GREEN METHODOLOGIES LEADING TO THE FORMATION OF NEW C-C AND C-HETEROATOM BONDS

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CONTENTS

PREFACE

This book is intended for advanced students, graduates, and researchers from both academia and industry working in the area of organic, heterocyclic or medicinal chemistry and looking for a survey on the synthetic methods, chemistry, and applications of favored green-chemistry methods of recent years.

Over the last few decades, concerns about the environmental impact of the growth of human society have become omnipresent and sustainability has appeared as an a priori problem in every field of human activity. The chemical industry plays an important role in human progress and, as usual, an increased pressure has been put on chemists to improve the sustainability of their methods. In this regard, the notion of Green Chemistry has been described as the design of chemical products and methods to decrease or remove the use and formation of hazardous materials and was advanced in principles to canalize the chemists in their search towards greenness.

Environmental pollution has become one of the main reasons for the deterioration of our ecosystem. In recent years, chemists have focused their attention on this issue and began to develop environmentally friendly methods for the design of chemical processes and industrial products. The primary aim is to prevent waste formation in the first place, rather than the end-of-pipe remediation approach, which contains elimination of waste after production. Different greener techniques are being improved as researchers proceed, enhancing alternatives to conventional chemical synthesis and transformations. The target approach for this purpose has been the design of new chemicals using environmentally friendly new strategies, unconventional energy sources, catalytic methods, and renewable materials. At the same time, it has been a reliable focus by chemists to achieve the desired conversion with minimum waste and to create alternative efficient conditions and develop environmentally friendly reaction conditions by eliminating the use of hazardous solvents as much as possible.

The toxic and volatile nature of solvents, which are the most frequently used chemicals in laboratories, means their impact on the environment is undeniable. Therefore, there has been an increasing effort to eliminate the use of these solvents or to use environmentally friendly solvents instead.

In recent years, solvent-free reactions - reactions in which water or ionic liquids are used as solvents - have emerged as environmentally friendly methods.

Nowadays, when we are facing an energy crisis, energy consumption in reactions that last for hours or even days in classical methods is one of the important environmental problems. In order to minimize or completely eliminate this energy consumption, the chemists have started to use greener methods such as microwave irradiation, ultrasonic sonication, mechanochemical synthesis, one-pot multi component reactions, and photocatalytic reactions. With these methods, the reaction times have been shortened and selective high yield products have been obtained.

This book contains information on the use of the above-mentioned environmental methods in the formation of C-C or C-heteroatom bonds in some important organic reactions such as Mannich, Petasis, Kabachnik-Fields Ugi, Passerini, Groebke-Blackburn-Bienaymé, Biginelli, Hantzsch, Suzuki–Miyaura, Mizoroki-Heck, Sonogashira-Hagihara, Michael, and Knoevenagel. The greener processes used in each reaction have been revealed by conducting a deep literature survey.

This research-oriented book is illustrated in depth with clearly drawn chemical structures. The highly scientific scope attributed to the subject makes this the most authoritative one-volume account of modern green chemistry. It also provides a comprehensive explanation of many reactions and their mechanisms, especially heterocyclic chemistry.

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We are very grateful to Cambridge Scholar Publishing for encouraging us to write this book and thanks to Helen Edwards for contacting us about this.

Hope it helps all readers.

INTRODUCTION

With the increasing environmental pollution and its detrimental impact on the ecosystem in mind, the development of new chemical strategies, which contain the use of eco-friendly chemicals, solvents, catalysts, atom economical procedures, and alternative energy inputs has gained considerable interest (Dekamin, Peyman, Karimi, Javanshir et al., 2016; Zarnegar and Safari, 2016). Since the emergence of sustainable concerns influencing nearly every aspect of daily life, green chemists have directed their attention to converting the chemical processes formulated at the outset of this century to eco-friendly procedures for the design of chemical and industrial products (Zarnegar and Safari, 2016; Alza, E.; Rodriguez E. C.; Sayalero, S.; Bastero et al., 2009; Chate, Rudrawar, Bondle, Sangeshetti, 2020). As a result, green chemistry has become a growing field of chemistry based on the principles, which have been established to develop cleaner and environmentally benign procedures. The ultimate target of green chemistry is to shift the traditional chemical processes, which use hazardous reagents, catalysts and/or toxic and volatile solvents, into environmentally innocent methodologies involving renewable and non-hazardous raw materials (Dekamin, Karimi, Latifidoost, Ilkhanizadeh, 2018; Dove, 2014; Vispute, Zhang, Sanna, Xiao et al. 2010; Khan, Khan, Shareef, Danish, 2018; Mohamadpour, 2021).

The varied character of the chemical world requires a variety of greener methods in our search for success criteria while developing new chemical processes. The main goal is to avoid waste formation in the first place, rather than the end-of-pipe remediation approach, which includes removal of waste after production. Different greener processes are being developed as we continue developing alternatives to traditional chemical synthesis and transformations. The target approach necessitates new environmentally benign strategies, unconventional energy sources, catalytic methods, and chemical products designed in a benign manner using renewable materials. One of the trustworthy approaches to accomplish this goal is to discover alternative efficient conditions and eco-friendly reaction media to achieve the desired transformation with minimized waste and eliminate the employment of hazardous solvents as far as possible (Varma, 2007).

The new challenges faced in the chemical industry are security, safety, and changing regulatory demands that dictate developments in production efficiency through the implementation of efficient eco-friendly ‘‘greener’’ technologies. These new technologies can improve the performance of a company via taking control of the costs of the products by speeding up the modification and waste reduction while complying with the regulations. Among various examples, a succinct synthesis of Ibuprofen, which is a commonly used analgesic, underlines the importance of the green chemistry concept by eliminating large quantities of waste through following a three-step atom-economical way instead of a six-step process (Varma, 2007).

1

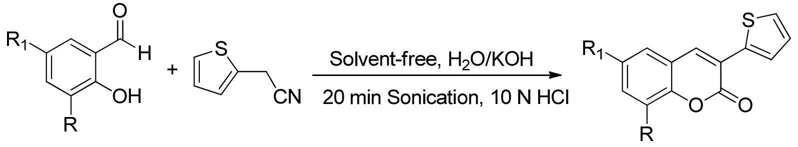
OVERVIEW OF GREEN TECHNIQUES

In this section, some green techniques have been discussed separately. However, it is difficult to classify most studies according to the technique they use. Because in the quest for environmental benignity and sustainability, the application of two or more green methodologies such as MW, US, solvent- and catalyst-free applications, etc. together have unquestionable significance. Most of the studies reported in recent years include such combinations. Therefore, the difference between techniques classified under different headings is not precise. For example, an MW-assisted method may also be solvent-free, catalyst-free, and/or multicomponent at the same time.

1.1. Solvent-Free Reactions

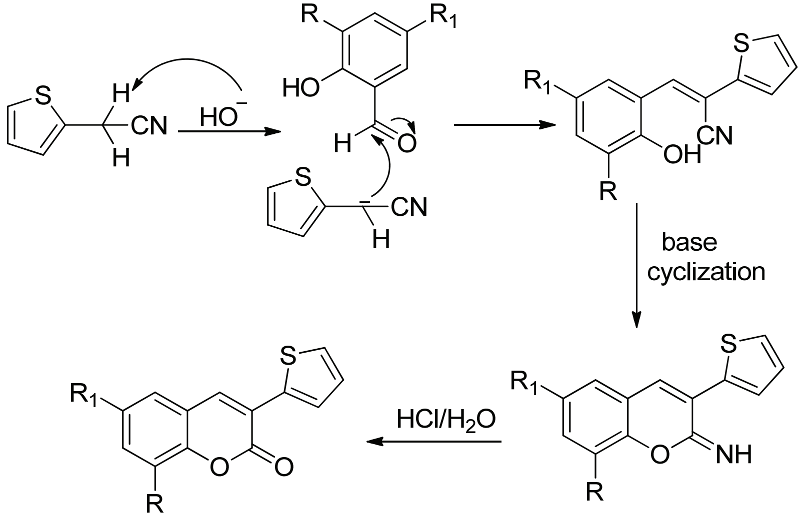
It is well known that solvents play an important role in the promotion of organic reactions. Besides enabling more efficient contact between reactants, solvents also transfer the thermal energy required for the reaction. However, the extensive industrial use of volatile, toxic, and hazardous solvents in nearly all chemical industries shows a negative impact on the environment. In terms of a green environment, an ideal solvent should be non-toxic, nonvolatile, non-corrosive, non-flammable, recoverable, renewable, and biodegradable. Furthermore, the green solvents should be cheap and easy to handle as well. Many different solvents such as water, ionic liquids, and supercritical fluids such as supercritical carbon dioxide (scCO_2) have emerged as alternatives to the hazardous solvents. However, there are some limitations to their application, such as product separation for water, solubility problems of highly hydrophobic substrates, lack of data about the biocompatibility and toxicity for ionic liquids, large production costs, and costly apparatuses for scCO_2. Therefore, it is crucial to search for new sustainable reaction media (Kordnezhadian, Shekouhy and Khalafi-Nezhad, 2020).

From a green environment perspective, it is clear that the reactions under solvent-free conditions and in solid-state have great importance serving the sustainable environment concept. Lower energy consumption, increased selectivity, minimized waste, cost and toxicity are some of the preferred properties of solvent-free reactions over traditional methods. As a result of these, solvent-free reactions are considered as another one of the green techniques (Bhat, Choudhury and Trivedi, 2013; Schneider, Szuppa, Stolle et al., 2009; Gu, 2012). Due to the difficulty of removing organic solvents from a reaction mixture, the elimination of them or the replacement by non-volatile, non-flammable, and green ones is the most relevant method in the sustainable chemistry aspect. In this connection, the discovery of solvent-free alternative procedures has been considered as the best solution, especially in case either one of the reagents or the products exist as a liquid and can be employed as a solvent. If the presence of a solvent is of great importance to a process, it is necessary to select ones having no or limited effect on the health and ecosystem. The employment of unconventional green solvents improves the sustainable properties of the reaction and also the synthetic efficacy by the stabilization of catalyst, altering the selectivity, or facilitating isolation procedures. Taking the benefits of the utilization of unconventional solvents, most of the known multicomponent reactions (MCRs) have been enhanced in terms of substrate variety, reaction yield, catalyst recycling, and isolation procedures. Besides water and ionic liquids, polyethylene glycol polymers (PEGs) have also been utilized as new green solvents. Moreover, water has been accepted as a unique reaction solvent conforming to current strict requirements on green chemistry. The literature survey has revealed that the reactions carried out on organic solvent-water interfaces are faster and also exhibit novel reactivity profiles and selectivity (Gu, 2012). As an example of solvent-free reactions, the reaction reported by Nagaraju et al. can be given. These authors have designed a short time synthesis of some coumarin derivatives under ultrasound (US) irradiated conditions at room temperature through a one-pot multi-component strategy (Scheme 1, Scheme 2). The coumarin derivatives synthesized in this study have been declared as an innovative category for the visualization of fingerprints (FPs) on the different non-porous material surfaces using a powder dusting method. The obtained images of FPs have high characteristics with high selectivity, sensitivity, low background hindrance, and better contrast. According to this, these coumarin derivatives can be used as promising small organic fluorescent tags for display applications and FPs (Kumar, Udayabhanu, Alghamdi, Mahadevan et al., 2021).



R$_1$= H, Cl; **R**= Cl

Scheme 1. Schematic representation of synthesis of CTFTs.

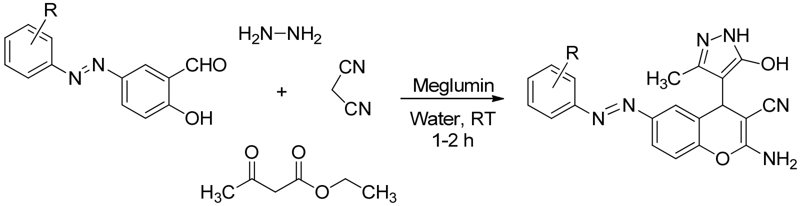


Scheme 2. Mechanism of Coumarin derivatives.

1.2. Water as a Reaction Solvent

As a non-hazardous, non-flammable, exclusively redox-stable, and cheap solvent, water has the added privilege of being almost easily accessible in nature, even in undeveloped countries. Moreover, the use of water as the reaction medium supplies the unique reactivity and selectivity. Hence, water is an almost perfect and green solvent. The use of water in reactions as the solvent has attracted widespread attention due to its large number of advantages involving its safety, environmentally friendly character, non-toxicity, cleanliness, and availability for many organic reactions. From the economical and also environmental points of view, water-mediated reactions have become very appealing methods. In this context, water as a universally accepted green solvent is the best choice to carry out organic transformations. Due to its exceptional physico-chemical superiorities, it enables the reaching of the requested reactivity or selectivity that cannot be achieved in any organic media. This is the reason why nature itself has chosen water as the solvent for life processes. The hydrophilic effect and hydrogen bonding potency of water is believed to accelerate the reaction rate in the water drastically despite its low ability to dissolve organic reagents.

Recently, the compounds containing the diazo group have been extensively studyed worldwide due to their exceptional medicinal, photophysical and photochemical features. Reversible *cis-trans* isomerization activated by light is observed in the azo bond leading to changes in the compounds having this function in the structural geometry-related properties such as the dipole moment and optical properties. Chromenes coupled with transition metals have been reported to display chemosensing features. In this connection and as an example of the reactions performed in water, Pore's group have reported the design and synthesis of Meglumine catalyzed one-pot synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-aryldiazenyl-4*H*-chromene-3-carbonitriles in aqueous medium at room temperature (Korade, Mhaldar, Kulkarni, Rashinkar et al., 2021) (Scheme 3).



R= 4-I, 2,3-benzo, 3-NO_2, 2-Cl, 4-Br, 2-Me, 3-Me, 3-MeO, 4-MeO, H.

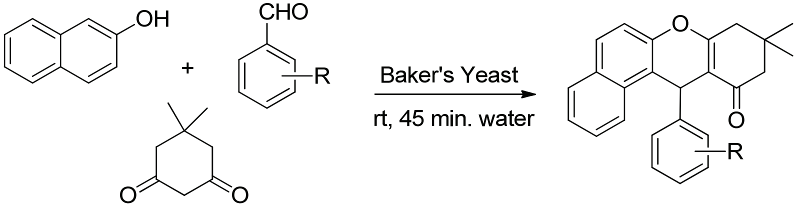
Scheme 3. Meglumin catalyzed one-pot four component syntheses of novel 2-amino-4-pyrazolyl-6-aryldiazenyl-4*H*-chromene-3-carbonitriles in water.

Atom economy, simple workup procedure avoiding tedious column chromatography, energy efficiency, and good to moderate yields have been specified as the main advantages of this water-mediated green method. The synthesized molecules have been proven to possess strong fluorescent properties with considerable stokes shift of 290–293 nm.

Another example of water mediated reactions has been reported by Chavan's group for the synthesis of tetrahydrobenzo[a]xanthene-11-ones and pyrazolo[3,4-b]quinolones. To perform such a study, these authors have been inspired by the fact that the compounds bearing both pyrazole and quinoline rings in their structures exhibit intensified antibacterial, antiviral, and antimalarial activities. Furthermore, the rapidly developing drug resistance rendering most antibiotics ineffective has forced humanity to face serious threats. Therefore, the development of new methodologies, which also are not detrimental to the ecosystem, for the synthesis of new and non-resistant therapeutic agents has become vital (Demirbas, Sahin, Demirbas and Alpay Karaoglu, 2009).

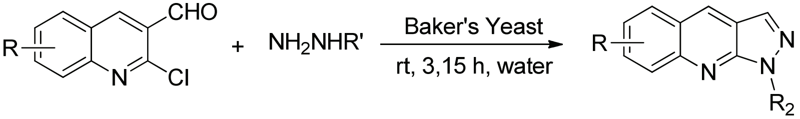
Besides their biological activities, pyrazoloquinolines have been found to possess electroluminescent potential. Two classical protocols have been known to afford pyrazoloquinolines. 2-Chloroquinoline-3-carbaldehyde has been condensed with substituted hydrazine hydrates in a polyol/aqueous medium under conventional heating or microwave irradiation. The clean one-pot condensation of 2-chloroquinoline-3-carbaldehyde and substituted hydrazines in the presence of p-toluene sulfonic acid under MW-promoted conditions has also been declared. Some other reports contain the conversion of quinoline-2-ones into 2-chloroquinoline-3-carbaldehyde intermediates, which then are subjected to a reaction with hydrazine hydrate/phenyl hydrazines under conventional heating in an organic solvent to yield pyrazoloquinolines.

The protocol containing the use of L-proline as the catalyst in the one-pot condensation of pyrazolones, anilines, and aldehydes has also been reported as the strategy leading to the formation of pyrazoloquinolines. The above-explained methods possess one or more drawbacks, and no study performed in water in the presence of biocatalysts, which accelerate one-pot multicomponent syntheses of benzoxanthones and pyrazoloquinolines, has been reported. Although enzymes have been known as biocatalysts for accelerating biotransformations, since the last decade of the 20th century, they have been explored as catalysts to activate various synthetic procedures. Generally, biocatalysts are isolated enzymes/coenzymes, either in pure or whole-cell crude form. Active baker's yeast is a rich source of the library of enzymes and is used as a whole-cell source of biocatalysts in various organic transformations. In this connection, Chavan and coworkers have described a one-pot condensation for the synthesis of tetrahydrobenzo[a]xanthene-11-ones and pyrazolo[3,4-b]quinolones. This reaction has been performed by the catalytic activation of baker's yeast and excellent yields have been accessed within 45 mins at room temperature in water. The attempts made have shown that the cyclocondensation has not been carried out in reasonable yields in the absence of baker's yeast, even at longer reaction times (Chavan, Kharat, Bhosle, Dhumal et al., 2021) (Scheme 4, Scheme 5).



R= 4-Cl, 4-OH, 4-Br, 2-NO_2, 4-OMe, 4-Me, 4-F

Scheme 4. Synthesis of tetrahydrobenzo[a]-xantene-11-ones.



R= H, 6-Me, 7-Me, 8-Me, 6-Cl, 6-OMe; R'= H, Ph

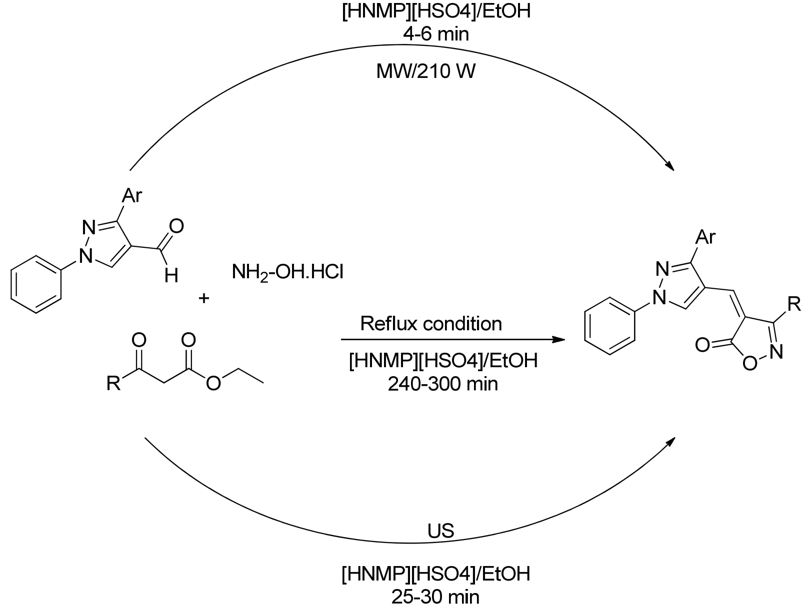
Scheme 5. Synthesis of pyrazolo[3,4-b]quinolines.

1.3. Ionic Liquids

As an important result of the meeting "The Paris UN Climate Conference 2015", the growth form of the world should be trustworthy, sustainable, and beneficial for all to overcome the climate change challenges. Therefore, academicians and industrial researchers have to make greater efforts towards the elimination of the detrimental effects of chemicals and chemical processes on the ecosystem. In recent years, the attempt to find durable developments in the chemistry field has become an essential task, one which can be achieved by implementing green chemistry techniques. The use of eco-friendly solvents with no or minimal impact on both aquatic organisms and the environment has been accepted as the significant criteria for innocent and sustainable chemical processes. Among the best alternative solvents are ionic liquids, which are organic salts with low melting points being in the liquid state at or near room temperature. They have also been known as designer solvents, solvents of the future, liquid organic salts, ionic melts, liquid electrolytes, fused salts, ionic fluids, liquid salts, and ionic glasses. The ionic liquids are green alternatives to organic solvents used in chemical procedures such as biotransformation and extraction. They are thermally stable, non-volatile and their solvation properties vary by changing the cation and the anion. These green solvents are the liquids that render new technologies possible through environmental applicability. However, they have some disadvantages involving poor biodegradability, high cost, sustainability, and biocompatibility (Gadilohar and Shankarling, 2017).

In the context of green chemistry concerns, the use of "safer solvents and efficient energy sources" has become an indispensable principle for chemical processes. In this regard, the employment of ionic liquids as the catalyst, co-catalyst, solvent, and/or co-solvent in combination with environmentally favorable energy inputs like microwave and ultrasound has attracted widespread attention to reach numbers of diverse molecular libraries in a green manner (Duan, Wang and Li, 2015). Ionic liquids (ILs) have some suitable properties such as good selectivity and high catalytic activity, broad liquid range, low vapor pressure, high ionic conductance, good thermal stability, and regulable chemical and physical properties, and these make them popular as catalysts, catalyst holders and solvents (Xu, Zhao, Song, Miao, Yang et al., 2015; Yazdani-Elah-Abadi, and Kangani, 2017; Wasserscheid, Keim, 2000). Ionic liquids display important properties involving broad liquid range, negligible vapor pressure, adequate ionic conductivity, capacity to dissolve a variety of organic and inorganic solids, and potentially recyclable properties. Acidic ionic liquids have been used in diverse areas owing to their superior physical and chemical properties. [HNMP][HSO_4] which is also a brønsted acidic IL has successfully been employed in various organic reactions involving Oxa-Michael additions, cyclocondensations reactions, trans-esterification reactions, and Prins reactions. The microwave (MW) and ultrasound (US) irradiated multicomponent reactions activated by various green catalysts such as nano-particles, zeolites, vitamins, and ionic liquids have been evaluated as fascinating, interesting, and environmentally benign protocols.

In this context, Shelke and coworkers have studied the synthesis of some isoxazolones through a MW or US supported multi-component condensation strategy in the presence of an *N*-Methyl-2-Pyrrolidonium Hydrogen Sulphate [HNMP][HSO_4] catalyst (Shirolea, Tambea and Shelke, 2020) (Scheme 6).



Scheme 6. Synthesis of isoxazolone derivatives.

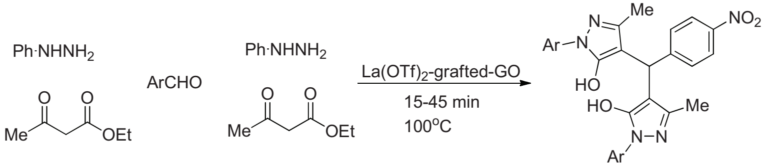
Despite the extensive use of ILs in the processes containing homogeneous catalysis, some drawbacks such as catalyst recovery, difficulty in the separation of reaction products from the ionic phase, and the high cost of relatively large quantities of ionic liquids have limited their usage.

To overcome these drawbacks, the method including immobilization of ILs onto the surface of various substances has been used with the intent to prepare supported IL catalysts (Xu, Zhao, Song, Miao, Yang et al., 2015; Li, Bhadury, Song and Yang, 2012). Magnetic materials, carbon nanotubes (CNTs), silica, nanosheets, inorganic materials, and graphene polymers, have been used as holders for the immobilization of ionic liquids. Immobilized ILs have the combination of the properties of both homogeneous and heterogeneous catalysts such as high system stability, good recyclability, easy separation, etc (Zarnegar, Safari, 2016; Li, Bhadury, Song and Yang, 2012; Ai, Wu, Li, Zhao et al., 2016; Safari, and Zarnegar, 2013; Pourjavadi, Hosseini, Doulabi, Fakoorpoor et al., 2012; Xu, Sheng, Wang, Liu et al., 2016). The development of multicomponent domino reactions (MDRs) in the presence of microwave irradiation and an ionic liquid catalyst has become an important topic for the synthesis of complex or simple bioactive compounds in the drug discovery field (Dömling and Ugi, 2000). Even so, accessing the active structures of polyheterocycylic scaffolds containing various functional groups has remained a challenging topic in modern organic chemistry (Yazdani-Elah-Abadi and Kangani, 2017).

1.4. Catalyzed Reactions

The employment of multifunctional catalysts in consecutive reactions, where two or more catalytic reactions take place in one pot, prevents the waste of time and yield during the synthesis procedures in sequential steps. Some advantages such as step-saving, low-cost, reduced waste production and energy, and limited solvents consumption make these procedures sustainable, green, and attractive. Acids and bases have been regarded as the most attractive catalysts in organic chemistry. However, the employment of acidic and basic groups in a homogeneous system is not suitable as they neutralize each other in so-called "wolf-and-lamb" reactions resulting in the formation of inactive salts. On the other hand, a heterogeneous multifunctional catalyst can solve this challenge by spatially separated incompatible active organic groups, avoiding their mutual neutralization. Clays, silica, and polymers are supporting materials used for the immobilization of basic and acidic functions. Graphene oxide (GO) is accepted as a very appealing carbon material due to its cheapness, high availability, benignity, and exhibiting interesting physical properties such as excellent mechanical and thermal stability. GO has a two-dimensional structure consisting of basal planes sp^2-bonded carbon with unique surface properties. Epoxy and hydroxyl groups are present on the GO planes, while the carboxylic acids are located on the sheet edges. Recently, graphene oxide has been employed as an acidic solid support for the immobilization of basic functional groups to obtain bifunctional catalysts having the ability to be recycled and reused without any difficulty (Sobhani, Zarifi and Skibsted, 2017).

Sobhani and coworkers have designed an immobilized lanthanum (III) triflate on amine-grafted grapheme oxide [$La(OTf)_2$-grafted-GO] as a new multifunctional catalyst (Scheme 7) and they have used it as the first reusable (Lewis and Brønsted) acid–base trifunctional catalyst for the tandem reaction of phenylhydrazine, ethyl acetoacetate, and arylaldehydes yielding bis(pyrazolyl)methane derivatives (Sobhani, Zarifi and Skibsted, 2017).

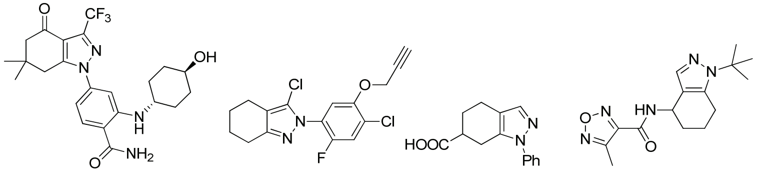


Ar: C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 2-OH-C_6H_4, 4-OH-C_6H_4, 2-thienyl, 2-furyl, 4-CHO-C_6H_4

Scheme 7. Synthesis of bis(pyrazolyl) methanes.

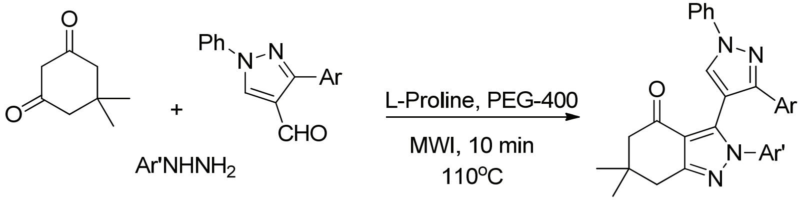
The synthesized multifunctional [(Lewis and Brønsted) acid−base] catalyst has been reported to display excellent catalytic performance and synergetic catalytic effects in this one-pot five-component reaction. Moreover, based on the FT-IR spectrum and TEM image data of this reusable catalyst, the morphology and structure of La(OTf)$_2$-grafted-GO has been reported to remain intact after 9 recoveries.

Recently, the use of organocatalysts for the activations of chemical reactions has provided a green approach for the effective synthesis of a wide range of molecular libraries. In particular, L-proline has been employed as an environmentally friendly, non-toxic, and non-hazardous catalyst in many reactions focused on green chemistry. A catalytic reaction, which is performed in an eco-friendly solvent allowing both solvent and catalyst recycling, has always been assessed as a cost-efficient procedure. The use of PEG supplying recyclable reaction medium has attracted a great demand in synthetic procedures because of its thermal stability, and its recoverable, biodegradable, inexpensive, and non-toxic properties. On the other hand, tetrahydroindazolones (THIs) have been reported to possess a broad spectrum of pharmacological and biological activities (Fig. 1). The THI itself constitutes a privileged structural unit of SNX-2122, which has been identified as a powerful heat shock protein 90 (HSP-90) inhibitor and demonstrates antiproliferative activities against multiple cancer cell lines in nanomolar quantities.



SNX-2122, HSP-90 inhibitor **herbicidal agent** **anti-inflammatory agent** **MTB inhibitor**

Figure 1. Bioactive tetrahydroindazolones.



Ar: C_6H_5, 4Cl-C_6H_4, 4OCH_3-C_6H_4, 3N-C_6H_3, 2S-C_6H_3, 4NH_2-C_6H_4, 4NO_2-C_6H_4;
Ar': C_6H_5, Br-C_6H_4.

Scheme 8. Synthesis of substituted pyrazolyl-tetrahydroindazolones.

Given these, Kamble et al. have reported a microwave irradiated three-component domino reaction yielding regioselective pyrazolyl-tetrahydroindazolones (Scheme 8). This condensation carried out in PEG-400 as a greener solvent in the presence of readily available L-proline as an organocatalyst has been defined as a powerful procedure leading to the preparation of a new scaffold-based 2-substituted THIs possessing a high potential for several applications in the medicinal chemistry field (Bayannavar, Kamble, Shaikh, Kumar et al., 2019).

1.5. Microwave Irradiated Reactions

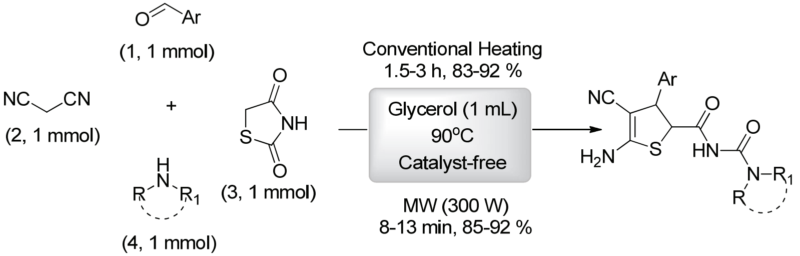
Because of the limitation of fossil energy sources, the application of renewable and more efficient energy sources to provide the requisite heat has become more significant. In this connection, the high efficiency of microwave irradiation in comparison with heat at driving chemical reactions has led to the fast-growing of its application in organic chemistry, polymer chemistry, nanotechnology, material sciences, biochemical processes, and peptide syntheses.

Among the environmentally benign methodologies, microwave (MW) irradiated reactions have also gained considerable attention mainly owing to their solvent- and catalyst-free characters providing an alternative way with minimum waste formation, shorter reaction times, isolation of relatively pure products, high yields, and easy work-up procedures. Hence they have been accepted as green alternatives to traditional synthetic procedures (Khan, Khan, Shareef and Danish, 2018; Mermer, Demirbas, Cakmak, Colak et al., 2019; Demirci, Demirbaş, Menteşe, Özdemir et al., 2018; Mermer, Demirbas, Demirbas, Colak et al., 2018; Mermer, Demirbaş, Şirin, Uslu et al., 2018; Mentese, Bayrak, Uygun, Mermer et al., 2013; War, Srivastava and Srivastava, 2017; Kappe, 2004; Henary, Kananda, Rotolo, Savino et al., 2020; Katritzky and Angrish, 2006; Naeimi and Moradi, 2006; Ramesh and Raghunathan, 2008).

The power of microwave as an easy-controlled and powerful heating resource has been used to speed the reactions and to supply efficient procedures leading to the formation of several important chemicals (Liu, You, Wu, Han, 2020; Lidström, Tierney, Wathey and Westmana, 2001; Rathi, Gawande, Zboril and Varma, 2015; Jagani, Sojitra, Vanparia, Patel, et al., 2012; Al-Hazimi and Al-Alshaikh, 2010; Desai, Satodiya, Rajpara, Joshi et al., 2017; Guan, Al-Misba'a and Huang, 2015). This new reaction tool is based on the microwave power reducing reaction times and energy consumption with increased yields and selectivity of the examined conversions. This technique also supplies a more benign and environmentally sustainable approach for organic synthesis (Zhu, Sun, Lou, An et al., 2015). Because of the benefits described above, the employment of microwave activation has become quite widespread among synthetic organic chemistry groups (Khalafi-Nezhad, 2020).

It is well known that microwave chemistry relies on the ability of the reaction mixture to absorb microwave energy efficiently, taking advantage of microwave dielectric heating phenomena such as dipolar polarization and ionic conduction mechanisms. Obviously, it depends on the polarity of the reaction media to absorb energy and then convert it into heat (Khalafi-Nezhad, 2020). The efficiency of such energy and heat dispersal is a function of the dielectric properties of the reactants and solvents. Hence, the molecules with higher dielectric constant values absorb MW energy more efficiently, while reagents with lower polarity or crystalline materials absorb less. However, the implementation of polar volatile and flammable solvents is highly dangerous. To avoid the explosion risk, the use of non-flammable and nonvolatile reaction media is essential. One of the probable problems in the use of microwave reactors is the explosion of the reactor flasks or tubes sometimes due to the pressure implemented by the reaction solvent during irradiation. Therefore, the elimination of the solvent has significant importance, which actually results in shorter reaction times and better yields. However, in some cases the use of a solvent may be unavoidable. Among the solvents suitable for this purpose, glycerol, a non-flammable and nonvolatile liquid, supplies high efficiency to absorb microwave energy and deliver to reactants. Therefore, glycerol can be a good option as a safe solvent to perform MW-mediated organic reactions under safe conditions. In this context, Kordnezhadian and coworkers have described the catalyst-free one-pot four-component microwave-accelerated synthesis of 2-(*N*-carbamoylacetamide)-substituted-2,3-dihydrothiophenes under MW irradiated conditions.

Glycerol has been used as a biodegradable, non-toxic, and highly efficient reusable reaction media (Khalafi-Nezhad, 2020) (Scheme 9).



Scheme 9. The catalyst-free one-pot four-component synthesis of 2-(*N*-carbamoylacetamide)-substituted-2,3-dihydrothiophenes in glycerol at 90ºC under conventional heating or MW irradiation.

Microwave-assisted organic synthesis (MAOS) also allows modifications in selectivity (chemo-, regio-, and stereo-selectivity) for the synthesis of complex heterocyclic molecules. Benzo[a]phenazine derivatives have been reported to act as dual inhibitors of topoisomerases I and II, while some act as anticancer and antitumor agents. Pyridazinophenazinediones and pyridophenazinediones have been known to possess the antitumor activity as well. Additionally, phenazines having a fluorescent feature have been employed as photosensitizers in photodynamic therapy where the combination of light and photo-sensitizing creates hydroxyl radicals or highly reactive oxygen species near the tumor for selective destroying of the targeted tissue. Moreover, 1,4-dihydropyridine (DHP) derivatives have been reported as a basically significant class of aza-heterocyclic molecules displaying several pharmacological, medical, and biological activities containing hepatoprotective, bronchodilator, antidiabetic, vasodilator, geroprotective, antitumor, anti-HIV, antiatherosclerotic and anticonvulsant features (Dehghan and Mohebat, 2020).

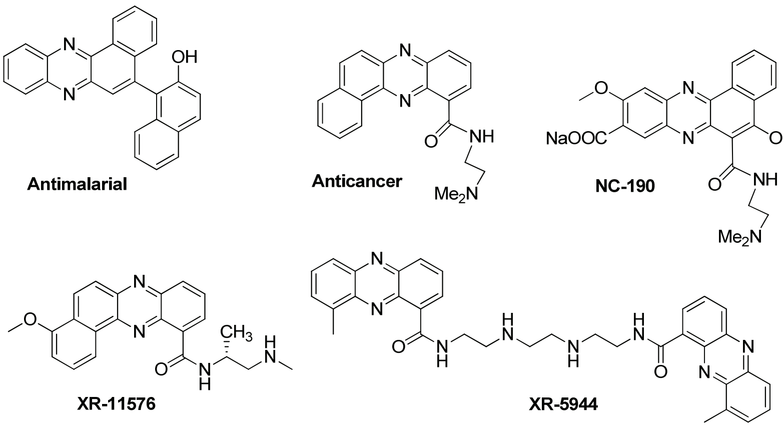
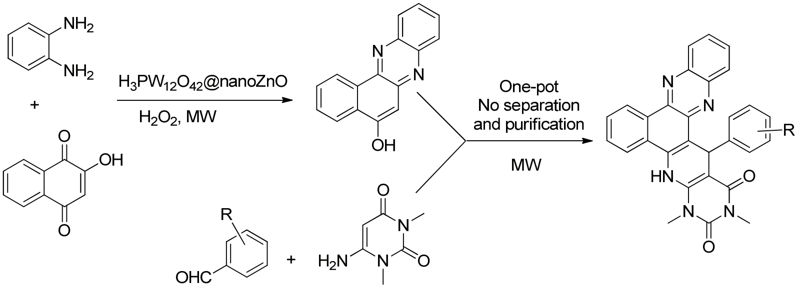


Figure 2. Biologically active phenazine derivatives.

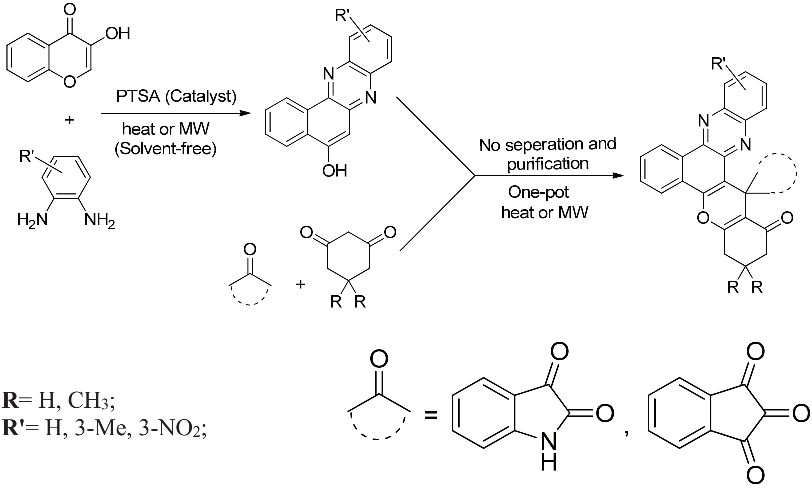
Very recently, Dehghan and Mohebat have reported the synthesis of complex benzophenazine derivatives by sequential single-pot four component reaction. This condensation has been performed through the condensation between 2-hydroxy-1,4-naphthoquinone, o-phenylenediamine, benzaldehydes, and 6-amino-1,3-dimethyluracil catalyzed by $H_3PW_{12}O_{40}$@nano-ZnO as a highly efficient, eco-friendly, and recyclable heterogeneous catalyst under microwave irradiation (MWI) (300 W, max. 100 °C) in H_2O (Dehghan and Mohebat, 2020) (Scheme 10).



