concerned about not being able to isolate the pure compounds (*vide supra*).

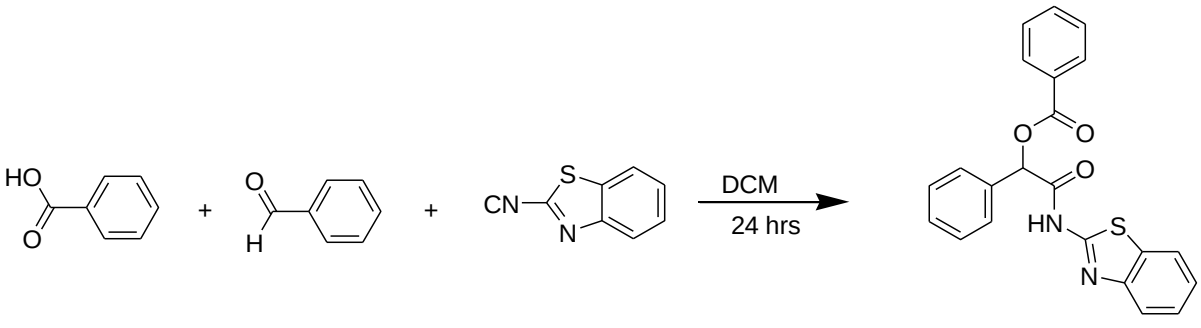
Table 2.2.3. Synthesized isocyanides via formamide dehydration utilizing the optimized reaction conditions with $POCl_3$ under solvent-free conditions (see above).

Entry	**Product**	**Yield %**	**Entry**	**Product**	**Yield %**
1.		98	2		85
3.		90	4.		86
5.		83	6.		85
7.		79	8		85
9		87	10		94

11		86	12		92
13		88	14		74
15		80	16		97
17		90	18		88
19		90	20		76
21		91	22		85
23		96	24		81
25		68	26		65

27		78	28		65
29		45	30		54
31		68	32		87
33		76	34		93

The remaining isocyanides, despite being stable enough to be isolated, decomposed rapidly at room temperature and could not be preserved for any length of time. The isolation of heterocycle-containing isocyanides was complicated because of their intrinsic instability. To verify that the herein obtained isocyanides can be used as *in situ* reactant in a 3-component Passerini reactions, we chose to proceed with the synthesis of MCR-derived compounds utilizing benzoic acid, benzaldehyde and 2-isocyanobenzothiazole as in situ reactant in a classical Passerini 3-components reaction (**Scheme 2.2.1**). Overall, the findings showed that minor impurities in the isocyanide have no significant impact on the subsequent transformation, suggesting that this approach could be used in other multicomponent processes. It is worth noting that these compounds have the potential to undergo the full range of multicomponent reactions for which isocyanides are known exemplified for example by the Passerini and Ugi reaction, and they have the desirable structural diversity and molecular complexity needed for fine-tuning biological activity.



Scheme 2.2.1. Synthesis of Passerini product using 2-isocyanobenzothiazole generated *in situ*

To highlight the superiority of our approach, we calculated the environmental factor (E-factor) and compared it to reported literature protocols for different dehydration reagents including *p*-toluenesulfonyl chloride (*p*-TsCl), phosphoryl trichloride ($POCl_3$) and the combination of triphenylphosphane (PPh_3) and iodine bearing in mind that the lower the E-factor, the better the process's overall performance. The excessive usage of organic solvent for the dehydration process and aqueous workups adopted during the purification step leads to the generation of more aqueous waste for other approaches thus resulting in a high E-factor **(Table 2.2.4)**.

Table 2.2.4. Comparison of various parameters for 100 mmol synthesis of various optimized conditions.

References	**Waibel 2020 [107]**	**Wang 2015 [108]**	**Domling 2009 [147]**	**Patil 2020 [95]**	**This method**
The solvent used (mL)	200	900	100	50	0
Aq. Waste generated (mL)	500	3000	300	0	0
% Yield	97	90	65	97	98
Reaction time (min)	120	60	300	12	5
Number of Operations	9	7	9	3	3
E-Factor	7.41	18.4	50.5	8.4	**5.5**

In addition, while our protocol is solvent-free, other approaches leverage on the use of organic solvent of about (50-300 mL) particularly DCM, which in turn jeopardized the process's sustainability **(Table 2.2.4)**. Furthermore, the results show that the other approaches require longer reaction times (30 min-2 hr) for efficient dehydration compared with the present protocol. Based on the number of operations and the experimental simplicity other approaches required about 7 to 9 workup steps, but our workup consists primarily of a simple silica filtration step followed by solvent evaporation. By avoiding aqueous workup and performing the reaction at higher concentrations under solvent-free conditions, we were able to achieve the lowest E-factor in our procedure resulting in minimal waste generation **(Figure 2.2.1)**. In general, the lower the E-factor, the less waste is generated [146]. As a result, our method is more environmentally friendly than any other known isocyanide synthesis method.

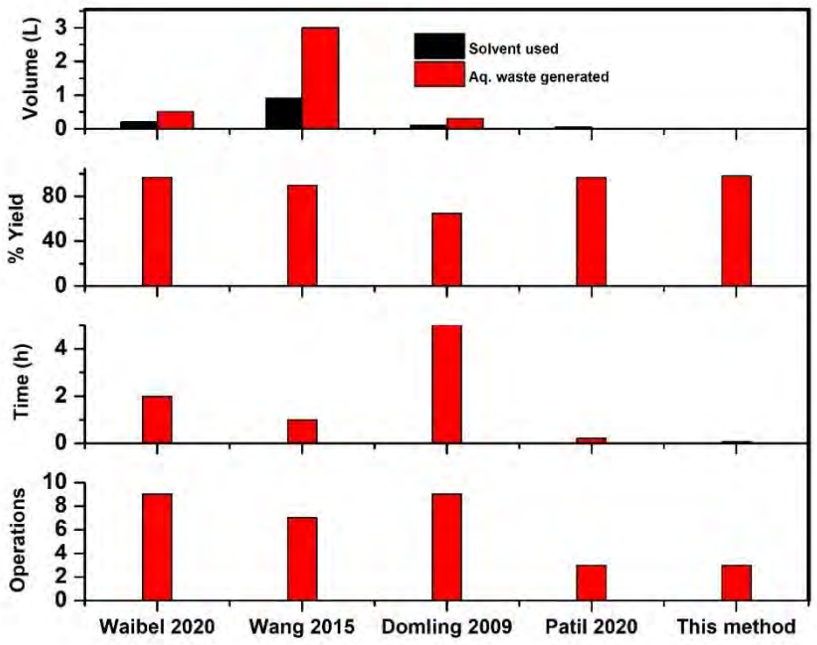


Figure 2.2.1. Graphical representation of various parameters for 100 mmol synthesis of various optimized conditions.

The mechanism of dehydration is illustrated as follows: In the presence of triethylamine, the double bond of the oxygen in the formamide group breaks and protonates the oxygen, which leads to the formation of an unstable complex, which, on further elimination of HCl and chloride ions furnishes the anticipated isocyanides [146].

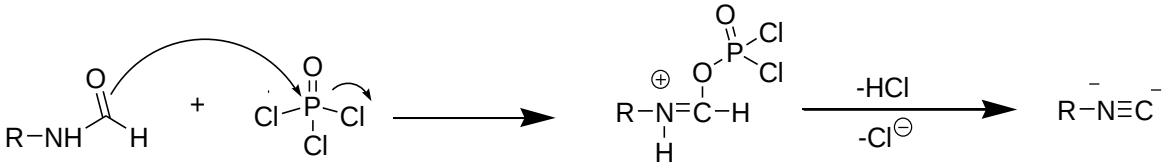


Figure 5. Mechanism of dehydration reaction using phosphorus oxychloride

Conclusion

The dehydration of various *N*-substituted formamides with phosphorus oxychloride afforded the corresponding isocyanides. Our approach allows the synthesis of various functionalized isocyanides in high purity and in almost quantitative yields in solvent-free conditions. This approach enables the *in situ* synthesis of unstable isocyanides, allowing unstable isocyanides to be used as reactants in many processes. As a result, we believe that this method is better when considering time, purity, yield, simplicity, safety, and sustainability. Our approach is more environmentally friendly than the previously reported isocyanide synthesis procedures.

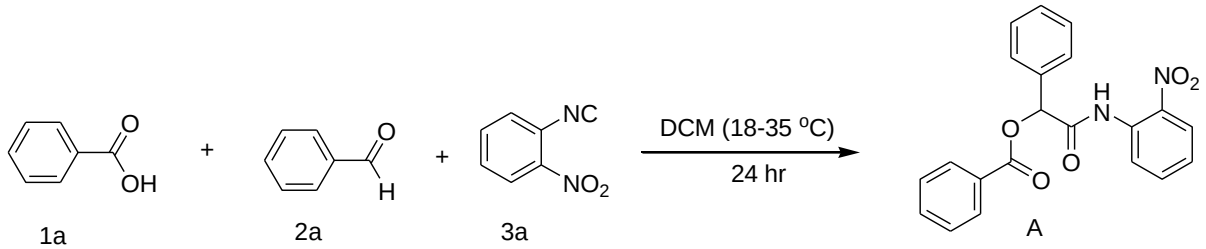
Chapter 3

Part A: This part forms the basis for three publications, see details below or visit https://doi.org/10.3390/ijms23179529, https://doi.org/10.1002/slct.202204325 and https://doi.org/10.1039/D2RA06189A

3.1. Immobilized Sulfuric Acid on Silica Gel as Highly Efficient and Heterogeneous Catalyst for the One-Pot Synthesis of Novel α-Acyloxycarboxamides in Aqueous Media

As an example of a one-pot MCR, the formation of α-acyloxycarboxamides from a carboxylic acid, an aldehyde, and substituted isocyanide was investigated in aqueous media. Usually, Passerini reactions are performed in an organic solvent such as CH_2Cl_2 or MeOH, and they can take 24 h or more for completion [16]. This is the case for most synthetic transformations, despite the many investigations into aqueous organic reactions. In addition to the negative environmental impact of using organic solvents and the inconvenience of the longer reaction time, this also makes them impractical for use in a typical three-hour undergraduate laboratory session. In an attempt to find suitable conditions, we could introduce MCR methodologies to our undergraduate classes, the organic solvent was substituted with water. Surprisingly, the Passerini reaction was completed in 15 min, and excellent yields were obtained. This method is significantly greener than the classical Passerini reaction because water is an ideal non-toxic, nonflammable, environmentally friendly, cheap, and readily available solvent. In aqueous media, several organic processes have shown significant increases in the rates of reaction, even though for many of these, the origins of these enhancement are still a mystery [17,18].

As part of the ongoing research on the synthesis of novel organic compounds utilizing immobilized sulfuric acid on silica gel (H_2SO_4-SiO_2) [26], we report the preparation of a new class of α-aryloxy amide derivatives by a novel three-component Passerini reaction of benzoic acid (**1a**), aldehydes (**2a**), and isocyanides (**3a**) in the presence of immobilized sulfuric acid on silica gel in aqueous media **(Scheme 3.1).** A clean, effective, and environmentally safe chemical reaction to generate novel α-acyloxycarboxamide derivatives was carried out in the presence of immobilized sulfuric acid on silica gel. This heterogeneous catalyst was used in a Passerini reaction for the first time in aqueous media under mild conditions.



1a 2a 3a A

Scheme 3.1. Passerini reaction involving benzoic acid (**1a**), benzaldehyde (**2a**), and 2-nitrophenylisocyanide (**3a**) in DCM.

2. Results and Discussion

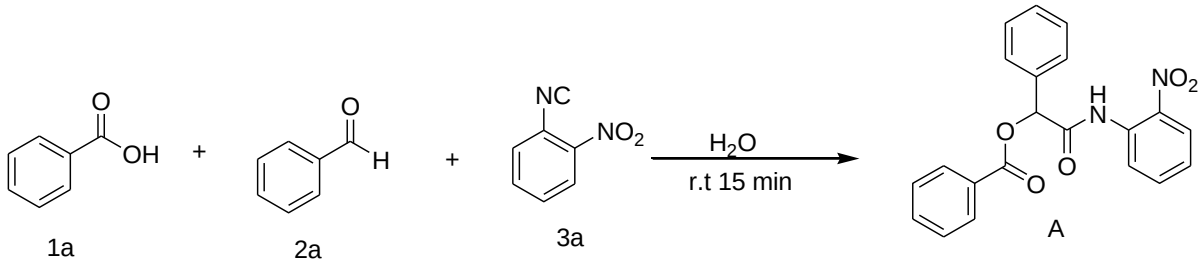
MCR have been characterized as efficient methods for synthesizing polyfunctional compounds with high diversity and complexity in a few steps. The reaction of benzoic acid **(1a)**, benzaldehyde **(2a)**, and 2-nitrophenylisocyanide **(3a)** was chosen as the model reaction in order to explore reaction conditions. These were firstly subjected to a typical Passerini reaction in DCM at room temperature (18–35 °C) for 24 h **(Table 3.1, entry 5)**. The desired product (A) was obtained in 85% yield.

To improve the efficiency of reaction, various reaction solvents were screened, such as diethyl ether, toluene, acetonitrile, ethyl acetate, DCM, ethanol, and methanol. Although the reaction occurs with all the solvents used, dichloromethane and methanol were the best among the tested solvents, producing 85 and 78% yields, respectively **(Table 3.1)**.

Table 3.1. Effect of different solvents on the yield of the Passerini reaction.

Entry	Solvent	Yield (%)
1	Diethyl ether	43
2	Toluene	65
3	Acetonitrile	58
4	Ethyl acetate	32
5	Dichloromethane	85
6	Ethanol	74
7	Methanol	78
8	Water	90

When the reaction was carried out in diethyl ether, toluene, acetonitrile, ethyl acetate, and ethanol, low to moderate amounts of the product were observed, producing product yields of 43, 65, 58, 32, and 74%, respectively which may have been due to solubility issues **(Table 3.1, entries 1–6)**. Therefore, DCM was found to be the best organic solvent for the current reaction, as it provided the desired product in 85% yield within 24 h **(Table 3.1, entry 5)**. At this point, it was necessary to carry out these reactions under green conditions. To our delight, when the solvent was replaced with water at room temperature, the Passerini reaction was completed in 15 min **(Scheme 3.1.1)**, and the product was obtained in 90% yield **(Table 3.1, entry 8)**. It was also discovered that extending the reaction time had little or no influence on the yield, as 15 min was found to be sufficient for completing the reaction with almost quantitative yield.



Scheme 3.1.1. Passerini reaction in aqueous media.

Isocyanides have been found to undergo slow spontaneous hydrolysis in the presence of water [27]. Following that observation, we then focused on the optimization of the water content. The reaction was explored by increasing the volume of water from 1 to 5 mL to acquire a better understanding of the effect of water on the model Passerini reaction. The best result, of 90% yield, was observed when 2 mL of water by volume was introduced to the reaction **(Table 3.1.1, entry 2)**. The effectiveness of the reaction declined dramatically when the amount of water was reduced **(Table 3.1.1, entry 1)**, while increasing the amount of water also resulted in a lower product yield **(Table 3.1.1, entries 3–5)**.

Table 3.1.1. Investigating the effect of water on the optimized Passerini reaction.

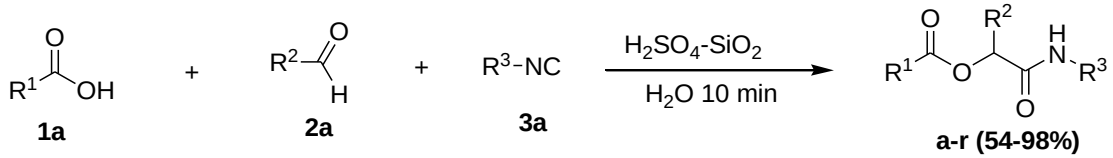
Entry	Volume of H_2O	Yield (%)
1	1 mL	57
2	2 mL	90
3	3 mL	82
4	4 mL	71
5	5 mL	53

To investigate the effect of a catalyst on the model Passerini reaction and to establish the best catalytic conditions, we started the condensation of benzoic acid (1 mmol), benzaldehyde (1 mmol), and 2-nitrophenylisocyanide (1 mmol) in the presence of H_2SO_4 immobilized on SiO_2 (0.01 g) as a catalyst at room temperature (18–35 °C) in aqueous media. The reaction furnished the corresponding Passerini adducts in 10 min, and a good yield (93%) of the product was obtained.

To enhance the reaction yields of the products, catalytic studies were carried out by increasing the catalyst amount from 0.01 g to 0.05 g at room temperature in aqueous media while keeping the other experimental parameters constant. The conversion rate gradually increased from 93% to 98% within 10 min when the catalyst amount was increased to 0.02 g **(Scheme 3.1.2)**. This is because more acidic sites became available as the catalyst concentration increased. The yield was unaffected by further increasing the catalyst loading (0.03–0.04 g). Further loading with 0.05 g of catalyst had a detrimental effect on the yield. As the catalyst amount was increased, the percentage conversion increased to a high point before gradually declining. An excessive amount of catalyst may obstruct conversion due to catalyst

poisoning caused by an excessive amount of reactants adhering to the catalyst surface. The amount of catalyst determines the availability of acidic sites, which when present in excess, may produce undesirable by-products, or promote the occurrence of the reversible reaction [28]. When the reaction was carried out in the presence of silica gel (without catalyst) the Passerini adducts were obtained in 64% yield within 15 min, which implies that the reaction rate depends greatly on the catalyst used. The optimal quantity of catalyst for the successful Passerini reaction in aqueous media was determined to be 0.02 g.

To demonstrate the catalytic significance of H_2SO_4-SiO_2 for this reaction, we applied this catalyst to synthesize α-acyloxycarboxamide derivatives under aqueous conditions utilizing a variety of aromatic isocyanides with a wide range of *ortho*, *meta*, and *para*-substitutions. Generally, the synthetic procedure involved stirring the equimolar mixture of benzoic acid (1a, 1 mmol), benzaldehyde (2a, 1 mmol), isocyanide (3a, 1 mmol), in the presence of H_2SO_4 immobilized on SiO_2 (0.02 g) in water (2 mL) for 10 min at room temperature (18–35 °C). The corresponding results are given in Scheme 3.1.2. We discovered that the reaction worked exceptionally well with either electron-releasing or electron-withdrawing substituents on the aryl ring of the isocyanide. Various functional groups, such as fluoro, chloro, methyl, and methoxy groups, were found to be well-tolerated (**Scheme 3.1.2.)**.



$R^1 = C_6H_5$ $R^2 = C_6H_5$

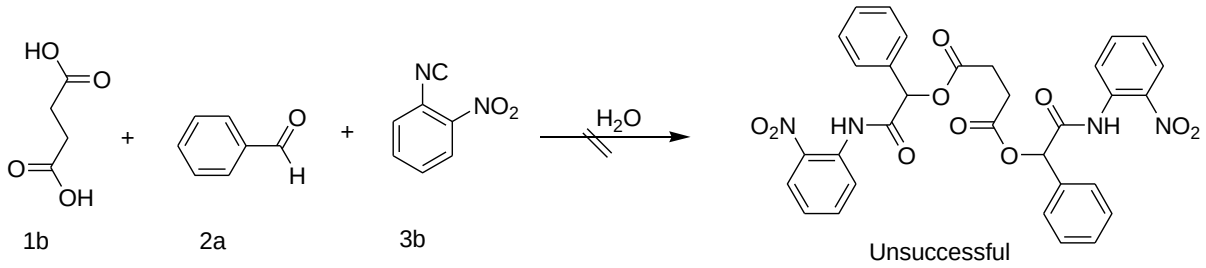
3a: R^3 =2-NO_2-C_6H_4
3b: R^3 =2-Br-C_6H_4
3c: R^3 =2-Cl-C_6H_4
3d: R^3 =3,4-F_2-C_6H_3
3e: R^3 =3,4-Cl_2-C_6H_3
3f: R^3 =3-CN-C_6H_4
3g: R^3 =4-CH_3-C_6H_4
3h: R^3 =3-CH_3-C_6H_4
3i: R^3 =3,5-$(CH_3)_2$-C_6H_3
3j: R^3 =2,4,6-$(CH_3)_3$-C_6H_2
3k: R^3 =2-NO_2, 4-$(CH_3)C_6H_3$
3l: R^3 =4-$(OCH)_3$-C_6H_4
3m: R^3 =(CH_2)-2-$(OCH)_3$-C_6H_3
3n: R^3 =(CH_2)-4-$(OCH)_3$-C_6H_3
3o: R^3 =2-$(COOC_2H_5)$-C_6H_4
3p: R^3 =1-C_8H_7
3q: R^3 =2-I-C_6H_4
3r: R^3 =3-(C_5H_4NS)

Scheme 3.1.2. Passerini reaction under the optimized catalytic conditions.

The obtained α-acyloxycarboxamide derivatives (a-r) **(Scheme 3.1.2)** were confirmed based on their NMR spectral data. The ^{1}H NMR spectra of this series showed NH signals ranging from δH = 8.00 to 11.00 ppm. The aromatic protons of carboxylic acid and aldehyde moieties also appeared in the expected range (δH 7.80–6.40 ppm). ^{13}C NMR spectra exhibited signals ranging from δC 161.0 to 173.0 ppm, corresponding to the two amido-ester C=O groups.

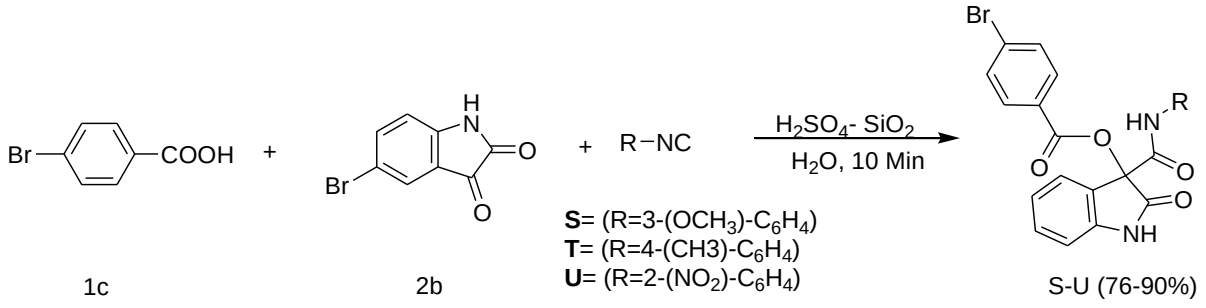
The Passerini reaction under the above optimized conditions for the synthesis of bis α-acyloxycarboxamide derivatives was unsuccessful in the case of phthalic acid **(1b)**. This may be attributed to the planarity of the phenyl ring preventing the second Passerini reaction due to steric hindrance. According to a literature review, succinic acid could be used to synthesize bis α-

acyloxycarboxamides [28]. The free rotation of the C-C bond between the two methylene groups was suggested as a strategy to increase the flexibility and avoid steric restriction around the -COOH. However, the synthesis of bis α-acyloxycarboxamides utilizing succinic acid **(1c)** under the above experimental conditions was unsuccessful; all trials led to the hydrolysis of the corresponding isocyanide **(Scheme 3.1.3)**.



Scheme 3.1.3. Unsuccessful attempts to synthesize bis α-acyloxycarboxamides.

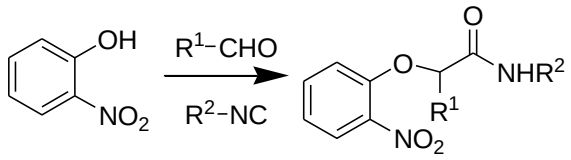
The versatility of the standardized Passerini reaction conditions for the synthesis of novel α-acyloxycarboxamides was also examined for the carbonyl component of the Passerini reaction while employing 5-bromoisatin **(2b)** (5-bromoindole 2,3-dione) as the carbonyl component and 4-bromobenzoic acid **(1c) (Scheme 3.1.4)**. It was observed that the developed reaction conditions were robust for accepting indole-2,3-dione. Thus, the reaction of isatin **(2b)**, benzoic acid (1a), and 3-methoxyphenylisocyanide **(3b)** under optimized reaction conditions led to the formation of (3-methoxyphenylcarbamoyl)(2-oxoindolin-3-yl)methyl benzoate in 90% yield **(Scheme 3.1.4)**.



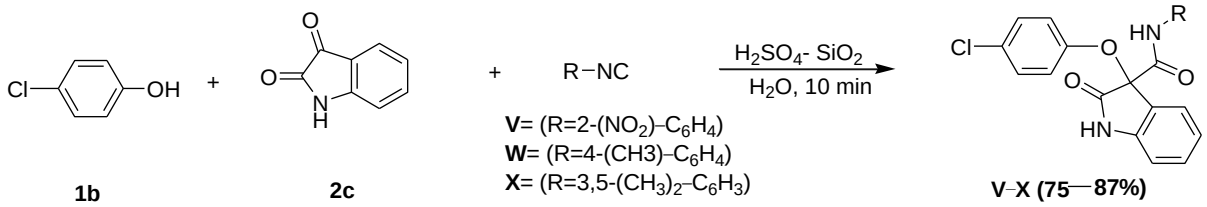
Scheme 3.1.4. Passerini reaction in aqueous media, employing 5-bromo isatin (5-bromoindole 2,3-dione) as the carbonyl surrogate.

Utility of 4-chlorophenol as an acid surrogate

The synthetic potential of this protocol was examined by utilizing electron-deficient phenols as the acid component in the reaction. Thus, the Passerini reaction involving isatins (2c) with 4-chlorophenol (1b) and 2-nitrophenylisocyanide (3a) under optimized reaction conditions resulted in the synthesis of an O-arylated oxindole derivative in good to excellent yields **(Scheme 3.1.6)**. In this reaction, the irreversible Smiles rearrangement of the intermediate phenoxyimidate adducts resulted in the formation of the *O*-arylated product, and this is an example of the application of the Smiles rearrangement in a Passerini reaction **(Scheme 3.1.5)**.



Scheme 3.1.5. Typical Passerini–Smiles reaction of 2-nitrophenol



1b **2c** **V–X (75—87%)**

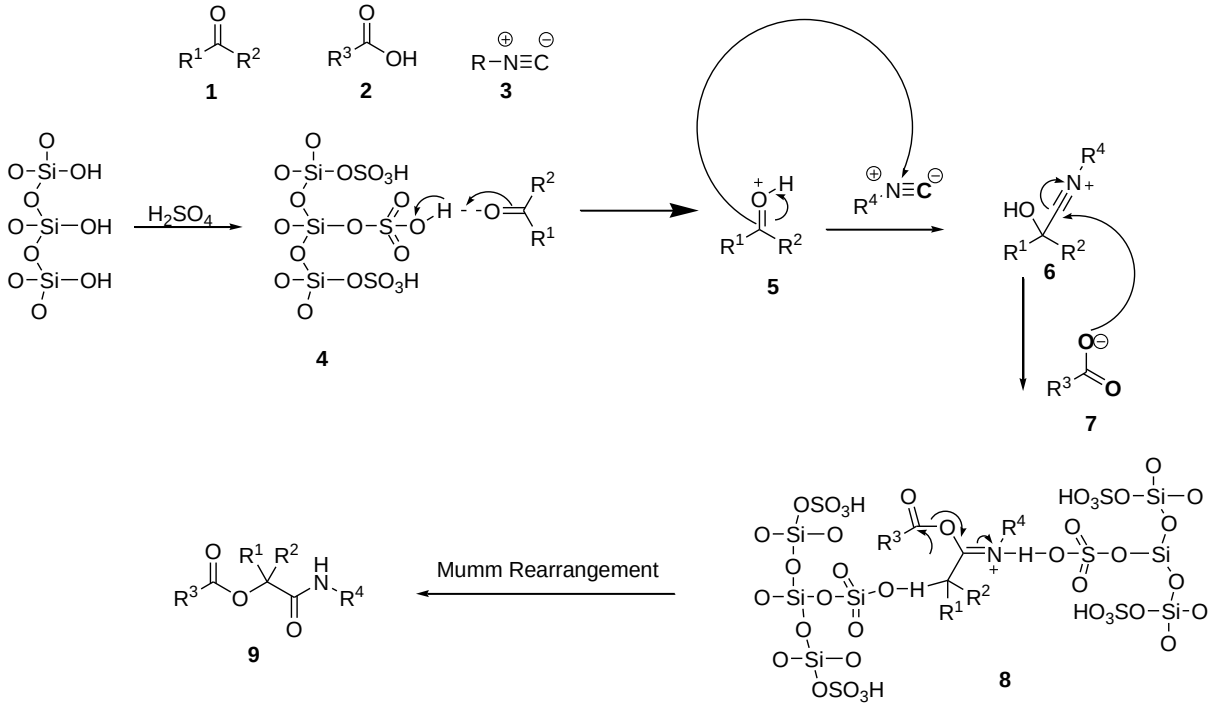
Scheme 3.1.6. Passerini reaction in aqueous media, employing 4-chlorophenol as the acid surrogate under catalytic conditions.

The recyclability and reusability effect of the $H_2SO_4 \cdot SiO_2$ catalyst in these reactions was also studied. After each reaction, the catalyst was filtered, cleaned with ethyl acetate, dried at 120 °C for three hours, and then utilized in another cycle of reactions. The catalyst reusability demonstrated that it was extremely effective in the synthesis of Passerini products. After five cycles, the percentage conversion efficiency under the optimum conditions dropped from 98% to 87%. The higher catalytic efficiency may be due to the higher acidity produced by the H-bond and hydrophobic core of the mesoporous catalyst. **(Table 3.1.2)**.

Table 3.1.2. Efficiency of the recycled catalyst in the model Passerini reaction

Entry	Turn	Yield (%)
1	1	98
2	2	96
3	3	93
4	4	91
5	5	87

The proposed reaction mechanism is illustrated in **Scheme 3.1.7**. for the formation of α-acyloxycarboxamide derivatives in the presence of SiO_2-H_2SO_4. The catalyst first activates the carbonyl group of the aldehydes **(4)**. Then, the isocyanide attacks the activated carbonyl **(5)** group nucleophilically, forming an intermediate known as nitrilium **(6)**. The intermediate **(6)** is then attacked by the carboxylate of **(7)**, which is followed by an acyl transfer by a Mumm rearrangement to generate derivatives of oxindole-based acyloxycarboxamides **(9)**.



Scheme 3.1.7. Proposed mechanism for the formation of α-acyloxycarboxamides in the presence of the immobilized sulfuric acid on silica gel (SiO_2-H_2SO_4)

Characterization of the catalyst

FT-IR spectral analysis

The FT-IR spectrum of the catalyst is shown in Figure 3.1. The catalyst was solid, and the solid-state IR spectrum was obtained by the attenuated total reflection (ATR) method. For each experiment, 16 scans were performed in the frequency range from 650 to 4000 cm^{-1}. The wide bands detected in the spectra (A) at 3511 and (C) 3486 cm^{-1} were attributed to superimposed stretching modes of Si–OH groups and hydroxyl groups (O–H). The peaks from Si–O–Si groups, which occur in the range of 1250–1000 cm^{-1} for asymmetric stretching, are a characteristic indicator of the silica structure. For silica (B, SiO_2) without a catalyst, the major peaks were broad asymmetric Si–O–Si stretching from 1200 to 1000 cm^{-1} and symmetric Si–O–Si stretching near 800 cm^{-1}.

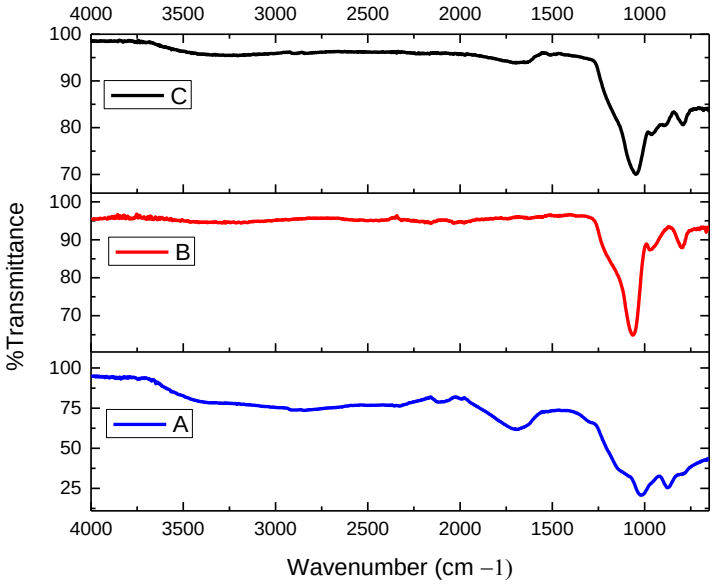


Figure 3.1. The FT-IR spectra of (A) the immobilized sulfuric acid on silica gel, (B) silica gel without catalyst, and (C) recovered catalyst after five cycles.

Powder X-ray diffraction (PXRD)

As shown in Figure 3.1.1, the PXRD pattern of (A), the immobilized sulfuric acid on silica gel, displayed a noticeable signal at a 2θ angle of 22.91° (a broad diffraction band), which is reminiscent of a typical amorphous silica diffraction pattern. The same broad diffraction band was noticed for the recovered catalyst (C) after five cycles **(Figure 3C)**. A certain conclusion can be made about the crystalline structure of the support, i.e., silica was not distorted during the preparation of the catalysts. Future reactions or research would take advantage of structured silicas, such as mesoporous or templated zeolites.

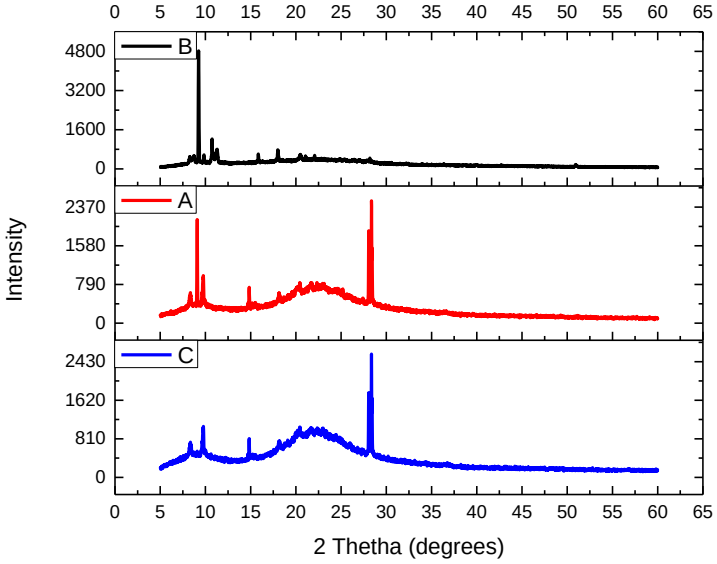


Figure 3.1.1. The PXRD of (A) the immobilized sulfuric acid on silica gel, (B) silica gel without catalyst, and (C) recovered catalyst after five cycles.

Conclusions

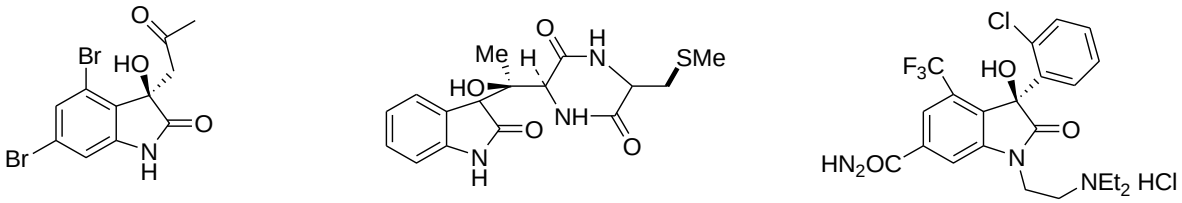
In this work, we have shown the reactivity, efficiency, and reusability of immobilized sulfuric acid on silica gel. This solid catalyst is applicable in MCRs as a heterogenous catalyst. The Passerini reaction was assayed in the presence of SiO_2-H_2SO_4 for the first time. Our findings also demonstrated that water is a good substitute for volatile organic solvents, which is in line with one of the green chemistry principles and important for future applications. The few benefits of this protocol are quick reaction times, high product yields, a simple workup, mild reaction conditions, environmental compatibility, and a lack of side products. Turning this into a standard undergraduate practical is still in progress.

Part B

3.2. Aqua-Mechano-Assisted Passerini Reactions: A Simple and Straightforward Access to Oxindole Derivatives

Attention has grown recently in the development of "greener" organic chemistry processes that make use of unconventional energy sources, such as microwave irradiation, ultrasonic activation, and more recently, high-speed ball-milling methods made possible by mechanochemical activation or by performing reactions in aqueous media [59, 94, 148, 53].

In the context of Passerini reactions of sterically hindered carbonyl compounds, we postulated that a MCR combining isatin derivatives, isocyanides, and carboxylic acids could allow access to oxindole derivatives. This is significant because oxindoles with a quaternary benzylic centre are a prominent structural motif in a wide range of natural products and pharmacologically active compounds [149]. Among them, oxindoles having a heteroatom at the benzylic position, such as the bioactive natural products (*R*)-convolutamydine A, maremycin B9, and the growth hormone secretion activator SM-130686, and are useful examples of this class of compounds **(Figure 3.2)** [150, 151]. In addition, following our modest success with aqua mediated synthesis, we set out to develop a mechanochemical technique for the synthesis of biologically important oxindole derivatives [152], and we decided to try the combination of aqua- or mechanochemical techniques separately for the synthesis of various functionalized oxindole derivatives.



(*R*)-convolutamydine A **maremycin B** **SM-130686**

Figure 3.2: Selected biologically active oxindole derivatives.

The applications of aqua- and mechanochemistry for rapid organic synthesis have found widespread use, owing to the reduction in time, improved yields and easier operation as compared to conventional methods. The Passerini three-component reaction utilizing isatin (indole-2,3-dione), substituted carboxylic acid and various functionalized isocyanides is a very important tool in the construction of diversity-oriented compound libraries. In this regard, an aqua- mechanochemical version of this transformation has been developed and is based on the use of water (aqueous reaction) and high-speed vibration milling with a double agate ball (6 mm diameter) in an agate jar and water as a liquid-assisted grinding agent to furnish the oxindole derivatives. The Passerini 3-CR (three-component reaction) is one of the transformations in this field that has received the most attention, according to the numerous

articles that have been published so far [37]. Interesting investigations have been published on the solvent-free synthesis of Passerini adducts using magnetic stirring, ultrasonic, microwave, and manual grinding [148, 45, 153]. However, none of them proved to be entirely satisfactory in terms of yield, reaction time, experimental simplicity, and functionalization scope. Nevertheless, the use of water and mechanochemical activation in isocyanide based multicomponent reactions (IMCRs) is still an issue that requires attention. In continuation of the ongoing efforts to develop more sustainable methodologies in organic synthesis, we report herein the synthesis of biologically important oxindole derivatives under simultaneous aqua (water) and mechanochemical conditions (liquid-assisted ball milling conditions).

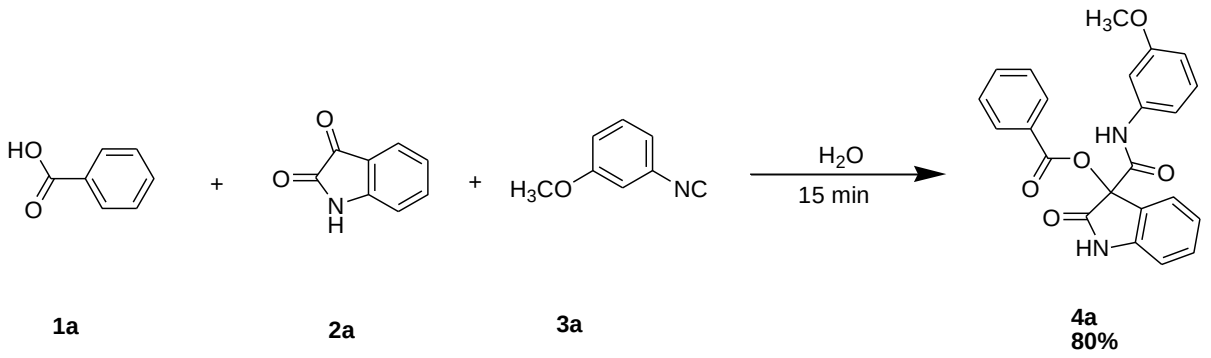
Results and Discussion

Passerini 3-CR Reaction in aqueous media

Prior to this investigation, the three main factors that influence the rate of the Passerini reaction were evaluated. The acidity of the medium, the concentrations of the reagents, and the polarity of the solvents [154]. Additionally, it was established that, in contrast to the Ugi reaction (another MCR using a ketone / aldehyde, an amine, an isocyanide and usually a carboxylic acid derivative), the Passerini reaction is accelerated in aprotic solvents [76]. The concentration of the reagents is another crucial aspect because all MCRs, including the Passerini reaction, perform better when the reactants are present at high concentrations [155]. In actuality, the low solubility of the reactants in water boosts the influence of the hydrophobic effect on the rate of the reaction, but dissolution reduces the yield of the three component reactions [156].

The Passerini multicomponent reaction (P-MCR) is typically carried out in a toxic aprotic organic solvent such as dichloromethane or toluene [157][85]. Pirrung, Das Sarma, and others have demonstrated that the P-MCR may be carried out effectively in water [158]. Due to the advantages of MCRs, their combination with aqueous media is one of the subclasses of an ideal synthesis that is recognized.

For the first set of experiments, we chose as model reaction of the P-MCR of benzoic acid **(1a)**, indole-2,3-dione **(2a)** and 1-isocyano-3-methoxybenzene **(3a)**. To compare results of the reaction under aqua conditions with those obtained under standard conditions (organic solvents), we studied the influence of different solvents on the reaction course **(Table 3.2)**.



1a **2a** **3a** **4a 80%**

Scheme 3.2: Model Passerini reaction in aqueous media.

As shown in **Table 3.2**, the organic solvents had a significant effect on the yield of (4a), and acetonitrile, tetrahydrofuran (THF), and ethanol, were found to be inefficient (**entries 1, 3 and 5**). The use of toluene resulted in a yield of 51%. However, the P-3CR proceeded smoothly in dichloromethane (CH_2Cl_2) and methanol (CH_3OH) with higher yields of 82% and 75% respectively **(entries 4 and 6)**.

Table 3.2: Effect of different solvents on the yield of Passerini reaction.

Entry	Solvent	Time	Yield %
1	Tetrahydrofuran	48 hr	No reaction
2	Toluene	24 hr	51
3	Acetonitrile	24 hr	12
4	Dichloromethane	48 hr	82
5	Ethanol	48 hr	24
6	Methanol	48 hr	75
7	Water	15 min	80
8	Methanol-Water Mixture	1 hr	43
9	DCM-water mixture	1 hr	71

We then focused our work on aqueous reaction systems and investigated the effect of water on the model Passerini reaction using **1a**, **2a**, **and 3a**. These reactions were undertaken in pure water, methanol-water mixture (1:1 added to allow dissolutions of the products) and in a biphasic system of DCM-water mixture (1:1). According to the observations reported in **Table 3.2 entries 8 and 9**, the reaction rate accelerates in a biphasic medium, producing a yield of 71% in 1 hr as opposed to a reaction carried out in a homogenous medium (water-methanol), which produced a yield of 43%. When the reaction was carried out in distilled water, good yield (80%) of the product was obtained in 15 min **(Table 3.2, entry 7).** It is important to underline the circumstances in which the unique properties of water can, through the hydrophobic effect, speed up organic reactions. While reaction uniformity may

be enhanced, as in the case of a mixture of methanol and water, the hydrophobic/cohesive pressure effect may be jeopardized. Therefore, it is important to strike a balance when adding organic cosolvents. Although there is no direct evidence to support this, mixtures of organic/water solvents have substantially lower surface tension than water alone, which is expected to have a reduced hydrophobic effect thus lowering the reaction yield as observed in **Table 3.2** above. Reactants must not be water-miscible to benefit from hydrophobic effects; as a result, all heterogeneous reactions, at least on a microscopic scale, and mixing effects on reaction efficiency are to be anticipated.

Then, we looked at the scenario where one of the reactants possesses amphiphilic properties and could, as a result, positively affect the reaction, for example, by increasing the reaction yield. Since many aldehydes and carboxylic acids are highly soluble in water, it was necessary to ascertain how much of the reactions take place "in water" as opposed to "on water". To examine whether this could be accomplished, we performed the Passerini reactions with three different acids. Partially water-soluble acid (benzoic acid **1a**), water-insoluble acid (4-bromobenzoic acid **1b**) and water-soluble acid (3,5-dibromosalicylic acid, **1c**). It is widely known from prior research that, depending on concentration, acid **1a** and **1b** self-assemble into micelles or vesicles in aqueous solution. The three carboxylic acids **(1a–c)** were reacted separately with isatin **(2a)** and 1-isocyano-3-methoxybenzene **(3a)** at room temperature for 15 min. It was discovered that in aqueous media (distilled water), the reaction yields strongly depended on the nature of carboxylic acid. For the reaction carried out with 3,5-dibromosalicylic acid **(1c)**, the yield of product **6a** was only 56%. Apart from the steric effect of **(1c)** this may also be due to the high solubility of 3,5-dibromosalicylic acid **(1c)**. However, for the water-insoluble acid **(1b)**, the reaction yield of product **5a** was 88%. Since all the reactants are insoluble in water, this reaction takes place "on water," which causes the reaction yield to significantly increase when compared to 3,5-dibromosalicylic acid which occurred in water. Interestingly, the reactions between the hydrophobic acid **(1b)** "on water" were complete after 15 min at room temperature in yield of (88%, product **5a**). On the other hand, more water-soluble acid **(1c)** gave the Passerini product **4c** in low yield (56%) within 15 minutes and extending the reaction time to 1 hr had no impact on the yield of **4c**. In addition, when the reaction occurred "in water," water also successfully competed with the carboxylate for the nucleophilic addition to the carbonyl atom thus resulting in lower yields of products as observed in **table 3.2.1.**

Table 3.2.1: The scope of carboxylic acid for the Passerini reaction "in water" and "on water".

Entry	Acid	Product	Solvent	Yield %
1	Benzoic acid (1a)	**4a**	Distilled water	80
2	4-Bromobenzoic acid (1b)	**5a**	Distilled water	88
3	3,5-Dibromosalicylic acid (1c)	**6a**	Distilled water	56

Reaction conditions: *carboxylic acid (**1a–c**, 1 mmol), indole-2,3-dione (**2a**, 1 mmol) and 1-isocyano-3-methoxybenzene (**3a**, 1 mmol) were stirred in distilled water (2 mL) for 15 min at room temperature. The progress of reaction was monitored by TLC.*

Generally, water-insoluble carboxylic acid **(1b)** gave the Passerini products in excellent yields (88%), while partially soluble carboxylic **(1a)** acid afforded the products in relatively high yield albeit slightly lower than **(1b)**, thus showing competition between the "in water" and "on water" reactions **(Table 3.2.1)**.

Considering this finding, we decided to investigate comparatively the influence of the pH value on the reaction yield with benzoic acid **(1a)**, 4-bromobenzoic acid **(1b)**, and 3,5-dibromosalicylic acid **(1c)** under the above experimental conditions. We began by measuring the pH of the individual reaction mixture before and after completion of reaction. The results showed that pH values of **1a**, **1b**, and **1c** in solution prior to the completion of reaction are **4.12**, **5.26**, and **3.92** respectively, which is expected to have a varied impact on the rate of reaction. The pH of the reaction involving **1a**, **1b**, and **1c** after completion of the reaction was **3.87**, **4.75**, and **3.11** correspondingly. It was suggested that the reduced yield of **6a** (56%) produced by reaction **(1c**, **2a**, **3a)** at pH = **3.11** was consistent with acid catalysed hydrolysis of isocyanides [159]. However, as the acidity decreases the yield of **4a** for the reaction **(1a**, **2a**, **3a)** carried out at pH = **3.87** was slightly higher (80%). Generally, it was observed that the more acidic the solution, the lower the reaction yield. The results showed that pH =**4.75** was optimal for this model reaction, providing product **5a** in 88% yield.

The distribution of reaction products revealed a considerable correlation between the hydrophobicity of the reactants, the more hydrophobic ones producing the typical Passerini product in high yields. These findings suggested that the reactivity "on water" might be different from that in water. To confirm whether this variation may be utilized in organic synthesis we decided to investigate the catalytic effect of the immobilized sulfuric acid on silica gel on the model Passerini reaction “in water” and “on water” with the aim of increasing the reaction yields. This heterogeneous catalyst has been utilized in Passerini reaction under mild conditions in aqueous media, for the first time. The catalyst SiO_2-H_2SO_4 was prepared by following the reported literature procedure [159]. It was found that, in the presence of SiO_2-H_2SO_4 at room temperature, the yield of the model Passerini reaction in water **(1c**, **2a**, **3a)** increases significantly from 56% to 73% of Passerini products within 10 min. (**Table 3.2.2, entry 11**). Also, when the reaction was performed in the presence of SiO_2-H_2SO_4 for the model Passerini reaction “on/in water” **(1a**, **2a**, **3a)** at room temperature, the reaction yield decreased slightly from 80 to 71% in 10 minutes **(Table 3.2.2, entry 3)**. There were no noticeable changes in the yield of reaction involving water insoluble acid **(1b**, **2a**, **3a)** except a shorter reaction time **(Table 3.2.2, entries 5-8)**. It is helpful to note that an increase in the reaction time (10-15 min) had no effect on the final yield of the product. Obviously, the advantages of immobilized sulfuric acid on silica for the model Passerini reaction is

short reaction times and ease of catalyst separation. These results show the ineffectiveness of the immobilized sulfuric acid on silica gel for the model reaction "on water" **(1a**, **2a**, **3a**, **& 1b**, **2a**, **3a)**, due to the decreased yield of product **4a** and the absence of a discernible change in the yield of product **5a**. As the reaction yield of product **4a** decreases in water in the presence of catalyst, which may be due to catalyst inactivation issue, we hypothesized that the catalyst is unnecessary or even detrimental to the Passerini reaction on water. However, we envisage that the catalyst is only compatible with the model Passerini reaction "in water" **(1c**, **2a**, **3a)**, thus we chose to explore the catalyst in our subsequent research on **1c**.

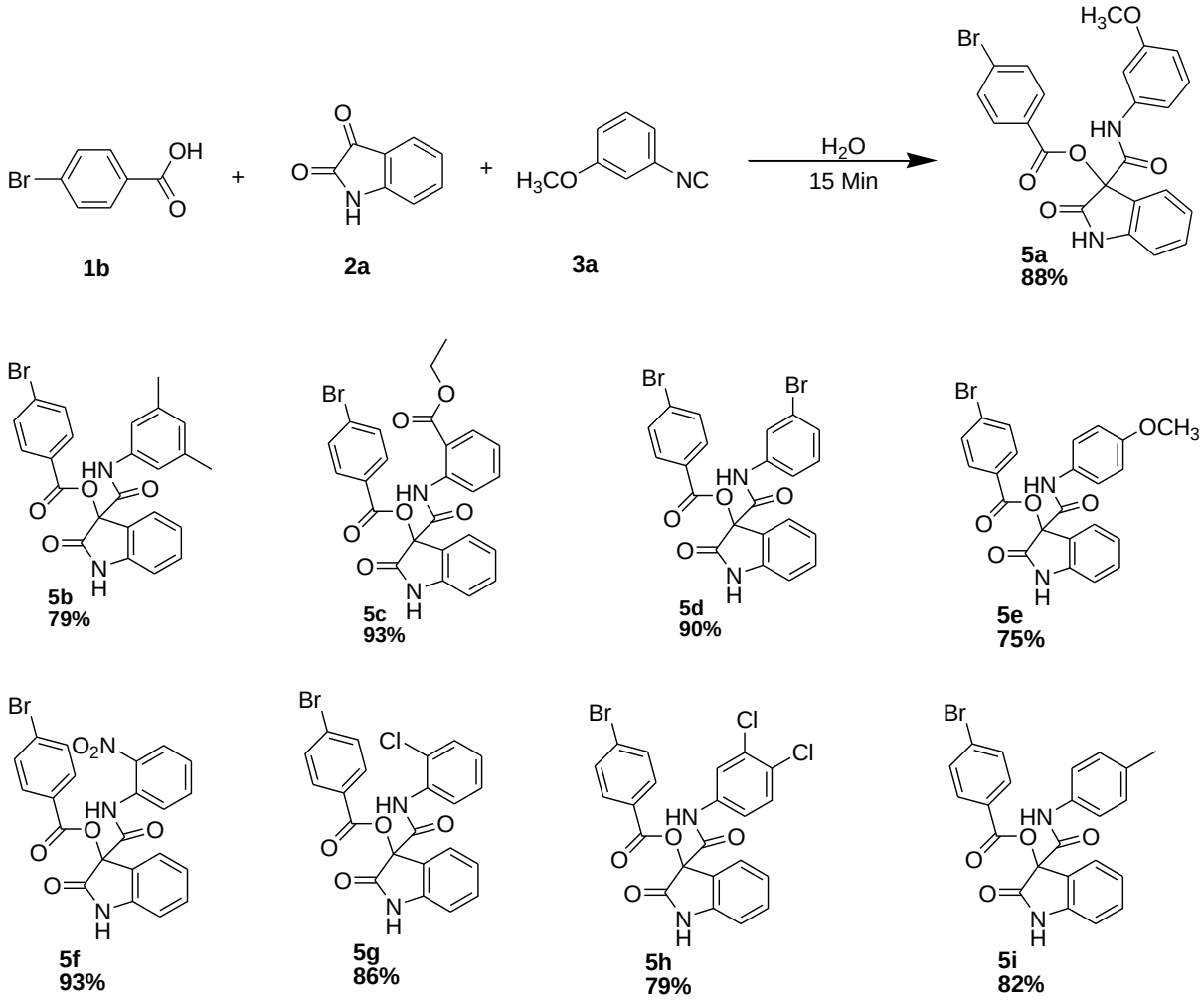
We next investigated the effect of the stoichiometry of the immobilized sulfuric acid on silica gel on the outcome of the reaction **(Table 3.2.2).** We found that excess SiO_2-H_2SO_4 was not helpful for faster conversion. On the other hand, a lower amount of SiO_2-H_2SO_4 led to substantially slower conversion. Using 0.02 g of SiO_2-H_2SO_4 led to the formation of product **(6a)** in 77% yield within 10 min for reaction carried out in water **(Table 3.2**, **entry 6)**. Accordingly, the best reaction efficiency was achieved in the presence of 0.02 g SiO_2-H_2SO_4 at room temperature in water for **(1c, 2a, 3a) (Table 3.2.2**, **entry 11)**.

Table 3.2.2: Screening for best reaction conditions.

Entry	Reaction Condition	Solvent	Catalyst (g)	Time (min)	Yield %
1.	(1a, 2a, 3a)	Distilled water	No catalyst	15	80
2	(1a, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.01)	10	74
3.	(1a, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	10	71
4.	(1a, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.03)	10	65
5	(1a, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	15	71
6.	(1b, 2a, 3a)	Distilled water	No catalyst	15	88
7.	(1b, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.01)	10	88
8.	(1b, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	10	88
9.	(1b, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.03)	10	88
10	(1b, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	15	88
11.	(1c, 2a, 3a)	Distilled water	No catalyst	15	56
12.	(1c, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.01)	10	60
13.	(1c, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	10	73
14.	(1c, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.03)	10	70
15.	(1c, 2a, 3a)	Distilled water	SiO_2-H_2SO_4 (0.02)	15	73

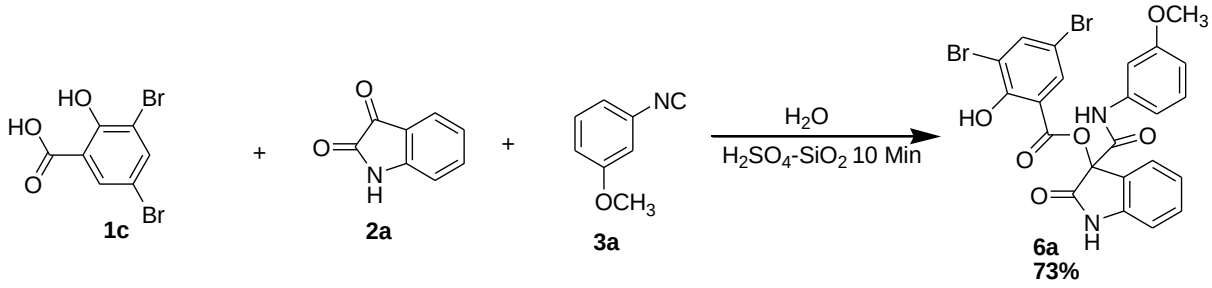
*The reaction was performed with different carboxylic acids (**1a–c**, 1 mmol), indole-2,3-dione (**2a,** 1 mmol), and 1-isocyanide 3-methoxybenzene (**3a**, 1 mmol) in the presence and absence of catalyst using water (2 ml) as solvent at room temperature. The progress of reaction was monitored by TLC.*

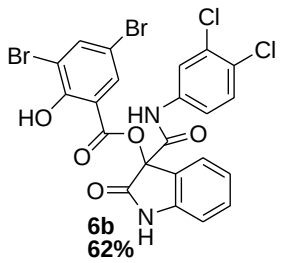
Under the optimized reaction conditions, the Passerini reaction carried out in the absence of catalyst with benzoic acid **(1a)** resulted in product **4a** with 80% yield. Products **(5a-i)** were obtained in high to excellent yields (65-94%) when the reactions **(1b**, **2a**, **3a-i)** were performed "on water" in the absence of catalyst. These results verify that micelle- and vesicle-forming **1b** are able to promote the Passerini reaction, in which they are simultaneously a part of the reactants. To study the efficiency and generality of the catalyst, new oxindole based α-acyloxycarboxamides derivatives **(6a-o)** were synthesized using **1c** (3,5-dibromosalicylic acid), indole-2,3-dione **(2a)** and different functionalized aromatic isocyanides **(3a-o)**, as shown in **Scheme 3.2.2**. The synthesized products, when compared to earlier studies of Passerini reactions without catalyst, had good yields and relatively shorter reaction times, which confirms the efficiency of the catalyst. The results are clearly demonstrated in **Table 3.2.2**.