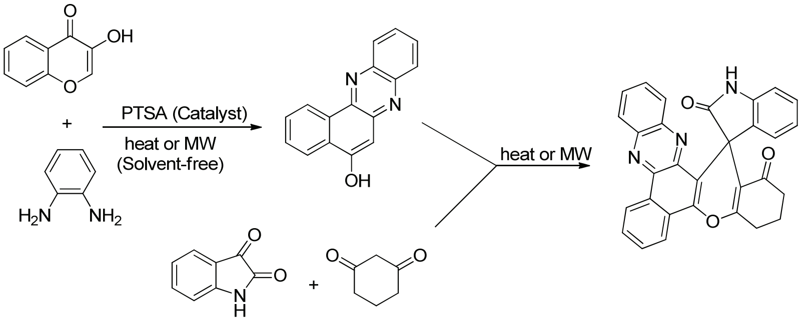
R= 4-NO_2, 4-Cl, 4-Br, 3-NO_2, 2-NO_2, -H, 4-Me, 4-MeO

Scheme 10. $H_3PW_{12}O_{40}$@nano-ZnO catalyzed sequential one-pot synthesis of 2,4-dimethyl-16-(4-aryl)-5,16-dihydrobenzo[a]pyrimido[50,40:5,6]pyrido[2,3-c]phenazine-1,3(2*H*,4*H*)-diones under MWI in water.

The effective construction of polyheterocyclic frameworks with diverse functionalities has remained a challenging topic in modern synthetic organic chemistry. Among these polyheterocyclic skeletons, phenazine derivatives have attracted considerable attention due to their biological activities involving fungicidal, trypanocidal, antiplatelet and antimalarial activities. Some benzophenazine derivatives have been reported as dual inhibitors of topoisomerase I and II, which are key enzymes impressing the topology of DNA at various points in the cell cycle. Also, chromene-annulated heterocyles constitute a substantial class of oxygen-containing heterocycles possessing considerable effects as pharmaceuticals, including antimicrobial and antifungal activities, and these are widely distributed in several edible fruits and vegetables. Therefore, compounds including phenazine and chromene units together have gained a lot of interest in drug discovery studies (Mohebat, Simin and Yazdani-Elah-Abadi, 2019) (Scheme 11).



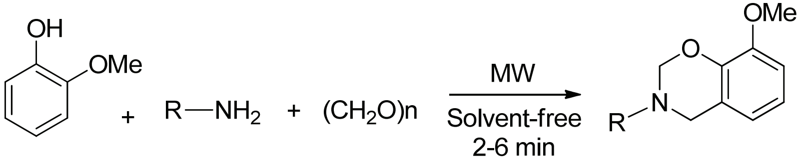
Scheme 11. One-pot four-component synthesis of novel spiro[benzo[α]chromeno[2,3-*c*]phenazine] derivatives in the presence of PTSA as an efficient solid acid catalyst.



Scheme 12. Synthesis of 3,4-dihydrospiro[benzo[α]chromeno[2,3-*c*]phenazine-16,3’-indoline]-1,2’(2*H*)-dione.

Considering the work in the development of new synthetic methods, Mohebat et al. have defined a new sequence of a one-pot, four-component domino cyclization between benzene-1,2-diamines, 2-hydroxy-1,4-naphthoquinone, cyclic 1,3-dicarbonyl compounds, and ninhydrin or isatin (Scheme 12). This reaction, yielding spiro[benzo[a]chromeno[2,3-c]phenazine] derivatives, has been carried out in the presence of PTSA under traditional and MW irradiated conditions and it has resulted in the formation of products with excellent yields and purities in very short reaction times. Several advantages of this method have been reported involving easy process, operational simplicity, the use of the non-toxic, inexpensive catalyst in minimum quantities without any by-product in solvent-free conditions. Thus, this procedure has been evaluated as an example of environmentally benign, since it requires the use of neither metal-containing catalyst nor solvent (Mohebat, Simin and Yazdani-Elah-Abadi, 2019).

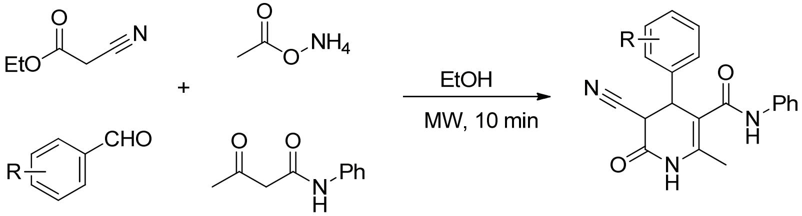
Another interesting example has been reported by Lomonaco’s group; this is the one-pot synthesis of benzoxazines, which are known as useful intermediates for the preparation of resins used in the area of synthetic materials and polymers, by means of an environment-friendly microwave-assisted strategy in solvent-free media. It is particularly striking that the duration of this reaction, which takes place with good yields, is very short (2-6 mins) (Kotzebue, Ribeiro, Mota, Zampieri et al., 2017) (Scheme 13).



R= Ph, 2-MeC_6H_4, 4-MeC_6H_4, cyclohex, furan-2-ylmethyl, tetrahydrofuran-2-ylmethyl

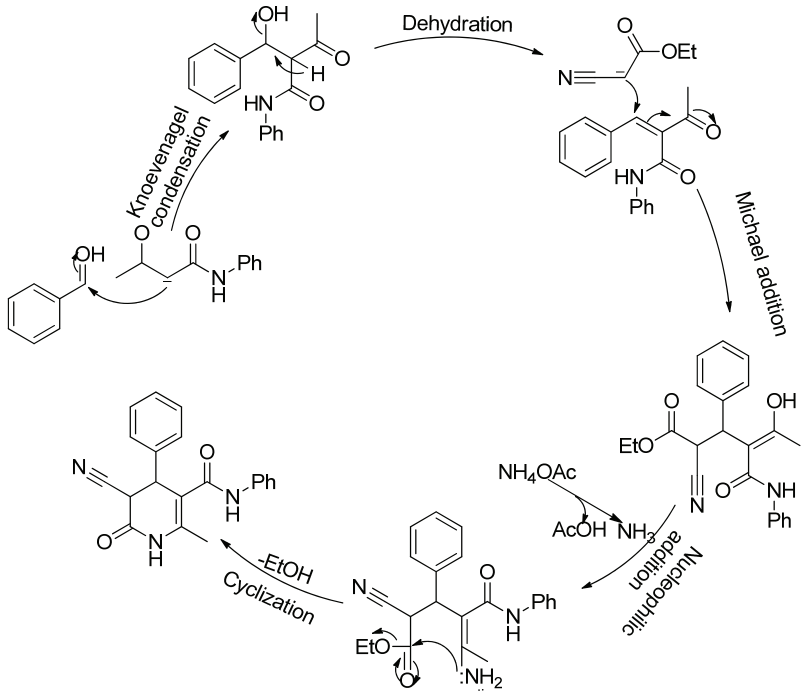
Scheme 13. Microwave synthesis of benzoxazines under solvent-free conditions.

The study reported by Jonnalagada and coworkers can be given as another green strategy containing the catalyst-free, one-pot multicomponent synthesis of tetrahydropyridine-3-carboxamides under microwave irradiated conditions (Khumalo, Maddila, Maddila And Jonnalagadda, 2020) (Scheme 14, Scheme 15).



R= 2-MeO, 2,4-diCl, 3,4,5-triMeO, 2-Cl-6-F, thiophen-2-yl, 4-OH, 2-CF_3, 2-Me, 2,4,5-triMe, 3-Cl, 2,5-diMeO

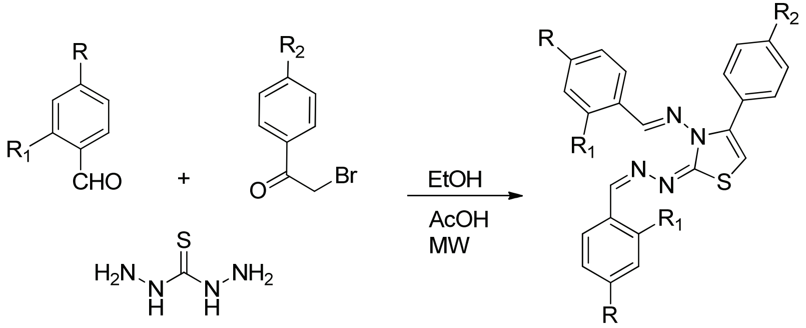
Scheme 14. Four-component green synthetic route for tetrahydropyridine-3-carboxamides.



Scheme 15. Probable mechasim for the formation of tetrahydropyridine-3-carboxamide.

The important advantages of this procedure have been reported as simple handling, environmental benignity, faster reaction, less toxicity, evading column chromatography, higher yields, and mild reaction conditions.

Considering the green chemistry concept, some thiazole derivatives have been synthesized via the application of an MW irradiated catalyst-free one-pot three-component protocol in ethanol (Mamidala, Mudigunda, Peddi, Bokara et al., 2020) (Scheme 16).



R= Cl, Br, OH; **R$_1$**= H, OH; **R$_2$**= H, F, Cl, Br, NO$_2$, OMe.

Scheme 16. Synthesis of thiazoles; reagents and conditions: EtOH, AcOH, microwave irradiation at 70°C and 210 W.

A study involving the comparison of the benefits of traditional and MW irradiation methods has been studied by Mermer et al. for the reactions involving the synthesis of new derivatives of fluoroquinolones, which are antibacterial drugs. These researchers have explained why this study was needed based on the following data.

The increasing multidrug resistance among bacteria, viruses, and fungi to currently used drugs has emerged as an alarming and reemerging microbial threat and has become a major public health concern worldwide with nearly 15 million deaths every year. Several pathogens which appeared to be under control have once again been fatal since they have developed a variety of strategies to enhance their survival skills in the presence of antimicrobial agents. Estimates suggested that unless significant progress is made, drug resistant infections may result in ten million deaths annually by 2050. In order to manage drug resistance, the development of novel chemotypes which act upon novel molecular targets, has emerged as an urgent and crucial requirement. However, only a few molecules with new modes of action to medical use have been prepared.

More recently, the molecular hybridization concept based on the combination of structural units of two or more drug fragments through the fusion in one molecular framework with improved properties has been adopted as a new and attractive strategy (Lal, Yadav, Kumar, Kumar et al., 2018; Ozdemir, Demirbas, Demirbas, Colak et al., 2018; Mentese, Demirbas, Mermer, Demirci et al., 2018; Demirci, Demirbas, Ulker, Alpay-Karaoglu et al., 2014; Siwek, Staczek and Stefanska, 2011). The key advantage of hybrid molecules consisting of several pharmacophore groups each with different modes of action is to inhibit bacterial targets via unique binding sites or via novel modes of action or to exhibit dual modes of action (Panda, Liaqat, Girgis, Samir et al., 2015; Li, Zhang, Plattner, Mao et al., 2013; Ceylan, Bektas, Bayrak, Demirbas et al., 2013; Chugunova, Akylbekov, Bulatova, Gavrilov et al., 2016; Ozdemir, Demirbas, Cebeci, Bayrak et al., 2017; Basoglu, Ulker, Alpay-Karaoglu and Demirbas, 2014; Zidar, Tomasic, Macut, Sirc et al., 2016). Moreover, molecular hybrids can display better pharmacokinetic profiles, therapeutic indexes and more importantly a low tendency to resistance.

Quinolones have been at the center of considerable scientific and clinical interest since their discovery in the early 1960s. This is because they potentially offer many of the attributes of an ideal antibiotic, involving high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues, and a potentially low incidence of side-effects. Much research has attempted to make these potential attributes real. After the first quinolone, nalidixic acid, was developed, it took more than a decade before additional compounds, such as flumequine, norfloxacin, and enoxacin, became available for clinical use. The main use for all these agents was the treatment of urinary tract infections. Since the discovery of norfloxacin (NFLX) by Koga et al. in the early 1980s, quinolones have become one of the most attractive agents in the chemotherapy of both community-acquired and serious hospital-acquired infections (Mentese, Demirci, Ozdemir, Demirbas et al., 2016; Itoh, Kuramoto, Amano, Kazamori et al., 2019). These drugs display their activity by binding to two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV. This causes permanent double stranded DNA breaks and results in cell death. However, the rapidly increasing level of resistance towards quinolone class antibacterial drugs has limited their therapeutic efficacy and led scientists to design either novel structural classes of inhibitors targeting gyrase and topoisomerase IV; or to discover new quinolone hybrids (Tomasic, Mirt, Barancokova, Ilas et al., 2017; Alagumuthu, 2017).

During the past 30 years, hundreds of quinolone derivatives have been discovered, and a large quantity of structure–activity relationship (SAR) has been accumulated. The activity of quinolone class antibacterial agents arises from the bicyclic heterocyclic ring and also the structure of peripheral substituents and their spatial relationship. These groups can provide additional affinity towards bacterial enzymes, enhance the cell penetration or alter pharmacokinetic properties. The *in silico* studies on quinolone class antibiotics have showed that the basic group at C-7 position is the most suitable site for chemical modifications. It constitutes an area with a great influence on potency, spectrum and safety and most of studies aiming at the discovery of new quinolone hybrids have been focused on the functionalization at C-7 in the quinolone skeleton (El-Din, Abuo-Rahma, Sarhan, Gad et al., 2009; Sharma, Jain, Yar, Pahwa et al., 2015; Mentese, Bayrak, Uygun, Mermer et al., 2013).

Considering these aforementioned statements, Demirbas's group has focused on the design, ecofriendly synthesis and antibacterial evaluation of new piperazine-azole-fluoroquinolone conjugates (Fig. 3). Phenyl piperazine scaffold has been selected as the key prototype structural unit and the combination of phenyl piperazine skeleton with azole and fluoroquinolone units has been achieved by both the conventional and microwave irradiated techniques (Mermer, Faiz, Demirbas, Demirbas et al., 2019).

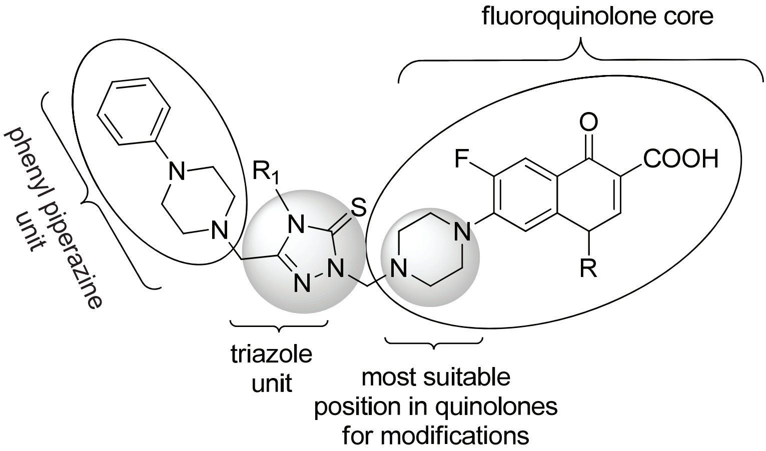
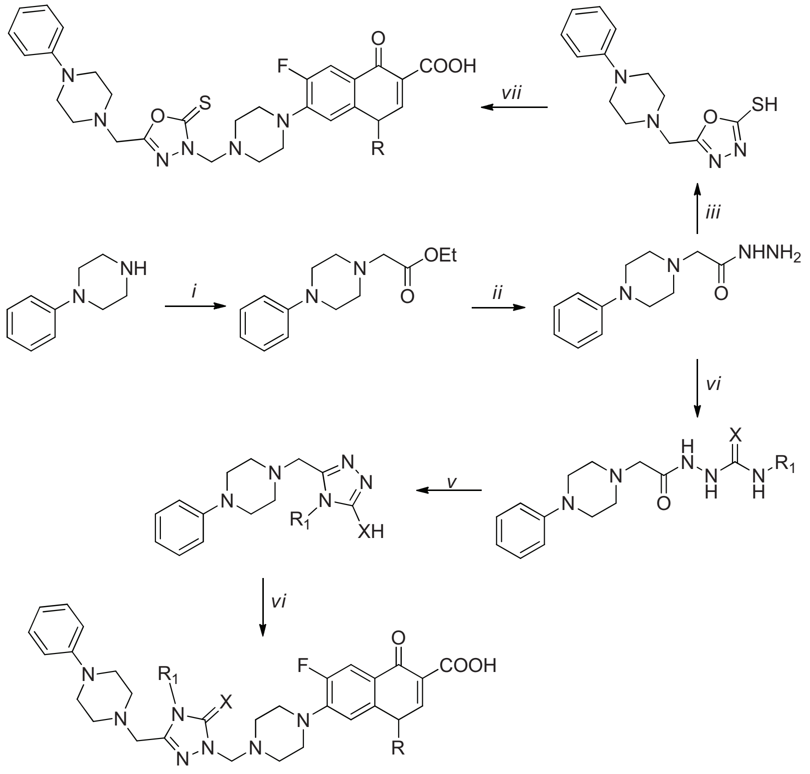


Figure 3. General representation of the target compounds.



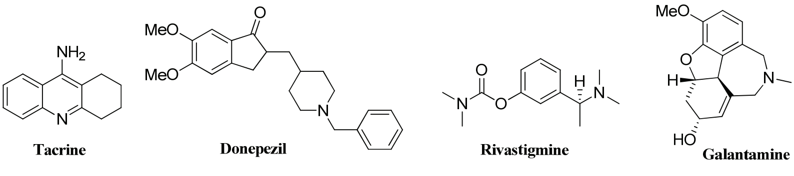
R= Ethyl, Cyclopropyl; **X**= O, S; **R$_1$**= Ph, Et, Bn, 4-FC_6H_4

Scheme 17. Synthesis of fluoroquinolone-triazole and fluoroquinolone-oxadiazole hybrid compounds. *i*: $BrCH_2COOEt$, TEA, THF; *ii*: $NH_2NH_2{\cdot}H_2O$, EtOH; *iii*: CS_2, KOH(aq), EtOH; *iv*: R_1NCX; *v*: NaOH(aq), EtOH; *vi*: HCHO, DMF, *vii*: Ciprofloxacin or Norfloxacin.

Compared to conventional methods, the use of the microwave irradiation method has significantly decreased the reaction time while the reaction yields have increased. At the same time, the results of optimization studies have shown that the reaction progress has not been affected by the presence of Lewis acids and solvent. The antibacterial activity screening studies have revealed that new hybrid molecules consisting of fluoroquinolone-azole-piperazine conjugation have good-to-excellent antibacterial activity against the test microorganisms. Furthermore, these hybrids have exhibited good DNA gyrase inhibition with the IC_{50} values varying between 0.134 and 1.84 μg/mL (Mermer, Faiz, Demirbas, Demirbas et al., 2019) (Scheme 17).

The same authors have performed the conventional and MW irradiated synthesis of some triazole-quinolone hybrid compounds with antioxidant and anticholinesterase activity (Mermer, Demirbas, Sirin, Uslu et al., 2018). Acetylcholinesterase (AChE) is known as a serine hydrolase enzyme managing the hydrolysis of acetylcholine (ACh), which is a significant neurotransmitter for the arrangement of cognition in animals (Shah, Khan, Ejaz, Afridi et al., 2017). Inhibition of AChE leads to the rise of ACh levels in cholinergic synapses. Thus, cholinesterase inhibitors are used in the treatment of various neuromuscular disorders which occur because of reduced cortical and hippocampal levels of ACh such as Alzheimer's disease (AD) which is a complex neurodegenerative disorder characterized by synapse dysfunction, neuronal death, and loss of memory and learning ability (Strelnik, Petukhov, Zueva, Zobov et al., 2016; Gilhus, Skeie, Romi, Lazaridis et al., 2016).

Current treatment approaches for AD continue to be principally symptomatic, with the major therapeutic AD, known as the cholinergic hypothesis, and specifically on cholinesterase inhibition. Various AChE inhibitors such as tacrine, donepezil, rivastigmine, and galantamine have been used contemporarily for the symptomatic treatment of AD. In recent years, novel cholinesterase inhibitors from natural resources or synthetic ways, which have coumarin, benzofuran, berberine, b-carboline, benzophenone, ferulic acid, naphthyridine, triazine, and quinolone scaffolds as the main pharmacophoric groups, have been reported (Saeed, Zaib, Ashraf, Iftikhar et al., 2015; Delogu, Matos, Fanti, Era, Medda et al., 2016).



Tacrine **Donepezil** **Rivastigmine** **Galantamine**

Figure 4. Molecular structures of FDA-approved AD-treatments.

Most of free radicals and reactive oxygen species (ROS) including superoxide anions and hydrogen peroxide are unstable species with unpaired valence electrons and capable of abstracting electrons from other molecules. In cells, the incomplete oxygen metabolism and release of free electrons result in the production of ROS and oxygen radicals which have been attributed to food oxidation and many diseases. Antioxidants whether they are natural or synthetic are capable of inhibiting the construction of reactive oxygen species (ROS) and free radicals. An imbalance between ROS and antioxidants causes oxidative stress leading to cancer, aging, neurological degeneration in Parkinson's, Alzheimer's, arthritis, inflammation, and ischemic injury (Basoglu-Ozdemir, Demirbas, Demirbas, Colak, et al., 2018).

Some new compounds possessing promising AChE inhibition activity have been obtained in the study reported by Mermer's group. This study has been declared to be established for the synthesis of new multipotent hybrid molecules which have a quinolone-triazole hybrid scaffold for the treatment of Alzheimer's disease (Mermer, Demirbas, Sirin, Uslu et al., 2018). Surprisingly, while the quinolone-triazole compounds have been expected to be more active, the inhibition results have demonstrated that the most active compounds are quinolone-carbothioamide derivatives. In this study, the use of MW has provided great advantages in terms of both reaction time and yields (Figure 5, Scheme 18).

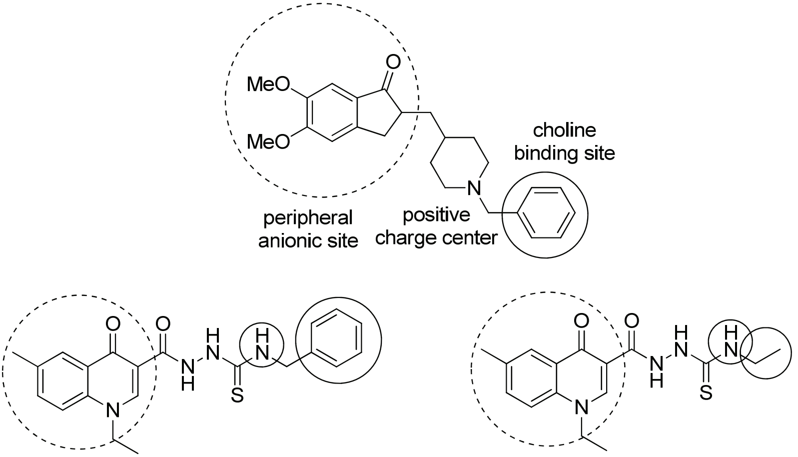
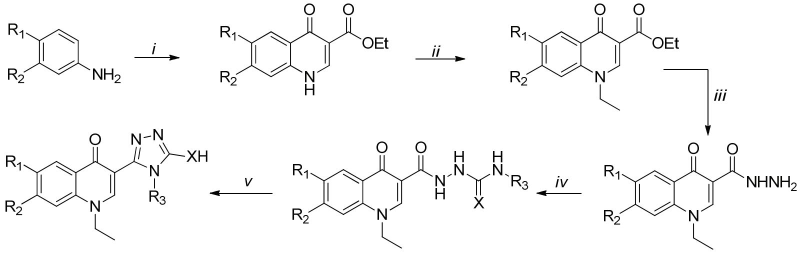


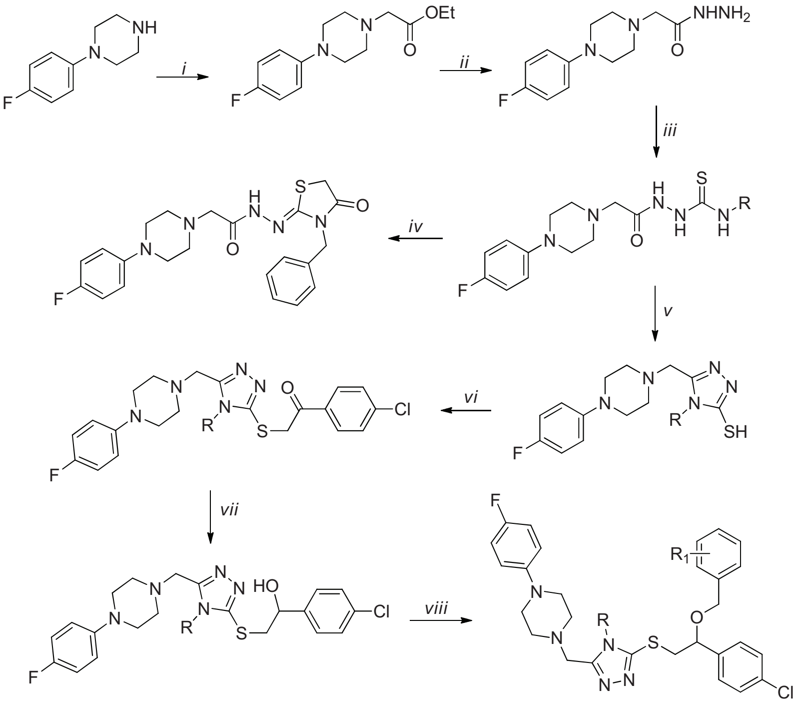
Figure 5. Structural hypothesis for AChE inhibitors.



R_1 = Me, F; **R_2** = H, Cl; **R_3** = Ph, Bn, Et, 4-FC_6H_4; X = S, O

Scheme 18. Synthetic pathway for the preparation of quinolone-1,2,4-triazole derivatives. *i*: diethyl ethoxymethylenemalonate, Ph_2O; *ii*: K_2CO_3, C_2H_5Br; *iii*: H_2NNH_2; *iv*: RNCX; NaOH, H_2O-EtOH.

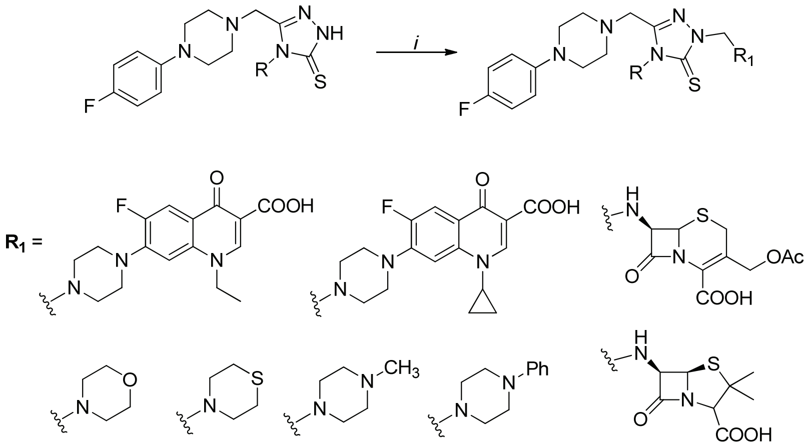
The synthesis of some new triazole-quinolone hybrids has been carried out in the study reported by Basoglu-Ozdemir and coworkers. In this procedure, both traditional and MW irradiated methods were used comparatively. The results obtained have demonstrated that the microwave-assisted method has proved a valuable technique for reducing reaction times, giving cleaner reaction profile, improved yields, simplified work-up, and designing energy-saving protocols (Basoglu-Ozdemir, Demirbas, Demirbas, Colak et al., 2018). The synthetic strategies adopted to obtain the target compounds are depicted in Scheme 19 and Scheme 20).



R = CH_2Ph, Ph; $\mathbf{R_1}$ = 4-Cl, 2,4-diCl, 2,6-diCl

Scheme 19. Synthesis of conazole derivatives. *i*: $BrCH_2COOEt$, Et_3N, THF, rt or MW; *ii*: H_2NNH_2, EtOH, reflux or MW; *iii*: RCNS, DCM, rt or MW; *iv*: $BrCH_2COOEt$, NaOAc, reflux or MW; *v*: NaOH, reflux or MW; *vi*: NaOEt, 2-bromo-1-(4-chlorophenyl)ethanone, reflux or MW; *vii*: $NaBH_4$, EtOH, reflux or MW; *viii*: NaH, benzyl chloride, THF, reflux.

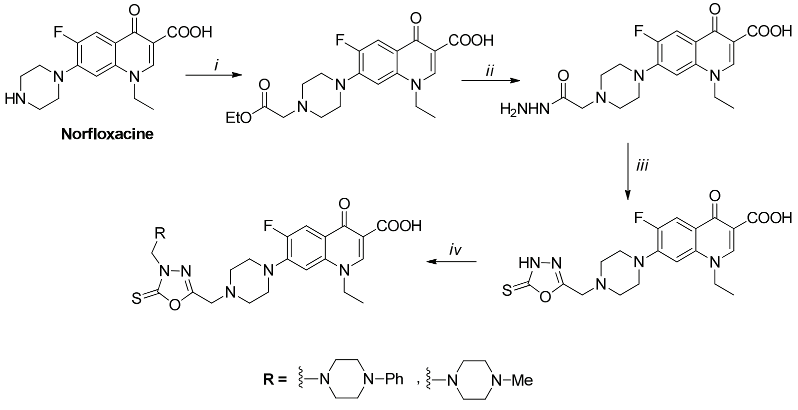
The antimicrobial, antiurease and antioxidant activity screening studies have also been performed in this study. The highest activity has been observed for compounds containing the fluoroquinolone nucleus on the test bacteria with the MIC values between 0.24-1.9 mg/mL. In addition, some of the newly synthesized compounds have shown good urease inhibition against Jack bean urease. Furthermore, some of them have displayed antioxidant and antifungal activity.



R = $CH_2C_6H_5$, Ph

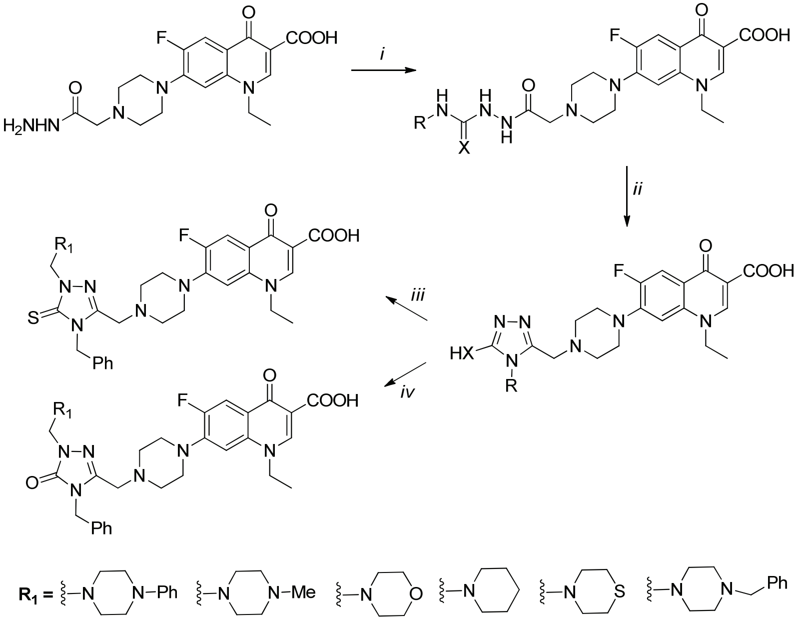
Scheme 20. Synthesis of novel Mannich base derivatives. *i*: HCHO, DMF, suitable amine, rt or MW.

It has been reported that the compounds obtained by molecular hybridization of several pharmacophore groups act by inhibiting two or more conventional targets simultaneously, and this multiple target strategy has resulted in the development of several bioactive hybrid molecules. The heterocyclic pharmacophores are selected on the basis of their known biological activity profiles (Chen, Wu, Lee, Chen et al., 2015; Panda, Liaqat, Girgis, Samir et al., 2015; Rajanarendar, Thirupathaiah, Ramakrishna and Nagaraju, 2015).



Scheme 21. Reagents and conditions: *i*: $BrCH_2CO_2Et$ in DMF, TEA, 24 h, rt. (method 1) or $BrCH_2CO_2Et$, EtOH, TEA, 15 min, 200 W (method 2); *ii*: H_2NNH_2, chloroform, 24 h, rt. (method 1) or 15 min 80 W MW irradiation MW (method 2); *iii*: KOH, CS_2, EtOH-H_2O, 10 h, reflux (method 1) or 20 min 150 W MW irradiation MW (method 2); *iv*: amine, DMF, HCHO, 24 h, rt.

The superior properties of microwave-irradiated techniques are attributed to both thermal and specific non-thermal effects induced by these irradiations, providing rapid and convenient chemical synthesis. Therefore, the combination of one-pot multicomponent reactions and microwave-irradiation techniques has been an attractive methodology for production of new bioactive compounds. The rationale of the study reported by Demirci et al. for developing new chemotherapeutic agents have based on the hybridization of two biologically active molecules into a single hybrid molecule. In this study, the use of microwave irradiation provided an efficient and green synthetic approach with dramatically reduced reaction times and improved yields (Demirci, Demirbaş, Menteşe, Başoğlu-Özdemir et al., 2018) (Scheme 21, Scheme 22). The results show that most of the newly synthesized compounds exhibit strong antibacterial activity compared with norfloxacin itself.



R= Et, Ph, CH_2Ph; X= O, S

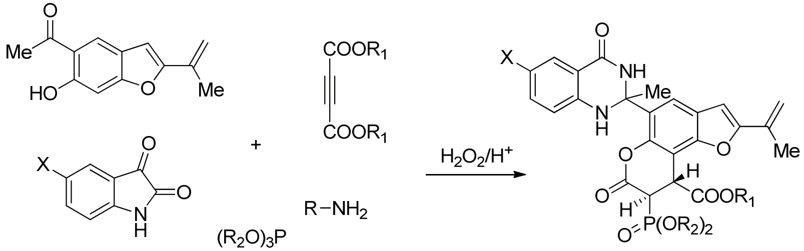
Scheme 22. Synthesis of 1,3,4-oxadiazole-norfloxacine and 1,2,4-triazole-norfloxacine derivatives via Mannich reaction under MW irradiation. *i*: DMF, 24 h stirring or MW (150 W), 5 min; *ii*: NaOH, EtOH, 18 h or MW (120 W), NaOH, 25 min; *iii*, *iv*: amine, DMF, HCHO, 24 h, rt.

1.6. Ultrasound-Supported Reactions

The ultrasound (US) supplies a specific cavitation in the reaction media which induces high temperature and pressure inside of the bubbles and enhances mass transfer and turbulent flow in the liquid (Cravotto and Cintas, 2006). This enables various organic reactions to perform in shorter reaction times than conventional heating (Chidurala, Jetti, Pagadala, Meshram et al., 2016; Bretanha, Teixeira, Ritter, Siqueira et al., 2011; Duarte, Cunico, Pereira, Flores et al., 2010; Machado, Lima, Rotta, Bonacorso et al., 2011; Mamaghani, Loghmanifar and Taati, 2011; Dabholkar and Ansari, 2010). The effect of ultrasonic irradiation has been attributed to its chemical or mechanical impacts or both of them. Furthermore, as a mechanical acoustic wave with frequency, it provides high energy by cavitation and secondary effects in reaction media (Khan, Khan, Iqbal and Yousuf, 2016; Khan, Khan and Sahoo, 2018). Cavitation, which is the most important mechanism of ultrasound intensity (Kikuta, Yoshida, Watanabe, Hashimoto et al., 2008), is a phenomenon containing the formation of vapor bubbles in a liquid (Ammar, Chtourou, Frikha and Trabelsi, 2015). The control and selection of the ultrasonic energy intensity and quantity of effective cavitation are the most important points for the efficient implementation of ultrasound irradiation. The cavitational activity is determined by the quantity of effective cavitation population. On the other hand, the energy intensity depends on the average behavior of bubbles (Ashokkumar, 2011).

In the context of developing new and green protocols for the generation of useful chemical products, the application of sonication has received significant interest as another unusual energy source because of its simplicity, efficacy, and benignity (Zarnegar and Safari, 2016). Various sonochemistry-based methods have been developed as a valuable and original strategy employing to accelerate organic reactions. This technique offers important features for organic reactions such as the formation of pure products with high yields, improvement of reaction rates, energy-saving, easier process, waste decreasing, etc (Ashokkumar, 2011).

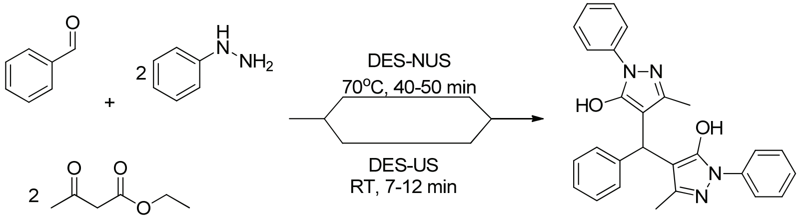
Phospohanes with optical activity have been known as valuable compounds exhibiting wide range of biological activities such as antipsoriatic, anti-influenza, antimicrobial and herbicidal. Quinazolinones constitute another class of medically important compounds displaying several activities such as antibacterial, antifungal and antitumor. Due to these important features, various procedures have been developed for the preparation of quinazolinone derivatives. In this context, Hossaini et al. have reported an ultrasound irradiated sequential one-pot five component procedure yielding diastereoizomeric phosphonate derivatives which also carry chromone and quinazolinone moieties. This reaction which contains the sequential treatment of isatin or its derivatives, primary amines, euparin, dialkyl acetylenedicarboxylates, trimethyl phosphite or triphenyl phosphite in the presence of acidic solution of hydrogen peroxide, has resulted in excellent yields in shorter reaction times (Sharafian, Hossaini, Rostami-Charati and Khalilzadeh, 2020) (Scheme 23).



X = H, CI, Me, NO2; **R** = Me, Et, *i*-Pr, *t*-Bu; **R1** = Me, Et; **R2** = Me, Et, Ph

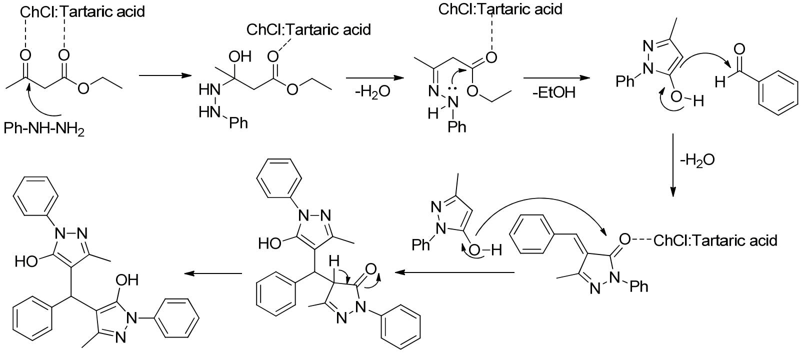
Scheme 23. Green synthesis of euparin-based quinazolinones under ultrasonic irradiation.

In the context of environmental benignity and sustainability, the use of a deep eutectic solvents (DES) and US techniques in tandem have undisputed importance. In this context, Kamble and Shankarling have designed a synthetic pathway leading to the formation of some new 4,4-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives starting from various aldehydes, phenyl hydrazine, and ethyl acetoacetate in water. ChCl: Tartaric acid, (as a DES), and ultrasonic irradiation have been used as activators together (Kamble and Shankarling, 2018) (Scheme 24).



Scheme 24. Synthesis of 4,4-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol.

When this reaction has been performed under ultrasonic irradiation without any DES in water, no product has formed. DES is a requisite first step for, for example, Knorr pyrazole synthesis. The combination of ultrasound and DES has caused a distinguished decrease in temperature and reaction time. Here, an acoustic cavitation and cage effects caused by ultrasonic irradiation have provided high temperature and pressure within seconds leading to the acceleration of the reaction rate. The cavitation contains the nucleation, growth, and temporal collapse of millions of vapor bubbles in microscopic nature, as a result of which, the surface area increases leading to a decrease in the reaction time (Kamble and Shankarling, 2018).



Scheme 25. Plausible mechanism.