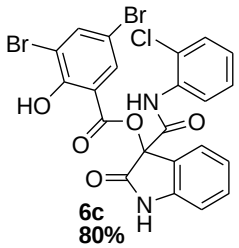


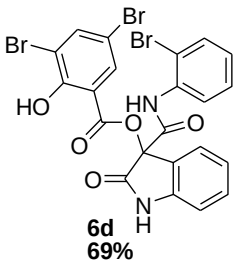
Scheme 3.2.1: Variation of isocyanide moieties with 4-bromobenzoic acid (1b)

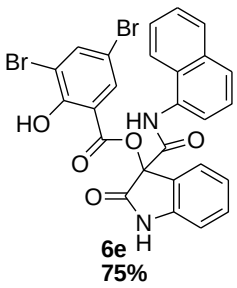
Generally, the reactions which were carried out with benzoic acid (partially water soluble **1a**,) in water resulted in products **4a** with yields of 80%. In the case of 4-bromobenzoic acid (water-insoluble **1b**) the yields **(5a-i)** obtained were 75-93%. The results demonstrated that in aqueous media the reaction results in the formation of products with equal or higher yields than under "standard conditions" (dichloromethane as solvent or neat). A variety of electron releasing and withdrawing groups at various positions of the aromatic ring of isocyanides are well tolerated, leading to the formation of the oxindole derivatives. Furthermore, the reactions **(1c, 2a, 3a-o)** performed in water (**entries 4–6**) in the presence of catalytic amounts of SiO_2-H_2SO_4 resulted in products **6a-o** in moderate to good yields 53–87% demonstrating the efficiency of the catalyst. Under the above catalytic conditions isocyanides with electron-donating groups afforded good yields of 53-80% of the desired products. The halogen (F, Cl, Br, I)-containing isocyanides offered better yields of corresponding products, ranging from 62 to 80%. Various functional groups such as ester, ether, halo, and nitro groups were found to react smoothly under the optimized reaction conditions and demonstrating good yields of the products. Finding a sustainable method for easy preparation of oxindole derivatives will surely benefit the drug discovery process.

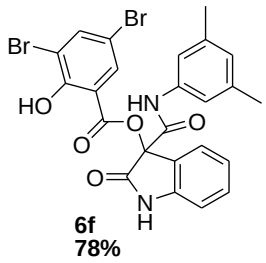


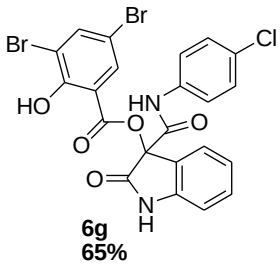


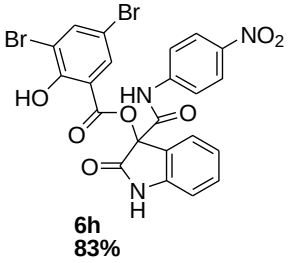


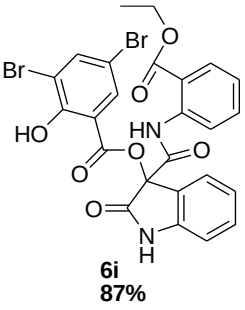


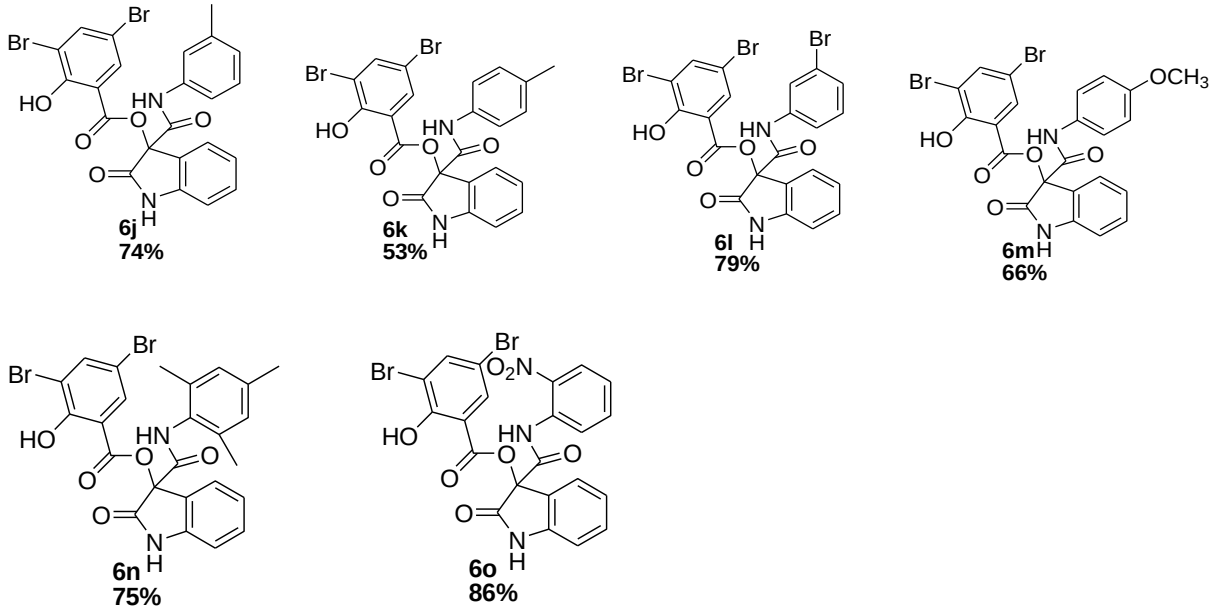






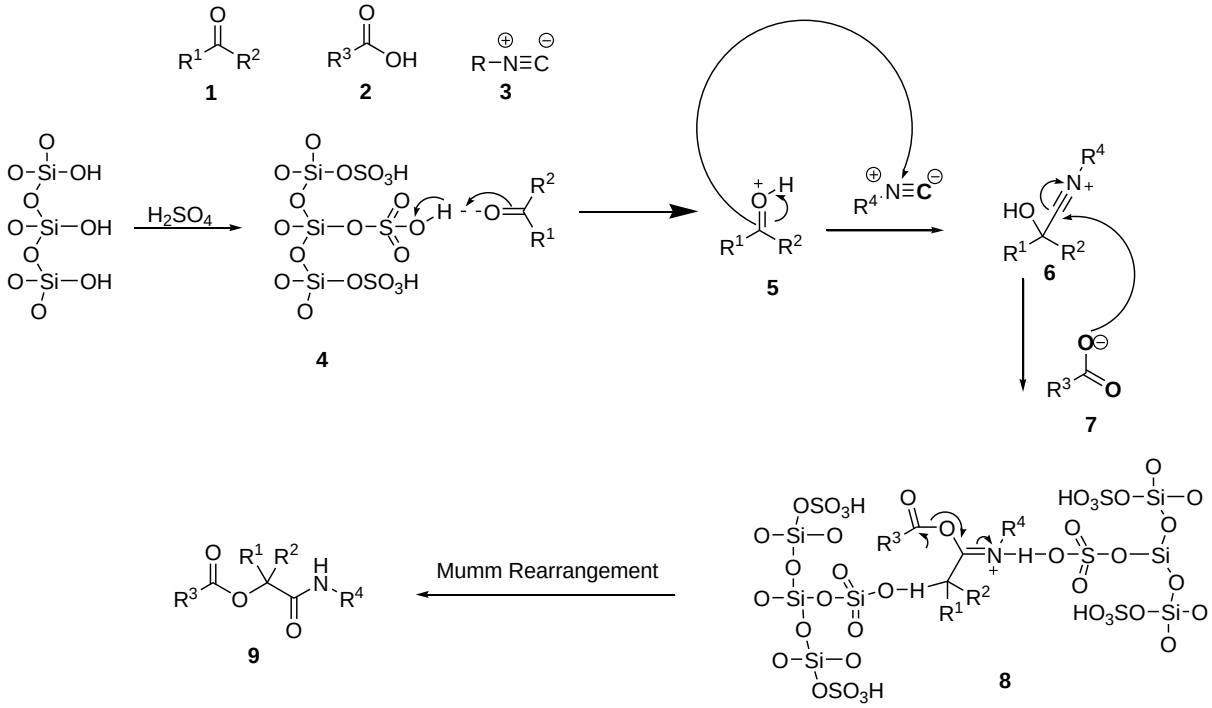






Scheme 3.2.2: Variation of isocyanide moieties with 3,5-dibromosalicylic acid **(1c)**

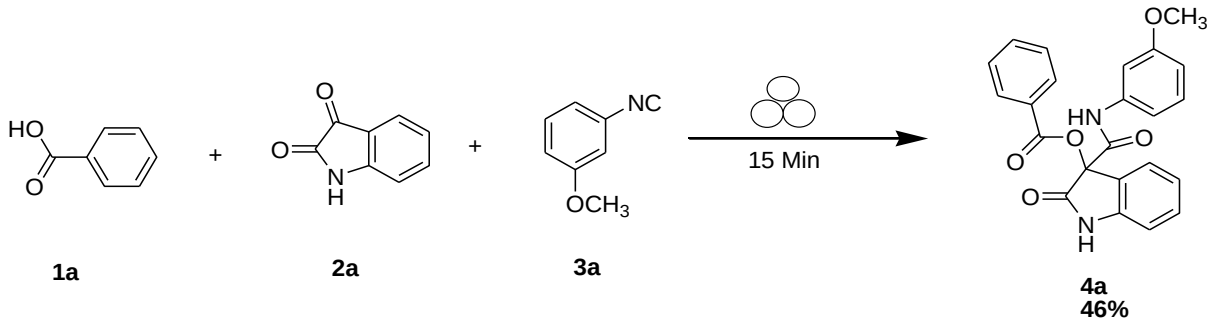
A suggested mechanism for the formation of α-acyloxycarboxamides derivatives **(9)** in the presence of immobilized sulfuric acid on silica gel is outlined in **scheme 5**. SiO_2-H_2SO_4 efficiency is better appreciated when considering its acid-base amphoteric character, as it serves as both a proton donor and acceptor during the reaction course. The catalyst first activates the carbonyl group of aldehydes **(4)**, followed by the nucleophilic attack of isocyanide to the activated carbonyl **(5)** group which Sresults in the formation of an intermediate called nitrilium **(6)**. The carboxylate of **(7)** then attacks intermediate **(6)**, followed by an acyl transfer through a Mumm rearrangement to produce oxindole based α-acyloxycarboxamides derivatives **(9)**.



Scheme 3.2.3: Proposed mechanism for the synthesis of α-acyloxycarboxamides in the presence of the immobilized sulfuric acid on silica gel (SiO_2-H_2SO_4).

Passerini reaction under mechanochemical conditions.

We began this study by evaluating the practicality of a solvent free Passerini 3-CR reaction under mechanochemical conditions. The synthesis of Passerini adduct 4a was chosen as our model reaction, which employed 1-isocyano-3-methoxybenzene **(3a)**, indole-2,3-dione **(2a)**, and benzoic acid **(1a)**, as the starting materials in a modified Makita (Jigsaw) ball mill under mechanochemical activation. The experiments under Method A, **(Met-A)** leverage on the use of a stainless-steel reactor (diameter: 2.0 cm; height: 2.0 cm; volume of reactor: 13.2 ml) that contained two balls of the same material (diameter: 6 mm; mass: 0.90 g) and a milling time of 15 min at 25 Hz. After purification by column chromatography, the anticipated Passerini adduct **4a** was isolated in 46 % yield (**Table 3.2.3, Entry 2**). The yield increases slightly to 53% when the milling time increases to 40 minutes, and further increase in the milling time to 50 min has no impact on the reaction yield of **4a** (**Table 3.2.3, Entries 4-6).** This compares with our previous synthesis under aqueous conditions with no mechanical activation, which yielded 53 to 93%, depending on the solvent (see **Table 3.2**).



Scheme 3.2.4: Model Passerini reaction under mechanical activation.

Encouraged by these findings, we conducted a series of experiments in a smaller stainless-steel reactor (**Met-B)** (0.6 cm in diameter, 2.0 cm in height, and 3.4 mL in volume) with two smaller milling balls of the same material (diameter: 4 mm; mass: 0.51 g). In this case, the desired product was obtained in 40% yield after milling for 30 min, at 30 Hz, (**Table 3.2.3**, **Entry 10**). Similar conversions were obtained by increasing the grinding time to 50 min (**Table 3.2.3**, **Entry 12**) suggesting that the operation is greatly dependent on the material of the reactor, as well as the surface area of the components, especially the balls and the internal reactor surface.

Table 3.2.3: Optimization of mechanochemical reaction parameters.

Entry	Reagents	Reactor type (d, (mm))	Time (min) Freq (Hz),	Yield %
1.	1a, 2a, 3a.	Met-A, (6)	10 (25)	32

2.	1a, 2a, 3a.	Met-A, (6)	15 (25)	46
3.	1a, 2a, 3a.	Met-A, (6)	20 (25)	46
4.	1a, 2a, 3a.	Met-A, (6)	30 (25)	49
5.	1a, 2a, 3a.	Met-A, (6)	40 (25)	53
6.	1a, 2a, 3a.	Met-A, (6)	50 (25)	53
7.	1a, 2a, 3a.	Met-B, (4)	10 (25)	28
8.	1a, 2a, 3a.	Met-B, (4)	15 (25)	34
9.	1a, 2a, 3a.	Met-B, (4)	20 (30)	34
10.	1a, 2a, 3a.	Met-B, (4)	30 (30)	40
11.	1a, 2a, 3a.	Met-B, (4)	40 (30)	40
12.	1a, 2a, 3a.	Met-B, (4)	50 (30)	40

[a] All reactions were carried out on a 1 mmol scale by using equimolar amounts of the reactants. [b] Reactor type: Met-A, stainless steel [diameter (d): 2.0 cm; height: 2.0 cm; volume of reactor: 13.2 mL]; Met-B, stainless steel (diameter: 1.2 cm; height: 2.0 cm; volume of reactor: 3.4 mL);

Noticing our earlier yield improvements with DCM, methanol, and water as solvents, we consequently investigated a liquid-assisted milling technique using the established optimized reaction conditions **(Table 3.2.4)**. Since DCM is typically used as the solvent in Passerini reactions, it was chosen initially for the strategy. This would also allow us to compare these results with those obtained previously for the same reaction in DCM. Various reaction solvents were also screened as before such as, toluene, and methanol. The reaction occurs in all the solvents tested producing 75, 62, 81% yields of the desired products **(4a)** (**Table 3.2.4, entries 1-3**). At this point, we thought of carrying out these reactions under aqua assisted milling conditions (this is only a small amount of water, not enough to dissolve the reagents). To our delight, when the solvent was replaced with water at room temperature, the Passerini adduct was obtained in 92% yield after milling for 15 min (**Table 3.2.4, entry 5)**. This may be due to the reactants' low water solubility, which amplifies the influence of the hydrophobic effects on the rate of reaction and resulted in a significant rise in the yield of **4a**. (**Table 3.2.4, entry 5**). The use of 50 µL (0.05 mL), 75 µL (0.075 mL), 100 µL (0.1 mL) of water as the additive for the LAG resulted in a slight improvement in yield (**Table 3.2.4, Entries 4-8)**. Conversely, a reduction in grinding time (**Table 43.2.3)**, and a rise in frequency **(Table 3.2.3)**, had a negative impact.

Table 3.2.4: Effect of solvent on the model mechanochemical reaction.

Entry	Reaction	Additive	Time (min)	Yield%
1.	1a, 2a, 3a.	DCM	15	75
2.	1a, 2a, 3a.	toluene	15	62
3.	1a, 2a, 3a.	methanol	15	81
4.	1a, 2a, 3a.	Water (50 µL)	10	79

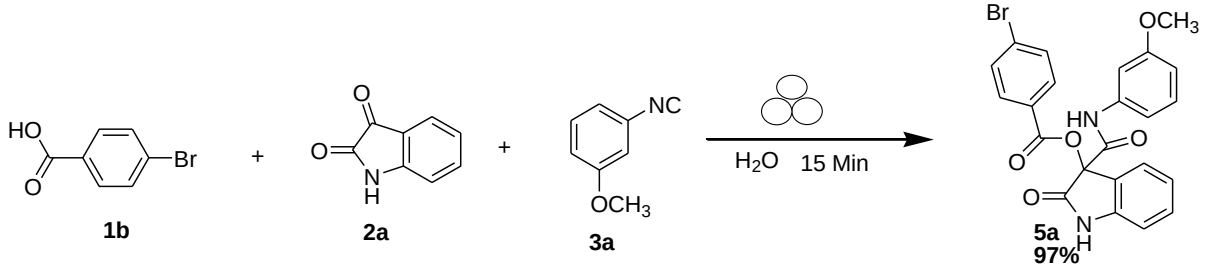
5.	1a, 2a, 3a.	Water (50 µL)	15	92
6.	1a, 2a, 3a.	Water (50 µL)	20	92
7.	1a, 2a, 3a.	Water (75 µL)	15	94
8.	1a, 2a, 3a.	Water (100 µL)	15	97

[a] All reactions were carried out on a 1 mmol scale by using equimolar amounts of reactants. [b] Reaction carried out using a frequency of 25 Hz. [c] Reaction was carried out with two balls (diameter: 6 mm).

With the optimized reaction conditions in hand, we then examined the substrate scope of this aqua assisted milling Passerini reaction. The scope of the carboxylic acid moiety was first examined (**Table 3.2.5)**. It was found that the unsubstituted **(1a)** and monosubstituted benzoic **(1b)** acids performed well resulting in the synthesis of the oxindole derivatives (**4a, 5a-i**) in high to excellent yield (90-97%), due to insolubility of **1a, 1c** and the rise in hydrophobic effect needed for rate enhancement. However, when 3,5-dibromosalicylic acid was used as an acid surrogate, despite the steric hindrances the reaction was completed in 15 minutes and the product **(6a)** was obtained in high yield (93%). This is surprising because of the solubility issue associated with 3,5-dibromosalicylic acid **(1c)** as explained in **Table 3.2.5**. In order to gain insight into the mechanism and the rate of this reaction, we investigated the stoichiometric effect of water on the model Passerini reaction involving (1c). We chose to perform the reaction under different stoichiometric volumes of water bearing in mind the maximum volume of water needed to make a slurry of reactant mixture under mechanical activation **(Table 3.2.5).** The result shows that the hydrophobicity of the reactant mixture increases at low water concentration, resulting in high yield of product **6a** (**Table 3.2.5, entry 6).** When the volume was increased to 100 µL (0.1ml), the yield declined slightly due to an increase in the solubility of **1c** in water (**Table 3.2.5, entry 4**). Generally, we observed that for water soluble reactants, the higher the volume of water the lower the influence of the hydrophobic effect and consequently the lower the reaction yield. It is important to note in this context that 3,5-dibromosalicylic acid afforded the expected products 6a-o in good to excellent yield demonstrating the versatility of the present method but underlying the need to control the amount of water in the case of water-soluble acids.

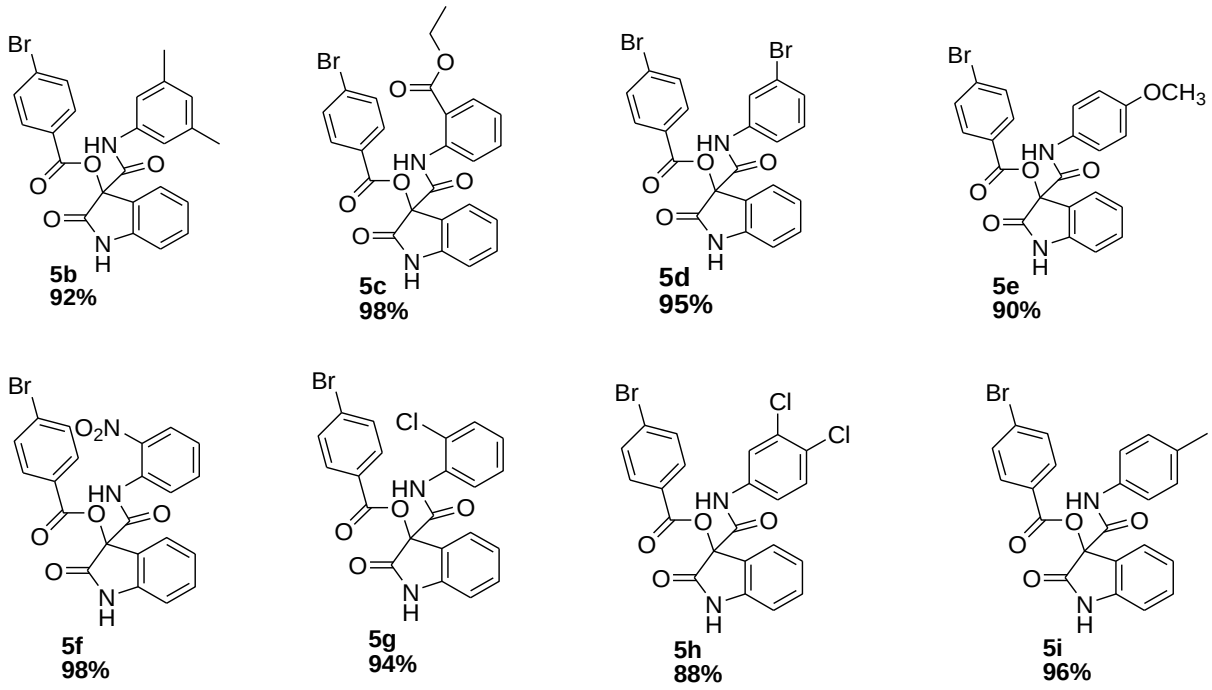
Table 3.2.5: Optimization of water content stoichiometry on the model reaction.

Entry	Reaction	Additive	Time (min)	Yield%



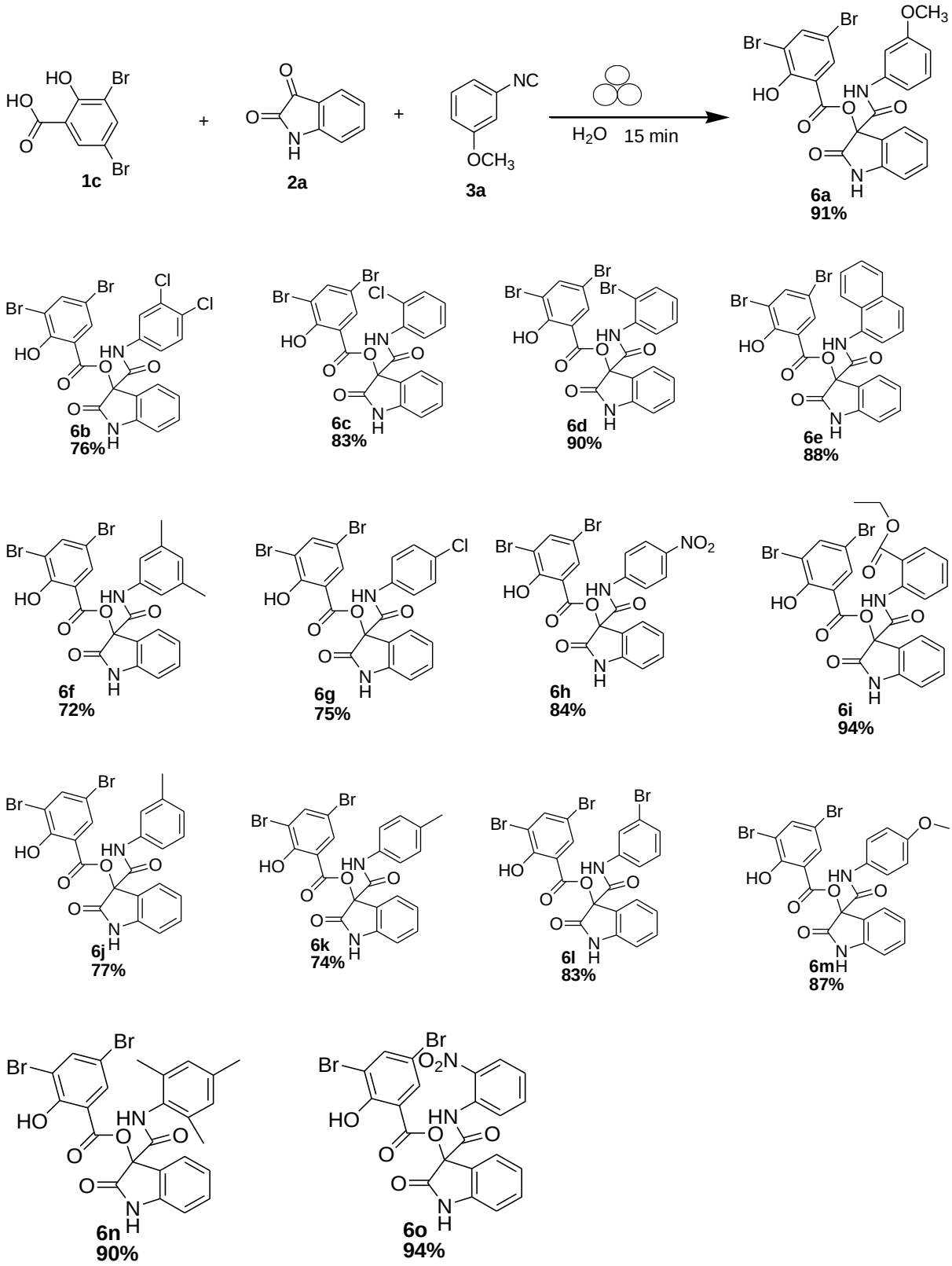
1.	1b, 2a, 3a.	Water (100 µL)	15	95
2.	1b, 2a, 3a.	Water (75 µL)	15	97
3.	1b, 2a, 3a.	Water (50 µL)	15	90
4.	1c, 2a, 3a.	Water (100 µL)	15	72
5.	1c, 2a, 3a.	Water (75 µL)	15	87
6.	1c, 2a, 3a.	Water (50 µL)	15	91

[a] All reactions were carried out on a 1 mmol scale by using equimolar amounts of reactants. [b] Reaction carried out using a frequency of 25 Hz. [c] Reaction was carried out with two balls (diameter: 6 mm).



Scheme 3.2.5: Variation of isocyanide moieties under mechanochemical conditions.

Next, we investigated the scope of this reaction with various substituted isocyanides. Under the above optimized reaction conditions, isocyanides with electron-donating groups afforded good yields of 70-97% of the desired products with milling times of 15 min. The halogen (F, Cl, Br, I)-containing isocyanides offered better yields of corresponding products, ranging from 75 to 90%. Similarly, electron-withdrawing groups react smoothly under the above conditions, exhibiting good yields of the desired products. In general, Passerini reaction involving electron-rich, or electron-deficient aromatic isocyanides afforded the products in excellent yields (70–97%). Generally, the above experimental details demonstrate the benefit of the techniques in terms of yields, minimization of solvent use and experimental simplicity.



Scheme 3.2.6: Variation of isocyanide moieties under mechanochemical conditions.

Summary and Conclusions

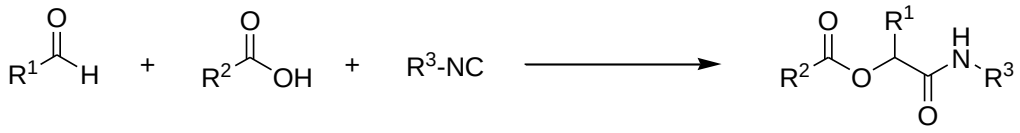
The mechanochemical reaction was compared to its water-based counterpart reaction, and it is significant to note that both protocols were found to have several key benefits, including simplicity of use, good yields, short reaction times, use of non-toxic solvent and non-conventional energy source and eco-friendly method. The procedures, in our opinion, offer a convenient and efficient alternative to the existing traditional methods. However, comparing the two protocols is useful in terms of reaction yield and experimental simplicity. As shown in **tables 3.2.4, and 3.2.5**, the reactions carried out under mechanochemical activation happen at comparatively faster rates with higher yields. While the same reactions carried out under aqueous conditions, gave a moderate to high yield within the same timeframe except where catalyst was employed (**Tables 3.2, 3.2.1, 3.2.2**). Notably, while the reaction involving sterically hindered water-soluble benzoic acid **1c** leverages on use of immobilized sulfuric acid for rate enhancement as observed in all related reactions of **1c**, it was evident that mechanochemical activation can speed up the reaction considerably to reduce the reaction time with higher yields even in the absence of catalyst. Thus, we found that liquid assisted mechanochemical activation was very effective and useful in our work, which was superior to the reaction carried out under aqueous conditions with respect to yields and experimental simplicity. Thus, we propose the application of aqua and mechanochemical methodologies as biologically and environmentally safe techniques to provide an eco-friendly and economical procedure for the synthesis of biologically important oxindole derivatives, which can be afforded in 10 to 15 min.

Part C

3.3. The *N*-formamides as carbonyl precursors in the catalytic synthesis of Passerini adducts under aqua and mechanochemical conditions.

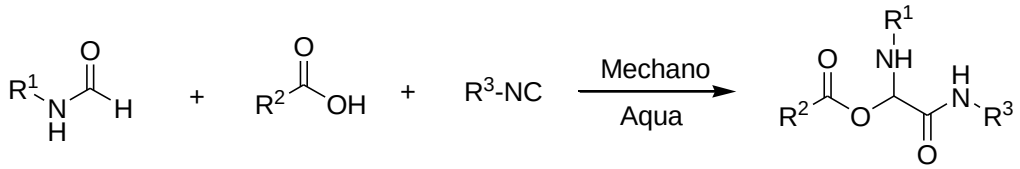
Passerini reaction have been known for over 80 years, but little is known about the scope of carbonyl-type electrophiles that undergo the reaction. The most studied candidates for this reaction are aldehydes and (to a lesser extent) ketones [160, 161]. On the other hand, the impact of including neighbouring reactive groups within the carbonyl component has not been investigated. Additionally, the application of alternative carbonyls such esters and formamides has not been studied. We set out to replace the carbonyl component, keeping in mind the potential effects of even minor functional modifications, by simply substituting *N*-formamides for the carbonyl in the Passerini reaction.

Typical Passerini reaction.



Scheme 3.3: Passerini 3-component reaction utilizing carboxylic acid, aldehyde, and isocyanide.

New synthetic route.



Scheme 3.3.1: Aqua/Mechano mediated Passerini reaction utilizing various heterocyclic *N*-formamides as a replacement for the carbonyl component.

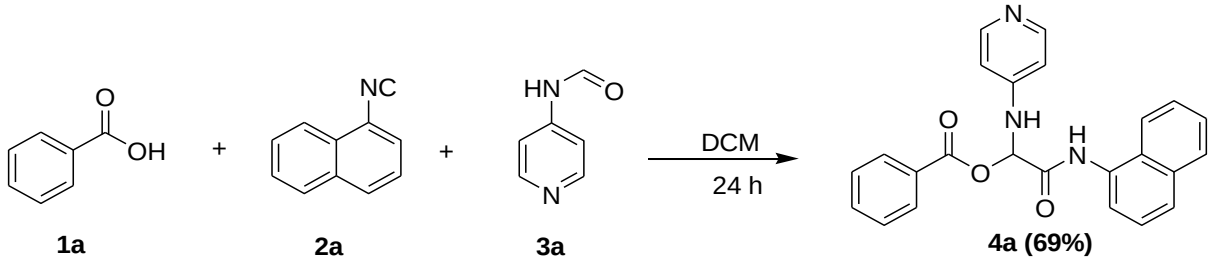
Aqua and mechanochemistry are widely used for organic synthesis because they take less time, produce better results, and are simpler to utilize than traditional techniques. A crucial tool in the construction of diversity-oriented compound libraries is the Passerini three-component reaction, which uses aldehyde, substituted carboxylic acid, and different functionalized isocyanides [77]. In this regard, mechanochemical and aqua versions of this transformation have been developed, and they are based on the use of water (aqueous reaction) and high-speed vibration milling with a double agate ball (6 mm diameter) in an agate jar and water as a liquid-assisted grinding agent to produce the carboxamide derivatives.

A heterogenous catalytic approach can be anticipated to be advantageous as an alternative to the commonly used metallocatalysis or organocatalysis due to the high efficiency, short reaction time, high

yield, and mild reaction conditions [162]. Bronsted acid catalysts have been used in several organic transformations to overcome limitations, such as toxicity, volatility, and hazardous nature of the conventional methods [163]. Catalysts are adsorbed on silica gel to provide the benefits and advantages of ready availability, simple work-up procedure, long catalytic life, environmental safety, excellent yields, and recyclability [27, 28]. The aim of the present work was to combine the activity of catalysts with the diversity offered by a Passerini reaction to obtain functionally distinct α-acyloxycarboxamide scaffolds with the feature of broad substrate scope and sufficient molecular diversity needed for fine tuning biological activity (using various substituted heterocyclic *N*-formamides as carbonyl surrogates).

Results and Discussion.

The Passerini reaction of benzoic acid (1mmol), 1-naphthylisocyanide (1 mmol) and 4-formamido pyridine (1mmol) as the carbonyl surrogate was chosen as the model reaction using dichloromethane as solvent (Scheme 1). Interestingly, a new product **4a** was observed and isolated in 69% yield **(Table 3.3 entry 4)**. This revealed the successful replacement of carbonyl by 4-formamido pyridine **3a** (*N*-formamides) in the Passerini reaction. We investigated the impact of various solvents on the reaction course first in the absence of catalyst, to determine the most suitable reaction conditions and to compare the results of the aqua conditions with those obtained under standard conditions (organic solvents). **(Table 1).**

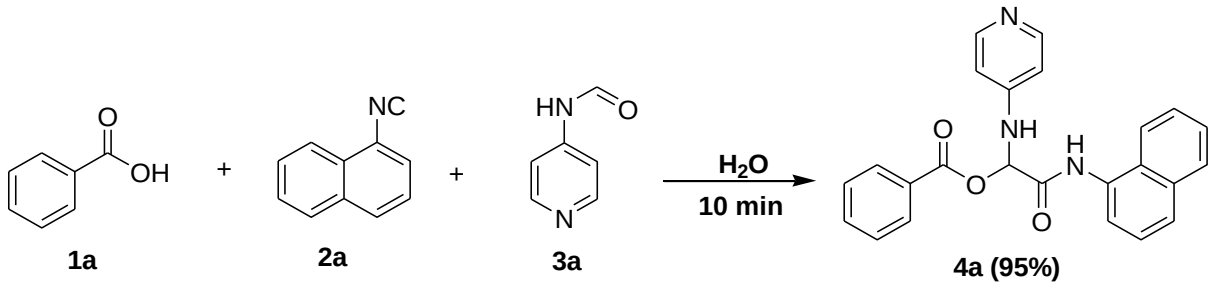


Scheme 3.3.2: Model Passerini reaction in dichloromethane without catalyst.

The P-3CR in the absence of H_2SO_4-SiO_2 proceeded smoothly in dichloromethane (CH_2Cl_2) and methanol (CH_3OH) with yields of 69% and 47% respectively **(Table 3.3 entries 4-5)**. Solvents such as tetrahydrofuran, toluene, and diethyl ether were ineffective even after 48 hours producing trace amount of the products (**Table 3.3 entry 1-3)**. When the reaction was carried out in water in the absence of catalyst, the product **4a** was obtained in high yield **(82%)** within 15 min **(Table 3.3 entry 6)**. The reaction products distribution showed strong dependency on the hydrophobicity of the reactants, according to Pirrung, Das Sarma, [52] while the more hydrophobic ones producing the typical Passerini product in high yield and at a faster rate.

Table 3.3: Effect of solvents on the scope of Passerini reaction in the presence/absence of catalyst.

Entry	Solvent	Catalyst (g)	Time	Yield %
1	Tetrahydrofuran	No	48 hr	14
2	Toluene	No	24 hr	23
3	Diethyl ether	No	48 hr	30
4	Dichloromethane	No	48 hr	69
5	Methanol	No	48 hr	47
6	Water	No	15 min	82
7	Tetrahydrofuran	SiO_2-H_2SO_4 (0.02)	24 hr	33
8	Toluene	SiO_2-H_2SO_4 (0.02)	6 hr	51
9	Diethyl ether	SiO_2-H_2SO_4 (0.02)	24 hr	44
10	Dichloromethane	SiO_2-H_2SO_4 (0.02)	6 hr	78
11	Methanol	SiO_2-H_2SO_4 (0.02)	6 hr	63
12	Water	SiO_2-H_2SO_4 (0.02)	10 min	95



Scheme 3.3.3: Model Passerini reaction in aqueous media in the presence of catalyst.

The model reaction was performed in the presence of 0.02g of H_2SO_4-SiO_2 in DCM at room temperature and 78% product yield was observed after 6 h **(Table 3.3, entry 10)**. Also, when the reaction was performed in the presence of 0.02 g of H_2SO_4-SiO_2 in methanol at room temperature, the yield decreases to 63% after 6 h **(Table 3.3, entry 11)**. The highest yield (95%) was obtained when the reaction was carried out in water in the presence of 0.02 g of the H_2SO_4-SiO_2 at room temperature **(Table 3.3, entry 12)**. Therefore, as indicated from the results the heterogenous catalyst (H_2SO_4-SiO_2) has higher efficiency and activity, consequently, reactions are carried out on a wider surface producing high yields of products in a very short time. The next survey of catalysts revealed that further increase in the catalyst amount has little or no effect on the yield of the reaction product **(4a)** as 0.02g was found sufficient to carry out the reaction with highest possible yields. Thus, the best reaction efficiency was achieved in the presence of 0.02 g H_2SO_4-SiO_2 in water (2ml) at room temperature **(Table 3.3, entry 12)**.

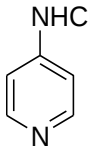
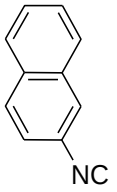
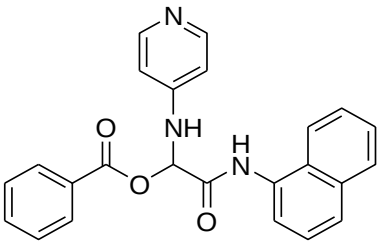
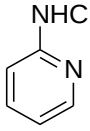
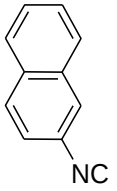
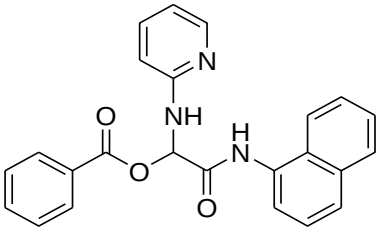
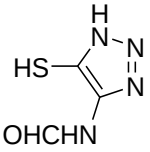
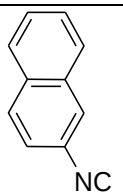
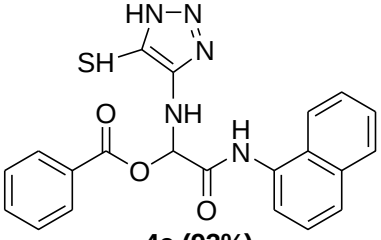
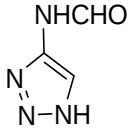
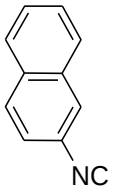
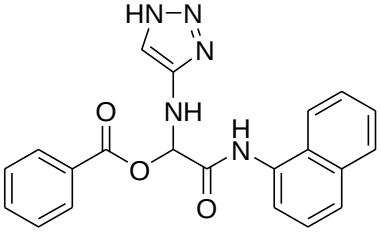
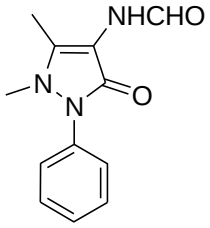
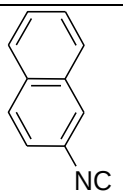
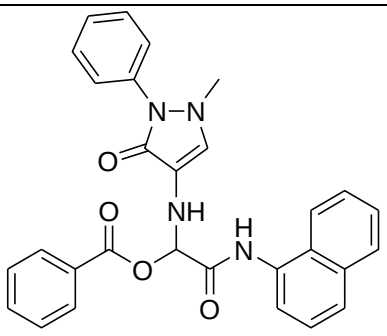
Table 3.3.1: Screening for best catalytic reaction conditions.

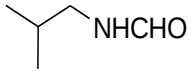
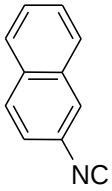
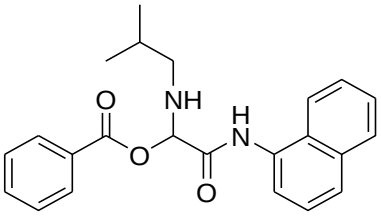
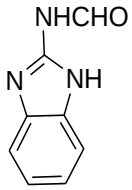
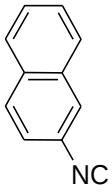
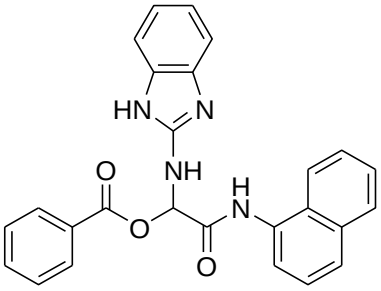
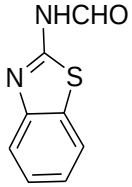
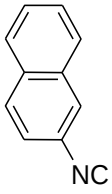
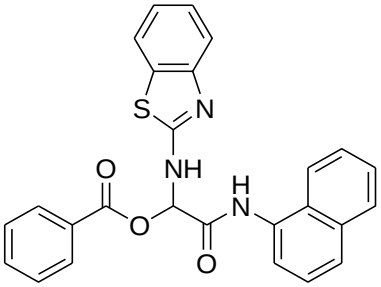
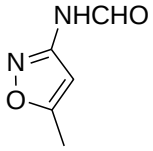
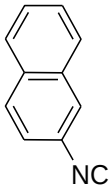
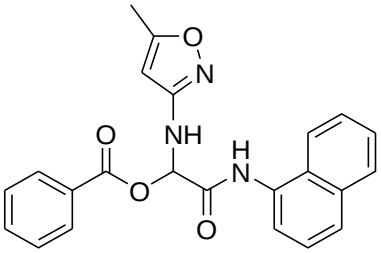
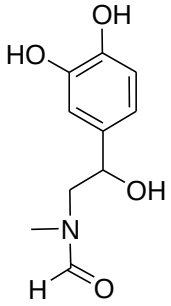
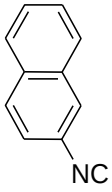
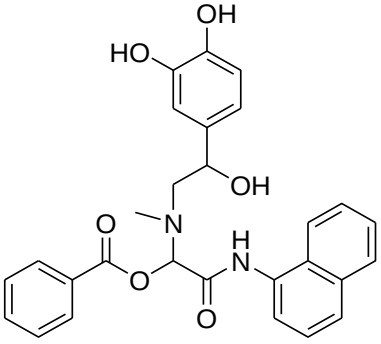
Entry	Reaction Condition	Solvent	Catalyst (g)	Time	Yield %
1	**(1a, 2a, 3a)**	Distilled water	SiO_2-H_2SO_4 (0.01)	10 min	93
2.	**(1a, 2a, 3a)**	Distilled water	SiO_2-H_2SO_4 (0.02)	10 min	95
3.	**(1a, 2a, 3a)**	Distilled water	SiO_2-H_2SO_4 (0.03)	10 min	95
4.	**(1a, 2a, 3a)**	Dichloromethane	SiO_2-H_2SO_4 (0.01)	6 hr	72
5.	**(1a, 2a, 3a)**	Dichloromethane	SiO_2-H_2SO_4 (0.02)	6 hr	78
6.	**(1a, 2a, 3a)**	Dichloromethane	SiO_2-H_2SO_4 (0.03)	6 hr	78

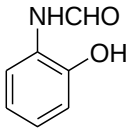
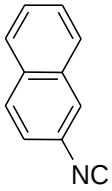
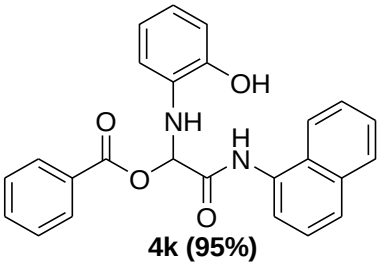
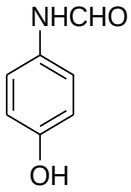
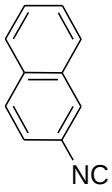
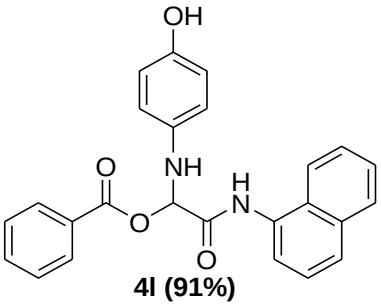
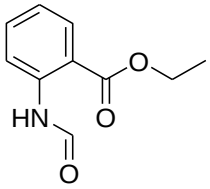
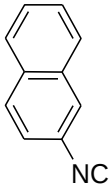
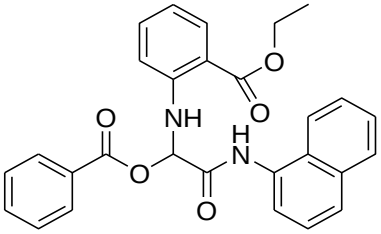
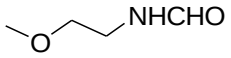
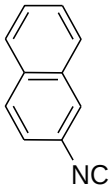
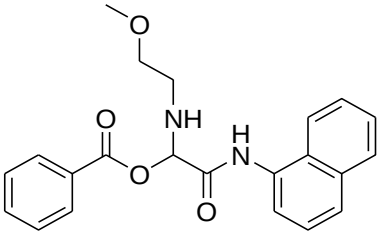
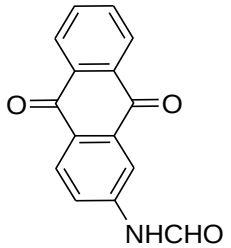
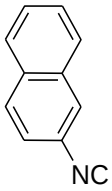
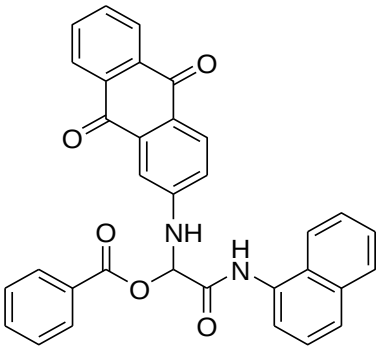
To study the effectiveness and generality of the catalyst, new functionalized α-acyloxyamide derivatives were synthesized using benzoic acid **1a**, 1-naphthylisocyanide **2a** and various heterocyclic N-formamides **3a-p**, as shown in **Table 3.3.1**. In comparison to conventional Passerini reaction that leverages on volatile organic solvent, the synthesized compounds exhibit good yields and considerably faster reaction times, which confirms the catalyst's effectiveness. The results are presented in **Table 3.3.1**. With the optimal conditions in hand **(Table 3.3, entry 12)**, sixteen **(16)** *N*-formamide derivatives **3a–p**, three **(3)** isocyanides **2a**, **2q**, **2r** and a benzoic acid **(1a)** were used to construct a series of analogues **4a–r.** All desired products were isolated by column chromatography, and the yields are ranging from 83–96% **(Table 3.3.2)**.

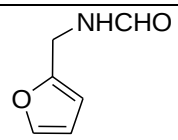
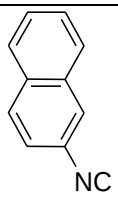
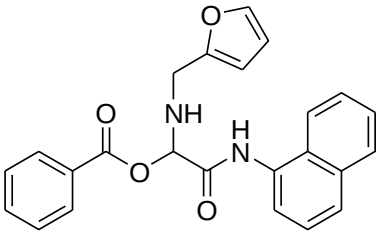
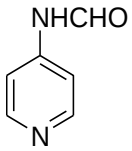
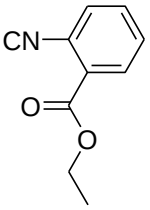
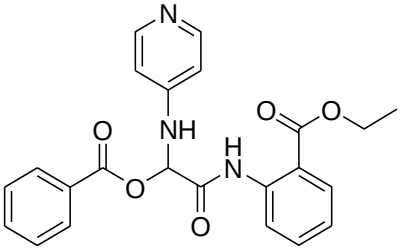
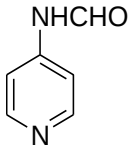
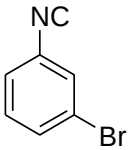
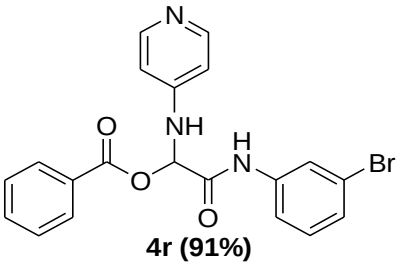
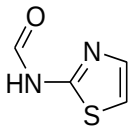
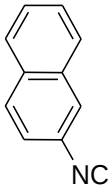
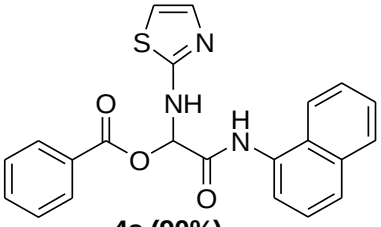
In the course of our investigation, we found that a variety of functionalized *N*-formamides containing heteroatoms could be used as beneficial inputs in Passerini MCRs to provide adducts in high to excellent yields. For example, the heterocyclic *N*-formamides of anthraquinone **3o**, antipyrine **3e**, isoxazole **3i**, ephedrine **3j**, thiazole **3s**, benzothiazole **3h**, benzimidazole **3g**, furfural **3p**, and 1,2,3-triazole **3c-d** moieties were each found to participate in Passerini MCRs that proceeded readily in one-pot operations in the presence of immobilized sulfuric acid on silica gel. To our knowledge, there are no reports in the literature employing this set of heterocyclic *N*-formamides in Passerini MCRs; thus, we present some novel functionalized Passerini adducts.

Table 3.3.2. New synthesized Passerini adducts under catalytic conditions.

Entry	*N*-formamides (3a-s)	Isocyanides	Acid	Product
1			R-COOH	 **4a (95%)**
2.			R-COOH	 **4b (87%)**
3.			R-COOH	 **4c (93%)**
4.			R-COOH	 **4d (90%)**
5.			R-COOH	 **4e (96%)**

6.			R-COOH	 **4f (92%)**
7.			R-COOH	 **4g (85%)**
8.			R-COOH	 **4h (95%)**
9.			R-COOH	 **4i (83%)**
10.			R-COOH	 **4j (89%)**

11.			R-COOH	 **4k (95%)**
12.			R-COOH	 **4l (91%)**
13.			R-COOH	 **4m (87%)**
14.			R-COOH	 **4n (84%)**
15.			R-COOH	 **4o (90%)**

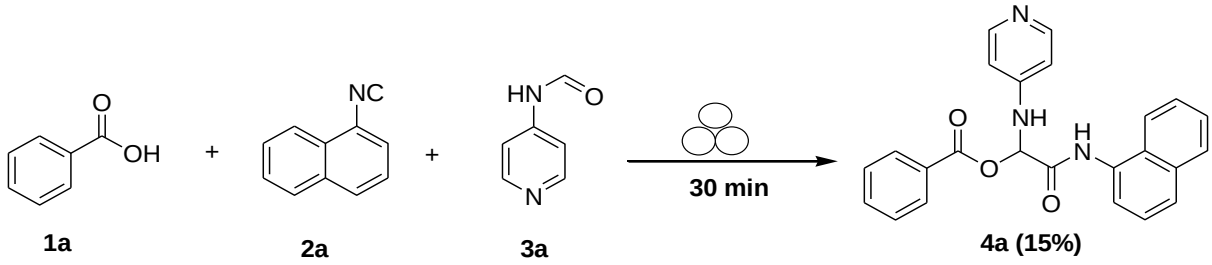
16.			R-COOH	 **4p (88%)**
17.			R-COOH	 **4q (94%)**
18.			R-COOH	 **4r (91%)**
19			R-COOH	 **4s (90%)**

Mechanochemical synthesis.

The physical state of the reactants is an important factor to consider in this experiment. For the first set of experiments (exp A), both reagents are liquids, hence a grinding auxiliary (typically an inert solid) was necessary to facilitate mixing and energy transfer. However, the reagents for the second experiment **(exp B)**, are solids, and the addition of a grinding agent could have a diluting impact.

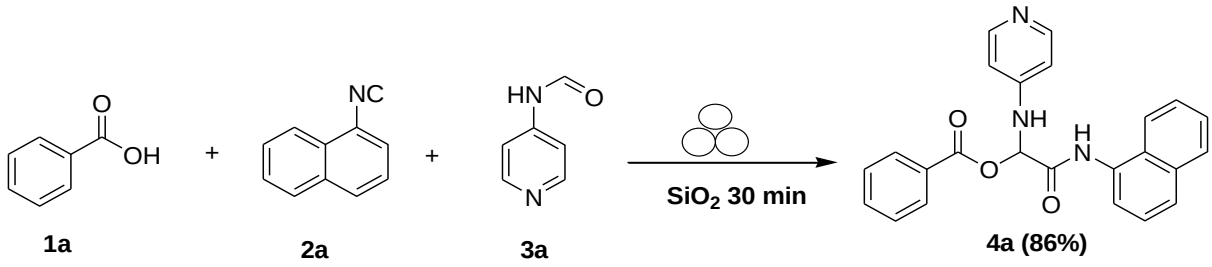
Initially the mechanochemical synthesis of various functionalized α-acylcarboxamide was investigated, we decided to employ fewer variables in this study by using the same jar and ball materials as in our earlier studies while also maintaining the same ball size, ball number, and jar size. Thus, the experiments **(Exp-A/B)** relied on the use of a stainless-steel reactor (diameter: 2.0 cm; height: 2.0 cm; volume of reactor: 13.2 ml) that contained two balls of the same material (diameter: 6 mm; mass: 0.90 g).

Experiment A. The model reaction first selected was the reaction between benzoic acid (1 mmol), 1-naphthylisocyanide (1 mmol), and 4-formamido pyridine (1 mmol). The three substrates were subjected to milling in the first series of experiments without using an auxiliary material, the yield of Passerini adduct **4a** obtained was dismal after 30 minutes at 25 Hz **(Table 3.3.3, entry 1)**.



Scheme 3.3.4. Model Passerini reaction with liquid substrate under mechanochemical activation.

Applying liquid substrates 2a, 3a, under these circumstances was disappointing because the yields of the resulting **4a** were much lower than those seen in the previously reported aqua mediated synthesis method (**Scheme 3.3.3**, **versus Scheme 3.3.4)**. A very watery slurry was visible when the ball mill jars for these reactions were opened after the milling, leading one to conclude that insufficient energy transfer had occurred. This limitation was removed by employing neutral alumina as a grinding auxiliary in the substrate combination. As a result, a dry, powdery crude product was produced, which supported our prediction because all products were now produced with noticeably better yields **(Scheme 3.3.5)**.

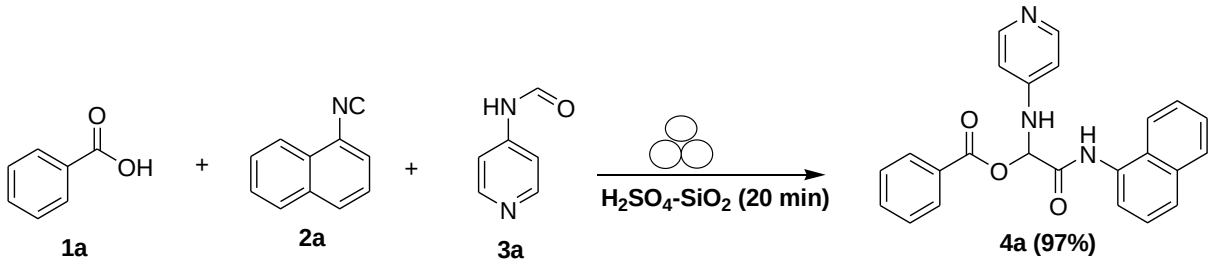


Scheme 3.3.5. Model Passerini reaction with liquid substrate and silica gel as grinding auxiliary.

Interestingly, introducing silica gel to the reaction mixture gave the desired Passerini product in 86% yield after milling for 30 minutes **(Table 3.3.3**, **entry 2)**. There may be numerous functions for the inclusion of a grinding auxiliary. Specifically, in mechanochemical processes where the reaction mixture might be defined as a gum, paste, or liquid, we believe that the main advantages pertain to enhanced mixing and enabling energy transfer. Notably, the same reaction carried out in aqueous media produced almost the same yield in the absence of catalyst **(Table 3.3, entry 6)**.

Table 3.3.3. Optimization of the model reaction conditions for (exp A).

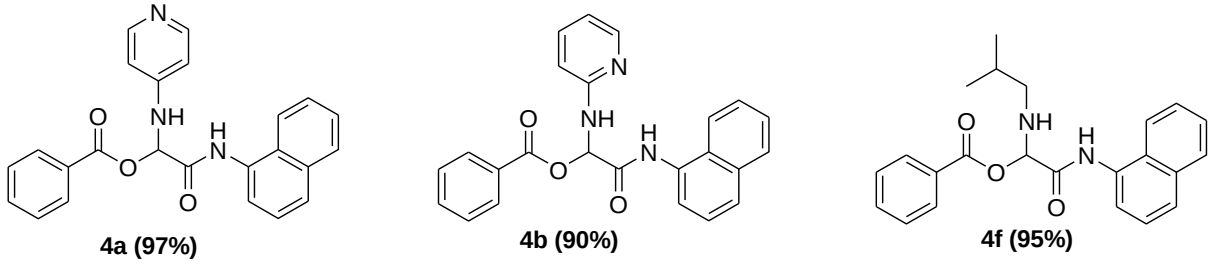
Entry	Reaction Condition	Catalyst (g)	Time min	Yield %
1	(1a, 2a, 3a)	No catalyst	30	15
2.	(1a, 2a, 3a)	SiO_2 (0.03)	30	86
3.	(1a, 2a, 3a)	SiO_2 (0.03)	40	86
4.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.01)	10	41
5.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.01)	20	55
6.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.01)	30	55
7.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.02)	10	74
8.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.02)	20	77
9.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.02)	30	77
10.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.03)	10	95
11.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.03)	20	97
12.	(1a, 2a, 3a)	SiO_2-H_2SO_4 (0.03)	30	97



Scheme 3.3.6. Model Passerini reaction with liquid substrate and immobilized sulfuric acid on silica gel as grinding auxiliary.

To further increase the yield of **4a**, we resorted to the employment of immobilized sulfuric acid on silica gel as a griding auxiliary instead of silica gel, since the positive impact of the catalyst in Passerini reaction has been established in our previous studies [159]. We started by subjecting the model substrates to milling in the presence of 0.01g of catalyst for 20 minutes. The yield of **4a** declines rapidly to 55%. Increase in the reaction time to 30 min had a negligible effect **(Table 3.3.3**, **entries 4–6)**. Then, the catalyst amount was varied. At this point the yield rose as the amount of catalyst utilized increased to 0.03g producing the Passerini product in 97% yield in milling time of 20 min **(Table 3.3.3, entries 7–12)**. It should be noted that the result was superior to those obtained under aqueous media in the presence of catalyst **(Table 3.3.3, entry 11, versus Table 2, entry 2**). Furthermore, in this case, the addition of more catalyst had an even greater impact on the yield, unlike the previous case where more than 0.02 g of catalyst had a detrimental effect. The catalyst in this situation probably serves as both a solid auxiliary for mechanochemical activation and a promoter system.

With the optimized conditions, we evaluated the scope of the liquid substrates via a Passerini reaction in the ball mill. Starting with pyridine moieties **(3a, 3b)** as carbonyl surrogate, 1-naphthylisocyanides and benzoic acid. The reaction proceeded smoothly producing the corresponding Passerini adducts in excellent yields **(90-97%)** after milling for 20 min under catalytic conditions. Similarly, liquid heterocyclic *N*-formamides containing ephedrine **(3j)**, and furan **(3p)** moieties also proved to be suitable for the multicomponent reaction in the ball mill, affording the products **(4j**, **4p)** preferentially. Finally, a set of experiments using 1-isocyano-3-bromo benzene **(2r)** and ethyl 2-isocyanobenzoate **(2q)** as isocyanide component with benzoic acid **(1a)** and 4-formamido pyridine **(3a) (Figure 3.3**, **4r**, **4q)** were also successful, highlighting the wide range of applicability for the mechanochemical method.



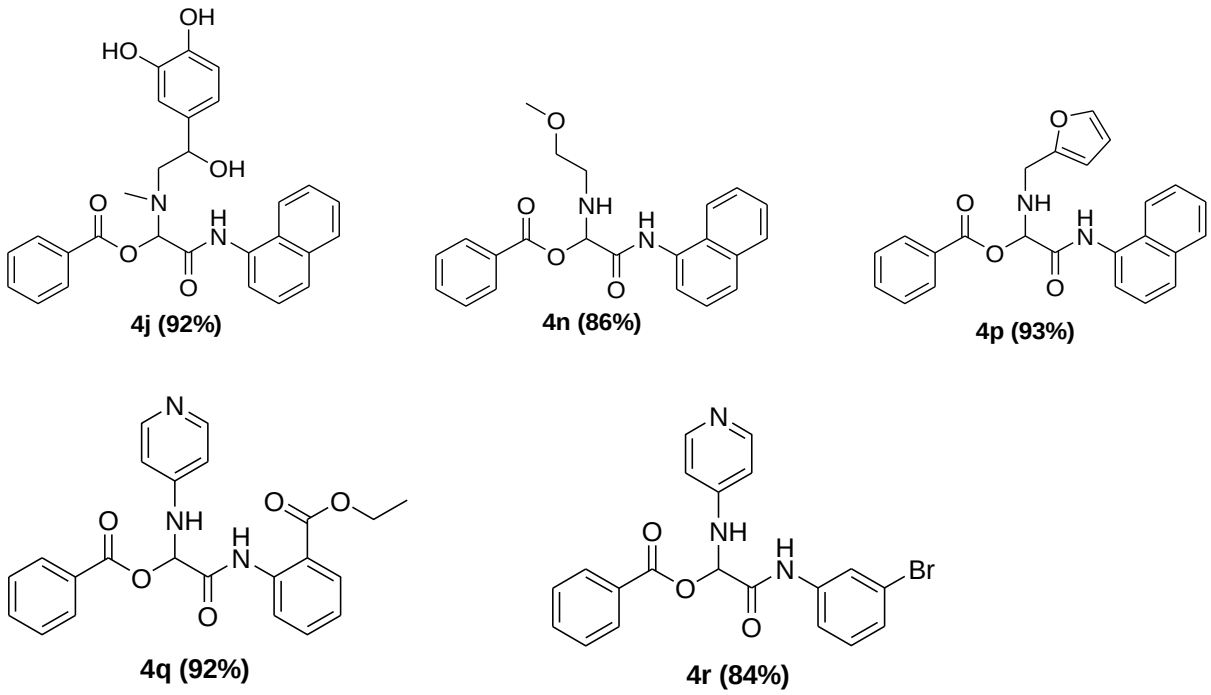
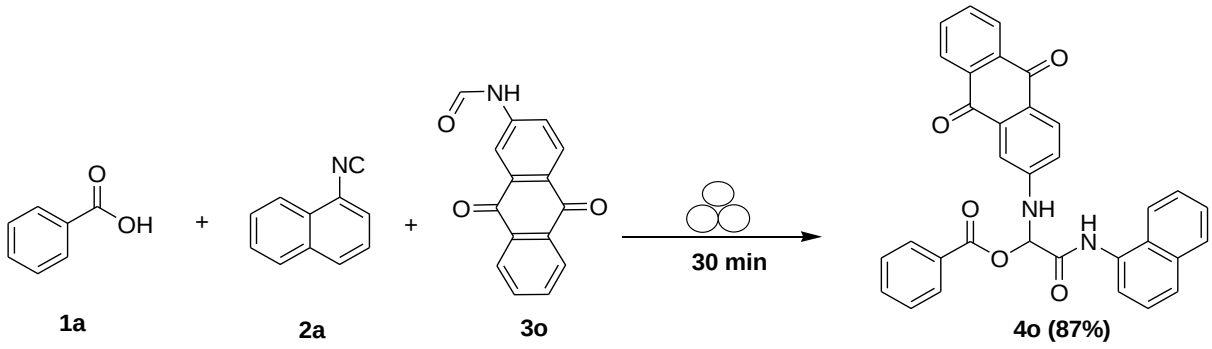


Figure 3.3: Variation of heterocyclic *N*-formamide moieties under mechanochemical activation.

Experiment B.

For the initial test reactions, benzoic acid **1a**, 1-naphthylisocyanide **2a** and 2-formamidoanthracene-9,10-dione **(3o)** were chosen as representative substrates (both reagents are solids). In the second experiment, both compounds were milled at 25 Hz for 20 min, and to our delight, product formation occurred providing the Passerini adducts **4o** in a yield of 71% **(Table 3.3.4**, **entry 1).** Increasing the milling time from 20 to 30 min improved the yield of **4o** to 87% and no further increase was observed at 40 min **(Table 3.3.4**, **entries 2-4)**. However, 30 minutes of milling at 25 Hz produced **4o** with an 87% optimum yield, but a shorter reaction time (10 min) had a detrimental impact on the yield of **4o** (79%) **(Table 3.3.4**, **entries 1-4)** respectively. At this point, the newly developed mechanochemical method for **4o** produced outcomes similar to those of the previously reported aqua-mediated procedure **(Table 3.3, entry 12)**, nonetheless, no solvent was employed this time yet.

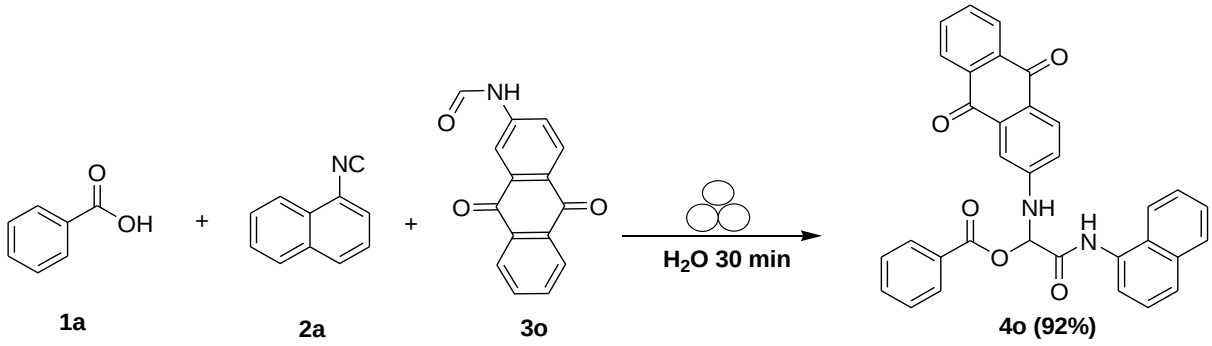


Scheme 3.3.7. Model Passerini reaction with solid substrate without grinding auxiliary.

Table 3.3.4. Optimization of the model reaction conditions for (exp B).

Entry	Reaction Condition	Additive	Time min	Yield %
1	(1a, 2a, 3o)	No additive	10	79
2.	(1a, 2a, 3o)	No additive	20	84
3.	(1a, 2a, 3o)	No additive	30	87
4.	(1a, 2a, 3o)	No additive	40	87
5.	(1a, 2a, 3o)	Water (50 µL)	30	89
6.	(1a, 2a, 3o)	Water (75 µL)	30	92
7.	(1a, 2a, 3o)	Water (100 µL)	30	72
8.	(1a, 2a, 3o)	Water (150 µL)	30	66
9.	(1a, 2a, 3o)	Aqueous HCl (75 µL)	30	69
10.	(1a, 2a, 3o)	Aqueous H_2SO_4 (75 µL)	10	74
11.	(1a, 2a, 3o)	Aqueous HNO_3 (75 µL)	20	81
12.	(1a, 2a, 3o)	Acetic acid (75 µL)	30	88

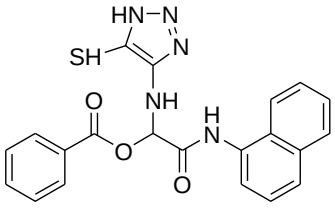
The idea of performing these reactions under liquid-assisted milling conditions was then entertained. We were thrilled to discover that when 75 µL water was employed as liquid auxiliary at room temperature after 30 minutes of milling, the yield of **4o** increases further to 92% of the Passerini adducts **(Table 3.3.4, entry 6)**. When 100 µL and 150 µL of water was used as an additive for the LAG, the yield decreased significantly to 72 and 66% respectively **(Table 3.3.4, Entries 7–8)**. The latter observation may be caused by the more liquid changing the reaction mixture's texture and so lessening effective mixing.



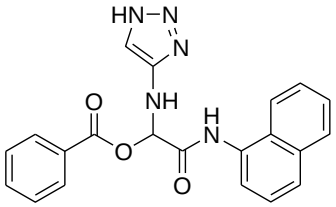
Scheme 3.3.8. Model Passerini reaction with solid substrate with water as grinding auxiliary.

In our previously reported Passerini reactions in aqueous media, the presence of immobilized sulfuric acid on silica gel had proven advantageous. We anticipate that using liquid acid in replacement of water (LAG) may have a beneficial effect on the reaction yield, so such effects on the formation of **4o** were therefore also investigated here under mechanochemical conditions. In each instance, 10 mol % of the

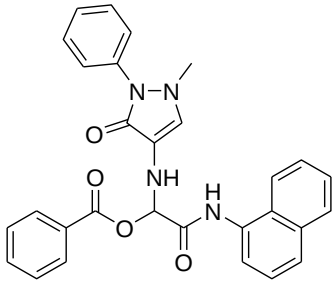
additive were used. The yield of **4o** decreased from the best yield of 92% **(Table 3.3.4)** to 69% in the presence of aqueous HCl **(Table 3.3.4, entry 9)**. Additionally, H_2SO_4 and HNO_3 had detrimental impacts, lowering the yield of **4o** to 74 and 81%, respectively **(Table 3.3.4, entries 10- 11)**. It was discovered that adding 75µl of Acetic acid slightly boosted the yield to 88%. Compound **4o** was now successfully produced with a yield of 88% with acetic acid (weak) compared to earlier trial with acids (strong) **(Table 3.3.4**, **entry 12)**. An alternative justification is that at higher acid loading, the 'on–off' activation of the formamide to nucleophilic attack is slow, meaning that the nucleophilicity is greatly retarded compared to lower acid loadings. Although good yield was obtained with weak acid (acetic acid), however the yield (88%) **(Table 3.3.4**, **entry 12)** is not comparable to that obtained using water (92%) **(Table 3.3.4**, **entry 6)** under the same milling conditions. Consequently, water was chosen as an additive of choice in this case and is explored further for subsequent research. Accordingly, the optimal mechanochemical conditions for the formation of **4o** involved a milling of **1a**, **2a,** and **3o** in the presence of water (75µl) at 25 Hz for 30 min at room temperature. At the end of the reaction, the crude mixture was subjected to column chromatography to furnish **4o** in 92% yield **(Figure 3.3.1)**.



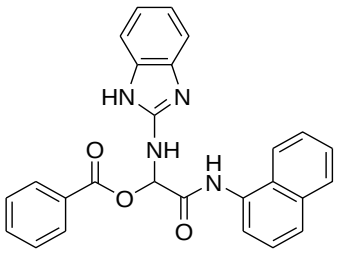
4c (82%)



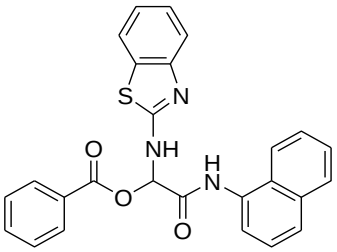
4d (94%)



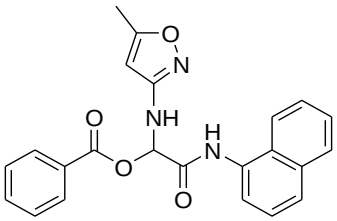
4e (86%)



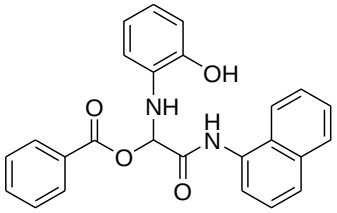
4g (80%)



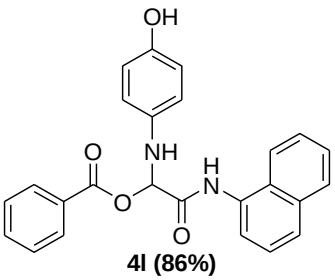
4h (88%)



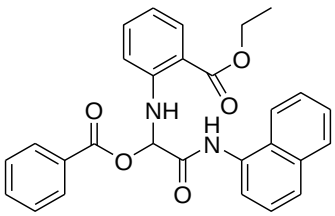
4i (83%)



4k (78%)



4l (86%)



4m (93%)

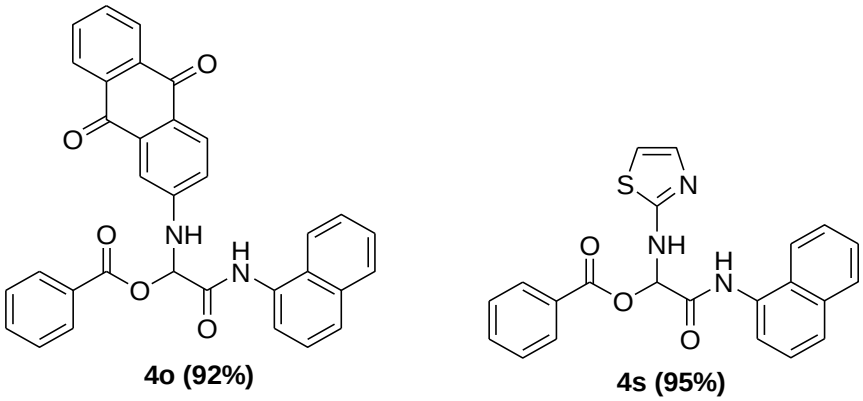


Figure 3.3.1: Variation of heterocyclic *N*-formamide moieties under mechanochemical activation.

With the optimized conditions at hand, we explored the scope of the method by using different substituted solid *N*-formamides such as those that contain the electron-donating groups 2-formamido phenol **(3k),** and 4-formamido phenol **(3l)**. The corresponding Passerini adducts **4k–l** were produced in good to excellent yields (78– 86 %). **(Figure 3.3.1)**. Heterocyclic *N*-formamides with five membered rings such as 1,2,3-triazole-5-thiol **(3c)**, 1,2,3-triazole **(3d)**, isoxazole **(3i)**, and thiazole **(3s)** moieties were also studied and found to furnish products **4c**, **4d**, **4i**, and **4s** in good to excellent yields (82–95 %). Additionally, heterocyclic aromatic *N*-formamides such as Antipyrine **(3e)**, benzimidazole **(3g)** and benzothiazole **(3h)**, generated the anticipated products **4e**, **4g**, and **4h** in good to excellent yields (80–88 %) after purification by column chromatography.

Conclusions

A practical synthesis of Passerini 3-CR adducts **(4a–s, 79–100% yield)** under aqua and mechanochemical (ball-milling) conditions was developed to demonstrate the usefulness of an aqueous organic reaction and mechanochemical activation for isocyanide-based multicomponent reactions. These protocols allow for the preparation of valuable molecules in good to excellent yields under catalytic conditions. Furthermore, these MCRs have high atom economy, experimental simplicity, short reaction times, and low energy costs. Additionally, our studies have opened the possible construction of diversity-oriented compound libraries and biologically relevant or natural-product-like molecular frameworks via the Passerini reaction from various heterocyclic *N*-formamides, benzoic acid and functionalized isocyanide. Finally, the Passerini processes could be scaled up to 100 mmol. We believe that these findings will offer value to the growing area of mechanochemistry and aqueous organic reactions undoubtedly.

Chapter 4

Part A.

Aqueous Microwave Assisted Novel Synthesis of Isothiocyanates by Amine Catalysed Sulfurization of Isocyanides with Lawesson's Reagent

Isothiocyanates are an important class of chemical compounds that have been discovered as subunits in both naturally occurring and biologically active compounds. Many isothiocyanate analogues possessing the isothiocyanate motif have been synthesized for possible medical applications after it was discovered that naturally occurring isothiocyanates play a key role in the cancer chemo-preventive activities of these plant species [164, 165]. Many epidemiological studies have discovered a connection between eating cruciferous vegetables like broccoli and lower cancer risk. The bioactive components of these cruciferous vegetables have been found to lower the expression of numerous cancer-related biomarkers in humans [166, 167]. The beneficial health effects of cruciferous vegetables are believed to be caused by the isothiocyanate (ITC) compounds, which are prevalent in these foods and are widely known for their ability to prevent cancer [168].

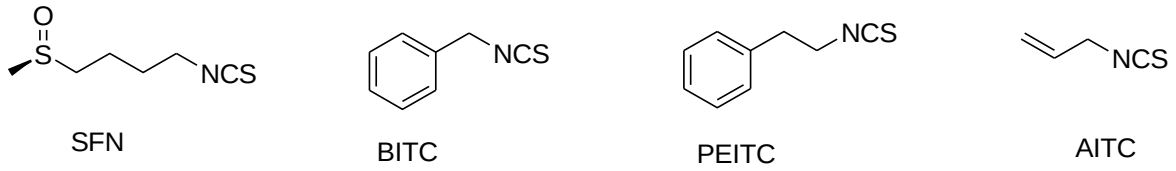


Figure 4.2. Some natural isothiocyanates found in cruciferous vegetables: sulforaphane (SFN), phenethylisothiocyanate (PEITC), benzyl isothiocyate (BITC) and allyl isothiocyanate (AITC).

Isothiocyanates and isocyanides possessing electron-withdrawing groups in the α-position can be deprotonated and react as formal dipoles due to the presence of an electrophilic atom and a nucleophilic carbanion in the functional groups of the isothiocyanate or isocyanide. Although many synthetic methods for the preparation of isothiocyanates have been reported from amines,[169] dithiocarbamates,[170] organic halides,[171] olefins[172], and aldoximes[173]. The most widely utilized method in the literature is the decomposition of dithiocarbamates using heavy metals,[174] or the use of thiophosgene,[175] iodine, ethyl chlorocarbonate, and claycop [176]. Most approaches of these approaches, however, suffer from low yields and the employment of ecologically unfriendly reagents [177]. The reaction of thiophosgene with amines, for example, is the most common method for producing isothiocyanates [178]. Due to thiophosgene's toxicity, it has been replaced by several alternatives "thiocarbonyl transfer" reagents, including thiocarbonylditriazole [179], thiocarbonyldiimidazole [180], *bis*-(trichloromethyl) carbonate, trichloromethyl chloroformates[181], and di-2-pyridyl thionocarbonate [182]. While these chemicals are much less toxic, they are however,

not commonly available, and the formation of thiourea as a byproduct limits the scope of these techniques. Several other functional groups can be transformed to ITCs, including isocyanides, which are often employed in multicomponent reactions (MCRs) and are particularly intriguing because they are less hazardous [113, 183]. The sulfurization of isocyanides was considered as an attractive alternative employing Lawesson's Reagent (LR) also known as 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide [184]. Lawesson's reagent, a well-known classic example of a molecule with distinctive structural characteristics and unique chemical behaviour, has a wide range of applications in synthetic organic chemistry [185]. Its main applications involved the thionation of various carbonyl groups early on, with great success. Lawesson's reagent, though, now plays a significantly different role in the synthesis, and its application can aid the chemistry community in comprehending novel concepts [186].

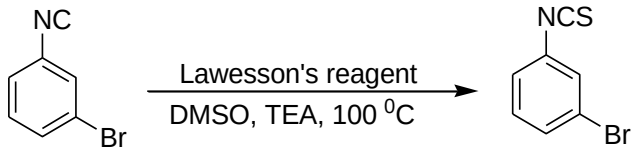
Although the sulfurization of isocyanates with Lawesson's reagent has been described in the literature for a few compounds [187], this reaction was reported to proceed under microwave irradiation and solvent-free conditions. Lawesson's Reagent has been effectively used to convert oxygen functionalities including amides [188], lactones [64], and esters, ketones, flavones, or isoflavones [65] into their thio analogues under microwave irradiation conditions.

Previously, Valletti and co-workers reported the conversion of oxygen to sulfur in the case of isocyanates using Lawesson's reagent (LR) under microwave irradiation. The reaction involves the conversion of oxygen from an isocyanate into an isothiocyanate (C=O to C=S [184]. Considering the effectiveness of Lawesson's Reagent (LR) for the sulfurization of isocyanates and that it is affordable on large scale, we speculated that it could also be effective and practical in the direct thionation of isonitriles to form isothiocyanates (R-NC to R-NCS). To the best of our knowledge, no reports of amine catalysed thionation of isonitriles with Lawesson's reagent have been published and for the first time, we present our findings here.

In this work, a variety of synthesis methods were investigated to develop a more efficient and broadly applicable method of converting isocyanides into isothiocyanates using Lawesson's reagent. The method is generic, broad in scope, and enables the synthesis of a wide range of functionalized aromatic ITCs.

Results and Discussion.

Our study is directed towards the sustainable conversion of isonitriles to isothiocyanates using Lawesson's reagent as thionation reagent under conventional heating and microwave irradiation conditions. To study and optimize the process, we selected a suitable model compound 3-bromophenyl isocyanide and reacted it with Lawesson's reagent in a stoichiometric amount in DMSO, under conventional heating, while monitoring the formation of the respective ITC **(Scheme 4.1)**.



Scheme 4.1: Optimization studies of the model 3-bromophenyl isocyanide

As soon as the base was added, the reaction mixture turned dark brown, indicating the formation of polysulfur chains. The consumption of suspended Lawesson's reagent (which is only partially soluble in DMSO) was also clearly observed as the reaction progressed. According to several reports, organic bases (especially tertiary amines) were more efficient during the sulfurization of isocyanides to isothiocyanates. Therefore, we started by evaluating the reactivity of several amines in the reaction of a model isocyanide including 1,8-diazabicyclo[5.4.0]undec-7-en (DBU), triethylamine (TEA), 1,4-diazabicyclo[2.2.2]octane (DABCO) and diisopropyl ethylamine. Among the common organic bases tested, a tertiary amines such as triethylamine proved to be more efficient resulting in 94% conversion **(Table 4.1**, **entry 2)**. DBU gave a quantitative yield of 81%. Triethylamine (TEA) was found to have the greatest conversion rate.

Table 4.1: Optimisation of reaction under different basic conditions

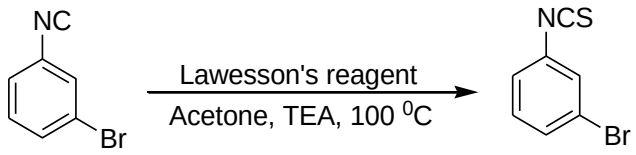
Entry	Solvent	Base	Time (L.R)	Yield (L.R)
1.	DMSO	(DBU)	2 hr	81%
2.	DMSO	Triethylamine	**1 hr**	**94%**
3.	DMSO	DABCO	2 hr	59%
4.	DMSO	(Diisopropyl ethylamine)	2 hr	67%

However, to generalise the protocol for the sulfurization of a large number of isocyanides with high structural diversity, the reaction was optimized by changing the temperature **(Table 4.1.1)**. The temperature was raised up to 100 ºC, which was found to be sufficient for carrying out the reaction with the highest possible yield of the required product **(Table 4.1.1**, **entry 5)**. When the reaction was conducted at room temperature only trace amounts of isothiocyanates after 3 h were obtained **(Table 4.1.1**, **entry 1)**. The results show that higher temperatures resulted in higher conversions. Therefore, we established optimized conditions for the sulfurization of isocyanides using Lawesson's reagent for the synthesis of isothiocyanates **(Table 4.1.1**, **entry 5)**.

Table 4.1.1: Effects of temperature on the model reaction.

Entry	Solvent	Temp	Time (L.R)	Yield (L.R)
1.	DMSO	r.t	3 hr	Traces
2.	DMSO	40	2 hr	48%
3.	DMSO	60	2 hr	78%
4.	DMSO	80	1 hr	87%
5.	DMSO	100	**1 hr**	**94%**

Various reaction solvents were screened such as DMSO, DCM, acetone, ethanol, water, and acetone/H_2O (1:1) **(Table 4.1.2)**. Among these, DMSO as a reaction solvent generated high yields probably due to its ability to dissolve and stabilize polysulfur chains **(Table 4.1.2**, **entry 1)**. However, in the context of sustainability, attention was given to greener alternatives for commonly used solvents according to greener solvent parameters. Polar solvents such as acetone, among others are listed as environmentally safe in the industrial SSGs and are at the top of the list of green chemicals. Acetone allowed full conversion to isothiocyanates after 1 hr in 86% yield and is a greener alternative if compared to DMSO (Table 3, entry 3). Furthermore, when the reaction was carried out in the presence of water (H_2O), the corresponding isothiocyanates were obtained in only 18% yield **(Table 4.1.2**, **entry 5).** However, When the reactions were conducted in the mixed solvents [H_2O/ acetone (1:1)], the products isothiocyanate was formed, albeit in a considerably lower yield of 55% **(Table 4.1.2**, **entry 6)**.



Scheme 4.1.1: Optimization studies of the model 3-bromophenyl isocyanide

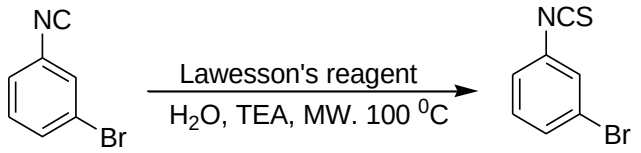
As a result, the established optimized conditions are as follows: 3-bromophenyl isocyanide (1.0 mmol), Lawesson's reagent (0.5 mmol), triethylamine (4 mmol), in (1 mL) of acetone reflux at 100 ºC for 1 hour.

Table 4.1.2: Optimization of the solvent parameter for the model reaction

Entry	Solvent	Time (L.R)	Yield (L.R)
1.	DMSO	1 hr	94%
2.	DCM	**2 hr**	**46%**
3.	Acetone	1 hr	86%
4.	Ethanol	1 hr	60%
5.	H_2O	2 hr	18%
6.	H_2O/ acetone (1:1)	2 hr	55%

At this point, we thought of carrying out these reactions under microwave irradiation. Following the already established optimization studies with conventional heating. Then the reaction mixture was subjected to irradiation in a pressure vial with MW (150 W power) at 60 °C for 10 min. Under these conditions the anticipated isothiocyanates were obtained in good yield. However, the process was further optimized with respect to temperature because it was necessary to improve the reaction yield (entry 1). The yield of the expected isothiocyanates increased from 85% to 98% when the temperature was raised to 100 °C **(Table 4.1.3**, **entry 1-3)**. Next, the amount of Et_3N was optimized. To guarantee optimal conditions for both steps of transformation, The amount of triethylamine was increased to 4 mmol, which was found to be sufficient for carrying out the reaction with the highest possible yield of the required product **(Table 4.1.3**, **entry 3)**. As Et_3N was gradually reduced from 4 to 2 mmol, the reaction's efficiency declined significantly **(Table 4.1.3**, **entries 7-9)**.

Furthermore, among the solvents tested, DMSO was the solvent of choice due to it's strong potential to absorb irradiation, however for the benefit of green chemistry, attention was given to green alternative solvents including acetone, and water. Surprisingly when the reaction was irradiated in the presence of water as solvent, isothiocyanates were obtained in 90% yield **(Table 4.1.3**, **entry 6)**. It is worth noting that the conditions that seem unsuitable for the conventional heating approach gave an excellent yield with microwave irradiation. According to literature, water has been proven to have a good ability to absorb microwaves, which allows for fast heating of reaction mixtures. Water also serves as a pseudo-organic solvent since the dielectric constant drastically decreases at higher temperatures. It appears that the combination of microwave irradiation and water as a solvent generated a significant synergistic effect.



Scheme 4.1.2: Optimized aqueous microwave irradiation conditions for the synthesis of isothiocyanates using Lawesson's reagent.

Thus, the optimal conditions were obtained by reacting 3-bromophenyl isocyanide (1.0 equiv.), and Lawesson's reagent (1 equiv.), were reacted under microwave irradiation using triethylamine (4 equiv.) as the base in 1ml of water at 100 ºC for 10 min.

Table 4.1.3: Effect of temperature, amount of the catalyst and solvent on the synthesis of model isothiocyanate.

Entry	Base (equiv)	Solvent	Temp/time ºC/min.	Yield
1.	Et_3N (5)	DMSO	60/10	85%
2.	Et_3N (4)	DMSO	80/10	94%
3.	Et_3N (4)	DMSO	100/10	98%
4.	Et_3N (4)	Acetone	100/10	93%
5.	Et_3N (5)	H_2O	100/10	87%
6.	**Et_3N (4)**	**H_2O**	**100/10**	**90%**
7.	Et_3N (3)	H_2O	100/10	81%
8.	Et_3N (2)	H_2O	100/10	66%
9.	Et3N (4)	H_2O/ Acetone	100/10	79%

Comparison between microwave and oil bath heating

Comparative studies were carried out to model sulfurization reaction of 3-bromophenylisocyanides with Lawesson's reagent to evaluate the efficiency of MW-assisted sulfurization over traditional heating. Thus, the reaction performed in aqueous media, with MW assistance afforded ITC in 90% **(Table 4.1.3 entry 6)**. On the contrary, a trace amounts of isothiocyanate was obtained in an aqueous medium with Lawesson's reagent under conventional heating **(Table 4.1.2**, **entry 5)**. Moreover, this may be due to the pseudo-organic behaviour of water at higher temperatures, as the dielectric constant is substantially reduced. In addition, product **(1B)** was obtained in 94% after 60 min at 100 ºC in DMSO under conventional heating. When the same reaction was performed under microwave irradiation, compound (**1A**) was obtained in an excellent yield (98%) within 10 minutes **(Table 4.1.3**, **entry 3)**. The results of experiments conducted under the above optimized conditions clearly show that the use of microwave

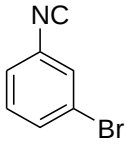
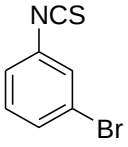
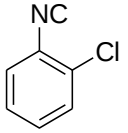
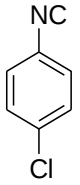
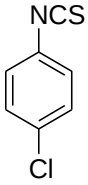
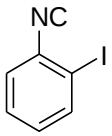
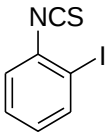
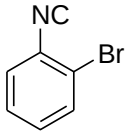
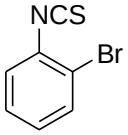
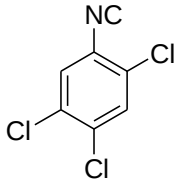
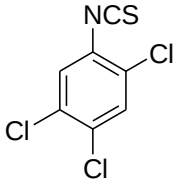
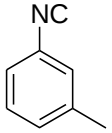
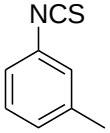
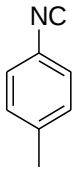
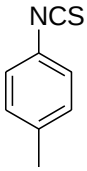
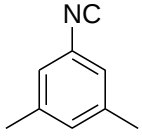
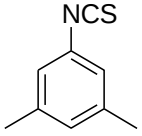
radiation facilitates higher yields of ITC and significantly decreases reaction times. In this way, reactions become cleaner and faster and are easy to manipulate. In all cases, it was generally observed that reactions conducted using microwave irradiation showed an improvement in yields in the range of 5–30% over the classical heating approach. Additionally, the Lawesson by-products are easy to separate because they are highly water soluble.

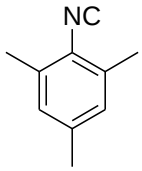
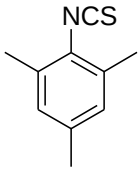
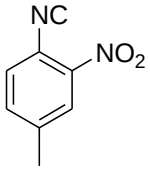
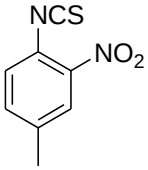
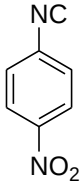
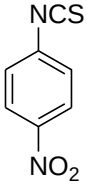
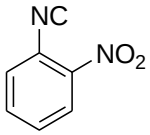
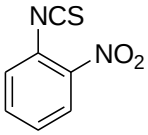
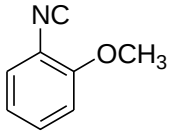
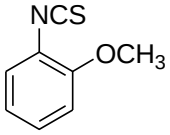
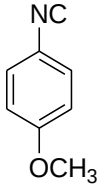
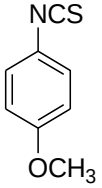
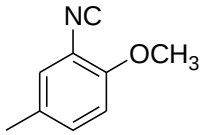
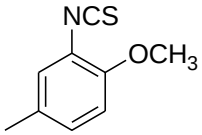
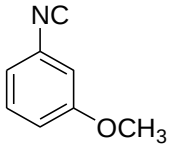
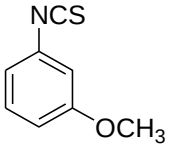
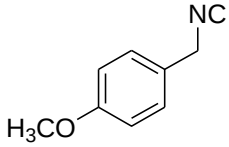
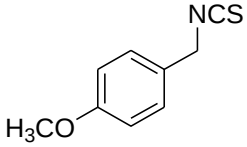
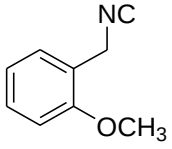
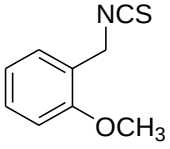
The Scope of Reaction.

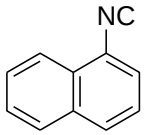
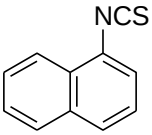
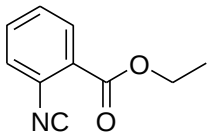
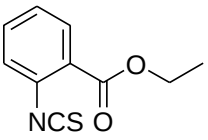
We investigated these processes using both thermal heating and microwave irradiation, as shown in **table 4.1.4**. When the experiment was conducted using conventional heating, it took about 1 hour for completion of the reaction. The optimization of the process was done by varying the temperature to obtain products with good yields and purity. At lower temperatures, lower chemical yields were observed. The use of microwave (MW) irradiation for carrying out reactions in the lab can be advantageous for the synthesis of a wide variety of compounds. When the method is properly applied, the most obvious benefits are quicker and cleaner reactions since there are fewer side reactions. As a result, it may be argued that MW-assisted synthesis is more economical. The best results were observed at 100 ^{o}C and 150 W. **Table 4.1.4** demonstrates how the yields of the products obtained by MW irradiation compared to thermal heating are higher with a striking decrease in reaction time because homogeneous heating (caused by vigorous agitation of reactant molecules) throughout the reaction media is achieved by MW irradiation as opposed to convectional thermal heating. Evidently, the reaction rate and yields were boosted by the MW irradiation.

Isothiocyanates with an aromatic ring **(1–21)** were obtained with up to 98% yield. A library of aromatic isothiocyanates **(1–21)** substituted at *ortho*, *meta*, or *para*-positions was obtained under the optimized conditions. In good to excellent yields **(45-98%)**, a wide range of N-aryl- isocyanides were transformed swiftly into the anticipated isothiocyanates under conventional heating and microwave irradiation. Substituted N-aryl substrates with an electron-withdrawing or electron-donating group **(1-21)** on the benzene ring performed satisfactorily. Under these conditions, ether **(18-20)**, halo **(1-8)**, nitro **(9-12)**, and ester **(22)**, the functional groups **(17)** were only slightly affected. Various mono, di, and trisubstituted isocyanides **(1-21)** also yielded good results, indicating that steric effects did not significantly hinder the reaction progress. Isolation of the corresponding pure ITCs was easy since the by-products are water-soluble. The purification involves a simple elution of crude product with hexane/DCM through a short pad of silica gel followed by solvent evaporation. As a result, we were able to obtain isothiocyanates in high yields and purity within a short period of time. In all cases, reaction times were reduced, and yields improved.

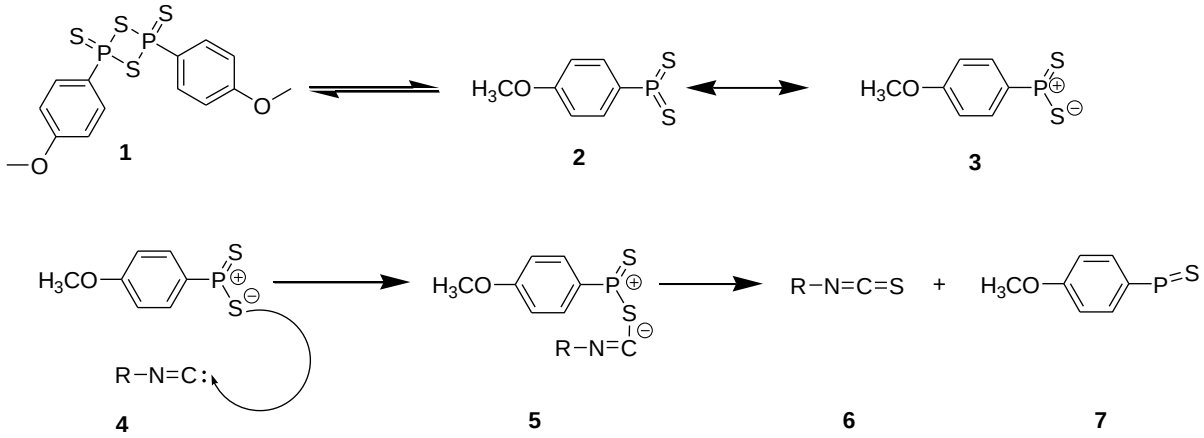
Table 4.1.4: Synthesized isothiocyanates utilizing Lawesson's reagent (L.R) under microwave irradiation (A) and conventional heating approach (B).

Entry	Isocyanides	Methods	Time (min)	Product	Yield %
1.		A B	10 60		94 86
2.		A B	10 60		89 72
3.		A B	10 60		76 61
4.		A B	10 60		91 78
5.		A B	10 60		85 83
6.		A B	10 60		77 60
7.		A B	10 60		95 92
8.		A B	10 60		90 75
9.		A B	10 60		85 64

10.		A B	10 60		92 70
11.		A B	10 60		83 58
12.		A B	10 60		80 77
13.		A B	10 60		96 89
14.		A B	10 60		70 81
15.		A B	10 60		83 62
16.		A B	10 60		82 75
17.		A B	10 60		87 66
18.		A B	10 60		69 53
19.		A B	10 60		61 53

20.		A B	10 60		95 78
21.		A B	10 60		94 80

Even though we have yet to prove the mechanism of isocyanide thionation using Lawesson's reagent in an experimental manner, Figure 4 show a possible explanation. It is known that Lawesson's reagent and the more reactive dithiophosphine ylide are usually in equilibrium in solution **(2, 3).** These reactive species **(2, 3)** interact readily with the electrophilic carbon to produce the intermediate **(5)** which further furnishes the corresponding isothiocyanates **(6)** after the elimination of (4-methoxyphenyl)sulfanylenephosphine **(7) (Scheme 4.1.3).**



Scheme 4.1.3: Proposed mechanism for the synthesis of isothiocyanates using Lawesson's reagent.

Conclusions

In summary, we have successfully developed a general, green, practical, and highly efficient protocol for the synthesis of a broad range of functionalized isothiocyanates from their corresponding isocyanides using Lawesson's reagent and a catalytic amounts of amine bases, particularly triethylamine under aqua assisted microwave irradiation and conventional heating conditions. The synthetic procedures presented in this study enabled the rapid and simple acquisition of a library of 21 structurally diverse isothiocyanates with good or very good yields **(53–96%),** in high purity. The simplicity of operation, the easy work-up procedure, high reaction rates, very mild conditions, excellent yields and environmentally benign conditions are the most important advantages of the present method. The newly developed method could convert a wide range of aryl-isocyanides into their corresponding isothiocyanates in excellent yields and it holds promise for future scale-up.

Part B

4.2. Aqua/mechanochemical mediated synthesis of novel spiro [indole-pyrrolidine] derivatives

Indoles are frequently found in nature and serve as the basic building block for several bioactive compounds. Numerous alkaloids and compounds derived from marine molluscs and shellfish, such as rhynchophylline, elegantine, formosanine, surogatoxin, neosurogatoxin, etc., **(Figure 4.2.1)** have recently been discovered to be heterocyclic compounds with a spiro system at the position 3 of the 2-indolinone skeleton. Many of these heterocycles are used as vital intermediates on the way to bioactive compounds [188, 189, 190].

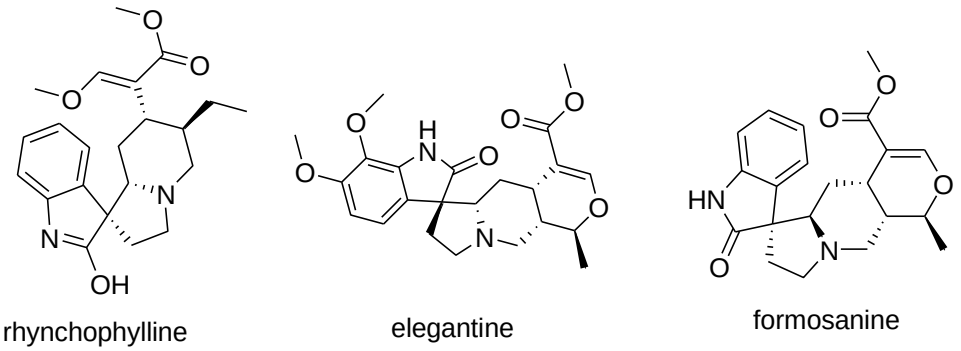


Figure 4.2.1. Examples of naturally occurring spirooxindoles.

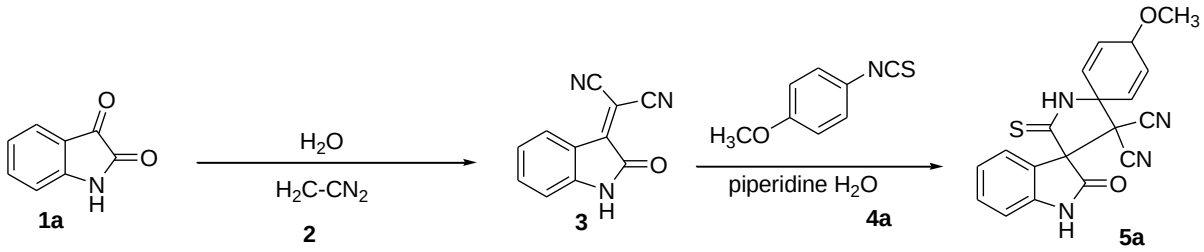
Due to their numerous biological functions, derivatives of isothiocyanates are also quite interesting. The 3-spiroindolines incorporating pyrrolidine moiety appear to be potentially biologically active compounds considering the useful range of biological activities associated with naturally occurring spiroindole pyrrolidine [191].

Aqua and mechanochemistry are commonly used for organic synthesis as they are faster, more efficient, and simpler to employ than traditional techniques. In this regard, the synthesis of spiroindole pyrrolidine derivatives has been developed under mechanochemical and aqua conditions, and they are based on the use of water (aqueous reaction) and high-speed vibration milling with a double agate ball (6 mm diameter) in an agate jar and piperidine as a liquid-assisted grinding agent.

Results and Discussion.

In continuation of our earlier interest in the synthesis of biodynamic heterocycles under aqua and mechanochemical conditions. We have investigated the reaction of indole-2,3-dione **(1a)** with malononitrile **(2)** to give 3-dicyanomethylene-2H-indol-2- ones **(3a)** that was cyclocondensed *in situ* with 4-methoxyphenyl isothiocyanates **(4a)** under aqua and mechanochemical conditions leading to the facile one pot synthesis of 2"-oxo-5'-sulfanylidene-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3"-indole]-2,5-diene-3',3'-dicarbonitrile **(5a)**.

The formation of **(5a)** was assumed to proceed via the Michael condensation, i.e., involving the attack of the carbanion nucleophile on the olefinic carbon of ylidene, followed by the cycloaddition of isothiocyanates on the cyano group to form the spiro compound.



Scheme 4.2: Synthesis of spiroindole-pyrrolidine derivative in aqueous media

The initial investigation began with the reaction between isatin **(1a),** malononitrile **(2**), and 4-methoxy isothiocyanate **(4a)** in methanol at room temperature for 6 hours in the presence of piperidine as the catalyst. Interestingly, a new product (**5a)** was observed and isolated in 70% yield **(Table 4.2 entry 1)**. We investigated the impact of various solvents on the reaction course to determine the most suitable reaction conditions and to compare results of the aqua conditions with those obtained under standard conditions (organic solvents). **(Table 4.2)**. The reaction proceeded smoothly in dichloromethane (CH_2Cl_2) and ethanol with high yields of 62% and 75% respectively **(Table 4.2 entries 3-4)**. Solvents such as toluene, and diethyl ether were ineffective even after 6 hours of producing trace amounts of the products (**Table 4.2 entries 2, 5.)**. When the reaction was carried out in water in the presence of two drops of piperidine, the product (**5a)** was obtained in high yield **(85%)** within 15 min **(Table 4.2 entry 6)**. Also, when the reaction was carried out in the absence of the catalyst (piperidine) the reaction fails to furnish the final spiro adduct, instead the intermediate **(3a)** was obtained. This implies that the cycloaddition of isothiocyanates **(4a)** with 3-dicyanomethylene-2H-indol-2- ones **(3a)** requires a base for activation.

Table 4.2: Effect of solvents on the scope of the reaction.

Entry	Solvent	Time	Yield %
1	Methanol	6 hr	70
2	Toluene	6 hr	28
3	Ethanol	6 hr	75
4	Dichloromethane	6 hr	62
5	Diethyl ether	6 hr	40
6	Water	15 min	85

Having established that the best optimal conditions for the one-pot synthesis of spiro pyrrolidine are the presence of piperidine as catalyst and water as reaction solvent carried out at room temperature.

We now investigate the scope of this one-pot mechanochemical process. The NMR data of the synthesized spiro compound **(a-h)** clearly show the existence of a mixture of diastereomers. The results indicate that all ^{1}H NMR and ^{13}C NMR peaks of compound **(5a-h)** are duplicated, revealing that the products **(5a-k)** exist as a mixture of diastereomers.

The reaction carried out for isatin/5-bromo isatin **(1a, 1b)** and isothiocyanates derivatives **(4a-k),** bearing electron-donating **(4)** as well as electron-withdrawing groups **(4b**, **4c**, **4g**, **4i**, **4j**, **4k)** furnished the corresponding 2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile derivatives and 5''-bromo-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile derivatives were obtained in excellent yields.

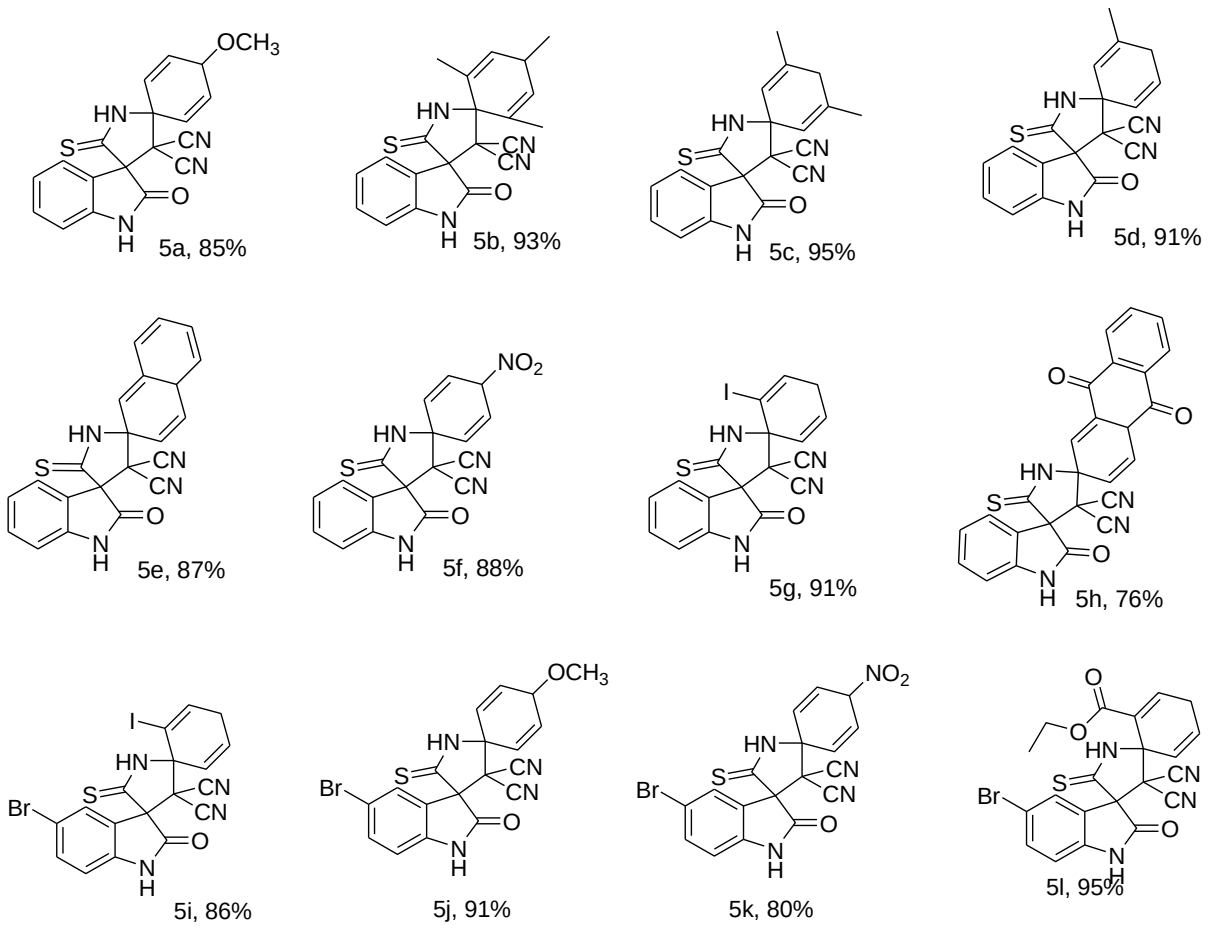
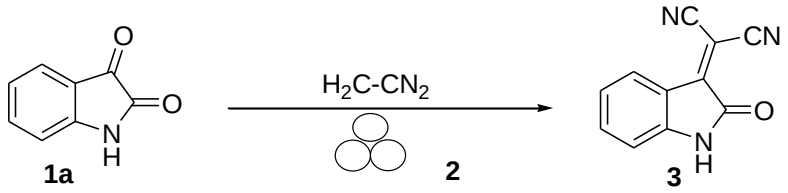


Figure 4.2.2: Variation of isothiocyanate moieties in the synthesis of spiroindoline pyrrolidine under aqua condition.

Mechanochemical Synthesis.

In this study, we developed our system utilizing the flexible methodology laid out by Dandia *et al.* [189] However, we found that high-energy ball milling was necessary to obtain satisfactory yields. In the initial experiment, a moderate yield (64%) was obtained by simply milling the two solids (isatin (1a), and malononitrile (2a) under neat conditions without the use of an auxiliary grinding material **(Table 4.2.1**, **entry 1)**.

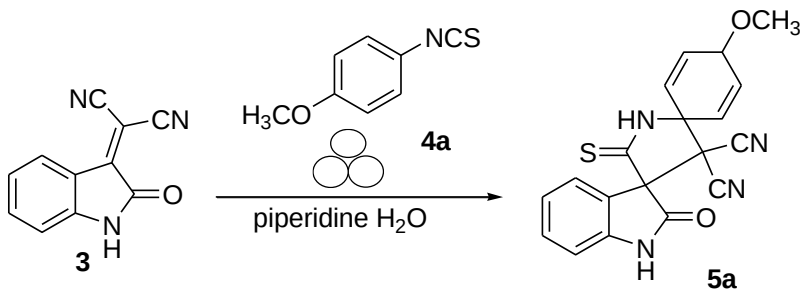


Scheme 4.2.1: Synthesis of 3-dicyanomethylene-2H-indol-2-ones **(3a)** under mechanochemical activation without any additive.

Pleasingly, treatment of isatin **(1a)** with one equivalent of malononitrile **(2)** in the presence of 2-3 drops of MeOH as an additive afforded the desired 3-dicyanomethylene-2H-indol-2- ones **(3a)** in 69% yield after milling for 10 minutes **(Table 4.2.1**, **entry 2)**. The yield increased further to 74% when DCM was employed as LAG **(Table 4.2.1**, **entry 3)**. To further boost the yield, the reaction was conducted in the presence of water as LAG agent, the yield of **(3a)** rose rapidly to 90% **(Table 4.2.1**, **entry 4)** extending the milling times to 15 minutes further increased the yield to 98% **(Table 4.2.1**, **entry 5)**. A grinding auxiliary could serve a variety of purposes, such as enhancing mixing and facilitating energy transfer. Early studies into the cyclocondensation of the isothiocyanates focused on determining the ideal reaction time for the isolated step rather than two-step, i.e., the 3-dicyanomethylene-2H-indol-2- ones **(3a)** was isolated from step one and purified before being subjected to this second reaction optimisation. Having achieved optimal conditions for the first step of the reaction, our attention turned to the second step.

Table 4.2.1. Optimization of the model reaction conditions for (Step A).