Besides the fact that enzymes and their activities are extremely necessary for life, the selective inhibition of critical enzymes has also considerable importance for chemotherapeutic intervention in some diseases. Unregulated high enzyme activity results in the formation of reaction products at abnormal levels which can cause specific pathologies. Nowadays, the strategy of selective enzyme inhibition gets attention in modern pharmaceuticals, and enzymes have become interesting targets in drug therapies. For this reason, many organic molecules have been synthesized as specific enzyme inhibitors and continue to be synthesized. Modeling methods for the three-dimensional structure and topology of the enzymes, active sites, and the organic molecules help the researcher to design new drug molecules or evaluate synthesized molecules for their enzyme inhibition potentials (Mermer, Demirbas, Colak, Ayazoglu-Demir, Kulabas et al. 2018). Carbonic Anhydrase enzymes (CAs), also known as carbonate dehydratases, catalyze the CO_2 hydration to produce bicarbonate and a proton, are zinc-containing metalloenzymes and present in all phyla which maintain pH homeostasis in the body. Carbonic anhydrases are divided into seven genetically distinct families depending on their localization in different organisms, catalytic activity, and sensitivity to different classes of inhibitors. However, only one class (α-class) is present in humans, which consists of 16 isoforms varying in tissue distribution and cellular localization (membrane, cytosol, mitochondria). Among these, five are cytosolic (CA I–III, CA VII, and CA XIII), two are mitochondrial

(CA VA and CA VB), four are membrane-bound (CA IV, CA IX, CA XII, and CA XIV) and one is secreted into saliva and milk (CA VI). The CA isoforms take part in several biochemical and physiological processes including acid-base regulation, bone resorption, calcification, ureagenesis, gluconeogenesis, and tumorigenicity (Yu, Hou, Tian et al., 2018; De Luca, Mancuso, Ferro, Buemi et al., 2018; Zołnowska, Sławinski, Szafranski, Angeli et al., 2018).

2-Thioxo-1,3-thiazolidin-4-one core, which has been commonly named rhodanine, constitutes a privileged scaffold having several biological activities including selective inhibition on various enzymes such as *β*-lactamase, HCV NS3 protease, aldose reductase, histidine decarboxylase, *N*-acetyltransferase, and histone acetyltransferase (Chauhan, Sharma, Saxena, Singh et al., 2013). Moreover, the rhodanine unit constitutes a central part of various heterocyclic moieties with a wide range of pharmacological activities such as antimalarial, antimicrobial, antiviral, anti-diabetic, and anticonvulsant effects (Song, Zheng, Deng, Wang et al., 2012; Sortino, Delgado, Juarez, Quiroga et al., 2007) (Fig. 6). Other applications of 5-acylidene- and 5-arylimino rhodanines are on dye sensitizers and optical materials. Additional applications of rhodanine-based compounds are in analytical chemistry including determinations of heavy metals in the amperiometric method. Synthetic methodologies which generate highly diverse molecules promptly are needed to design and development new and efficient structures in drug discovery studies.

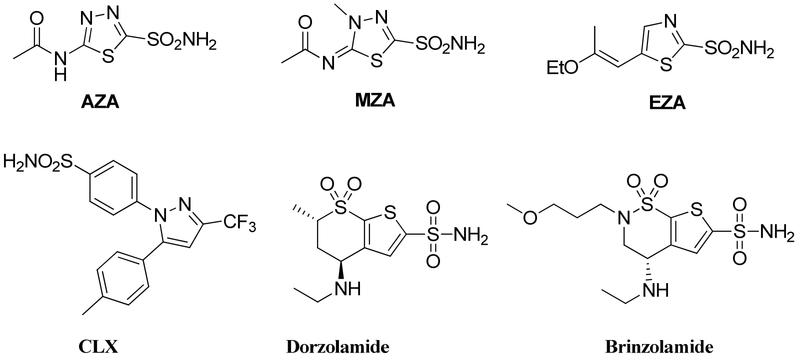
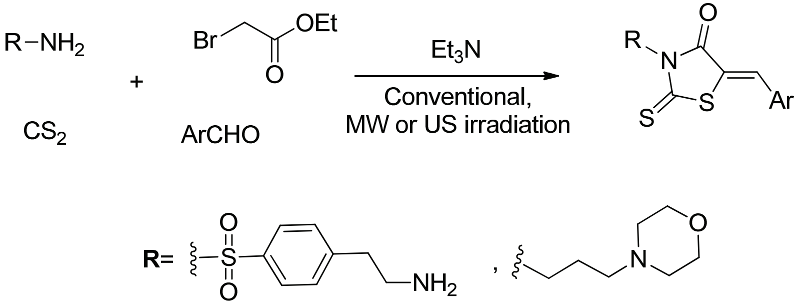


Figure 6. Molecular structure of sulfonamide-based drugs.



Ar: 2OH-C_6H_4, 4MeO-C_6H_4, 4CF_3-C_6H_4, 4F-C_6H_4, 3F-C_6H_4, 2F-C_6H_4, 2N-C_6H_3, 3N-C_6H_3, 4N-C_6H_3, 2,6-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 2,6-$ClFC_6H_3$, 4NO_2-C_6H_4, 3OH, 4MeO-C_6H_3, 3Br,4Cl-$Cl_2C_6H_3$, C_6H_5

Scheme 26. Synthetic pathway for the preparation of target compounds.

In the light of this information, Mermer and coworkers have designed the one-pot four component synthesis of new sulfonamide- and morpholine-based 5-arylidenerhodanines as effective CA (II) inhibitors. To compare the reactions in terms of reaction time and yield, the reaction has been carried out in conventional, MW, and US irradiated conditions (Scheme 26). The results obtained have shown that the advantages of MW and US-supported methods were very close to each other but provided a great advantage when compared with the traditional method. Thus, the combination of the one-pot four-component reaction of cheap and commercially available compounds with US and MW irradiation techniques has made this new strategy highly green and effective in diversity-oriented strategies. The newly synthesized compounds were also subjected to screens for their CA II inhibition capacity. IC50 values of some of the examined molecules were determined and it was found that they were nanomolar level except one, and lower than that of the reference molecule. Silico studies showed that all of the rhodanine derivatives have a higher affinity than reference ligand against the binding site, while none of the compounds have demonstrated any interaction with Zn^{2+} as with the classical sulfonamides (Mermer, Demirbas, Colak, Ayazoglu-Demir et al., 2018; Mermer, Demirbas, Cakmak, Colak et al., 2019).

1.7. One-pot Multicomponent Reactions

Numerous cascading chemical reactions are involved in the hemostasis process, which causes the stopping of bleeding. These kinds of biological processes constitute examples of self-sorting methods in systems biology. On the other hand, system chemistry studies offer the primary comprehension of the self-sorting principles of molecular networks that help us to access new systems with various properties and functions, unlike any traditional substance (Sahoo, Bose and Mal, 2015). For today, with the discovery of high-speed parallel synthesis, the multi-component reaction (MRC) has been widely used for the generation of arrays possessing high molecular diversity, rapidly. When coupled with another modification, the power of these transformations is increased even further, causing plenty of complex processes, especially the production of pharmacologically appropriate compound classes for screening purposes (Schwerkoske, Masquelin, Perun and Hulme, 2005).

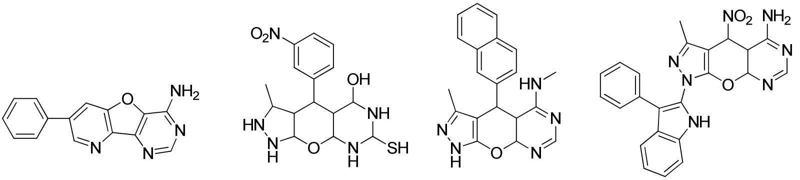
Substantial efforts have been dedicated to the discovery of new strategies yielding structurally complex and diverse molecules in the field of synthetic organic chemistry. Multicomponent reactions (MCRs) providing important advantages over conventional linear type methods enable a molecule to be produced from three or more components in a one-pot procedure. Due to this ability to generate several libraries of molecules with various biological activities, the MCRs have become an important strategy in medicinal, combinatorial, and organic chemistry. Multicomponent domino reactions can be more efficiently carried out when they have been implemented together with other green techniques such as ultrasonic irradiation. This green technique has been known to possess appealing impacts on both heterogeneous and homogeneous reactions including the formation of pure compounds with better yields and shorter reaction times in milder conditions (Chidurala, Jetti, Pagadala, Meshram et al., 2016; Ammar, Chtourou and Frikha, Trabelsi, 2015; Pagadala, Maddila and Jonnalagadda, 2014; Yadav, Lim, Kim and Jeong, 2021).

The development of new efficient and atom economic methodologies under solvent- and catalyst-free conditions based on ultrasound or microwave irradiated multicomponent reaction (MCR) strategy has taken its place in the center of green chemistry (Khan, Khan, Shareef and Danish, 2018). Given current research, MCRs, which can give one product from at least three components in a single operation, have been considered as an ideal tool in synthetic organic chemistry with high bond-forming efficiency, shortness, and structural diversity (Khan, Khan, Iqbal, and

Yousuf, 2016; Khan, Khan and Sahoo, 2018; Khan, Yousuf and Khan, 2015; Hadjebi, Hashtroudi, Bijanzadeh and Balalaie, 2011; Moslemine, Anaraki-Ardakani, 2009; Patravale, Gore, Patil, Kolekar et al., 2014; Hajighasemi, Abadi and Shams, 2020; Feng, Wang, Daya and Zhou, 2019; Khan and Iqbal, 2016). Compared with conventional methodologies, the structural diversity, the convergent and atom economic character, the easy applicability of a one-pot operation, which requires no isolation of intermediates, the accessibility to complex molecules with the formation of new C-C, C-heteroatom bonds, the minimized waste formation, and high selectivity are the main superiorities of one-pot multicomponent reactions (Zarnegar and Safari, 2016; Khan, Khan and Sahoo, 2018; Triggle, Langs and Janis, 1989; Aruoma, Smith, Cecchini, Evans et al., 1991; Chaudhary, 2020; Kotadia and Soni, 2014; Wei and Li, 2004). The multiple bond-forming efficiencies make a multicomponent reaction capable of generating new molecules with structural complexity and diversity starting from readily available materials (Zare and Barazandehdoust, 2019; Ramón and Yus, 2005; Marek, 2005; Ganem, 2009).

Given economic and environmental perspectives, MCRs have become efficient tools for the construction of industrial and medicinal libraries with high structural complexity. Combining multicomponent reactions with other environmental techniques such as solvent-free media, MW, or US support not only simplifies procedures but also displays more positive effects on the protection of the ecosystem than their individual application (Fu, Yang, Lai, Ma et al., 2015; Cerulli, Banfi, Basso, Rocca et al., 2012; Estevez, Villacampa and Menendez, 2010).

Certain heterocyclic compounds including pyrimidine, pyrazole, and pyrano units have been reported to possess diverse pharmacological and biological properties. The fused pyrano ring has been considered an important structural motif taking place in the structures of various bioactive compounds such as anticancer, antifungal, antibacterial, anti-HIV, anticoagulant, and anti-malarial agents. Pyrimidine derivatives represent another class of biologically important molecules possessing analgesic and anti-inflammatory activities. They act as potential kinase inhibitors, as well. Substituted pyrazolo pyranopyrimidines have become substantial structural motifs in organic synthesis due to their wide range of applications such as antibacterial, anti-inflammatory, anti-tubercular, kinase inhibitor, analgesic, and antipyretic activities (Figure 7).

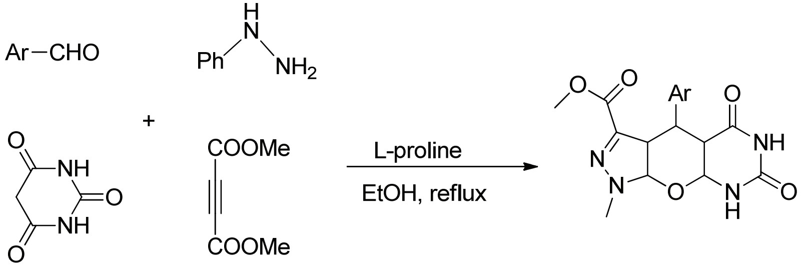


Kinase inhibitor **Anti-tuberculosis** **Anti-inflammatory** **Anti-bacerial**

Figure 7. Some biologically active pyrazolo pyranopyrimidines.

Several methods have been reported leading to the formation of pyrazolopyranopyrimidines. The most commonly employed way contains the condensation of ethyl acetoacetate with benzaldehyde, barbituric acid, and hydrazine hydrate in acidic media. Pyrazolopyranopyrimidine derivatives have also been synthesized utilizing titanium dioxide nanowires (TiO_2 NWs) and Nano-porous acid catalysts (SBAPr-SO_3H) under reflux conditions. Recently Meglumin catalyzed reactions yielding pyrazolopyranopyrimidines derivatives have been reported as well.

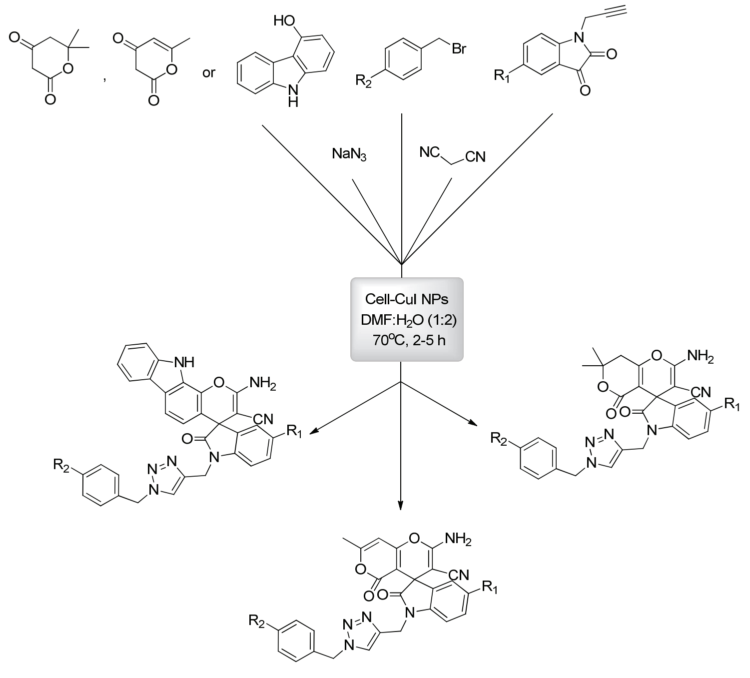
L-Proline acts as the catalyst with high stereoselectivity in many reactions including Michael, Mannich, and aldol condensations. It is also used as a chiral modifier in heterogeneous catalysis in hydrogenation reactions. L-proline has been successfully used in the synthesis of polysubstituted pyridines, thiopyrans, pyrans, quinolones, and pyranopyrazoles. Besides being highly soluble in water and many common organic solvents, L-proline has additional advantages of being inexpensive and commercially available.



Scheme 27. L-Proline catalyzed one-pot four component synthesis of pyrano[2,3-d]pyrimidine-3-carboxylates.

In this context, some pyrano[2,3-d]pyrimidine-3-carboxylates have been synthesized through a completely new protocol containing the one-pot four-component condensation of dimethyl but-2-ynedioate, phenylhydrazine, barbituric acid, and aromatic aldehyde in L-proline mediated ethanol solvent (Yadav, Lim, Kim and Jeong, 2021) (Scheme 27).

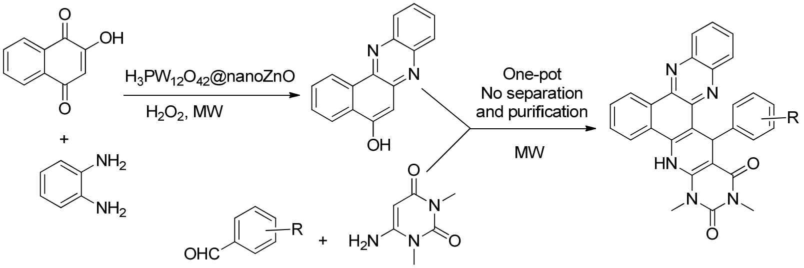
There are numerous MCRs named after people, such as the well-known Petasis, Ugi, Passerini, Biginelli, Groebke-Blackburn-Bienaymé (GBB), Hantzsch, and Huisgen reactions, most of which are three- or four-component transformations. MCRs with five or more components have been called high-order MCRs, which are more efficient than ordinary MCRs in the construction of complex structures. However, the numbers of high-order MCRs are limited, because the increased number of competitive reactions giving byproducts makes it harder to incorporate all the components in an orderly sequence to generate target products. In the 5CRs, if a component has two reaction centers, this reaction becomes a 6-center 5-component reaction (6C5CR). It should not be forgotten that MCRs have only a single operational step to place all the components in the reaction media. When components are introduced in a stepwise manner at different stages of the reaction, they are called one-pot reactions instead of MCRs (Ma, Zhi and Zhang, 2021).



Scheme 28. 6C5CR yielding spirochromenocarbazole-tethered 1,2,3-triazoles.

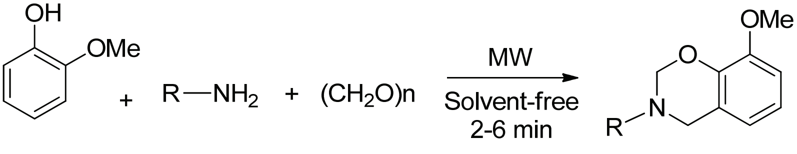
Desai and coworkers have reported a multicomponent reaction of *N*-propargyl isatins, benzyl halides, malononitrile, sodium azide, and 5,5-dimethyl-1,3-cyclohexanedione, 6-methyl-2*H*pyran-2,4(3*H*)-dione or 4-hydroxycarbazole for the synthesis of 1,2,3-triazoletethered spirochromenocarbazoles. Cellulose-supported CuI nanoparticles (Cell-CuI NPs) have been used as reusable catalysts in this condensation (Scheme 28). This is a 6-centered-5-component reaction (6C5CR) since *N*-propargyl isatins have 2-reaction centers. All the synthesized products have been screened against Mycobacterium tuberculosis, Mycobacterium bovis, as well as a panel of cancer cell lines. Some products exhibited antimycobacterial, antitubercular, antibacterial, and anti-proliferative activities (Chavan, Pandit, Desai, Wadgaonkar et al., 2017; Chavan, Desai, Wadgaonkar, Tapase et al., 2019).

Very recently, Dehghan and Mohebat have reported the synthesis of complex benzophenazine derivatives by a sequential single-pot four component reaction. This conversion has been performed through the condensation between 2-hydroxy-1,4-naphthoquinone, o-phenylenediamine, benzaldehydes, and 6-amino-1,3-dimethyluracil in the presence of $H_3PW_{12}O_{40}$@nano-ZnO as a highly efficient, eco-friendly, and recyclable heterogeneous catalyst under microwave irradiation (MWI) (300 W, 100°C) in H_2O (Dehghan and Mohebat, 2020) (Scheme 29).



Scheme 29. $H_3PW_{12}O_{40}$@nano-ZnO catalyzed sequential one-pot synthesis of 2,4-dimethyl-16-(4-aryl)-5,16-dihydrobenzo[a] pyrimido [50,40:5,6]pyrido[2,3-c]phenazine-1,3(2*H*,4*H*)-diones under MWI in water.

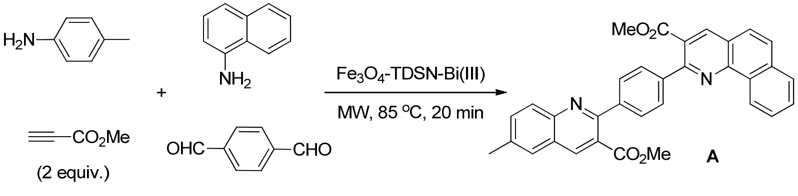
Another interesting example has been reported by Lomonaco's group including the one-pot synthesis of benzoxazines by means of an environment-friendly microwave-assisted strategy in solvent-free media. It is particularly striking that the duration of this reaction, which affords useful intermediates for the preparation of resins used in synthetic materials and polymers with good yields, is very short (2-6 mins) (Kotzebue, Ribeiro, Mota, Zampieri et al., 2017) (Scheme 30).



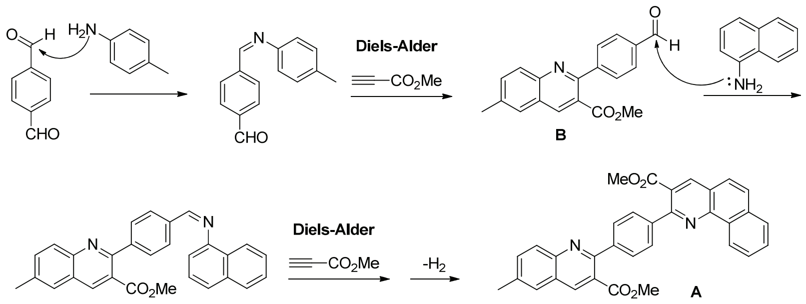
R= Ph, 2-MeC_6H_4, 4-MeC_6H_4, cyclohex, furan-2-ylmethyl, tetrahydrofuran-2-ylmethyl

Scheme 30. Microwave synthesis of benzoxazines under solvent-free conditions.

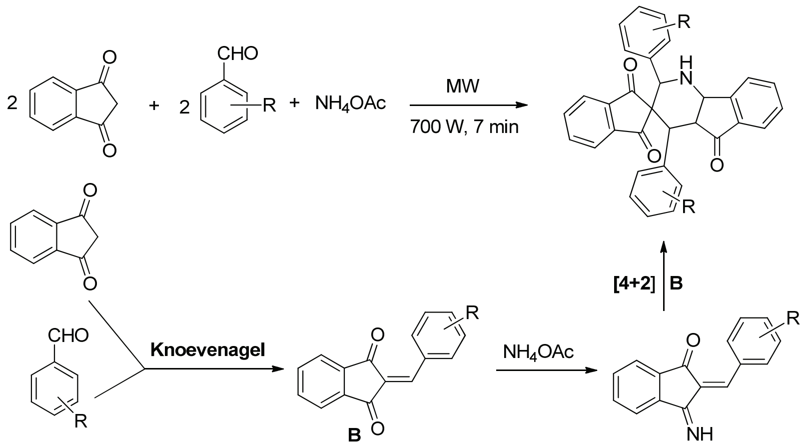
Another one-pot five component reaction performed under microwave heating and solvent-free conditions have been reported by Mohammadpoor-Baltork and coworkers. Two equivalents of methyl propiolate and one equivalent each of terephthaldialdehyde, naphthalen-1-amine, and p-toluidine have been used in this reaction yielding biquinoline **A** in the presence of a reusable Fe_3O_4-TDSN-Bi(III) catalyst (Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles). The synthesis may involve the condensation of terephthaldialdehyde and *p*-toluidine followed by Diels–Alder reaction and aromatization to form **B**. The reaction of **B** and naphthalen-1-amine followed by another Diels–Alder reaction affords biquinoline **A** after aromatization. It is a 6C5CR, since terephthaldialdehyde is a 2-centered reactant (Asadi, Landarani-Isfahani, Mohammadpoor-Baltork, Tangestaninejad et al., 2017) (Scheme 31, Scheme 32).



Scheme 31. 6C5CR yielding biquinoline.



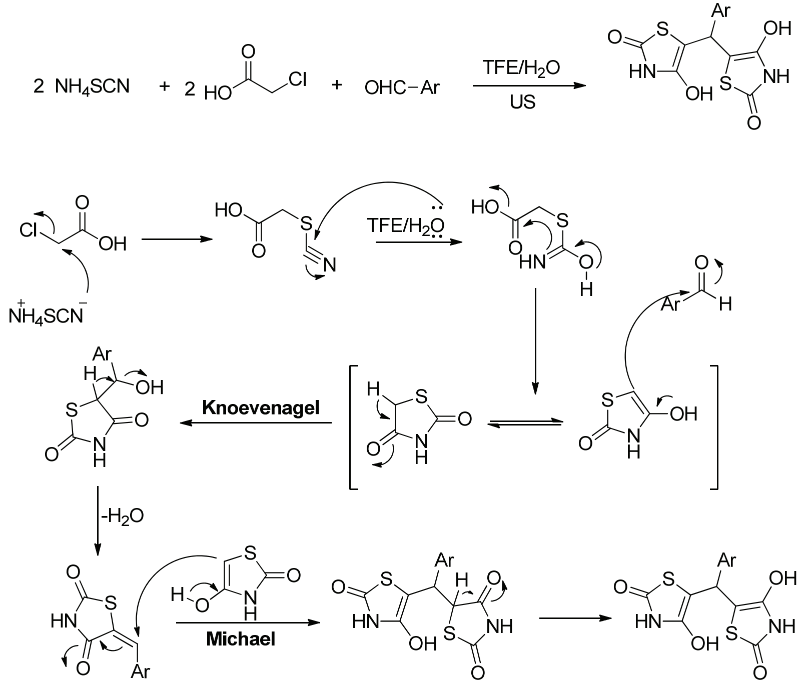
Scheme 32. Mechanism for the formation of biquinoline **A**.



R = H, 2-Cl, 4-Cl, 3-Br, 4-Br, 4-F, 2,4-Cl_2, 3-NO_2, 4-NO_2, 2-Me, 3-Me, 4-Me

Scheme 33. Synthetic pathway for the synthesis of spiroindenotetrahydropyridine derivatives (**A**).

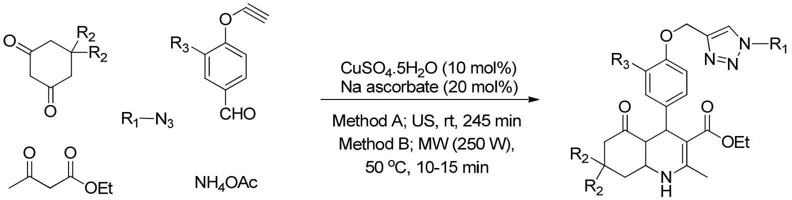
An example of US irradiated room temperature condensation has been developed by Heravi and coworkers. This reaction yielding 5,50-(arylmethylene)-bis(4-hydroxythiazole-2(3*H*)-one) derivatives contains the five-component interaction of one equivalent of aryl aldehydes and two equivalents each of monochloroacetic acid and ammonium thiocyanate in TFE/water (1:1) (Scheme 34). In this reaction, the condensation between monochloroacetic acid and ammonium thiocyanate followed by hydrolysis and cyclization has produced thiazolone. Knoevenagel condensation of thiazolone with aromatic aldehydes followed by Michael addition and tautomerization then has generated the final products (Heravi and Naghilou, 2017).



Ar = Ph, 4-MePh, 4-NO_2Ph, 3-NO_2Ph, 2-ClPh, 3-ClPh, 4-ClPh, 2,4-diClPh, 4-BrPh, 4-OHPh

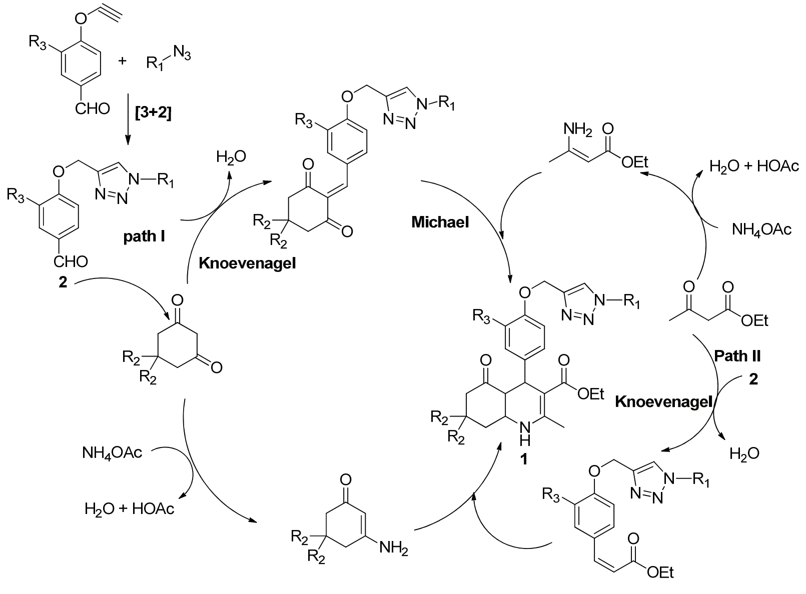
Scheme 34. 5CR affording thiazole derivatives.

Khurana et al. have described the synthesis of 1,2,3-triazole-linked 1,4-dihydropyridines **1** under microwave or ultrasonic irradiation in PEG-400 (Scheme 35, Scheme 36). The obtained compounds have been evaluated for their antifungal, antibacterial, and antioxidant activities, and for photophysical properties. In the reaction mechanism proposed by these authors, the first step is a 1,3-dipolar cycloaddition between aryl azides and propargylated benzaldehydes to form 1,2,3-triazoles **2**. The next step (path I) is the Knoevenagel reaction of 1,2,3-triazoles **2** with 1,3-cyclohexanediones, followed by the Michael reaction of the enamine from ethyl acetoacetate and ammonium acetate to afford the products **1**. Another pathway (path II) is the Knoevenagel reaction of 1,2,3-triazoles **2** and ethyl acetoacetate, followed by Michael reaction of the enamine to afford products **1**. It is a 6C5CR, since propargylated benzaldehydes have 2-reaction centers (Singh, Sindhu, Khurana, Sharma et al., 2013).



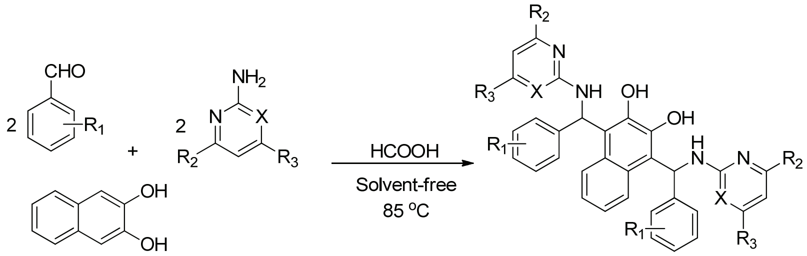
R$_1$= Ph, 4-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-FC$_6$H$_4$, 4-F-3-ClC$_6$H$_3$,1-Naphthyl, 3-ClC$_6$H$_4$, **R**$_2$ = H, Me, **R**$_3$ =H, OMe

Scheme 35. One-pot five-component synthesis of 1,2,3 triazole-linked pentasubstituted 1,4-dihydropyridines (PEG: polyethylene glycol, US: ultrasonication, MWI: microwave irradiation).



Scheme 36. 6C5CR for triazole-linked pentasubstituted 1,4-dihydropyridines.

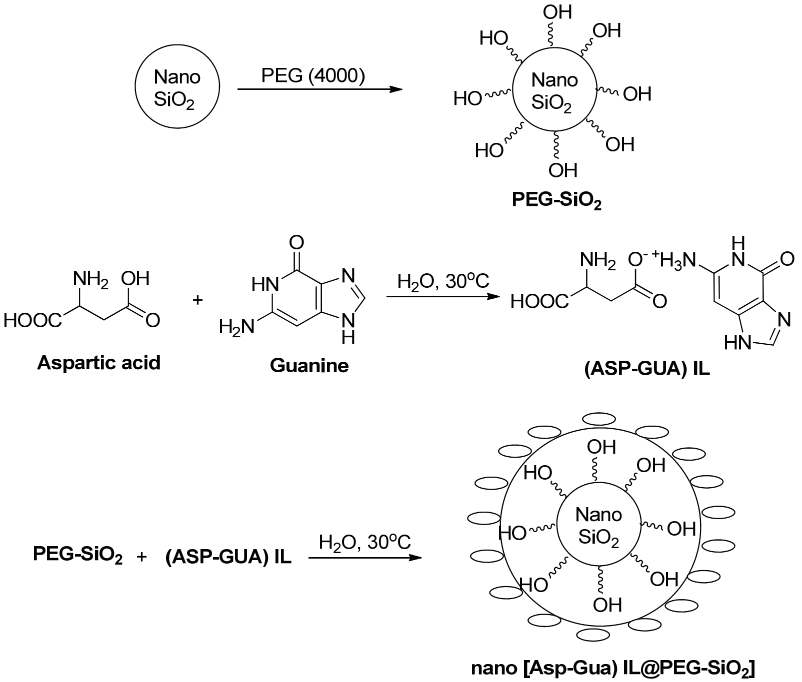
Olyaei and coworkers have described a solvent-free 6C5CR leading to the formation of bisBetti bases (bis(1-aminomethyl-2-hydroxy)naphthalenes) between the interaction of two equivalents each of aryl aldehydes and heteroaryl amines and one equivalent of 2,3-dihydroxynaphthalene under the catalytic activity of formic acid at 80ºC (Olyaei, Abforushha, and Khoeiniha, 2017) (Scheme 37).



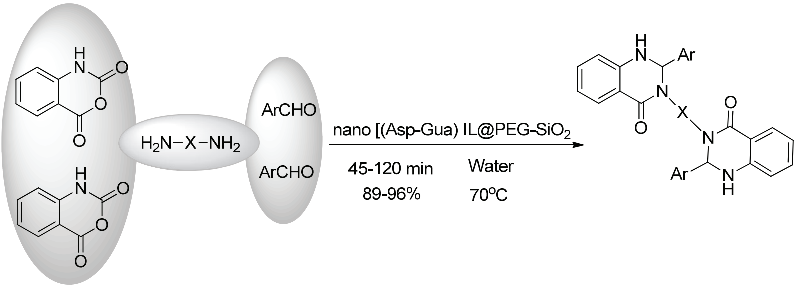
R$_1$ = H, 2-Cl, 3-Cl, 3-Br, 4-Me; **R**$_2$ = H, Cl, Me; **R**$_3$ = H, Me; X = N, C-NO_2

Scheme 37. 6C5CR for bis(1-aminomethyl-2-hydroxy)naphthalenes.

The study carried out by Nikoofar and Shahriyari can be given as an example of the ionic liquid mediated multicomponent reactions. The authors have placed aspartic acid-guanine ionic liquid on the hydroxylated nano-silica face to obtain a novel bio-based core-shell organic-inorganic nanocatalyst (Asp-Gua) IL@PEG-SiO_2 (Scheme 38). The catalytic performance of the newly synthesized catalyst has been proven for the synthesis of two classes of interesting heterocycles that are bis(2,3-dihydroquinazolin-4(1*H*)-one) derivatives (Scheme 39) and tricarboxamides (Scheme 40) via a pseudo five-component reaction under solvent-free conditions (Nikoofar and Shahriyari, 2020).

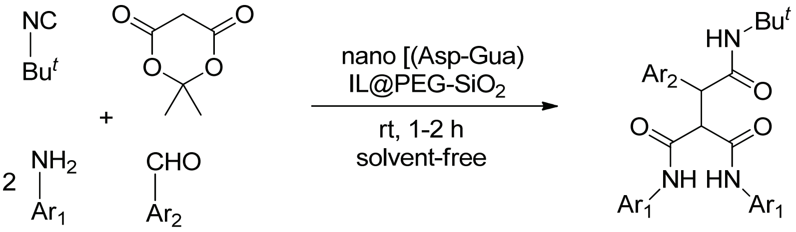


Scheme 38. Schematic synthetic route of nano [(Asp-Gua) IL@PEG-SiO$_2$.



X= -C_6H_4-, -$(CH_2)_6$-, -$(CH_2)_2$-, -$(CH_2)_0$-;
Ar= C_6H_5, $CH_2C_6H_5$, 4-ClC_6H_4, 2-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-MeC_6H_4, 4-HOC_6H_4, 2-HOC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, naphtalen-2-yl, benzyl, indol-3-yl

Scheme 39. Synthesis of 3,30-(1,4-phenylene)bis(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one) derivatives.

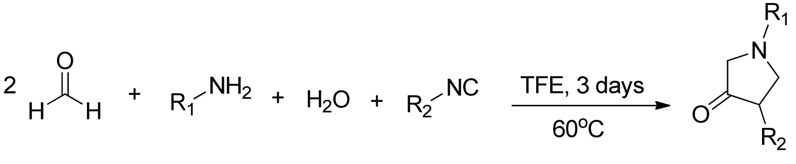


Ar₁ = 4-BrPh, 4-MePh, 3-HOPh, 2-NO$_2$Ph, **Ar₂** = 2-ClPh, 2-OH-3-MePh, 4-OMePh

Scheme 40. Synthesis of tricarboxamides.

Some advantages of the strategies depicted in Scheme 39 and Scheme 40 have been reported as high yields, simple work-up procedure, access to the desired products without any by-product formation, performing the condensation under green conditions besides the possibility to prepare a wide range of pharmaceutically active heterocycles, and recovery and reusability of the catalyst without loss of activity. This reaction has been examined in the presence of different solvents, water, and solvent-free media. The results obtained have demonstrated that the best solvent is water as a green and economic media. After completion of the condensation, the nanocatalyst has been separated by adding methanol to the reaction mixture and further filtration followed by air-drying. The recovered nanostructure, (Asp-Gua) IL@PEG-SiO$_2$, has been used for two more cycles without important activity loss.

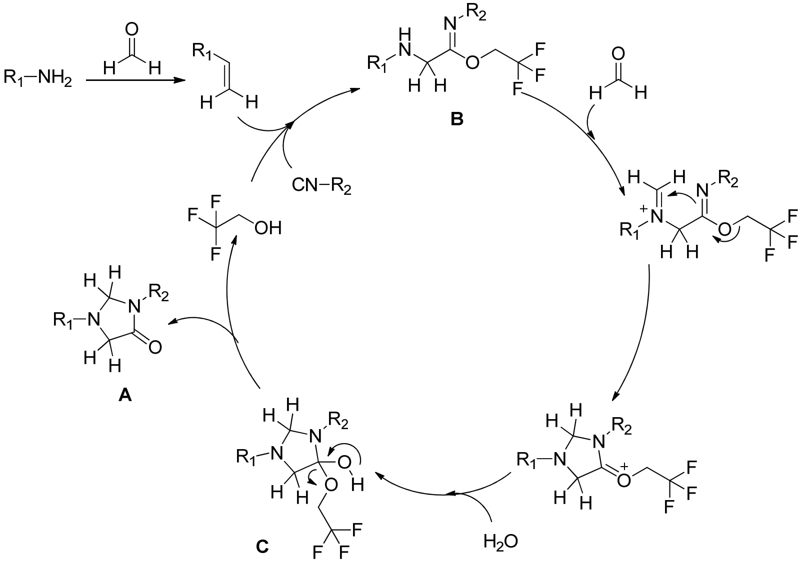
A study, where water is a reagent and also solvent, has been reported by Ramírez et al. This five-component reaction contains the condensation of two equivalents of formaldehyde and one equivalent each of primary amine, water, and isocyanide to afford *N,N*'-disubstituted-4-imidazolidinones **A**. Imines generated in situ from formaldehyde and amines react with isocyanides and TFE to give amines **B** which then react with second formaldehyde followed by an intramolecular nucleophilic attack and addition of water to form hemiorthoamides **C**. Releasing TFE from **C** gives 4-imidazolidinone **A** (Attorresi, Bonifazi, Ramirez and Gola, 2018) (Scheme 41, Scheme 42).



A

R$_1$= 4-MeC$_6$H$_4$; 2-CF$_3$C$_6$H$_4$; 3,5-F$_2$C$_6$H$_4$; 4-ClC$_6$H$_4$; 4-FC$_6$H$_4$; dodecyl, prop-2-yn-1-yl, 4-acetoxyphenyl;
R$_2$ = *n*-Bu, *i*-Bu, *t*-Bu, 4-FC$_6$H$_4$; 4-ClC$_6$H$_4$; 4-MeOC$_6$H$_4$; dodecyl, Bn, phenethyl, prop-2-yn-1-yl

Scheme 41. Synthesis of *N,N*'-disubstituted-4-imidazolidinones.