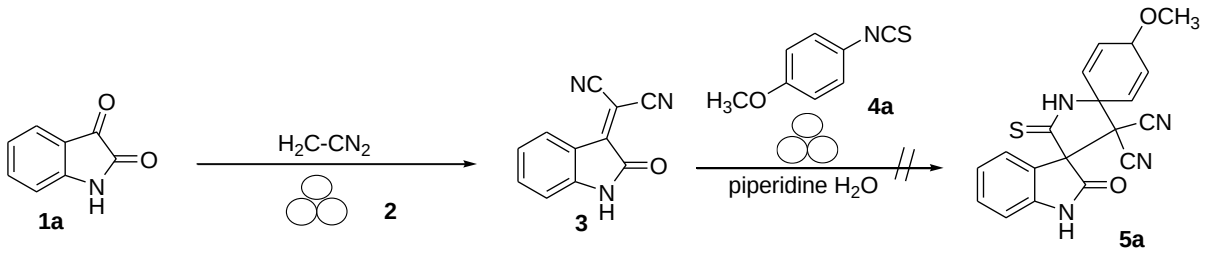
Entry	Reaction Condition	Additive	Time min	Yield %
1	(1a, 2)	No additive	10	64
2.	(1a, 2)	Methanol	10	69
3.	(1a, 2)	DCM	10	74
4.	(1a, 2)	Water	10	90
5.	(1a, 2)	Water	20	98



Scheme 4.2.2: Synthesis of spiroindole-pyrrolidine derivative **(5a)** under mechanochemical activation.

For the second step of the reaction, we started with cyclocondensation of isothiocyanates **(4a)** with intermediate **(3a)** which furnishes the corresponding spiroindole-pyrrolidine in 83% yield after milling for 10 minutes in the presence of piperidine as additive. An increase in the milling time had a positive effect on the reaction yield, since the yield increases further to 97% at the milling time of 20 min. When the reaction was carried out in the absence of a catalyst (piperidine), the reaction did not afford the anticipated product even after 1h milling time.

The scope of the one-pot mechanochemical process was investigated following the established optimized reaction conditions **(Scheme 4.2.2)**. After 15 minutes of milling, the combined two-steps procedure was unable to furnish product **5a** as anticipated. The reaction's conditions remain unaffected by extending the milling time to an hour. As the reaction progressed, intermediate 3-dicyanomethylene-2H-indol-2-ones **(3a)** was obtained rather than the desired final spiro adducts **(5a)**. This is due to the electron donating resonance effect of indole of nitrogen which decreases the electrophilicity of isothiocyanates carbon preventing the final cyclocondensation reaction to furnish compound **5a**.



Scheme 4.2.3: Unsuccessful one-step synthesis of spiroindole-pyrrolidine derivative (**5a**) under mechanochemical activation.

The synthesis of 3-dicyanomethylene-2H-indol-2-ones **(3a)** according to the first step is experimentally simple, leading to the formation of the analytically pure compounds in 98% yield. The structures were confirmed by ^{1}H and ^{13}C NMR, IR spectroscopy, and mass spectrometry. We demonstrated that the cyclocondensation of isothiocyanates **(4a-h)** with 3-dicyanomethylene-2H-indol-2-ones **(3a)** in the presence of piperidine as catalyst afforded spiro compounds in excellent yield after 15 minutes milling at room temperature.

The Knoevenagel condensation of 5-bromo, isatin **(1b)** and malononitrile **(2**) afforded the corresponding 5-bromo, 3-dicyanomethylene-2H-indol-2-ones **(3b).** Subsequent cyclo-condensation with isothiocyanates **(4i-l)** furnished the anticipated spiro-pyrrolidine derivatives **(5i-l)** in excellent yield after 30 minutes of milling.

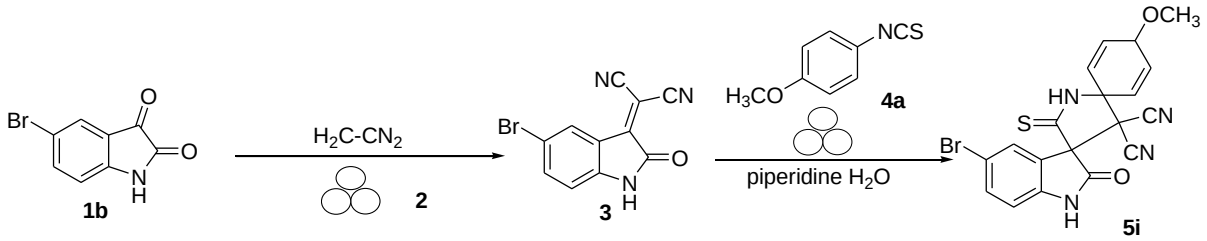


Figure 4.2.3. Synthesis of spiroindole-pyrrolidine derivative (**5i**) using 5-bromo isatin **(1b)** under mechanochemical activation.

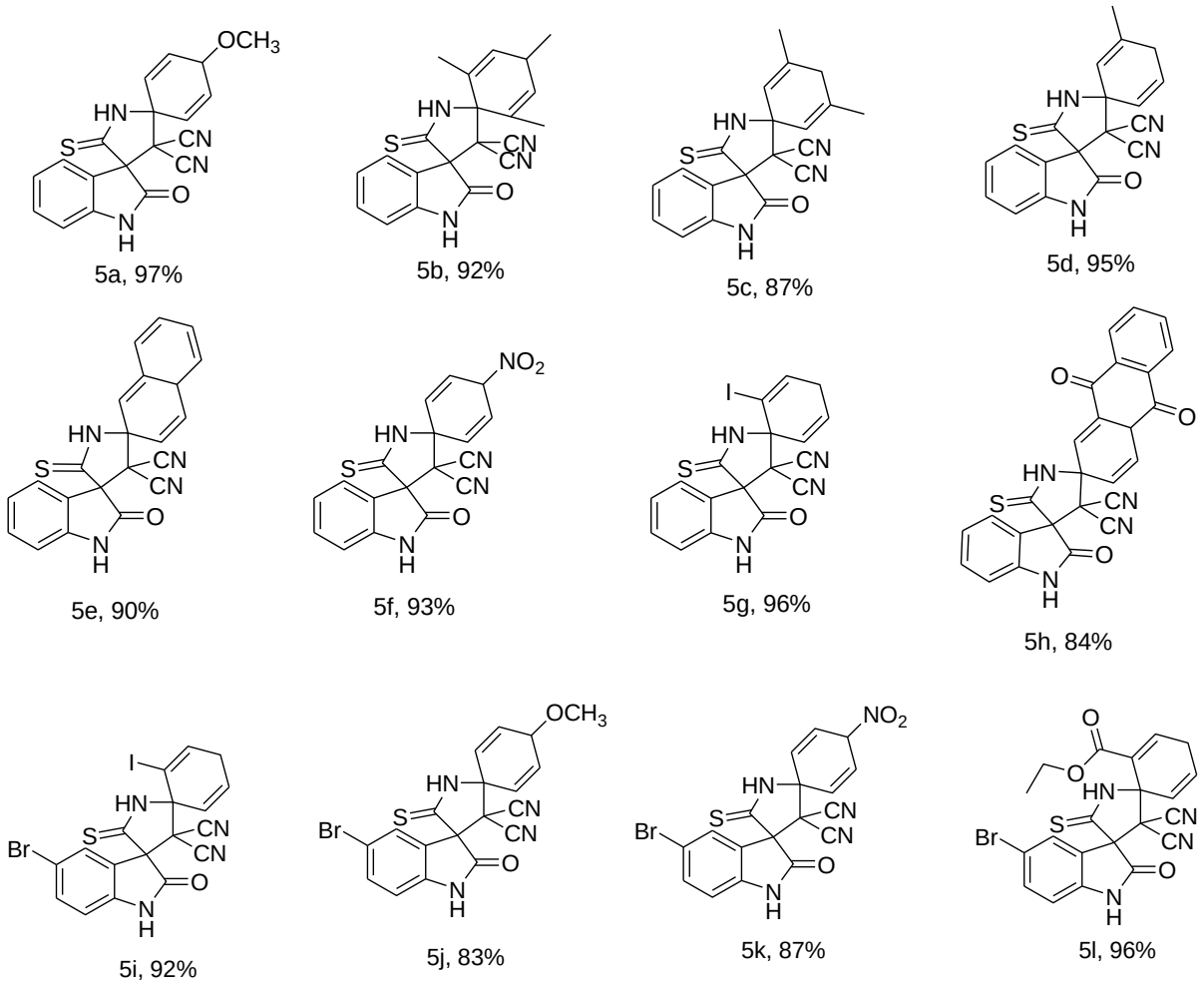


Figure 4.2.4: Variation of isothiocyanate moieties in the synthesis of spiroindole pyrrolidine under aqua condition.

With the optimized reaction conditions in hand, we then examined the scope and limitations of the reaction. First, we examined the variation of the intermediate moiety. The parent 3-dicyanomethylene-2H-indol-2-ones **(2)** underwent a smooth reaction with different functionalized isothiocyanates, and the corresponding spiroindole-pyrrolidine derivatives are formed with excellent yield, **(3a-h**). Moreover, the substitution at the 5-position for 5-bromo 3-dicyanomethylene-2H-indol-2-ones **(3b**) did not affect the reaction outcome, and the desired product was formed in good to excellent yield and selectivity **(5i−l).** Next, we focused on the scope of the isothiocyanate component. The isothiocyanate with electron-donating and electron-withdrawing groups of *N*-aryl ring **(4a-h)** is well tolerated, and the desired product was formed in good yield with moderate diastereoselectivity **(5a-h).** Additionally, cyclocondensation of 5-bromo, 3-dicyanomethylene-2H-indol-2-ones with 2-iodophenylisothiocyanate afforded the corresponding product in moderate yield with a mixture of diastereomers **(5i).** Additionally, the 2",9,10-trioxo-5'-sulfanylidene-1",2",9,10- tetrahydro-4aH-dispiro[anthracene-2,2'-pyrrolidine-4',3"-indole]-3',3'-dicarbonitrile synthesized from 2-isothiocyanatoanthracene-9,10-dione **(4h)** and 3-dicyanomethylene-2H-indol-2-ones **(3a)** underwent a smooth reaction leading to the formation of the desired products in high yield **(5h).**

Conclusions

In this section we showed the facile synthesis of some new derivatives of spiro pyrrolidine compounds via a Michael condensation of 3-dicyanomethylene-2H-indol-2-ones **(3a)** or 5-bromo, 3-dicyanomethylene-2H-indol-2-ones **(3b)** with isothiocyanates derivatives under aqua and mechanochemical conditions. The described procedure is an appealing methodology for the Michael and Knoevenagel reaction due to the short reaction time, operational simplicity, high yield, and environmentally benign conditions. These spiro systems contain a range of functional groups, making them crucial building blocks for the diversity-oriented synthesis of spiro heterocyclic libraries with the potential to be employed as bioactive compounds.

Chapter 5

5. Materials and methods

Mechanochemical experiments were carried out in an in-house ball mill constructed from a Makita Jigsaw to which was attached a ball milling capsule. This consisted of one of two possible types of reactors. The method A (Met-A) (had a diameter: 2.0 cm; height: 2.0 cm; the volume of reactor: 13.2 mL) or the Met-B (diameter: 1.2 cm; height: 2.0 cm; the volume of reactor: 3.4 mL) stainless steel jars equipped with stainless steel balls (diameter: 6 mm; mass: 0.90 g; diameter: 4 mm; mass: 0.51 g;). Powder X-ray diffraction measurements were performed using a D8 Advance diffractometer made by a Bruker AXS company in Germany. Microwave irradiation reactions were performed in a microwave oven, Anton Paar (Monowave 450) Power (W) 850. A PerkinElmer Spectrum 100 FT-IR Spectrometer was used for the FT-IR analysis. The IR spectra were obtained by the attenuated total reflection (ATR) method. For each experiment, 16 scans were performed in the frequency range from 650 to 4000 cm^{-1}. Melting points of all the compounds were determined using a Koffler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker Advance III 400 spectrometer using CDCl3 or DMSO-d6 as a solvent with tetramethyl silane used as the internal standard. LC-MS/MS data were recorded on a Bruker Compact quadrupole time of flight (QToF) mass spectrometer. Raw mass spectrometry data were processed using MZmine software (version 2.38). The solvents and chemicals used were of analytical grade and were purchased from Sigma Aldrich and used without further purification. The purity determination of the starting materials and reaction monitoring was performed by thin-layer chromatography (TLC) on Merck silica gel G F254plates.

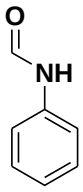
5.1. Experimental Part: Chapter 2

5.1.1 Preparation of sulphuric acid adsorbed on silica gel (H_2SO_4–SiO_2)

The preparation of H_2SO_4–SiO_2 was carried out by following the reported procedure [25]. To a suspension of silica gel (29.5 g, 230– 400 mesh size) in EtOAc (60 mL) was added H_2SO_4 (1.5 g, 15.5 mmol, 0.8 mL of a 98% aq. solution of H_2SO_4) and the mixture was stirred magnetically for 30 min at room temperature. The EtOAc was removed under reduced pressure (rotary evaporator) and the residue was heated at 100 ºC for 72 h under vacuum to afford H_2SO_4–SiO_2 as a free-flowing powder.

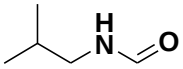
5.1.2. A General Procedure for *N*-formylation of Amines with Triethyl orthoformate Promoted by immobilized H_2SO_4 on Silica gel.

5.1.2.1. *N*-phenyl formamide



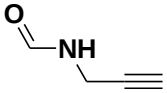
To a mixture of aniline (0.548 mL 6 mmol) and triethyl orthoformate (24 mmol). The immobilized H_2SO_4 on silica gel (1.2 g) was then added and the reaction mixture was stirred under reflux conditions (65 °C). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with EtOAc (20 mL), filtered, water (30 mL) added, the solution extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography and eluted with (EtOAc-Pet Ether (3:1)) to afford *N*-phenylformamide **(1)**. (0.52g 95 %). Dark brown liquid. IR (NaCl) $\nu(cm^{-1})$ 3349, 3213, 3150, 2896, 1700, 1686, 1530, 1436, 1350, 1261. Mixture of rotamers were observed. ^1H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.45 (brs, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 8.5, 0.9 Hz, 2H), 7.12 – 6.95 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 137.1, 129.2, 124.8, 118.9. ^1H NMR (400 MHz, $CDCl_3$) Minor rotamer: δ 9.15 (d, J = 10.0 Hz, 1H), 8.59 (d, J = 10.4 Hz, 1H), 7.46 (dd, J = 8.5, 0.9 Hz, 2H), 7.27 – 7.15 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 137.5, 129.7, 125.3, 120.4

5.1.2.2. *N*-isobutylformamide



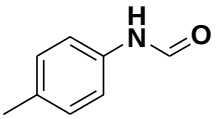
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using isobutylamine (0.596 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford as a yellow oil *N*-isobutylformamide **(2)**. (0.48g 80.5 %). IR (NaCl) $\nu(cm^{-1})$ 3312, 2951, 1936, 1653, 1534, 1463, 1368. The mixture of rotamers was observed. ^1H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 7.57 (brs, 1H), 7.42 (1H), 3.65 – 2.65 (m, 2H), 1.70 – 1.18 (m, 1H), 0.96 – 0.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 47.3, 28.0, 20.6. ^1H NMR (400 MHz, $CDCl_3$) Minor rotamer: δ 7.18 (1H), 6.86 (brs, 1H), 2.62 – 1.70 (m, 4H), 1.18 – 0.96 (m, 4H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 46.1, 30.4, 19.2.

5.1.2.3. *N*-(prop-2-ynyl)formamide.



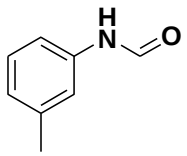
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using proparglamine (0.36 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow oil *N*-(prop-2-ynyl)formamide **(3)** (0.28g 78%). IR (NaCl) ν(cm^{-1}) 3390, 3047, 2923, 2356, 1645, 1524, 1379, 1235, 1031. The mixture of rotamers was observed. Major rotamer: 1H NMR (400 MHz, CDCl3) δ 8.32 (s, 1H), 8.02 (brs, 1H). 3.91 (s, 2H), 2.22 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 79.2, 71.0, 27.5. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 12.6 Hz, 1H), 5.12 (d, J = 12.8 Hz, 1H), 3.65 (s, 1H), 2.35 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 79.5, 70.1, 31.8.

5.1.2.4. *N-p*-tolylformamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using p-toluidine (0.644 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N-p*-tolylformamide **(4)** (0.61g 95%); m.p. 50–54 ºC, IR (NaCl) ν(cm^{-1}) 3360, 2913, 2854, 1686, 1515, 1368, 1211. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 9.19 (d, J = 10.7 Hz, 1H), 8.65 (d, J = 11.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 134.9, 130.5, 120.8, 20.9. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (brs, 1H), 8.30 (s 1H), 7.13 (dd, J = 14.5, 8.3 Hz, 4H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 133.0, 129.3, 119.1, 20.9.

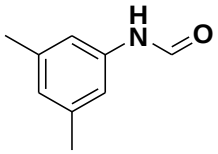
5.1.2.5. *N-m*-tolylformamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using m-toluidine (0.63 mL 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a brown liquid *N-m*-tolylformamide **(5)** (0.57g 90%). IR

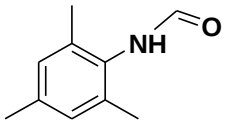
(NaCl) v(cm-1) 3366, 2920, 2860, 1670, 1519, 1368, 1211. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 9.14 (d, *J* = 8.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.10 (dd, *J* = 10.6, 8.0 Hz, 2H), 6.82 (t, *J* = 6.3 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163, 139, 136, 129, 125, 119, 115, 20.8. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (brs, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.31 (s, 1H), 7.14 – 7.05 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 138.5, 128.1, 125.3, 120.6, 117.1, 20.4.

5.1.2.6. *N*-(3,5-Dimethylphenyl)formamide.



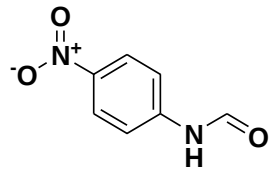
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3,5-dimethyl aniline (0.748 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow solid *N*-(3,5-dimethyl) phenylformamide **(6)** (0.73g 97%) m.p 168-170 ºC. IR (NaCl) *v*(cm^{-1}) 3321 3013 2918 1669 1601 1396 1282. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.57 (brs, 1H), 7.35 (s, 1H), 6.78 (d, *J* = 7.1 Hz, 2H), 2.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 149.4, 139.1, 117.3, 113.2, 21.6. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (brs, 1H), 8.78 (d, *J* = 10.6 Hz, 1H), 8.29 (s, 1H), 6.88 (d, *J* = 14.4 Hz, 2H), 2.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 145.2, 139.7, 137.1, 126.0, 120.4, 118.2, 14.4.

5.1.2.7. *N*-mesitylformamide.



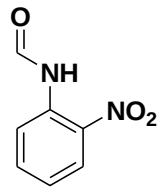
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2,4,6-trimethylaniline (0.8 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-mesitylformamide **(7)** (0.66g 82.5%) m.p 179-180 °C. IR (NaCl) *v*(cm^{-1}) 3389, 2970, 2915, 2868, 1653, 1532, 1489, 1391, 1254, 1012. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.31 (brs, 1H), 6.91 (d, *J* = 2.1 Hz, 2H), 6.09 (s, 1H), 2.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 139.5, 137.1, 134.1, 18.6, 17.2. ^{1}H NMR (400 MHz, $CDCl_3$) Minor rotamer: δ 8.03 (d, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 9.9 Hz, 1H), 7.27 (brs, 1H), 6.78 (s, 1H), 2.21 (s, 3H), 2.17 (d, *J* = 5.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 131.2, 129.1, 122.3, 21.2, 20.4.

5.1.2.8. *N*-(4-nitrophenyl) formamide



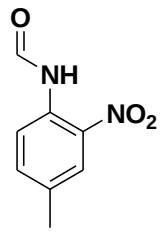
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-nitroaniline (0.83 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford yellow solid *N*-(4-nitrophenyl)formamide **(8)** (0.81g 97%) m.p 196-198 ºC. IR (NaCl) $\nu(cm^{-1})$ 3481, 3343, 3116, 2946, 1732, 1624, 1581, 1444, 1275. ^1H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 10.3 Hz, 2H), 6.71 (brs, 1H), 6.58 (d, J = 10.3 Hz, 1H), 3.38 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 155.4, 144.2, 135.9, 126.2, 112.8.

5.1.2.9. *N*-(2-nitrophenyl) formamide



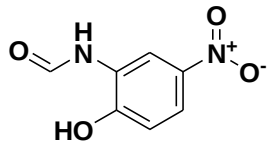
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-nitro aniline (0.83g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow solid *N*-(2-nitrophenyl) formamide **(9)** (0.74g 90%) m.p 175-177 ºC. IR (NaCl) $\nu(cm^{-1})$ 3470, 3341, 3275, 2946, 2360, 2126, 1715, 1684, 1489, 1246. The mixture of rotamers was observed. ^1H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.57 (brs, 1H), 8.05 (dd, J = 8.6, 1.5 Hz, 1H), 7.36 – 7.28 (m, 2H), 6.80 (dd, J = 8.4, 1.2 Hz, 1H), 5.93 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.0, 135.1, 133.5, 126.2, 124.1, 1183. Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ 10.29 (brs, 1H), 8.75 (d, J = 8.1 Hz, 1H), 8.19 (dd, J = 8.5, 1.5 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.20 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 144.3, 136.9, 131.7, 125.2, 122.5, 116.3.

5.1.2.10. *N*-(4-methyl-2-nitrophenyl)formamide.



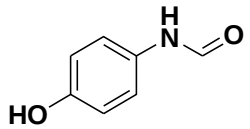
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-methyl-2-nitroaniline (0.9g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a reddish brown solid *N*-(4-methyl-2-nitrophenyl)formamide **(10)** (0.86g 96%) m.p 124-126 ºC. IR (NaCl) *v*(cm^{-1}) 3470, 3349, 3251, 2923, 1704, 1672, 1563, 1407, 1332, 1231, 1149. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 10.17 (brs, 1H), 8.62 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.44 (d, *J* = 10.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 142.3, 136.1, 130.5, 124.4, 122.1, 20.6. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (brs, 1H), 8.84 (s, 1H), 8.53 (s, 1H), 7.85 (s, 1H), 7.15 (d, *J* = 10.5 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161, 153, 135, 131, 126, 118, 19.

5.1.2.11. *N*-(2-hydroxy-5-nitrophenyl) formamide



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-hydroxy-5-nitroaniline (0.925g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow solid *N*-(2-hydroxy-5-nitrophenyl) formamide **(11)** (0.83g 90%) m.p 116-118 ºC. IR (NaCl) *v*(cm^{-1}) 3118 2915 1632 1510.6 1349 1120.7. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.35 (brs, 1H), 8.27 (s, 1H), 7.72 (d, *J* = 10.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 153.4, 145.2, 140.1, 122.9, 117.1, 111.3.

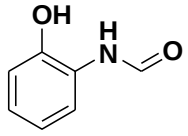
5.1.2.12. *N*-(4-hydroxyphenyl)formamide



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-aminophenol. (0.654 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/Pet-Ether (3:1)) was then evaporated under reduced pressure to afford a brown solid *N*-(4-hydroxyphenyl)formamide **(12)** (0.49g 75%) m.p 136-138 ºC. IR (NaCl) *v*(cm^{-1}) 3308 3118 2970 2808 1720 1653 1505 1401 1244. The mixture of rotamers was observed.^{1}H NMR (400 MHz, DMSO). Major rotamer: δ 9.25 (brs, 1H), 8.34 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 3.36 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 163.1, 153.4, 148.1, 130.5, 121.2, 115.1. ^{1}H NMR (400 MHz, DMSO).

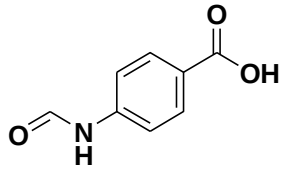
Minor rotamer: δ 9.90 (brs, 1H), 8.51 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 163.4, 153.1, 141.9, 130.2, 120.2, 115.0.

5.1.2.13. *N*-(2-Hydroxy phenyl) formamide



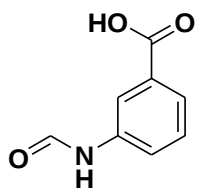
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-aminophenol. (0.654g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/Pet-Ether) (3:1)) was then evaporated under reduced pressure to afford a white solid *N*-(2-Hydroxy phenyl) formamide **(13)** (0.53 g 81%. m.p. 128-130 ºC. IR (NaCl) *v*(cm^{-1}) 3481, 3343, 3145, 2961, 1720, 1624, 1581, 1444, 1275. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.20 (d, *J* = 1.7 Hz, 1H), 7.56 (brs, 1H), 7.13 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.08 (td, *J* = 7.9, 1.5 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.83 (td, *J* = 7.8, 1.3 Hz, 1H), 4.27 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 159.2, 147.0, 127.5, 121.2, 120.0, 119.5. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 11.6 Hz, 1H), 6.74 (d, *J* = 11.4 Hz, 1H), 6.73 – 6.68 (m, 2H), 6.66 – 6.58 (m, 2H), 2.46 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 159.2, 143.5, 124.4, 120.2, 119.1.

5.1.2.14. 4-Formamidobenzoic acid



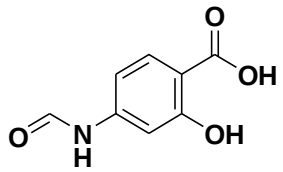
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3-aminobenzoic acid (0.823 g 6 mmol) and triethyl orthoformate (24 mmol) or and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid 4-formamidobenzoic acid **(14)** (0.71g 86%). m.p 250-252 ºC. IR (NaCl) *v*(cm^{-1}) 3457, 3363, 3128, 2874, 1655, 1596, 1416, 1287. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.0 (s, 1H). 7.61 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 2H), 5.87 (brs, 1H), 3.37 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.0, 153.5, 131.2, 117.6, 112.0.

5.1.2.15. 3-Formamidobenzoic acid



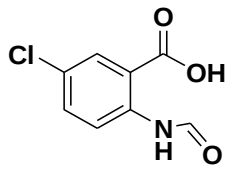
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3-aminobenzoic acid (0.823 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (Pet/EtOAc 3:1) was then evaporated under reduced pressure to afford 3-formamidobenzoic acid **(15)** (0.77g 94%). m.p. 155-158 ºC. IR (NaCl) ν(cm^{-1}) 3300, 3125, 2918, 2250, 1644, 1558, 1382, 1220. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 10.38 (brs, 1H), 10.29 (d, J = 10.9 Hz, 1H), 8.85 (d, J = 10.9 Hz, 1H), 8.27 (d, J = 5.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.46 (dt, J = 15.9, 8.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.5, 159.7, 138.2, 131.1, 129.6, 124.5, 123.1, 119.4.

5.1.2.16. 4-formamido-2-hydroxybenzoic acid



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-amino salicylic acid (0.91 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (Pet-Ether/EtOAc (1:3)) was then evaporated under reduced pressure to afford a yellow viscous liquid 4-formamido-2-hydroxybenzoic acid **(16)** (0.68g 75%). IR (NaCl) ν(cm^{-1}) 3384, 3126, 2890, 1748, 1648, 1558, 1377, 1215. ^{1}H NMR (400 MHz, DMSO) δ 7.41 (d, J = 8.6 Hz, 1H), 6.07 (dd, J = 8.6, 2.0 Hz, 2H), 5.96 (d, J = 2.0 Hz, 2H), 3.63 (s, 1H), 3.34 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.0, 163.3, 155.1, 131.5, 106.2, 98.9.

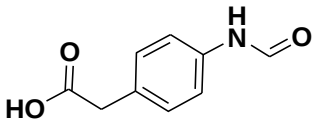
5.1.2.17. 5-chloro-2-formamidobenzoic acid.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino-5-chlorobenzoic acid (1.02 g, 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid 5-chloro-2-formamidobenzoic acid **(17)** (7.45g 73%) m.p 204-206 ºC. IR (NaCl) ν(cm^{-1}) 3469, 3351, 2808, 1667, 1586, 1472, 1201. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, DMSO) Major rotamer: δ 10.98 (s, 1H), 8.56 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.62 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.3, 161.0, 150.1, 133.7, 130.2, 122.4, 118.6, 110.5. Minor rotamer: ^{1}H NMR (400 MHz, DMSO) δ 10.49 (s, OH), 8.98 (brs, 1H), 8.51 (s, 1H), 7.66 (dd, J

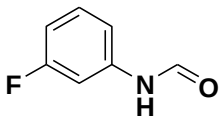
= 8.9, 2.5 Hz, 1H), 7.25 (dd, *J* = 8.9, 2.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 167.2, 161.8, 150.3, 138.7, 130.3, 127.2, 117.1.

5.1.2.18. 2-(4-formamidophenyl)acetic acid.



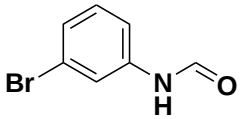
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-amino phenyl acetic acid (0.906 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid 2-(4-formamidophenyl)acetic acid **(18)** (0.77g 85%) m.p 142-144 ºC. The mixture of rotamers was observed. Major rotamer: ^{1}H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 7.27 (d, *J* = 11.0 Hz, 4H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.46 (d, *J* = 11.2 Hz, 2H), 3.72 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 174, 163, 136, 131, 129, 119, 115, 48, 47, 39. Minor rotamer: ^{1}H NMR (400 MHz, MeOD) δ 7.98 (s, 1H), 7.02 (brs, 1H), 6.86 (d, *J* = 11.0 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 3.68 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 174.2, 160.6, 131.2, 130.1, 129.5, 118.0, 115.1. m/z (ESI-HRMS) calculated for $C_9H_9NO_3$ $[M+H]^+$: 180.0582; found $[M+H]^+$: 180.0697.

5.1.2.19. *N*-(3-fluoro-phenyl) formamide



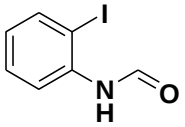
The experimental procedure described for the synthesis of *N*-Phenyl formamide **1** was followed using 3-fluoro aniline (0.576 mL 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/Pet (2:1)) was then evaporated under reduced pressure to afford 3-Fluorobenzylformamide **(19)** (0.56 g 97%) m.p 53-55 ºC. IR (NaCl) ν(cm^{-1}) 3304, 3032, 2944, 1684, 1598, 1442, 1278, 1149, 861. The mixture of rotamers was observed. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (brs, 1H), 8.38 (s, 1H), 7.61 (s, 1H), 7.49 (d, *J* = 10.6 Hz, 1H), 7.35 – 7.22 (m, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 159.2, 138.5, 131.0, 115.3, 112.4, 107.3. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 11.2 Hz, 1H), 7.49 (d, *J* = 10.8 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.86 (dt, *J* = 18.1, 8.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 138.2, 130.5, 114.6, 111.7, 106.2.

5.1.2.20. *N*-(3-bromo-phenyl) formamide



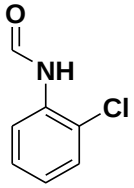
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3-bromoaniline (0.6 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(3-bromophenyl)formamide **(20)** (0.47g 78%) m.p 100-103 ºC. IR (NaCl) $\nu(cm^{-1})$ 3355, 2889, 1749, 1749, 1677, 1463, 1283. The mixture of rotamers was observed. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 11.0 Hz, 1H), 8.68 (d, J = 11.2 Hz, 1H), 7.79 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 9.8 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 138.0, 131.4, 128.0, 123.4, 118.1. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (brs, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.29 (d, J = 9.8 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 138.3, 130.1, 127.5, 121.2, 117.0.

5.1.2.21. *N*-(2-Iodo-phenyl) formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-iodo aniline (0.7 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/Pet (4:1)) was then evaporated under reduced pressure to afford a white solid *N*-(2-Iodo-phenyl) formamide **(21)** (0.66 g 94%) m.p 116-118 ºC. IR (NaCl) $\nu(cm^{-1})$ 3313 2902 2647 1748 1658 1515 1434 1396 1201.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.8 Hz, 1H), 8.38 (brs, 1H), 8.18 (d, J = 7.3 Hz, 1H), 7.73 (dd, J = 17.5, 7.0 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.48 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 159.1, 146.1, 139.4, 139.2, 137.1, 129.3, 108.2.

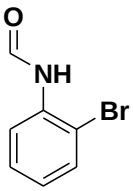
5.1.2.22. *N*-(2-chlorophenyl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-chlorooaniline (0.76 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(2-chlorophenyl)formamide **(22)** (0.69g

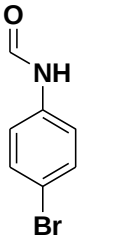
91%) m.p 80-82 ºC. IR (NaCl) ν(cm^{-1}) 3343, 3103, 3040, 2903, 1700, 1665, 1532, 1438, 1399, 1297, 1160, 1036. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.50 (d, *J* = 1.4 Hz, 1H), 8.06 (brs, 1H), 7.37 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.24 (d, *J* = 1.1 Hz, 1H), 7.06 (td, *J* = 7.9, 1.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 130.4, 129.1, 127.3, 125.1, 122.6, 119.3. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 11.1 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 5.5 Hz, 1H), 7.13 (dt, *J* = 8.6, 4.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 133.2, 128.5, 126.0, 124.2, 122.6.

5.1.2.23. *N*-(2-bromophenyl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-bromoaniline (1.03 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(2-bromophenyl)formamide **(23)** (0.87g 84%) m.p 92-94 ºC. IR (NaCl) ν(cm^{-1}) 3351, 2907, 1696, 1655, 1575, 1516, 1395, 1289, 1160, 1120. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.39 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.80 (brs, 1H), 7.56 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.02 (td, *J* = 7.9, 1.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 135.4, 132.2, 128.6, 126.3, 122.5, 113.2. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 11.1 Hz, 1H), 8.39 (d, *J* = 9.5 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 135.3, 133.2, 129.7, 126.5, 119.4, 115.1.

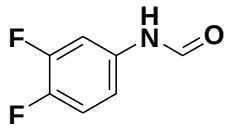
5.1.2.24. *N*-(4-bromophenyl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-bromoaniline (0.8 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(4-bromophenyl)formamide **(24)** (0.65g 81%) m.p 115-117 ºC. IR (NaCl) ν(cm^{-1}) 3355, 3185, 3114, 3052, 2864, 1747, 1395, 1307, 1250. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.36 (brs, 1H), 7.83

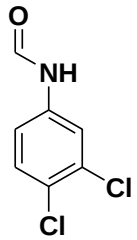
(s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 145.4, 135.2, 132.9, 121.3, 117.2. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 9.2 Hz, 1H), 8.63 (d, J = 11.3 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 11.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 145.2, 135.1, 131.4, 120.1, 118.2, 110.2.

5.1.2.25. *N*-(3,4-difluorophenyl) formamide



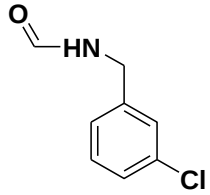
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3,4-difluoroaniline (0.77 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(3,4-difluorophenyl) formamide **(25)** (0.44g 56%). m.p 165-170 ºC. IR (NaCl) ν(cm^{-1}) 3560, 2880, 1700, 1662, 1505, 1334, 1206. ^{1}H NMR (400 MHz, DMSO) δ 7.97 (brs, 1H), 7.16 – 7.04 (m, 2H), 6.93 (s, 1H), 6.75 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 152.4, 149.1, 146.0, 118.2, 115.1, 108.3.

5.1.2.26. *N*-(3,4-dichlorophenyl)formamide



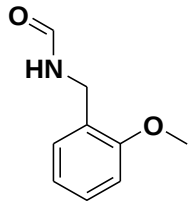
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3,4-dichoro aniline (0.97 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(3,4-dichlorophenyl)formamide **(26)** (0.78g 81%) m.p 105-107 ºC. IR (NaCl) ν(cm^{-1}) 3373, 3007, 2892, 1672, 1594, 1473, 1309, 1129, 812. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, DMSO) Major rotamer: δ 8.49 (d, J = 4.0 Hz, 2H), 8.29 (brs, 1H), 7.49 – 7.30 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 160.2, 138.2, 131.7, 126.3, 121.4, 119.6. Minor rotamer: ^{1}H NMR (400 MHz, DMSO) δ 8.68 (d, J = 11.0 Hz, 1H), 7.88 (brs, 1H), 8.08 (s, 1H), 7.06 (dd, J = 8.7, 2.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 162.4, 138.5, 132.1, 127.4, 120.2, 118.5.

5.1.2.27. 3-chlorobenzylformamide



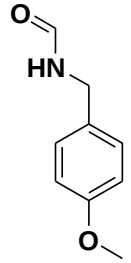
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3-chlorobenzylamine (1.0g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow viscous liquid 3-chlorobenzylformamide **(27)** (0.82 g 82%). IR (NaCl) $\nu(cm^{-1})$ 3216, 2899, 2790, 2700, 2645, 1731, 1665, 1579, 1489, 1371, 1211, 1098, 773. ^{1}H NMR (400 MHz, DMSO) δ 8.40 (brs, 1H), 8.17 (s, 1H), 7.58 (s, 1H), 7.49 – 7.13 (m, 2H), 4.32 (d, J = 6.1 Hz, 1H), 4.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.4, 141.2, 137.6, 133.4, 130.0, 128.4, 41.5.

5.1.2.28. *N*-[(2-Methoxyphenyl)methyl]formamide.



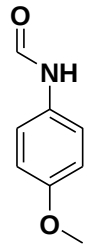
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-methoxybenzylamine (1.00 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(2-methoxybenzyl)formamide **(28)** (0.85g 85%) m.p 78-80 °C. IR (NaCl) $\nu(cm^{-1})$ 3355, 2837, 2329, 2091, 1655, 1489, 1235, 1024. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.14 (brs, 1H), 8.11 (s, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 10.3 Hz, 1H), 6.95 – 6.83 (m, 2H), 4.45 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 157.1, 129.4, 128.2, 125.6, 110.3, 55.3, 37.1. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (brs, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.03 – 6.94 (m, 1H), 6.75 (s, 1H), 4.31 (d, J = 4.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 130.4, 129.1, 125.2, 120.6, 41.4, 36.4.

5.1.2.29. *N*-(4-methoxybenzyl)formamide.



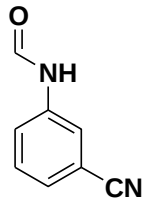
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-methoxybenzylamine (0.82 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(4-methoxybenzyl)formamide **(29)** (0.786 g 96%). m.p. 77-79 ºC . IR (NaCl) ν(cm^{-1}) 3390, 2913, 2623, 2219, 1651, 1514, 1244. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.14 (brs, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.64 (s, 1H), 4.34 (d, J = 5.9 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 158.2, 133.6 129.2, 114.5, 55.1, 41.3. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 11.9 Hz, 2H), 7.17 (d, J = 34.2 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 4.27 (d, J = 6.2 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 150.4 133.9, 130.4, 122.6, 59.4, 45.0.

5.1.2.30. *N*-(4-methoxyphenyl)formamide



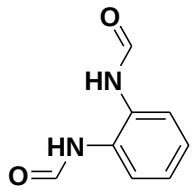
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using *p*-anisidine (0.74 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(4-methoxyphenyl)formamide **(30)** (0.693g 94%) m.p 77-79 ºC. IR (NaCl) ν(cm^{-1}) 3379, 3009, 2829, 1907, 1641, 1516, 1379, 1246, 1035. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.57 (brs, 1H), 8.19 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 159.1, 156.5, 129.2, 122.4, 114.1, 55.3. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 9.5 Hz, 1H), 8.47 (d, J = 11.0 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 164.0, 157.2, 129.5, 121.1, 114.4, 60.2.

5.1.2.31. *N*-(3-cyanophenyl)formamide.



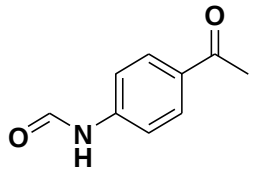
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 3-aminobenzo nitrile (0.71 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-(3-cyanophenyl)formamide **(31)** (0.66g 93%) m.p 115-117 ºC. IR (NaCl) v(cm^{-1}) 3300, 3025, 2972, 2223, 1669, 1590, 1469, 1301. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, DMSO) Major rotamer: δ 10.32 (brs, 1H), 10.17 (d, J = 10.6 Hz, 1H), 7.86 (s, 1H), 7.40 – 7.15 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.5, 139.1, 130.4, 127.2, 123.5, 122.1, 118.9, 111.5. Minor rotamer: ^{1}H NMR (400 MHz, DMSO) δ Major rotamer: 8.69 (d, J = 10.8 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.71 – 7.51 (m, 3H), 7.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 162.4, 139.2, 130.5, 127.2, 122.6, 120.1, 112.5.

5.1.2.32. *N*-(2-formamidophenyl)formamide.



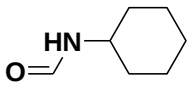
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using benzene-1,2-diamine (0.65 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH (2:1)) was then evaporated under reduced pressure to afford a brown liquid *N*-(2-formamidophenyl)formamide **(32)** (0.64 g 96%). IR (NaCl) v(cm^{-1})) 3417, 2899, 1772, 1680, 1453, 1410, 1239. ^{1}H NMR (400 MHz, Acetone) δ 8.69 (brs, 1H), 8.44 (s, 1H), 7.84 (d, J = 6.2 Hz, 3H), 7.75 (s, 1H), 7.33 (d, J = 9.0 Hz, 2H). ^{13}C NMR (101 MHz, Acetone) δ 163.0, 159.6, 140.1, 134.4, 122.6, 114.3.

5.1.2.33. *N*-(4-acetyl phenyl) formamide.



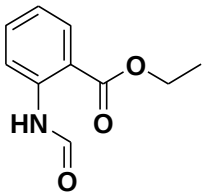
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-aminoacetophenone (0.8 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow solid *N*-(4-acetyl phenyl) formamide **(33)** (0.76g 95%) 158-160 ºC. IR (NaCl) ν(cm^{-1}) 3293, 2884, 1669, 1662, 1582, 1529, 1268, 1058. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.42 (brs, 1H), 8.35 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 159.1, 151.4, 141.2, 133.5, 129.2, 119.1, 113.4, 25.1. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 11.2 Hz,2H), 8.59 (d, *J* = 9.4 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 161.6, 151.3, 141.5, 133.2, 130.1, 127.5, 117.2, 26.1.

5.1.2.34. *N*-(cyclohexyl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using cyclohexylamine (0.69 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/Pet ether (3:1)) was then evaporated under reduced pressure to afford viscous colourless liquid *N*-(cyclohexyl)formamide **(34)** (0.60g 86%). IR (NaCl) ν(cm^{-1}) 3289, 2940, 2858, 2204, 1640, 1538, 1334. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer δ 8.41 (brs, 1H), 2.97 (s, 1H), 1.97 (d, *J* = 11.8 Hz, 2H), 1.72 (d, *J* = 11.8 Hz, 2H), 1.39 – 1.19 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 77.5, 50.3, 31.2, 24.1. Minor rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 3.77 (s, 1H), 1.85 (d, *J* = 15.6 Hz, 2H), 1.58 (d, *J* = 12.2 Hz, 3H), 1.13 (dd, *J* = 25.0, 13.0 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 77.1, 48.4, 33.2, 25.0.

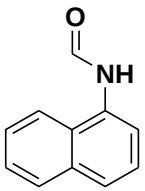
5.1.2.35. Ethyl 2-formamidobenzoate.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using ethyl 2-aminobenzoate (0.99 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid ethyl 2-formamidobenzoate **(35)** (0.92g 93%) m.p 58-60 ºC. IR (NaCl) ν(cm^{-1}) 3284, 2904, 1681, 1582, 1515, 1244. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (brs, 1H), 8.39 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.13 (t,

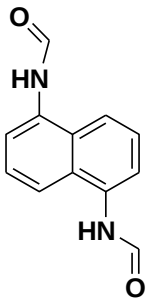
J = 8.3 Hz, 1H), 6.53 (t, *J* = 8.7 Hz, 2H), 4.24 – 4.16 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 159.2, 150.1, 140.4, 134.6, 131.0, 121.2, 116.4, 110.7, 60.1, 13.0. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 10.9 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.35 – 4.21 (m, 3H), 1.30 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 161.8, 146.3, 134.6, 130.1, 121.0, 115.4, 61.2, 29.5.

5.1.2.36. *N*-(naphthalen-1-yl)formamide



This reaction was carried out by treating 1-Naphthylamine (0.86 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford faint purple solid *N*-(naphthalen-1-yl)formamide **(36)** (0.84g 98%) m.p 135-137 ºC. IR (NaCl) *v*(cm^{-1}) 3250, 3051, 2968, 1658, 1567, 1391, 1296. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.30 (brs, 1H), 8.17 (d, *J* = 7.0 Hz, 2H), 7.87 – 7.74 (m, 2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.35 (m, 2H), 6.75 (dd, *J* = 6.8, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 142.1, 134.8, 128.3, 127.2, 126.4, 125.1, 124.5, 119.2, 110.4. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.61 (d, *J* = 10.0 Hz, 1H), 8.55 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 10.4 Hz, 1H), 7.27 (dt, *J* = 15.0, 7.7 Hz, 2H), 7.17 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 141.5, 134.2, 131.4, 128.3, 127.5, 124.1, 120.5, 119.0, 106.4.

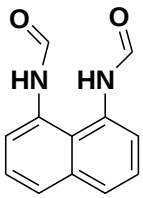
5.1.2.37. *N*-(5-formamidonaphthalen-1-yl)formamide.



The desired product was prepared by using 1,5-diaminonaphthalene (0.94 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a brown solid *N*-(5-formamidonaphthalen-1-yl)formamide **(37)** (0.60g 64%) m.p 130-133 ºC. IR (NaCl) *v*(cm^{-1}) 3224, 3005, 2903, 1641, 1528, 1395, 1262, 1215, 1149. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, MeOD) Major rotamer: δ 8.39 (d, *J* = 4.9 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.79

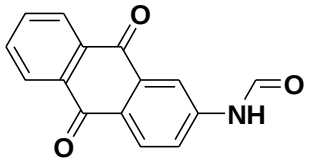
(d, *J* = 8.6 Hz, 1H), 7.33 – 7.26 (m, 4H), 6.76 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 161.3, 144.5, 131.1, 126.3, 123.1, 119.0. Minor rotamer: ^{1}H NMR (400 MHz, MeOD) δ 8.45 (brs, 1H), 8.36 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 165.4, 131.7, 127.1, 124.3, 120.5, 110.2.

5.1.2.38. *N,N'*-(naphthalene-1,8- diyl)diformamide



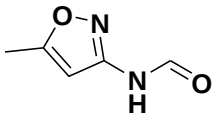
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 1,8-diaminonaphthalene (0.94 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a brown solid *N*-(8-formamidonaphthalen-1-yl)formamide **(38)** (0.86g 91%) m.p 146-148 ºC**.** IR (NaCl) *ν*(cm^{-1}) 3036, 2943, 2329, 1739, 1681, 1336, 1219. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (brs, 1H), 7.44 (s, 1H), 7.09 – 7.00 (m, 2H), 6.46 (dd, *J* = 6.0, 2.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 145.2, 137.1, 128.0, 120.3, 108.5. m/z (ESI-HRMS) calculated for $C_9H_9NO_3$ $[M+Na]^+$: 237.0639; found $[M+Na]^+$: 237.0698.

5.1.2.39. *N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)formamide



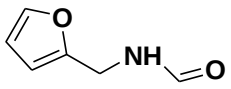
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino anthraquinone (1.34 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH (1:2) was then evaporated under reduced pressure to afford an orange solid *N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)formamide**(39)** (1.17g 98%) m.p 266-268 ºC. IR (NaCl) *ν*(cm^{-1}) 3249, 3108, 1706, 1667, 1589, 1538, 1287, 1240, 1177. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (brs, 1H), 8.35 (s, 1H), 8.34 (s, 1H), 8.33 – 8.31 (m, 3H), 8.30 (d, *J* = 1.7 Hz, 1H), 8.29 – 8.24 (m, 3H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.81 (dd, *J* = 5.8, 3.3 Hz, 4H), 7.75 (td, *J* = 7.2, 1.6 Hz, 3H), 7.45 (d, *J* = 2.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7, 181.2, 168.3, 135.4, 133.6, 132.3, 129.1, 127.0, 124.5.

5.1.2.40. *N*-(5-methylisoxazol-3-yl) formamide



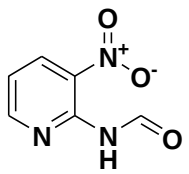
The experimental procedure described for the synthesis of *N*-phenylformamide **1** was followed using 3-amino-5-methylisoxazol (0.589 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (Pet-ether/EtOAc (2:1)) was then evaporated under reduced pressure to afford a yellow solid *N*-(5-methylisoxazol-3-yl) formamide **(40)** (0.56g 95%) m.p 120-122 ºC. IR (NaCl) ν(cm^{-1}) 3213, 3151, 2918, 1686, 1548, 1396, 1249. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer δ 8.40 (brs, 1H), 6.70 (s, 1H), 5.53 (s, 1H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 164.4, 159.0, 94.5, 13.2. Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (brs, 1H), 8.80 (d, J = 11.0 Hz, 1H), 5.91 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 162.2, 157.8, 97.4, 12.6.

5.1.2.41. *N*-(Furan-2yl)methyl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using (furan-2-yl)methanamine (0.53 ml 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a brown liquid *N*-((furan-2-yl)methyl) formamide **(41)** (0.521g 98%). IR (NaCl) ν(cm^{-1}) 3375, 3044, 2919, 2853, 2333, 2083, 1661, 1504, 1383, 1199, 1012. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 7.47 (brs, 1H), 7.30 (d, J = 1.7 Hz, 1H), 7.26 (s, 1H), 6.19 (dd, J = 35.5, 2.0 Hz, 1H), 4.35 – 4.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 150.7, 142.2, 110.4, 34.8. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.98 (d, J = 3.9 Hz, 1H), 7.00 (s, 1H), 6.26 (d, J = 1.7 Hz, 1H), 5.56 (d, J = 3.7 Hz, 1H), 4.28 – 4.22 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 142.4, 128.7, 107.1, 38.4.

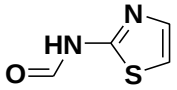
5.1.2.42. 2-Formamido-3-nitropyridine.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino-3-nitropyridine (0.84 g 6 mmol) and triethyl orthoformate (24 mmol) or and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent

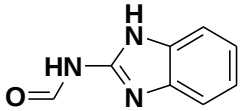
(EtOAc/Pet-Ether (4:1)) was then evaporated under reduced pressure to afford a yellow solid 2-Formamido-3-nitropyridine **(42)** (0.77g 92%). m.p 140-141 ºC. IR (NaCl) ν(cm^{-1}) 3460, 3089, 2913, 2846, 2328, 1643, 1567, 1505, 1429, 1206. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.3, 1.6 Hz, 1H), 8.35 (dd, J = 4.5, 1.6 Hz, 1H), 6.74 (dd, J = 8.3, 4.5 Hz, 1H), 1.75 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 153.5, 145.7 135.3, 128.1, 113.5.

5.1.2.43. *N*-(thiazol-2-yl)formamide.



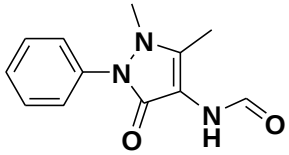
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-aminothiazole (0.6 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH (2:1)) was then evaporated under reduced pressure to afford a white solid *N*-(thiazol-2-yl)formamide **(43)** (0.40g 67%) m.p 155-157 ºC. IR (NaCl) ν(cm^{-1}) 3400, 3267, 3087, 3014, 2809, 1700, 1645, 1520, 1172. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (brs, 1H), 7.47 (d, J = 3.6 Hz, 1H), 7.05 (d, J = 3.6 Hz, 1H), 6.54 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 146.7, 137.5, 114.3.

5.1.2.44. 2-Formamido benzyimidazole.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino benzyimidazole (0.8 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH1:2) was then evaporated under reduced pressure to afford a white solid 2-Formamido benzimidazole **(44)** (0.63g 79%) m.p 165–167 ºC. IR (NaCl) ν(cm^{-1}) 3567, 3065, 1694, 1538, 1475, 1377, 1326, 1193, 1036. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (brs, 1H), 7.13 (dd, J = 5.8, 3.2 Hz, 2H), 6.90 (dd, J = 5.8, 3.2 Hz, 2H), 6.71 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.5, 165.2, 154.6, 136.1, 119.5, 110.2.

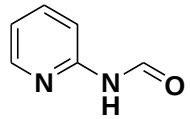
5.1.2.45. 4-formamido-antipyrine.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-amino antipyrine (1.22 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH

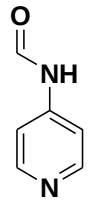
(1:1)) was then evaporated under reduced pressure to afford a yellow solid 4-formamido-antipyrine **(45)** (0.93g 76%) m.p 136-137 ºC. IR (NaCl) ν(cm^{-1}) 3359, 3157, 3054, 2873, 2501, 2157, 1687, 1640, 1303. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (brs, 1H), 8.61 (s, 1H), 7.98 (d, J = 51.9 Hz, 3H), 7.68 – 6.98 (m, 5H), 2.97 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 163.6, 162.9, 149.5, 133.3, 129.5, 125.1, 104.4, 77.2, 34.8, 11.2.

5.1.2.46. *N*-(Pyridine -2-yl) formamide.



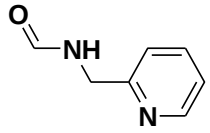
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-aminopyridine (0.56 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH (1:1)) was then evaporated under reduced pressure to afford a white solid *N*-(Pyridine -2-yl) formamide **(46)** (0.44g 79%) m.p 72-73 ºC. IR (NaCl) ν(cm^{-1}) 3384, 3271, 3048, 2907, 2731, 2305, 2071, 1758, 1642, 1516, 1438, 1282. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, MeOD) Major rotamer: δ 9.31 (brs, 1H), 8.29 (d, J = 3.8 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.81 – 7.66 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 164.6, 152.2, 149.2, 139.8, 121.5, 115.3. Minor rotamer: ^{1}H NMR (400 MHz, MeOD) δ 8.39 (brs, 1H), 8.25 (d, J = 4.0 Hz, 1H), 7.11 (dd, J = 12.3, 7.2 Hz, 2H), 6.93 (d, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 161.5, 151.2, 148.9, 139.2, 120.5, 112.3.

5.1.2.47. *N*-(Pyridine -4-yl) formamide.



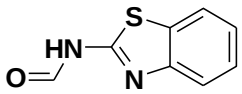
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 4-aminopyridine (0.56 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc/EtOH (1:1)) was then evaporated under reduced pressure to afford a yellow liquid *N*-(Pyridine -4-yl) formamide **(47)** (0.40g 71%). IR (NaCl) ν(cm^{-1}) 3387, 3101, 1694, 1628, 1526, 1338, 1201. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (brs, 1H), 10.11 (d, J = 7.3 Hz, 2H), 9.48 (s, 1H), 8.92 (d, J = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 161.5, 141.8, 111.5.

5.1.2.48. *N*-((pyridine-2-yl)methyl)formamide.



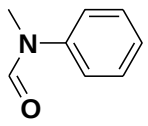
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-picolyl amine (0.65 mL 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow oil *N*-((pyridine-2-yl)methyl)formamide **(48)** (0.61g 94%). IR (NaCl) $\nu(cm^{-1})$ 3263, 3044, 2927, 2853, 2333, 2094, 1668, 1594, 1532, 1379, 1231, 1153. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 10.10 (d, J = 7.0 Hz, 1H), 8.46 (d, J = 6.8 Hz, 1H), 8.12 (s, 1H), 7.75 (td, J = 7.7, 1.5 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.29 – 7.25 (m, 1H), 4.55 (d, J = 6.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 155.6, 147.5, 139.1, 123.4, 42.2. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.3 Hz, 1H), 8.20 (brs, 1H), 7.85 (s, 1H), 7.72 – 7.63 (m, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.24 – 7.18 (m, 2H), 4.76 (d, J = 6.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 156.6, 148.6, 137.7, 126.5, 121.9, 46.4.

5.1.2.49. *N*-(benzo[d]thiazol-2-yl)formamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino benzothiazole (0.90 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid 2-formamido benzothiazole **(49)** (0.79 g 87%) m.p 74-76 ^{o}C. IR (NaCl) $\nu(cm^{-1})$ 3351, 3179, 2713, 2282, 1690, 1620, 1518, 1444. ^{1}H NMR (400 MHz, DMSO) δ 8.13 (brs, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.19 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 168.2, 164.8, 152.3, 130.5, 126.9, 122.1, 121.4, 118.2.

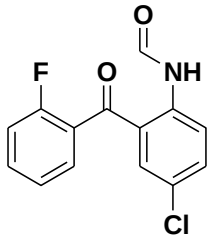
5.1.2.50. *N*-methyl-N-phenylformamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using N-methylaniline (0.65mL 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford *N*-methyl-*N*-phenylformamide **(50)** (0.48g 73%) m.p 123-

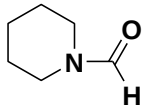
125 ºC. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.39 (brs, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.13 – 7.04 (m, 3H), 6.53 (dd, *J* = 8.6, 1.0 Hz, 3H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 149.3, 128.8, 122.3, 112.0, 31.5. Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.23 – 7.16 (m, 1H), 6.66 – 6.59 (m, 2H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 142.7, 129.5, 126.1, 117.8, 32.2.

5.1.2.51. *N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]formamide.



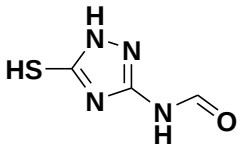
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using 2-amino-5-chloro-2-fluoro benzophenone (1.5 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow solid *N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]formamide **(51)** (1.22g 81%) m.p 79-81 ºC. IR (NaCl) *v*(cm^{-1}) 3446 3341.4 2923 1640.5 1477.5 1215.8 1154. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 8.64 (d, *J* = 9.0 Hz, 1H), 8.53 (brs, 1H), 8.46 (d, *J* = 14.5 Hz, 1H), 7.96 (s, 1H), 7.58 (d, *J* = 6.6 Hz, 1H), 7.35 (td, *J* = 7.6, 1.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 9.4 Hz, 1H). 4.04 (q, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 170.3, 160.1, 158.6, 145.9, 134.3, 132.8, 130.4, 126.1, 124.9, 120.5, 116.3, 64.6. Minor rotamer:^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.64 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 6.6 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.07 (t, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5, 174.3, 161.1, 159.7, 151.4, 133.0, 131.5, 127.3, 123.6, 118.2.

5.1.2.52. Piperidine-1-carbaldehde



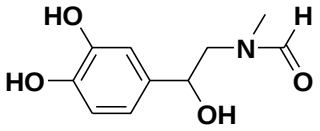
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using piperidine (0.79 mL 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellow oil Piperidine-1-carbaldehde **(52)** (0.67 mL 85%). IR (NaCl) *v*(cm^{-1}) 3371, 2944, 2772, 2540, 1726, 1694, 1585, 1338. ^{1}H NMR (400 MHz, D_2O) δ 8.38 (brs, 1H), 3.15 – 2.98 (m, 4H), 1.69 (dt, *J* = 5.8 Hz, 4H), 1.57 (dd, *J* = 11.0, 5.7 Hz, 2H). ^{13}C NMR (101 MHz, D_2O) δ 170.5, 44.1, 22.8, 21.5.

5.1.2.53. *N*-(5-mercapto-1H-1,2,4-triazol-3- yl)formamide



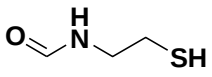
The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using piperidine (0.67 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid 3-formamido-1,2,4-triazole-5-thiol **(53)** (0.60 g 90%) m.p 198-200 ºC. IR (NaCl) ν(cm^{-1}) 3398, 3316, 3191, 3050, 2725, 1636, 1593, 1209. The mixture of rotamers was observed. ^{1}H NMR (400 MHz, DMSO) Major rotamer: δ 8.93 (brs, 1H), 7.95 (s, 1H), 7.47 (s, 2H), 5.84 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 163.8, 160.4, 144.9. Minor rotamer: ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.44 (s, 1H), 8.34 (s, 1H), 7.47 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.6, 156.0, 148.3. m/z (ESI-HRMS) calculated for $C_9H_9NO_3$ $[M+H]^+$: 145.0106; found $[M+H]^+$: 145.0218.

5.1.2.54. *N*-[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]-N- methylformamide.



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using (-)-Epinephrine (1.09 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a brown viscous liquid *N*-[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]-*N*- methylformamide **(54)** (0.816g 75%). IR (NaCl) ν(cm^{-1}) 3245, 3003, 2787, 2137, 1734, 1636, 1538, 1334. ^{1}H NMR (400 MHz, D_2O) δ 8.17 (brs, 1H), 6.84 – 6.62 (m, 2H), 6.59 (d, J = 7.9 Hz, 1H), 6.50 (d, J = 7.8 Hz, 1H), 4.71 (s, 3H), 2.99 (d, J = 8.1 Hz, 1H), 2.60 (s, 1H), 2.55 (s, 2H). ^{13}C NMR (101 MHz, D_2O) δ 168.2, 144.7, 132.0, 118.5, 116.2, 113.6, 68.4, 54.3, 32.8.

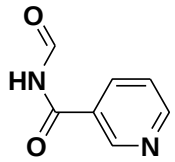
5.1.2.55. *N*-(2-mercaptoethyl)formamide



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using cysteamine (0.46 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a yellowish liquid *N*-(2-mercaptoethyl)formamide **(55)** (0.39 g 85%). IR (NaCl) ν(cm^{-1}) 3363, 3148, 2783, 1671, 1593, 1393. ^{1}H NMR (400 MHz, D_2O) δ 8.27 (brs, 1H),

7.96 (s, 1H), 4.71 (s, 4H), 3.07 (t, J = 6.6 Hz, 1H), 2.71 (t, J = 6.6 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 168.3, 164.2, 41.8, 21.4.

5.1.2.56. *N*-formylnicotinamide



The experimental procedure described for the synthesis of *N*-phenyl formamide **1** was followed using nicotinamide (0.73 g 6 mmol) and triethyl orthoformate (24 mmol) and (1.2 g) of immobilized H_2SO_4 on silica gel. The mixture was subjected to purification and the eluted solvent (EtOAc) was then evaporated under reduced pressure to afford a white solid *N*-formylpyridine-3-carboxamide **(56)** (0.68g 93%) m.p 98-100 ºC. IR (NaCl) ν(cm^{-1}) 3245, 3003, 2787, 2137, 1734, 1636, 1538, 1334. ^{1}H NMR (400 MHz, D_2O) δ 8.65 (d, J = 1.9 Hz, 1H), 8.47 (d, J = 6.4 Hz, 1H), 8.27 (brs, 1H), 8.02 (dd, J = 9.9, 1.8 Hz, 1H), 7.39 (dd, J = 8.0, 5.1 Hz, 1H), 4.70 (s, 1H). ^{13}C NMR (101 MHz, D_2O) δ 169.7, 151.3, 146.1, 137.0, 128.2, 124.7.

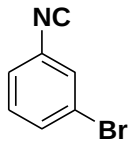
5.2 Experimental: Chapter 2.1. (Part B)

5.2.1 Synthesis of Isocyanide from *N*-Formamide.

5.2.2 General Procedure.

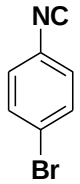
To a solution of *N*-(3-bromophenyl)formamide (0.25 mL 2 mmol) in triethylamine (2 ml) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford the product in high yield with minimal solvent consumption. The products obtained were known compounds and identified by melting point and ^{1}H NMR spectroscopy and the spectral data were compared with the literature values.

5.2.2.1. 1-bromo-3-isocyanobenzene.



To a solution of *N*-(3-bromophenyl)formamide (0.25 mL 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 ºC. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown liquid 1-bromo-3-isocyanobenzene (0.235 g 94%). IR (NaCl): 2125 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.51 – 7.46 (m, 1H), 7.32 – 7.23 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 133.0, 131.0, 129.6, 127.9, 125.3, 122.9.

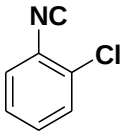
5.2.2.2. 4-bromo-1- isocyanobenzene.



To a solution of *N*-(4-bromo phenyl)formamide (0.4g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 4-bromo phenyl isocyanide (0.35 g; 85%) m.p 98-100 ºC. IR (NaCl): 2114 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.8 Hz, 2H), 7.18 (d, J =

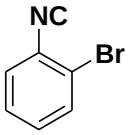
8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 132.5, 127.3, 125.2, 123.1

5.2.2.3. 1-chloro-2-isocyanobenzene.



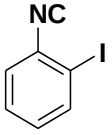
To a solution of *N*-(2-chlorophenyl)formamide (0.3g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford brown liquid 1-chloro-2-isocyanobenzene (0.27 g; 90%) m.p 26-28 ºC. IR (NaCl): 2141 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.9, 1.4 Hz, 1H), 7.35 (dd, J = 7.7, 1.4 Hz, 1H), 7.27 (td, J = 7.7, 1.9 Hz, 1H), 7.22 (td, J = 7.6, 1.5 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 130.7, 130.3, 130.1, 127.9, 127.5.

5.2.2.4. 1-bromo-2-isocyanobenzene.



To a solution of *N*-(2-bromophenyl)formamide (0.4g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow liquid 1-bromo-2-isocyanobenzene (0.34 g; 86%) m.p 39-40 ºC. IR (NaCl): 2145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.27 (td, *J* = 7.7, 1.4 Hz, 1H), 7.19 (td, *J* = 7.8, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 133.8, 130.7, 128.2, 119.8.

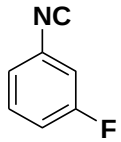
5.2.2.5. 1-iodo-2-isocyanobenzene.



To a solution of *N*-(2-iodophenyl)formamide (0.49 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction,

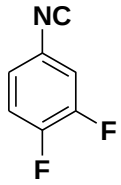
the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a green liquid 1-iodo-2-isocyanobenzene (0.36 g; 83%). IR (NaCl): 2121 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 6.1, 5.1 Hz, 2H), 6.98 (ddd, *J* = 8.2, 5.9, 3.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 139.3, 130.6, 128.8, 127.5, 94.2.

5.2.2.6. 1-fluoro-3-isocyanobenzene.



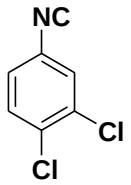
To a solution of *N*-(3-fluorophenyl)formamide (0.28 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow liquid 1-fluoro-3-isocyanobenzene (0.24 g; 85%). IR (NaCl): 2106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (td, *J* = 8.1, 6.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.15 – 7.08 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.6, 161.8, 131.7, 123.3, 117.7, 114.6.

5.2.2.7. 1,2-difluoro-4-isocyanobenzene.



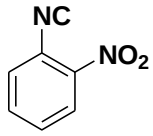
To a solution of *N*-(3,4-difluorophenyl)formamide (0.314 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow liquid 1,2-difluoro-4-isocyanobenzene (0.25 g; 79%). IR (NaCl): 2137 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.9 Hz, 1H), 7.28 (s, 1H), 7.24 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 151.9, 149.1, 123.0, 122.9, 117.9, 116.0, 115.8.

5.2.2.8. 1,2-dichloro-4-isocyanobenzene.



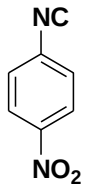
To a solution of *N*-(3,4-dichlorophenyl)formamide (0.38 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 1,2-dichloro-4-isocyanobenzene (0.24 g; 85%) m.p 32-33 ºC. IR (NaCl): 2125 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 3.4 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 162.6, 139.5, 130.5, 127.3, 123.9, 120.0, 111.2.

5.2.2.9. 1-Isocyano-2-nitrobenzene.



To a solution of *N*-(2-nitrophenyl)formamide (0.33g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 ml were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow liquid 1-Isocyano-2-nitrobenzene (0.29 g; 87%). IR (NaCl): 2121 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.06 (m, 1H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.66 – 7.53 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 144.7, 135.6, 129.9, 126.1, 118.4.

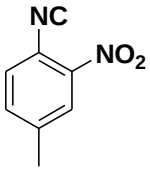
5.2.2.10. 4-Nitro phenyl isocyanide.



To a solution of *N*-(4-Nitrophenyl)formamide (0.33g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 ºC. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 4-Nitro phenyl isocyanide (0.31 94%) m.p 96-98 ºC. IR (NaCl): 2117 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ 7.98 (d, *J* = 12.3 Hz, 2H), 6.62 (d, *J* = 5.3 Hz,

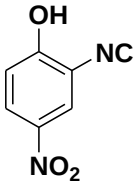
2H). ^{13}C NMR (101 MHz, MeOD) δ 156.4, 138.2, 127.4, 113.0.

5.2.2.11. 4-methyl-2-nitro phenyl isocyanide.



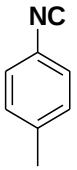
To a solution of *N*-(4-methyl-2-nitrophenyl)formamide (0.36 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 15 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 4-methyl-2-nitro phenyl isocyanide (0.31 g; 86%). m.p 103-104 ºC. IR (NaCl): 2127 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 7.89 (s, 1H), 7.50 – 7.46 (m, 1H), 6.73 (d, J = 8.5 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 143.4, 136.7, 129.3, 126.19, 124.83, 118.88, 20.85.

5.2.2.12. 2-isocyano-4-nitrophenol.



To a solution of 2-formamido 4-nitrophenol (0.36 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 2-isocyano-4-nitrophenol (0.33 g; 92%). m.p 116-119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.39 (d, *J* = 8.9 Hz, 1H), 8.28 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 153.9, 145.4, 140.9, 122.3, 117.8, 111.8.

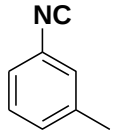
5.2.2.13. 1-isocyano-4-methylbenzene.



To a solution of *p*-tolyformamide (0.27 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for

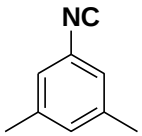
about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown solid 1-isocyano-4-methylbenzene (0.24 g; 88%) m.p 20-21 ºC. IR (NaCl): 2125 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 139.4, 130.0, 126.5, 29.9.

5.2.2.14. 1-isocyano-3-methylbenzene.



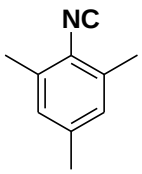
To a solution of *m*-tolyformamide (0.27 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown liquid 1-isocyano-3-methylbenzene (0.20 g; 74%). IR (NaCl): 2133 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.19 (t, *J* = 8.3 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 140.0, 130.5, 129.4, 127.4, 123.9, 30.4.

5.2.2.15. 3,5-dimethyl phenyl isocyanide.



To a solution of 3,5-dimethyl phenyl formamide (0.30 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 3,5-dimethyl phenyl isocyanide (0.24 g; 80%). m.p 53-55 ºC. IR (NaCl): 2157 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.99 (s, 2H), 2.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 139.5, 131.5, 124.4, 29.6.

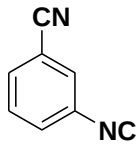
5.2.2.16. 2-isocyano-1,3,5-trimethylbenzene.



To a solution of 2,4,6-trimethylphenyl formamide (0.32 g; 2 mmol) in triethylamine (2 mL) and

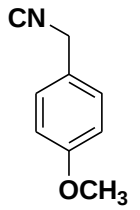
subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry packed column. 100 % diethyl ether was used as the mobile phase to afford a colourless liquid 2-isocyano-1,3,5-trimethylbenzene (0.31 g 97%). IR (NaCl): 2121 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 2.36 (s, 3H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 139.1, 134.5, 128.6, 21.5.

5.2.2.17. 3-isocyanobenzonitrile.



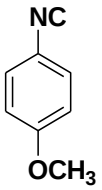
To a solution of 3-formamido benzonitrile (0.29 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a white solid 3-isocyanobenzonitrile (0.26 g; 90%). m.p 88-90 ºC. IR (NaCl): 2141 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 132.4, 130.3, 129.3, 116.3, 113.5.

5.2.2.18. 1-(isocyanomethyl)-4-methoxybenzene.



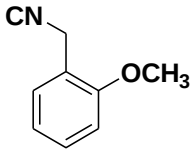
To a solution of 4-methoxy benzyl formamide (0.33 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a white solid 1-(isocyanomethyl)-4-methoxybenzene (0.29 g; 88%) m.p 32-34 ºC. IR (NaCl): 2153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.42 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.9, 127.4, 124.0, 113.5, 54.7.

5.2.2.19. 1-isocyano-4-methoxy benzene.



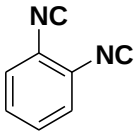
To a solution of *N*-(4-methoxyphenyl)formamide (0.30 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 1-isocyano-4-methoxy benzene (0.27 g; 90%) m.p 33-34 ºC. IR (NaCl): 2161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 160.0, 127.9, 114.8, 55.8.

5.2.2.20. 1-(isocyanomethyl)-2-methoxybenzene.



To a solution of 2-methoxy benzyl formamide (0.33 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a dark green solid 1-(isocyanomethyl)-2-methoxybenzene (0.25 g; 76%) m.p 110-112 ºC. IR (NaCl): 2145 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.17 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.78 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.53 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 130.6, 129.6, 127.5, 125.4, 120.9, 111.0, 55.09, 41.05.

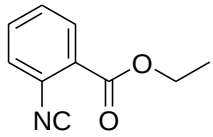
5.2.2.21. 1,2-diisocyanobenzene.



To a solution of o-phenelenediformamide (0.32 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was

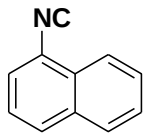
used as the mobile phase to afford a brown liquid 1,2-diisocyanobenzene (0.29 g; 91%). IR (NaCl): 2157 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.02 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 130.1, 127.6, 124.3.

5.2.2.22. Ethyl-2 isocyanobenzoate.



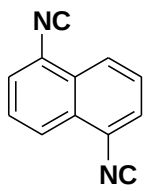
To a solution of Ethyl 2-formamidobenzoate (0.39 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a colourless liquid Ethyl-2 isocyanobenzoate (0.33 g; 85%). IR (NaCl): 2125 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.38 (td, J = 7.7, 1.6 Hz, 1H), 7.35 – 7.20 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 163.2, 132.1, 131.0, 128.5, 126.5, 62.1, 13.4.

5.2.2.23. 1-isocyanonaphthalene.



To a solution of *N*-(1-naphthy)formamide (0.34 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 ◦C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a green liquid 1-isocyanonaphthalene (0.32 g; 96%). IR (NaCl): 2129 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.1, 5.1 Hz, 2H), 7.48 – 7.30 (m, 3H), 7.23 – 7.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 133.4, 129.7, 128.2, 127.3, 124.77, 124.3, 122.6.

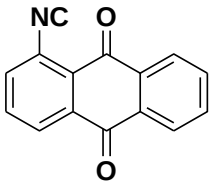
5.2.2.24. 1,5-diisocyanonaphthalene.



To a solution of *N*-(5-formamidonaphthalen-1-yl)formamide (0.37 g; 2 mmol) in triethylamine (2 mL)

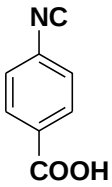
and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown solid 1,5-diisocyanonaphthalene (0.30 g; 81%) m.p 148-150 ºC. IR (NaCl): 2125 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 128.2, 127.1, 125.8, 125.1, 114.6.

5.2.2.25. 2-Isocyano anthracene-9, 10 dione.



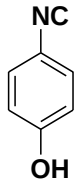
To a solution of 2-Formamido anthraquinone (0.50 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford an orange colour solid 2-Isocyano anthracene-9, 10 dione (0.34 g; 68%). m.p 135-137 ºC. IR (NaCl): 2121 cm^{-1}. ^{1}H NMR (400 MHz, DMSO) δ 7.73 (s, 1H), 7.60 (dd, *J* = 65.1, 17.0 Hz, 3H),7.39 (s, 2H), 7.28 – 7.17 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 182.7, 181.3, 168.3, 135.4, 133.7, 132.3, 129.2, 127.1, 124.3.

5.2.2.26. 4-Isocyanobenzoic acid.



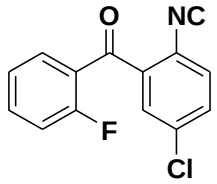
To a solution of 4-formamido benzoic acid (0.33 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a white liquid 4-isocyanobenzoic acid (0.21 g; 64%). ^{1}H NMR (400 MHz, MeOD) δ 9.83 (d, J = 10.8 Hz, 1H), 9.26 (d, J = 8.7 Hz, 1H), 9.12 (d, J = 8.5 Hz, 1H), 9.04 (d, J = 2.0 Hz, 1H), 5.11 (s, 1H). ^{13}C NMR (101 MHz, MeOD) δ 171.6, 166.4, 139.26, 133.3, 128.8.

5.2.2.27. 4-isocyano phenol.



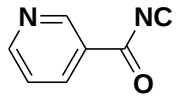
To a solution of 4-formamido phenol (0.27 ml; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown liquid 4-isocyano phenol (0.21 g; 78%). ^{1}H NMR (400 MHz, MeOD) δ 8.37 (s, 1H), 7.65 (d, *J* = 14.4 Hz, 2H), 7.31 (d, *J* = 11.9 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 164.8, 161.3, 150.1, 134.0, 124.2, 121.4.

5.2.2.28. (5-chloro-2-isocyanophenyl)(2-fluorophenyl)methanone.



To a solution of *N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]formamide (0.56 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid (5-chloro-2-isocyanophenyl)(2-fluorophenyl)methanone (0.36 g; 65%). m.p 130-132 ºC. IR (NaCl): 2110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.35 (m, 2H), 7.28 – 7.11 (m, 4H), 6.66 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 160.0, 157.9, 149.5, 134.8, 133.0, 132.0, 129.63, 127.8, 123.9, 120.1, 118.4, 116.3.

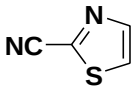
5.2.2.29. Isocyano(pyridine-3-yl)methanone.



To a solution of *N*-formylpyridine-3-carboxamide (0.29 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a colourless liquid Isocyano(pyridine-3-yl)methanone (0.13 g;

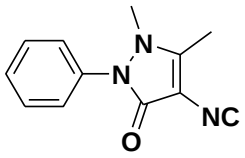
45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.75 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 151.8, 138.8, 123.2, 116.0, 109.5.

5.2.2.30. 2-Isocyano Thiazole.



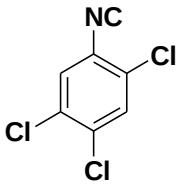
To a solution of *N*-(thiazol-2-yl)formamide (0.26 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a brown liquid 2-isocyano thiazole (0.14 g; 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 3.7 Hz, 1H), 7.07 (d, *J* = 3.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 134.8, 113.8.

5.2.2.31. 4-isocyano-antipyrine.



To a solution of 4-formamido antipyrine (0.5 g; 2 mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow solid 4-isocyano-antipyrine (0.34 g; 68%). m.p 92-94 ºC. IR (NaCl): 2131 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.8 Hz, 1H), 7.48 (s, 2H), 7.46 (t, *J* = 1.9 Hz, 2H), 7.39 (t, *J* = 1.2 Hz, 1H), 7.38 (t, *J* = 1.9 Hz, 1H), 7.36 (t, *J* = 1.2 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 3H), 7.30 (t, *J* = 1.7 Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.86, 159.0, 150.6, 133.7, 129.3, 128.2, 125.4, 35.1, 10.6.

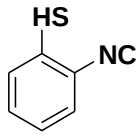
5.2.2.32. 1,2,4-trichloro-5-isocyanobenzene



To a solution of *N*-(2,4,5-trichlorophenyl)formamide (0.45 g; 2mmol) in triethylamine (2 mL) and

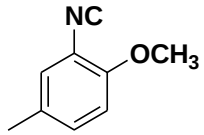
subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a dark brown solid 1,2,4-trichloro-5-isocyanobenzene (0.39 g; 87%). m.p 121-123 ºC. IR (NaCl): 2134 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 18.6 Hz, 1H), 5.21 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 134.6, 131.9, 129.7, 128.9.

5.2.2.33. 2-isocyanobenzenethiol.



To a solution of *N*-(2-mercaptophenyl)formamide (0.31 ml; 2mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a yellow liquid 2-isocyanobenzenethiol (0.23 mL; 76%). IR (NaCl): 2127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 153.2, 133.7, 126.2, 125.5, 123.5, 121.9.

5.2.2.34. 2-isocyano-1-methoxy-4-methylbenzene.



To a solution of *N*-(2-methoxy-5-methylphenyl)formamide (0.33 g; 2mmol) in triethylamine (2 mL) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for about 5 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured directly into a dry-packed column. 100 % diethyl ether was used as the mobile phase to afford a colourless liquid 2-isocyano-1-methoxy-4-methylbenzene (0.31 ml; 93%). IR (NaCl): 2136 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 7.00 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 6.71 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 152.7, 130.7, 130.0, 127.6, 111.4, 56.2, 20.0.

5.2.3. General procedure for Passerini product using conventional method.

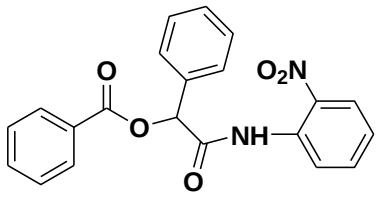
To a solution of 2-formamido-benzothiazole (2 mmol) in triethylamine (5 mmol) and subsequently phosphorus oxychloride (2 mmol) 0.2 mL were added at 0 °C. The reaction mixture was stirred for 5 min. The progress of the reaction was monitored by TLC. After the completion of reaction, DCM (2 ml), benzoic acid (2 mmol), benzaldehyde (2 mmol) were added. The reaction mixture was stirred at room temperature for 24 hours. Upon the completion of reaction as indicated by TLC the resultant mixture was extracted with DCM. The combined organic solution was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification of crude mass on silica gel eluting with DCM) afforded MCR products in good yield.

5.3. Experimental: Chapter 3.1. (Part A)

5.3.1 General Experimental Procedures for Passerini reaction in aqueous media under catalytic condition.

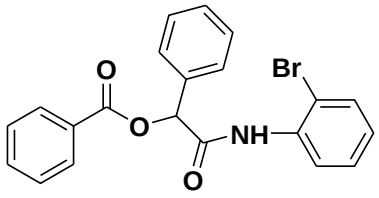
A mixture of benzoic acid (0.122 g, 1 mmol), benzaldehyde (0.10 mL, 1 mmol), and isocyanide (0.15 g 1 mmol) was vigorously stirred in 2 mL of water at room temperature for 10 min in the presence of 0.02 g of immobilized sulfuric acid on silica gel (SiO_2-H_2SO_4). Upon completion, the organic layer was separated and collected by a separating funnel. The combined organic phases were concentrated under reduced pressure, and the residue was purified by column chromatography using DCM/hexane (3:1) as an eluent to afford the desired products. Typical yields ranged from 60 to 98%. All other products (A-W) were obtained by a similar approach.

5.3.1.1. (2-nitrophenylcarbamoyl)(phenyl)methyl benzoate (A).



Prepared from 1-isocyano-2-nitrobenzene (0.15 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol,) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (98% yield); mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H, NH), 8.71 (d, J = 8.4 Hz, 1H, Ar-H), 8.15 (d, J = 9.8 Hz, 1H, Ar-H), 8.04 (d, J = 8.4 Hz, 3H, Ar-H), 7.64–7.48 (m, 2H, Ar-H), 7.39 (t, J = 7.7 Hz, 3H, Ar-H), 7.26 (t, J = 7.7 Hz, 1H, Ar-H), 7.14 (t, J = 7.8 Hz, 1H, Ar-H), 6.72 (d, J = 8.4 Hz, 1H, Ar-H), 6.60 (d, J = 7.2 Hz, 1H, (O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, (NH-CO), 159.8, (O-C=O), 144.6, 136.2, 135.7, 133.8, 133.6, 130.2, 129.3, 128.5, 126.2, 125.9, 124.0, 122.8, 118.7, 116.8. HR-MS (ESI): [M+H$^+$] calculated for $C_{21}H_{17}N_2O_5$: 377.1211, found: 377.2603.

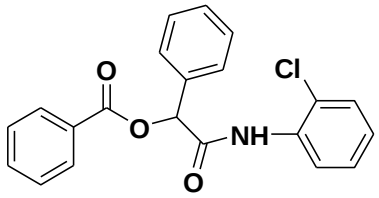
5.3.1.2. (2-bromophenylcarbamoyl)phenyl)methyl benzoate (B).



Prepared from 1-bromo-2-isocyanobenzene (0.18 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol,) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (76% yield); m.p 100–102

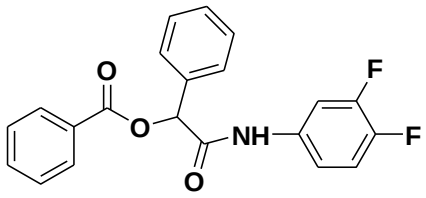
°C; IR (NaCl) v(cm^{-1}) 3253 (NH), 1712 (CO) ester, and 1628 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.31 (d, J = 8.2 Hz, 1H, NH), 8.13 (d, J = 7.3 Hz, 1H, Ar-H), 8.03 (d, J = 7.2 Hz, 2H, Ar-H), 7.52 (dd, J = 15.8, 8.3 Hz, 1H, Ar-H), 7.44–7.29 (m, 3H, Ar-H), 7.20 (t, J = 7.7 Hz, 1H, Ar-H), 6.89 (t, J = 8.3 Hz, 1H, Ar-H), 6.45 (s, 1H, O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, (NH-CO), 164.6, (O-C=O), 135.1, 134.8, 134.0, 133.9, 132.2, 130.4, 130.2, 130.0, 129.3, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 128.1, 128.2, 127.4, 125.7, 121.6, 113.5, 76.2. HR-MS (ESI): [M+H^+] calculated for $C_{21}H_{16}BrNO_3$: 410,0325, found: 410.0331.

5.3.1.3. (2-chlorophenylcarbamoyl)(phenyl)methyl benzoate (C).



Prepared from 1-chloro-2-isocyanobenzene (0.14 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (96% yield); m.p 143–145 °C; IR (NaCl) v(cm^{-1}) 3300 (NH), 1715 (CO) ester, and 1675 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, NH), 8.35 (d, J = 8.2 Hz, 1H, Ar-H), 8.12 (d, J = 7.4 Hz, 2H, Ar-H), 7.56 (t, J = 8.0 Hz, 3H, Ar-H), 7.43 (t, J = 7.7 Hz, 2H, Ar-H), 7.37 (s, 1H, Ar-H), 7.33 (dd, J = 9.8, 7.3 Hz, 3H, Ar-H), 7.28 (d, J = 8.0 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.19–7.15 (m, 1H, Ar-H), 6.97 (dd, J = 11.2, 4.3 Hz, 1H, Ar-H), 6.44 (s, 1H, (O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, (NH-CO), 164.3, (O-C=O), 135.2, 133.9, 133.8, 129.9, 129.0, 128.9, 127.9, 127.4, 125.2, (Ar-Cl), 122.8, 121.3, 76.18 (O-(CH)CO). HR-MS (ESI): [M+H^+] calculated for $C_{21}H_{16}ClNO_3$: 366.0831, found: 366.1302.

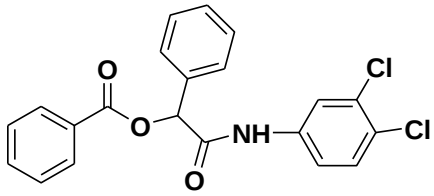
5.3.1.4. (3,4-difluorophenylcarbamoyl)(phenyl)methyl benzoate (D).



Prepared from 1,2-difluoro-4-isocyanobenzene (0.14 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (66% yield); m.p 150–151 °C; IR (NaCl) v(cm^{-1}) 3273 (NH), 1732 (CO) ester, and 1671 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H, (NH), 8.17 (d, J = 7.7 Hz, 1H, Ar-H), 8.11 (d, J = 8.3 Hz, 1H, Ar-H), 7.72–7.57 (m, 2H,

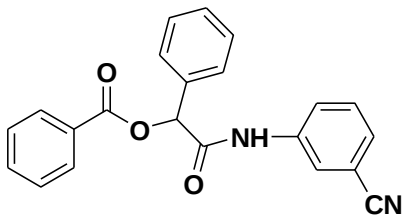
Ar-H), 7.52 (dd, J = 12.6, 4.8 Hz, 1H, Ar-H), 7.46 (dd, J = 10.9, 5.5 Hz, 2H, Ar-H), 7.15–6.98 (m, 1H, Ar-H), 6.45 (s, 1H, (O-(CH)CO).). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, (NH-CO), 165.4, (O-C=O), 151.0 (NH-R-C-F), 148.9, 134.6, 134.0, 133.7, 130.1, 129.9, 129.4, 129.0, 128.7, 128.5, 127.4, 117.3, 109.8, 76.1, (O-(CH)CO). HR-MS (ESI): [M+H+] calculated for $C_{21}H_{15}F_2NO_3$: 368,1015, found: 368.1022.

5.3.1.5. (3,4-dichlorophenylcarbamoyl)phenyl)methyl benzoate (E).



Prepared from 1,2-dichloro-4-isocyanobenzene (0.17 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow solid (73% yield); m.p 152–153 °C; IR (NaCl) v(cm^{-1}) 3273 (NH), 1722 (CO) ester, and 1671 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, NH), 8.05 (d, J = 8.2 Hz, 3H, Ar-H), 7.65 (s, 1H, Ar-H), 7.54 (dd, J = 7.1 Hz, 3H, Ar-H), 7.41 (dd, J = 15.7, 7.9 Hz, 4H, Ar-H), 7.34 (d, J = 6.4 Hz, 2H, Ar-H), 7.27–7.14 (m, 2H, Ar-H), 6.34 (s, 1H, O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, (NH-CO), 165.6, (O-C=O), 136.5, 134.5, 134.0, 133.7, 132.8, 130.4, 130.2, 129.9, 129.5, 129.0, 128.8, 128.7, 128.5, 128.0, 127.5, 121.7, 119.2, 76.2, (O-(CH)CO). HR-MS (ESI): [M+H^+] calculated for $C_{21}H_{15}Cl_2NO_3$: 427.0346, found: 427.1105.

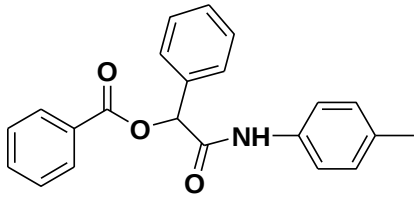
5.3.1.6. (3-cyanophenylcarbamoyl)phenyl)methyl benzoate (F).



Prepared from 3-isocyanobenzonitrile (0.13 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (89% yield); m.p 136–137 °C; IR (NaCl) v(cm^{-1}) 3350 (NH), 1730 (CO) ester, and 1687 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H, NH), 8.14–7.82 (m, 2H, Ar-H), 7.66–7.57 (m, 1H, Ar-H), 7.57–7.51 (m, 2H, Ar-H), 7.48 (t, J = 7.9 Hz, 1H, Ar-H), 7.40 (t, J = 7.7 Hz, 2H, Ar-H), 6.36 (s, 1H, O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, (NH-CO), 167.4, (O-C=O), 133.8, 132.9, 130.7, 130.2, 129.8, 129.4, 128.5, 127.6, 116.6, (C-CN), 113.9, 76.3, (O-(CH)CO). HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{16}N_2O_3$: 357.1172, found:

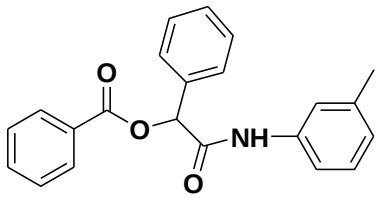
356.9086.

5.3.1.7. (p-tolycarbamoyl)phenyl)methyl benzoate (G).



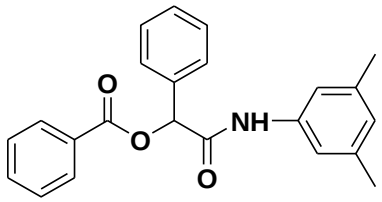
Prepared from 1-isocyano-4-methylbenzene (0.12 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (94% yield); m.p 148–149 °C; IR (NaCl) v(cm^{-1}) 3285 (NH), 1730 (CO) ester, and 1642 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H, NH), 8.07 (d, J = 6.9 Hz, 2H, Ar-H), 7.96 (d, J 6.7 Hz, 1H, Ar-H), 7.71-7.72 (m, 3H, Ar-H), 7.57 (m, 3H Ar-H), 7.48 (s, 6H, Ar-H), 7.10 (s, 2H, Ar-H), 6.26 (s, 1H, O-(CH)CO), 2.23 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 167.8 (NH-C=O), 166.8 (O-C=O), 136.4, 135.7, 134.2, 133.3, 133.2, 131.2, 129.9, 129.7, 129.6, 129.5, 129.3, 129.3, 129.1, 129.0, 127.8, 119.8, 76.3, (O-(CH)CO), 20.8 (CH3). HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{19}NO_3$: 346.1318, found: 346.1315.

5.3.1.8. (*m*-tolylcarbamoyl)(phenyl)methyl benzoate (H).



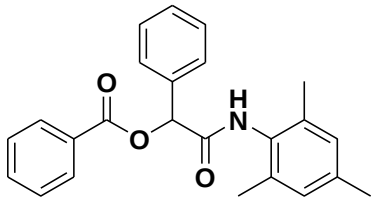
Prepared from 1-isocyano-3-methylbenzene (0.12 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (75% yield); IR (NaCl) v(cm^{-1}) 3273 (NH), 1718 (CO) ester, and 1675 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.4 Hz, 1H, (NH), 7.80 (s, 1H, Ar-H), 7.55 (dd, J = 14.0, 6.9 Hz, 2H, Ar-H), 7.43 (t, J = 7.7 Hz, 1H, Ar-H), 7.40–7.26 (m, 2H, Ar-H), 7.21 (d, J = 8.1 Hz, 1H, Ar-H), 7.11 (t, J = 7.8 Hz, 1H, Ar-H), 6.86 (d, J = 7.5 Hz, 1H), 6.37 (s, 1H, (O-(CH)CO), 2.23 (s, 2H, CH_3), 2.09 (s, 1H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, (NH-CO), 165.0, (O-C=O), 139.0, 138.0, 136.8 (NH-R-CH_3), 135.2, 133.8, 130.4, 129.9, 129.2, 128.9, 128.7, 127.4, 120.7, 117.1, 76.1, (O-(CH)CO), 21.4, (CH_3). HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{19}NO_3$: 346.1340, found: 346.1836.

5.3.1.9. (3,5-dimethylphenylcarbamoyl)(phenyl)methyl benzoate (I).



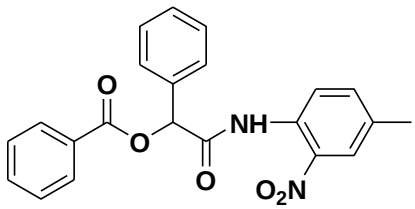
Prepared from 3,5-dimethyl phenyl isocyanide (0.13 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (94% yield); m.p 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H, NH), 8.03 (dd, J = 14.1, 7.5 Hz, 3H, Ar-H), 7.54 (t, J = 7.4 Hz, 2H, Ar-H), 7.40 (t, J = 7.7 Hz, 3H, Ar-H), 7.28 (d, J = 7.1 Hz, 1H, Ar-H), 6.95–6.84 (m, 1H, Ar-H), 6.82 (t, J = 7.4 Hz, 1H, Ar-H), 6.75 (d, J = 8.1 Hz, 1H, Ar-H), 6.32 (s, 1H, (O-(CH)CO), 4.44 (d, J = 5.9 Hz, 1H, CH_3), 3.61 (s, 1H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, NH(CO), 164.7, (O-C=O), 135.5, 133.7, 130.2, 129.8, 129.3, 128.9, 128.6, 127.5, 120.8, 110.2, 75.9, (O-(CH)CO), 55.1, 40.0. HR-MS (ESI): [M+H$^+$] calculated for $C_{23}H_{21}NO_3$: 361.1522, found: 361.1936.

5.3.1.10. (mesitylcarbamoyl)(phenyl)methyl benzoate (J).



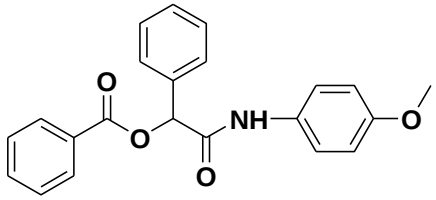
Prepared from 2-isocyano-1,3,5-trimethylbenzene (0.15 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a colorless liquid (60% yield); IR (NaCl) ν(cm^{-1}) 3257 (NH), 1730 (CO) ester, and 1604 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 6.77 (m, 3H), 2.25 (s, 7H), 2.17 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 162.3, 138.8, 136.4, 134.5, 133.8, 131.3, 130.5, 129.6, 129.3, 128.8, 128.4, 126.9, 21.1, 18.7. HR-MS (ESI): [M+H$^+$] calculated for $C_{24}H_{23}NO_3$: 374.1655, found: 374.2118.

5.3.1.11. (4-methyl-2-nitrophenylcarbamoyl)phenyl)methylbenzoate (K).



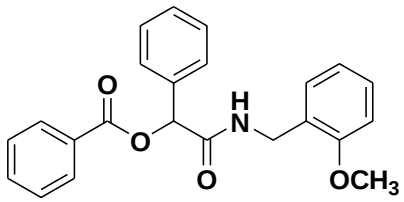
Prepared from 4-methyl-2-nitro phenyl isocyanide (0.16 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow solid (92% yield); m.p 126–129 °C; IR (NaCl) v(cm^{-1}) 3343 (NH), 1694 (CO) ester, and 1641 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H, NH), 8.60 (d, J = 8.6 Hz, 1H, Ar-H), 8.19 (d, J = 7.3 Hz, 2H, Ar-H), 7.95 (s, 1H, Ar-H), 7.56 (d, J = 7.7 Hz, 3H Ar-H), 7.35 (d, J = 7.6 Hz, 4H, Ar-H), 7.11 (d, J = 10.2 Hz, 2H, Ar-H), 6.66 (d, J = 8.5 Hz, 2H, Ar-H), 6.43 (s, 1H, O-(CH)CO), 2.42 (s, 3H, CH3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, (NH-CO), 167.5, (O-C=O), 143.9, 142.7, 137.2, 136.3, 135.0, 134.3, 133.8, 131.8, 130.0, 129.5, 128.7, 127.1, 126.6, 125.2, 122.0, 118.8, 76.3, (O-(CH)CO), 21.3. HR-MS (ESI): [M+H+] calculated for $C_{22}H_{18}N_2O_5$: 391.1383, found: 391.3062.

5.3.1.12. (4-methoxyphenylcarbamoyl)phenyl)methyl benzoate (L).



Prepared from 1-isocyano-4-methoxy benzene (0.13 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (94% yield); IR (NaCl) v(cm^{-1}) 3293 (NH), 1734 (CO) ester, and 1671 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 10.42 (s, 1H, NH), 8.08 (d, J = 7.2 Hz, 2H, Ar-NH), 7.70 (d, J = 7.3 Hz, 3H), 7.58 (t, J = 7.7 Hz, 2H), 7.52–7.46 (m, 4H), 7.43 (dd, J = 14.5, 7.4 Hz, 2H), 6.88 (d, J = 9.1 Hz, 2H), 6.22 (s, 1H, O-(CH)CO), 3.70 (s, 3H, OCH3). ^{13}C NMR (101 MHz, DMSO) δ 166.5 (NHC=O), 165.6 (O-C=O), 155.9 (R-C-O-CH_3), 135.8, 134.2, 132.0, 129.9, 129.7, 129.5, 129.3, 129.1, 129.0, 127.8, 121.2, 114.3, 76.2 (O-(CH)CO), 55.6 (OCH_3). HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{19}NO_4$: 362.1346, found: 362.1319.

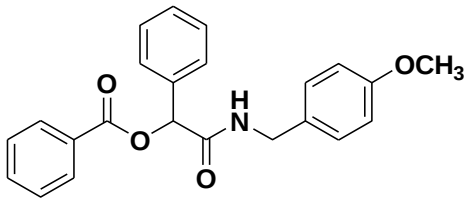
5.3.1.13. (2-methoxybenzylcarbamoyl)phenyl)methyl benzoate (M).



Prepared from 1-(isocyanomethyl)-2-methoxybenzene (0.15 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a colorless liquid (94% yield); IR (NaCl)

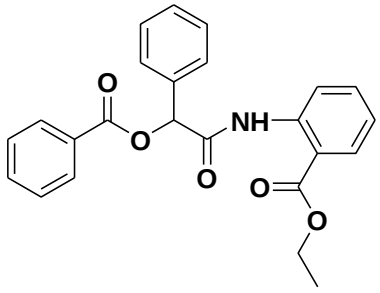
v(cm^{-1}) 3273 (NH), 1722 (CO) ester, and 1663 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.04 (m, 1H, NH), 8.02 (dd, J = 8.4, 1.2 Hz, 1H, Ar-H), 7.60–7.49 (m, 1H, Ar-H), 7.48–7.35 (m, 2H, Ar-H), 7.29 (d, J = 7.0 Hz, 1H, Ar-H), 7.23–7.12 (m, 1H, Ar-H), 6.83 (td, J = 7.4, 0.7 Hz, 1H, Ar-H), 6.76 (d, J = 8.2 Hz, 1H, Ar-H), 6.30 (s, 1H, O-(CH)CO)), 4.44 (d, J = 5.9 Hz, 1H, (NH-CH-R), 3.67 (d, J = 6.2 Hz, 1H, (NH-CH-R), 3.63 (s, 1H, O-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, (NH-CO), 167.9, (O-C=O), 157.6, (C-O-CH_3), 135.7, 133.7, 130.2, 129.8, 129.3, 128.9, 128.7, 128.6, 127.4, 125.5, 120.8, 110.2, 75.9, (O-(CH)CO), 55.1, (O-CH_3) 39.9, (NH-(CH_2)R. HR-MS (ESI): [M+H^+] calculated for $C_{23}H_{21}NO_4$: 376.1435, found: 376.1560.

5.3.1.14. (4-methoxybenzylcarbamoyl)phenyl)methyl benzoate (N).



Prepared from 1-(isocyanomethyl)-4-methoxybenzene (0.15 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (98% yield); m.p 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, NH), 8.09–7.93 (m, 2H, Ar-H), 7.47 (dt, J = 15.6, 9.4 Hz, 1H, Ar-H), 7.43–7.31 (m, 2H, Ar-H), 7.26–7.16 (m, 1H, Ar-H), 7.08 (dd, J = 14.6, 9.1 Hz, 1H, Ar-H), 6.80–6.55 (m, 1H, Ar-H), 6.25 (d, J = 30.0 Hz, 1H, (O-(CH)CO), 4.69 (s, 1H, OCH_3), 4.62 (s, 1H), 4.36–4.28 (m, 1H, (NH-CH-R), 3.68–3.62 (m, 1H, (NH-CH-R). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, (NH-CO), 161.8, (O-C=O), 159.1, 143.0, 133.7, 130.4, 130.1, 129.5, 129.2, 129.0, 128.8, 128.4, 127.8, 127.4, 123.3, 114.4, 114.3, 114.1, 114.1, 113.9, 76.0, (O-(CH)CO), 55.2, (OCH_3), 41.8, (NH-CH_2). HR-MS (ESI): [M+H^+] calculated for $C_{23}H_{21}NO_4$: 376.1402, found: 376.2408.

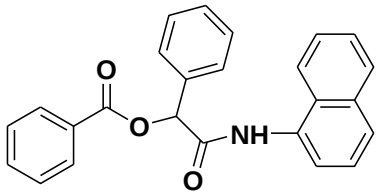
5.3.1.15. ethyl 2-[2-(benzoyloxy)-2-phenylacetamido]benzoate (O).



Prepared from ethyl-2 isocyanobenzoate (0.18 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column

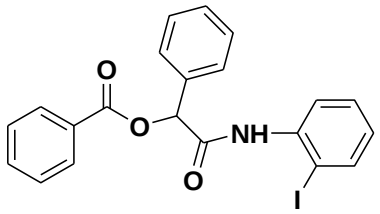
chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (88% yield); m.p 130–132 °C; IR (NaCl) v(cm^{-1}) 3242 (NH), 1730 (CO) ester, and 1683 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H, NH), 8.65 (d, J = 8.6 Hz, 1H, Ar-H), 8.27 (d, J = 7.5 Hz, 2H, Ar-H), 7.93 (dd, J = 14.6, 8.6 Hz, 1H, Ar-H), 7.59 (d, J = 7.2 Hz, 2H Ar-H), 7.53 (t, J = 7.4 Hz, 1H, Ar-H), 7.48–7.36 (m, 4H, Ar-H), 7.37–7.24 (m, 3H, Ar-H), 7.01 (t, J = 7.6 Hz, 1H, Ar-H), 6.38 (s, 1H, O-(CH)CO), 4.37 (q, J = 7.1 Hz, 1H, CH), 4.31–4.19 (m, 2H, CH2), 1.29 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 O-C=O benzoate), 167.4 (NH-CO), 165.0 (O-C=O ester), 140.8, 135.7, 134.5, 133.5, 131.3, 130.7, 129.2, 128.8, 128.3, 127.2, 123.0, 120.5, 115.8, 62.0, 61.4, 14.1. HR-MS (ESI): [M+H+] calculated for $C_{25}H_{21}NO_6$: 431.1317, found: 431.1020.

5.3.1.16. (naphthalen-3-ylcarbamoyl)(phenyl)methyl benzoate (P).



Prepared from 1-isocyanonaphthalene (0.15 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white powder (80% yield); m.p 171–172 °C; IR (NaCl) v(cm^{-1}) 3422 (NH), 1713 (CO) ester, and 1623 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 8.15 (d, J = 7.4 Hz, 1H, (NH), 7.99–7.90 (m, 1H, Ar-H), 7.85 (d, J = 7.3 Hz, 1H, Ar-H), 7.80 (d, J = 8.0 Hz, 1H, Ar-H), 7.77–7.67 (m, 1H, Ar-H), 7.59 (dd, J = 9.7, 5.6 Hz, 2H, Ar-H), 7.57–7.51 (m, 1H, Ar-H), 7.52–7.43 (m, 1H, Ar-H), 6.53 (s, 1H, O-(CH)CO). ^{13}C NMR (101 MHz, DMSO) δ 168.1, (NH-CO), 165.8, (O-C=O), 136.0, 134.2, 134.1, 133.1, 130.0, 129.6, 129.4, 129.3, 129.2, 128.6, 128.6, 127.9, 126.6, 126.4, 126.0, 122.9, 122.8, 76.4, (O-(CH)CO). HR-MS (ESI): [$M+H^+$] calculated for $C_{25}H_{20}NO_3$: 382.1339, found: 382.1316.

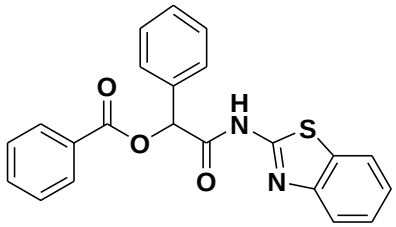
5.3.1.17. (2-iodophenylcarbamoyl)phenyl)methyl benzoate (Q).



Prepared from 1-iodo-2-isocyanobenzene (0.23 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a green solid (85% yield); m.p 104–106

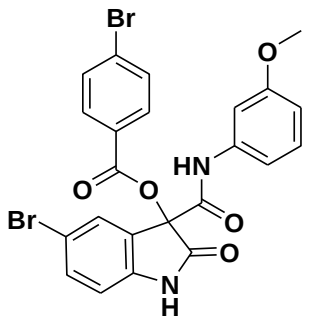
°C; IR (NaCl) v(cm^{-1}) 3249 (NH), 1730 (CO) ester, and 1679 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, NH), 8.24 (d, J = 8.3 Hz, 1H, Ar-H), 8.18 (d, J = 7.2 Hz, 2H, Ar-H), 7.82 (d, J = 8.0 Hz, 1H, Ar-H), 7.69 (d, J = 6.7 Hz, 2H, Ar-H), 7.57 (t, J = 7.6 Hz, 4H, Ar-H), 7.43 (t, J = 7.7 Hz, 3H, Ar-H), 7.27 (dd, J = 12.1, 4.8 Hz, 2H, Ar-H), 7.08–7.01 (m, 1H, Ar-H), 6.79 (td, J = 7.9, 1.5 Hz, 2H, Ar-H), 6.46 (s, 1H, O-(CH)CO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, (NH-CO), 164.8, (O-C=O), 139.5, 138.8, 137.3, 135.2, 133.9, 130.4, 130.2, 129.4, 129.3, 128.8, 128.6, 127.6, 127.4, 126.4, 121.6, 76.1, O-(CH)CO). HR-MS (ESI): [M+H^+] calculated for $C_{21}H_{16}INO_3$: 458.0158, found: 458.0715.

5.3.1.18. (benzo[d]thiazol-2-ylcarbamoyl)(phenyl)methyl benzoate (R).



Prepared from 2-isocyanobenzo[d]thiazole (0.16 g, 1 mmol), benzaldehyde (0.11 mL, 1 mmol), and benzoic acid (0.122 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a white solid (63% yield); m.p 122–124 °C; IR (NaCl) v(cm^{-1}) 3286 (NH), 1710 (CO) ester, and 1679 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H, NH), 8.09 (d, J = 7.4 Hz, 1H, Ar-H), 7.96 (d, J = 7.4 Hz, 1H, Ar-H), 7.79 (d, J = 7.6 Hz, 1H, Ar-H), 7.61 (t, J = 7.5 Hz, 1H, Ar-H), 7.57–7.50 (m, 1H, Ar-H), 7.45 (dd, J = 16.4, 8.4 Hz, 2H, Ar-H), 7.33 (t, J = 7.6 Hz, 1H, Ar-H), 7.25 (t, J = 9.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, (NH-CO), 164.3, (O-C=O), 161.3, (Ar-C=S), 133.5, 132.1, 130.9, 130.7, 129.5, 129.2, 128.9, 128.8, 128.0, 127.9, 126.7, 125.2, 123.0, 122.0, 120.6, 120.5, 119.7. HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{17}N_2O_3S$: 389.0861, found: 389.2442.

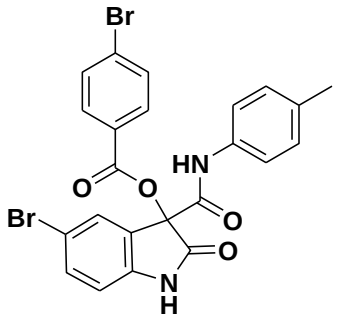
5.3.1.19. 3-(3-methoxyphenylcarbamoyl)-5-bromo-2-oxoindolin-3-yl 4-bromobenzoate (S).



Prepared from 1-isocyano-3-methoxybenzene (1.33 mL, 1 mmol), 5-bromo isatin (0.23 g, 1 mmol), and 4-bromobenzoic acid (0.21 g, 1 mmol) according to the general procedure. Purification: column

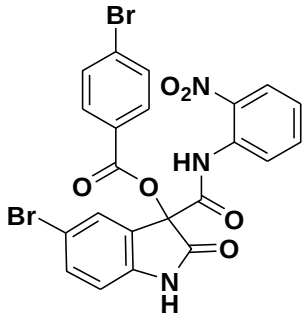
chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (90% yield); IR (NaCl) v(cm^{-1}) 3286 (NH), 1710 (CO) ester, and 1679 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H, (NH-amide)), 8.75 (s, 1H, (NH-indole)), 7.98 (dd, J = 14.9, 7.7 Hz, 3H, (Ar-H), 7.49 (dd, J = 12.7, 7.2 Hz, 2H, (Ar-H)), 7.35 (dd, J = 16.1, 8.2 Hz, 2H, (Ar-H)), 7.16 (dd, J = 6.0, 8.0 Hz, 3H, (Ar-H)), 6.97 (dd, J = 17.5, 8.8 Hz, 2H, (Ar-H)), 6.85 (d, J = 7.8 Hz, 1H, (Ar-H)), 6.62 (dd, J = 8.2, 1.7 Hz, 1H, (Ar-H)), 5.18 (s, NH-indole), 3.68 (s, 3H, (O-CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, (-CO-indole), 171.0, (-CO-ester), 163.8, (CO-amide), 161.8, (C-OCH_3), 160.2, 142.3, 138.3, 134.3, 133.4, 131.1, 130.1, 129.7, 128.7, 128.4, 124.9, 123.4, 112.3, 111.4, 105.6, 55.3. HR-MS (ESI): [M+H^+] calculated for $C_{23}H_{18}Br_2N_2O_6$: 575.9202, found: 575.6714.

5.3.1.20. 3-(p-tolylcarbamoyl)-5-bromo-2-oxoindolin-3-yl 4-bromobenzoate (T).



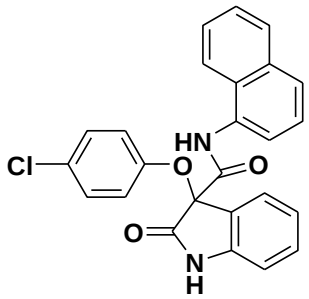
Prepared from 1-isocyano-4-methylbenzene (0.13 mL, 1 mmol) 5-bromo isatin (0.23 g, 1 mmol), and 4-bromobenzoic acid (0.21 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as yellow liquid (76% yield); IR (NaCl) v(cm^{-1}) 3244 (NH), 1718 (CO) ester, and 1682 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.12 (d, J = 40.1 Hz, 1H, NH-amide), 10.09 (d, J = 23.3 Hz, 1H, NH-indole), 8.71 (d, J = 11.1 Hz, 1H, (Ar-H), 8.23 (s, 1H, Ar-H), 7.87 (d, J = 8.4 Hz, 1H, Ar-H), 7.77–7.61 (m, 1H, Ar-H), 7.47 (d, J = 8.3 Hz, 2H, Ar-H), 7.09 (dd, J = 17.5, 8.0 Hz, 3H, Ar-H), 6.87 (d, J = 8.3 Hz, 1H, Ar-H), 2.25 (s, 3H, CH3). ^{13}C NMR (101 MHz, DMSO) δ 167.1 (CO-indole), 162.9 (CO-amide), 159.8 (CO-ester), 159.4, 140.4, 136.2, 133.1, 133.0, 132.1, 131.7, 130.2, 129.7, 127.3, 119.5, 118.1, 114.7, 20.9. HR-MS (ESI): [M+H^+] calculated for $C_{23}H_{16}Br_2N_2O_4$: 541.9416, found: 541.4483.

5.3.1.21. 3-(2-nitrophenylcarbamoyl)-5-bromo-2-oxoindolin-3-yl 4-bromobenzoate (U).