Scheme 42. Reaction mechanism for pseudo-5CR of *N,N*'-disubstituted-4-imidazolidinones.

1.8. Mechanochemical Reactions

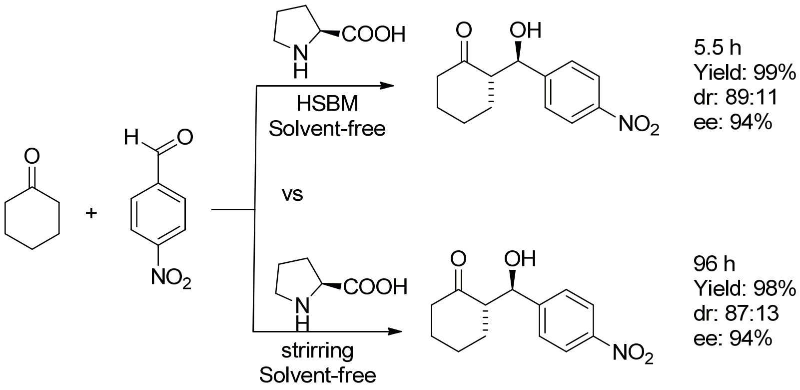
As known, with the outbreak of the energy crisis and the development of green chemistry methodologies, scientists have directed their attention to minimizing the use of hazardous reagents in industry. They have also put great efforts into eliminating waste and recycling as much as possible and so obtaining products in a greener and environmentally benign manner.

Mechanochemistry is described as the use of mechanical energy to perform chemical reactions. Mechanochemical reactions have been reported to supply phases, compounds, and microstructures, which are different from the products of ordinary reactions. In this way, the reactions that cannot take place in thermal conditions become possible, similar to the reactions induced by the energy of photons under photochemical conditions. The characteristics of mechanochemistry involving the improvement of catalyst utilization, reducing toxic solvents, and energy consumption have placed this technique in the center of green chemistry.

Since Toda and coworkers have exhibited for the first time that many reactions in any solvent can also be carried out in solid-state, solvent-free techniques have evolved rapidly, particularly in the unsymmetric organic synthesis field (Wu, Wang, Li, Feng et al., 2021).

Solid-state chemistry containing mechanochemical reactions has become a rapidly growing area. Several technological applications have emerged where mechanochemical forces have been successfully used in achieving chemical reactions. Such reactions taking place between two macroscopic solid particles are believed to proceed via liquefaction by forming a eutectic mixture (Varma, 2007).

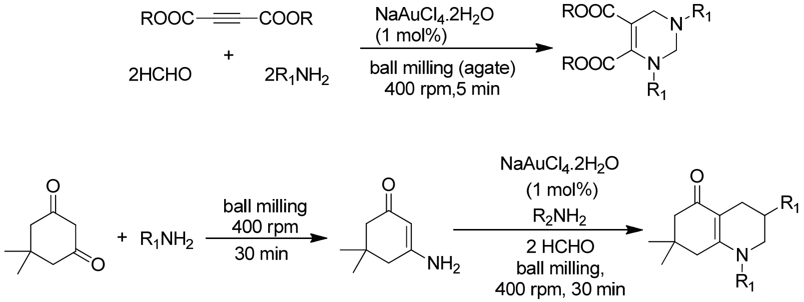
The simplest equipment used to achieve a mechanochemical reaction is a mortar with its pestle, dating back to the Stone Age. Today, there are different grinding equipments automated for their appropriate and trustworthy use in laboratory (small scale) or industrial (large scale) processes. The most widely used are high speed ball mills (HSBMs), planetary mills and screw mills. In the reaction mixture, the stress created by the friction and the knocking of balls in the mill reactor generates high-temperature microsites supporting the breaking of substrate bonds and the formation of a new bond to yield the target compound. In organic chemistry, the aldol reaction constitutes one of the most thoroughly organocatalytic reactions since it offers one of the most beneficial strategies leading to the formation of new C-C bonds. In a seminal work reported by Bolm et al. in 2006, chiral organocatalyzed asymmetric aldol reactions have been carried out in a ball mill with excellent results (Rodríguez and Bolm, 2006). These experiments, where the solvent has been eliminated and also the reaction times have considerably been shortened relative to those in solution, have clearly displayed the advantages of the employment of mechanochemistry in the enantioselective organocatalyzed aldol reactions (Avila-Ortiz and Juaristi, 2020) (Scheme 43).



Scheme 43. Asymmetric aldol reaction organocatalyzed by (S)-proline. Comparison between conventional stirring in solution and high-speed ball milling (HSBM) conditions. dr, diastereomeric ration; ee, enantiomeric excess.

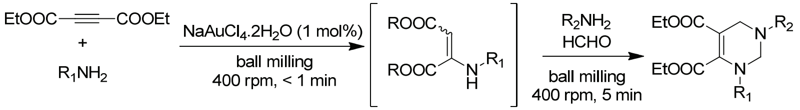
Within the purpose of sustainable improvement, the current fields of interest involve the synthesis of complex molecular scaffolds through a multicomponent reaction strategy including solvent-free- or water-mediated transformations with unconventional energy inputs.

Some advantages including operational simplicity, reduction of intermediate isolation as well as purification steps, the synthesis of complex molecules from readily available starting materials, and minimization of cost/time/waste constitute the superiorities of one-pot multicomponent reactions over multistep synthesis. In this context, a solvent-free one-pot five-component procedure has been defined by Praven et al. under mechanochemical conditions in the presence of a gold catalyst (Vadivelu, Raheem, Sugirdha, Bhaskar et al., 2018) (Scheme 44, Scheme 45, Scheme 46).



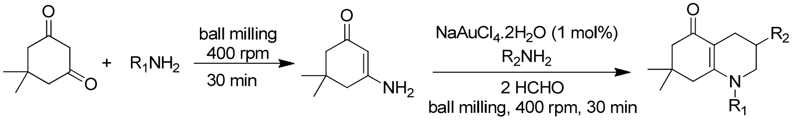
$\mathbf{R}$ = Et or Me; $\mathbf{R_1}$ = Ph, Bn, *t*-Bu, 2-ClPh, 4-BrPh

Scheme 44. Synthesis of 1,3-symmetrically substituted tetrahydropyrimidines.



$\mathbf{R_1}$ = Ph, Bn, 2-ClPh, $\mathbf{R_2}$ = Ph, Bn, *t*-Bu, 2-ClPh

Scheme 45. Synthesis of 1,3-symmetrically substituted tetrahydropyrimidines.

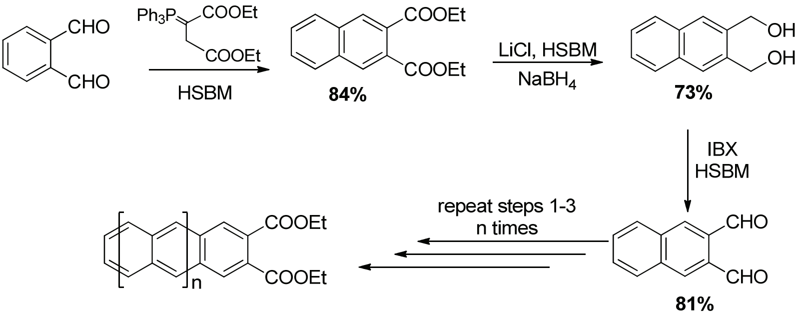


$\mathbf{R_1}$= Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$;
$\mathbf{R_2}$ = Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_4$, 2-MeOC$_6$H$_4$, Bn, 4-BrC$_6$H$_4$

Scheme 46. Synthesis of 5-oxo-octahydroquinazoline derivatives.

The low quantity of the catalyst loading, excellent product yields, a short reaction time, and solvent-free media has been reported as the beneficial features of this strategy. This method has also provided a safe and clean procedure and has the potential to be used to generate a wide range of structurally attractive complex molecules (Vadivelu, Raheem, Sugirdha, Bhaskar et al., 2018).

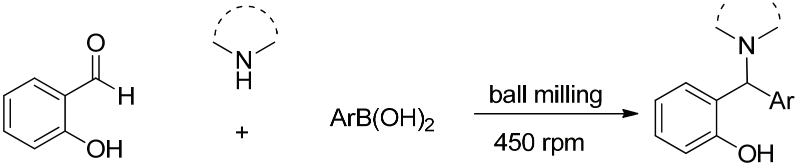
In an especially useful implementation of mechanochemistry, Mack and coworkers have developed a methodology yielding polyaromatic compounds. These compounds are important in synthetic organic chemistry because of their different applications in nanotechnology. However, the synthesis of them constitutes an ecological and technical challenge, because polyaromatic compounds are generally insoluble in most of the solvents. Mechanochemistry supplies the advantage that reagents can be treated under solvent-free conditions. Several steps of the synthetic procedure developed by Mack and coworkers have been performed in a ball mill (HSBM) under solvent-free conditions, making this methodology an environmentally benign alternative way (Wang, Hill, Theard and Mack, 2019) (Scheme 47).



Scheme 47. Synthesis of polyaromatic compounds under solvent-free HSBM.

High-Speed Ball Milling (HSBM) which is a process that works on the same principle as a mortar and pestle has been effectively utilized for the enhancement of environmentally benign reactions (Dove, 2014; Vispute, Zhang, Sanna, Xiao et al., 2010). This technique is based on solvent-free reaction approaches, as well. In this context, secondary and tertiary aminophenol derivatives have been synthesized via Petasis boronic Mannich reaction under HSBM conditions and α-Al_2O_3 has been used as the grinding auxiliary, as well (Khan, Khan, Shareef and Danish, 2018).

In the study reported by Hosseinzadeh et al., secondary and tertiary alkyl, cyclic or aromatic amines and aryl boronic acids and salicylaldehyde have been used to obtain the target compounds (Hosseinzadeh, Lasemi, Oloub and Pooryousef, 2017) (Scheme 48).

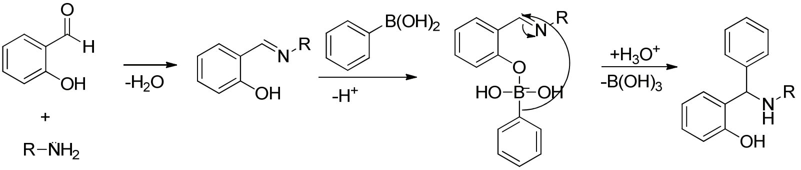


Amine: Morpholine, piperidine, piperazine, diphenylamine, methylbenzylamine, benzylamine, aniline, 4-CN-aniline, 4-NO_2-aniline, 4-OMe-aniline.

Ar: Ph, 3-MeC_6H_4, 4-*t*BuC_6H_4, 4-$OMeC_6H_4$, 6-OMe-2-naphtyl, 4-ClC_6H_4.

Scheme 48. Preparation of secondary and tertiary aminophenols under Ball-milling conditions.

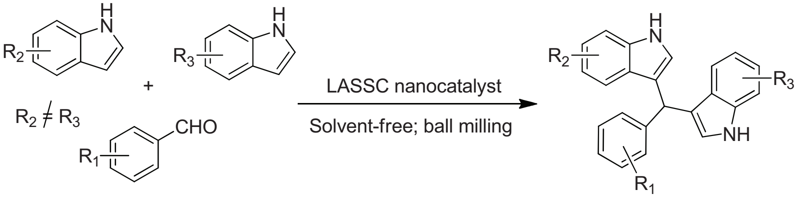
Looking into the proposed mechanism of the reaction, it is seen that salicylaldehyde reacts with a primary amine to form an imine in the first step, followed by a quaternary boronate salt form. After the formation of the quaternary boronate salt, the boron substituent is transferred to the imine moiety to yield the secondary amine (Hosseinzadeh, Lasemi, Oloub and Pooryousef, 2017) (Scheme 49).



Scheme 49. Mechanism of Petasis boronic Mannich reaction with primary amines.

Liquid-assisted grinding (LAG) has emerged as a continuation of the conventional solvent-free mechanochemical method, where a small quantity of a liquid is used as a support to control the selectivity or to increase the reaction rate. Although it has an important role in organic and inorganic chemistry, its mechanism of action is still more complicated or even unclear. In addition, its product yields have not been significantly improved. Current studies have displayed that the mechanism of LAG may be related to liquid polarity or molecular migration (Wu, Wang, Li, Feng et al., 2021).

Wu and coworkers have disclosed a three-component reaction using mechanochemical grinding. This reaction catalyzed by the Lewis acid-surfactant-SiO_2 combined catalyst (LASSC) is a Friedel-Crafts alkylation between indoles and aldehydes, where the unsymmetrical bis(indolyl)methane derivatives have been obtained in a short time with higher yields. The advantages of LASSC as a catalyst have been reported as the ready availability of its composition, nontoxicity, no solvent required, and reusability multiple times. This catalytic process has demonstrated a certain selectivity for the indole with different groups. Additionally, as shown by the excellent yields from the gram-scale synthesis, this protocol has provided a potential strategy to scale up the synthesis of unsymmetrical bis(indolyl)methanes with some advantages such as mild reaction conditions, operational simplicity, and recycling. Thus, the synthesis of unsymmetrical bis(indolyl) methane derivatives has been achieved for the first time through a micro-nano chiral environment constructed by achiral catalysts using a mechanochemical strategy (Wu, Wang, Li, Feng et al., 2021) (Scheme 50).



R$_1$= 4-Cl, 3-NO$_2$, 2-NO$_2$, 4-Me, 4-MeO-3-MeO, 4-MeO, 4-CN, 4-OH, furan-2-yl, n-butyl, 3-phenylpropyl, pyridine-2-yl; **R$_2$**= 6-H, 6-CN, 6-NO$_2$, 6-OMe, 5-MeO, 6-NH$_2$, 6-F, 6-OH;
R$_3$ = 6-Br, 6-Cl, 7-Br or 1-Me.

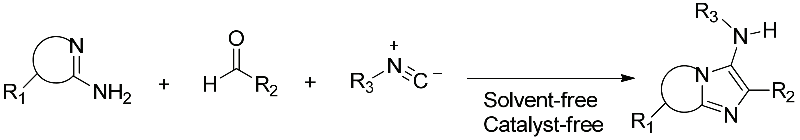
Scheme 50. LASSC-catalyzed synthesis of unsymmetrical bis(indolyl) methane derivatives.

1.9. Photocatalytic Reactions

In recent years, the use of light as an energy source for chemical activation has become a rapidly growing area being supported by the presence of efficient light sources with precise wavelengths which are cheap and quite powerful, such as light-emitting diodes (LED). In this context, visible light irradiation has become a trustworthy approach in the meaning of green chemistry because of its abundant energy reserves, low cost, and renewable source of energy for the benign methodologies giving organic compounds.

Photocatalysis using visible light has various applications in the synthesis of organic compounds through cycloaddition reactions, florinations, cross coupling reactions, etc. Comparison of these methodologies with conventional ones has showed that photocatalysis often allows reactions to take place under milder reaction conditions, like at ambient temperatures. In photocatalysis, generally catalytic amounts of metallic complexes that are toxic and expensive or organic pigments that may not be recyclable should be used.

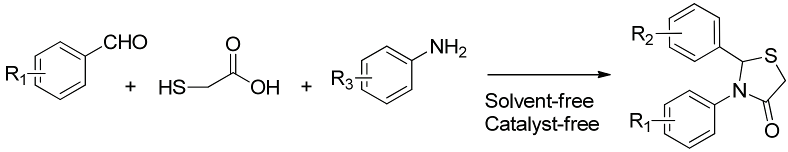
Consequently, synthetic organic chemistry researchers have been studying the development of eco-friendly processes that may be performed via photo-organocatalytic processes. Therefore, photocatalysis has become a topic of current interest generating many publications. However, very few studies on the usage of this strategy under solvent-free conditions have been reported. In 2018, Siddiqui et al. developed a photocatalyzed method for the synthesis of imidazole pyridines and imidazole thiazoles with excellent yields. In this reaction, only visible light was used as an activator under solvent-free media and without any catalyst (Shivhare, Jaiswal, Srivastava, Tiwari et al., 2018) (Scheme 51).



R$_1$= H, 3-$NO_2C_6H_4$, 3-MeC_6H_4; **R**$_2$= Ph, benzyl, 2-$CH_3C_6H_4$, 4-$Me_2NC_6H_4$, 4-CNC_6H_4, 4-$NO_2C_6H_4$,
4-*i*-proC_6H_4, pyridine-4-yl, furan-2-yl; **R**$_3$= cyclohex, 2-OH-5-BrC_6H_3, cyclohexylamino, *t*-butylamino.

Scheme 51. Photocatalytic synthesis of imidazolopyridines and imidazolothiazoles under solvent-free conditions. The yellow bulb-shaped sign indicates irradiation with visible light.

Imidazol-pyridines and imidazole-thiazoles have been attracting attention as intermediates in drug synthesis. The method reported by these authors is a simple and green alternative as it does not require any catalyst or solvent. In 2020, Siddiqui's group described the photocatalytic synthesis of 1,3-thiazolidin-4-ones without any solvent. This multi-component reaction proceeded under photochemical activation in metal catalyst-free media. This procedure has resulted in excellent yields for a variety of substrates. As compared with those previously reported, this strategy has superior properties because it does not require the use of any solvent, high temperatures, or toxic and expensive metal catalysts. In conclusion, the search for methodologies matching with the "Green Chemistry Principles" has stimulated scientists to develop effective alternatives to carry out the chemical activation of various synthetic procedures. Microwave activation, solvent-free mechanochemistry, the combination of enzymatic catalysis with mechanochemical activation, and solvent-free mechanochemistry have been regarded as among the most beneficial alternatives. The reactions performed by using these methodologies usually result in good yields, require mild reaction conditions, and allow scale-up processes. In traditional methods, the isolation of products and the subsequent purification procedures often involve column chromatography or at least filtration followed by recrystallization, which requires the use of solvents. Nevertheless, when carried out in solvent-free media, non-traditional strategies such as microwave activation, mechanochemistry, sonication, and photochemistry, certainly result in more efficient synthetic procedures and contribute remarkably to the overall atom economy, minimum waste formation, and sustainability of the process (Nazeef, Shivhare, Ali, Ansari et al., 2020) (Scheme 52).



R$_1$= C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2,4-$Me_2C_6H_4$,
R$_2$= C_6H_5, 4-FC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, pyridine-2-yl, pyridine-4-yl, thiophene-2-yl.

Scheme 52. Photocatalytic synthesis of 1,3-Thiazolidin-4-ones under solvent-free conditions.

Benzo[a]phenazine derivatives have been reported to act as dual inhibitors of topoisomerases I and II, while some act as anticancer and antitumor agents. pyridazinophenazinediones and pyridophenazinediones have been known to possess the antitumor activity as well. Additionally, phenazines having a fluorescent feature have been employed as photosensitizers in photodynamic therapy where the combination of light and photo-sensitize creates hydroxyl radicals or highly reactive oxygen species near the tumor for selective destruction of the targeted tissue. Moreover, 1,4-dihydropyridine (DHP) derivatives have been reported as a significant class of aza-heterocyclic molecules displaying several pharmacological, medical, and biological activities containing hepatoprotective, bronchodilator, antidiabetic, vasodilator, geroprotective, antitumor, anti-HIV, antiatherosclerotic and anticonvulsant features (Fig. 8) (Mohamadpour, 2021).

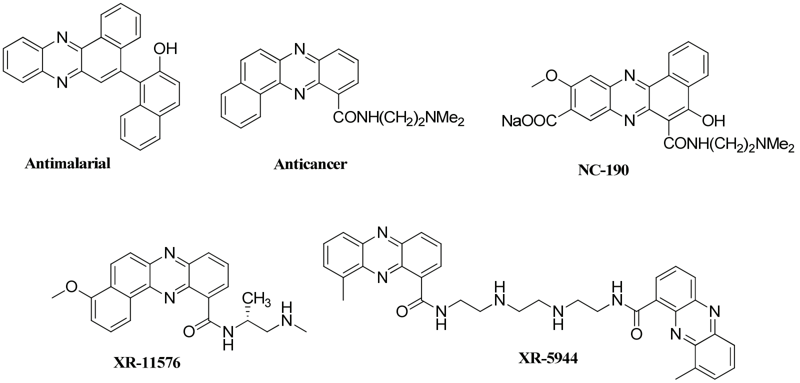
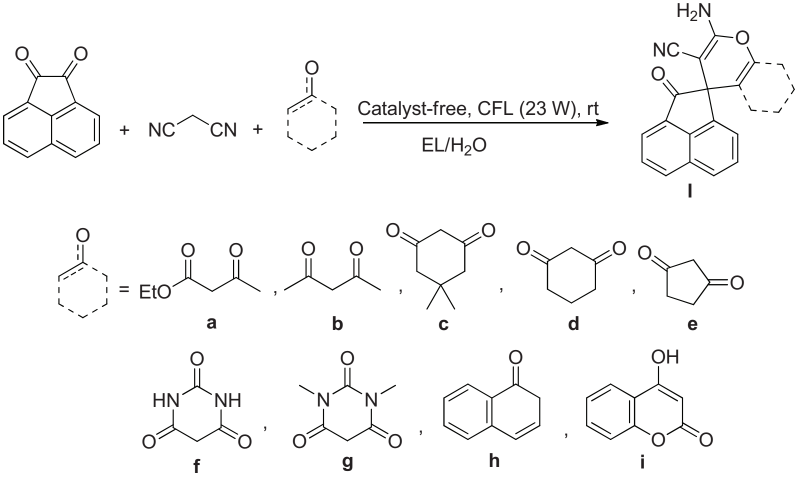
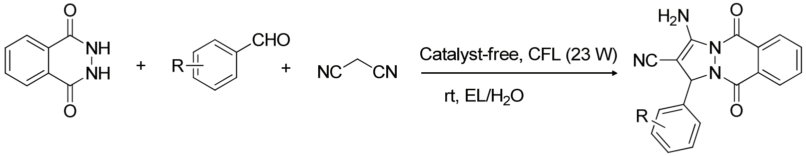


Figure 8. Biologically active phenazine derivatives.

Mohamadpour has used light-emitting diodes and compact fluorescent lights as the sources of visible light for the catalyst-free, one-pot three-component synthesis of spiroacenaphthylenes and 1*H*-pyrazolo[1,2-b]phthalazine-5,10-diones (Scheme 53, Scheme 54).

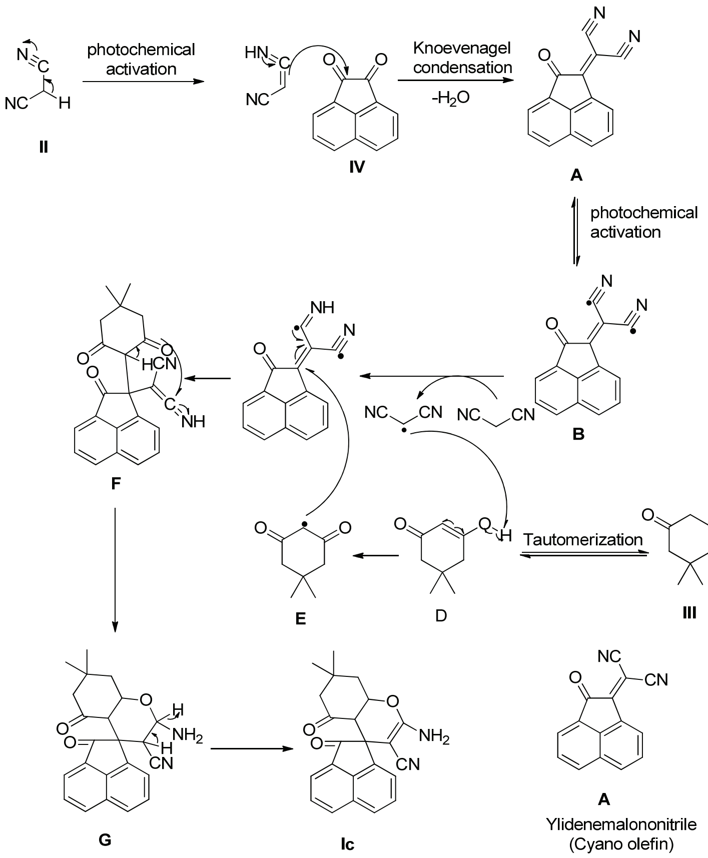


Scheme 53. Synthesis of spiroacenaphthylenes.



R= 2-OMe, 2-Cl, 3-Cl, 4-Cl, 3-Br, -H, 2-Me, 3-Me, 4-Me, 4-NO$_2$, 3-NO$_2$, 2-NO$_2$, 4-F, 2-F, 3,4,5-(OMe)$_3$, 3,4-(OMe)$_2$

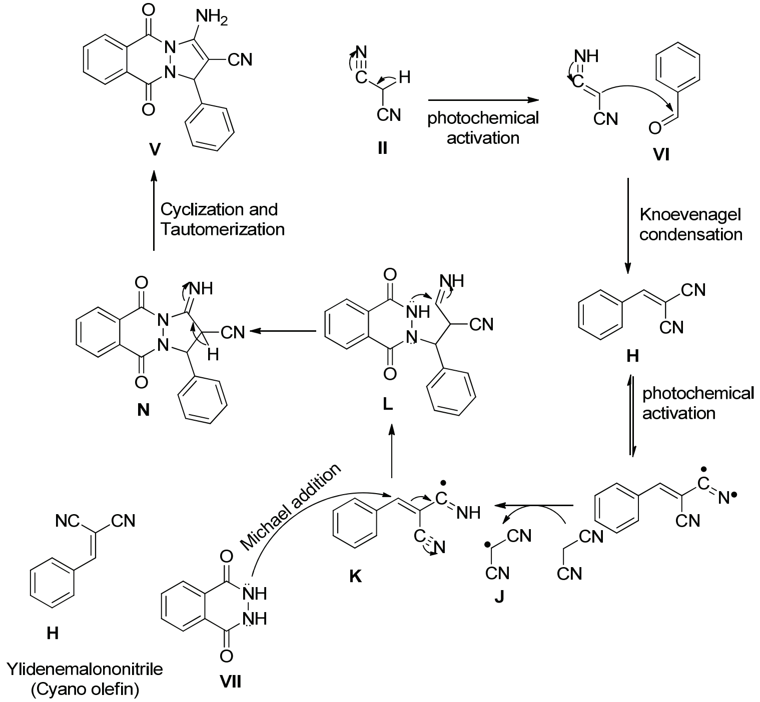
Scheme 54. Synthesis of 1*H*-pyrazolo-[1,2-*b*]phthalazine-5,10-diones.



Scheme 55. The mechanistic path recommended by the authors for synthesizing spiroacenanaphthylenes.

The proposed mechanism for the synthesis of **Ic** has been presented in Scheme 55. In the beginning, the active methylene compound **II** was formed by the tautomerization of malononitrile irradiated with visible light in EL/H_2O. Activated methylene **II** and acenaphthequinone **IV** have been subjected to a Knoevenagel condensation in solution to yield a cyanoolefin **A** by removing water. Then, a free radical **B** has been formed by light-activation of the cyanoolefin. The intermediate **B** has abstracted methylene hydrogen from malononitrile, and has given a malononitrile radical, which has accepted hydrogen from dimedone **III** to generate the intermediate **E**. Thus, the intermediate **B** has converted to intermediate **C**. Subsequently, the intermediate **E** has reacted with the intermediate **C** via a Michael addition to give the intermediate **F**, followed by an intra-molecular cycle to generate the desired product **Ic**.

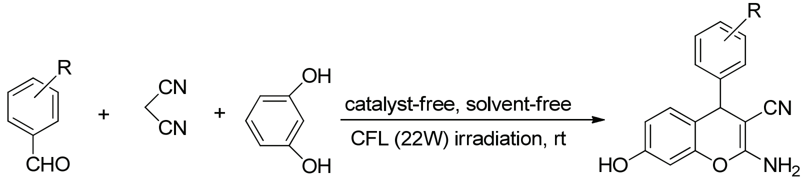
The proposed mechanism for the reaction giving compounds **V** has been submitted in Scheme 56. The intermediate ylidenemalononitrile (cyano olefin) **H** has been readily formed via Knoevenagel condensation between active methylene compound **II** and aryl aldehyde **VI** under the activation effect of the visible light irradiation in EL/H_2O solvent. Then, visible light could activate the mediator to form a free radical intermediate **J**. Intermediate **J** accepts hydrogen from methylene malononitrile **II**, and thus converts malononitrile to radical malononitrile. The Michael addition of phthalhydrazide **VII** to intermediate **K** produces iminomethylene derivative intermediate **L**. Finally, the synthesis of the targetted compounds **V** has been carried out by intramolecular cyclization and collaboration with tautomerization of Michael's additive **L** (Scheme 56).



Scheme 56. The mechanistic path recommended by the authors for synthesizing 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives.

As a result, Mohamadpour's study has submitted a visible light irradiated catalyst-free protocol for the synthesis of spiroacenaphthylenes and 1*H*-pyrazolo[1,2-b]phthalazine-5,10-diones, which constitute two classes of biologically important scaffolds. This reaction has been performed in aqueous ethyl lactate at room temperature as a low-cost and green methodology. An efficient feature of the reaction with excellent yields and metal-free character, is to use CFL irradiation as a green endorsing media sufficiently remarking the rising potential of CFL (compact floating lamp) irradiation in organic synthesis (Mohamadpour, 2021).

The synthesis of 4*H*-chromenes, a biologically significant scaffold, given in Scheme 57 is another example of the reactions employing light-emitting diodes and compact fluorescent lights (Mohamadpour, 2021).



R= H, 4-Me, 3-NO_2, 4-Br, 2-Cl, 3-MeO, 4-F, 4-OH, 4-Cl, 4-NO_2, 3-F, 4-OMe, 3-OH, 2-Me, 2-furanyl, 3,4-diMe, 4-diMeN, 2-thienyl, 2,4-diCl

Scheme 57. Catalyst- and solvent-free visible light irradiated synthesis of 4*H*-chromenes through a Knoevenagel–Michael cyclocondensation.

At first, this reaction was performed in different solvents such as a small amount of EtOH, $CHCl_3$, H_2O, DMF, MeOH, H_2O/EtOH (1:1), EtOAc, DMSO, THF, and DCM. However, extraordinary improvements have been obtained under solvent-free conditions.

The significant results of the study have been reported as the use of solvent- and catalyst-free non-hazardous reaction conditions, operational simplicity, and relatively cheap starting compounds. In addition, the separation of pure products, which obtained excellent yields, by an easy filtration process, has eliminated the need for column chromatography, which is a laborious and time-consuming operation. Another key feature of the existing study is to use CFL irradiation as a green and low-cost activator sufficiently remarking the rising potential of CFL irradiation in organic synthesis (Mohamadpour, 2021).

2

SOME NAMED ONE-POT MULTICOMPONENT REACTIONS AND THEIR DIVERSE APPLICATIONS UNDER GREEN CONDITIONS

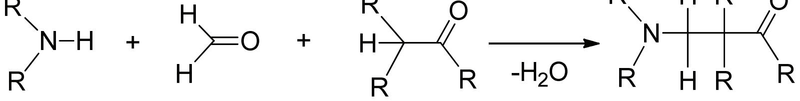
2.1. Mannich Reaction

2.1.1. Classical Mannich Reaction

The Mannich reaction, which is a three-component condensation reaction, has been regarded as one of the most important reactions leading to the formation of a new C-C bond. This reaction yielding aminomethylated products has been widely used as a key step for the synthesis of a wide number of natural products and pharmaceuticals (Chaudhary, Tupe and Deshpande, 2013; Nikalje, Ghodke, Khan and Sangshetti, 2015; Nimbalkar, Tupe, Seijas-Vazquez et al., 2016).

The Mannich reaction generally contains the one-pot condensation of an aldehyde (generally formaldehyde), a primary or secondary amine and an active hydrogen component (ketones, nitroalkanes, *β*-keto esters, *β*-cyanoacids, etc.).

The Mannich reaction involves condensation between the carbonyl compound that has an acidic proton next to the carbonyl group, formaldehyde and a primary or secondary amine or ammonia. The formed product, a *β*-amino-carbonyl compound, is also known as the Mannich base (Blicke, 2011).

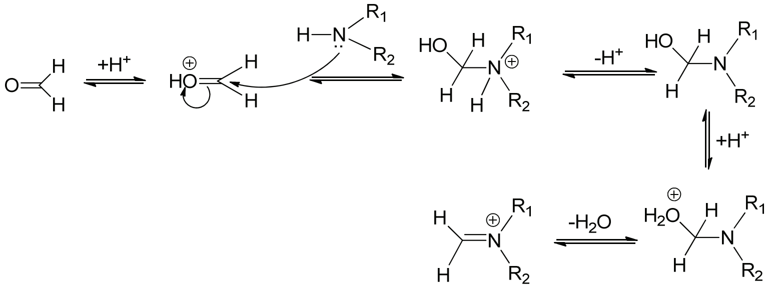


Scheme 58. Mannich reaction.

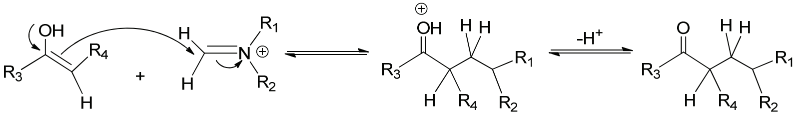
The Mannich reaction is a nucleophilic addition containing the nucleophilic attack of amine-nitrogen to the carbonyl group. The imine compound forms following dehydration. In the second step, the imine compound acts as an electrophile in the electrophilic addition reaction to a compound including an acidic proton.

In this condensation reaction, primary or secondary amines or ammonia have been used for the activation of formaldehyde. Tertiary amines cannot be used due to the lack of an NH proton that is necessary to form the intermediate enamine. Nitriles, carbonyl compounds, aliphatic nitro compounds, acetylenes, imines or α-alkyl-pyridines constitute the examples of α-CH-acidic compounds (nucleophiles). Electron-rich heterocycles such as thiophene, pyrrole, furan and activated phenyl groups can also been used. Indoles are particularly suitable for the reactions yielding gramine derivatives (Cromwell, Soriano and Doomes, 1980; Girreser, Heber and Schütt, 1998).

The Mannich reaction starts with the formation of an iminium ion from the reaction between the amine and formaldehyde. However, there is a problem in the mechanism shown below: The pka of protonated oxygen is approximately -2. This means that the reaction stops by the deprotonation of carbonyl group by the amine. Therefore, it is imperative to perform this reaction at a pH of approximately 4-5. The appropriate mechanism starts with a nucleophilic attack of amine-nitrogen to carbonyl carbon.



In this step, the compound having activated α-CH tautomerizes to enol form then it attacks to imminium ion (Blicke, 2011) (Scheme 59).



Scheme 59. Mechanism for Mannich reaction.

Although the Mannich reaction has been established as one of the protocols for the preparation of *β*-amino carbonyl compounds, some drawbacks such as long reaction times and harsh reaction conditions have limited their applicability. To avoid many of the drawbacks of the presence of Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_4$, etc.) in the stoichiometric ratio for conjugate addition reaction, several reactions employing the catalyst in minimum quantities in the reactions which use the readily available and economic substrates with minimum toxicity have been developed in the past few years. By following this purpose, several catalysts including $InCl_3$, palladium, $CeCl_3$/NaI, $CeCl_3$/NaI, $Bi(OTf)_3$, $Bi(NO_3)_3$, copper salts, and acidic clays have been employed successfully to catalyze aza-Michael addition (Yang, Ji, Gu, Shen et al., 2005).

The literature data on the Mannich reaction containing oxadiazole thiones has demonstrated that these compounds undergo both *N*-aminomethylation and *S*-aminomethylation depending on the reaction conditions (Nimbalkar, Tupe, Vazquez, Khan et al., 2016).

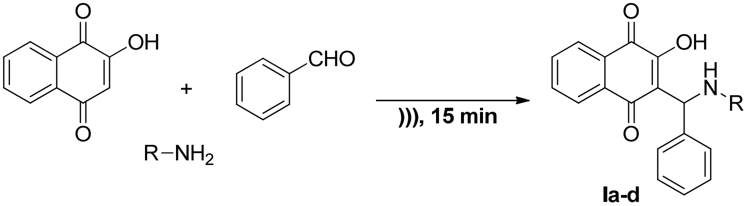
It has been reported that the reaction time of a classical Mannich reaction, which takes place in organic solvents, is between 3-10 hours. Recently some microwave supported Mannich reactions have been described as more efficient (Ram and Pandey, 1974; Mermer, Demirci, Ozdemir, Demirbas et al., 2017; Mentese, Demirci, Ozdemir, Demirbas et al., 2016; Ozdemir, Demirbas, Demirbas, Colak et al., 2018; Basoglu-Ozdemir, Demirbas, Demirbas, Ayaz et al., 2018).

N-Mannich bases obtained from amines, amides, imides, urea, and hydantoin derivatives have been used as potential prodrug candidates. It is reported that the group linked to the parent amine by the Mannich reaction increases the lipophilicity of the molecule at physiological p*H* values by decreasing their protonation, and this limitation of protonation causes an increase in absorption through bio-membranes (Ozturkcan, Turhan and Turgut, 2012).

Naphthoquinones which exist in different families of plants, some animals, and fungi have been accepted as important compounds having some biological activities such as antifungal, antimalarial, antiviral, trypanocidal, antibacterial, anticancer, insecticidal and leishmanicidal properties. 2-Hydroxy-1,4-naphthoquinone (lawsone), one of the important members of this class, also known as henna, has been used in cosmetics as a tattoo dye, body paint, and hair dye.

Acting as a UV filter in sunscreens is another interesting feature of henna, the leaves of which have been used as a prophylactic against skin diseases. Antifungal, antitumor and antibacterial activities of lawsone have also been reported. The first Mannich base derivative of lawsone was first reported in 1947 by Leffler and Hathaway. The antimalarial activity of this Mannich base has also been described.

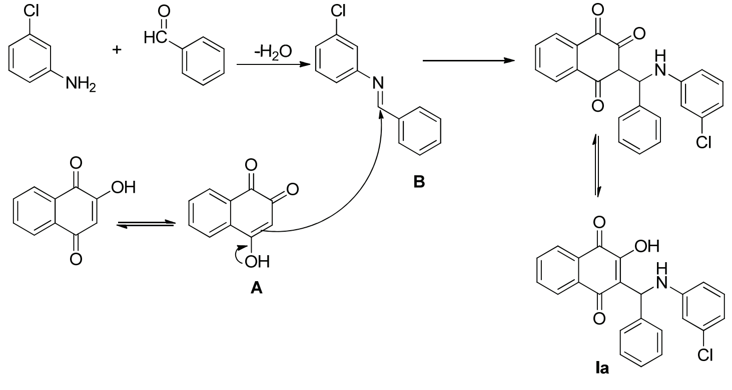
Lopez et al. have explained an ultrasound-mediated, three-component reaction between lawsone, benzaldehyde, and primary amines yielding the corresponding Mannich bases (Peng, Dou, Song and Jiang, 2005) (Scheme 60).



R: Ia= 3-ClC$_6$H$_4$, **Ib**= 4-NO$_2$C$_6$H$_4$, I**c**= 2,4-diClC$_6$H$_3$; I**d**= (CH$_2$)$_5$CH$_3$.

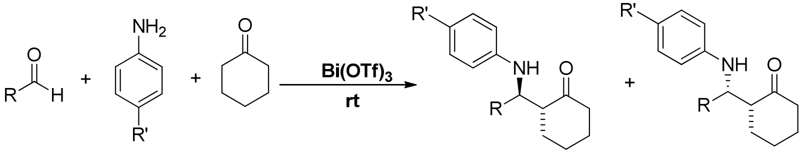
Scheme 60. Ultrasound irradiated one-pot tree component synthesis of Mannich base derives of Lawsone.

A reasonable mechanism for the formation of **Ia** has been presented in Scheme 61. The nucleophilic attack of 3-chloroaniline to the carbonyl carbon of benzaldehyde with the subsequent H$_2$O elimination afforded the imine intermediate **B**. Afterwards, the enol form of lawsone (**A**), which has been promoted by the excess of amine, attacks the imine **B** to afford the target product (**Ia**) (Lopez-Lopez, Nery-Flores, Sáenz-Galindo and de Loera, 2017).