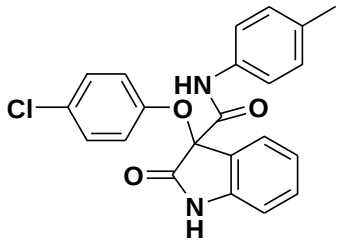
Prepared from 1-isocyano-2-nitrobenzene (0.15 g, 1 mmol), 5-bromo isatin (0.23 g, 1 mmol), and 4-bromobenzoic acid (0.21 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (85% yield); IR (NaCl) v(cm^{-1}) 3280 (NH), 1712 (CO) ester, and 1676 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, NH-amide), 8.20 (d, J = 8.2 Hz, 1H NH-indole), 7.93 (d, J = 8.6 Hz, 3H, Ar-H), 7.88–7.80 (m, 3H, Ar-H), 7.73 (t, J = 7.6 Hz, 1H, Ar-H), 7.66 (d, J = 8.4 Hz, 1H, Ar-H), 7.55 (t, J = 7.7 Hz, 1H, Ar-H), 7.49–7.41 (m, 6H, Ar-H), 7.36 (t, J = 7.7 Hz, 4H, Ar-H), 7.01 (t, J = 6.8 Hz, 4H, Ar-H), 6.87 (t, J = 11.5 Hz, 1H, Ar-H), 6.58 (t, J = 7.7 Hz, 3H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.86 (-CO-indole), 172.4 (-CO-ester), 167.1 (-CO-amide), 159.8 (-C-NO2), 151.1, 146.6, 144.1, 138.7, 136.1, 135.5, 132.0, 131.7, 130.6, 127.3, 125.8, 125.0, 123.1, 119.6, 115.8, 112.6. HR-MS (ESI): [M+H+] calculated for $C_{22}H_{13}Br_2N_3O_6$: 575.9320, found: 575.6714.

5.3.1.22. 3-(4-chlorophenoxy)-N-(naphthalen-1-yl)-2-oxoindoline-3-carboxamide (V).



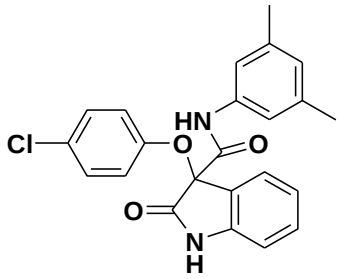
Prepared from 1-isocyano-naphthalein (0.15 mL, 1 mmol), isatin (0.147 g, 1 mmol), and 4-chlorophenol (0.13 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (80% yield); IR (NaCl) v(cm^{-1}) 3295 (NH), 1053 (CO), and 1679 (CO) amide. 1H NMR (400 MHz, DMSO) δ 11.06 (s, 2H, NH-amide), 10.34 (s, 1H, NH-indole), 9.71 (s, 1H, Ar-H), 8.59 (d, J = 10.5 Hz, 1H, Ar-H), 8.49 (s, 1H, Ar-H), 8.22–8.05 (m, 1H, Ar-H), 7.98 (dd, J = 25.7, 7.5 Hz, 1H, Ar-H), 7.83 (dd, J = 26.9, 7.8 Hz, 1H, Ar-H), 7.72 (dd, J = 16.1, 7.8 Hz, 1H, Ar-H), 7.58 (t, J = 7.6 Hz, 3H, Ar-H), 7.50 (d, J = 7.3 Hz, 2H, Ar-H), 7.19 (d, J = 8.8 Hz, 2H, Ar-H), 7.06 (t, J = 7.5 Hz, 2H, Ar-H), 6.91 (d, J = 7.9 Hz, 2H, Ar-H), 6.77 (d, J = 8.8 Hz, 2H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (CO-indole), 160.7 (CO-amide), 159.8, 156.7, 151.1, 138.8, 134.1, 133.0, 129.6, 128.8, 126.5, 126.1, 125.2, 125.1, 123.2, 122.7, 122.2, 119.7, 118.2, 117.3, 112.6. HR-MS (ESI): [M+H+] calculated for $C_{22}H_{13}Br_2N_3O_6$: 573.93, found: 573.80.

5.3.1.23. 3-(4-chlorophenoxy)-2-oxo-N-p-tolylindoline-3-carboxamide (W).



Prepared from 1-isocyano-4-methylbenzene (0.13 mL, 1 mmol), isatin (0.147 g, 1 mmol), and 4-chlorophenol (0.13 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (87% yield); IR (NaCl) v (cm^{-1}) 3259 (NH), 1048 (CO), and 1680 (CO) amide. 1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, NH-amide), 10.11 (s, 1H, NH-indole), 9.72 (s, 2H, Ar-H), 8.71 (d, J = 11.1 Hz, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 7.58 (t, J = 7.7 Hz, 1H, Ar-H), 7.55–7.41 (m, 2H, Ar-H), 7.19 (d, J = 8.7 Hz, 4H, Ar-H), 7.14–6.99 (m, 3H, Ar-H), 6.91 (d, J = 7.9 Hz, 1H, Ar-H), 6.77 (d, J = 8.7 Hz, 4H, Ar-H), 2.25 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (CO-indole), 162.9 (CO-amide), 159.8, 156.7, 151.1, 138.8, 136.2, 133.1, 129.6, 125.1, 123.2, 122.7, 119.5, 118.2, 117.3, 112.6, 20.9. HR-MS (ESI): [M+H^+] calculated for $C_{22}H_{17}ClN_2O_3$: 573.0911, found: 393.2902.

5.3.1.24. 3-(4-chlorophenoxy)-N-(3,5-dimethylphenyl)-2-oxoindoline-3-carboxamide (X).



Prepared from 1-isocyano-3,5-dimethylbenzene (0.131 mL, 1 mmol), isatin (0.147 g, 1 mmol), and 4-chlorophenol (0.13 g, 1 mmol) according to the general procedure. Purification: column chromatography on silica gel (3:1 DCM/hexane). Isolated as a yellow liquid (87% yield); IR (NaCl) v(cm^{-1}) 3283 (NH), 1050 (CO), and 1679 (CO) amide. 1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, NH-indole), 10.05 (s, 1H, NH-amide), 9.72 (s, 2H, Ar-H), 8.75 (d, J = 11.0 Hz, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 7.59 (t, J = 7.7 Hz, 1H, Ar-H), 7.50 (d, J = 7.4 Hz, 1H, Ar-H), 7.19 (d, J = 8.8 Hz, 6H, Ar-H), 7.07 (t, J = 7.5 Hz, 1H, Ar-H), 6.91 (d, J = 7.8 Hz, 1H, Ar-H), 6.78 (t, J = 8.7 Hz, 5H, Ar-H), 6.71 (s, 1H, Ar-H), 2.23 (s, 5H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (CO-indole), 159.9 (CO-amide), 159.8, 156.7, 151.1, 138.8, 138.5, 138.3, 129.6, 125.6, 125.1, 123.2, 122.7, 118.2, 117.3, 117.2, 115.6, 112.6, 21.5. HR-MS (ESI): [M+H^+] calculated for $C_{23}H_{19}ClN_2O_3$: 406.1136, found: 406.4155.

5.4 Experimental for Chapter 3, part two.

5.4.1. General Experimental Procedures for the Aqua Synthesis of Oxindole derivatives (4a, 5a–i,).

A mixture of benzoic acid (1a, 1b, 1 mmol) indole-2,3-dione (0.10 mL, 1 mmol), and isocyanide (1 mmol) was vigorously stirred in 2 mL water at room temperature for 15 minutes. Upon completion, the organic layer was separated and collected by a separating funnel. The combined organic phases were concentrated under reduced pressure and the residue was purified by column chromatography using DCM/Hexane (3: 1) as eluent to afford the desired products. Typical yields range from 60 to 98%. All other products (A-T) were obtained by similar approach.

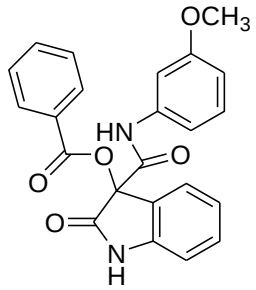
5.4.2. General Procedures for the Aqua Synthesis of Oxindole derivatives (6a–o,) in the presence of catalyst.

A mixture of 3,5-dibromo salicylic acid (1c, 1 mmol) indole-2,3-dione (1 mmol), and isocyanide (1 mmol) was vigorously stirred in 2 mL water at room temperature for 15 minutes in the presence of 0.02g of immobilized sulfuric acid on silica gel. Upon completion, the organic layer was separated and collected by separating funnel. The combined organic phases were concentrated under reduced pressure and the residue was purified by column chromatography using DCM/Hexane (3: 1) as eluent to afford the desired products.

5.4.3. General Procedure for the Mechanochemical Synthesis of Oxindole derivatives (4a, 5a–i, 6a-o).

A mixture of benzoic acid (1 mmol), indole-2,3-dione (1 mmol), isocyanides (1 mmol), and additive (water 100 μL) was milled in a 13.2 mL stainless steel milling vessel containing two balls of the same material (diameter: 6 mm; mass: 0.90 g) at 25 Hz for 15 min. After the milling was complete, the content of in the milling vessel was transferred into a beaker using a small amount of organic solvent (DCM). Then, purification was done by column chromatography to afford the corresponding oxindole derivatives in high yield.

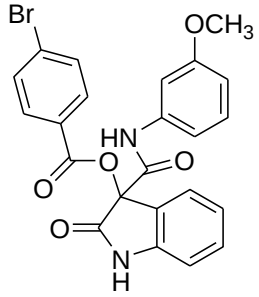
5.4.3.1. 3-(3-methoxyphenylcarbamoyl)-2-oxoindolin-3-yl benzoate (4a).



yellow liquid (Yield: Exp A 80%, Exp B, 97%); IR (NaCl) ν(cm^{-1}) 3324 (NH), 1730 (CO) ester, and 1643 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 33.8 Hz, 1H, NH amide), 8.75 (s, 1H NH-

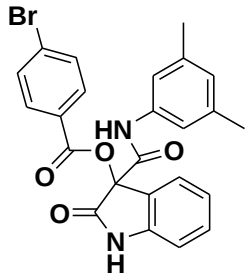
indole), 8.08 – 7.84 (m, 4H, Ar-H), 7.56 – 7.42 (m, 2H, Ar-H), 7.43 – 7.26 (m, 6H, Ar-H), 7.23 – 7.07 (m, 3H, Ar-H), 7.07 – 6.91 (m, 2H, Ar-H), 6.82 (dd, *J* = 25.3, 6.5 Hz, 1H, Ar-H), 6.65 – 6.52 (m, 1H, Ar-H), 5.18 (s, 1H), 3.73 – 3.64 (m, 3H, O-CH_3). 13C NMR (101 MHz, DMSO) δ 173.4 (-CO-indole), 171.0 (-CO-ester), 163.9 (-CO-amide), 160.1 (-C-O-CH_3), 142.3, 138.2, 134.2, 133.5, 130.1, 129.9, 129.6, 128.9, 128.4, 127.9, 124.9, 123.4, 112.3, 111.4, 105.6, 81.7, 55.3 (O-CH_3), 31.0. HR-MS (ESI): [M+H^+] calcd for $C_{23}H_{18}N_2O_5$: 403.4013, found: 403.4026.

5.4.3.2. 3-(3-methoxyphenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5a).



yellow liquid (Yield: Exp A 88%, Exp B, 97%); IR (NaCl) *v*(cm^{-1}) 3355 (NH), 1747 (CO) ester, and 1639 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H, NH-amide), 8.84 (d, *J* = 10.6 Hz, 1H, NH-indole), 8.62 (d, *J* = 11.4 Hz, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 7.87 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.54 – 7.37 (m, 1H, Ar-H), 7.27 – 7.05 (m, 3H, Ar-H), 6.99 (dd, *J* = 15.0, 7.7 Hz, 1H, Ar-H), 6.85 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.71 – 6.50 (m, 2H, Ar-H), 3.71 (d, *J* = 9.4 Hz, 3H, O-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8 (-CO-indole), 169.2 (-CO-ester), 163.1 (-CO-amide), 160.6 (C-OCH_3), 159.6, 149.9, 138.7, 138.1, 137.9, 131.7, 130.6, 129.8, 125.6, 123.8, 117.9, 112.7, 112.2, 110.9, 105.9, 104.8, 55.4 (O-CH_3). HR-MS (ESI): [M+H^+] calcd for $C_{23}H_{17}BrN_2O_5$: 481.3002, found: 481.3075.

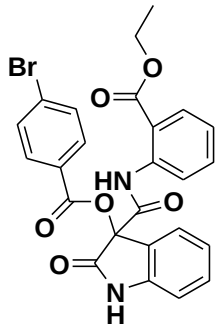
5.4.3.3. 3-(3,5-dimethylphenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5b).



yellow liquid (Yield: Exp A 79%, Exp B, 92%); IR (NaCl) *v*(cm^{-1}) 3328 (NH), 1726 (CO) ester, and 1614 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H, NH-amide), 8.60 (d, *J* = 11.5 Hz, 1H, NH-indole), 8.41 – 8.17 (m, 2H, Ar-H), 7.90 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.53 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.23 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.89 – 6.78 (m, 1H, Ar-H), 6.78

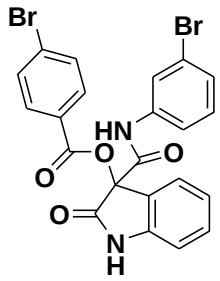
(d, J = 11.9 Hz, 1H, Ar-H), 6.74 – 6.67 (m, 1H, Ar-H), 6.68 – 6.58 (m, 2H, Ar-H), 6.55 (s, 1H, Ar-H), 6.37 (s, 1H, Ar-H), 6.29 (s, 1H, Ar-H), 5.23 (s, 1H, Ar-H), 2.20 (d, J = 35.7 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (-CO-indole), 162.9 (-CO-ester), 159.0 (-CO-amide), 140.2, 139.6, 139.0, 138.9, 136.6, 134.1, 131.7, 127.0, 126.5, 122.7, 120.8, 117.7, 115.2, 113.3, 111.6, 21.2 (CH_3). HR-MS (ESI): [M+H^+] calcd for $C_{24}H_{19}BrN_2O_4$: 480.3318, found: 480.3327.

5.4.3.4. {[2-(ethoxycarbonyl)phenyl]carbamoyl}-2-oxo-2,3-dihydro-1H-indol-3-yl 4-bromobenzoate (5c).



yellow liquid (Yield: Exp A 93%, Exp B, 98%); IR (NaCl) ν(cm^{-1}) 3324 (NH), 1713 (CO) ester, and 1690 (CO) amide. ^1H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H, NH-amide), 10.41 (d, J = 9.7 Hz, 1H, NH-indole), 8.80 (dd, J = 25.1, 8.7 Hz, 1H, Ar-H), 8.56 (d, J = 8.5 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 7.87 (dd, J = 18.7, 7.8 Hz, 2H, Ar-H), 7.45 – 7.28 (m, 3H, Ar-H), 6.97 (t, J = 7.7 Hz, 1H, Ar-H), 4.30 (q, J = 7.1 Hz, 1H), 4.25 (d, J = 7.1 Hz, 2H), 1.34 – 1.20 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8 (-CO-indole), 169.5 (-CO-ester), 167.8, (-CO-ester), 166.9 (-CO-amide), 163.9 (C-COO-), 161.4, 159.6, 150.2, 140.3, 138.4, 134.3, 132.9, 131.7, 130.7, 129.2, 127.8, 125.3, 123.2, 122.9, 120.9, 117.8, 61.8 (O-CH_2), 14.0 (CH_3). HR-MS (ESI): [M+H^+] calcd for $C_{25}H_{19}BrN_2O_6$: 522.2404, found: 522.2418.

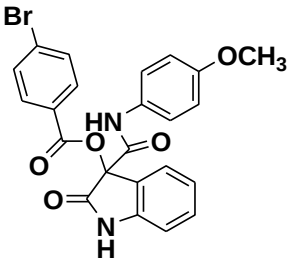
5.4.3.5. 3-(3-bromophenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5d).



yellow liquid (Yield: Exp A 90%, Exp B, 95%); IR (NaCl) ν(cm^{-1}) 3332 (NH), 1738 (CO) ester, and 1679 (CO) amide. ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 11.2 Hz, 1H), 8.44 (s, 1H, NH-amide), 8.34 (d, J = 8.2 Hz, 2H, NH-indole), 7.66 (s, 3H, Ar-H), 7.37 (d, J = 8.0 Hz, 1H, Ar-H), 7.32 (d, J = 8.0 Hz, 2H, Ar-H), 7.22 (t, J = 8.4 Hz, 2H, Ar-H), 7.13 – 7.04 (m, 1H, Ar-H), 7.01 (t, J = 7.7 Hz, 2H, Ar-

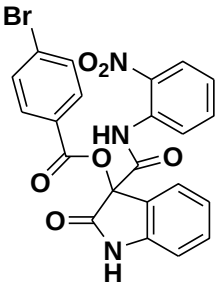
H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (-CO-indole), 158.8 (-CO-ester, amide), 144.0, 141.3, 138.6, 133.6, 130.3, 129.5, 128.0, 127.8, 125.9, 125.1, 124.1, 122.5, 121.9, 118.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{22}H_{14}Br_2N_2O_4$: 531.1017, found: 531.1025.

5.4.3.6. 3-(4-methoxyphenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5e).



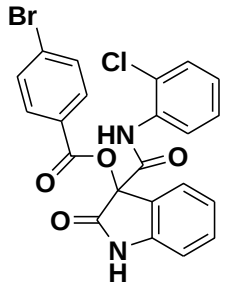
yellow liquid (Yield: Exp A 75%, Exp B, 90%); IR (NaCl) ν(cm^{-1}) 3352 (NH), 1780 (CO) ester, and 1671 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 11.4 Hz, 1H NH-amide), 8.53 – 8.42 (m, 1H), 8.29 (s, 1H, NH-amide), 7.62 (s, 1H, NH-ester), 7.21 – 7.17 (m, 1H, Ar-H), 7.17 – 7.10 (m, 1H, Ar-H), 6.95 (d, J = 8.0 Hz, 1H, Ar-H), 6.66 (d, J = 2.0 Hz, 1H, Ar-H), 6.66 – 6.59 (m, 2H, Ar-H), 6.56 (s, 1H), 3.74 (s, 3H, O-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (-CO-indole), 160.6 (-CO-ester), 160.1 (-CO-amide), 159.2 (C-OCH_3), 138.6, 138.1, 137.9, 130.6, 129.8, 125.7, 123.8, 112.6, 112.0, 110.9, 110.5, 110.4, 105.8, 104.8, 55.4 (OCH_3). [M+H$^+$] calcd for $C_{23}H_{17}BrN_2O_5$: 481.3330, found: 481.3326.

5.4.3.7. 3-(2-nitrophenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5f).



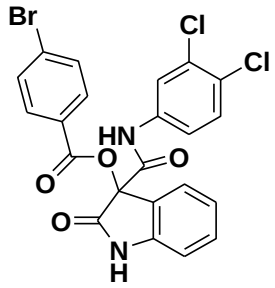
yellow liquid (Yield: Exp A 93%, Exp B, 98%); IR (NaCl) ν(cm^{-1}) 3359 (NH), 1703 (CO) ester, and 1628 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, NH-amide), 8.20 (d, J = 8.2 Hz, 1H NH-indole), 7.93 (d, J = 8.6 Hz, 2H, Ar-H), 7.88 – 7.80 (m, 2H, Ar-H), 7.73 (t, J = 7.6 Hz, 1H, Ar-H), 7.66 (d, J = 8.4 Hz, 1H, Ar-H), 7.55 (t, J = 7.7 Hz, 1H, Ar-H), 7.49 – 7.41 (m, 2H, Ar-H), 7.36 (t, J = 7.7 Hz, 2H, Ar-H), 7.01 (t, J = 6.8 Hz, 1H, Ar-H), 6.87 (t, J = 11.5 Hz, 1H, Ar-H), 6.58 (t, J = 7.7 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 172.4 (-CO-ester), 167.1 (-CO-amide), 159.8 (-C-NO_2), 151.1, 146.6, 144.1, 138.7, 136.1, 135.5, 132.0, 131.7, 130.6, 127.3, 126.1, 125.8, 123.1, 119.6, 115.8, 112.6. [M+H$^+$] calcd for $C_{22}H_{14}BrN_3O_6$: 495.1465, found: 495.1499.

5.4.3.8. 3-(2-chlorophenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5g).



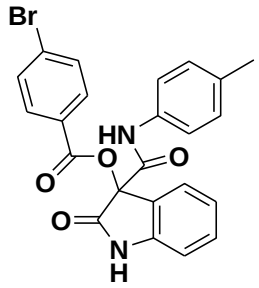
yellow liquid (Yield: Exp A 86%, Exp B, 94%); IR (NaCl) ν(cm^{-1}) 3308 (NH), 1718 (CO) ester, and 1629 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.37 (s, 1H -NH-amide), 8.12 (d, *J* = 8.1 Hz, 1H, -NH-indole), 7.87 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.70 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.57 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.49 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.33 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.15 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.05 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.91 (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 167.1 (-CO-ester), 164.0 (-CO-amide), 160.8, 159.8, 151.1, 138.8, 134.7, 132.1, 131.7, 130.5, 129.9, 128.6, 127.3, 126.3, 125.9, 123.9, 118.2, 112.6. [M+H^{+}] calcd for $C_{22}H_{14}BrClN_2O_4$: 485.5072, found: 485.5061.

5.4.3.9. 3-(3,4-dichlorophenylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5h).



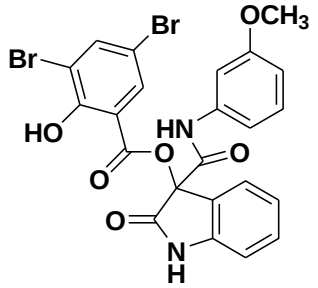
yellow liquid (Yield: Exp A 79%, Exp B, 88%); IR (NaCl) ν(cm^{-1}) 3334 (NH), 1714 (CO) ester, and 1671 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.19 (s, 1H, NH- amide), 10.54 (d, *J* = 33.9 Hz, 1H, Ar-H), 10.33 (d, *J* = 10.6 Hz, 1H, Ar-H), 8.84 (d, *J* = 10.7 Hz, 1H, Ar-H), 8.31 (s, 1H, NH-indole), 7.95 (s, 2H, Ar-H), 7.84 (s, 1H), 7.64 – 7.37 (m, 2H, Ar-H), 7.18 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.12 – 6.96 (m, 1H, Ar-H), 6.93 – 6.76 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 170.8 (-CO-ester), 163.1 (-CO-amide), 160.5 (-C-Cl), 159.8 (-C-Cl), 157.7, 140.0, 138.7, 138.6, 131.5, 131.2, 125.6, 123.1, 120.8, 119.6, 117.8, 116.6, 110.0. [M+H^{+}] calcd for $C_{22}H_{13}BrCl_2N_2O_4$: 520.1116, found: 520.1135.

5.4.3.10. 3-(p-tolylcarbamoyl)-2-oxoindolin-3-yl 4-bromobenzoate (5i).



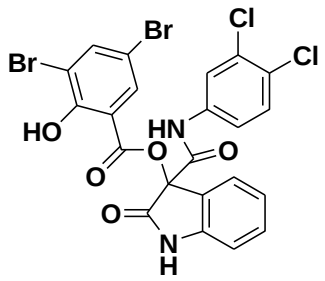
yellow liquid (Yield: Exp A 82%, Exp B, 96%); IR (NaCl) ν(cm^{-1}) 3316 (NH), 1702 (CO) ester, and 1651 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H, NH-amide), 8.64 (d, *J* = 11.5 Hz, 1H, Ar-H), 8.38 (s, 1H, -NH-indole), 8.15 (d, *J* = 10.9 Hz, 1H, Ar-H), 7.98 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.63 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.59 (dd, *J* = 15.7, 8.0 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.17 (t, *J* = 9.1 Hz, 2H, Ar-H), 7.01 (d, *J* = 8.2 Hz, 2H, Ar-H), 6.95 (d, *J* = 7.9 Hz, 1H, Ar-H), 2.20 (s, 3H CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (-CO-ester), 158.9 (-CO-amide), 144.2, 138.7, 133.6, 135.3, 134.5, 133.9, 131.7, 130.2, 129.6, 125.8, 123.9, 120.0, 119.2, 112.4, 31.0 (-CH_3). [M+H^+] calcd for $C_{23}H_{17}BrN_2O_4$: 464.2130, found: 464.2122.

5.4.3.11. 3-(3-methoxyphenylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6a).



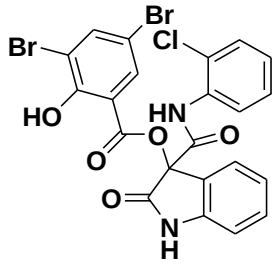
yellow liquid (Yield: Exp A 73%, Exp B, 91%); IR (NaCl) ν(cm^{-1}) 3482 (OH), 3326 (NH), 1709 (CO) ester, and 1622 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1H, -OH), 10.20 (s, 1H, NH-amide), 8.81 (d, *J* = 10.9 Hz, 1H, Ar-NH), 8.27 (s, 1H, NH-indole)), 7.87 (d, *J* = 15.3 Hz, 2H, Ar-H), 7.55 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.47 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.30 (s, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 15.7, 7.7 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.76 (d, *J* = 8.9 Hz, 1H, Ar-H), 6.63 (d, *J* = 7.9 Hz, 1H, Ar-H), 2.06 (s, 3H, O-CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 170.8 (-CO-ester), 163.0 (-CO-amide), 160.5 (-C-OCH_3), 159.9 (C-OH), 158.1, 151.1, 140.0, 139.8, 138.7, 132.0, 130.6, 125.0, 123.1, 118.2, 117.3, 112.6, 112.0, 111.8, 110.0, 109.3, 103.7, 55.4 (O-CH_3). [M+H^+] calcd for $C_{23}H_{16}Br_2N_2O_6$: 573.7593, found: 573.7582.

5.4.3.12. 3-(3,4-dichlorophenylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6b).



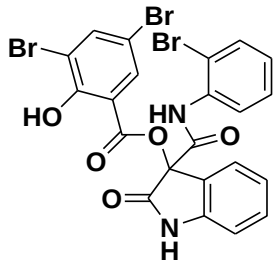
yellow liquid (Yield: Exp A 62%, Exp B, 76%); IR (NaCl) ν(cm^{-1}) 3450 (OH), 3329 (NH), 1714 (CO) ester, and 1605 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.11 (s, 1H, -OH), 10.57 (s, 1H -NH-amide), 8.38 (s, 1H, NH-indole), 7.92 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.77 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.65 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.56 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.12 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.96 (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 167.1 (-CO-ester), 159.8 (-CO-amide), 151.1 (-C-OH), 140.5, 138.8, 132.1, 131.3, 131.7, 130.4, 127.3, 126.2, 125.1, 123.2, 120.3, 118.2, 116.5, 115.3 113.5, 112.6, 110.6. HR-MS (ESI): [M+H^{+}] calcd for $C_{22}H_{12}Br_2Cl_2N_2O_5$: 615.1784, found: 615.1783.

5.4.3.13. 3-(2-chlorophenylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6c).



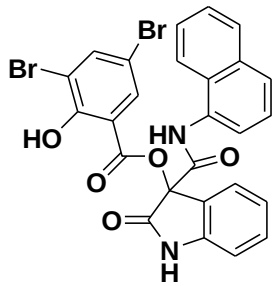
yellow liquid (Yield: Exp A 80%, Exp B, 83%); IR (NaCl) ν(cm^{-1}) 3477 (OH), 3344 (NH), 1725 (CO) ester, and 1618 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.06 (s, 1H, -OH), 9.89 (s, 1H, NH-amide), 8.48 (d, *J* = 10.7 Hz, 1H, Ar-H), 8.36 (s, 1H, -NH-indole), 8.11 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 7.87 (s, 1H, Ar-H), 7.57 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.32 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.14 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.05 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.90 (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 170.9 (-CO-ester), 164.0 (-CO-amide), 159.8 (-C-OH), 157.6, 151.1, 140.2, 138.8, 134.7, 132.1, 130.4, 129.9, 128.6, 127.0, 125.9, 125.1, 123.9, 123.2, 118.2, 116.4, 112.6, 110.2. HR-MS (ESI): [M+H^{+}] calcd for $C_{22}H_{13}Br_2ClN_2O_5$: 580.3561, found: 580.3540.

5.4.3.14. 3-(2-bromophenylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6d).



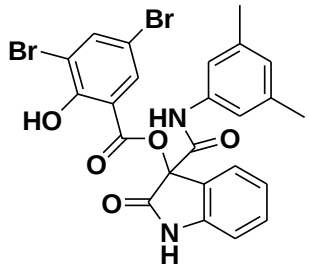
yellow liquid (Yield: Exp A 69%, Exp B, 90%); IR (NaCl) ν(cm^{-1}) 3308 (OH), 3276 (NH), 1718 (CO) ester, and 1679 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H, -OH)), 11.08 (s, 1H, -NH-amide), 10.67 (s, 1H, -NH-indole), 8.35 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar-H), 8.12 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.62 – 7.50 (m, 2H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.39 – 7.31 (m, 2H, Ar-H), 7.28 (dt, *J* = 9.5, 4.7 Hz, 2H, Ar-H), 7.18 (t, *J* = 3.7 Hz, 2H, Ar-H), 6.98 (d, *J* = 7.7, 1.2 Hz, 1H, Ar-H), 6.45 (s, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (-CO-ester), 164.5 (-CO-amide), 155.7, 144.0, 140.5, 134.5, 133.9, 133.8, 132.1, 129.9, 129.3, 129.0, 128.9, 128.7, 127.9, 127.3, 125.1, 122.8, 121.3, 113.4, 112.8, 110.6, 76.2. HR-MS (ESI): [M+H+] calcd for $C_{22}H_{13}Br_2ClN_2O_5$: 622.8284, found: 622.8289.

5.4.3.15. 3-(naphthalen-1-ylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6e).



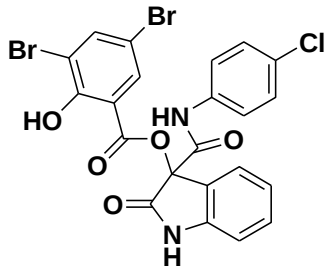
brown liquid (Yield: Exp A 75%, Exp B, 88%); IR (NaCl) ν(cm^{-1}) 3312 (OH), 3196 (NH), 1713 (CO) ester, and 1687 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H, -OH), 9.41 (s, 1H, -NH-amide), 8.56 – 8.33 (m, 1H, Ar-H), 8.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.85 – 7.79 (m, 2H, Ar-H), 7.77 (q, *J* = 3.0 Hz, 1H, Ar-H), 7.73 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.64 – 7.59 (m, 2H, Ar-H), 7.55 – 7.49 (m, 2H, Ar-H), 7.42 (d, *J* = 3.8 Hz, 1H, Ar-H), 7.26 – 7.21 (m, 1H, Ar-H), ^{13}C NMR (101 MHz, DMSO) δ 184.9 (-CO-indole), 171.0 (-CO-ester), 164.5 (-CO-amide), 159.8 C-OH), 157.8, 151.1, 140.0, 138.7, 134.2, 133.0, 132.1, 128.7, 126.9, 126.6, 126.2, 125.9, 125.0, 123.1, 122.9, 119.8, 118.5, 112.6. HR-MS (ESI): [M+H+] calcd for $C_{26}H_{16}Br_2N_2O_5$: 593.9418, found: 593.9432.

5.4.3.16. (3,5-dimethylphenylcarbamoyl)(2-oxoindolin-3-yl)methyl3,5-dibromo-2 hydroxybenzoate (6f).



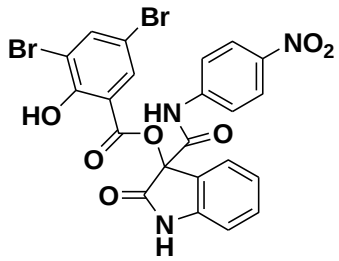
yellow liquid (Yield: Exp A 78%, Exp B, 72%); IR (NaCl) ν(cm^{-1}) 3410 (OH), 3328 (NH), 1702 (CO) ester, and 1608 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1H, -OH), 10.06 (s, 1H, -NH-amide), 8.74 (d, *J* = 11.0 Hz, 1H, Ar-H), 8.23 (s, 1H, -NH-indole), 7.82 (d, *J* = 6.5 Hz, 1H, -Ar-H), 7.59 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.06 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.91 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 2.22 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 162.9 (-CO-ester), 159.9 (-CO-amide), 151.1 (-C-OH), 139.0, 138.8, 138.6, 138.5, 138.5, 138.3, 131.9, 125.6, 125.5, 123.2, 121.4, 120.6, 119.0 118.2, 117.2, 115.6, 112.1, 108.1, 21.5 (CH_3), 21.4 (CH_3). HR-MS (ESI): [M+H+] calcd for $C_{24}H_{18}Br_2N_2O_5$ 574.2022, found: 574.2018.

5.4.3.17 (4-chlorophenylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6g).



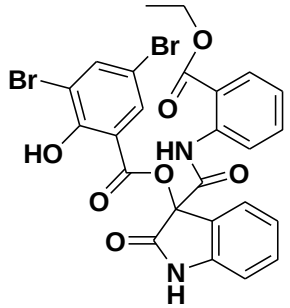
yellow liquid (Yield: Exp A 65%, Exp B, 75%); IR (NaCl) ν(cm^{-1}) 3439 (OH), 3251 (NH), 1726 (CO) ester, and 1616 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H, -OH), 8.75 (s, 1H, -NH-amide), 8.57 (d, *J* = 11.3 Hz, 1H, Ar-H), 8.43 (d, *J* = 8.9 Hz, 1H, Ar-H), 8.34 (s, 1H, -NH-indole), 7.97 (t, *J* = 3.5 Hz, 1H, Ar-H), 7.66 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.50 (dd, *J* = 11.3, 7.7 Hz, 1H, Ar-H), 7.47 – 7.38 (m, 2H, Ar-H), 7.33 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.02 – 6.90 (m, 2H, Ar-H), 6.85 (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (-CO-indole), 162.6 (-CO-ester), 159.7 (-CO-amide), 159.2 (C-OH), 157.4, 149.5, 140.3, 139.3, 138.7, 136.8, 135.4, 132.8, 130.8, 129.8, 129.1, 125.7, 124.0, 121.8, 121.2, 119.8, 118.0, 112.5. HR-MS (ESI): [M+H^+] calcd for $C_{22}H_{13}Br_2ClN_2O_5$: 580.4761, found: 580.4740.

5.4.3.18. (4-nitrophenylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6h).



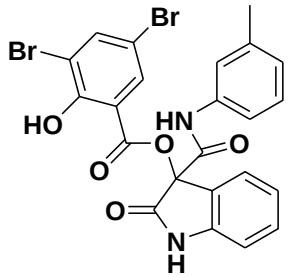
yellow liquid (Yield: Exp A 83%, Exp B, 84%); IR (NaCl) ν(cm^{-1}) 3477 (OH), 3355 (NH), 1739 (CO) ester, and 1641 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H, -OH), 10.52 (s, 1H, NH-amide), 9.09 (dd, J = 35.9, 8.9 Hz, 1H, Ar-H), 8.41 (s, 1H, NH-indole), 8.38 – 8.28 (m, 2H, Ar-H), 8.21 (t, J = 10.9 Hz, 2H, Ar-H), 7.89 (dd, J = 11.9, 5.7 Hz, 3H, Ar-H), 7.85 – 7.78 (m, 2H, Ar-H), 7.42 (d, J = 8.7 Hz, 1H, Ar-H) ^{13}C NMR (101 MHz, DMSO) δ 170.4 (-CO-indole), 168.6 (-CO-ester), 167.2 (-CO-amide), 163.1 -C-NO_2), 158.6 (-C-OH), 147.9, 144.6, 142.9, 139.2, 132.0, 130.8, 128.5, 125.9, 125.6, 125.5, 119.5, 117.0, 112.1, 108.9.

5.4.3.19. {[2-(ethoxycarbonyl)phenyl]carbamoyl}(2-oxo-2,3-dihydro-1H-indol-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6i).



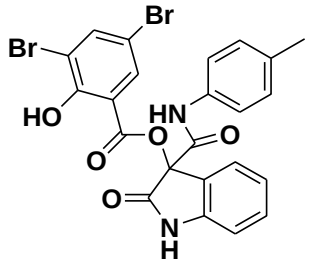
yellow liquid (Yield: Exp A 87%, Exp B, 94%); IR (NaCl) ν(cm^{-1}) 3447 (OH), 3324 (NH), 1690 (CO) ester, and 1622 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H, -OH), 10.50 (d, J = 8.2 Hz, 1H, NH-amide), 8.88 (d, J = 11.0 Hz, 1H, Ar-H), 8.62 (d, J = 8.4 Hz, 1H, Ar-H), 8.44 (d, J = 1.5 Hz, 1H, Ar-H), 7.98 (dd, J = 8.0, 1.6 Hz, 1H, Ar-H), 7.92 (d, J = 2.4 Hz, 1H, Ar-H), 7.79 (dd, J = 8.0, 1.5 Hz, 1H, Ar-H), 7.74 (d, J = 2.4 Hz, 1H, Ar-H), 7.52 – 7.40 (m, 1H, Ar-H), 7.17 (ddd, J = 8.5, 7.1, 1.4 Hz, 1H, Ar-H), 7.11 – 7.01 (m, 1H, Ar-H), 4.24 (t, J = 7.1 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (-CO-indole), 168.2 (-CO-ester), 168.1 (-CO-amide), 166.8 (-CO-ester), 159.8 (-C-OH), 157.8, 150.4, 140.7, 140.3, 134.5, 134.3, 133.9, 132.2, 131.8, 131.2, 130.8, 123.5, 123.2, 121.2, 116.7, 116.2, 110.5, 77.3, 61.5 (CH_2), 30.9 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{25}H_{18}Br_2N_2O_7$: 615.1394, found: 615.1383.

5.4.3.20. (*m*-tolylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6j).



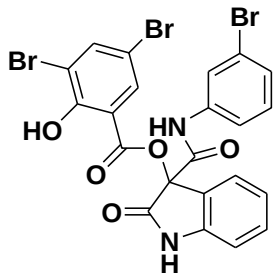
yellow liquid (Yield: Exp A 74%, Exp B, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H, -OH), 8.30 (s, 1H, -NH-amide), 8.18 (d, *J* = 19.4 Hz, 1H, -NH-indole), 8.16 – 8.05 (m, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.79 (d, *J* = 10.5 Hz, 1H, Ar-H), 7.70 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.31 (dd, *J* = 18.5, 10.9 Hz, 2H, Ar-H), 7.05 – 6.84 (m, 1H, Ar-H), 6.81 (t, *J* = 7.6 Hz, 1H, Ar-H), 5.31 – 5.13 (m, 1H, Ar-H), 1.84 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (-CO-indole), 167.7 (-CO-ester), 157.8 (-CO-amide), 144.5, 141.5, 140.1, 139.1, 138.8, 137.3, 131.4, 129.4, 127.6, 126.5, 122.0, 120.8, 114.5, 112.7, 110.8, 90.3, 84.4, 24.6 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{23}H_{16}Br_2N_2O_5$: 558.9094, found: 558.9035.

5.4.3.21. (*p*-tolylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6k).



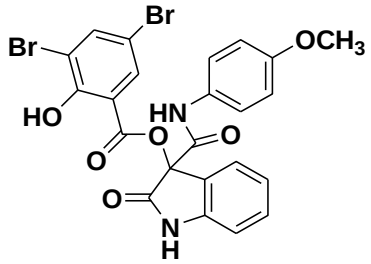
yellow liquid (Yield: Exp A 53%, Exp B, 74%); IR (NaCl) *v*(cm^{-1}) 3316 (OH), 3255 (NH), 1702 (CO) ester, and 1651 (CO) amide.^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, OH), 10.09 (d, *J* = 18.4 Hz, 1H, Ar-H), 8.70 (d, *J* = 11.1 Hz, 1H, Ar-H), 8.22 (s, 1H, -NH-amide), 7.82 (s, 1H, -NH-indole), 7.58 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.48 (dd, *J* = 12.7, 7.9 Hz, 2H, Ar-H), 7.19 – 6.98 (m, 3H, Ar-H), 6.91 (d, *J* = 7.9 Hz, 1H, Ar-H), 2.24 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 159.8 (-CO-ester, amide), 151.1 (-C-OH), 138.8, 138.4, 136.2, 132.9, 131.9, 130.2, 129.6, 125.1, 123.2, 119.5, 118.2, 118.1, 112.6, 112.1, 108.1, 20.9 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{23}H_{16}Br_2N_2O_5$: 558.5694, found: 558.5635.

5.4.3.22. 3-(3-bromophenylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6l).



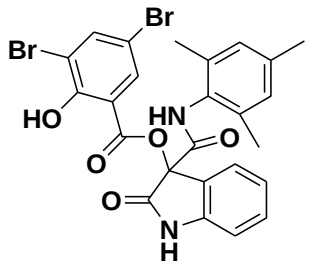
yellow liquid (Yield: Exp A 79%, Exp B, 83%); ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, -OH), 10.38 (s, 1H, NH-amide), 10.27 (d, *J* = 10.6 Hz, 1H, Ar-H), 8.97 – 8.62 (m, 1H, Ar-H), 8.30 (s, 1H, -NH-indole), 7.94 (s, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.55 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.52 – 7.36 (m, 2H, Ar-H), 7.26 (dd, *J* = 15.2, 7.3 Hz, 1H, Ar-H), 7.03 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.90 (d, *J* = 7.8 Hz, 1H, Ar-H), 5.73 (s, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 170.8 (-CO-ester), 163.0 (-CO-amide), 159.8 (-C-OH), 158.0, 151.1, 140.6, 140.2, 139.8, 138.7, 132.1, 131.6, 126.6, 125.1, 123.1, 122.7, 120.1, 118.3, 117.0, 116.5, 112.0, 109.8. HR-MS (ESI): [M+H^{+}] calcd for $C_{22}H_{13}Br_3N_2O_5$: 621.2784, found: 621.2742.

5.4.3.23 (4-methoxyphenylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6m).



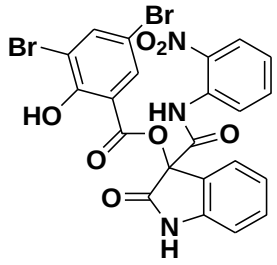
yellow liquid (Yield: Exp A 66%, Exp B, 87%); IR (NaCl) *ν*(cm^{-1}) 3385 (OH), 3324 (NH), 1725 (CO) ester, and 1643 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.56 (d, *J* = 22.9 Hz, 1H, -OH, NH)), 7.93 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.92 – 7.82 (m, 1H, Ar-H), 7.84 – 7.69 (m, 1H, Ar-H), 7.55 (dd, *J* = 15.7, 5.6 Hz, 1H, Ar-H), 7.46 – 7.30 (m, 2H, Ar-H), 6.99 – 6.77 (m, 2H, Ar-H), 5.23 (s, 1H, NH-indole), 3.93 – 3.59 (m, 4H-O-CH_3), 1.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (-CO-indole), 166.4 (-CO-ester), 157.7 (-CO-amide), 157.4 (-C-OH), 144.2, 140.6, 139.6, 128.7, 127.5, 123.5, 116.9, 114.4, 113.7, 110.3, 77.3, 77.0, 76.7, 55.5 (O-CH_3). HR-MS (ESI): [M+H^{+}] calcd for $C_{23}H_{16}Br_2N_2O_6$: 573.1617, found: 573.1618.

5.4.3.24. 3-(mesitylcarbamoyl)-2-oxoindolin-3-yl 3,5-dibromo-2-hydroxybenzoate (6n).



yellow liquid (Yield: Exp A 75%, Exp B, 90%); ^{1}H NMR (400 MHz, DMSO) δ 9.36 (s, 1H, -OH), 8.22 (s, 1H, -NH-amide), 8.00 (s, 1H -NH-indole), 7.93 (d, *J* = 11.6 Hz, 1H, Ar-H), 7.86 (s, 2H, Ar-H), 7.57 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.05 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.95 – 6.80 (m, 4H, Ar-H), 2.16 (s, 3H -CH_3), 2.10 (s, 6H- CH_3). ^{13}C NMR (101 MHz, DMSO) δ 184.8 (-CO-indole), 170.9 (-CO-ester), 165.2 (-CO-amide), 159.9 (-C-OH), 157.6, 151.1, 140.2, 138.8, 136.3, 135.9, 135.1, 134.8, 131.7, 129.2, 128.7, 125.1, 123.2, 118.2, 116.4, 112.1, 20.9 (CH_3), 18.7 (CH_3), 18.6 (CH_3). HR-MS (ESI): [M+H+] calcd for $C_{25}H_{21}Br_2N_2O_5$ 585.2347, found: 585.2359.

5.4.3.25. (2-nitrophenylcarbamoyl)(2-oxoindolin-3-yl)methyl 3,5-dibromo-2-hydroxybenzoate (6o).



yellow liquid (Yield: Exp A 86%, Exp B, 94%);IR (NaCl) *v*(cm^{-1}) 3481 (OH), 3359 (NH), 1730 (CO) ester, and 1628 (CO) amide. ^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H, -OH), 10.87 (s, 1H, NH-amide), 10.59 (s, 1H -NH-indole), 8.40 (s, 1H, Ar-H), 8.27 – 7.98 (m, 3H, Ar-H), 7.98 (dd, *J* = 25.8, 9.4 Hz, 2H, Ar-H), 7.83 (d, *J* = 25.9 Hz, 1H, Ar-H), 7.71 (dd, *J* = 22.9, 15.7 Hz, 1H, Ar-H), 7.52 (dt, *J* = 57.5, 17.4 Hz, 1H, Ar-H), 7.40 – 7.19 (m, 2H, Ar-H), 7.16 – 6.97 (m, 2H, Ar-H), 6.90 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.70 – 6.43 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δ 184.5 (-CO-indole), 170.5 (-CO-ester), 159.7 (-CO-amide), 158.0 (-C-OH), 151.3, 146.7, 140.1, 138.7, 135.9, 132.1, 130.3, 125.8, 125.1, 123.0, 119.5, 118.1, 115.6, 112.9, 111.8, 110.0. HR-MS (ESI): [M+H^{+}] calcd for $C_{23}H_{13}Br_2N_3O_7$: 591.9205, found: 591.8710.

5.5. Experimental for Chapter 3, part three.

5.5.1. General Experimental Procedures for the Aqua Synthesis of Passerini adducts (4a-s) in the presence of a catalyst.

A mixture of benzoic acid (1a, 1 mmol) 1-naphthylisocyanides (2a, 1 mmol), and 4-formamido pyridine (3a, 1 mmol) was vigorously stirred in 2 mL water at room temperature for 10 minutes in the presence of 0.02g of SiO_2-H_2SO_4. Upon completion, the organic layer was separated, the combined organic phases were concentrated under reduced pressure and the residue was purified by column chromatography using DCM/Hexane (3: 1) as eluent to afford the desired products. Typical yields range from 83 to 96%.

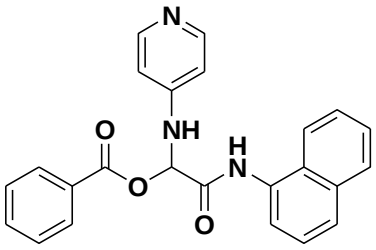
5.5.2. General Procedure for the Mechanochemical Synthesis of Passerini adducts (4a-b, 4f, 4j, 4n, 4p).

Experiment A. A mixture of benzoic acid (1a, 1 mmol) 1-naphthylisocyanides (2a, 1 mmol), and *N*-(pyridin-4-yl)formamide (3a, 1 mmol) and additive (SiO_2-H_2SO_4 0.02g) was milled in a 13.2 mL stainless steel milling vessel contained two balls of the same material (diameter: 6 mm; mass: 0.90 g) at 25 Hz for 20 min. After the milling was complete, the content in the milling vessel was transferred into a beaker using a small amount of organic solvent (DCM). Then, purification was done by column chromatography to afford the corresponding Passerini adducts in high to excellent yield.

5.5.3. General Procedure for the Mechanochemical Synthesis of Passerini adducts (4c-e, 4g-i, 4k-m, 4o, 4s).

Experiment B. A mixture of benzoic acid (1a, 1 mmol) 1-naphthylisocyanides (2a, 1 mmol), and 2-formamidoanthracene-9,10-dione (3o, 1 mmol) and additive (water 75 µL) was milled in a 13.2 mL stainless steel milling vessel contained two balls of the same material (diameter: 6 mm; mass: 0.90 g) at 25 Hz for 30 min. After the milling was complete, the content in the milling vessel was transferred into a beaker using a small amount of organic solvent (DCM). Then, purification was done by column chromatography to afford the corresponding oxindole derivatives in high yield.

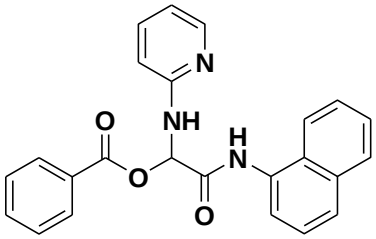
5.5.3.1. [(naphthalen-1-yl)carbamoyl](pyridin-4-ylamino)methyl benzoate (4a).



white solid (Yield: Met A 95%, Met B, 97%); m.p 107-109 ºC. IR (NaCl) ν(cm^{-1}) 3324 (NH), 1730 (CO) ester, and 1643 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (d, J = 9.9 Hz, 1H, NH-amide),

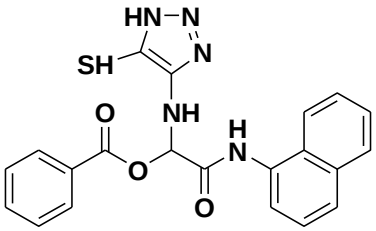
8.48 (d, *J* = 10.9 Hz, 1H, NH), 8.00 (t, *J* = 9.6 Hz, 3H, Ar-H), 7.71 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.63 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.50 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.43 (td, *J* = 11.8, 3.8 Hz, 2H, Ar-H), 7.31 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.26 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.14 (d, *J* = 7.3 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (CO-ester), 166.1 (CO-amide), 134.2, 133.7, 132.2, 130.4, 129.9, 128.5, 128.3, 128.0, 127.9, 127.4, 126.9, 126.3, 126.1, 125.5, 124.9, 122.9, 121.7, 120.8, 118.8. HR-MS (ESI): [M+H$^+$] calcd for $C_{24}H_{19}N_3O_3$: 398.2514, found: 398.2521.

5.5.3.2. [(naphthalen-1-yl)carbamoyl][(pyridin-2-yl)amino]methyl benzoate (4b).



white solid (Yield: Met A 87%, Met B, 90%); m.p 132-134 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (d, *J* = 7.4 Hz, 1H, NH-amide), 8.51 (d, *J* = 10.9 Hz, 1H, NH), 8.06 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.03 (t, *J* = 8.7 Hz, 2H, Ar-H), 7.76 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.55 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.51 – 7.41 (m, 1H, Ar-H), 7.41 – 7.26 (m, 2H, Ar-H), 7.23 – 7.09 (m, 1H, Ar-H), 4.80 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (CO-ester), 166.1 (CO-amide), 134.3, 133.8, 133.6, 132.2, 130.2, 129.8, 129.5, 128.5, 128.0, 127.9, 127.7, 127.3, 127.1, 126.7, 126.6, 125.5, 124.9, 122.9, 121.7, 118.7. HR-MS (ESI): [M+H$^+$] calcd for $C_{24}H_{19}N_3O_3$: 398.1410, found: 398.1424.

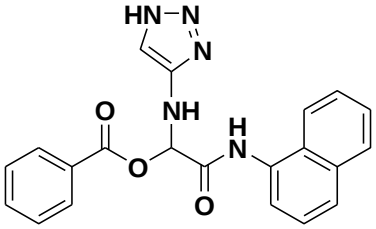
5.5.3.3. [(naphthalen-1-yl)carbamoyl][(5-sulfanyl-1H-1,2,3-triazol-4-yl)amino]methyl benzoate (4c).



white solid (Yield: Met A 93%, Met B, 82%); m.p 133-135 ºC. IR (NaCl) *ν*(cm^{-1}) 3330 (NH), 1660 (CO) ester, and 1628 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H, NH-amide), 10.42 (d, J = 4.4 Hz, 1H, NH), 9.60 (d, J = 8.5 Hz, 1H, Ar-H), 9.51 (d, J = 8.4 Hz, 1H, Ar-H), 9.25 (d, J = 4.4 Hz, 1H, Ar-H), 9.19 (t, J = 7.6 Hz, 1H, Ar-H), 9.02 (t, J = 7.6 Hz, 1H, Ar-H), 8.13 (s, 1H, SH), 7.91 (d, J = 4.5 Hz, 1H, Ar-H), 7.56 (d, J = 4.5 Hz, 1H, Ar-H), 7.35 (d, J = 2.3 Hz, 1H, Ar-H), 4.87 (s, 5H, Het-H), 4.67 (d, J = 5.2 Hz, 1H, Het-H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8 (CO-ester), 187.8

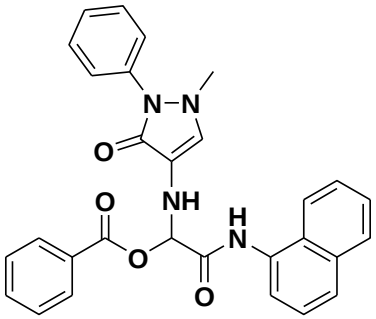
(CO-amide), 186.0, 171.6, 167.9, 167.2, 164.5, 163.8, 162.6, 156.5, 155.9, 145.5, 144.5, 133.5, 129.1, 128.2, 103.4, 87.0. HR-MS (ESI): [M+H$^+$] calcd for $C_{21}H_{17}N_5O_3S$: 419.1916, found: 419.1918.

5.5.3.4. [(naphthalen-1-yl)carbamoyl][(1H-1,2,3-triazol-4-yl)amino]methyl benzoate (4d).



white solid (Yield: Met A 90%, Met B, 94%); m.p 130-132 ºC. IR (NaCl) ν(cm^{-1}) 3222 (NH), 1687 (CO) ester, and 1655 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H, NH-amide), 8.58 (d, J = 1.3 Hz, 1H, NH), 8.49 (d, J = 10.9 Hz, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 8.00 (d, J = 7.4 Hz, 2H, Ar-H), 7.73 (d, J = 8.2 Hz, 3H, Ar-H), 7.64 (d, J = 8.3 Hz, 1H, Ar-H), 7.49 – 7.39 (m, 12H, Ar-H), 7.32 (t, J = 7.8 Hz, 20H, Ar-H), 7.18 – 7.07 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, CDCl3) δ 172.2 (CO-ester), 166.2 (CO-amide), 156.2, 149.0, 145.8, 134.2, 133.7, 129.8, 128.5, 127.7, 127.3, 127.1, 126.9, 125.5, 124.9, 122.9, 121.7, 120.7, 118.8, 114.0. HR-MS (ESI): [M+H$^+$] calcd for $C_{21}H_{17}N_5O_3$: 388.2013, found: 388.2043.

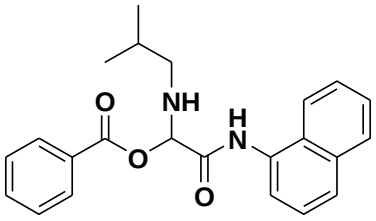
5.5.3.5. [(1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4e).



brown solid (Yield: Met A 96%, Met B, 86%); m.p 128-130 ºC. IR (NaCl) ν(cm^{-1}) 3328 (NH), 1720 (CO) ester, and 1618 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (d, J = 10.2 Hz, 1H), 9.63 (s, 1H, NH-amide), 9.30 (s, 1H, NH), 8.50 (d, J = 11.0 Hz, 1H, Ar-H), 8.05 (d, J = 8.4 Hz, 1H, Ar-H), 7.99 (d, J = 7.8 Hz, 2H, Ar-H), 7.86 (d, J = 7.5 Hz, 1H, Ar-H), 7.75 (d, J = 7.8 Hz, 1H, Ar-H), 7.65 (d, J = 8.3 Hz, 1H, Ar-H), 7.54 (d, J = 8.1 Hz, 1H, Ar-H), 7.45 (t, J = 7.3 Hz, 1H, Ar-H), 7.32 (t, J = 7.5 Hz, 2H, Ar-H), 7.23 (d, J = 7.4 Hz, 1H, Ar-H), 7.17 (t, J = 7.1 Hz, 1H, Ar-H), 2.98 (s, 1H, CH_3), 2.17 (s, 1H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (CO-amide), 165.7 (CO-hetero), 161.0 (CO-ester), 148.6, 134.2, 133.4, 132.3, 130.1, 129.9, 128.4, 128.0, 127.7, 127.4, 127.0, 126.8, 125.7, 124.6, 122.8,

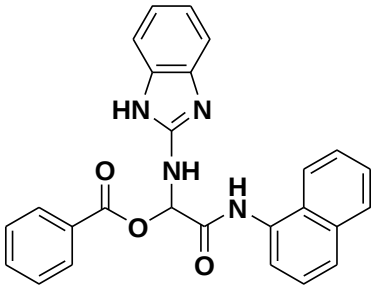
121.7, 120.8, 118.8, 106.2, 35.4 (CH_3), 12.2 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{30}H_{26}N_4O_4$: 507.2238, found: 507.2301.

5.5.3.6. [(2-methylpropyl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4f).