Scheme 61. Plausible mechanism leading to the formation of **Ia**.

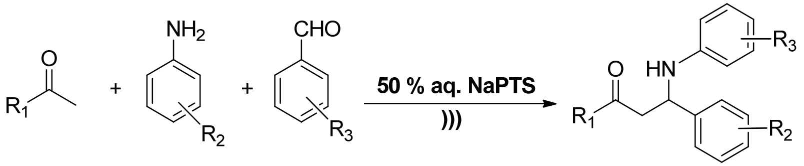
A literature survey has revealed that Lewis acid catalysts have been needed for activating some Mannich reactions, even when ultrasound-assisted. A Bismuth(III) triflate catalyzed Mannich reaction has been performed by Ozturkcan et al. in water at room temperature under ultrasound irradiated conditions (Ozturkcan, Turhan and Turgut, 2012) (Scheme 62).



R= 4-bromophenyl, 4-chlorophenyl, 4-nitrophenyl, 2-thienyl
R'= CH_3, CH_2CN.

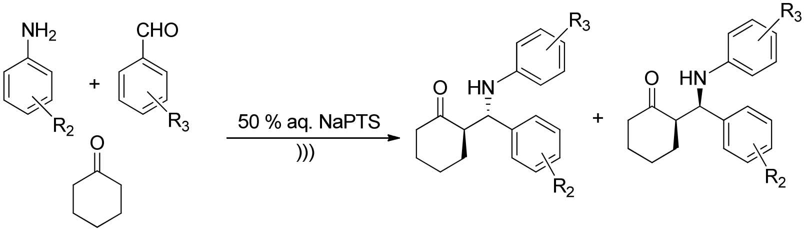
Scheme 62. $Bi(OTf)_3.4H_2O$ catalyzed Mannich reaction affording *β*-aminoketones.

The expression "hydrotropes" refers to various classes of water-soluble surface-active compounds which increase the solubility of organic substrates in the aqueous phase even at higher concentration. Hydrotropes generally consist of hydrophilic and hydrophobic parts. The hydrophobic part should be too small to induce micelle formation. Kamble et al. have reported the aqueous hydrotropic solution mediated synthesis of *β*-amino carbonyl compounds under ultrasonic irradiation (Kamble, Kumbhar, Rashinkar et al., 2012) (Scheme 63, Scheme 64).



R₁= Ph, $4\text{-}ClC_6H_4$, $n\text{-}C_3H_7$; **R₂**= H, $4\text{-}OCH_3$, 4-Cl, $3\text{-}NO_2$,
R₃= H, $3\text{-}NO_2$, $4\text{-}CH_3$, 4-COOH, 4-Cl, $4\text{-}NO_2$.

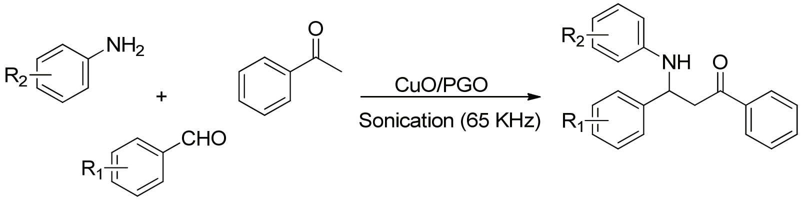
Scheme 63. Ultrasound promoted synthesis of *β*-aminocarbonyl compounds in the presence of NaPTS (50% aq).



NaPTS: sodium *p*-toluene sulphonate
R₂= H, 3-OCH₃-4-OH; **R₃**= 4-Cl, 4-CH₃, 2-Cl

Scheme 64. Ultrasound promoted synthesis of *β*-aminocarbonyl compounds derived from cyclohexanone in NaPTS solution (50% aq).

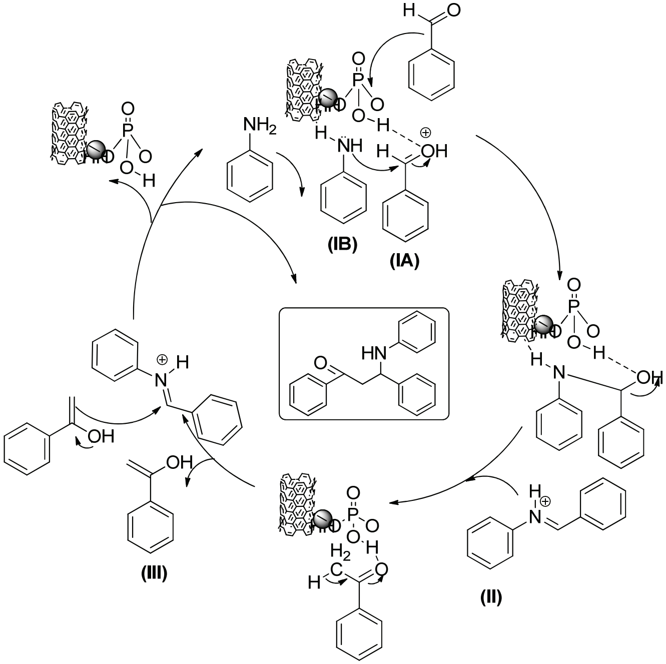
Since both acids and metal oxide nanoparticles have been successfully applied for the synthesis of *β*-amino carbonyl compounds, it could be considered that modifying metal oxide nanoparticles on an acidic GO (PGO) surface would potentially make a novel nanocatalyst for this type of Mannich reaction. In this regard, Dash's group has developed a more environmentally friendly and highly efficient heterogeneous nanocatalyst, CuO/PGO (CuO Phosphate Graphene Oxide) (Acharya, Pratap Nayaka, Barika et al., 2020). The target compounds have been obtained via condensation of benzaldehyde, acetophenone and aniline in the presence of the designed nanocatalyst (CuO/PGO) under ultrasound sonication as given in Scheme 65. It is observed that the designed nanocatalyst is extremely active towards all the reactions within a shorter period of time as compared to other traditionally available catalysts with less consumption of energy.



R₁=H, 4-OCH₃, 4-CH₃, 4-Cl, 4-Br, 4-OH, 3-OH, 4-NO₂, 3-NO₂; **R₂**=H, 4-CH₃

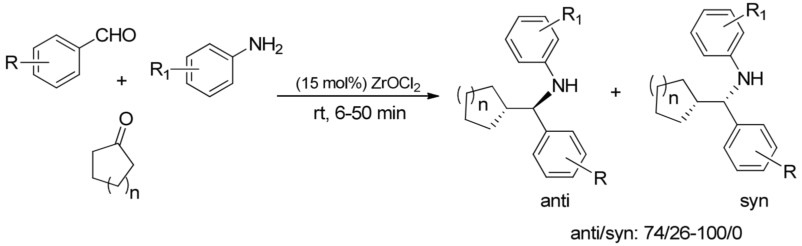
Scheme 65. Ultrasonic-assisted green synthesis of 3-anilino-1,3-diphenyl-1-propanones by CuO/PGO nanoparticles via Mannich reaction.

Looking into the plausible mechanism, the acidic nature (both Brönsted and Lewis) of the catalyst and efficient chemical adsorption of reactant molecules on the catalyst surface initiate the interaction of acidic groups with aldehyde (**IA**) and amine substrates under US activation. Because of this interaction, the carbonyl group is protonated and activated (mostly by the Brönsted acidic sites present on CuO/PGO). Meanwhile, the aniline molecule (**IB**) also is activated by the Lewis acidic site (Cu^{2+}) (Botteselle, Godoi, Galetto, Bettanin et al., 2012). Later, the nucleophilic attack on activated aldehyde occurs to be an iminium intermediate (II) via dehydration. The intermediate is stabilized by both the acidic sites through intermolecular bonding with −OH and −NH groups which further enhance its electrophilicity. The intermediate then gets nucleophilic attack by the activated acetophenone to form the desired product. At the same time, CuO nanoparticles bind properly with the organic substrates lowering the energy barrier required for all the intermediate steps (Babu, Priyadarsini and Karvembu, 2011). Overall, the presence of both Cu^{2+} and phosphate groups help in the activation, stabilization, and formation of the *β*-amino carbonyl compound (Scheme 66).



Scheme 66. Plausible reaction mechanism for the synthesis of 3-anilino-1, 3-diphenyl-1-propanone.

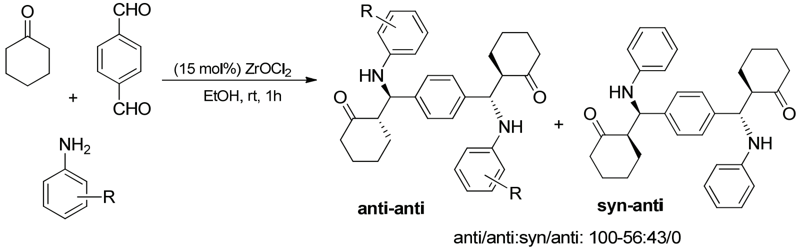
A Mannich type reaction between anilines, in situ, formed aldimines, and ketones under solvent-free conditions are catalyzed effectively by zirconium oxychloride. This condensation proceeds speedily with excellent stereoselectivity and good to high yields. The catalyst can be reused for subsequent conversions without appreciable loss of efficacy (Nikoofar and Khademi, 2016) (Scheme 67).



Scheme 67. Mannich reaction between aldimines and ketones.

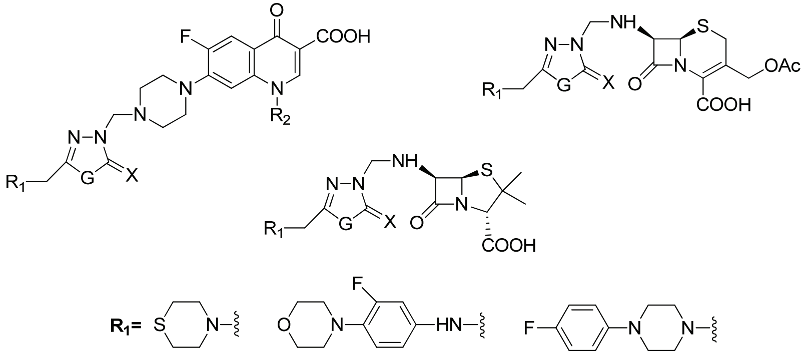
$ZrOCl_2$ has also been employed as a catalyst for the synthesis of amidoalkyl naphthols via a Mannich-type reaction between aromatic aldehydes, β-naphthols, urea, or amides (Nagawade, Shinde, 2007).

The Mannich reaction of terephthalaldehyde, cyclohexanone, and anilines has been reported to be efficiently catalyzed by $ZrOCl_2.8H_2O$ yielding bis-β-amino ketones. This condensation has taken place in ethanol at room temperature and has resulted in good to high yields with anti-selectivity (Nikoofar and Khademi, 2016) (Scheme 68).



Scheme 68. $ZrOCl_2.8H_2O$ Catalyzed Mannich reaction between cyclohexane and anilines.

Some MW-assisted Mannich reactions have been reported by the Demirbas research group. Based on the molecular hybridization concept and to obtain new drug candidates with a lesser tendency to antibacterial resistance, these authors have introduced two or more biologically active units such as triazole, piperazine, and morpholine into fluoroquinolone, penicillin, or cephalosporine skeletons, which are antibiotics used for the treatment of bacterial infections, through MW-mediated Mannich reaction (Basoglu-Ozdemir, Demirbas, Demirbas, Ayaz et al., 2018; Uygun-Cebeci, Demirbas, Basoglu-Ozdemir, Bayrak et al., 2018; Demirci, Mermer, Ak, Aksakal, Colak et al., 2017; Uygun-Cebeci, Basoglu-Ozdemir, Ceylan, Bayrak et al., 2017).

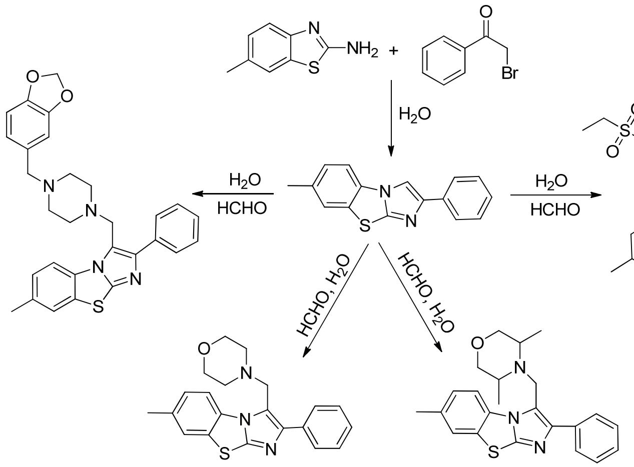


R$_2$= ethyl, cyclopropyl; **X**= O, S; **G**= O, NPh, $NCH_2C_6H_5$, NC_2H_5

Scheme 69. MW-assisted synthesis of fluoroquinolone, penicillin, or cephalosporine derivatives

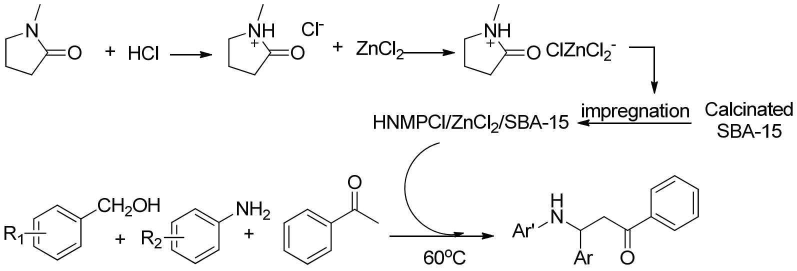
For the synthesis of the compounds given in Scheme 69, two methods involving conventional treatment and MW irradiation have been applied. The reaction time shortened from hours to minutes with better yields when MW irradiation was used. More importantly, the MW-assisted method has not required the presence of any reaction solvent.

In the study reported by Maddili and coworkers, water has been used as the solvent for the synthesis of novel imidazo[2,1-b]benzothiazole derivatives via a multi-component Mannich reaction (Maddili, Yandrati, Siddam, Kannekanti et al., 2017). In this reaction, benzothiazole has been chosen as a starting compound and it has been allowed to react with 2-bromoacetophenone in water at 100°C to form imidazo[2,1-b]benzothiazole. Then, the obtained compound has undergone a Mannich reaction with secondary cyclic or aliphatic amine and formaldehyde again in water (Scheme 70). The obtained compounds have been investigated further for their antifungal, antimicrobial, and anti-inflammatory activities.



Scheme 70. Synthesis of imidazo[2,1-b]benzothiazoles derivatives using water as a solvent via Mannich reaction.

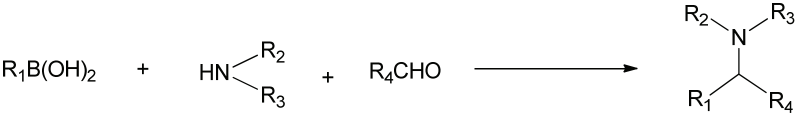
Deep eutectic solvents (DESs), which are a new kind of ionic solvent introduced in 2003 by Abbott and coworkers, are primarily low melting mixtures of a quaternary ammonium salt (e.g., choline chloride) and hydrogen-bond acceptors such as urea, carboxylic acids, or polyols. The properties of DESs are similar to those of ionic liquids and include negligible vapor pressure and low flammability while also overcoming several limitations associated with ILs such as intolerance to humidity. The main advantages of DESs include their straightforward synthesis, comparatively low cost, high biodegradability, and low toxicity. These interesting features of DESs have made these natural green solvents more popular in electrochemistry, material chemistry, and organic synthesis. In this context, Azizi and Edrisi have synthesized Mannich bases using deep eutectic solvent immobilized on SBA-15 as a novel separable catalyst (Azizi, Edrisi, 2017) (Scheme 71).



Scheme 71. The synthesis of HNMPCl/ZnCl₂ DES and impregnation onto the surface of SBA-15 and synthesis of novel Mannich bases.

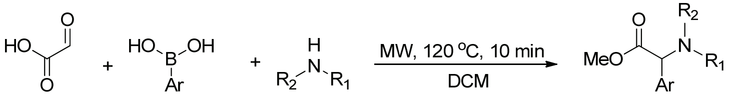
2.1.2. Petasis Reaction

The Borono-Mannich reaction named also as the Petatis reaction is a classical three-component reaction containing the condensation of an aldehyde, an amine, and a boronic acid (Nun, Martinez and Lamaty, 2010) (Scheme 72).



Scheme 72. The Petatis reaction.

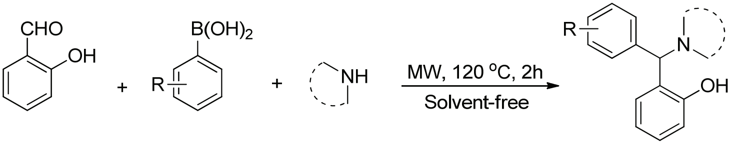
Several green methodologies have been enhanced to improve Petasis reaction conditions - such as reaction time and reactivity - and to reduce the environmental effect. Among them, McLean and coworkers have focused on a green method including microwave irradiation, to advance Petasis reaction conditions (McLean, Tye and Whittaker, 2004). Glyoxylic acid has been used as an aldehyde source while various phenylboronic acids and secondary amines have been selected (Scheme 73).



Ar: Ph,3-OMe-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-*t*Bu-C_6H_4, 2-ThioC_6H_4, 2-benzofuranyl, 1-naphtyl;
Amine: Morpholine, 2-aminodiphenylmethane, diethylamine, dibenzylamine, *p*-anisidine.

Scheme 73. Petasis reaction of glyoxylic acid, substituted boronic acid and secondary amines under MW irradiation.

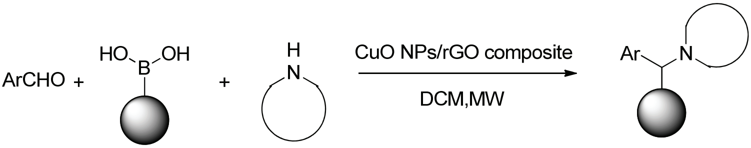
Nun and coworkers have described a Petasis reaction with the solvent-free condition under microwave irradiation (Nun, Martinez and Lamaty, 2010). For this purpose, salicylaldehyde, substituted phenylboronic acid derivatives, and three kinds of secondary amines (morpholine, piperidine, and dibenzyl amine) have been used for the reactions. This reaction has required 24 hours for completion at room temperature, while it has taken 2 hours under solvent-free MW conditions (Scheme 73).



R= H, 4-Me, 3-Me, 2-Me, 3,4,5-OMe, 3-NO_2,
Amine: morpholine, piperidine, dibenzylamine.

Scheme 73. Microwave assisted Petasis reaction.

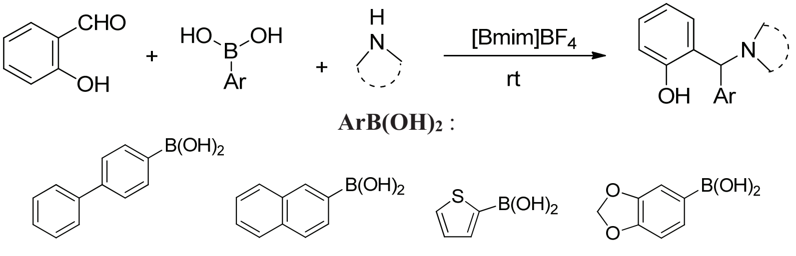
Considering the rationale behind the improvement of sophisticated and sustainable methodologies and researchers' attention on the discovery of the expeditious synthesis of nanomaterials and heterocyclic compounds, Dandia et al. have reported the synthesis, characterization, and catalytic application of a CuO NPs–rGO composite for the Petasis reaction of boronic acids, salicylaldehydes, and amines under microwave irradiation (Dandia, Bansal, Sharma, Rathore et al., 2018) (Scheme 74). The catalytic activity of the CuO NPs/rGO composite under MW has been observed to be 12-fold higher than the conventional method. The microwave method coupled with the use of the CuO NPs/rGO composite offers several advantages including cleaner reaction profiles, a highly economical and environmentally benign methodology with shorter time durations, high yields, and simple experimental and work up procedures.



Ar: Ph, 5-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, **RB(OH)$_2$**: Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-OMeC$_6$H$_4$, 2-ThioC$_6$H$_4$;
Amine: piperidine, morpholine

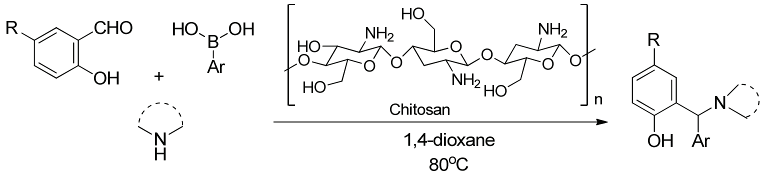
Scheme 74. CuO NPs/rGO composite catalyzed synthesis of alkylaminophenols under MW.

As it is well known, ionic liquids have been finding growing applications in organic synthesis due to their green credentials and capacity to boost reaction rates and selectivities. However, there were no reports on the use of ionic liquids to promote the Petasis reaction until 2007. Based on this purpose, Yadav and coworkers have focused on the use of ionic liquids as recyclable solvents for the Petasis–Mannich reaction of aryl boronic acids, 2-hydroxy aryl aldehydes, and secondary amines to obtain alkylaminophenols in high yields under mild and neutral conditions (Yadav, Reddy and Lakshmi, 2007) (Scheme 75).



Scheme 75. Petasis multi-component coupling reaction in ionic liquid [Bmim]BF$_4$.

The direct utilization of natural materials for catalytic applications has become a very attractive strategy in most organic reactions due to their environmental benignity and being easily separable and recyclable. Chitosan is one of the most used natural materials as a catalyst in various reactions, and in this direction, it has been utilized as a green catalyst in several Petasis reactions (Reddy et al., 2004). In the citosane catalyzed study reported by Reddy's group, unlike methods such as the conventional and microwave irradiation, the time of this reaction has been further reduced and the yield has been enhanced to the range of 86-95% (Scheme 76).

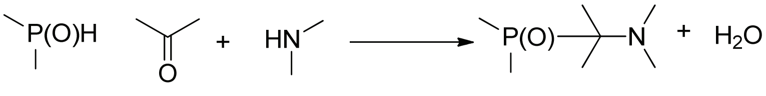


R= H, OMe; **Ar**: Ph, 4-ClC_6H_4, 4-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 2-MeC_6H_4, 4-MeC_6H_4;
Amine: morpholine, pyrrolidine, piperazine, 3-thiophene, 4-$OMeC_6H_4$, 3,4-OMe-C_6H_3

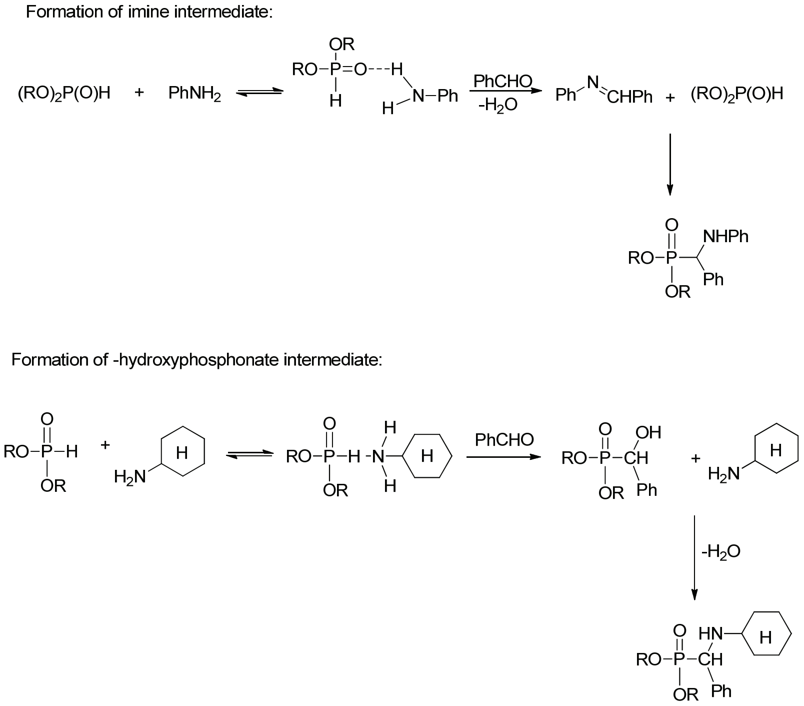
Scheme 76. Chitosan catalyzed synthesis of alkylaminophenols via Petasis reaction.

2.1.3. Kabachnik-Fields Reaction

The Kabachnik-Fields reaction, which is commonly known as phospha-Mannich condensation, is a milestone in organophosphorus synthesis yielding amino phosphonates and their derivatives (Scheme 77). This breakthrough condensation was first reported in 1952 by Kabachnik and Medved and Fields independently. The scientists proposed a three-component mechanism between a carbonyl compound, an amine, and a hydrophosphoryl compound giving α-amino phosphonates. The reasonable mechanism giving a P-C-N moiety was described in 1998 by Cherkasov and coworkers. According to the descriptions of these authors, the α-hydroxyphosphonate is formed by the addition of the dialkylphosphite to the carbonyl group of the oxo component, and then the hydroxyphosphate undergoes substitution by the amine to furnish the α-aminophosphonate (Scheme 78). Later, it was proved that the nature of the substrate decides the progress of the reaction as a competitive hard-soft nucleophile-electrophile interaction (Keglevich and Bálint, 2012).

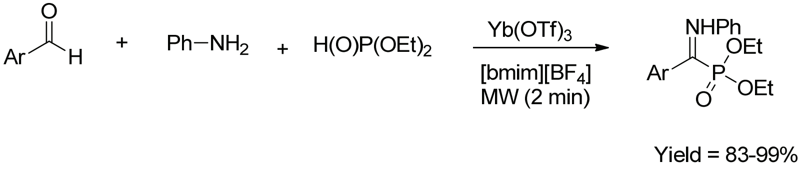


Scheme 77. The Kabachnik-Fields reaction.



Scheme 78. The mechanism of Kabachnik-Fields reaction via an imine intermediate or α-hydroxyphosphonate intermediate.

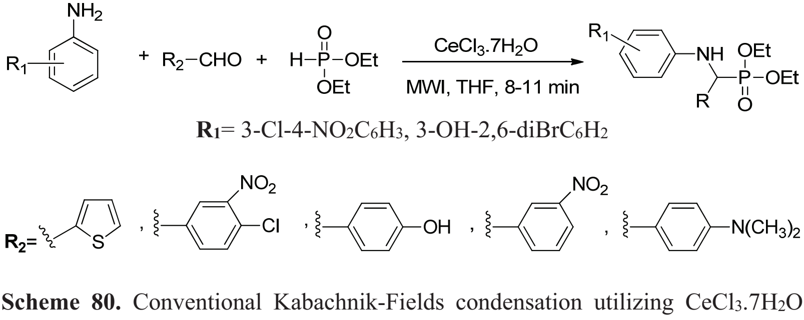
The Kabachnik-Fields (KF) reaction has become a pioneering strategy in synthetic organic chemistry. However, most of the reactions require the use of toxic and expensive solvents or catalysts in stoichiometric quantities. Otherwise, limited contributions have been reported under catalyst-free conditions (Shilpa, Harry, Ujwaldev and Anilkumar, 2020) (Scheme 79).



Ar = Ph, 4-OMePh, 2-MePh, 3-MePh, 4-MePh, 4-FPh, 1-Np

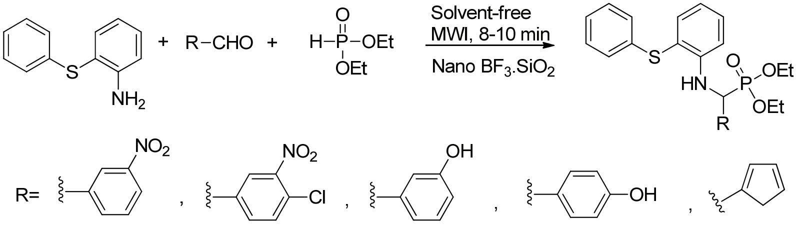
Scheme 79. $Yb(OTf)_3$ catalysed MW-assisted three component reaction of aldehydes, aniline and diethylphosphite with $[bmim][BF_4]$ as the ionic liquid.

Synthetic chemists have been searching for better alternatives. In this connection lanthanide halides, especially Ce(III) salts have been described as cost-efficient, less toxic, air/water stable and can easily recoverable catalysts. Doddaga's group has developed a straightforward approach yielding a new class of α-aminophosphonates using $CeCl_3.7H_2O$ as the catalyst. 4-Chloro-3-nitrobenzaldehyde, 4-amino-2,6-dibromophenol, and diethylphosphite in THF have reacted via the KF reaction pathway to give the desired product under MW irradiation conditions (Scheme 80). Different aldehydes with electron-rich groups, electron-deficient groups, and heteroaryl groups, have reacted conveniently to afford the desired products in excellent yields. The interpretation of the mechanism has clearly demonstrated that the catalyst has a dual role in the in-situ formation of the imine intermediate and facilitating the attack of the diethylphosphite on the imine. It has been reported that the designed compounds have displayed exceptional in vitro antimicrobial and antifungal activities (Shilpa, Harry, Ujwaldev and Anilkumar, 2020).



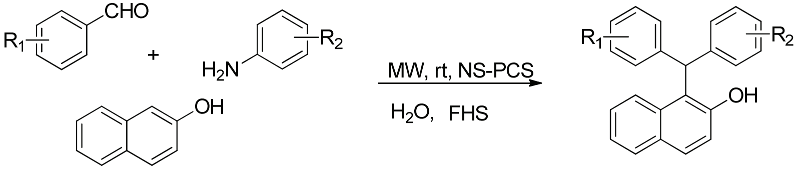
Scheme 80. Conventional Kabachnik-Fields condensation utilizing $CeCl_3.7H_2O$ catalyst.

As evinced from the previous studies, a one-pot KF condensation has been a great challenge for synthetic organic chemists because of the water formation, which has ceased the reaction either by deactivating or decomposing the catalyst. Despite the presence of several Lewis acid catalysts, most of the methods have suffered from numerous drawbacks. In this context, Rajasekhar et al. in 2013 proposed an eco-friendly one-pot three-component coupling of aryl aldehydes, 2-(phenylthio)aniline, and diethylphosphite, catalyzed by nano-$BF_3.SiO_2$, a cheap, versatile, and ecofriendly bench-top catalyst (Scheme 81). The enhanced surface area of the nanocatalyst enables the reactants to approach the active sides smoothly. The obtained results have revealed that excellent yields have been accessed with electron-poor aryl aldehydes rather than with electron-rich aldehydes (Shilpa, Harry, Ujwaldev and Anilkumar, 2020).



Scheme 81. SiO_2 supported BF_3 catalysis of α-aminophosphonates exhibiting antibacterial as well as antifungal properties.

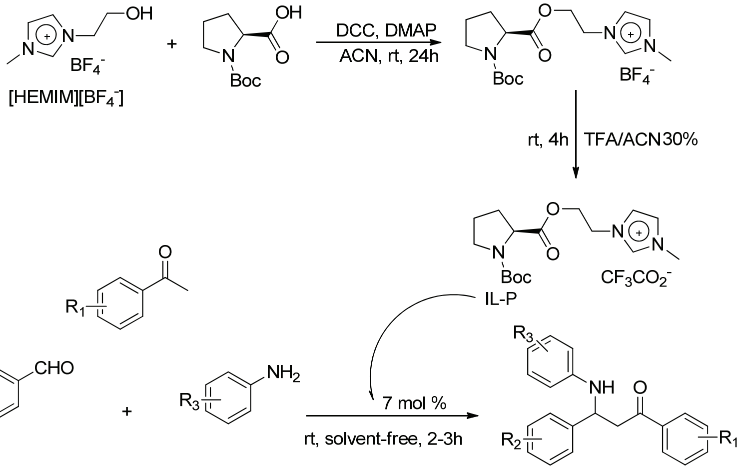
Porous Carbon Spheres (PCSs), which have great appeal as a catalyst on account of their unique physical and chemical properties, are a spherically shaped carbon material. Eshghi's group has reported the synthesis of novel Betti bases via PCSs and a ferric hydrogen sulfate (FHS) catalyzed Mannich reaction (Mansoori, Eshghi and Lari, 2020). Water has been used as a cheap and non-toxic solvent (Scheme 82). This clean and one-pot economic procedure, which is the three-component Mannich reaction improved by the employment of NS-PCS and FHS under the aqueous condition, is attractive from a green chemistry point of view. Mild reaction conditions, a short reaction time, and perfect yields of the products make this methodology stunning and considerable.



R_1= H, 3-Cl, 4-NO_2, 4-CH_3, 3-CH_3; **R_2**= 2-Cl, 4-Cl, 4-CH_3, 4-OCH_3, 4-Pr.

Scheme 82. Synthesis of Betti bases via a green methodology.

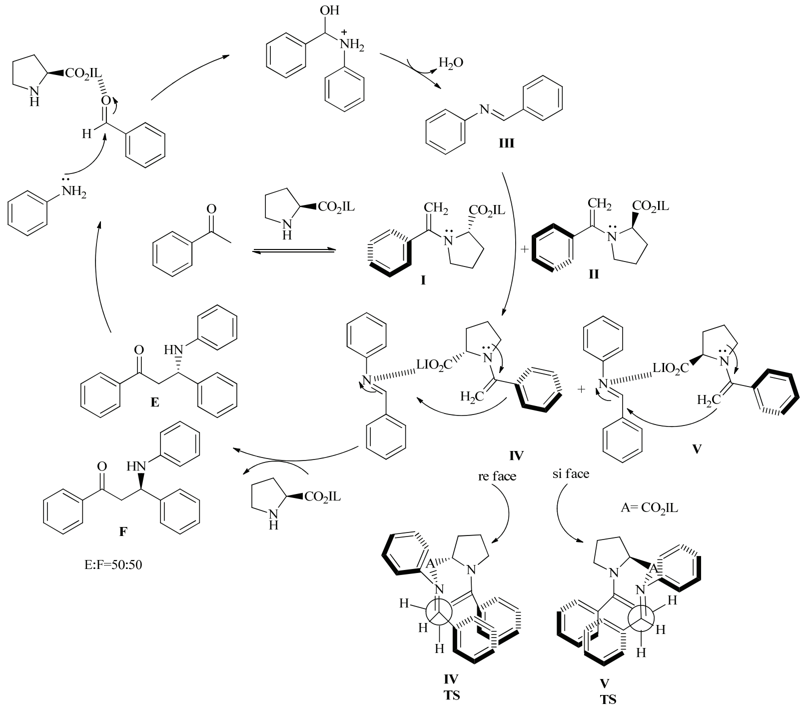
The employment of ionic liquids as a reaction medium in Mannich reactions, as in many synthetic routes, presents a suitable remedy for both solvent emission and catalytic recycling problems. Prabhakara and Maita have specified a highly efficient, clean, and simple procedure for the synthesis of *β*-amino carbonyl derivatives using ionic liquid-immobilized proline(s) organocatalyst under solvent-free conditions This methodology, as MW or US methods, has been reported to procure many benefits such as mild reaction conditions, short reaction time, low catalyst loading percentage, multicomponent approach, and transition metal-free and solvent-free synthesis. Additionally, the used ionic liquid-immobilized proline(s) organocatalyst could be recycled and reutilized many times without a crucial loss of its catalytic activity (Prabhakara and Maiti, 2020) (Scheme 83).



R_1= H, **R_2**= H, 4-CH_3, **R_3**= H, 4-Cl, 2-Cl, 3-Cl, 4-CH_3, 4-NO_2, 4-OCH_3

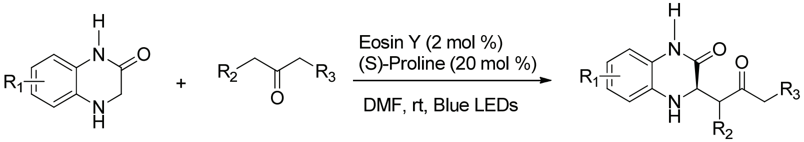
Scheme 83. Synthesis of *β*-carbonyl derivatives via Ionic liquid-immobilized proline(s) under solvent-free conditions.

The possible mechanism for the IL-P catalyzed reaction giving the target products has been presented in Scheme 84. When the IL-P organocatalyst has been used, the formation of enantiopure Mannich bases is possible. However, in this study, no enantiomeric forms of the main products have been observed. Perhaps, the mechanism of the reaction can be advanced by a series of reactions such as imine and enamine formation of acetophenone with IL-P organocatalyst, imine activation by an IL-P catalyst and C-C bond formation reaction. At first, the aldehyde is activated by an IL-P organocatalyst which reacts with substituted arylamine to give the intermediate imine (**III**). At the same time, the acetophenone reacts with the IL-P organocatalyst to create imine and enamine (**I**) and (**II**). The imine (**III**) is activated by the IL-P catalyst and reacts with the enamine (**I**) and (**II**) to give the transition states (**IV**) and (**V**). Possibly, the transition states (**IV**) and (**V**) are deliberated to be the rate-determining step. Probably, during the reaction of acetophenones with the IL-P organocatalyst, the phenyl ring of acetophenone and the proline moiety will arrange in a perpendicular plane to avoid the steric hindrance. Therefore, enamine formations (**I**) and (**II**) are possible. Next, the transition states **IV** and **V** will have equal energy which leads to the re- and si-face attack of enamine of acetophenone (**I**) and (**II**) with imine (**III**) by the formation of the C-C bond.



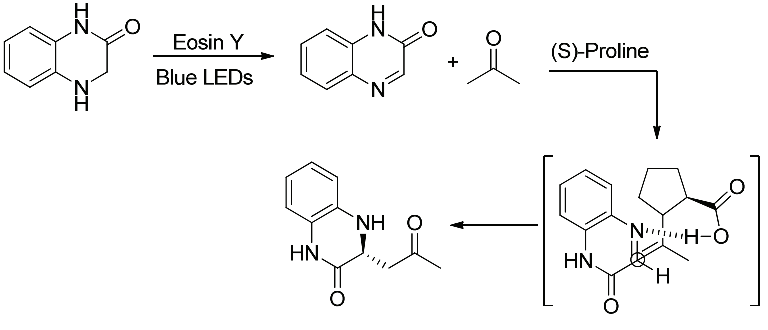
Scheme 84. Plausible mechanism and transition state for Mannich reaction using IL-P organocatalyst.

The application of visible-light photoredox catalysis has become an exciting subject in many fields of chemistry in the past decade, owing to its remarkable benefits such as low cost, safety, renewability, abundance, and environmental friendliness (König, 2013; Yoon, Prier, Rankic and MacMillan, 2013; Romero and Nicewicz, 2016). Moreover, controlling chirality has become one of the guiding principles in the chemical society over the last number of years. One of the major objectives of organic chemistry is utilizing the whole potential of synthetic chemistry to constitute and check chiral structures with different types of functions (Kane-Maguire and Wallace, 2010). In this connection, asymmetric catalysis supplies many possibilities for economical and efficient access to chiral compounds in the enantiomerically pure form (Walsh, Patrick, Kozlowski and Marisa, 2008). Thus, interfacing visible-light photochemical activation with asymmetric catalysis has provided new opportunities for the development of synthetic methods for the efficient, convenient, and green synthesis of nonracemic chiral molecules (Wang and Lu 2015; Silvi and Melchiorre, 2018). With this approach, Vila and coworkers have synthesized dihydroquinoxalinone derivatives using different aliphatic or cyclic ketones via a combination of visible-light organophotoredox catalysis and asymmetric organocatalysis (Rostoll-Berenguer, Blay, Muñoz, Pedro and Vila, 2019). Eosin Y as photocatalyst and (*S*)-proline as an organocatalyst have been chosen for synthesizing the quinoxalinone derivatives with good reaction yields and excellent enantioselectivities under very mild conditions (Scheme 85). Further, the reaction has been carried out under blue LED irradiation, so the oxidation has been faster than other light sources. Looking into the plausible mechanism of the reaction, initially under the irradiation of visible light and in the presence of Eosin Y and oxygen, dihydroquinoxalin-2-one is oxidized to quinoxalin-2(1*H*)-one. Then, the (S)-proline reacts with the ketone to create an enamine. The formed enamine attacks the re- face of the quinoxalin-2(1*H*)-one. The enantioselectivity is further controlled by H-bonding between the proline carboxylic acid and cyclic amine (Scheme 86).



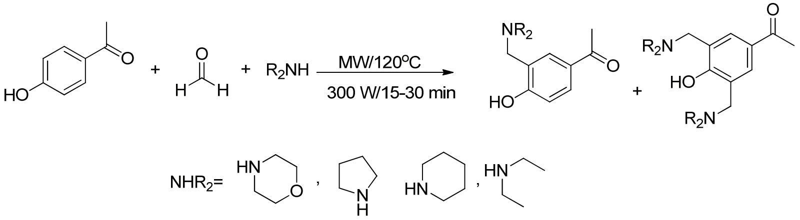
R₁= 7-CH_3, 6-CH_3, 5-CH_3, 7-OCH_3, 7-CF_3, 7-F, 6,7-diCH_3; **R₂**= H, OH; **R₃**= H, CH_3, $(CH_2)_7CH_3$.

Scheme 85. Enantioselective photooxidative Mannich reaction for quinoxalinone derivatives.



Scheme 86. Plausible stereochemical pathway.

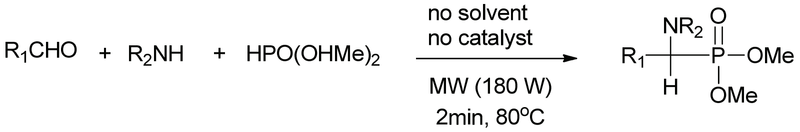
Mono- and disubstituted 4-hydroxyacetophenone derivatives have been obtained via microwave-assisted Mannich Reaction Aljohani and coworkers (Aljohani, Said, Lentz, Basar et al, 2019) (Scheme 87).



Scheme 87. One-pot multi-component Mannich reaction under MW irradition to form 4-hydroxy acetophenone derivatives.

2.1.3.1. Greener Accomplishments in KF Condenzations

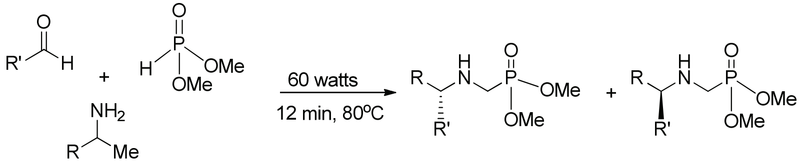
A catalyst- and solvent-free KF reaction was accomplished by Zou’s group in 2006 via the subjection of the reaction mixture to MW irradiation at 80°C, 180 W, for 2 hours (Mu, Lei, Zou and Zhang, 2006) (Scheme 88).



R$_1$= 4-NO$_2$-phenyl, *i*-propyl, furan-2-yl, tert-butyl
R$_2$ = Ph, 2-Cl-phenyl, 3-Br-phenyl, 4-Cl-phenyl, 4-Me-phenyl, naphthyl, cyclohexyl

Scheme 88. MW technique for the synthesis of α-aminophosphonates via classical Kabachnik-Fields reaction.

The presence of a chiral center in aminophosphonates has motivated synthetic chemists to expand their studies to yield optically pure compounds. Ordonez and coworkers in 2012 developed a green and one-pot protocol leading to the selective synthesis of α-aminophosphonates. In this reaction, aromatic aldehydes as well as aliphatic aldehydes, dimethylphosphite and chiral amines have undergone condensation under solvent- and catalyst-free MW irradiated conditions (Shilpa, Harry, Ujwaldev and Anilkumar, 2020) (Scheme 89).

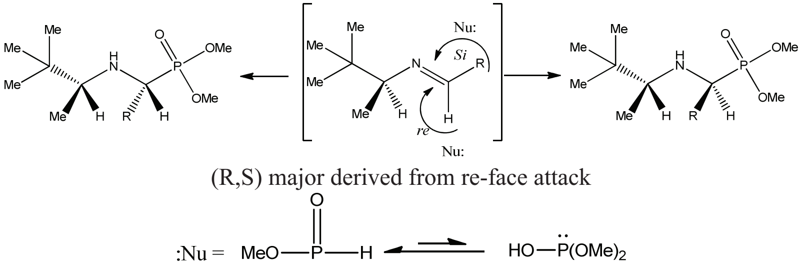


Yield = 66-86% R,S: S,S = >70:30

R = Ph, *p*-ClPh, *p*-OMePh, *i*-Bu, *i*-Pr, *t*-Bu; **R'** = Ph, *t*-Bu

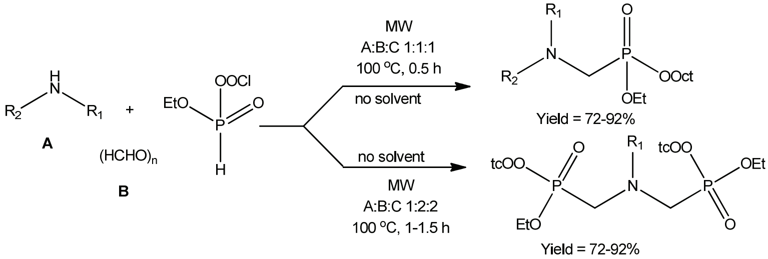
Scheme 89. General scheme for the synthesis of diastereomeric α-aminophosphonates.

The mechanistic studies have evidenced that the imine from (S)-3,3-dimethyl-2-butylamine adopts a low energy conformation and is captured by the imine π bond so that the nucleophilic attack takes place preferably from the less hindered side (Scheme 90). This method has a special advantage since it enables the performing of the reaction in a short time (Balint, Fazekas, Drahos and Keglevich, 2013).



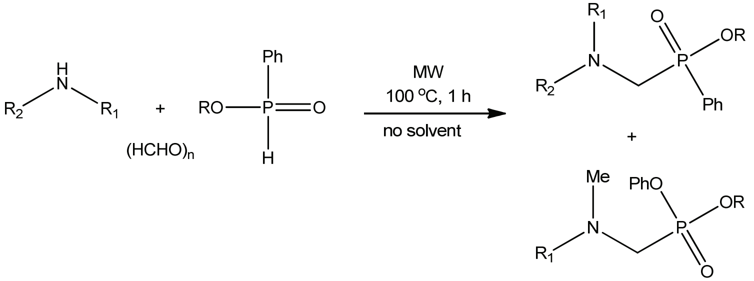
Scheme 90. Plausible mechanism for nucleophilic attack of $(MeO)_2P(O)H$ onto Schiff bases.

In 2016, the synthesis of α-aminophosphonates and a diastereomeric mixture of bis(ethyloctylphosphonomethyl)amines was reported via MW mediated KF condensation of paraformaldehyde, primary or secondary amines, and ethyl octyl phosphite (EOP) without any solvent and catalyst (Scheme 90). When one equivalent of paraformaldehyde was employed, the use of synthetically obtained alkyl-*H*-phenylphosphinate as the P reagent displayed a high tendency to give *N*-methylated by-products besides the expected product (Scheme 91). Moreover, two equivalents of this P reagent have been used for the synthesis of bis (alkoxyphenylphosphinylmethyl)amines, where the mixture of 1:1 diastereomers has been obtained (Scheme 92). Furthermore, trialkyl orthoformate has been employed for the condensation of primary or secondary amines with dialkyl phosphite or diphenylphosphine oxide to afford amino-methylenebisphosphine oxides and amino-methylenebisphosphonates respectively (Scheme 93). To obtain α-aminophosphonates with chiral *N*-scaffolds, Balint and coworkers have employed various dialkylphosphites (Scheme 94), paraformaldehyde, and (S)-α-phenylethylamine through catalyst- and solvent-free KF reaction by MW radiations. The synthesis of optically active bis(aminophosphonates) has been performed via the implementation of the same strategy in the presence of higher equivalents of paraformaldehyde and P reagents (Balint, Fazekas, Drahos and Keglevich, 2013; Matveeva, Podrugina, Tishkovskaya, Tomilova et al., 2003; Kabachnik, Zobnina and Beletskaya, 2005; Bhagat and Chakraborti, 2007) (Scheme 95).



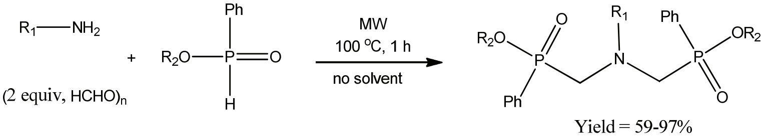
R₁/R₂ = *n*-Pr/H, *n*-Bu/H, Cyclohexyl/H, Bn/H, Et/Et, *n*-Bu/*n*-Bu, *n*-Bu/Me, Cyclohexyl/Me, Bn/Me

Scheme 90. MW-assisted Kabachnik-Fields condensation using ethyloctylphsophite in a catalyst and solvent-less medium.



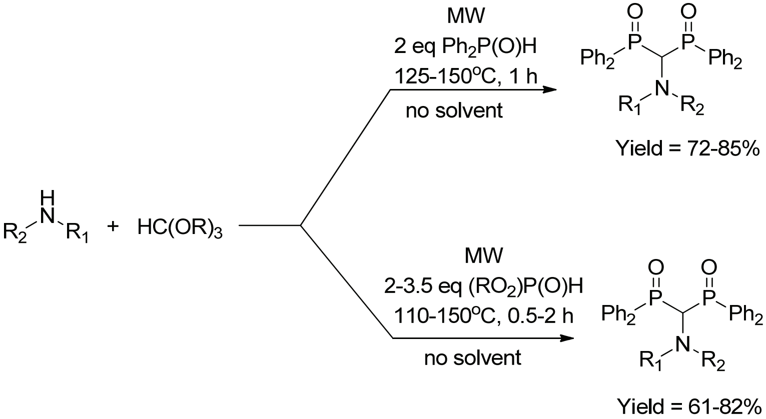
R₁/R₂ = *n*-Pr/H, *n*-Bu/H, Cyclohexyl/H, Bn/H, Et/Et, *n*-Bu/*n*-Bu, *n*-Bu/Me, Cyclohexyl/Me, Bn/Me; **R** = Et, Pr, Bu

Scheme 91. MW-assisted Kabachnik-Fields condensation using alkyl-H-phenylposphinate in a catalyst and solvent-free medium.



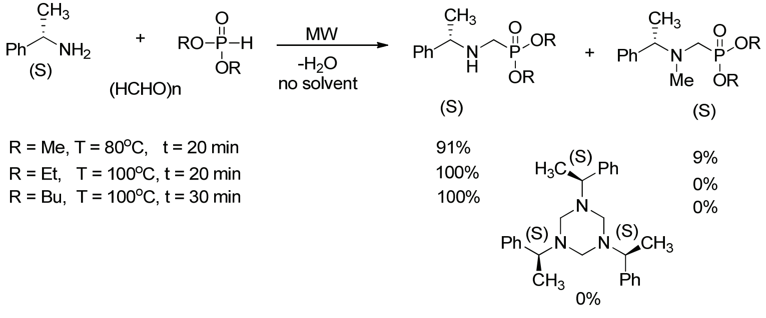
R₁ = *n*-Pr, *n*-Bu, Cyclohexyl, Bn; **R₂** = Et, Pr, Bu

Scheme 92. Double Kabachnik-Fields condensation using alkyl-*H*-phenylpjosphinate to obtain bis(alkoxyphenylphosphinylmethyl)amines.

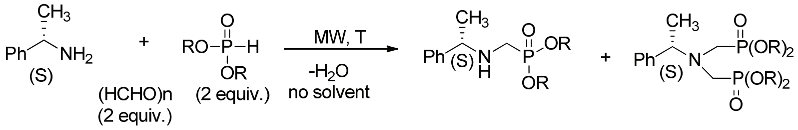


R₁/R₂ = *n*-Pr/H, *n*-Bu/H, Cyclohexyl/H, Bn/H, Et/Et, *n*-Bu/nBu, *n*-Bu/Me, Cyclohexyl/Me, Bn/Me

Scheme 93. Three-component condensation between primary or secondary amines, trialkyl orthoformate and dialkylphosphite or diphenylphosphine oxide.

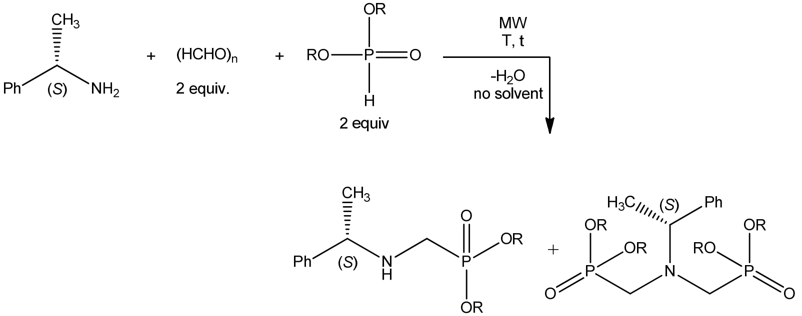


Scheme 94. Synthesis of chiral dialkyl-(*S*)-α-phenylethylaminomethyl phosphonates.



R = Me, T = 80°C, t = 1 h	98%	0%
R = Et, T = 100°C, t = 1.1 h	100%	0%
R = Bu, T = 120°C, t = 1.5 h	100%	0%

Scheme 95. Chiral double Kabachnik-Fields synthesis of (S)-bis(phosphonoylmethyl)-α-phenylamines.

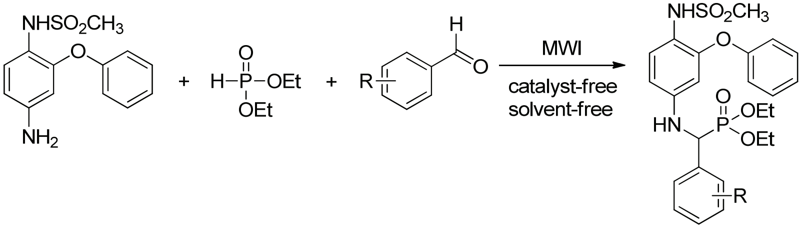


R= Me	T= 80°C, t= 1h	98%	0%
R= Et	T= 100°C, t= 1.1h	100%	0%
R= Bu	T= 120°C, t= 1.5h	100%	0%

Scheme 96. Chiral double Kabachnik-Fields synthesis of (*S*)-bis(phosphonoylmethyl)-α-phenylethylamines.

The synthesis of a new class of α-aminophosphonates possessing superior anti-inflammatory properties has been carried out starting from diethylphosphite, *N*-(4-amino-2-phenoxy phenyl)methanesulfonamide, and various aldehydes through an MW mediated one-pot KF condensation (Scheme 96).

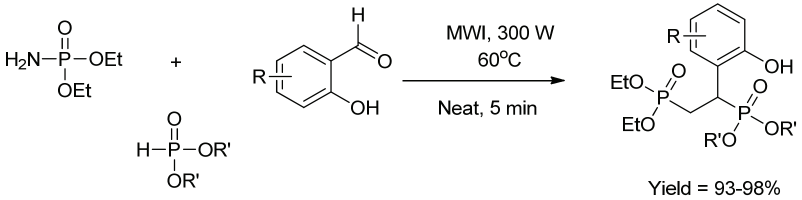
In another study, diethylphosphoramidate containing an amide moiety has been used instead of a primary or secondary amine to react diethyl- or dimethylphosphite and differently substituted salicylaldehydes in an MW induced KF condensation (Balint, Fazekas, Pinter, Szollosy et al., 2012) (Scheme 97).



R = 4-F, 3-NO$_2$, -Cl, 3-OH, 3-NO$_2$-4-Cl, 2-thienyl

Scheme 97. MW-assisted synthesis of some novel α-aminophosphonates with anti-inflammatory properties.

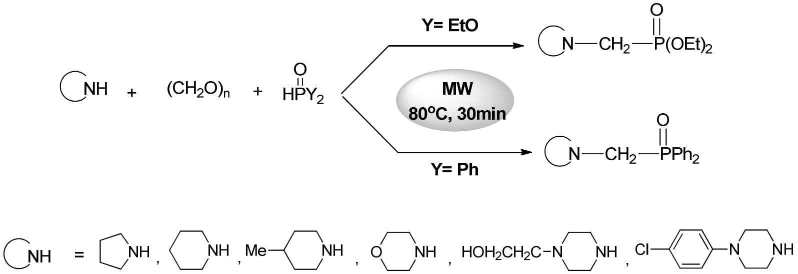
Another MW-mediated Kabachnik-Fields condensation, where dietilfosforamidate has been used as one of the reagents, has been reported by Anilkumar and coworkers (Shilpa, Harry, Ujwaldev and Anilkumar, 2020) (Scheme 98).



R = *p*-NO$_2$, *p*-OMe, *p*-Br, *p*-Cl, 3,5-dibutyl; R' = ethyl, methyl.

Scheme 98. Three-component Kabachnik-Fields reaction using diethylphosphoramidate.

A phospha-Mannich-type reaction yielding the phosphomethylation products of imidazole derivatives at 80–100°C under traditional heating for 6-8 hours with the yields 73-92% have been described. An analog reaction of morpholine and piperidine in benzene in the presence of *p*-toluenesulfonic acid as a catalyst under reflux conditions for 1.5 hours has afforded the corresponding phosphonomethylated derivatives with the yield 70-88%. Prauda et al. have reported the microwave irradiated phosphono- and phosphinoxidomethylation reactions of piperidine, pyrrolidine, piperazine and morpholine derivatives containing the reaction of the corresponding substrates with paraformaldehyde and diethyl phosphite under solvent-free conditions (Prauda, Greiner, Ludanyi and Keglevich, 2007) (Scheme 99).

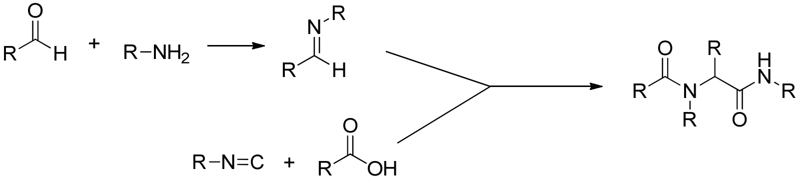


Scheme 99. Microwave irradiated phosphono- and phosphinoxidomethylation reactions of piperidine, pyrrolidine, piperazine and morpholine derivatives under solvent free conditions.

2.2. Isonitrile-Based Multicomponent Reactions

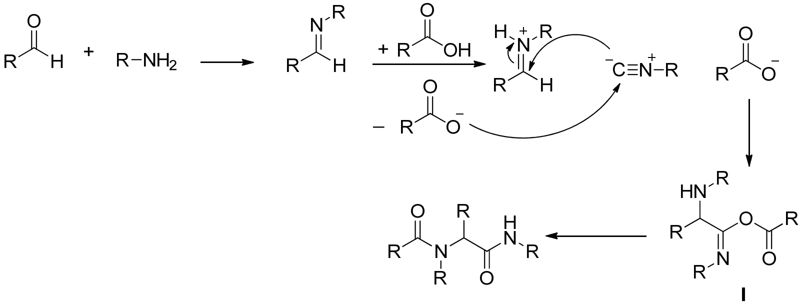
2.2.1. Ugi Reaction

The one-pot condensation between an amine, an aldehyde, an isocyanide, and a carboxylic acid, namely the four-component Ugi reaction (U-4CC), allows the rapid access to α-aminoacyl amide derivatives. The Ugi products illustrate a wide range of substituent patterns and form peptidomimetics that can display potential pharmaceutical applications. Thus, it enables the generation of very important compound libraries for screening studies (Scheme 100).



Scheme 100. General representation of the Ugi reaction.

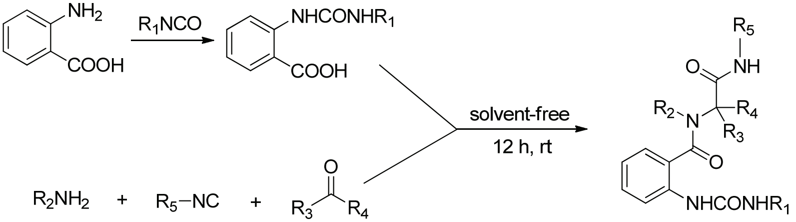
The mechanism is accepted to contain a prior formation of an imine from the condensation of the amine with the aldehyde, followed by the addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon; the resulting acylated isoamide rearranges by acyl transfer to generate the final product (Scheme 101).



Scheme 101. Mechanism of Ugi reaction.

The intermediate **I** has functional groups suitable for further reactions. This reaction keeps on without the need for isolation of the intermediate **I** in catalyst-free media. In this multi-component condensation based on isocyanides, all five starting compounds have been mixed in one pot within short intervals to maximize bond formation for complexity generation and diversification. The introduction of three components (isonitrile, amine, carbonyl compound) takes place a half-hour after mixing the two starting materials (phenyl isocyanate and benzoic acid), which leads to the separation of the product as a precipitate.

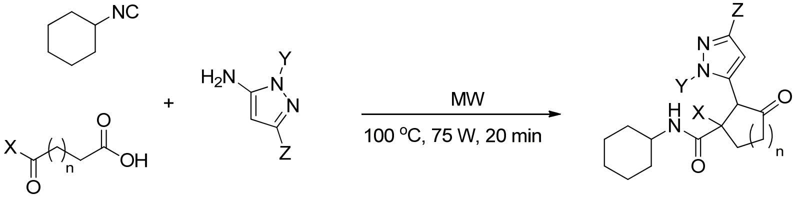
An example of solvent-free Ugi reactions has been reported by Azizian et al. This procedure yielding new urea derivatives contains the one-pot five-component condensation of 2-amino benzoic acid, phenyl isocyanate, primary amines, oxo compound, and isocyanides at room temperature (Azizian, Yadollahzadeh, Tahermansouri, Khoei et al., 2012) (Scheme 102).



R$_1$= H, 4-MeO; **R**$_2$= Et, Bn; **R**$_3$= Me, Et, *t*-Bu, cyclopentyl, cyclohexyl, Ph, 4-$NO_2C_6H_4$; **R**$_4$= H, Me, *t*-Bu; *n*-Bu, cyclohexyl.

Scheme 102. Synthesis of urea derivatives *via* a five-component reaction.

Pyrazole derivatives have been defined by a broad range of pharmacological activities including anti-inflammatory, antimicrobial, anti-tubercular, anticancer, anti-HIV, antiproliferative, and many more. The combination of pyrazole and oxopyrrolidine units generates versatile building blocks in organic chemistry with prominent pharmaceutical properties. Several methods on the synthesis of pyrazoleoxopyrrolidine derivatives use expensive catalysts, toxic organic solvents, and proceed via multiple steps affording the desired products with unsatisfactory yields. Among the methods focusing on such challenges, multicomponent reactions (MCRs) performed under microwave irradiation have come forward. In this context, Jassem et al. have reported the efficient synthesis of new pyrazole-oxopyrrolidine derivatives with antimicrobial potential via a MW irradiated (4C-3C) Ugi reaction starting from different aminopyrazoles, ketoacids, and cyclohexylisocyanide (Jassem, Almashal and Jaber, 2020) (Scheme 103).

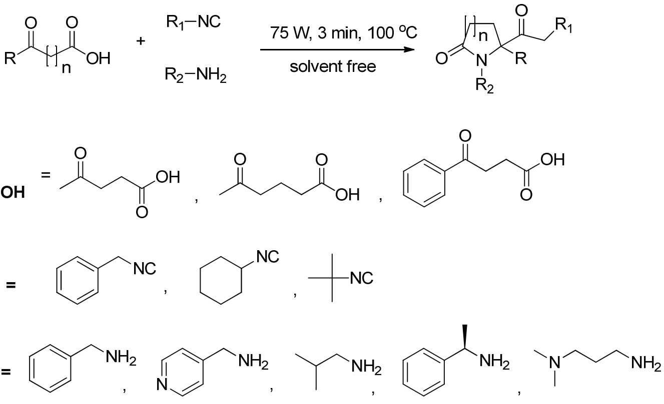


X = CH_3, $CH_3CH_2CH_2CH{=}CH_2$; **Y**= CH_3, Ph; **Z**= CH_3, Ph, n=1, 2, 3.

Scheme 103. Microwave assisted solvent free synthesis of *N*-cyclohexyl-2-(1*H*-pyrazol-5-yl)- carboxamide derivatives.

The synthesis of five- and six-membered lactams via the intramolecular 4-center-3-component Ugi reaction (U-4C-3CR) has been reported as the reaction affording useful compounds. Classically, this reaction has been carried out in methanol at room temperature with reaction times of up to 48 hours. In a variation of this method supported by microwave irradiation, Tye and coworkers have synthesized five-membered lactams derived from levulinic acid with a shorter reaction time of 30 mins.

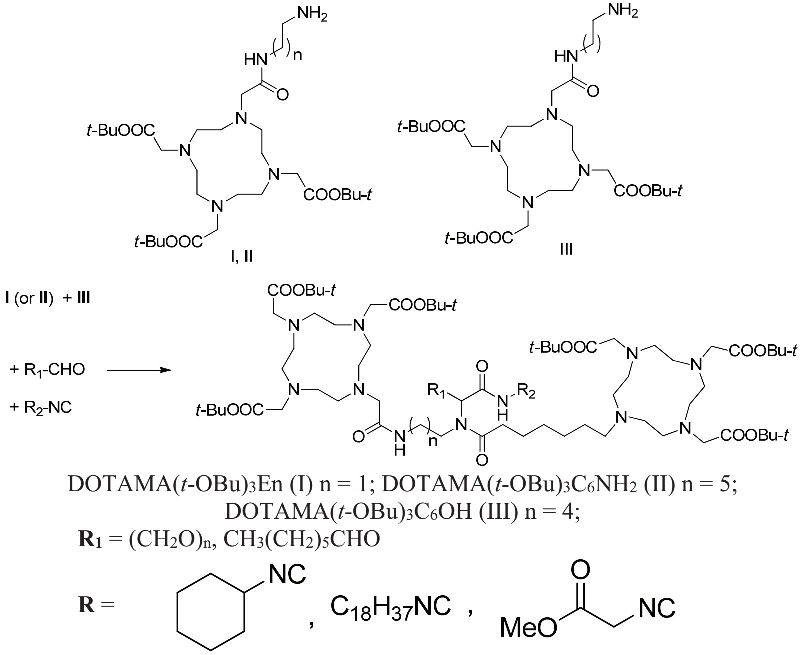
Recently, Deprez-Poulain et al. have reported an efficient solvent-free synthesis of the five- and six-membered lactams through a 4-center-3-component Ugi reaction (Scheme 104) from levulinic acid or 5-ketohexanoic acid, isocyanide, and amine under MW irradiated conditions. These reactions have been performed at 100°C for 3 mins under 75 W. A set of structurally different amines and isocyanides have been combined with both levulinic and 5-ketohexanoic acid to yield structurally different lactam derivatives. This method has also been used successfully for the synthesis of lactame 6 starting from 3-benzoylpropionic acid with a bulkier structure. The authors have disclosed that this microwave assisted procedure has provided a much better way than the classical methods in the literature for giving six-membered lactams (Jida, Malaquin, Deprez-Poulain, Laconde and Deprez, 2010).



Scheme 104. U-4C-3CR from isocyanide, ketoacid and amine.

It is accepted that the one-pot synthesis of various substituted macrocyclic ligands led to the elimination of the chemical- and time-consuming steps. Indeed, through the capability of combining more than two reactants in an organized process, MCRs present not only great structural diversity and complexity per step but also the probability of the introduction of matched functional groups suitable for further transformations. Actually, the combination of an MRC to biomolecules or macromolecules through an efficient post-transformation can submit a powerful way for affording molecular probes useful for biomedical applications. In a parallel context, the synthesis of functionalized polyazacycloalkanes has been attracting growing interest, because they represent chelating agents, which are able to compose stable complexes with various metal ions ranging from transition metals to lanthanides and other heavy metals. The utilization of these chelates as radiopharmaceuticals as contrast-enhancing agents (CAs) for magnetic resonance imaging (MRI) and for the diagnosis and therapy of tumors presents the most appropriate biomedical applications. A substantial challenge in the development of new chelates has been reported as the improvement of their capability to target tissues and organs to allow certain delivery to specific cellular targets. The general strategy involves the synthesis of a chelating unit bearing a suitable group through which it can be bound covalently to the specific biological transporter, giving the compounds which are called bifunctional chelating agents (BFCAs). Macrocyclic BFCAs are generally based on DOTA or DOTAmonoamide (DOTA=1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid) derivatives incorporating a large variety of functional groups available for integration such as amines, carboxyls, ketones or aldehydes, maleimides, isothiocyanates, alkynes and vinyl sulfones.

In this context, the synthesis of multimeric BFCAs, which can combine the search for more efficient CA and the targeting of these CA to specific receptors, has not been studied yet. Therefore, Hulme et al. have handled this problem using Ugi 4CR, which has allowed the synthesis of a series of dimeric ligands containing a hydrophobic chain or different functional groups. The synthesis has been performed by utilization of simple monomeric BFCAs with a primary amino group in one case and a carboxylic acid in another and by changing the aldehyde and/or the isocyanide used in the Ugi 4CR (Scheme 105).



DOTAMA(*t*-OBu)$_3$En (I) n = 1; DOTAMA(*t*-OBu)$_3$C$_6$NH$_2$ (II) n = 5;
DOTAMA(*t*-OBu)$_3$C$_6$OH (III) n = 4;

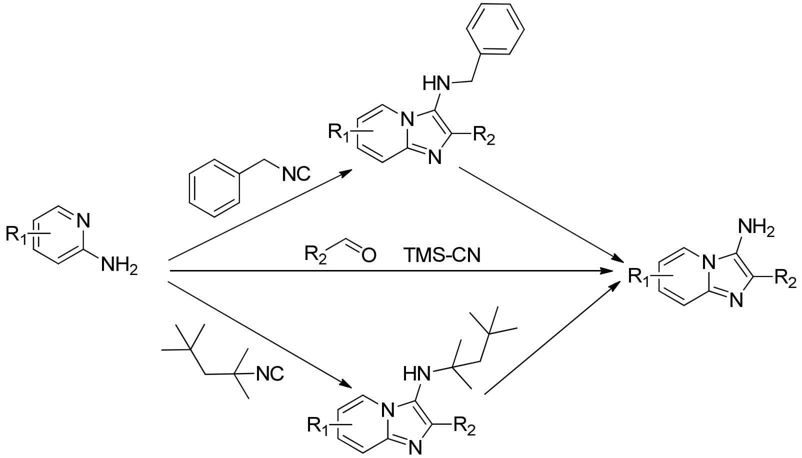
R$_1$ = $(CH_2O)_n$, $CH_3(CH_2)_5CHO$

R =

Scheme 105. General synthesis of ditopic bifunctional chelating agents through Ugi 4CR.

As a result, this Ugi four-component reaction performed in a single pot has been employed to obtain bifunctional ditopic chelators from DOTA monoamide derivatives such as amino and acid components. Several advantages of this approach have been reported: *i*) short reaction times with reasonable yields; *ii*) the possibility to modulate the chemical properties of the chelator (charge, denticity, ligating groups) and the pendant central functional moiety; *iii*) the increased possibility to produce a large number of derivatives to satisfy the different chemical requirements (Tei, Gugliotta, Avedano, Giovenzana et al., 2009).

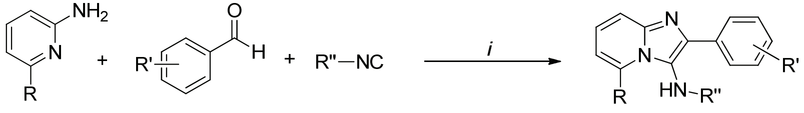
The unique application of TMSCN as a non-classical, yet functional, isonitrile equivalent, giving 3-aminoimidazo[1,2-a]pyridines, (Scheme 106) has been presented in the paper reported by Hulme et al. This method obviates the need for an acid mediated de-protection strategy. The studies reported previously on the application of KCN have disclosed that this strategy has given the desired products in low yield and with moderate purity. Additional methods yielding this class of compound have also been defined, including hydrogenation of *N*-benzyl compounds and the condensation of a-halocarbonyls with 2-aminopyridines, followed by nitrosation and reduction. However, the latter methods have low capability to synthesize a wide range of libraries (Hulme and Lee, 2008).



R1= 2-Me, 3-Me, 3-Et, 3-Ph; **R2**= Ph, cyclohex; *i*-Bu, thiophen-2-yl, *n*-bu.

Scheme 106. Synthesis of 3-aminoimidazol[1,2-a]pyridine derivatives.

Certain transition metals such as ruthenium and its complexes have been attracting substantial interest in various organic processes as catalysts. The use of the $RuCl_3.3H_2O$ complex in organic transformations requires the presence of electron donor ligands such as phosphines (P(III)) and amines (nitrogen-based ligands). As is well-known, MCRs have been attracting much attention from the point of view of combinatorial chemistry because of some superior features such as productivity, convergence, generally high yields of products, and facile execution. In this area, isocyanide-based MCRs such as the versatile Ugi and Passerini reactions have a major importance. The synthesis of aminoimidazopyridines, which are placed among the most important class of pharmaceuticals due to their wide range of biological activity, has been attracting widespread interest. For this purpose, several MCRs have been developed containing the condensation of an isocyanide, an aldehyde, and a 2-aminoazine in the presence of protic acids such as $HClO_4$, AcOH, cellulose sulfuric acids, p-toluenesulfonic acids, or Lewis acids such as $Sc(OTf)_3$, $MgCl_2$, $SnCl_2$, $ZrCl_4$, or $ZnCl_2$ in a Groebke–Blackburn three-component reactions. However, some drawbacks of these methods have been reported such as long reaction times, low yields of the products, harsh reaction conditions, the requirement for an inert atmosphere, tedious workup leading to the generation of large amounts of toxic metal-containing waste, and the use of stoichiometric or relatively expensive reagents. As a result, the development of new strategies has remained an attractive goal. To overcome these drawbacks, Rostamnia and Hassankhani have developed an Ugi-type method leading to the synthesis of aminoimidazole derivatives in solvent-free media in the presence of $RuCl_3.3H_2O$ without any ligands or other additives. This solvent-free condensation, using commercially available $RuCl_3.3H_2O$, is economically affordable concerning the Ru sources and does not require the presence of expensive ligands. The condensation of aldehydes, 2-aminopyridines, and isocyanides has supplied simple one-pot access into the preparation of aminoimidazole derivatives with a green pharmaceutical manner. This method also has the advantage of being carried out in neutral conditions (Rostamnia and Hassankhani, 2013) (Scheme 107).

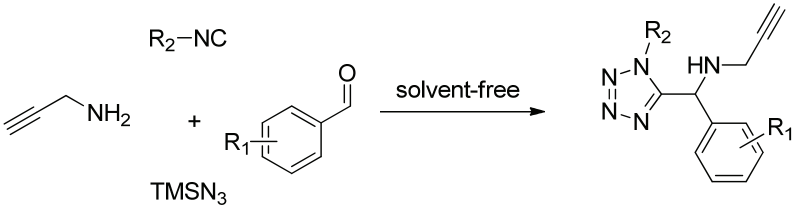


i= Ru (5 mol%), solvent-free, 40°C.
R= H, Me; **R'**= H, 4-NO_2, 4-Cl, 3-NO_2; **R''**= *t*-Bu, Ph

Scheme 107. $RuCl_3$-catalyzed solvent-free Ugi-type synthesis of aminoimidazoles.

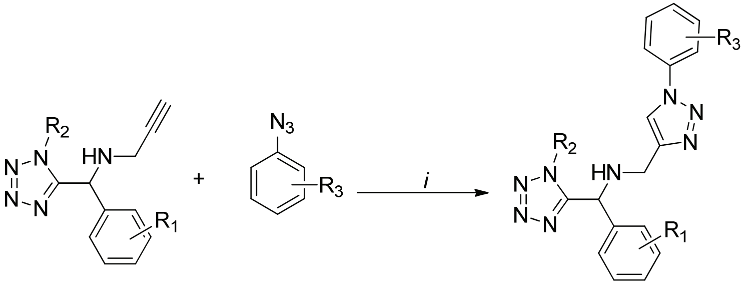
Molecular hybridization has been considered as an effective strategy for the development of new compounds with biological activity. This approach helps to discover more efficient drug candidates, particularly hybrid compounds containing two or more biologically active units acting synergistically. An efficient approach for the synthesis of such compounds is a multicomponent reaction (MCR)/post-condensation, which enables access to several biological and pharmacological active scaffolds. In recent years, the Ugi-azide reaction has been proven to be a useful tool for the generation of hybrid systems containing the 1,5-disubstituted tetrazole (1,5-DS-T) scaffold via a one-pot manner or a few steps. 1,2,3-Triazoles and 1,5-DS-T have been known as synthetic five-membered, nitrogen-containing heterocycles that act as amide bonds and cis-amide bonds of peptide bioisosteres, respectively. The biological activities of both heterocycles, which are considered privileged scaffolds, have been well documented.

Given the above considerations, García et al. have developed a new synthetic strategy for the preparation of 1,5-DS-T (1,5-disubstituted tetrazole) linked 1,2,3-triazole through an Ugi-azide reaction followed by a copper-catalyzed alkyne-azide (CuAAC) reaction as a post condensation process for the Ugi-azide reaction under solvent-free conditions. This post-transformation process has been clarified in the classical Ugi 4-component reaction (Aguilar-Morales, de Loera, Contreras-Celedón, Cortés-García et al., 2019) (Scheme 108, Scheme 109).



R₁= H, 2-F, 4-F, 4-Br, 2-Br, 2-Cl, 4-MeO, 2,4,5-triMe; **R₂**= *t*-Bu, Cy

Scheme 108. Solvent-free synthesis of 1,2,3-triazole derivatives via classical Ugi condensation.



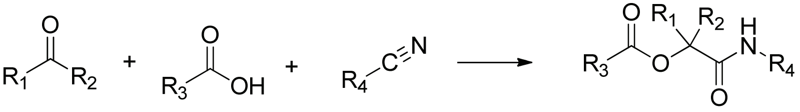
i= CuAAC, t-BuOH:H_2O (1:1), $CuSO_4.5H_2O$, Sodium ascorbate
R_1= H, 4-F, 4-Br, 4-MeO, 2-Cl, 2,4,5-triMe; **R_2**= t-Bu, Cy; **R_3**= 4-CN, 4-Cl, 4-NHCOMe

Scheme 109. 1,5-DS-T-1,2,3-triazoles synthesized using the CuACC reaction as a post-condensation process.

2.2.2. Passerini Reaction

The classic Passerini reaction, discovered in 1921 by Mario Passerini, is one of the oldest multicomponent reactions and is another isonitrile-based MCR that yields a-acyloxy carboxamides in a one-pot synthesis from an aldehyde, isonitrile, and carboxylic acid. In this reaction, the acid is always a carboxylic acid, and the product alpha-acyloxy amides (Banfi and Riva, 2005).