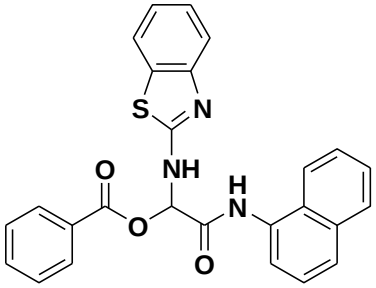
yellow solid (Yield: Met A 92%, Met B, 95%); m.p 115-117 ºC. IR (NaCl) ν(cm^{-1}) 3386 (NH), 1703 (CO) ester, and 1627 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, J = 9.3 Hz, 1H, NH-amide), 8.55 (d, J = 11.1 Hz, 1H, NH), 8.05 (d, J = 7.6 Hz, 5H, Ar-H), 7.83 (d, J = 8.3 Hz, 1H, Ar-H), 7.73 (d, J = 8.3 Hz, 1H, Ar-H), 7.59 – 7.48 (m, 4H, Ar-H), 7.40 (d, J = 7.7 Hz, 2H, Ar-H), 7.25 (d, J = 7.2 Hz, 1H, Ar-H), 3.08 (t, J = 6.6 Hz, 1H, CH_2), 1.78 (dt, J = 13.4, 6.7 Hz, 1H, CH_3), 0.87 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.74 (CO-ester), 165.37 (CO-amide), 160.07, 134.24, 133.68, 132.16, 130.31, 129.58, 128.49, 127.78, 127.17, 126.89, 125.52, 121.59, 120.53, 118.97, 47.07 (CH_2), 28.42 (CH_2), 20.09 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{23}H_{24}N_2O_3$: 377.3018, found: 377.3052.

5.5.3.7. [(1H-1,3-benzodiazol-2-yl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4g).



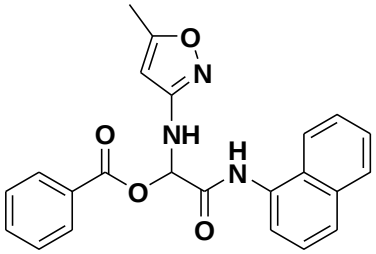
white solid (Yield: Met A 85%, Met B, 80%); m.p 132-144 ºC. IR (NaCl) ν(cm^{-1}) 3273 (NH), 1696 (CO) ester, and 1624 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 10.03 (d, J = 9.5 Hz, 1H), 8.59 (s, 1H, NH-amide), 8.54 (d, J = 11.0 Hz, 1H, NH), 8.05 (d, J = 8.2 Hz, 3H, Ar-H), 7.81 (d, J = 8.2 Hz, 1H, Ar-H), 7.72 (d, J = 8.3 Hz, 1H, Ar-H), 7.53 (t, J = 7.4 Hz, 2H, Ar-H), 7.39 (t, J = 7.6 Hz, 3H, Ar-H), 7.24 (d, J = 7.3 Hz, 1H, Ar-H), 5.20 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (CO-ester), 165.9 (CO-amide), 134.3, 133.8, 132.2, 130.1, 129.4, 128.4, 127.8, 127.2, 127.1, 126.9, 125.5, 121.6, 121.1, 120.3, 118.8, 113.3 111.7. HR-MS (ESI): [M+H$^+$] calcd for $C_{26}H_{20}N_4O_3$: 437.1525, found: 437.1520.

5.5.3.8. [(1,3-benzothiazol-2-yl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4h).



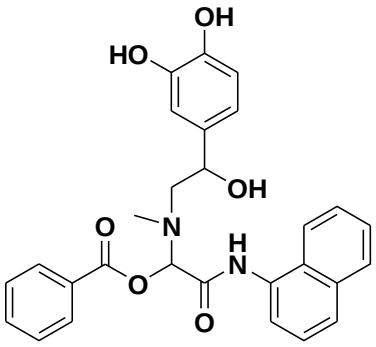
white solid (Yield: Met A 95%, Met B, 88%); m.p 136-138 ºC. IR (NaCl) ν(cm^{-1}) 3406 (NH), 1683 (CO) ester, and 1626 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H, NH-amide), 9.67 (d, J = 9.5 Hz, 1H, NH), 8.64 (s, 1H), 8.53 (d, J = 10.8 Hz, 1H, Ar-H), 8.35 (d, J = 8.4 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.09 (d, J = 8.4 Hz, 1H, Ar-H), 8.04 (d, J = 7.9 Hz, 2H, Ar-H), 7.99 (d, J = 8.1 Hz, 1H, Ar-H), 7.90 (d, J = 7.5 Hz, 1H, Ar-H), 7.80 (d, J = 8.1 Hz, 1H, Ar-H), 7.68 (dd, J = 18.8, 8.5 Hz, 1H, Ar-H), 7.57 (d, J = 8.0 Hz, 1H, Ar-H), 7.54 – 7.44 (m, 2H, Ar-H), 7.37 (t, J = 7.8 Hz, 3H, Ar-H), 7.22 (d, J = 7.2 Hz, 1H, Ar-H), 7.18 – 7.09 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (CO-amide), 165.5 (CO-ester), 160.0 (C-C Hetero), 154.1 (C-S, Hetero), 138.9, 134.2, 133.4, 132.2, 130.1, 129.8, 128.4, 128.2, 127.4, 127.1, 126.8, 126.1, 125.7, 124.9, 124.6, 122.9, 121.5, 120.1, 118.9, 116.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{26}H_{19}N_3O_3S$: 454.2011, found: 454.2028.

5.5.3.9. [(5-methyl-1,2-oxazol-3-yl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4i).



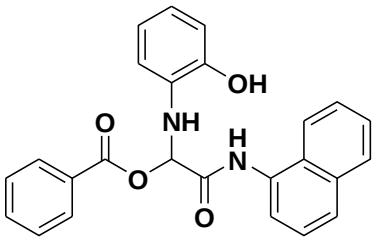
brown solid (Yield: Met A 83%, Met B, 83%); m.p 125-127 ºC. IR (NaCl) ν(cm^{-1}) 3258 (NH), 1690 (CO) ester, and 1625 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H, NH-amide), 10.12 (s, 1H, NH), 8.53 (d, J = 10.9 Hz, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 8.03 (d, J = 7.9 Hz, 2H, Ar-H), 7.79 (d, J = 8.0 Hz, 1H, Ar-H), 7.69 (d, J = 8.2 Hz, 1H, Ar-H), 7.50 (t, J = 7.4 Hz, 1H, Ar-H), 7.37 (t, J = 7.7 Hz, 2H, Ar-H), 7.22 (d, J = 7.3 Hz, 1H, Ar-H), 6.69 (s, 1H,), 2.31 (s, 1H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (CO-ester), 166.0 (CO-amide), 159.0 (C-C-Hetero), 133.7, 132.2, 130.2, 129.5, 128.5, 127.7, 127.1, 126.8, 125.5, 124.1, 123.8, 122.2, 121.7, 118.8, 97.1, 12.6 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{23}H_{19}N_3O_4$; 402.1014, found: 402.1009.

5.5.3.10. {[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl](methyl)amino}[(naphthalen-1-yl)carbamoyl]methyl benzoate (4j).



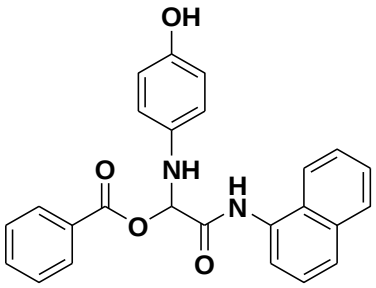
brown solid (Yield: Met A 89%, Met B, 92%); m.p 140-142 ºC. IR (NaCl) ν(cm^{-1}) 3469 (OH), 3246 (NH), 1703 (CO) ester, and 1620 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (d, J = 10.1 Hz, 1H, NH-amide), 9.39 (s, 1H, -OH), 8.46 (d, J = 10.8 Hz, 1H, -OH), 7.96 (d, J = 7.7 Hz, 2H, Ar-H), 7.68 (d, J = 7.9 Hz, 1H, Ar-H), 7.59 (d, J = 8.3 Hz, 1H, Ar-H), 7.42 (ddd, J = 22.5, 15.5, 7.0 Hz, 2H, Ar-H), 7.29 (d, J = 7.6 Hz, 2H, Ar-H), 7.22 (t, J = 7.8 Hz, 1H, Ar-H), 7.11 (d, J = 7.3 Hz, 1H, Ar-H), 4.79 (s, 1H, -CH (chiral)), 3.97 (q, J = 7.1 Hz, 1H, CH_2), 1.89 (s, 1H, CH_3), 1.09 (t, J = 7.2 Hz, 1H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO-ester), 167.0 (CO-amide), 166.1 (C-OH), 161.3 (C-OH), 134.2, 133.6, 132.2, 130.1, 129.8, 129.6, 128.4, 128.3, 128.0, 127.4, 127.0, 126.8, 125.4, 124.9, 124.5, 122.8, 121.7, 118.7, 60.6, 21.0, 14.9. HR-MS (ESI): [M+H^+] calcd for $C_{28}H_{26}N_2O_6$; 487.2917, found: 487.2910.

5.5.3.11. [(2-hydroxyphenyl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4k).



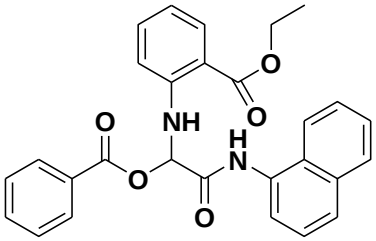
brown solid (Yield: Met A 95%, Met B, 78%); m.p 136-138 ºC. IR (NaCl) ν(cm^{-1}) 3451 (OH), 3234 (NH), 1679 (CO) ester, and 1628 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, J = 11.3 Hz, 1H, NH-amide), δ 8.59 (s, 1H, OH), 8.55 (d, J = 11.0 Hz, 1H, NH), 8.06 (d, J = 7.9 Hz, 4H, Ar-H), 8.00 (d, J = 8.2 Hz, 1H, Ar-H), 7.84 (d, J = 7.9 Hz, 1H, Ar-H), 7.74 (d, J = 8.3 Hz, 1H, Ar-H), 7.58 – 7.49 (m, 4H, Ar-H), 7.41 (t, J = 7.6 Hz, 5H, Ar-H), 7.26 (d, J = 7.3 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (CO-ester), 164.9 (CO-amide), 159.5 (C-OH), 134.2, 133.7, 132.1, 130.2, 129.4, 128.5, 127.7, 127.2, 127.1, 126.8, 126.3, 125.5, 121.4, 120.2, 118.9, 116.4. HR-MS (ESI): [M+H^+] calcd for $C_{25}H_{20}N_2O_4$; 413.1407, found: 413.1400.

5.5.3.12. [(4-hydroxyphenyl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4l).



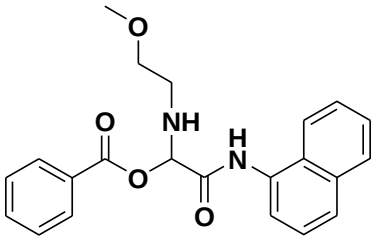
brown solid (Yield: Met A 91%, Met B, 86%); m.p 131-133 ºC. IR (NaCl) ν(cm^{-1}) 3417 (OH), 3330 (NH), 1655 (CO) ester, and 1624 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 10.5 Hz, 1H, NH-amide), 8.31 (s, 1H, NH), 7.96 (s, 1H, C-OH), 7.92 (d, J = 9.0 Hz, 1H, Ar-H), 7.82 (dd, J = 15.3, 8.0 Hz, 1H, Ar-H), 7.73 (d, J = 8.3 Hz, 1H, Ar-H), 7.66 (d, J = 8.3 Hz, 1H, Ar-H), 7.57 – 7.49 (m, 2H, Ar-H), 7.48 – 7.43 (m, 1H, Ar-H), 7.40 (t, J = 6.7 Hz, 1H, Ar-H), 7.26 (d, J = 7.3 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0 (CO-ester), 159.6 (CO-amide), 134.2, 131.9, 128.9, 128.6, 127.7, 127.1, 127.1, 126.8, 126.5, 126.2, 126.1, 125.7, 125.5, 121.2, 120.9, 120.3, 119.2. HR-MS (ESI): [M+H$^+$] calcd for $C_{25}H_{20}N_2O_4$; 413.2114, found: 413.2126.

5.5.3.13. ethyl 2-{[(benzoyloxy)[(naphthalen-1-yl)carbamoyl]methyl]amino}benzoate (4m).



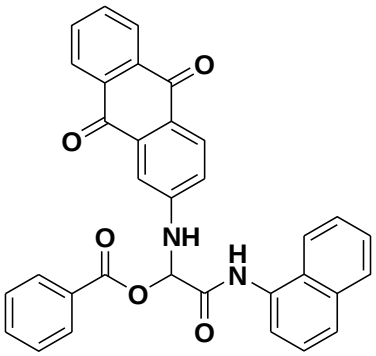
White solid (Yield: Met A 87%, Met B, 93%); m.p 119-121 ºC. IR (NaCl) ν(cm^{-1}) 3277 (NH), 1687 (CO) ester, and 1608 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H, NH-amide), 10.60 (s, 1H, NH), 8.98 (d, J = 11.1 Hz, 1H, Ar-H), 8.73 (d, J = 8.4 Hz, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 8.19 (d, J = 8.4 Hz, 1H, Ar-H), 8.14 (d, J = 7.5 Hz, 2H, Ar-H), 8.07 (d, J = 7.6 Hz, 1H, Ar-H), 7.91 (d, J = 8.2 Hz, 1H, Ar-H), 7.68 (t, J = 7.5 Hz, 1H, Ar-H), 7.60 (dt, J = 7.0, 5.6 Hz, 2H, Ar-H), 7.55 (d, J = 7.7 Hz, 1H, Ar-H), 7.52 – 7.40 (m, 3H, Ar-H), 7.38 (d, J = 8.3 Hz, 1H, Ar-H), 7.14 (t, J = 7.6 Hz, 1H, Ar-H), 4.39 (q, J = 7.1 Hz, 2H, CH_2), 1.43 (t, J = 7.1 Hz, 4H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (CO-ester), 168.1 (CO-benzoate), 159.9 (CO-amide), 140.3, 134.6, 133.6, 130.9, 130.1, 129.8, 129.6, 128.4, 128.3, 128.0, 127.4, 124.9, 124.6, 123.2, 122.9, 121.2, 115.8, 115.5, 61.6 (CH_2), 14.1 (CH_3). HR-MS (ESI): [M+H$^+$] calcd for $C_{28}H_{24}N_2O_5$; 469.1735, found: 469.1726.

5.5.3.14. [(2-methoxyethyl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4n).



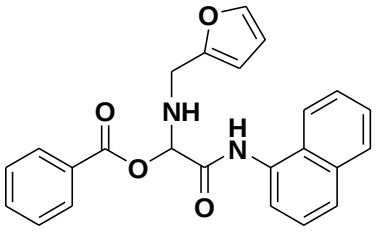
white solid (Yield: Met A 84%, Met B, 86%); m.p 127-129 ºC. IR (NaCl) ν(cm^{-1}) 3344 (NH), 1660 (CO) ester, and 1604 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H, NH-amide), 10.07 (d, J = 9.9 Hz, 1H, NH), 8.50 (d, J = 10.1 Hz, 1H, Ar-H), 8.11 – 7.92 (m, 4H, Ar-H), 7.92 – 7.85 (m, 1H, Ar-H), 7.75 (d, J = 8.1 Hz, 3H, Ar-H), 7.66 (d, J = 8.3 Hz, 1H, Ar-H), 7.52 (dd, J = 14.4, 6.4 Hz, 2H, Ar-H), 7.43 (d, J = 6.3 Hz, 1H, Ar-H), 7.30 (dd, J = 14.1, 6.2 Hz, 2H, Ar-H), 7.17 (d, J = 7.3 Hz, 1H, Ar-H), 1.87 (s, 1H,), 1.14 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (CO-ester), 165.8 (CO-amide), 134.2, 133.7, 132.2, 130.2, 129.8, 129.6, 128.5, 128.0, 127.4, 127.1, 126.9, 125.5, 124.9, 124.6, 122.9, 121.6, 118.7, 82.5, 24.9. HR-MS (ESI): [M+H$^+$] calcd for $C_{22}H_{22}N_2O_4$; 379.1640, found: 379.1658.

5.5.3.15. [(9,10-dioxo-9,10-dihydroanthracen-2-yl)amino][(naphthalen-1-yl)carbamoyl]methyl benzoate (4o).



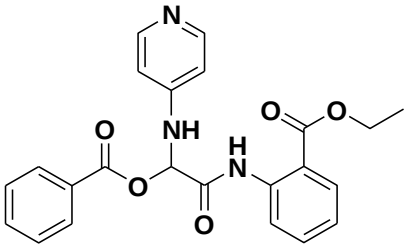
brown solid (Yield: Met A 90%, Met B, 92%); m.p 148-150 ºC. IR (NaCl) ν(cm^{-1}) 3328 (NH), 1714 (CO) ester, and 1633 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (d, J = 10.2 Hz, 1H, NH-amide), 10.07 (s, 1H, NH), 8.49 (d, J = 10.9 Hz, 1H, Ar-H), 8.01 (t, J = 10.6 Hz, 3H, Ar-H), 7.72 (d, J = 8.1 Hz, 1H, Ar-H), 7.63 (d, J = 8.3 Hz, 1H, Ar-H), 7.55 – 7.36 (m, 3H, Ar-H), 7.38 – 7.21 (m, 3H, Ar-H), 7.25 – 7.11 (m, 1H, Ar-H), 4.76 (s, 1H, CH), 1.12 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (CO-anthraquinone), 166.0 (CO-ester), 161.1 (CO-amide), 134.2, 133.7, 132.2, 130.2, 129.8, 129.5, 128.5, 128.3, 128.0, 127.4, 127.2, 127.1, 126.8, 125.5, 124.9, 124.6, 122.9, 121.7, 118.8, 114.7, 60.6, 13.8. HR-MS (ESI): [M+H$^+$] calcd for $C_{33}H_{22}N_2O_5$; 527.1523, found: 527.1517.

5.5.3.16. {[(furan-2-yl)methyl]amino}[(naphthalen-1-yl)carbamoyl]methyl benzoate (4p).



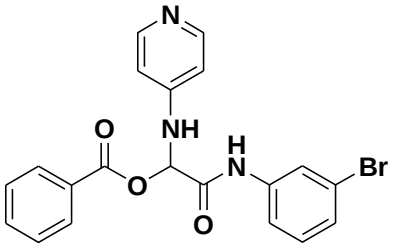
yellow solid (Yield: Met A 88%, Met B, 93%); m.p 118-120 ºC. IR (NaCl) ν(cm^{-1}) 3226 (NH), 1660 (CO) ester, and 1600 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H, NH-amide), 10.18 (d, J = 9.9 Hz, 1H, NH), 8.47 (d, J = 10.9 Hz, 1H, Ar-H), 7.99 (t, J = 10.0 Hz, 3H, Ar-H), 7.71 (d, J = 7.0 Hz, 1H, Ar-H), 7.62 (d, J = 8.2 Hz, 1H, Ar-H), 7.50 (d, J = 7.1 Hz, 1H, Ar-H), 7.44 (t, J = 7.7 Hz, 3H, Ar-H), 7.28 (dt, J = 23.2, 7.7 Hz, 3H, Ar-H), 7.13 (d, J = 7.3 Hz, 1H, Ar-H), 4.33 (d, J = 5.7 Hz, 1H), 1.88 (d, J = 21.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (CO-ester), 166.1 (CO-amide), 161.1 (C-hetero), 134.2, 133.7, 132.2, 130.2, 129.8, 129.6, 128.5, 128.0, 127.4, 127.1, 126.8, 125.5, 124.9, 124.6, 122.9, 121.7, 118.8, 35.2. HR-MS (ESI): [$M+H^+$] calcd for $C_{33}H_{22}N_2O_5$; 527.1572, found: 527.1720.

5.5.3.17. ethyl 2-[2-(benzoyloxy)-2-[(pyridin-4-yl)amino]acetamido]benzoate (4q).



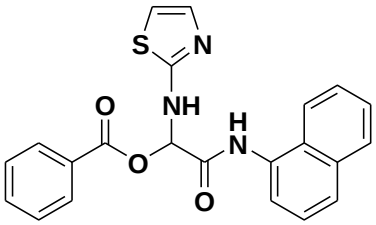
white solid (Yield: Met A 94%, Met B, 92%); m.p 125-127 ºC. IR (NaCl) ν(cm^{-1}) 3236 (NH), 1688 (CO) ester, and 1612 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H, NH-amide), 10.48 (d, J = 9.5 Hz, 1H, NH), 8.83 (d, J = 11.1 Hz, 1H, Ar-H), 8.76 – 8.57 (m, 1H, Ar-H), 8.57 (d, J = 8.5 Hz, 1H, Ar-H), 8.40 (s, 1H, Ar-H), 7.97 (d, J = 8.0 Hz, 2H, Ar-H), 7.89 (d, J = 8.0 Hz, 1H, Ar-H), 7.48 – 7.33 (m, 2H, Ar-H), 7.30 (t, J = 7.5 Hz, 2H, Ar-H), 7.22 (d, J = 8.1 Hz, 1H, Ar-H), 7.04 – 6.88 (m, 1H, Ar-H), 4.21 (q, J = 7.1 Hz, 3H, CH_2), 1.25 (t, J = 7.1 Hz, 4H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (CO-ester), 167.9 (CO-amide), 160.1 (CO-ester), 140.2, 134.4, 133.4, 131.7, 130.8, 130.0, 129.7, 128.3, 126.5, 123.1, 121.1, 115.4, 61.5, 60.2, 14.0. HR-MS (ESI): [$M+H^+$] calcd for $C_{23}H_{21}N_3O_5$; 420.1406, found: 420.1410.

5.5.3.18. [(3-bromophenyl)carbamoyl][(pyridin-4-yl)amino]methyl benzoate (4r).



yellow solid (Yield: Met A 91%, Met B, 84%); m.p 134-136 ºC. IR (NaCl) ν(cm^{-1}) 3351 (NH), 1683 (CO) ester, and 1604(CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.61 (d, J = 10.9 Hz, 1H), 8.32 (s, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.73 (s, 1H), 7.54 (t, J = 7.3 Hz, 3H), 7.40 (dd, J = 13.9, 6.5 Hz, 7H), 7.31 – 7.21 (m, 2H), 7.15 (dt, J = 16.9, 8.7 Hz, 3H), 7.00 (d, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (CO-ester), 159.2 (CO-amide), 137.9, 133.7, 131.1, 130.4, 130.2, 129.5, 128.5, 127.9, 123.3, 122.9, 122.7, 121.8, 118.4, 117.3. HR-MS (ESI): [M+H$^+$] calcd for $C_{20}H_{16}BrN_3O_3$; 426.3103, found: 426.3106.

5.5.3.19. [(naphthalen-1-yl)carbamoyl][(1,3-thiazol-2-yl)amino]methyl benzoate (4s).



brown solid (Yield: Met A 90%, Met B, 95%); m.p 127-129 ºC. IR (NaCl) ν(cm^{-1}) 3241 (NH), 1695 (CO) ester, and 1638 (CO) amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H, NH-amide), 10.00 (d, J = 10.1 Hz, 1H, NH), 8.65 – 8.39 (m, 1H, Ar-H), 8.02 (t, J = 10.0 Hz, 2H, Ar-H), 7.90 (d, J = 7.5 Hz, 1H, Ar-H), 7.80 (d, J = 7.6 Hz, 1H, Ar-H), 7.69 (d, J = 8.2 Hz, 1H, Ar-H), 7.50 (t, J = 7.2 Hz, 1H, Ar-H), 7.45 – 7.29 (m, 3H, Ar-H), 7.21 (d, J = 7.5 Hz, 1H, Ar-H), 6.91 (d, J = 3.6 Hz, 1H, Ar-H), 6.70 (d, J = 7.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (CO-ester0, 165.6 (CO-amide), 158.7 (C-thiazole), 135.6, 134.2, 133.5, 132.3, 130.0, 128.4, 127.7, 127.1, 126.8, 126.3, 125.9, 124.9, 121.6, 120.8, 118.8, 113.9, 109.9. HR-MS (ESI): [M+H$^+$] calcd for $C_{22}H_{17}N_3O_3S$; 404.1040, found: 404.1018.

5.6. Experimental for Chapter 4, Part One.

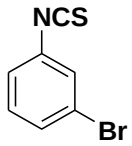
5.6.1. General Procedure for the preparation of isothiocyanates under conventional heating.

The corresponding isocyanide (1mmol) was dissolved in 2mL acetone and (0.2g; 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 ml of triethylamine (TEA). the reaction mixture was stirred for 1 hour under reflux at 100 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction (1 h), the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford the corresponding isothiocyanates.

5.6.2. General Procedure for the preparation of isothiocyanates under microwave irradiation.

The corresponding isocyanide (1mmol) was dissolved in 2mL water and (0.2g; 0.5 mmol. of Lawesson's reagent) was added. After addition of 1 mL of triethylamine (TEA (4 mmol), the reaction was irradiated in a microwave oven at a power of 850 W at 100 ºC. The progress of the reaction was monitored by TLC. After the completion of the reaction (10 min), the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford the corresponding isothiocyanates.

5.6.2.1. 1-bromo-3-isothiocyanatobenzene.

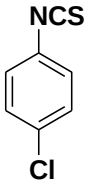


1-Bromo-3-isocyanobenzene (0.182g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-bromo-3-isothiocyanatobenzene (MW; 0.17 ml 94%, C.H; 0.15g 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 132.7, 130.7, 130.4, 128.8, 124.3, 122.8.

5.6.2.2. 1-chloro-2-isothiocyanatobenzene

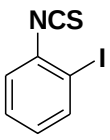
1-Chloro-2-isocyanobenzene (0.14g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-chloro-2-isothiocyanatobenzene (MW; 0.12 ml 89%, C.H; 0.1g 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.2 Hz, 1H), 7.19 – 7.04 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 131.7, 130.1, 129.7, 128.0, 127.6, 126.6.

5.6.2.3. 1-chloro-4-isothiocyanatobenzene



1-Chloro-2-isocyanobenzene (0.14g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 ml of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-chloro-4-isothiocyanatobenzene (MW; 0.12 ml 89%, C.H; 0.1g 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 129.8, 126.9.

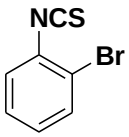
5.6.2.4. 1-iodo-2-isothiocyanatobenzene



1-Isocyano-2-iodobenzene (0.23 g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol.

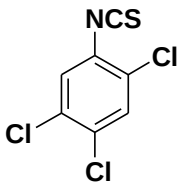
of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mMol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-iodo-2-isothiocyanatobenzene (MW; 0.21 g 91%, C.H; 0.18g 78%). IR (NaCl): 2121 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 6.90 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 134.9, 129.2, 128.3, 127.0, 94.1.

5.6.2.5. 1-bromo-2-isothiocyanatobenzene.



1-Bromo-3-isocyanobenzene (0.182g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After addition of 1 ml of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using heating mantle for conventional synthesis and by microwave irradiation (850 W) using microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-bromo-2-isothiocyanatobenzene (MW; 0.17 ml 94%, C.H; 0.15g 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 132.7, 130.7, 130.4, 128.8, 124.3, 122.8.

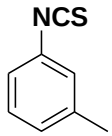
5.6.2.6. 1,2,4-trichloro-5-isothiocyanatobenzene.



1,2,4-Trichloro-5-isocyanobenzene (0.21g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 ml of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress

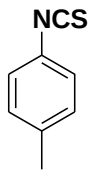
of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1,2,4-trichloro-5-isothiocyanatobenzene (MW; 0.16 g 77%, C.H; 0.13g 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 4.7 Hz, 1H), 7.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 131.8, 131.7, 131.5, 131.0, 130.7, 130.6, 127.4.

5.6.2.7. 1-isothiocyanato-3-methylbenzene



1-Isocyano-3-methylbenzene (0.12g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of the reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-isothiocyanato-3-methylbenzene (M.W; 0.11 g 95%, C.H; 0.1g 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 7.1 Hz, 2H), 7.06 – 6.92 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 130.9, 129.3, 128.0, 126.2, 122.7, 21.3.

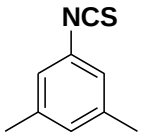
5.6.2.8. 1-isothiocyanato-4-methylbenzene.



1-Isocyano-3-methylbenzene (0.12g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford oil 1-isothiocyanato-4-methylbenzene (MW; 0.11 ml 90%, C.H; 0.09g 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (q, *J* = 8.4 Hz, 4H), 2.25 (s, 3H).

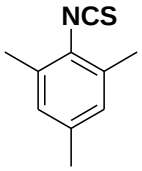
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 130.0, 128.3, 125.5, 21.5.

5.6.2.9. 1-isothiocyanato-3,5-dimethylbenzene.



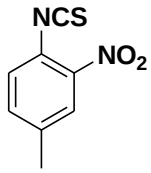
1-Isocyano-3,5-dimethylbenzene (0.13g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-1-isothiocyanato-3,5-dimethylbenzene (MW; 0.11 g 85%, C.H; 0.08g 64%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 6.4 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 134.2, 130.7, 129.2, 123.3, 21.1.

5.6.2.10. 2-isothiocyanato-1,3,5-trimethylbenzene.



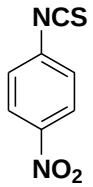
2-Isocyano-1,3,5-trimethylbenzene (0.14g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 2-isothiocyanato-1,3,5-trimethylbenzene (MW; 0.13 ml 92%, C.H; 0.1g 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 2H), 2.20 (s, 6H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 134.5, 128.7, 126.8, 20.8, 18.4.

5.6.2.11. 1-isothiocyanato-4-methyl-2-nitrobenzene.



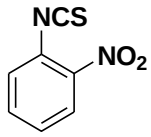
1-Isocyano-4-methyl-2-nitrobenzene (0.162 g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-isothiocyanato-4-methyl-2-nitrobenzene (MW; 0.13 g 83%, C.H; 0.07g 58%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 137.0, 131.8, 126.5, 125.1, 118.8, 20.1.

5.6.2.12. 1-isothiocyanato-4-nitrobenzene.



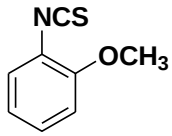
1-Isocyano-4-nitrobenzene (0.15g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford 1-isothiocyanato-4-nitrobenzene (MW; 0.12 g 80% C.H; 0.12g 77%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 129.9, 129.8, 126.9.

5.6.2.13. 1-isothiocyanato-2-nitrobenzene.



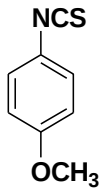
1-Isocyano-2-nitrobenzene (0.15g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-isothiocyanato-2-nitrobenzene (MW. 0.14 ml 96%, C.H 0.13g 89%). IR (NaCl): 2121 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 135.6, 132.1, 126.1, 118.8, 116.7.

5.6.2.14. 1-isothiocyanato-2-methoxybenzene.



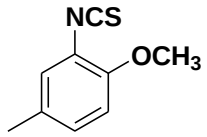
1-isocyano-2-methoxybenzene (0.15g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-isothiocyanato-2-methoxybenzene (MW; 0.11 g 70%, C.H; 0.12 g 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 2H), 6.65 (s, 1H), 3.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 135.6, 132.0, 130.0, 118.1, 113.5, 111.0, 55.1.

5.6.2.15. 1-isothiocyanato-4-methoxybenzene.



1-Isocyano-4-methoxybenzene (0.133mL 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil **1**-isothiocyanato-4-methoxybenzene (MW; 0.09 g 83%, C.H; 0.11g 66%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 133.5, 127.2, 123.3, 115.0, 55.5.

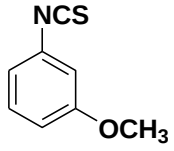
5.6.2.16. 2-isothiocyanato-1-methoxy-4-methylbenzene.



2-isocyano-1-methoxy-4-methylbenzene (0.15g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 2-isothiocyanato-1-methoxy-4-methylbenzene (MW; 0.12 g 82%, C.H; 0.11g 75%).

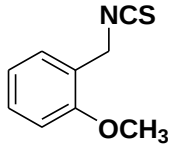
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 6.71 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 152.7, 130.7, 130.0, 127.6, 111.4, 56.2, 20.0.

5.6.2.17. 1-isothiocyanato-3-methoxybenzene.



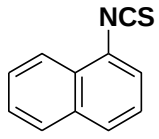
1-Isocyano-4-methoxybenzene (0.133 mL 1mMol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 ml of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil **1**-isothiocyanato-3-methoxybenzene (MW; 0.09 g 83%, C.H; 0.11g 66%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.2 Hz, 2H), 6.75 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 132.1, 130.3, 118.1, 113.5, 111.0, 55.5.

5.6.2.18. 1-isothiocyanato-2-methoxy-1-methylbenzene.



1-Isocyano-4-methoxy-1-methylbenzene (0.163 mL 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a yellow oil 1-isothiocyanato-2-methoxy-1-methylbenzene (MW; 0.09 g 61%, C.H; 0.08g 53%). IR (NaCl): 2121 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.2 Hz, 2H), 6.75 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 134.6, 130.8, 119.1, 115.2, 113.5, 111.9, 55.4.

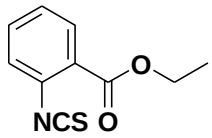
5.6.2.19. 1-isothiocyanatonaphthalene.



1-isocyanonaphthalene (0.15g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the

reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil 1-isothiocyanatonaphthalene (MW; 0.14 ml 95%, C.H; 0.12g 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 6.0, 3.3 Hz, 1H), 7.51 (dt, *J* = 14.8, 7.0 Hz, 2H), 7.33 (dd, *J* = 8.3, 5.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 129.2, 128.4, 127.7, 127.4, 127.4, 127.1, 125.4, 123.5, 122.7.

5.6.2.20. ethyl 2-isothiocyanatobenzoate.



Ethyl 2-isocyanobenzoate (0.18g 1mmol) was dissolved in (2mL acetone/water) and (0.2g 0.5 mmol. of Lawesson's reagent) was added. After the addition of 1 mL of triethylamine (TEA 4 mmol). The reaction was carried out by reflux using a heating mantle for conventional synthesis and by microwave irradiation (850 W) using a microwave oven for microwave-assisted synthesis. The progress of the reaction was monitored by TLC. After the completion of reaction (reflux=1 h, microwave=10 min) the reaction mixture was poured directly into a dry-packed column. A mixture of dichloromethane and hexane (3:1) was used as the mobile phase to afford a colourless oil ethyl 2-isothiocyanatobenzoate (MW; 0.17 ml 94%, C.H; 0.14g 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.25 (dd, *J* = 16.1, 8.0 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 133.7, 133.1, 131.6, 131.0, 130.2, 127.7, 126.8, 123.2, 61.8, 14.3.

5.7. Experimental for Chapter 4, Part Two.

5.7.1. General Experimental Procedures for the Aqua Synthesis of spiro [indole-pyrrolidine] adducts in the presence of piperidine.

A mixture of isatin/5-bromo isatin (1a/1b, 1 mmol) malononitrile (2, 1 mmol), and 4-methoxyphenyl isothiocyanate (4a, 1 mmol) was vigorously stirred in 2 mL water at room temperature for 15 minutes in the presence of 2-3 drops of piperidine. Upon completion, the organic layer was separated, and the combined organic phases were concentrated under reduced pressure and the residue was purify by column chromatography using DCM/Hexane (3: 1) as eluent to afford the desired products. Typical yields range from 80 to 95%. All other products **(5a-l)** were obtained by similar approach.

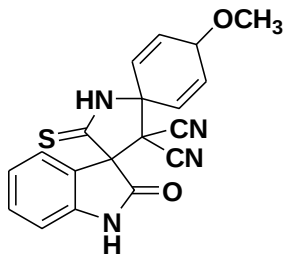
5.7.2. General Procedure for the Mechanochemical Synthesis of spiro [indole-pyrrolidine] adducts (3a/3b).

Step 1. A mixture of isatin/5-bromo isatin (1a/1b, 1 mmol), malononitrile (2, 1 mmol), and additive (water 50 μL) was milled in a 13.2 mL stainless steel milling vessel containing two balls of the same material (diameter: 6 mm; mass: 0.90 g) at 25 Hz for 20 min. After the milling was complete, the content in the milling vessel was transferred into a beaker using a small amount of organic solvent (DCM). Then, purification was done by column chromatography to afford the corresponding Passerini adducts in high to excellent yield.

5.7.3. General Procedure for the Mechanochemical Synthesis of spiro [indole-pyrrolidine] adducts (5a-l).

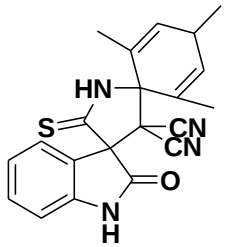
Experiment B. A mixture of 3-dicyanomethylene-2H-indol-2-ones / 5-bromo, 3-dicyanomethylene-2H-indol-2-ones (3a/3b, 1 mmol) and 4-methoxyphenyl isothiocyanate (4a, 1 mmol) with 2-3 drops of piperidine was milled in a 13.2 mL stainless steel milling vessel contained two balls of the same material (diameter: 6 mm; mass: 0.90 g) at 25 Hz for 20 min. After the milling was complete, the content in the milling vessel was transferred into a beaker using a small amount of organic solvent (DCM). Then, purification was done by column chromatography to afford the corresponding oxindole derivatives in high yield.

5.7.3.1. 4-methoxy-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3'' indole]-2,5-diene-3',3'-dicarbonitrile (5a).



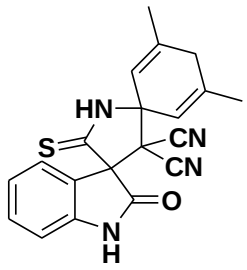
brown solid (Yield: Met A 85%, Met B, 97%); m.p 142-144 ºC. IR (NaCl) ν(cm^{-1}) 3324 (NH), 2220 (CN), and 1710 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 9.06 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 3.96 – 3.77 (m, 1H), 3.74 (s, 1H), 1.59 (d, J = 33.4 Hz, 2H), 1.23 (s, 4H). ^{13}C NMR (101 MHz, DMSO) δ 181.5, 164.6, 156.9, 151.0, 147.1, 138.0, 134.6, 127.8, 126.1, 123.7, 119.1, 113.2, 112.1, 81.0, 61.5, 55.5, 49.2, 29.6, 25.7, 22.2. HR-MS (ESI): [M+H^{+}] calcd for $C_{19}H_{14}N_4O_2S$: 362.0837 found: 362.0998.

5.7.3.2. 2,4,6-trimethyl-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (5b).



brown solid (Yield: Met A 93%, Met B, 92%); m.p 131-132 ºC. IR (NaCl) ν(cm^{-1}) 3336 (NH), 2225 (CN), and 1720 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 8.68 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 3.88 (s, 2H), 2.23 (s, 2H), 2.08 (s, 3H), 1.63 (t, *J* = 13.8 Hz, 2H), 1.54 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 180.7, 164.2, 151.0, 146.6, 138.0, 136.5, 128.5, 126.2, 123.3, 118.8, 113.3, 112.2, 81.2, 49.2, 25.8, 24.4, 20.9. HR-MS (ESI): [M+H^{+}] calcd for $C_{21}H_{18}N_4OS$: 374.1201 found: 374.1265.

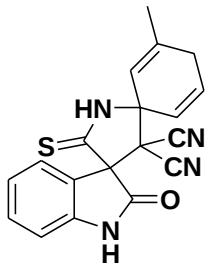
5.7.3.3. 3,5-dimethyl-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (5c).



brown solid (Yield: Met A 95%, Met B, 87%); m.p 140-142 ºC. IR (NaCl) ν(cm^{-1}) 3362 (NH), 2218 (CN), and 1708 (CO). 1H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 10.56 (s, 1H), 10.47 (s, 1H), 10.03 (s, 1H), 9.59 (s, 1H), 8.22 (s, 1H), 7.87 (s, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.12 (dd, J = 15.7, 7.9 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 7.04 – 6.96 (m, 1H), 6.94 (d, J = 6.8 Hz, 1H), 6.87 – 6.79 (m, 1H), 6.76 (s, 1H), 6.70 (s, 1H), 6.59 (s, 1H), 5.76 (s, 1H), 3.56 (d, J = 5.1 Hz, 1H), 2.23 (d, J = 6.0 Hz, 3H), 1.65 (t, J = 18.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 184.9,

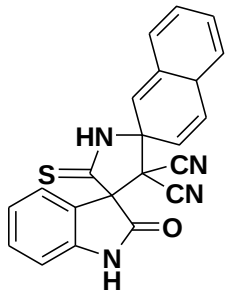
179.7, 167.8, 165.0, 159.7, 151.3, 140.1, 139.6, 139.4, 139.3, 138.3, 137.9, 128.6, 126.6, 125.5, 123.7, 121.8, 121.4, 120.8, 119.5, 117.2, 116.2, 115.6, 114.3, 114.0, 113.6, 109.7, 109.5, 106.4, 56.5, 53.7, 52.4, 44.2, 26.5, 26.2, 23.5, 21.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{20}H_{16}N_4OS$: 360.1044 found: 360.1296.

5.7.3.4. 3-methyl-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (5d).



brown solid (Yield: Met A 91%, Met B, 95%); m.p 138-140 ºC. IR (NaCl) ν(cm^{-1}) 3304 (NH), 2217 (CN), and 1710 (CO). ^{1}H NMR (400 MHz, Acetone) δ 10.02 (s, 1H), 9.76 (s, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.27 (d, J = 8.3 Hz, 1H), 7.16 (s, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.0 Hz, 1H), 5.49 (s, 1H), 4.40 (d, J = 33.9 Hz, 2H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 188.1, 171.3, 164.3, 151.3, 147.1, 138.0, 129.6, 126.1, 123.3, 122.3, 119.1, 118.4, 113.5, 111.8, 81.0, 75.4, 72.9, 67.4, 64.9, 21.2, 17.3, 14.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{19}H_{14}N_4OS$: 347.0888 found: 347.1008.

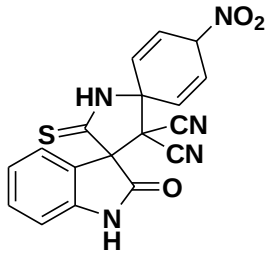
5.7.3.5. 2-oxo-5'-sulfanylidene-1,2-dihydro-4''aH-dispiro[indole-3,4'-pyrrolidine-2',2''-naphthalene]-3',3'-dicarbonitrile (5e).



brown solid (Yield: Met A 87%, Met B, 90%); m.p 156-158 ºC. IR (NaCl) ν(cm^{-1}) 3355 (NH), 2220 (CN), and 1715 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 11.05 (s, 1H), 10.53 (s, 1H), 10.44 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.21 – 7.07 (m, 2H), 7.06 (t, J = 8.6 Hz, 1H), 6.94 (s, 1H), 6.92 (t, J = 8.4 Hz, 2H), 6.83 (d, J = 7.7 Hz, 1H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.7, 167.8, 164.9, 164.1, 159.8, 152.5, 151.0, 147.0, 140.0, 139.3, 138.8, 138.2, 128.6, 126.6, 126.1, 125.1, 123.3, 121.3, 120.8, 119.4, 119.0, 114.2,

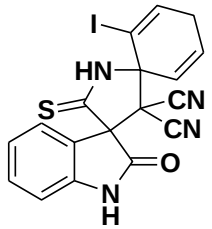
112.1, 109.7, 109.6, 81.0, 53.7, 52.4, 48.0, 23.2. HR-MS (ESI): [M+H$^+$] calcd for $C_{22}H_{14}N_4OS$: 382.1888 found: 382.1886.

5.7.3.6. {3',3'-dicyano-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-dien-4-yl}azinic acid (5f).



brown solid (Yield: Met A 88%, Met B, 93%); m.p 153-155 ºC. IR (NaCl) ν(cm^{-1}) 3328 (NH), 2212 (CN), and 1730 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.44 (s, 1H), 11.24 (s, 1H), 11.17 (s, 1H), 11.06 (s, 1H), 10.58 (s, 1H), 10.48 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.54 – 7.45 (m, 1H), 7.42 (dd, J = 14.6, 6.6 Hz, 1H), 7.25 (d, J = 10.9 Hz, 1H), 7.17 (dd, J = 17.1, 7.8 Hz, 3H), 7.08 (ddd, J = 18.4, 11.9, 4.5 Hz, 3H), 7.01 (dd, J = 14.7, 7.1 Hz, 2H), 6.93 (dd, J = 14.8, 7.2 Hz, 3H), 6.83 (d, J = 7.7 Hz, 3H), 6.17 (s, 1H), 4.03 (dd, J = 14.2, 7.1 Hz, 1H), 3.81 (d, J = 5.0 Hz, 2H), 3.56 (d, J = 5.3 Hz, 5H), 2.73 – 2.56 (m, 2H), 2.09 (s, 21H), 1.68 (d, J = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 207.0, 184.8, 169.7, 167.8, 165.0, 164.2, 159.8, 151.2, 146.9, 140.1, 139.3, 138.8, 138.2, 131.9, 128.7, 126.6, 125.1, 123.6, 123.3, 122.9, 121.4, 120.8, 118.3, 116.3, 115.3, 114.3, 112.6, 109.7, 106.3, 81.0, 65.6, 60.3, 53.8, 48.1, 31.1, 23.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{18}H_{12}N_5O_3S$: 379.0739 found: 379.0714

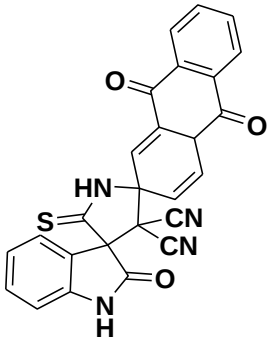
5.7.3.7. 2-iodo-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (5g).



brown solid (Yield: Met A 91%, Met B, 96%); m.p 130-132 ºC. IR (NaCl) ν(cm^{-1}) 3337 (NH), 2220 (CN), and 1718 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 10.07 (s, 1H), 9.56 (s, 1H), 9.47 (s, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.9 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 6.12 (dd, J = 14.5, 6.7 Hz, 2H), 6.08 (d, J = 8.1 Hz, 1H), 5.93 (t, J = 7.5 Hz, 2H), 5.84 (d, J = 7.6 Hz, 1H), 0.69 (d, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 172.7, 168.9, 164.3, 155.7, 151.4, 143.1, 130.9, 129.9,

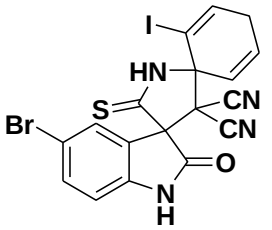
128.0, 126.1, 123.7, 118.3, 116.7, 114.3, 85.8, 58.5, 57.2, 31.4, 28.2. HR-MS (ESI): [M+H$^+$] calcd for $C_{18}H_{11}IN_4OS$: 457.9698 found: 457.9610.

5.7.3.8. 2'',9,10-trioxo-5'-sulfanylidene-1'',2'',9,10-tetrahydro-4aH-dispiro[anthracene-2,2'-pyrrolidine-4',3''-indole]-3',3'-dicarbonitrile (5h).



brown solid (Yield: Met A 76%, Met B, 84%); m.p 157-159 ºC. IR (NaCl) ν(cm^{-1}) 3346 (NH), 2230 (CN), and 1715 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 11.01 (s, 1H), 10.51 (d, J = 38.1 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.14 (dq, J = 15.8, 7.7 Hz, 2H), 7.02 (dt, J = 15.6, 8.2 Hz, 1H), 6.93 (t, J = 6.7 Hz, 2H), 6.83 (d, J = 7.7 Hz, 1H), 5.54 (s, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.59 (dd, J = 23.0, 11.6 Hz, 2H), 2.51 (s, 2H), 1.67 (d, J = 8.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 207.0, 204.2, 175.8, 170.9, 167.8, 163.9, 151.0, 147.1, 143.6, 139.8, 138.4, 130.3, 128.6, 126.9, 123.3, 121.2, 118.8, 113.6, 111.8, 110.4, 109.3, 106.2, 81.3, 60.4, 53.4, 51.9, 48.1, 45.6, 30.3, 26.0, 23.6, 21.2, 14.2. HR-MS (ESI): [M+H$^+$] calcd for $C_{26}H_{14}N_4O_3S$: 462.0786 found: 462.0796.

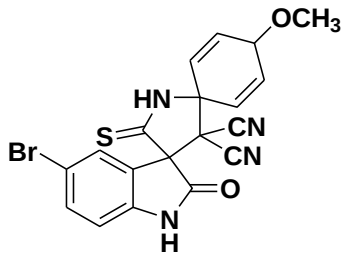
5.7.3.9. 5''-bromo-2-iodo-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (51).



brown solid (Yield: Met A 86%, Met B, 92%); m.p 130-132 ºC. IR (NaCl) ν(cm^{-1}) 3323 (NH), 2214 (CN), and 1726 (CO). ^{1}H NMR (400 MHz, CD3CN) δ 9.05 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 9.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.06 (q, J = 7.1 Hz, 1H), 2.28 (s, 6H), 1.24 (d, J = 14.9 Hz, 1H), 1.21 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, CD3CN) δ 163.5, 149.7, 145.2, 140.3, 138.2, 128.6, 126.7, 124.1, 120.9, 115.6,

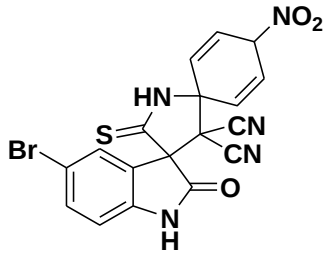
113.9, 112.6, 112.1, 111.3, 83.6, 60.7, 20.7, 14.0. HR-MS (ESI): [M+H$^+$] calcd for $C_{18}H_{10}BrIN_4OS$: 535.8803 found: 535.8825.

5.7.3.10. 5''-bromo-4-methoxy-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile (5j).



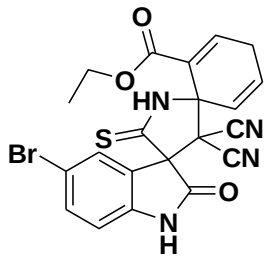
brown solid (Yield: Met A 91%, Met B, 83%); m.p 151-153 ºC. IR (NaCl) *v*(cm^{-1}) 3361 (NH), 2225 (CN), and 1710 (CO). 1H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 11.23 (s, 1H), 11.16 (d, J = 3.7 Hz, 1H), 7.91 (s, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 6.94 (t, J = 6.6 Hz, 1H), 5.58 (s, 1H), 4.09 – 3.94 (m, 1H), 2.09 (s, 8H), 1.99 (s, 1H), 1.23 (s, 1H), 1.18 (t, J = 7.1 Hz, 1H). 13C NMR (101 MHz, DMSO) δ 207.0, 163.9, 149.9, 146.1, 140.1, 128.2, 123.3, 120.9, 113.9, 113.2, 111.8, 82.7, 60.0, 31.3, 21.2, 14.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{19}H_{13}BrN_4O_2S$: 439.9942 found: 439.9904.

5.7.3.11. {5''-bromo-3',3'-dicyano-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-dien-4-yl}azinic acid (5k).



brown solid (Yield: Met A 80%, Met B, 87%); m.p 157-159 ºC. IR (NaCl) *v*(cm^{-1}) 3345 (NH), 2220 (CN), and 1708 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 11.23 (s, 1H), 10.63 (d, J = 28.5 Hz, 1H), 7.89 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 6.7 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.61 (d, J = 5.3 Hz, 1H), 3.48 (s, 1H), 2.09 (s, 3H), 1.99 (s, 1H), 1.70 (d, J = 13.9 Hz, 2H), 1.18 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 207.0, 163.5, 149.9, 145.7, 140.1, 127.9, 120.9, 114.2, 112.9, 111.8, 82.4, 60.4, 54.1, 52.7, 30.9, 26.4, 20.8, 14.5. HR-MS (ESI): [M+H$^+$] calcd for $C_{18}H_{12}BrN_5O_3S$: 457.9844 found: 457.9835.

5.7.3.12. ethyl-5''-bromo-3',3'-dicyano-2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-2-carboxylate (5l).



brown solid (Yield: Met A 95%, Met B, 96%); m.p 150-152 ºC. IR (NaCl) ν(cm^{-1}) 3358 (NH), 2220 (CN), and 1725 (CO). ^{1}H NMR (400 MHz, DMSO) δ 11.11 (s, 1H), 10.56 (d, J = 28.2 Hz, 1H), 7.68 (s, 1H), 7.52 (s, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.09 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 5.69 (s, 1H), 5.51 (s, 1H), 3.96 (q, J = 7.1 Hz, 1H), 3.54 (s, 2H), 3.41 (s, 2H), 2.01 (s, 1H), 1.92 (s, 1H), 1.61 (s, 6H), 1.11 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 204.2, 175.4, 170.8, 167.6, 164.6, 142.9, 138.7, 133.1, 130.1, 129.4, 128.4, 127.8, 126.9, 125.5, 125.2, 123.8, 121.7, 113.9, 112.5, 111.7, 110.2, 103.9, 60.2, 54.1, 52.7, 48.7, 30.0, 26.5, 23.4, 23.2, 14.5. HR-MS (ESI): [M+H^{+}] calcd for $C_{21}H_{15}BrN_4O_3S$: 482.0048 found: 482.0027.

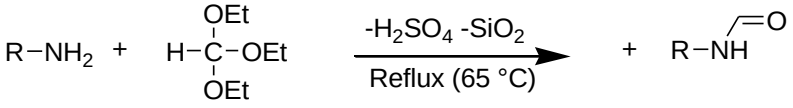
6. Chapter 6.

6.1. Summary and conclusions.

The major aim and objectives of this thesis was the exploration of new sustainable multicomponent reactions involving isocyanide and isothiocyanates. Initial exploration of the classical Passerini reaction allowed for the discovery of conditions that were widely applicable to different reagents and permitted further development into new sustainable methodologies in spiro-heterocyclic compound synthesis.

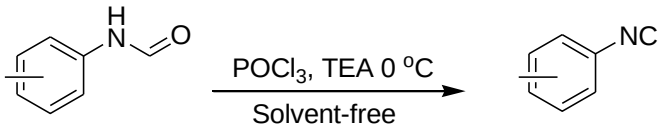
A two-steps method for the synthesis of isocyanides from amines has been developed. Firstly, the amine is converted to the *N*-formamide, followed by dehydration to the corresponding isocyanide.

It all starts from developing a simple, green, and highly efficient protocol for the *N*-formylation of various amines carried out in the presence of the immobilized sulfuric acid on silica gel as a promoter system (H_2SO_4–SiO_2). All reactions were performed in refluxing triethyl orthoformate (65 °C). The product formamides were obtained in high to excellent yields within 4 min. The approach is advantageous due to its solvent-free state, short reaction time, and high yields. The catalyst is recyclable with no significant loss in catalytic activity **(Scheme 6.1).**



Scheme 6.1. *N*-formylation of amines with triethyl orthoformate.

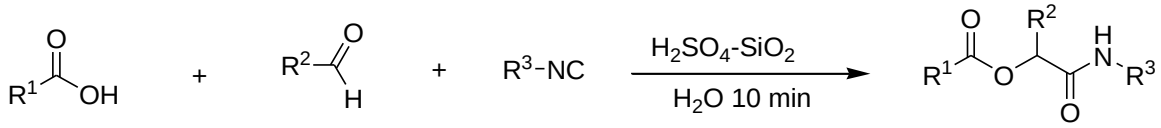
We later proceeded to dehydration of the resultant formamides using phosphorus oxychloride in the presence of triethylamine. To optimize the technique for $POCl_3$-based formamide dehydration and gain access to a large number of isocyanides with a wide structural diversity. We developed a more sustainable method for the synthesis of isocyanide under solvent-free condition in the presence of triethylamine as base. The product isocyanides were obtained in high purity and excellent yields in less than 5 minutes. The advantages of the protocol include increased synthesis speeds, very mild conditions, rapid access to large numbers of functionalized isocyanides, increased yields, high purity, and less reaction waste **(Scheme 6.2).**



Scheme 6.2. Dehydration of *N*-(3-bromophenyl)formamide to 3-bromo-1-isocyanobenzene.

Furthermore, as an example of a one-pot multicomponent reaction, the formation of α-acyloxycarboxamides from a carboxylic acid, an aldehyde and substituted isocyanide was investigated

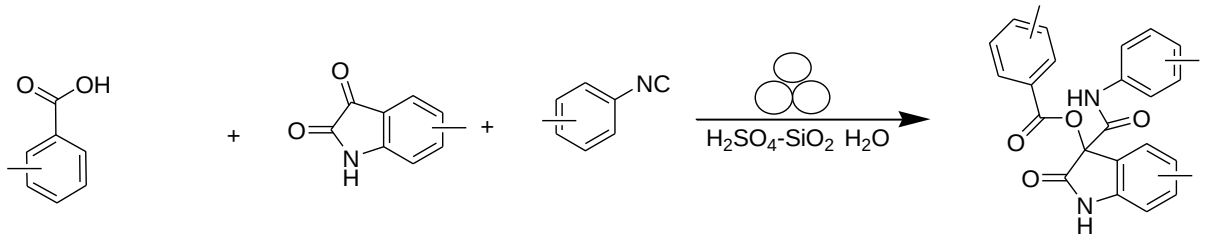
in aqueous media. Passerini reactions were completed in 10 minutes in the presence of the immobilized sulfuric acid on silica gel in aqueous media and excellent yields were observed. This method is significantly greener than the classical Passerini reaction because water is non-toxic, non-flammable, environmentally friendly, cheap, and readily available **(Scheme 6.3).** The simplicity of this method will form the basis of a new laboratory practical. This will allow not only the introduction of things like MCR but Green Chemistry and even Mechanochemistry.