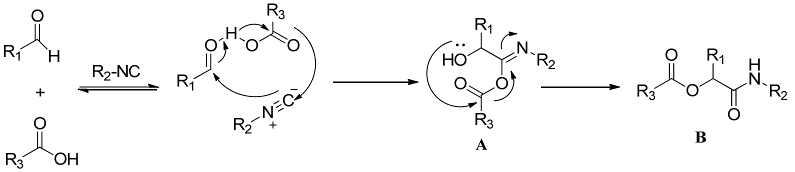
This methodology has been attracting a growing interest in recent years due to the usefulness of multicomponent reactions in synthetic procedures. Although it constitutes still probably the best process for generating α-acyloxy amides in a highly convergent way, its synthetic content has been enhanced lately using a bifunctional substrate, which can undergo secondary reactions. Thus, a larger range of compounds can be synthesized and complex biologically active substances can be accessed rapidly (Banfi, Basso and Riva 2010; Baker and Stanonis 1951). The carbonyl compound is one of the most important reactants among the three components due to the clear reactivity towards the C(sp^2) electrophilic center of the divalent isonitrile carbon atom. This reaction takes place slowly with low yields unless strong carboxylic acids or carbonyl compounds with unusual electrophilicity are not used (Xia and Ganem 2002) (Scheme 110).



Scheme 110. The representation of classic Passerini reaction.

A comprehensive examination has been focused on finding the Passerini reaction mechanism, and various literatures have indicated the different intermediates, such as hemiacetals, carbocation, and hydrogen-bonded adducts (Banfi and Riva, 2005). The formation of the hydrogen-bonded intermediate is the most admitted mechanism for this reaction (Scheme 111).

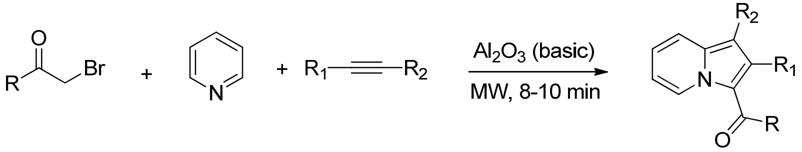
It comprises the activation of an aldehyde by the carboxylic acid, followed by the addition of an isocyanide to generate nitrilium intermediate (**A**). This (**A**) is trapped by the carboxylate, which then undergoes Mumm type rearrangement to afford the final α-acyloxy amide product (**B**).



Scheme 111. The proposed mechanism for the Passerini-3CR.

To succeed in more appropriate conditions for the synthesis of Passerini products, various reaction conditions have been examined such as microwave irradiation, ultrasound sonication, solvent-free media, reusable nanoparticles, and water as a solvent. The examples below include studies carried out with the Passerini reaction using green chemistry techniques.

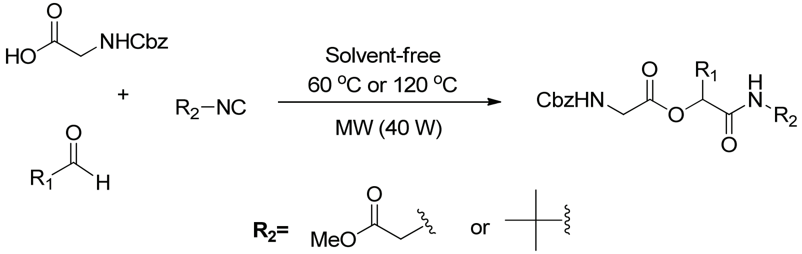
The practicability of microwave energy has led Bora and coworkers to use it for establishing the suitability of the three-component reaction (3-CR) involving the 1,3-dipolar cycloaddition reaction between an in situ generated dipole (R bromoacetophenone and pyridine) and acetylene (Bora, Saikia and Boruah, 2003). Thus, the authors have synthesized indolizine derivatives via a microwave-promoted solid-phase heterogeneous reaction. Phenacyl bromide, pyridine, and ethyl propiolate have been thoroughly mixed in basic alumina and irradiated at 2450 MHz for 8 min to give 3-benzoyl- 1-carbethoxy-indolizine with the 92% yield (Scheme 112). A sharp decrease in yield has been observed when basic alumina has been removed from the reaction medium to optimize the reaction conditions. At the same time, the use of different solvents such as THF, toluene, and DMF instead of pyridine has resulted in decreased reaction yields. On the other hand, the combination of the organic solvent, triethylamine, and alumina under microwave irradiation has afforded good results. Further, the refluxing of the same reagents and Et_3N thermally in different solvents without basic alumina for 6 h has caused lower reaction yields.



R= Ph, *p*-tolyl, styryl; **R_1**= H or COOMe; **R_2**= COOMe or COOEt

Scheme 112. Microwave-mediated three-component synthesis of indolizine derivatives catalysed by basic alumina.

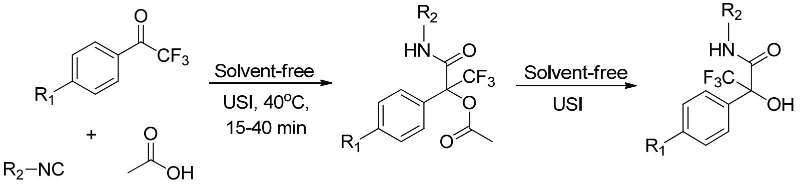
In another study, the researchers have investigated Passerini reactions via microwave irradiation under solvent-free conditions (Barreto, Vercillo and Andrade, 2011). The simplicity of the reaction conditions, its effect and the perfect outcomes (short reaction time; 0.5 min to 5 min) acquired using two different temperatures (60°C and 120°C), under solvent-free conditions, have created an appealing contribution among the existing methods (Scheme 113).



R_1 = Ph, 4-NO_2-Ph, 4-Cl-Ph, 3-OMe-Ph, 2-OMe-Ph, 2-Cl-Ph

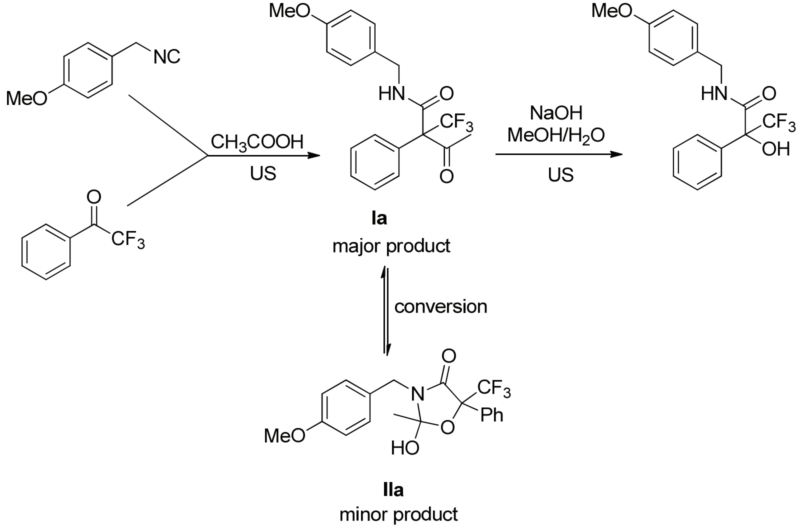
Scheme 113. Microwave assisted Passerini reaction under solvent-free condition.

Until 2012, there was no report on the Passerini reaction using the ultrasonic sonication method. Considering this situation, Cui and coworkers have put the hypothesis of whether the ultrasound can accelerate hindered Passerini reactions. To define the efficacies of USI on this reaction, the experiments have been performed using a sonic horn as an ultrasound source, while the other conditions are the same as those reported in the literature (Cui, Zhu, Du, Zhi-Peng et al., 2012). It has been concluded that the reaction time decreases from 16.5 h to 40 min and the reaction yield increases from 6% to 41%. Besides, it has investigated the solvent effect on reaction, and the solvents such as DCM, EtOAc, THF, H_2O, and $LiCl_{(aq)}$ used in Passerini reactions in classical method have not accelerated the reaction (Scheme 114). However, a higher reaction yield has been obtained in the study in solvent-free medium (same temperature and same ultrasonic irradiation conditions).



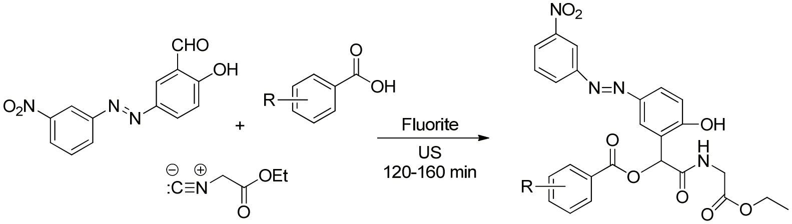
R_1= H, 4-MeO, 4-PhO or 4-Ph; **R_2**= 2-NO_2-4-$MeOC_6H_3$, 2-($PhCO_2$)C_6H_4, 2-NO_2-4-$MeOC_6H_3CH_2$, 4-$FC_6H_3CH_2$; 4-ClC_6H_4, 4-MeC_6H_4, 4-$ClC_6H_3CH_2$, 2-$MeOC_6H_3CH_2$ or 4-$MeOC_6H_4$

Scheme 114. Passerini reactions via USI under solvent-free condition.



Scheme 115. Conversion between the two Passerini products.

In 2013, an ultrasound-promoted one-pot Passerini/hydrolysis reaction sequence was enhanced for the synthesis of trifluoroatrolactamide derivatives using a diverse range of trifluoroacetophenones and isonitriles in acetic acid. In the following year, an ultrasound-promoted one-pot Passerini/hydrolysis reaction sequence has been enhanced for the synthesis of trifluoroatrolactamide derivatives using a diverse range of trifluoroacetophenones and isonitriles in acetic acid (Yu, Zhu, Bian, Cui et al., 2014). Parallel synthesis in a centrifuge tube using a noncontact ultrasonic cell crusher has been utilized in this study as an efficient process for the rapid generation of combinatorial trifluoroatrolactamide. Unlike the above study, here the authors have deduced that a ring closure product has been formed when they observe a minor impurity in TLC and performed characterization studies. This ring closing phenomenon in the Passerini reaction has not been reported previously for a three-component intermolecular Passerini reaction, although a similar phenomenon has been reported for an intramolecular Passerini reaction conducted in the presence of catalytic amine (Baker and Stanonis, 1951). It has been stated that the reaction temperature and equivalent of the used catalyst play an important role for the ratio of major and minor products. When the reaction has been performed at 60°C, the **Ia/IIa** ratio has gone up to 3:7.24 after 40 min. When tributyl amine (0.2 equivalents) has been used as the amine at 40°C, a ratio of 3:2.07 of **Ia/IIa** (NMR ratio) has been observed. When the temperature has been increased to 60°C under the same conditions, the ratio of **Ia/IIa** has gone up to 3:26.6. Furthermore, when 1 equivalent of tributyl amine has been used at 60°C, the ratio of **Ia/IIa** has increased further to 3:50.0. Further increases in the amount of catalyst have not led to an increase in the ratio of **Ia/IIa** (Scheme 115).

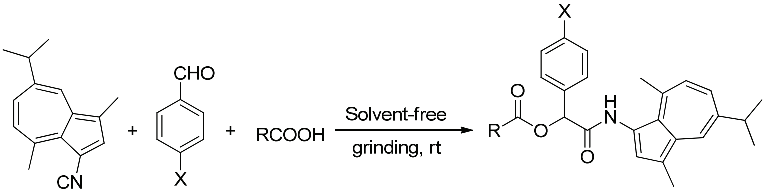


R = 4-NH_2, 4-OH, 4-NO_2, 4-Cl, 4-OCH_3

Scheme 116. Ultrasound promoted P-3CR using Fluorite catalyst.

Mohanram and coworkers have focused on synthesizing a series of novel one-pot synthesis of a three-component Passerini reaction using an aldehyde, carboxylic acid and an isonitrile with natural fluorite as a catalyst under ultrasonication (Mohanram, Meshram and Jogi, 2015) (Scheme 116). The fluorite has been used as a Lewis acid in the reaction, and it can be easily obtained after the completion of the reaction and was benign, efficient, and reusable.

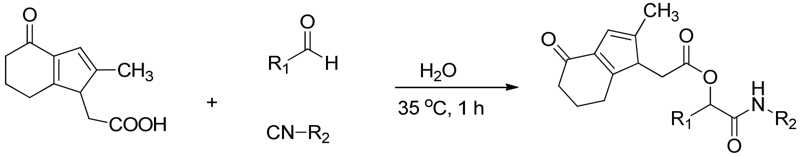
The reactivity is usually enhanced because of the closeness of the reagents in solvent-free reactions using mechanical grinding. By this approach, an environmentally friendly process yielding azulene derivatives bearing a carboxamide unit has been developed through a solvent-free Passerini reaction (Sato, Ozu, Takenaga, 2013) (Scheme 117). Although different solvents have been used to optimize the reaction conditions, the highest reaction yield has been accessed in a solvent-free medium in 20 min.



X= Cl, Br; **R**= Ph, 1-Naphthyl, 2-ClC_6H_4, 3-Cl C_6H_4, 4-Cl C_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-$OMeC_6H_4$, 3-$OMeC_6H_4$, 4-$OMeC_6H_4$

Scheme 117. The synthesis of azulene derivatives via grinding process under solvent-free condition.

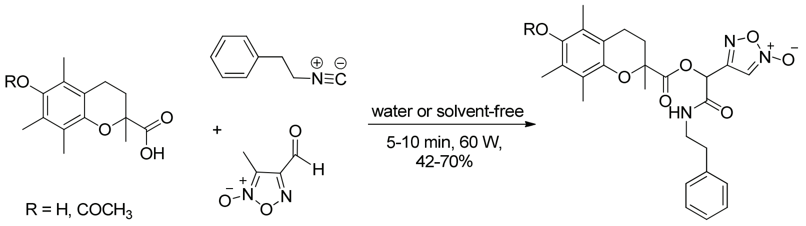
A novel water-mediated synthetic methodology leading to the formation of indolone-*N*-amino acid derivatives has been implemented by Li et al. using a Passerini three-component reaction (Yan, Wang, Zhang, Li, 2016) (Scheme 118).



R₁= H, Et, *n*-Pr, *i*-Pr, *i*-Bu, *n*-Hexyl, Cyclohexyl, 3-ClC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4;
R₂= 4-ClC_6H_4, CH_2COOEt.

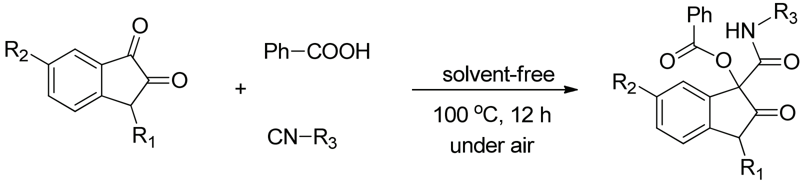
Scheme 118. Synthetic routes for the indolone-*N*-amino acid derivatives.

Ingold and coworkers have reported the synthesis of tocopherol analogs via the Passerini reaction in water or solvent-free conditions under MW irradiation (Ingold, Lopez and Porcal, 2014) (Scheme 119).



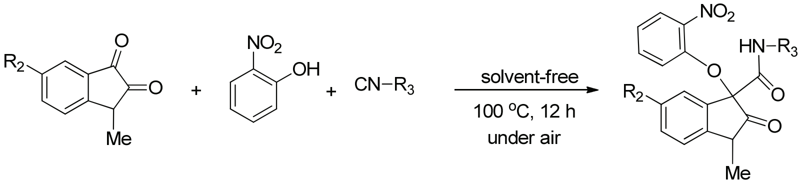
Scheme 119. Synthesis of α-acyloxycarboxamides via Passerini reaction.

A facile, atom-economic and environmentally benign protocol for the synthesis of biologically important oxindole derivatives in high yields has been demonstrated by utilizing isatins as carbonyl compound surrogates in a Passerini reaction implemented under solvent-free conditions. Moreover, electron-deficient phenols can also be used as the acid component in this reaction (Scheme 120 and 121) (Kaicharla, Yetra, Roy and Biju, 2013).



R$_1$= Me, Allyl, Bn; **R**$_2$= H, NO_2, F, Cl, Br; **R**$_3$= t-Bu, cyclohex, *i*-Pro, CH_2COOEt.

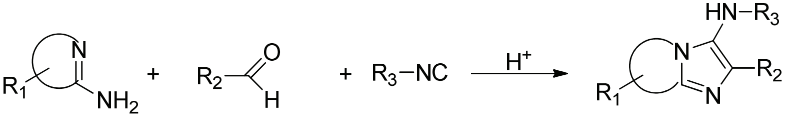
Scheme 120. One-pot synthesis of oxindoles under air and solvent-free conditions.



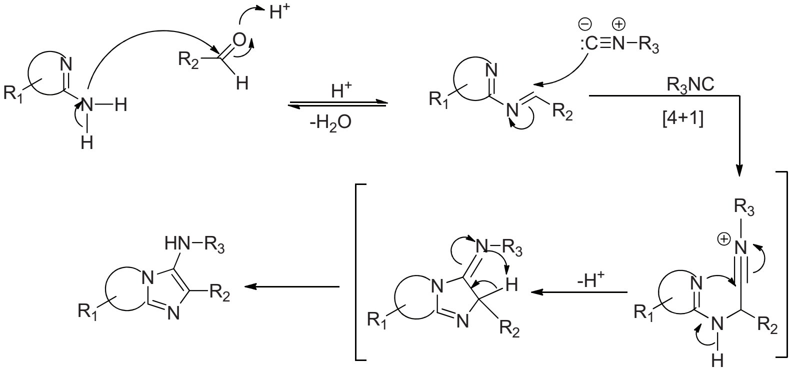
R$_2$= H, Br

Scheme 121. One-pot P-3CR synthesis of oxindoles with a free OH group at the benzylic position.

2.2.3. Groebke-Blackburn-Bienaymé reaction (GBBR)



Scheme 122. General representation of Groebke–Blackburn–Bienaymé multicomponent reaction.

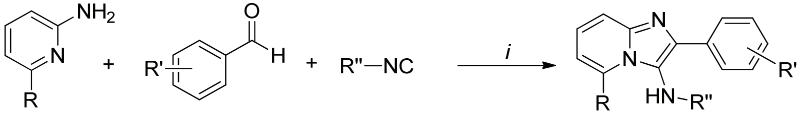


Scheme 123. Mechanism of Groebke–Blackburn–Bienaymé reaction.

As it is well-known MCRs have been attracting much attention from the point of view of combinatorial chemistry due to their superior features such as productivity, convergence, generally high yields of products, and facile execution. Certain transition metals such as ruthenium and its complexes have been attracting substantial interest in various organic processes as catalysts. The use of the $RuCl_3.3H_2O$ complex in organic transformations requires the presence of electron donor ligands such as phosphines (P(III)) and amines (nitrogen-based ligands).

In this area, isocyanide-based MCRs such as the versatile Ugi and Passerini reactions have major importance. The synthesis of aminoimidazopyridines, which are among the most important class of pharmaceuticals, has been attracting widespread interest due to their wide range of biological activities. For this purpose, several MCRs have been developed containing the condensation of an isocyanide, an aldehyde, and a 2-aminoazine in the presence of protic acids such as $HClO_4$, AcOH, cellulose sulfuric acids, *p*-toluenesulfonic acids, or Lewis acids such as $Sc(OTf)_3$, $MgCl_2$, $SnCl_2$, $ZrCl_4$, or $ZnCl_2$ in the Groebke–Blackburn three-component reaction (Rostamnia and Hassankhani, 2013).

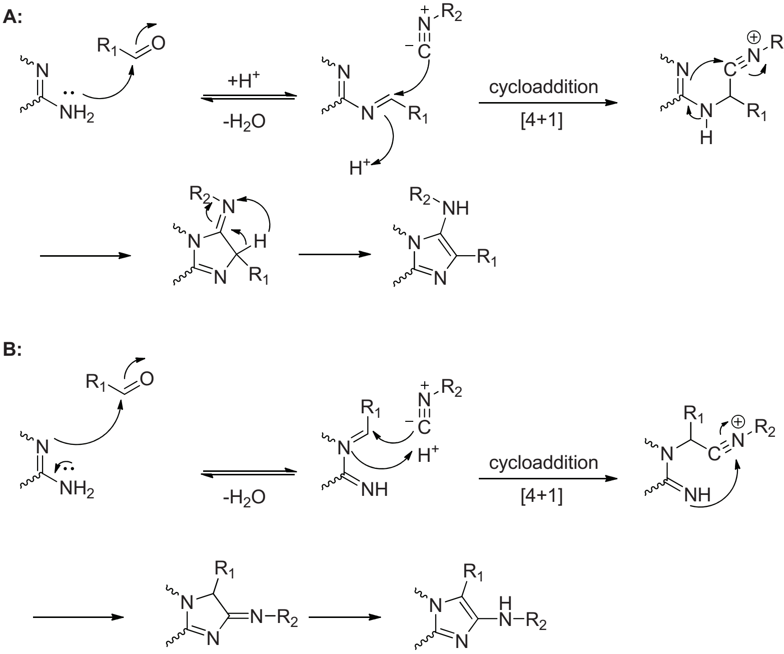
However, some drawbacks of these methods have been reported incluing long reaction times, low yields of the products, harsh reaction conditions, the requirement for an inert atmosphere, tedious workup procedures resulting in the formation of large amounts of toxic metal-containing waste, and the use of stoichiometric or relatively expensive reagents. As a result, the development of new strategies has remained an attractive goal. To overcome these drawbacks, Rostamnia and Hassankhani have developed an Ugi-type method leading to the synthesis of aminoimidazole derivatives in the solvent-free media in the presence of $RuCl_3.3H_2O$ without any ligand or other additives. This solvent-free condensation, employing commercially available $RuCl_3.3H_2O$ is economically affordable concerning the Ru sources and does not require the presence of expensive ligands. The condensation of aldehydes, 2-aminopyridines, and isocyanides has supplied simple one-pot access into the preparation of aminoimidazole derivatives with a green pharmaceutical manner. This method also has the advantage of being carried out in neutral conditions (Rostamnia and Hassankhani, 2013) (Scheme 124).



i= Ru (5 mol%), solvent-free, 40°C.
R= H, Me; **R'**= H, 4-NO_2, 4-Cl, 3-NO_2; **R''**= *t*-Bu, Ph

Scheme 124. $RuCl_3.3H_2O$ Catalyzed solvent-free synthsis of aminoimidazole derivatives.

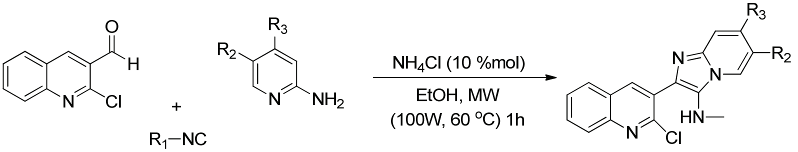
The Groebke-Blackburn-Bienaymé reaction (GBBR) has been used for the one-pot synthesis of therapeutically relevant fused imidazoles bridgehead nitrogen compounds from readily available aldehyde, isocyanide, and amidine building blocks. The reaction is driven by a wide range of catalysts and can be performed either under solvent or solvent-free conditions or under microwave irradiation. The GBBR products can be used for the synthesis of a variety of more complex scaffolds via post-modification reactions involving cyclization and nucleophilic substitution as well as further MCRs. The GBBR reaction has found diverse applications in combinatorial and medicinal chemistry and its products are of great use in drug discovery studies (Blackburn et al., 1998; Bienaymé and Bouzid, 1998; Groebke, Weber and Mehlin, 1998).



Scheme 125. Intramolecular nonconcerted GBB reaction mechanism.

The GBB reaction is thought to progress through an intramolecular incompatible mechanism similar to the Ugi reaction; however, cyclization takes place with the formation of a new ring system, unlike the flexible peptide-like Ugi product. The mechanism contains the in-situ formation of iminium species followed by a non-concerted [4+1] cycloaddition with the isocyanide to give the corresponding fused imidazoles (Hulme and Lee, 2008; Parenty and Song, 2007) (Scheme 125A). It is also known that the reaction with the reagents used (aldehydes, isocyanides, and 2-aminoazine derivatives) is not always easy and some by-products may form in the reaction mixture. In such a situation, the reaction starts from endocyclic nitrogen and the ratio of the two regioisomers depends on the nature of the substrate and the type of catalyst used (Scheme 125B).

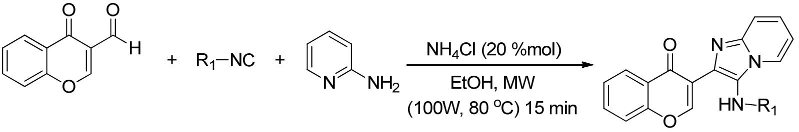
Groebke-Blackburn-Bienaymé-MCR is the most adopted method yielding the imidazo[1,2-a] class of compounds. Hereby, some of the more thematic studies are debated, indicating important developments, and several reaction conditions used such as solvent-free, microwave irradiation, or ultrasonication have been defined to completely understand the versatile character of the GBB-3CR. For instance, Montaño and Lopez have synthesized imidazo[1,2-a]pyridine analogs including quinoline moiety via the MW irradiation method (Ramírez-López and Gámez-Montaño, 2019). 2-Chloro-3-formylquinoline, isocyanides, 2-aminopyridin derivatives, and NH_4Cl (as the catalyst) have been used to obtain target compounds. To optimize the MW conditions, various temperature and reaction times have been performed, and the best condition has been found as 60°C, and 1 h in good-moderate yields (Scheme 126).



R₁ = *t*-Bu, 2,6-diMePh, 4-MeOPh; **R₂** = H, CN; **R₃** = H, AcOMe

Scheme 126. Synthesis of 2-chloroquinoline imidazol[1,2-a]pyridine derivatives.

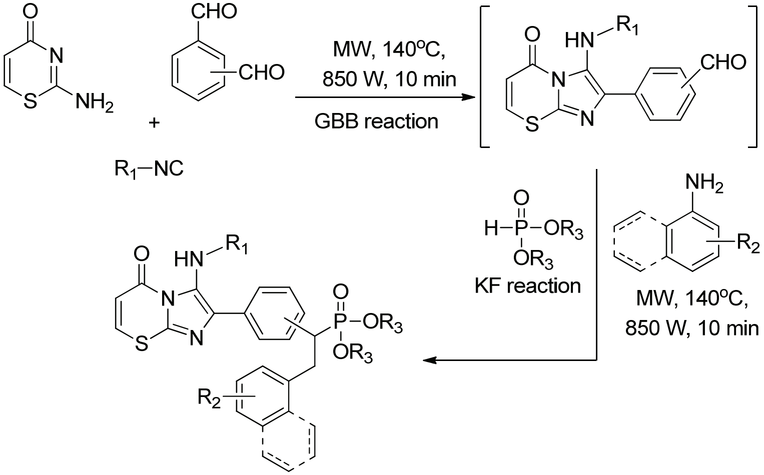
Montaño and coworkers have synthesized imidazo[1,2-a]pyridine-chromone derivatives with the above approach by changing only the aldehyde source (Gámez-Montaño et al., 2020). Unlike the above reaction, the reaction time and temperature have been changed to optimize the conditions (Scheme 127).



R₁= *t*-Bu, Ph, Bn, 4-MeOPh, 3,4-diOMePh

Scheme 127. Synthesis of imidazo[1,2-a]pyridine-chromone derivatives under MW conditions.

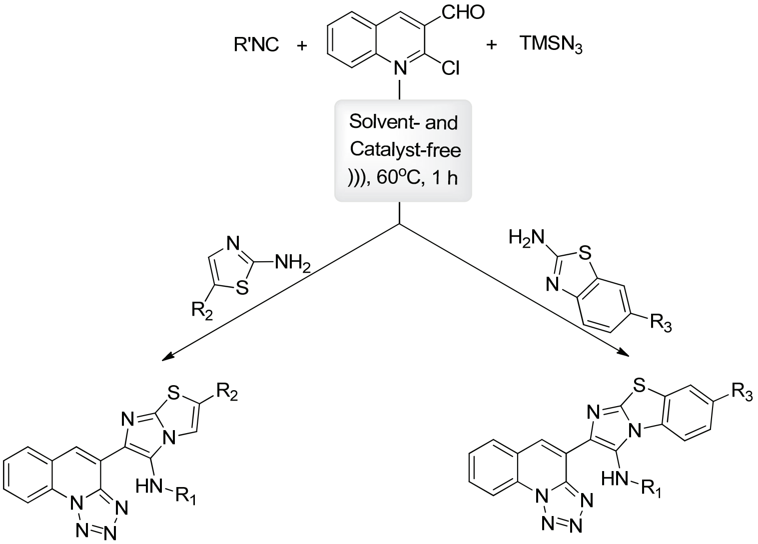
In another study, Sharma's group have reported an efficient catalyst-free, domino four-component strategy for the efficient construction of highly functionalized imidazo[2,1-b][1,3]thiazin-5-ones under catalyst- and solvent-free microwave irradiation conditions (Kaur, Saha, Singh, Singh et al., 2016). Interestingly, it has been figured out that the use of dialdehydes such as terephthalaldehyde and isophthalaldehyde resulted in the products with the retained aldehydic component. This result allowed two sequential multicomponent reactions to be carried out in one pot from the unreacted carbonyl end of the aldehyde used. Thus, bis-heterocyclic imidazo-thiazinyl-α-aminophosphonate scaffolds have been obtained using amines and dialkyl/arylphosphites via Kabachnik Field's (KF) reaction (Scheme 128).



R$_1$= *t*-Bu, 2,6-diMeC_6H_3, 1,1,3,3-tetramethylbutyl; **R**$_2$= Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4, 2-IC_6H_4, 4-AcC_6H_4, naphtyl; **R**$_3$= OET, OMe, OBn, *i*-Pr.

Scheme 128. Synthesis of dialkyl/aryl-((4-(3-alkylamino)-5-oxo-5*H*-imidazo[2,1-b][1,3]thiazin-2-yl) phenyl (alkylamino)phosphonates via one-pot 5-component reaction under solvent- and catalyst-free microwave conditions.

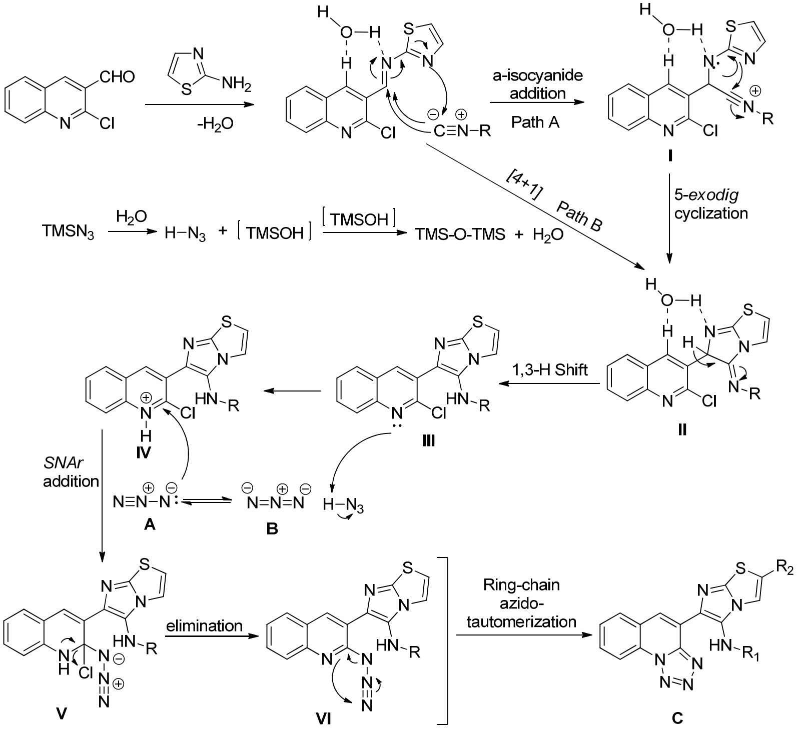
The synthesis of bound-type bis-heterocycles containing imidazo[2,1-b]thiazole or benzo[d]imidazo[2,1-b]-thiazole scaffolds and their analogs coupled with a complex heterocyclic substituent at the C-3 position of the imidazole ring was first performed by Catalan and coworkers under green conditions via solvent- and catalyst-free GBBR assisted by ultrasound irradiation (USI) (Claudio-Catalan, Pharande, Quezada-Soto, Kishore et al., 2018). Contrary to all previously reported multicomponent reaction processes yielding fused tetrazolo[1,5-a]quinolines analogs, this strategy is the first where the tetrazole ring has been formed in situ via the GBBR under green conditions. Further, the high complexity of the substituent at the C-3 position of the quinoline ring has been explained to have resulted from the functionalization of the aldehyde. Imidazo or benzo[d]imidazo[2,1-b]thiazoles and 1,5-DsT with quinoline moiety have been synthesized under solvent- and catalyst-free conditions via the strategy one-pot GBBR/post-transformation (Scheme 129).



R$_1$= cyclohex; *t*-Bu, C_6H_4Et, 4-$MeOC_6H_4$, **R$_2$**= H, CN; **R$_3$**= H, F

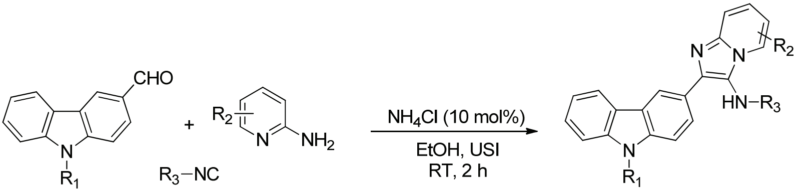
Scheme 129. Synthesis of tetrazolo[1,5-*a*]quinoline derivatives with ecofriendly methods.

It is seen that the GBBR mechanism begins with the reaction of 2-amino-thiazole with the aldehyde to generate an imine, which may follow two possible steps to yield the expected GBBR compound. It emphasizes the major role of the acidic proton at the C-4 position of the quinoline ring and the condensed water in the stabilization of imine, letting the α-isocyanide addition to form nitrilium intermediate **I**. This subsequently undergoes 5-exodig cyclization to give precursor **II**, followed by a spontaneous 1,3-hydride shift to give the GBBR product **III**. Next, HN_3 protonates the nitrogen of quinoline GBB compound **III** to generate iminium ion **IV** which undergoes S_NAr addition by the azide anion B to generate intermediate **V**. The later elimination of chloride ion in **V** occurs to form precursor **VI**, in which the azide group undergoes ring-chain azido-tautomerization to provide the tetrazolo[1,5-a]quinoline σ-bound with the imidazo[2,1-b]thiazole structure **C** (Scheme 130).



Scheme 130. Plausible One-Pot GBBR/SNAr/Ring-Chain Azido-Tautomerization Mechanism.

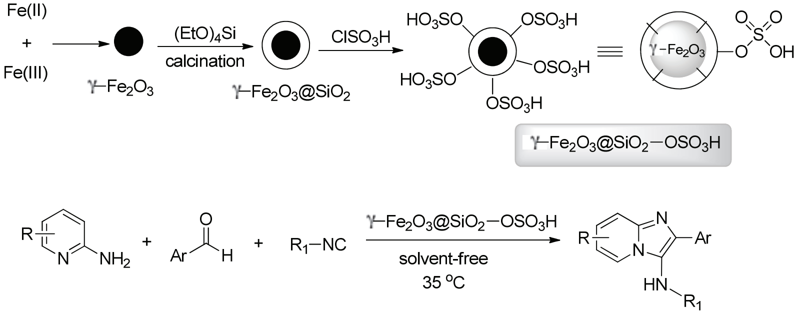
In another ultrasound-assisted study, bis-heterocyclic carbazolyl imidazo[1,2-*a*]pyridine derivatives have been synthesized (Kurva, Pharande, Quezada-Soto and Gámez-Montaño, 2018). This novel, potent and mild method has properties such as being a green, inexpensive and easily available catalyst, and solvent at room temperature (Scheme 131).



R₁= C_8H_{17}, C_3H_7; **R₂**= H, 7-Me, 8-Cl, 6-BnO, 9-Br, 8-CN; **R₃**= cyclohex, *t*-Bu, 4-$MeOC_6H_4$

Scheme 131. Synthesis of 3-amino fused imidazo[1,2-a]pyridines *bis*-heterocycles via green GBBR.

Magnetic nanoparticles, which have practical applications in many fields, are also frequently used in the synthesis of organic compounds. They are promising catalysts due to their advantages such as ease of use and easy separation. With this approach, Rostamnia and coworkers have used nanomagnetically modified sulfuric acid (γ-Fe_2O_3@SiO_2-OSO_3H) which is an efficient, fast, and reusable green catalyst to synthesize imidazo[2,1-*b*]thiazole derivatives via the Ugi-like GBB three-component reaction under solvent-free conditions (Rostamnia, Lamei, Mohammadquli, Sheykhan et al., 2012) (Scheme 132).

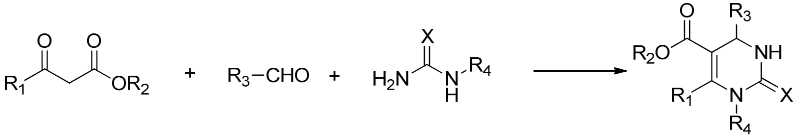


Scheme 132. One-pot synthesis of imidazo[1,2-a]pyridines with a green catalyst via the Ugi-like GBB three-component reaction under solvent-free conditions.

2.3. (Thio)urea or NH_3 Based Multicomponent Reactions

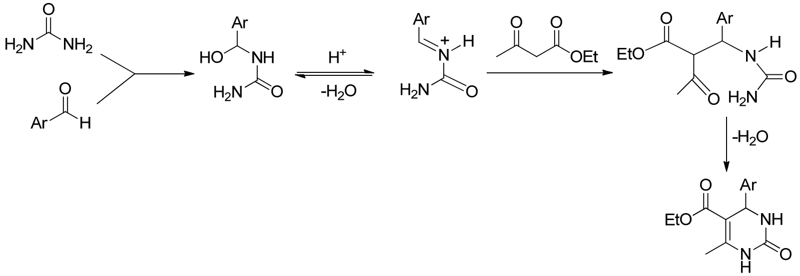
2.3.1. Biginelli Reaction

The Biginelli reaction has been described as an acid-catalyzed three-component reaction of an aldehyde, a *ß*-ketoester, and urea leading to the formation of dihydropyrimidones, which have been considered as useful tools with potential pharmacological activities. These reactions are convergent, where three or more starting compounds are combined to yield a single product, and basically all or most of the atoms are included in the product structure. As is well known, MCRs are efficient procedures by themselves, due to their important advantages in comparison to the conventional synthetic procedures that generally require more than one step and consecutive purification processes. On the other hand, solvent-free reactions provide a green process free of hazardous organic solvents with lower toxicity levels. Combining these two techniques in one process or even combined with other green techniques such as MW, US, etc., constitutes a much better approach to sustainability (Portilla-Zuñiga, Sathicq, Martínez, Fernandes et al., 2018) (Scheme 133).



Scheme 133. Biginelli reaction of *ß*-ketocarboxylic esters, aldehydes, and urea derivatives.

The reaction begins via the condensation between an aldehyde and urea, with some similarities to the Mannich reaction. The formed iminium intermediate acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to yield the cyclized product (Bose, Manhas, Pednekar, Ganguly et al., 2005; Vdovina and Mamedov, 2008; Bose, Sudharshan and Chavhan, 2005; Kappe, 1993).

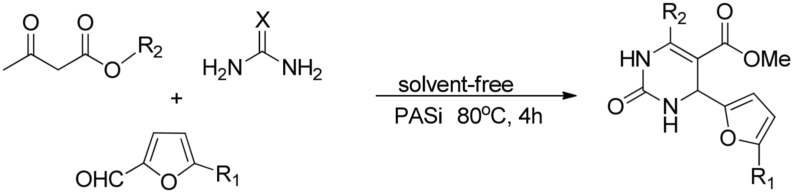


Scheme 134. The mechanism of Biginelli reaction suggested by Kappe.

According to Scheme 134, the rate determining the nucleophilic addition of urea to aldehyde initiates the reaction. The ensuing acid catalyzed condensation generates the imine compound. Then, the *β*-ketoester joins to the imine bond and the ring closure takes place by the nucleophilic attack of amine onto the carbonyl group. This final step ensures a second condensation and gives the Biginelli compound.