Scheme 6.3. Passerini reaction under the optimized catalytic conditions.

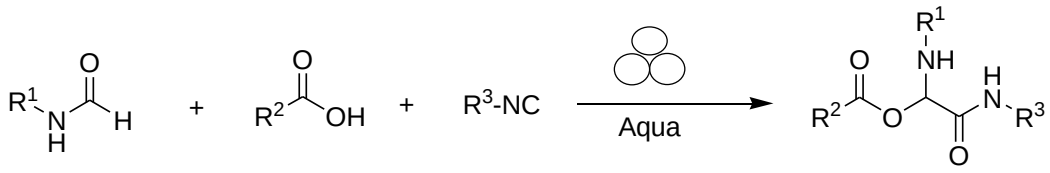
Following our success on the aqua organic reaction, we developed another sustainable technique for the subsequent synthesis of various Passerini adducts via mechanochemistry, according to IUPAC this is the latest emerging technique that would change the world.

Under this aqua and mechanochemical conditions, a protocol based on Passerini multi-component reaction has been developed for facile, efficient, environmentally benign, and economic atom synthesis of a small library of biologically important oxindole derivatives employing isatin, substituted benzoic acid and various functionalized isocyanides. This is interesting because oxindoles having a quaternary benzylic centre represent a common structural motif in many natural products and biologically active compounds **(Scheme 6.4).**



Scheme 6.4: Model Passerini reaction in aqueous media.

Furthermore, we investigated the scope of the carbonyl component in the Passerini reaction, and developed a simple, efficient, and environmentally friendly protocol for the catalytic synthesis of α-acyloxycarboxamides using *N*-formamides as a carbonyl precursor under aqua and mechanochemical conditions. The immobilized sulfuric acid on silica gel was employed for the synthesis of desired products, via the reaction of benzoic acid, 1-napthylisocyanide and various heterocyclic *N*-formamides **(Scheme 6.5).**



Scheme 6.5: Aqua/Mechano mediated Passerini reaction utilizing various heterocyclic *N*-formamides as a replacement for the carbonyl component.

In the final part of the project, we explored the novel synthesis of isothiocyanates using Lawesson's reagent and their application in spiro-heterocyclic chemistry. A general, practical, and highly efficient protocol for the preparation of a broad range of functionalized isothiocyanates has been developed from their corresponding isocyanides using Lawesson's reagent and a catalytic amount of amine bases, particularly triethylamine under microwave irradiation conditions **(Scheme 6.6).** As opposed to established approaches that employ toxic or volatile electrophilic liquids (thiophosgene, its derivatives, or CS_2).

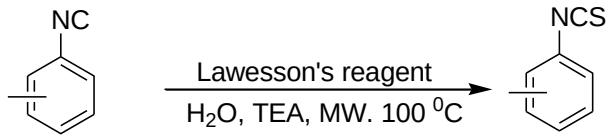
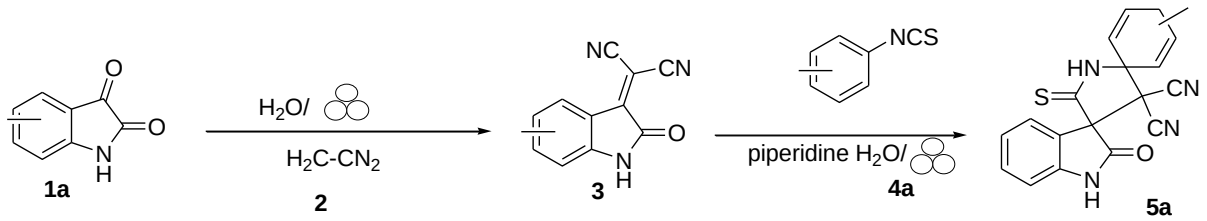


Figure 6.6: Aqueous microwave irradiation conditions for the synthesis of isothiocyanates using Lawesson's reagent.

The final part of the manuscript deals with the development of a more sustainable methodology towards the synthesis of spiroindole-pyrrolidine derivatives using isothiocyanates as a formal dipole in [3+2] cycloaddition under aqua and mechanochemical conditions **(Scheme 6.7).** We have investigated the reaction of indole-2,3-dione **(1a)** with malononitrile **(2)** to give 3-dicyanomethylene-2H-indol-2- ones **(3)** that was cyclocondensed *in situ* with isothiocyanates **(4a)** leading to the facile one-pot synthesis of 2''-oxo-5'-sulfanylidene-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-4',3''-indole]-2,5-diene-3',3'-dicarbonitrile **(5a).**



Scheme 6.7: Aqua/Mechanochemical mediated synthesis of spiroindole-pyrrolidine derivatives.

In conclusion, isocyanides are versatile synthesis building blocks, and this thesis proves that despite decades of intensive study, there is still plenty of potential for new chemistry to be developed utilizing them.

Acknowledgement:

This research was funded by the National Research Foundation of South Africa (TWAS/NRF) with grant number 116109.

Supplementary File

The link to the supplementary file can be accessed via the link below.

https://support.google.com/drive/answer/2424384?hl=en

References

[1] Tiwari, T.; and Talreja, S. Green Chemistry and Microwave Irradiation Technique: *J. Pharm. Res. Int.*, **2022**, 34, 74–79, doi: 10.9734/jpri/2022/v34i39a36240.

[2] Alfonsi, K.; Colberg, J.; Peter J.D.; Thomas F.; Sandra J.; Timothy A. J.; Peter K.; Craig K.; Mark A.N.; David A.P.; and Mark S. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation," *Green Chem.*, **2008**, 10, 31–36, doi: 10.1039/b711717e.

[3] Prat, D.; Hayler, J.; and Wells, A. A survey of solvent selection guides, *Green Chem.*, **2014**, 16, 10, 4546–4551, 2014, doi: 10.1039/c4gc01149j.

[4] Ran N.; Zhai L.; Chen Z.; Tao J. Recent application of biocatalysis in developing green chemistry for chemical synthesis at the industrial scale. *Green Chem,* **2008**, 16, 361-372.

[5] Ingold, M.; Colella, L.; Dapueto, R.; López, G.V.; and Porcal, W. Ugi Four-component Reaction (U-4CR) Under Green Conditions Designed for Undergraduate Organic Chemistry Laboratories," *World J. Chem. Educ.*, **2017**, 5, 153–157. doi: 10.12691/wjce-5-5-2.

[6] Draye, M.; Chatel, G.; and Duwald, R. Ultrasound for drug synthesis: A green approach, *Pharmaceuticals*, **2020**, 13, 2. doi: 10.3390/ph13020023.

[7] M. O. Simon and C. J. Li. Green chemistry oriented organic synthesis in water, *Chem. Soc. Rev.*, **2012**, vol. 41, 4, 1415–1427, doi: 10.1039/c1cs15222j.

[8] Denis P.; Andy W.; John H.; Helen S.; Robert M.; Abou-Shehada, S.; Peter J.D. Chem 21 selection guide of classical- and less classical-solvents, *Green Chem.*, **2015**, 18, 288–296, doi: 10.1039/c5gc01008j.

[9] Cioc, R.C.; Ruijter, E.; and Orru, R.V.A. Multicomponent reactions: Advanced tools for sustainable organic synthesis, *Green Chem.*, **2014**, 16, 2958–2975, doi: 10.1039/c4gc00013g.

[10] Hernández, J.G.; and Juaristi, E. Recent efforts directed to the development of more sustainable asymmetric organocatalysis, *Chem. Commun.*, **2012**, 48, 44, 5396–5409, doi: 10.1039/c2cc30951c.

[11] Watson, W. Green chemistry metrics, *Chim. Oggi/Chemistry Today*, **2014**, 32, 14–15, doi: 10.1007/s10098-009-0264-x.

[12] Parveen, K.; Banse, V.; and Ledwani, L. Green synthesis of nanoparticles: Their advantages and disadvantages, *AIP Conf. Proc.*, **2016**, 1724. doi: 10.1063/1.4945168.

[13] Kitanosono, T.; Masuda, K.; Xu, P.; and Kobayashi, S. Catalytic Organic Reactions in Water

toward Sustainable Society, *Chem. Rev.*, **2018**, 118, 679–746, doi: 10.1021/acs.chemrev.7b00417.

[14] Pirrung, M.C.; and Das Sarma, K. Aqueous medium effects on multi-component reactions, *Tetrahedron*, **2005**, 61, 48, 11456–11472. doi: 10.1016/j.tet.2005.08.068.

[15] Irwansyah, F.S.; Noviyanti, A.R.; Eddy, D.R.; Risdiana, R. Green Template-Mediated Synthesis of Biowaste Nano-Hydroxyapatite: A Systematic Literature Review. *Molecules* **2022**, 27, 5586. https://doi.org/10.3390/ molecules27175586

[16] Francisco García Calvo-Flores Dr. Sustainable Chemistry Metrics, *ChemsusChem,* **2009**, 2, 10, 905-919. https://doi.org/10.1002/cssc.200900128.

[17] Akbari, J. Synthesis of α-amino nitriles through Strecker-type reaction using SO 3H - functionalized ionic liquid as a homogeneous and water tolerant-acidic catalyst, *Comptes Rendus Chim.*, **2012**, 15, 6, 471–473, doi: 10.1016/j.crci.2011.12.005.

[18] Massah, A.R,; Azadi, D.; Aliyan, H.; Momeni, A.R..; Naghash, H.J.; and Kazemi, F. An efficient method for the synthesis of N-acylsulfonamides: One-pot sulfonylation and acylation of primary arylamines under solvent-free conditions, *Monatshefte fur Chemie*, **2008**, 139, 233–240, doi: 10.1007/s00706-007-0783-2.

[19] Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z.; and Salavati, H. Chemoselective synthesis of 2-aryloxazines and 2-aryltetrahydropyrimidines using nano-SiO2 as a reusable solid acid catalyst under thermal conditions and microwave irradiation, *J. Iran. Chem. Soc.*, **2011**, 8, 17–27, doi: 10.1007/bf03254278.

[20] Kannasani, R.K.; Peruri, V.V.S.; and Battula, S.R. "$NaHSO_4$-SiO_2 as an efficient and chemoselective catalyst, for the synthesis of acylal from aldehydes under, solvent-free conditions, *Chem. Cent. J.*, **2012**, 6, 1, doi: 10.1186/1752-153X-6-136.

[21] Abhishek, D.; Nadavala, S.K.; Mehul K.; Ahmed S.A.; Ahmed A.I.; Anis H.F.; Hiren P.; and Rohit L.V. Silica-immobilized ionic liquid Brønsted acids as highly effective heterogeneous catalysts for the isomerization of: N -heptane and n -octane, *RSC Adv.*, **2020**, 10, 26, 15282–15292, doi: 10.1039/d0ra00556h.

[22] Maleki, B.; Keshvari Shirvan, H.; Taimazi, F.; and Akbarzadeh, E. Sulfuric Acid Immobilized on Silica Gel as Highly Efficient and Heterogeneous Catalyst for the One-Pot Synthesis of 2,4,5-Triaryl-1H-imidazoles, *Int. J. Org. Chem.*, **2012**, 02, 93–99, doi: 10.4236/ijoc.2012.21015.

[23] Kiasat, A.R.; Mouradzadegun, A.; Elahi, S.; and Fallah-Mehrjardi, M. ChemInform Abstract: $Al(HSO_4)_3$/Silica Gel as a Novel Catalytic System for the Ring Opening of Epoxides with

Thiocyanate Anion under Solvent-Free Conditions., *ChemInform*, **2010**, 41, 26, p. doi: 10.1002/chin.201026062.

[24] Ma'mani, L.; Sheykhan, M.; Heydari, A.; Faraji, M.; and Yamini, Y. Sulfonic acid supported on hydroxyapatite-encapsulated-γ-Fe2O3 nanocrystallites as a magnetically Brønsted acid for N-formylation of amines, *Appl. Catal. A Gen.*, **2010**, 377, 64–69, doi: 10.1016/j.apcata.2010.01.020.

[25] Rasheed, S.; Rao, D.N.; Reddy, A.S.; Shankar, R.; and Das, P. Sulphuric acid immobilized on silica gel ($H2SO_4$-SiO_2) as an eco-friendly catalyst for transamidation," *RSC Adv.*, **2015**, 5, 10567–10574, 2015, doi: 10.1039/c4ra16571c.

[26] Suresh and Sandhu, J.S. Past, present and future of the Biginelli reaction: A critical perspective," *Arkivoc*, 2012, **2012**, 66–133, doi: 10.3998/ark.5550190.0013.103.

[27] Price, P.M.; Clark, J.H.; and Macquarrie, D.J. Modified silicas for clean technology, *J. Chem. Soc. Dalt. Trans.*, **2008**, 2, 101–110.

[28] Pramanik, A.; and Bhar, S. Silica-sulfuric acid and alumina-sulfuric acid: versatile supported Brønsted acid catalysts, *New J. Chem.*, **2021**, 45, 16355–16388, doi: 10.1039/d1nj02887a.

[29] Štrukil, V.; Margetic, D.; Igrc, M.D.; Eckert-Maksic, M.; and Frišcic, T. Desymmetrisation of aromatic diamines and synthesis of non-symmetrical thiourea derivatives by click-mechanochemistry, *Chem. Commun.*, **2012**, 48, 9705–9707, doi: 10.1039/c2cc34013e.

[30] Gómez-C.J.; Sánchez, J.D.; González, J.F.; and Menéndez, J.C. Mechanochemical Synthesis of Primary Amides, *J. Org. Chem.*, **2021**, 86, 14232–14237, doi: 10.1021/acs.joc.1c02350.

[31] Banerjee, M.; Bhosle, A.A.; Chatterjee, A.; and Saha, S. Mechanochemical Synthesis of Organic Dyes and Fluorophores, *J. Org. Chem.*, **2021**, 86, 13911–13923, doi: 10.1021/acs.joc.1c01540.

[32] Brindaban C.R.; Tanmay C.; and Nirmalya M. Carbon–Heteroatom Bond Forming Reactions and Heterocycle Synthesis under Ball Milling. *RSC Green Chem,* **2014**, 1-33, doi: 10.1039/9781782621980-00001

[33] Rightmire, N.R.; and Hanusa, T.P. Advances in organometallic synthesis with mechanochemical methods, *Dalt. Trans.*, **2016**, 45, 6, 2352–2362, doi: 10.1039/c5dt03866a.

[34] Gomollón-Bel, F. Ten Chemical Innovations That Will Change Our World, *Chem. Int.*, **2020**, 42, 4, 3–9, doi: 10.1515/ci-2020-0402.

[35] Pérez-Venegas, M.; and Juaristi, E. Mechanochemical and Mechanoenzymatic Synthesis of Pharmacologically Active Compounds: A Green Perspective, *ACS Sustain. Chem. Eng.*, **2020**, 8, 24, 8881–8893, doi: 10.1021/acssuschemeng.0c01645.

[36] Friščić, T. Supramolecular concepts and new techniques in mechanochemistry: Cocrystals, cages, rotaxanes, open metal–organic frameworks, *Chem. Soc. Rev.*, **2012**, 41, 9, 3493–3510, doi: 10.1039/c2cs15332g.

[37] Polindara-García, L.A.; and Juaristi, E. Synthesis of Ugi 4-CR and Passerini 3-CR Adducts under Mechanochemical Activation," *European J. Org. Chem.*, **2016**, 6, 1095–1102, doi: 10.1002/ejoc.201501371.

[38] Hernández, J.G.; and Friščić, T. Metal-catalyzed organic reactions using mechanochemistry, *Tetrahedron Lett.*, **2015,** 56, 29, 4253–4265, doi: 10.1016/j.tetlet.2015.03.135.

[39] Hernández, J.G.; Frings, M.; and C. Bolm, C. Mechanochemical Enzymatic Kinetic Resolution of Secondary Alcohols under Ball-Milling Conditions, *ChemCatChem*, **2016**, 8, 10, 1769–1772, doi: 10.1002/cctc.201600455.

[40] Kleine, T.; Buendia, J.; and Bolm, C. Mechanochemical degradation of lignin and wood by solvent-free grinding in a reactive medium, *Green Chem.*, **2013**, 15, 1, 160–166, doi: 10.1039/c2gc36456e.

[41] Sandra M.H.; Carolin G.; David T.R.;, Joshua H.T.; Eric J.B.; Caroline B.; and Richard G.B. Mechanocatalysis for biomass-derived chemicals and fuels. *Green Chem.*, **2010**, 12, 3, 468–47, doi: 10.1039/b923079c.

[42] Meine, N.; Rinaldi, R.; and Schüth, F. Solvent-Free catalytic depolymerization of cellulose to water-soluble oligosaccharides, *ChemSusChem*, **2012**, 5, 8, 1449–1454, doi: 10.1002/cssc.201100770.

[43] Rodríguez, B.; Bruckmann, A.; Rantanen, T.; and Bolm, C. Solvent-free carbon-carbon bond formations in ball mills, *Adv. Synth. Catal.*, **2007**, 349, 14–15, 2213–2233, doi: 10.1002/adsc.200700252.

[44] Hernández, J.G.; Turberg, M.; Schiffers, I.; and Bolm, C. Mechanochemical Strecker Reaction: Access to α-Aminonitriles and Tetrahydroisoquinolines under Ball-Milling Conditions, *Chem. - A Eur. J.*, **2016**, 22, 41, 14513–14517, doi: 10.1002/chem.201603057.

[45] Wang, G.W. Mechanochemical organic synthesis, *Chem. Soc. Rev.*, **2013**, 42, 18, 7668–7700, doi: 10.1039/c3cs35526h.

[46] Krunoslav, U.; Vjekoslav, S.; Cristina, M.; Patrick, A. J.; Andreas, P.; Tomislav, F.; and Ivan, H. Exploring the Effect of Temperature on a Mechanochemical Reaction by in Situ Synchrotron Powder X-ray Diffraction, *Cryst. Growth Des.*, **2016**, 16, 4, 2342–2347, doi: 10.1021/acs.cgd.6b00137.

[47] Mathijs F. J.; Anja R. A.; and Meijer E.W. Solute–Solvent Interactions in Modern Physical Organic Chemistry: Supramolecular Polymers as a Muse, *J. Am. Chem. Soc.* **2020**, 142, 47, 19781–19798

[48] Arani C.; and Valery V.F. Organic Synthesis ‘ On Water , *Chem. Rev.,* **2014**, 109, 2, 725–748, doi: 10.1021/cr800448q.Organic.

[49] Tomiichi H.; Y.; Akiomi U.; Masaki G. Continuous organic synthesis in water around micro-orifices after flows, *Heliyon,* **2020**, 6, 3, 2405-8440, https://doi.org/10.1016/j.heliyon.2020.e03630.

[50] Insuasty, D.; Castillo, J.; Becerra, D.; Rojas, H.; and Abonia, R. “Synthesis of biologically active molecules through multicomponent reactions, *Molecules*, **2020**, 25, 3,1–71, doi: 10.3390/molecules25030505.

[51] Safaei, H.R.; and Shekouhy, M. Eco-friendly multi-component synthesis of γ-spiroiminolactones in water, *Acta Chim. Slov.*, **2017**, 64, 4, 1020–1029, doi: 10.17344/acsi.2017.3773.

[52] Pirrung, M.C.; Das Sarma, K.; and Wang, J. Hydrophobicity and mixing effects on select heterogeneous, water-accelerated synthetic reactions, *J. Org. Chem.*, **2008**, 73, 22, 8723–8730, doi: 10.1021/jo801134r.

[53] Hooper, M.M.; and De Boef, B. A green multicomponent reaction for the organic chemistry laboratory: The aqueous passerini reaction, *J. Chem. Educ.*, **2009**, 86, 9, 1077–1079, doi: 10.1021/ed086p1077.

[54] Sela, T.; and Vigalok, A. Salt-controlled selectivity in ‘on water’ and ‘in Water’ passerini-type multicomponent reactions, *Adv. Synth. Catal.*, **2012**, 354, 13, 2407–2411. doi: 10.1002/adsc.201200448.

[55] Narayan, S.; Muldoon, J.; Finn, M.G.; Fokin, V.V.; Kolb, H.C.; and Sharpless, K.B.; On Water’: Unique Reactivity of Organic Compounds in Aqueous Suspension, *Nature*, **2005**, 3, 3275–3279. doi: 10.1002/anie.200462883.

[56] Sijbren O.; Jan B.F.; Engberts, N.; and Jan C.T.K. Million-Fold Acceleration of a Diels - Alder Reaction due to Combined Lewis Acid and Micellar Catalysis in Water, *J. Am. Chem. Soc.*, **1998**, 7863, 8, 9517–9525.

[57] Cortes-Clerget, M.; Yu, J.; Kincaid, J.R.A.; Walde, P.; Gallou, F.; and Lipshutz, B.H. Water as the reaction medium in organic chemistry: From our worst enemy to our best friend, *Chem. Sci.*, **2021**, 12, 12, 4237-4266, doi: 10.1039/d0sc06000c.

[58] Madje, B.R.; Shelke, K.F.; Sapkal, S.B.; Kakade, G.K.; and Shingare, M.S. An efficient one-pot synthesis of anthraquinone derivatives catalyzed by alum in aqueous media, *Green Chem. Lett. Rev.*, **2010**, 3, 4, 269–273, doi: 10.1080/17518251003776877.

[59] Van der Eycken, E.V. Aqueous Microwave Assisted Chemistry. Synthesis and Catalysis. *Angew. Chemie Int. Ed.*, **2010**, 49, 52, 10039–10040, doi: 10.1002/anie.201006427.

[60] De La Hoz, A., Díaz-Ortiz, A.; and Prieto, P. *Microwave-assisted green organic synthesis*, *Green Chem.,* **2016**, 2016, 47.

[61] Lu, X.; Wang, H.; Gao, R.; Sun, D.; and Bi, X. Microwave-assisted synthesis of asymmetric disulfides," *RSC Adv.*, **2014**, 4, 54, 28794–28797, doi: 10.1039/c4ra03592e.

[62] Desai, B.; Danks, T.N.; and Wagner, G. Thermal and microwave-assisted N-formylation using solid-supported reagents, *Tetrahedron Lett.*, **2005**, 46, 6, 955–957, doi: 10.1016/j.tetlet.2004.12.044.

[63] Varma, R.S. Greener chemical syntheses using mechanochemical mixing or microwave and ultrasound irradiation, *Green Chem. Lett. Rev.*, **2007**, 1, 1, 37–45, doi: 10.1080/17518250701756991.

[64] Filippi, J.J.; X. Fernandez, X.; Lizzani-Cuvelier, L.; and Loiseau, A.M. Solvent-free thionation of γ-lactones under microwave irradiation, *Tetrahedron Lett.*, **2003**, 44, 35, 6647–6650, doi: 10.1016/S0040-4039(03)01636-8.

[65] Varma, R.S.; and Kumar, D. Microwave-accelerated solvent-free synthesis of thioketones, thiolactones, thioamides, thionoesters, and thioflavonoids, *Org. Lett.*, **1999**, 1, 5, 697–700, doi: 10.1021/ol990629a.

[66] Wöhler, F.; Ueber künstliche Bildung des Harnstoffs, *Ann. Phys.*, **1828**, 88, 2, 253–256, doi: 10.1002/andp.18280880206.

[67] Ping, W.; Suwei D.; John A.B.; Karthik I.; Steven D.T.; Qiang, Z.; Ronald C.H.; JaeHung S.; Malcolm A.S.M.; Samuel J.D. Erythropoietin as a single glycoform," *Angew. Chemie - Int. Ed.*, **2012**, 51, 46, 11576–11584, doi: 10.1002/anie.201206090.

[68] Cioc, R.C.; Ruijter, E.; and Orru, R.V.A. Multicomponent Reactions: Advanced Tools for Sustainable Organic Synthesis *Green Chem.*, **2014**, 16, 1–18.

[69] Cores, Á.; Clerigué, J.; Orocio-Rodríguez, E.; Menéndez, J.C. Multicomponent Reactions for the Synthesis of Active Pharmaceutical Ingredients. *Pharmaceuticals*, **2022**, 15, 1009. https://doi.org/10.3390/ ph15081009

[70] Gjalt, W.H.; David G. Towards novel processes for the fine-chemical and pharmaceutical

industries, *Current Opinion in Biotechnology,* **2002**, 13, 4, 352-358, https://doi.org/10.1016/S0958-1669(02)00335-X.

[71] Touré, B.B.; and Hall, D.G. Natural product synthesis using multicomponent reaction strategies, *Chem. Rev.*, **2009**, 109, 9, 4439–4486, doi: 10.1021/cr800296p.

[72] Patil, Pravin. "From isocyanide based multicomponent reactions to heterocyclic synthesis." *PhD diss.,* Ecole Polytechnique X, **2012**.

[73] Ugi, I.; Werner, B.; and Dömling, A. The chemistry of isocyanides, their multicomponent reactions and their libraries, *Molecules*, **2003**, 8, 1, 53–66, doi: 10.3390/80100053.

[74] Maeda, S.; Komagawa, S.; Uchiyama, M.; and Morokuma, K. Finding reaction pathways for multicomponent reactions: The passerini reaction is a four-component reaction," *Angew. Chemie - Int. Ed.*, **2011**, 50, 3, 644–649. doi: 10.1002/anie.201005336.

[75] Wang, G.W. and Li, J.X.. Novel multicomponent reaction of fullerene: the first example of 1, 4-dipolar cycloaddition reaction in fullerene chemistry. *Org. & Bio. Chem.,* **2006**, 4, 22, 4063-4064.

[76] Dömling, A.; and Ugi, I. Multicomponent reactions with isocyanides, *Angew. Chemie - Int. Ed.*, **2000**, 39, 18, 3168–3210, doi: 10.1002/1521-3773(20000915)39:18<3168

[77] Koopmanschap, G.; Ruijter, E.; and Orru, R.V.A. Isocyanide-based multicomponent reactions towards cyclic constrained peptidomimetics, *Beilstein J. Org. Chem.*, **2014**, 10, 544–598, doi: 10.3762/bjoc.10.50.

[78] Eckert, H.; and Ugi, I. *The Role of Isocyanides in the Synthesis of β-Lactam Antibiotics and Related Compounds*, *Elsevier B.V.,* **1993**, 12, 10.

[79] Douguet, D. A computational-aided drug design web server, *Nucleic Acids Res.*, **2012**, 38, 2, 615–621, doi: 10.1093/nar/gkq322.

[80] Zarganes-Tzitzikas, T.; Chandgude, A.L.; and Doemling, A. ChemInform Abstract: Multicomponent Reactions, Union of MCRs and Beyond, *ChemInform*, **2015**, 46, 52, doi: 10.1002/chin.201552205.

[81] Dömling A. Innovations and Inventions: Why Was the Ugi Reaction Discovered Only 37 Years after the Passerini Reaction?. *J. Org. Chem,.* **2022**.

[82] Chen, W., Peng, X.W., Zhong, L.X., Li, Y. and Sun, R.C. Lignosulfonic acid: A renewable and effective biomass-based catalyst for multicomponent reactions. *ACS Sus. Chem. & Eng.,* **2015**, 3, 7, 1366-1373.

[83] Habibi-Khorassani, S.M., Shahraki, M. and Talaiefar, S. Full Kinetics and Mechanism Investigation for Generating 4-Substituted 1, 4-Dihydropyridine Derivatives in the Presence of Green Catalyst and Aqueous Medium: Experimental Procedure. *Curr. Org. Syn,* **2021**, 18, 6, 598-613.

[84] Maxwell, M.J., Arnold, A., Sweeney, H., Chen, L., Lih, T.S.M., Schnaubelt, M., Eberhart, C.G., Rubens, J.A., Zhang, H., Clark, D.J. and Raabe, E.H. Unbiased proteomic and phosphoproteomic analysis identifies response signatures and novel susceptibilities after combined MEK and mTOR inhibition in BRAFV600E mutant glioma. *Molecular & Cellular Proteomics,* **2021**, 20.

[85] Ayoup, M.S., Wahby, Y., Abdel-Hamid, H., Teleb, M., Abu-Serie, M.M. and Noby, A. Design, synthesis and biological evaluation of novel α-acyloxy carboxamides via Passerini reaction as caspase 3/7 activators. *Eur. J. Med. Chem.,* **2019**, 168, 340-356.

[86] Pirrung, M.C.; Ghorai, S.; and Ibarra-Rivera, T.R. Multicomponent reactions of convertible isonitriles, *J. Org. Chem.*, **2009**, 74, 11, 4110–4117, doi: 10.1021/jo900414n.

[87] Dolzhenko, Anton V. "Microwave-assisted multicomponent reactions." Green Sustainable Process for Chemical and Environmental Engineering and Science. *Elsevier,* **2021**, 205-229.

[88] Mocci, R.; Murgia, S.; De Luca, L.; Colacino, E.; Delogu, F.; and Porcheddu, A. Ball-milling and cheap reagents breathe green life into the one hundred-year-old Hofmann reaction, *Org. Chem. Front.*, **2018**, 5, 4, 531–538, doi: 10.1039/c7qo01006k.

[89] Stinson, S.; Organic chemistry, *Chem. Eng. News*, **1984**, 62, 6, 18–19, doi: 10.1021/cen-v062n006.p018.

[90] Chéron, N.; El Kaïm, L. Grimaud, L.; and Fleurat-Lessard, P. A density functional theory study of the nef-isocyanide reaction: Mechanism, influence of parameters and scope, *J. Phys. Chem. A*, **2011**, 115, 35, 10106–10112, doi: 10.1021/jp205909d.

[91] BZhang, O.; and Studer, A. Recent advances in the synthesis of nitrogen heterocycles via radical cascade reactions using isonitriles as radical acceptors, *Chem. Soc. Rev.*, **2015**, 44, 11, 3505–3521, doi: 10.1039/c5cs00083a.

[92] Gulevich, A.V.; Zhdanko, A.G.; Orru, R.V.A.; and Nenajdenko, V.G. Isocyanoacetate derivatives: Synthesis, reactivity, and application, *Chem. Rev.*, **2010**, 110, 9, 5235–5331, doi: 10.1021/cr900411f.

[93] Shirini, F.; Zolfigol, M.A.; and Safari, A. Efficient acetylation and formylation of alcohols in the presence of $Zr(HSO_4)_4$, *J. Chem. Res.*, **2006**, 3, 154–156, doi:

10.3184/030823406776330819.

[94] Chandgude, A.L.; and Dömling, A. An efficient Passerini tetrazole reaction (PT-3CR), *Green Chem.*, **2016**, 18, 3718–3721, doi: 10.1039/c6gc00910g.

[95] Patil, P.; Ahmadian-Moghaddam, M.; and Dömling, A. Isocyanide 2.0, *Green Chem.*, **2020**, 22, 20, 6902–6911, doi: 10.1039/d0gc02722g.

[96] Ugi, I.; Dömling, A.; Gruber, B.; and Almstetter, M. Multicomponent Reactions and Their Libraries - A New Approach to Preparative Organic Chemistry, *Croat. Chem. Acta*, **1997**, 70, 2, 631–647.

[97] Ivachtchenko, A.V., Ivanenkov, Y.A., Kysil, V.M., Krasavin, M.Y. and Ilyin, A.P. Multicomponent reactions of isocyanides in the synthesis of heterocycles. *Russ. Chem. Rev.,* **1997**, 79, 9, 787.

[98] Hald, P., Becker, J., Bremholm, M., Pedersen, J.S., Chevallier, J., Iversen, S.B. and Iversen, B.B. Supercritical propanol–water synthesis and comprehensive size characterisation of highly crystalline anatase TiO_2 nanoparticles. *J. Solid State Chem.*, **2006**,179, 8, 2674-2680.

[99] Wanzlick, H.W.; Lehmann-Horchler, M.; Mohrmann, S.; Gritzky, R.; Heidepriem, H.; and Pankow, B. New Methods of Preparative Organic Chemistry IV, *Angew. Chemie Int. Ed. Eng*, **1964**, 3, 6, 401–408, doi: 10.1002/anie.196404011.

[100] Niznik, G.E.; and Walborsky, H.M. Isocyanide Reductions. A Convenient Method for Deamination," *J. Org. Chem.*, **1978**, 43, 12, 2396–2399, doi: 10.1021/jo00406a020.

[101] Keita, M.; Vandamme, M.; Mahé, O.; and Paquin, J.F. Synthesis of isocyanides through dehydration of formamides using XtalFluor-E, *Tetrahedron Lett.*, **2015**, 56, 2, 461–464, doi: 10.1016/j.tetlet.2014.11.128.

[102] Waibel, K.A.; Nickisch, R.; Möhl, N.; Seim, R.; and Meier, M.A.R. A more sustainable and highly practicable synthesis of aliphatic isocyanides, *Green Chem.*, **2020**, 22, 3, 933–941, doi: 10.1039/c9gc04070f.

[103] Sankar, K.G.; Garima, P.; Vikas, C.; Darshan, R.S.; Tapan, M.S.; Nikita, P.B. One-pot preparation of isocyanides from amines and their multicomponent reactions: Crucial role of dehydrating agent and base, *RSC Adv*. **2013**, 3, 10867–10874.

[104] Lentz, D. Fluorinated Isocyanides. More than Ligands with Unusual Properties," *Angew. Chemie Int. Ed. English*, **1994**, 33, 13, 1315–1331, doi: 10.1002/anie.199413151.

[105] Pirrung, M.C.; and Ghorai, S. Versatile, fragrant, convertible isonitriles, *J. Am. Chem. Soc.*, **2006**, 128, 36, 11772–11773, doi: 10.1021/ja0644374.

[106] Ley, S.V.; and Taylor, S.J. A polymer-supported [1,3,2]oxazaphospholidine for the conversion of isothiocyanates to isocyanides and their subsequent use in an Ugi reaction, *Bioorganic Med. Chem. Lett.*, **2002**, 12, 14, 1813–1816, doi: 10.1016/S0960-894X(02)00269-X.

[107] Salami, S.A., Siwe-Noundou, X. and Krause, R.W.M. A More Sustainable Isocyanide Synthesis from N-Substituted Formamides Using Phosphorus Oxychloride in the Presence of Triethylamine as Solvent. *Molecules*, **2022**, 27, 20, p.6850.

[108] Wang, X.; Wang, Q.G.; and Luo, Q.L. Synthesis of isonitriles from *N*-substituted formamides using triphenylphosphine and iodine, *Synth.*, **2015**, 47, 1, 49–54, doi: 10.1055/s-0034-1379111.

[109] Zhang, X.; Evanno, L.; and Poupon, E. Biosynthetic Routes to Natural Isocyanides, *European J. Org. Chem.*, **2020**, 13, 1919–1929, doi: 10.1002/ejoc.201901694.

[110] Shen, Y.; Huang, B.; Zeng, L.; and Cui, S. Single Reactant Replacement Approach of Passerini Reaction: One-Pot Synthesis of β-Acyloxyamides and Phthalides, *Org. Lett.*, **2017**, 19, 17, 4616–4619, doi: 10.1021/acs.orglett.7b02232.

[111] Sornay, C., Hessmann, S., Erb, S., Dovgan, I., Ehkirch, A., Botzanowski, T., Cianferani, S., Wagner, A. and Chaubet, G. Investigating Multicomponent Approaches for the Site-Selective Conjugation of Native Proteins. *Chem. - A Eur. J.*, **2020**, 26, 61, 13797–13805, doi: 10.1002/chem.202002432.

[112] Ramozzi, R.; and Morokuma, K. Revisiting the passerini reaction mechanism: Existence of the nitrilium, organocatalysis of its formation, and solvent effect, *J. Org. Chem.*, **2015**, 80, 11, 5652–5657, doi: 10.1021/acs.joc.5b00594.

[113] Erian, A.W.; Sherif, S.M.; and Gaber, H.M. The chemistry of α-haloketones and their utility in heterocyclic synthesis, *Molecules*, **2003**, 8, 11, 793–865, doi: 10.3390/81100793.

[114] Chupakhin, E.; Babich, O.; Prosekov, A.; Asyakina, L.; and Krasavin, M. Spirocyclic motifs in natural products, *Molecules*, **2019**, 24, 22, doi: 10.3390/molecules24224165.

[115] Smith, L.K.; and Baxendale, I.R. Total syntheses of natural products containing spirocarbocycles, *Org. Biomol. Chem.*, **2015**, 13, 39, 9907–9933, doi: 10.1039/c5ob01524c.

[116] Laviós, A.; Sanz-Marco, A.; Vila, C.; Blay, G.; and Pedro, J.R. Asymmetric Organocatalytic Synthesis of aza-Spirocyclic Compounds from Isothiocyanates and Isocyanides, *European J. Org. Chem.*, **2021**, 16, 2268–2284, doi: 10.1002/ejoc.202100232.

[117] Khanna, P.; Panda, S.S.; Khanna, L.; and Jain, S.C. Aqua Mediated Synthesis of Spirocyclic Compounds, *Mini. Rev. Org. Chem.*, **2014**, 11, 1, 73–86, 2014, doi: 10.2174/1570193x1101140402101831.

[118] Soeta, T.; and Ukaji, Y. Carboxylic acid free novel isocyanide-based reactions, *Chem. Rec.*, **2014**, 14, 1, 101–116, doi: 10.1002/tcr.201300021.

[119] Holt, J.; and Fiksdahl, A. Nitropyridyl isocyanates in 1,3-dipolar cycloaddition reactions, *J. Heterocycl. Chem.*, **2007**, 44, 2, 375–379, doi: 10.1002/jhet.5570440215.

[120] Dawson, P.E. and Kent, S.B., Synthesis of native proteins by chemical ligation. *Annual review of biochemistry,* **2000**, 69, 923-960.

[121] Cao, Y.M.; Zhang, F.T.; Shen, F.F.; and Wang, R. Catalytic enantioselective ring-opening reaction of meso-aziridines with α-isothiocyanato imides, *Chem. - A Eur. J.*, **2013**, 19, 29, 9476–9480, doi: 10.1002/chem.201300297.

[122] Tan, B.; Zeng, X.; Leong, W.W.Y.; Shi, Z.; Barbas, C.F.; and Zhong, G., Core structure-based design of organocatalytic [3+2]-cycloaddition reactions: Highly efficient and stereocontrolled syntheses of 3,3′-pyrrolidonyl spirooxindoles, *Chem. - A Eur. J.*, **2012**, 18, 1, 63–67, doi: 10.1002/chem.201103449.

[123] Liu, X.L.; Han, W.Y.; Zhang, X.M.; and Yuan, W.C. Highly efficient and stereocontrolled construction of 3,3′- pyrrolidonyl spirooxindoles via organocatalytic domino Michael/cyclization reaction, *Org. Lett.*, **2013**, 15, 6, 1246–1249, doi: 10.1021/ol400183k.

[124] Habibi, D.; Nasrollahzadeh, M.; and Sahebekhtiari, H., Green synthesis of formamides using the Natrolite zeolite as a natural, efficient and recyclable catalyst, *J. Mol. Catal. A Chem.*, **2013**, 378, 148–155, doi: 10.1016/j.molcata.2013.04.001.

[125] Khatri, C.K.; and Chaturbhuj, G.U., Sulfated polyborate-catalyzed *N*-formylation of amines: a rapid, green and efficient protocol, *J. Iran. Chem. Soc.*, **2017**, 14, 12, 2513–2519, doi: 10.1007/s13738-017-1186-x.

[126] Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjaneyulu, B.; and Nandan Kumar, D., A remarkably simple *N*-formylation of anilines using polyethylene glycol, *Tetrahedron Lett.*, **2008**, 49, 14, 2225–2227, doi: 10.1016/j.tetlet.2008.02.050.

[127] Roberts, R.M.; and Vogt, P.J. Ortho esters, imidic esters and amidines. VII. N-alkylformanilides from alkyl orthoformates and primary aromatic amines; Rearrangement of alkyl N-arylformimidates, *J. Am. Chem. Soc.*, **1956**, 78, 18, 4778–4782, doi: 10.1021/ja01599a063.

[128] Swaringen, R.A.; Eaddy, J.F.; and Henderson, T.R. Reaction of Ortho Esters with Secondary Amines, *J. Org. Chem.*, **1980**, 45, 20, 3986–3989, doi: 10.1021/jo01308a007.

[129] Dhake, K.P.; Tambade, P.J.; Singhal, R.S.; and Bhanage, B.M. An efficient, catalyst- and solvent-free *N*-formylation of aromatic and aliphatic amines, *Green Chem. Lett. Rev.*, **2011**, 4,

2, 151–157, doi: 10.1080/17518253.2010.524168.

[130] Huffman, C.W. Formylation of Amines, *J. Org. Chem.*, **1958**, 23, 5, 727–729, doi: 10.1021/jo01099a023.

[131] Jung, S.H.; Ahn, J.H.; Park, S.K.; and Choi, J.K., A practical and convenient procedure for the *N*-formylation of amines using formic acid," *Bull. Korean Chem. Soc.*, **2002**, 23, 1, 149–150, doi: 10.5012/bkcs.2002.23.1.149.

[132] Ganapati Reddy, P.; Kishore Kumar, G.D.; and Baskaran, S. A convenient method for the N-formylation of secondary amines and anilines using ammonium formate, *Tetrahedron Lett.*, **2000**, 41, 47, 9149–9151, doi: 10.1016/S0040-4039(00)01636-1.

[133] Patre, R.E., Mal, S., Nilkanth, P.R., Ghorai, S.K., Deshpande, S.H., El Qacemi, M., Smejkal, T., Pal, S. and Manjunath, B.N. First report on bio-catalytic N-formylation of amines using ethyl formate. *Chem. Comm*, **2017**, 53, 2382-2385.

[134] Zeynizadeh, B.; and Abdollahi, M., The immobilized $NaHSO_4 \cdot H_2O$ on activated charcoal: a highly efficient promoter system for *N*-formylation of amines with ethyl formate, *Curr. Chem. Lett.*, **2016**, 5, 51–58, doi: 10.5267/j.ccl.2016.1.002.

[135] Kaboudin, B.; and Khodamorady, M. Organic reactions in water: A practical and convenient method for the *N*-formylation of amines in water, *Synlett*, **2010**, 19, 2905–2907, doi: 10.1055/s-0030-1259029.

[136] Yu, H., Wu, Z., Wei, Z., Zhai, Y., Ru, S., Zhao, Q., Wang, J., Han, S. and Wei, Y. N-formylation of amines using methanol as a potential formyl carrier by a reusable chromium catalyst. *Comm. Chem.,* **2019**, 2, 1-7. doi: 10.1038/s42004-019-0109-4.

[137] Lam, R.H.; McQueen, C.M.A.; Pernik, I.; McBurney, R.T.; Hill, A.F.; and Messerle, B.A. Selective formylation or methylation of amines using carbon dioxide catalysed by a rhodium perimidine-based NHC complex, *Green Chem.*, **2019**, 21, 3, 538–549, doi: 10.1039/c8gc03094d.

[138] Pathare, S.P.; Sawant, R.V.; and Akamanchi, K.G. Sulfated tungstate catalyzed highly accelerated *N*-formylation, *Tetrahedron Lett.*, **2012**, 53, 26, 3259–3263, doi: 10.1016/j.tetlet.2012.04.058.

[139] Mvthukur Bhojegowd, M.R.; Nizam, A.; and Pasha, M.A,. Amberlite IR-120: A reusable catalyst for N-formylation of amines with formic acid using microwaves, *Cuihua Xuebao/Chinese J. Catal.*, **2010**, 31, 5, 518–520, doi: 10.1016/s1872-2067(09)60064-4.

[140] Kim, J.G.; and D. O. Jang, D.O. Indium-catalyzed *N* -formylation of amines under solvent-free

conditions, *Synlett*, **2010**, 8, 1231–1234, doi: 10.1055/s-0029-1219784.

[141] Krishnakumar, B.; and Swaminathan, M. A convenient method for the N-formylation of amines at room temperature using TiO_2-P25 or sulfated titania, *J. Mol. Catal. A Chem.*, **2011**, 334, 1–2, 98–102, doi: 10.1016/j.molcata.2010.11.002.

[142] Habibi, D.; Sahebekhtiari, H.; Nasrollahzadeh, M.; and Taghipour, A., A Very Simple, Highly Efficient and Catalyst-free Procedure for the N-Formylation of Amines Using Triethyl orthoformate in Water Under Ultrasound-irradiation, *Lett. Org. Chem.*, **2013**, 10, 3, 209–212, doi: 10.2174/1570178611310030012.

[143] Hu, D.X.; Grice, P.; and Ley, S.V. Rotamers or diastereomers? An overlooked NMR solution, *J. Org. Chem.*, **2012**, 77, 11, 5198–5202, doi: 10.1021/jo300734r.

[144] Cechová, L.; Procházková, E.; Císarová, I.; Dracínský, M.; and Janeba, Z. Separation of planar rotamers through intramolecular hydrogen bonding in polysubstituted 5-nitrosopyrimidines, *Chem. Commun.*, **2014**, 50, 94, 14892–14895, doi: 10.1039/c4cc06978a.

[145] Giustiniano, M., Basso, A., Mercalli, V., Massarotti, A., Novellino, E., Tron, G.C. and Zhu, J., To each his own: isonitriles for all flavors. Functionalized isocyanides as valuable tools in organic synthesis. *Chem. Soc. Rev.*, **2017**, 46, 5, 1295–1357, 2017, doi: 10.1039/c6cs00444j.

[146] (a) Sheldon, R.A. Fundamentals of Green Chemistry : Efficiency in Reaction Design *Electron. Suppl. Mater. Chem. Soc. Rev.*, 2011, 1–64. (b) Brunelli, F., Aprile, S., Russo, C., Giustiniano, M. and Tron, G.C., In-water synthesis of isocyanides under micellar conditions. *Green Chemistry,* **2022**, 24, pp.7022-7028.

[147] Dömling, A. Novel synthesis of praziquantel. WO2009115333, 24 September **2009**.

[148] Leonardi, M.; Villacampa, M.; and Menéndez, J.C. Multicomponent mechanochemical synthesis, *Chem. Sci.*, **2018**, 9, 8, 2042–2064, doi: 10.1039/c7sc05370c.

[149] Kaicharla, T.; Yetra, S.R.; Roy, T.; and Biju, A.T., Engaging isatins in solvent-free, sterically congested Passerini reaction, *Green Chem.*, **2013**,15, 6, 1608–1614, doi: 10.1039/c3gc40454d.

[150] Martinez, S.T.; and Ferreira, V.F., The Isatins of professor angelo," *Rev. Virtual Quim.*, **2017**, 9, 3, 1154–1183, doi: 10.21577/1984-6835.20170069.

[151] Rouatbi, F.; Askri, M.; Nana, F.; Kirsch, G.; Sriram, D.; and Yogeeswari, P. Synthesis of new spirooxindole derivatives through 1,3-dipolar cycloaddition of azomethine ylides and their antitubercular activity, *Tetrahedron Lett.*, **2016**, 57, 2, 163–167, doi: 10.1016/j.tetlet.2015.11.056.

[152] Carstens, T.; Haynes, D.A.; and Smith, V.J., Cocrystals: Solution, Mechanochemistry, and

Sublimation, *Cryst. Growth Des.*, **2020**, 20, 2, 1139–1149, doi: 10.1021/acs.cgd.9b01450.

[153] Rostamnia, S.; and Hassankhani, A. $RuCl_3$-catalyzed solvent-free Ugi-type Groebke-Blackburn synthesis of aminoimidazole heterocycles, *RSC Adv.*, **2013**, 3, 40, 18626–18629, doi: 10.1039/c3ra42752h.

[154] Mironov, M.A.; Ivantsova, M.N.; Tokareva, M.I and Mokrushin, V.S., Acceleration of the Passerini reaction in the presence of nucleophilic additives, *Tetrahedron Lett.*, **2005**, 46, 23, 3957–3960, doi: 10.1016/j.tetlet.2005.04.050.

[155] Ugi, I., The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions. *Angewandte Chemie International Edition in English,* **1962**, 1, 8-21.

[156] Jenner, G., Effect of pressure on sterically congested cyanoalkylation reactions of alcohols, *Tetrahedron*, **2002**, 58, 21, 4311–4317, doi: 10.1016/S0040-4020(02)00347-2.

[157] El Kaim, L.; Gizolme, M.; and Grimaud, L. O-arylative Passerini reactions, *Org. Lett.*, **2006**, 8, 22, 5021–5023, doi: 10.1021/ol0617502.

[158] Pirrung, M.C.; and Das Sarma, K. Multicomponent Reactions are Accelerated in Water, *J. Am. Chem. Soc.*, **2004**, 126, 2, 444–445, doi: 10.1021/ja038583a.

[159] Paprocki, D., Wilk, M., Madej, A. Catalyst-free synthesis of α-acyloxycarboxamides in aqueous media. *Environ Chem Lett,* 2019,17, 1011–1016. https://doi.org/10.1007/s10311-018-0797-5

[160] Salami, S.A., Siwe-Noundou, X. and Krause, R.W., Catalytic Performance of Immobilized Sulfuric Acid on Silica Gel for *N*-Formylation of Amines with Triethyl Orthoformate. *Molecules,* **2022**, 27, 4213.

[161] Simila, S.T.M.; and Martin, S.F. Applications of the Ugi reaction with ketones, *Tetrahedron Lett.*, **2008**, 49, 29–30, 4501–4504, doi: 10.1016/j.tetlet.2008.05.073.

[162] Salvador, C.E.M.; and Andrade, C.K.Z. A Mild, Fast, and Scalable Synthesis of Substituted α-Acyloxy Ketones via Multicomponent Reaction Using a Continuous Flow Approach, *Front. Chem.*, **2019**, 7, 2–11, doi: 10.3389/fchem.2019.00531.

[163] Ansari, M.I.; Hussain, M.K.; Yadav, N.; Gupta, P.K.; and Hajela, K. Silica supported perchloric acid catalyzed rapid *N*-formylation under solvent-free conditions, *Tetrahedron Lett.*, **2012**, 53, 16, 2063–2065, doi: 10.1016/j.tetlet.2012.02.027.

[164] Kaur, M.; Sharma, S.; and Bedi, P.M.S. Silica supported Brönsted acids as catalyst in organic transformations: A comprehensive review," *Cuihua Xuebao/Chinese J. Catal.*, **2015**, 36, 4, 520–549, doi: 10.1016/S1872-2067(14)60299-0.

[165] Dufour, V.; Stahl, M.; and Baysse, C. The antibacterial properties of isothiocyanates, *Microbiol*, **2015**, 161, 2, 229–243, doi: 10.1099/mic.0.082362-0.

166. Oesophageal Cancer in Africa. Denver H, Parker MI. **2002**, *IUBMB Life,* 53 (4-5), 263-268.

167. Prevalence of Oesophageal Cancer. UK Cancer Research. [Online] [Cited: 12 May 2016.] :http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/index.html(link is external).

168. Dietary Sulforaphane, a Histone Deacetylase Inhibitor for Cancer Prevention. Emily H, John DC, Roderick HD., *The American Institute of Nutrition,* **2009**, p. 34.

[169] Wong, R.; and Dolman, S.J. Isothiocyanates from tosyl chloride mediated decomposition of in situ generated dithiocarbamic acid salts, *J. Org. Chem.*, **2007**, 72, 10, 3969–3971, doi: 10.1021/jo070246n.

[170] Hodgkins, J.E.; and Ettlinger, M.G., The synthesis of isothiocyanates from amines, *J. Org. Chem.*, **1956**, 21, 4, 404–405, doi: 10.1021/jo01110a006.

[171] Bian, G.; Shan, W.; and Su, W., A one-pot preparation of isothiocyanates from amines using two phosgene substitutes: bis-(trichloromethyl) carbonate and trichloromethyl chloroformates, *J. Chem. Res.*, **2005**, 9, 585–586, doi: 10.3184/030823405774308862.

[172] Cho, C.G.; and Posner, G.H. Alkyl and aryl isothiocyanates as masked primary amines, *Tetrahedron Lett.*, **1992**, 33, 25, 3599–3602, doi: 10.1016/S0040-4039(00)92512-7.

[173] Kitamura, T.; Kobayashi, S.; and Taniguchi, H. Photolysis of Vinyl Halides. Reaction of Photogenerated Vinyl Cations with Cyanate and Thiocyanate Ions, *J. Org. Chem.*, **1990**, 55, 6, 1801–1805, doi: 10.1021/jo00293a025.

[174] Kim, J.N.; Jung, K.S.; Lee, H.J.; and Son, J.S. A facile one-pot preparation of isothiocyanates from aldoximes, *Tetrahedron Lett.*, **1997**, 38, 9, 1597–1598, doi: 10.1016/S0040-4039(97)00121-4.

[175] Bian, G.; Qiu, H.; Jiang, J.; Wu, J.; and G. Lai, G., A new method for the synthesis of isothiocyanates from dithiocarbamates or alkyl amines using chlorosilanes as decomposition reagents, *Phosphorus, Sulfur Silicon Relat. Elem.*, **2007**, 182, 3, 503–508, doi: 10.1080/10426500600977379.

[176] Vermeulen, M.; Zwanenburg, B.; Chittenden, G.J.F.; and Verhagen, H. Synthesis of isothiocyanate-derived mercapturic acids, *Eur. J. Med. Chem.*, **2003**, 38, 7–8, 729–737, doi: 10.1016/S0223-5234(03)00141-7.

[177] Mesheram, H.M.; Dale, S.; and Yadav, J.S. A general synthesis of isothiocyanates from

dithiocarbamates using claycop, *Tetrahedron Lett.*, **1997**, 38, 50, 8743–8744, doi: 10.1016/S0040-4039(97)10158-7.

[178] Kuotsu, N.B.; Jamir, L.; Phucho, T.; and Sinha, U.B. A novel one-pot synthesis of isothiocyanates and cyanamides from dithiocarbamate salts using environmentally benign reagent tetrapropylammonium tribromide, *Acta Chim. Slov.*, **2017**, 64, 4, 832–841, doi: 10.17344/acsi.2017.3342.

[179] Nath, J.; Jamir, L.; and Patel, B.K. Improved procedure for the preparation of isothiocyanates via iodine-mediated desulfurization of dithiocarbamic acid salts, *Green Chem. Lett. Rev.*, **2011**, 4, 1–34, doi: 10.1080/17518253.2010.486773.

[180] Smith, L.A., Rates of elemental sulphur oxidation and associated oxygen and sulphur isotope fractionation*, Doctoral dissertation,* **2009**.

[181] Larsen, C.; and D. N. Harpp, D.N. Thiocarbonyl Transfer Reagent Chemistry. Selective Displacements with Formaldehyde Hydrazones and Other Nucleophiles, *J. Org. Chem.*, **1981**, 46, 12, 2465–2466, doi: 10.1021/jo00325a007.

[182] Cotarca, L.; Geller, T.; and Répási, J. Bis(trichloromethyl)carbonate (BTC, Triphosgene): A Safer Alternative to Phosgene?, *Org. Process Res. Dev.*, **2017**, 21, 9, 1439–1446, doi: 10.1021/acs.oprd.7b00220.

[183] Seelam, M.; Shaik, B.; and Kammela, P.R. Cobalt mediated by desulfurization toward the synthesis of isothiocyanates, *Synth. Commun.,* **2016**, 46, 21, 1759–1765, doi: 10.1080/00397911.2016.1224351.

[184] Z. Fu, W. Yuan, N. Chen, Z. Yang, and J. Xu, $Na_2S_2O_8$-mediated efficient synthesis of isothiocyanates from primary amines in water, *Green Chem.*, **2018**, 20, 19, 4484–4491, doi: 10.1039/c8gc02261e.

[185] Valette, L.; Poulain, S.; Fernandez, X.; and Lizzani-Cuvelier, L. Efficient and solvent-free microwave-accelerated synthesis of isothiocyanates using Lawesson's reagent, *J. Sulfur Chem.,* **2005**, 26, 2, 155–161, doi: 10.1080/17415990500070144.

[186] Ozturk, T.; Ertas, E.; and Mert, O. Use of Lawesson's reagent in organic syntheses, *Chem. Rev.,* **2007**, 107, 11, 5210–5278, doi: 10.1021/cr040650b.

[187] Khatoon, H.; and Abdulmalek, E. A focused review of synthetic applications of lawesson's reagent in organic synthesis, *Molecules,* **2021**, 26, 22, doi: 10.3390/molecules26226937.

[188] Boeini, H.Z.; and Khajeh, A. Direct and efficient conversion of tertiary thioamides to S-2-oxo thioesters under solvent-free conditions, Bull. *Korean Chem. Soc.,* **2011**, 32, 4, 1201–1203, doi:

10.5012/bkcs.2011.32.4.1201.

[189] Dandia, A.; Singh,R.; Sachdeva, H.; Gupta, R.; and Paul, S. Microwave promoted and improved thermal synthesis of spiro[indole- pyranobenzopyrans] and spiro[indole-pyranoimidazoles], *J. Chinese Chem. Soc.*, **2003**, 50, 2, 273–278, doi: 10.1002/jccs.200300041.

[190] Gupta, A.K.; Bharadwaj, M.; Kumar, A.; and Mehrotra, R. Spiro-oxindoles as a Promising Class of Small Molecule Inhibitors of p53–MDM2 Interaction Useful in Targeted Cancer Therapy, *Top. Curr. Chem.*, **2017**, 375, 1–25, doi: 10.1007/s41061-016-0089-0.

[191] Soria-Castro, S.M.; Caminos, D.A.; and Peñéñory, A.B. An expedient route to heterocycles through α-arylation of ketones and arylamides by microwave induced thermal SRN1 reactions, *RSC Adv.*, **2014**, 4, 34, 17490–17497, doi: 10.1039/c4ra00120f.