This reaction is originally catalyzed by mineral acids in protic solvents such as ethanol and water or aprotic solvents such as dioxane, tetrahydrofuran, or acetonitrile. In some cases, acetic acid is needed. Various starting compounds have been used for the reaction, including different types of esters and 3-oxoalkanoic thioesters, tertiary acetamides, protected thioureas, monosubstituted alkyl ureas, and guanidines. In the case of aldehydes, the reaction takes place with difficulty in the presence of aliphatic aldehydes, while aromatic aldehydes work in this reaction. On the other hand, the aldehydes containing thiophene, furan, and pyridine nuclei generate DHPMs with tolerable yields (Quan, Da, Zhang and Wang, 2009; Fazaeli, Tangestaninejad, Aliyan and Moghadam et al., 2006; Jauk, Pernat and Kappe, 2000; Nair, 2005; Yu, Liu, Liu, Jiang et al., 2007; Nadaraj, Thamarai, Abirami and Thangadurai, 2014).

A wide range of industrial compounds can be produced using furfural, such as furfurylamine, furfuryl alcohol, and its tetrahydro derivatives furanacrylic acid and furoic acid, tetrahydro furan, and furan itself (Subbiah, Simeonov, Esperança, Rebelo et al., 2013). Furfural is also used as a starting material for the synthesis of DHPMs (Joseph, Jain and Sain, 2006) which have a pyrimidine unit and are one of the major pharmacophores in medicinal chemistry. Most synthetic procedures leading to the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones and thiones (Kadre, Jetti, Bhatewara, Paliwal et al., 2006) require the presence of protic acid, Lewis acid, or ionic liquid as the catalyst. A procedure for the synthesis of DHP derivatives via a Biginelli reaction has been reported by Zuniga et al. The reaction has been performed using ethyl or methyl acetoacetate, furfural derivatives and urea or thiourea under solvent-free conditions in the presence of Preyssler heteropolyacids encapsulated in silica frameworks, with PASi ($PCSiO_2$) as a solid catalyst. This reaction has been performed under microwave irradiation or traditional heating (Portilla-Zuñiga, Sathicq, Martínez, Fernandes et al., 2018) (Scheme 135).



R_1= H, CH_2OH, NO_2; **R_2**= Me, Et

Scheme 135. Reaction and conditions for the Biginelli reaction.

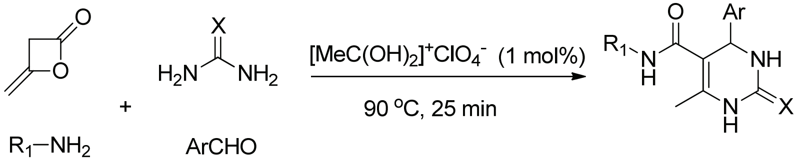
Historically, the MCR to emerge as a beneficial and powerful strategy to establish significant complex structures from simple and readily available materials is the Biginelli reaction, which was discovered in 1893 by an Italian chemist, Pietro Biginelli. The initial procedure of this reaction to get dihydropyrimidinones has been carried out in an acidic alcoholic solution via heating a mixture consisting of three components at reflux temperature.

The great effort of academic and industrial laboratories to discover improved and powerful conditions for the Biginelli reaction has facilitated the overcoming of most of the problems in the synthesis of dihydropyrimidin-2-ones (DHPMs). Since the discovery of this reaction, a number of improved catalytic systems have been developed, such as metal Lewis acids, Brønsted acids or bases, heterogeneous catalysts and organocatalysts.

Aryl substituted 3,4-dihydropyrimidin-2-one (DHPMs) derivatives have received great attention in recent years because of their enormous application in the Medicinal chemistry field. They also exhibit a wide range of biological activities and have been used extensively in the pharmaceutical industry as antihypertensive, α-antagonist, antiviral, antibacterial, anti-inflammatory, antitumor, and anti-HIV agents as well as calcium channel blockers (Shobha, Chari, Mano, Selvan et al., 2009).

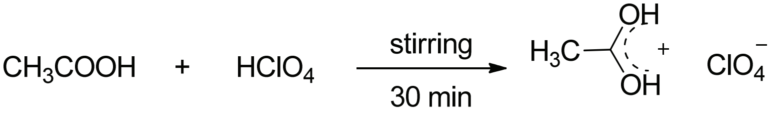
Recently, several synthetic methodologies yielding DHPMs have been developed to modify and improve this reaction. These approaches involve the application of ultrasound or microwave irradiation, and the use of various Brønsted acids, Lewis acids, organocatalysts or ionic liquids in solvent-free conditions. The search for new and efficient procedures involving the use of easily accessible and reusable catalysts has still been pursued and remarkable advances have been achieved in this field. However, more efforts have been required to make the reaction efficient, environmentally benign and substrate compatible. The two main issues that needed to be addressed have been declared. (1) Most of the reported Biginelli reactions have focused of the aromatic aldehydes. In the case of aliphatic aldehydes, the product yields are much lower than those from aromatic aldehydes; (2) most of the reported methods have been conducted in organic solvents and/or employed metal-based catalysts, which causes product and environmental pollution. Therefore, further improvements targeting the improvement of the Biginelli-type condensation conditions are highly needed. Wang and coworkers have described a Biginelli-type condensation for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones where several aliphatic and aromatic aldehydes have been used under optimized conditions. The obtained results have shown that the Biginelli reaction of aliphatic aldehydes proceeded smoothly to yield the desired products, 3,4-dihydropyrimidin-2-(1*H*)-ones, in good to excellent yields within 60 minutes. The employment of methyl acetoacetate and acetylacetone instead of ethyl acetoacetate has also afforded the formation of the desired compounds in high yields. In this study, the use of thiourea has afforded the corresponding thio derivatives of dihydropyrimidinones, which are also of interest owing to their therapeutic properties. In addition, aromatic aldehydes having different functional groups have displayed excellent reactivity towards the reaction, supplying better yields in less reaction time. Moreover, the advantages of this procedure are not only to preserve the simplicity of the Biginelli reaction but also to provide good yields of the product with high purity (Wang, Zhou, Chen and He, 2012).

Wang and coworkers have extended this protocol to the synthesis of 5-unsubstituted 3,4-dihydropyrimidinones via Biginelli-type condensation under the optimized conditions. A variety of functional groups have demonstrated good compatibilities and the reaction of acetophenone, aldehydes, and (thio)urea has rapidly proceeded within 20 minutes affording the desired products with good to excellent yields. Finally, taking into account also their biological activities, the authors have performed the synthesis of 5-carboxamide substituted 3,4-dihydropyrimidine-2(1*H*)one derivatives in good yields via a four-component Biginelli-type reaction taking place between diketene, amine, (thio)urea, and aromatic aldehyde in the presence of $[MeC(OH)_2]^+ClO_4^-$ as the catalyst (Scheme 136).

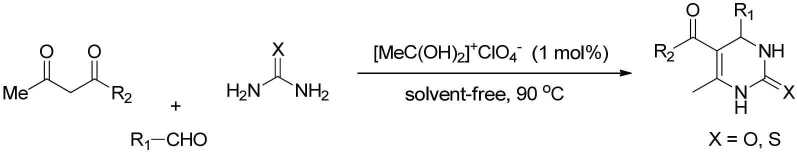


R₁= Bn, allyl; **Ar** = 4-ClC_6H_4, 4-BrC_6H_4, Ph; **X** = O, S

Scheme 136. Synthesis of dihydropyrimidine-5-carboxamides via four-component reaction.

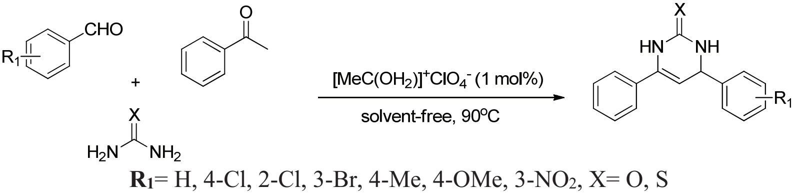


Scheme 137. Preparation of super acidic ionic liquid.



R₁= H, ethyl, propyl, izopropyl, *n*-hexyl, cyclohexyl, *n*-heptyl, phenyl, 4-methoxyphenyl, 4-chlorophenyl; **R₂**= OEt, OMe, Me; **X**= O, S.

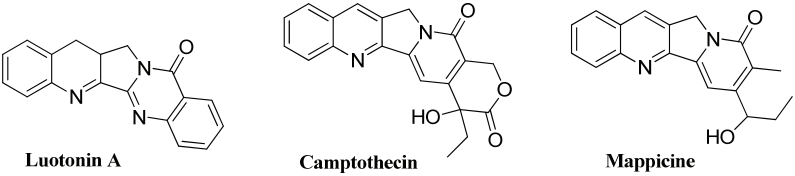
Scheme 138. Super acidic ionic liquid catalysed the Biginelli-type reactions under solvent-free conditions.



R₁= H, 4-Cl, 2-Cl, 3-Br, 4-Me, 4-OMe, 3-NO_2, X= O, S

Scheme 139. Synthesis of 5-unsubstituted 3,4-dihydropyrimidinone using $[MeC(OH)_2]^+ClO_4^-$.

Quinazolinone core consists of two fused rings and exhibit a variety of biological activities (Mohamadpour, 2021) (Fig 10).

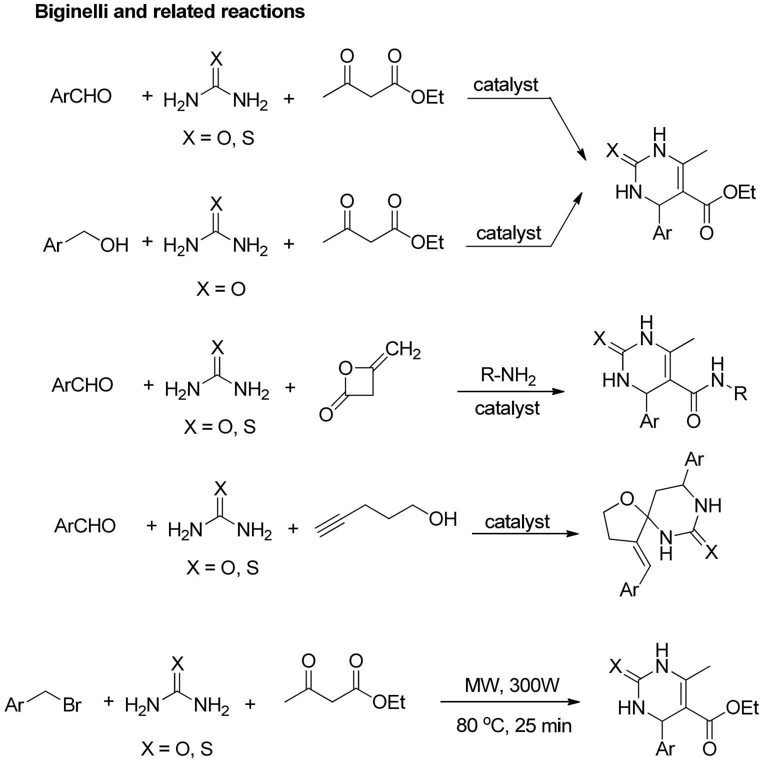


Luotonin A **Camptothecin** **Mappicine**

Figure 10. Medicinally important compounds involving a nitrogen-ring linkage.

The dihydropyrimidone nucleus also constitutes a key structural unit of some natural alkaloids such as Betzallidine A and B, which inhibit the binding of HIV GP-120 to CD4 cells. Their diverse therapeutic applications have made DHPMs the center of attention and have stimulated synthetic and medicinal organic chemists to develop more efficient methodologies giving these compounds (Malik, Dangroo and Ara, 2020). Some serious drawbacks such as lower yields (20–60%) and longer reaction time (24–36 h) have been reported for the traditional approach consisting of an HCl-catalyzed three-component cyclocondensation reaction. The important therapeutical values of this privileged scaffold have led to a great interest in the minds of organic chemists. This has caused the development of synthetic approaches with a variety of catalysts (Bahekar, Sarode, Wadekar and Chandak, 2017).

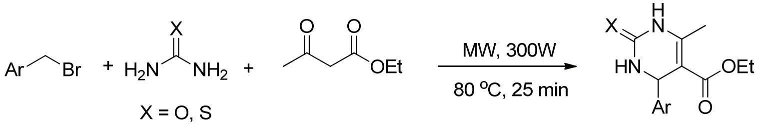
Among these methods, Biginelli and related reactions involving the condensation of (thio) urea, an aldehyde, and an enolizable carbonyl compound offer several powerful strategies leading to the formation of DHMP derivatives (Malik, Dangroo and Ara, 2020) (Scheme 140).



Scheme 140. Synthesis of dihydropyrimidones.

Several non-conventional techniques involving the use of ultrasound, microwave, high pressure, and mechanochemistry have also been employed to develop efficient and green synthetic strategies yielding DPHMs. In these methods, the scope of the Biginelli reaction is limited only by the aldehyde substrate. Great efforts have been dedicated to broadening the substrate scope to access new and more beneficial DHMPs with therapeutic significance. Although the developed methods are efficient, most of them require the presence of expensive catalysts, prolonged reaction time, and tiresome work-up procedures, and column purification, which reduces the yield, ultimately. Therefore, the development of the new Biginelli reaction employing a new carbonyl component and proceeding under milder conditions is highly desirable to access DHMPs.

Considering their biological significance, Dangroo and coworkers have developed a new and straightforward approach for the synthesis of dihydropyrimidone derivatives through sequential Kornblum oxidation followed by Biginelli reaction (Malik, Dangroo and Ara, 2020) (Scheme 141).



Ar= Ph, 4-BrPh, 3-BrPh, 3-HOPh, 4-HOPh, 4-FPh, 3-FPh, 2-CNPh, 3-NO_2Ph, 4-NO_2Ph, 2-ClPh, 2-MePh, 4-IPh, 2-FPh, 3-MePh, pyridine-2-yl, pyrrol-2-yl

Scheme 141. MW irradiated synthesis of dihydropyrimidone derivatives through sequential Kornblum oxidation and Biginelli reaction.

The protocol involves consecutive in situ oxidation and cyclocondensation starting from benzyl halides in a one-pot tandem manner under catalyst-free and base-free microwave irradiated conditions. Thus, this method enlarges the applicability of the Biginelli condensation via not limiting one of the components being an aldehyde. Furthermore, this approach has a broad substrate scope and submits the opportunity to access dihydropyrimidones under mild conditions with good yields. The recrystallization technique implemented for the purification of the products synthesized in this study eliminates the use of column chromatography requiring large quantities of volatile and toxic organic solvents, usually (Malik, Dangroo and Ara, 2020).

Luotonin A is a quinazoline based ring system consisting of five fused rings and is used as a drug for the treatment of abscesses, inflammation, and rheumatism (Mohamadpour, 2021). Similarly, 1,2,4-triazole compounds also display various biological properties such as antifungal, antihypertensive, anticholinergic, analgesic, diuretic, anti-inflammatory, antitumor, and antibacterial activities. The 1,2,4-triazole core takes part in the structures of numerous functionalized molecules having various applications in material science and medicinal chemistry and as an organocatalyst. This scaffold constitutes the building blocks of some drugs such as alprazolam, fluconazole, triazolam, rizatriptan, etc (Mohamadpour, 2021; Chaudhary and Tupe, 2013; Nikalje, Ghodke, Khan and Sangshetti, 2015; Nimbalkar, Tupe, Vazquez, Khan et al., 2016) (Fig 11).

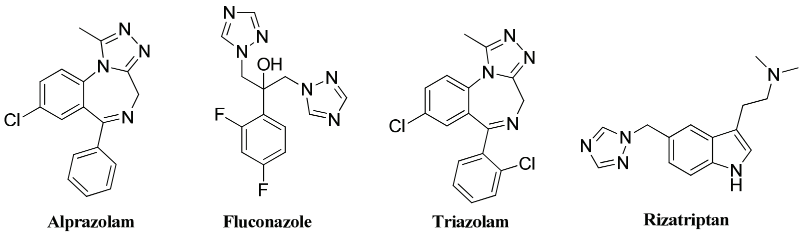
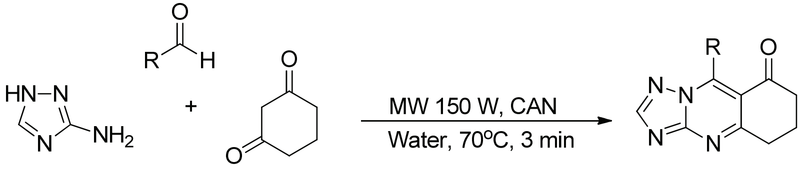


Figure 11. The structures of some 1,2,4-triazole containing drugs.

With the aim to combine these scaffolds, both of which have individually promising bioactivities, Sompalle and Roopan have synthesized a triazolo-quinazolinone hybrid via the one-pot multicomponent strategy under MW irradiated conditions in the presence of ceric ammonium nitrate (CAN) as catalyst (Scheme 142). The most common method giving these hybrids contains the condensation of substituted aldehyde and 3-amino-1,2,4-triazole with cyclic β-diketone in the presence of different catalysts before an oxidation step using various oxidizing agents in several solvents. Although various other processes affording these hybrid compounds containing 1,2,4-triazole and quinazoline units together have been reported, most of these suffer from several disadvantages such as the use of organic solvents, the requirement of multiple steps, tiresome experimental protocols, prolonged reaction times, expensive catalysts, and inadequate yields. Hence, literature data shows that an environmentally benign method for the synthesis of these compounds has not been developed before the study of Sompalle and Roopan (Sompalle and Roopan, 2016).

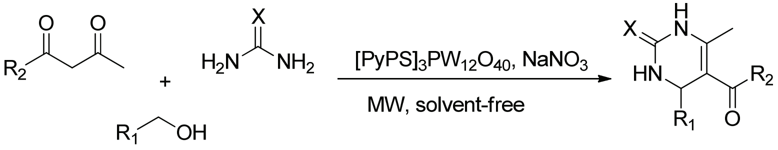


R= C_6H_5, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-*i*-proC_6H_4, 4-MeC_6H_4, 3,4-diMeOC_6H_3, 2,4-diMeOC_6H_4, 4-MeOC_6H_4, 3-MeOC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4

Scheme 142. CAN catalyzed synthesis of 9-aryl-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5*H*)-ones.

Recently, the employment of microwave-enhanced protocols and/or solvent-free systems catalyzed by inorganic acidic catalysts from strong Lewis acids to mild Bronsted acids for the synthesis of DHPMs have made the Biginelli reaction one of the most attractive and most studied areas. Today, most of the multi-step procedures lack the conceptual and experimental convenience of the one-pot Biginelli reaction. Therefore, none of these methods has great importance and cannot compete with the Biginelli condensation (Shumaila and Al-Thulaia, 2019).

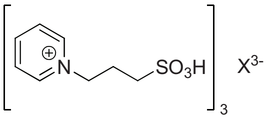
In one of the studies into the development of sustainable and beneficial synthetic procedures, Fu and coworkers have reported efficient and environmentally benign tandem oxidation processes (TOPs) for the Biginelli reaction, including the oxidation of alcohols and the following trapping of carbonyl intermediates with suitable nucleophiles in a one-pot operation. This condensation starting directly from alcohols has been carried out under MW and solvent-free conditions using heteropolyanion-based ionic liquids (HPAILs) as catalysts and $NaNO_3$ as an oxidant (Scheme 143). This methodology has provided compatibility with various functional groups and resulted in moderate to excellent yields to generate DHPMs in a two-step one-pot process. Short reaction times and reusability of the catalysts have been highlighted as the main advantages of this procedure (Fu, Yang, Ma, Sun et al., 2017).



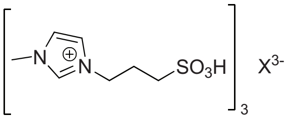
R₁= Ph, 4-OMeC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-OHC_6H_4, 2-OHC_6H_4, 2-furyl, *n*-C_6H_{13}, *i*-Pr; **R₂**= OEt, OMe, X= S, O.

Scheme 143. Tandem oxidation process (TOP) for the Biginelli reaction starting directly from alcohols.

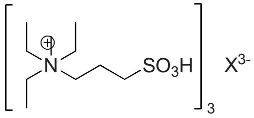
Heteropolyanions-based ILs (HPAILs) used in oxidation processes have been presented in Figure 12.



X= PW12O40, 1-(3-Sulfopropyl)pyridinium phosphotungstate ([PyPS]3PW12O40);
X= PMo12O40, 1-(3-Sulfopropyl)pyridinium phosphomolybdate ([PyPS]3PMo12O40);



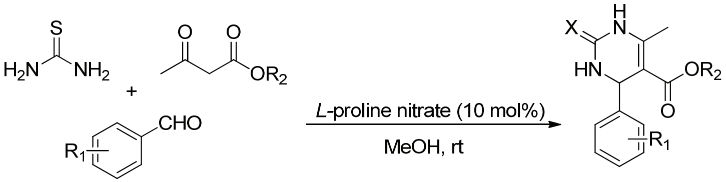
X= PW12O40, 1-methyl-3-(3-Sulfopropyl)imidazolium phosphotungstate ([MlMPS]3PW12O40);
X= PMo12O40, 1-Methyl-3--(3-Sulfopropyl)imidazolium phosphomolybdate ([PyPS]3PMo12O40);



X= PW12O40, Triethyl-(3-Sulfopropyl) aminium phosphotungstate ([TEAPS]3PW12O40);
X= PMo12O40, Triethyl-(3-Sulfopropyl)imidazolium phosphomolybdate ([TEAPS]3PMo12O40);

Figure 12. *N*-Substituted imidazole, pyridine and triethylamine based heteropolyanion-based ionic liquids (HPAILs).

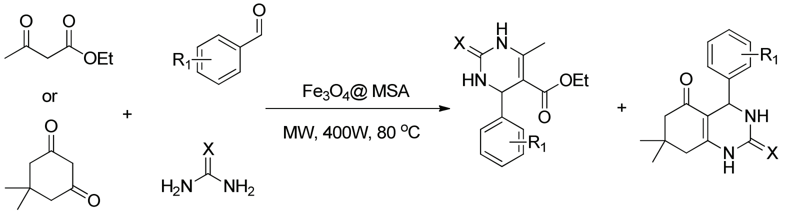
Considering the role of L-proline in enamine and amine catalysis, Chandak and coworkers have reported a simple, efficient, and recyclable procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones. They have used L-proline nitrate as a non-volatile, non-toxic, operationally simple, thermally stable (low melting temperature and high decomposition temperature), and recyclable catalyst. Another additional green aspect of the methodology has been explained as avoiding an aqueous workup leading to large amounts of water expenditure. The successful combination of eco-friendly solvents and catalysts is considered fascinating and is likely to open the gateway for the development of new green reaction strategies for other basic organic transformations (Bahekar, Sarode, Wadekar and Chandak, 2017) (Scheme 144).



R$_1$= C_6H_5, 4-$OMeC_6H_4$, 4-ClC_6H_4, $(CH_3)_2NC_6H_4$, 3,4,5-tri$OMeC_6H_2$, $(CH_3)_2CHC_6H_4$, 4-MeC_6H_4, 3-ClC_6H_4, 2-$NO_2C_6H_4$, 4-OHC_6H_4, **R$_2$**= OEt, OMe; **X**= O, S.

Scheme 144. L-Proline nitrate mediated synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones.

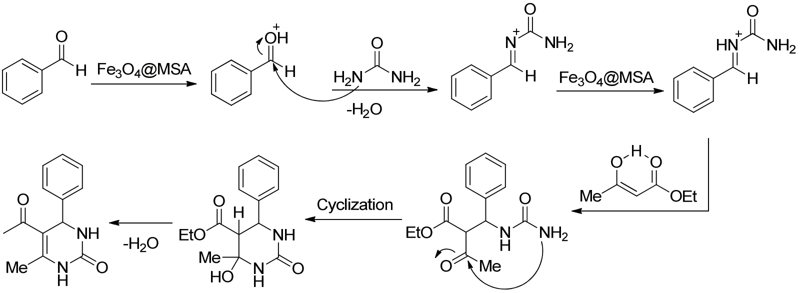
The development of acid systems using clean, inexpensive, commercially available, and environmentally benign catalysts has remained a challenge in organic syntheses. Moradi and Tadayon have prepared Fe_3O_4@meglumine sulfonic acid (Fe_3O_4@MSA) as a highly efficient, new, and green solid acid catalyst and used it for the synthesis of 3,4-DHPs under MW irradiation (Scheme 145, Scheme 146). Although some reactions employing Nano Fe_3O_4-supported sulfonic acid catalyst under solvent-free conventional heating conditions have been reported, this approach has supplied faster reaction conditions with an excellent yield of products under microwave irradiation. Besides, in comparison with other solid acid catalysts, high-performance reusable solid acid nanocatalyst with a high percentage of sulfonic acid groups has provided a green strategy for Biginelli condensation owing to the special structure of meglumine, which is an amino sugar derived from glucose. The noticeable advantages of this method performed in water-ethanol (being relatively green solvents) are the easy workup procedure, the reusability of the catalyst used in minimized quantities in the reaction media, the good to high yields ranging from 72-98%, and most importantly, the reaction times taking 40-60 seconds (Moradi and Tadayon, 2018).



MSA: Meglumine sulfonic acid

R₁= 4-Cl, 2,4-diCl, 4-OMe, 4-OH, 4-Me, 2-thiophenyl, 2-Me, 3-NO_2, H, 4-NO_2;
X= O, S

Scheme 145. Synthesis of 3,4-DHPs using Fe_3O_4@MSA.



Scheme 146. Plausible mechanism for the Biginelli reaction in the presence of Fe_3O_4@MSA.

The use of heterocyclic building blocks instead of urea in the Biginelli condensation makes this reaction more exhaustive leading to the formation of more complex products. In the Biginelli reaction, where 3-amino-1,2,4-triazole have been used as a 1,3-binucleophile, 4,7-dihydro-1,2,4-triazolo[1,5-a]-pyrimidines have been obtained as the main products under harsh reaction conditions. A Biginelli-type condensation employing both 3-amino-1,2,4-triazoles and salicylic aldehydes has displayed different reaction pathways depending on the structure of the third substrate and the applied reaction conditions. However, the altering of the conditions and different substituents on substrates can turn the progress of the reaction into the formation of other product types, which form as side reaction products or intermediates during the formation of compound **2** (Figure 13).

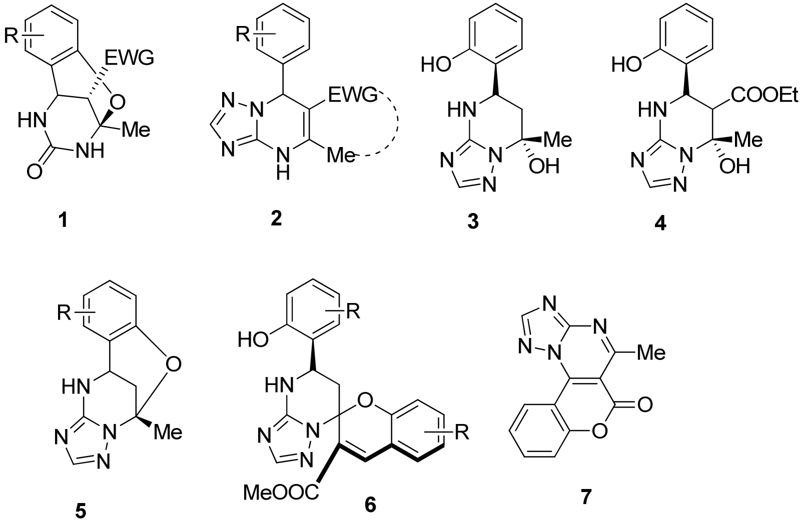
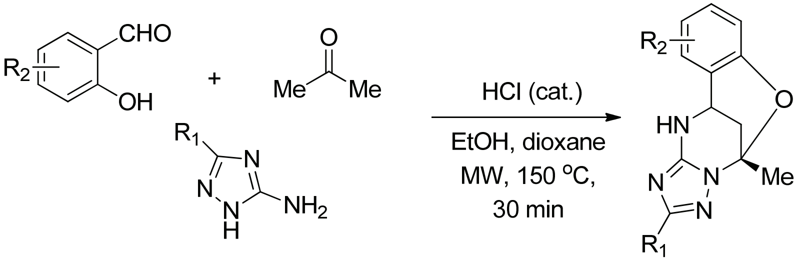


Figure 13. Different reaction products of modified Biginelli reactions using salicylic aldehydes and 3-amino-1,2,4-triazole as unconventional building blocks. Relative configuration of the stereogenic centers is shown.

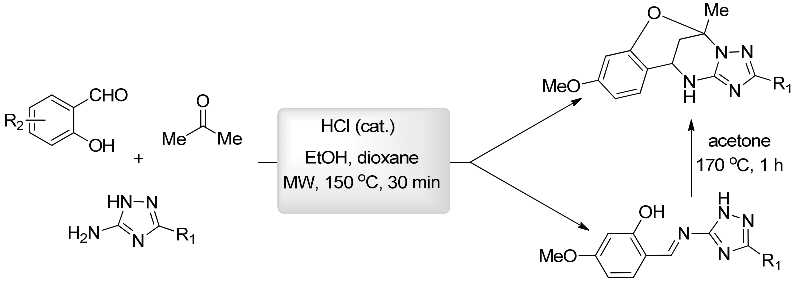
Interestingly, the formation of type **3** products in the presence of substrates without the o-hydroxy group on the aromatic ring takes place in acetone and requires a much higher temperature under MW irradiation giving moderate yields in the presence of TsOH. The type of compound **5** containing a tetrahydropyrane nucleus has been obtained by MW heating at 150°C for 30 min in acidic media. The spiro compounds (**6**) have been obtained as the main product by heating for 20h accompanied by 3-acetylcoumarin as a by-product.

In a modified Biginelli reaction, Gümüş et al. have designed a strategy containing one-pot three-component condensation of 5-substituted 3-amino-1,2,4-triazoles, salicylic aldehydes, and acetone under microwave irradiated conditions giving methano[1,2,4]triazolo[1,5-c][1,3,5]-benzoxadiazocine derivatives (Gümüş, Gorobets, Sedash, Chebanov et al., 2017) (Scheme 147, Scheme 148).



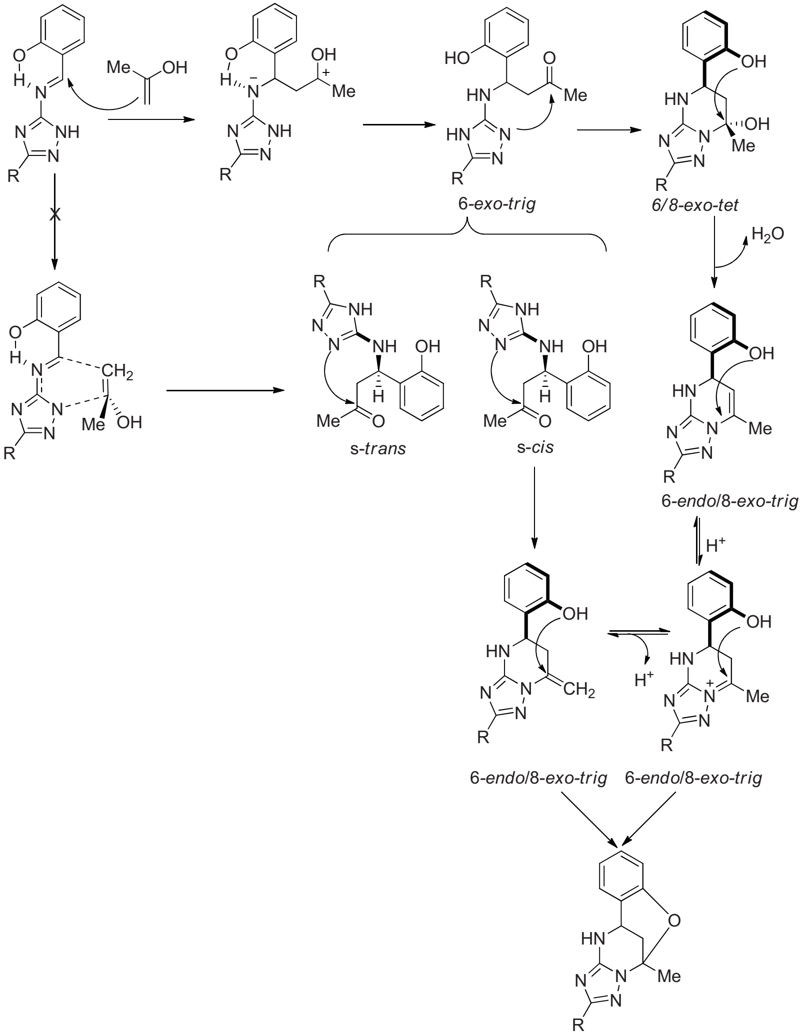
R₁= Me, n-C_5H_{11}, Ph, 2-Py, 3-Py, 4-Py; **R₂** = H, 3-OMe, 3-OEt, 4-OMe, 5-Br.

Scheme 147. The synthetic pathway for one-pot three-component condensation of 5-substituted 3-amino-1,2,4-triazoles, salicylic aldehydes, and acetone under microwave irradiated conditions.



R₁ = 2-Py, 3-Py, 4-Py

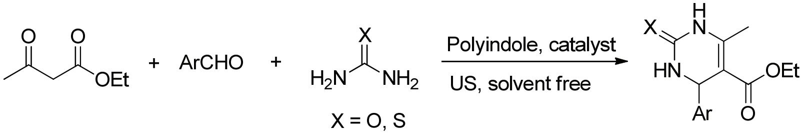
Scheme 148. MW irradiated synthesis of methano[1,2,4]triazolo[1,5-c][1,3,5]-benzoxadiazocine derivatives.



Scheme 149. The proposed reaction mechanism.

The proposed reaction mechanism contains the formation of imine compounds between salicylic aldehydes and 3-amino-1,2,4-triazoles followed by the further reaction with the enol form of acetone to form the tetrahydropyrimidines yielding benzoxadiazocine derivatives.

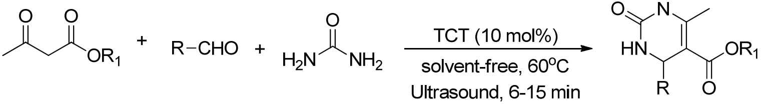
Another green methodology yielding some new dihydropyrimidinones performed in the presence of solid heterogeneous polyindole catalyst under solvent-free ultrasound radiation conditions (Scheme 150) has been reported by Handore's group. The synergistic effect of the polyindole catalyst, which was easily synthesized by the reaction of the indole monomer with copper (II) chloride in the aqueous phase, with ultrasonic irradiation has provided an ambidextrous and straightforward approach for the synthesis of various DHPM derivatives. As a result, the combination of ultrasonic conditions with a polyindole catalyst, which can be easily isolated by filtration and reused up to four cycles without significant loss in catalytic activity, has made this procedure environmentally and economically acceptable (Handore, Chabukswar, Pawar and Dallavalle, 2021).



Ar: Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, CH=CHC_6H_4, $(Me)_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-thyenyl, 4-OHC_6H_4, 3(OH)4(MeO) 4-ClC_6H_3

Scheme 150. Synthesis of DHPM using polyindole as a catalyst.

2,4,6-Trichloro-1,3,5-triazine (TCT) has been regarded as a low toxic, inexpensive, and less corrosive substance with potential uses in synthetic organic chemistry over various organic solvent-mediated Lewis acid catalytic systems. Lalitha and coworkers have described an efficient and appropriate method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a one-pot, solvent-free manner in the presence of TCT as an HCl source under ultrasonic irradiation (Scheme 151).

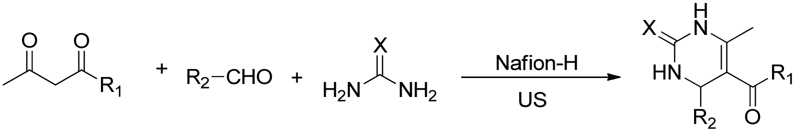


R= Ph, 2-F-4-BrC_6H_4, 3-Me-4-FC_6H_4, 3-Br-4-FC_6H_4, 1-naphtyl, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-$ClOC_6H_4$, 2,4-di$MeOC_6H_3$, 2-OH-4-$MeOC_6H_3$; **R_1**= Et, Bn

Scheme 151. TCT Catalyzed synthesis of DHPM under solvent-free, US irradiated conditions.

The reported reaction has worked well in the presence of 10 mol% TCT as an effective catalyst acting as an HCl source. An extensive range of functional group tolerance, good yield of products, and absence of any organic solvents have made this strategy economically and environmentally appropriate (Ramesh, Ramesh, Malecki and Lalitha, 2019).

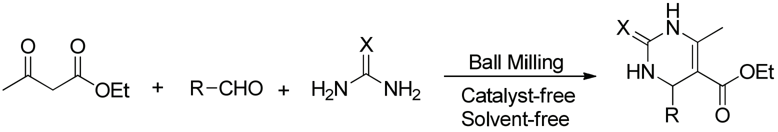
Taking into account the synergistic activation effect of the combination of ultrasound irradiation and solvent-free conditions, Wang and Pei have designed an efficient one-pot procedure for the synthesis of dihydropyrimidinones or thiones in the presence of perfluorinated resin sulfonic acid (Nafion-H) under ultrasound mediated solvent-free conditions. Nafion-H is an insoluble resin catalyst being inert to corrosive environments, stable up to 201°C, and easy to recover and reuse. In this study, the products have been obtained in high purity not requiring any chromatographic separation. Most significantly, the whole operation has not required the presence of any organic solvent at any stage. The rapid conversion, mild and green reaction conditions, simple experimental procedure, high yields, and catalyst reusability have been identified as notable advantages of this method (Wang and Pei, 2010) (Scheme 152).



R$_1$= OEt, OMe; **R**$_2$= Ph, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-OHC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, Me, furan-2-yl, CH=CHC_6H_4; **X**= O, S

Scheme 152. The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by nafion-H under ultrasound irradiation.

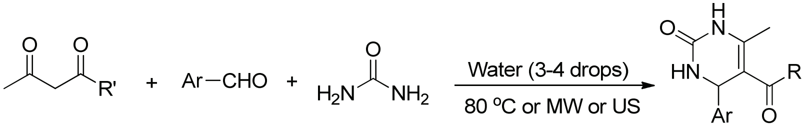
M'hamed and coworkers have reported a highly efficient and green strategy for the one-pot Biginelli synthesis of 3,4-dihydropyrimidine derivatives under ball milling catalyst-free and solvent-free conditions (Scheme 153). The other substantial advantage of this efficient technique is to supply the possibility to access the desired 3,4-dihydropyrimidine derivatives in pure mode with excellent yields in a short reaction time, as well as its simplicity and not requiring solvents and catalysts (M'hamed, Alshammari, Lemine et al., 2016).



R= Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, 4-OHC_6H_4, 4-$NO_2C_6H_4$; X= O, S.

Scheme 153. Mechanochemical synthesis of 3,4-dihydropyrimidines under catalyst- and solvent-free conditions.

The Jains group has described a simple, efficient, and green water-assisted procedure for the synthesis of medicinally important 3,4-DHMPs with excellent yields under conventional, ultrasound and microwave irradiated conditions not requiring additional solvent and an acid catalyst (Scheme 154). At first, this Biginelli reaction was performed in the presence of various aldehydes both aromatic and heterocyclic, *β*-dicarbonyl compounds, and urea (3-4 drops) by conventional heating at 80ºC for 45-75 min. On the other hand, the application of microwave irradiation to the same reaction mixture has resulted in the decrease of the reaction time to 2 min, while this condensation has been completed within 30-50 min under the ultrasound-mediated conditions. To evaluate the effect of water on the progress of this condensation, the reaction between ethyl acetoacetate, 4-chlorobenzaldehyde, and urea has been selected as the model, and the reaction has been performed without water using conventional heating, microwave irradiation, and ultrasound. In the case of conventional heating, this transformation has proceeded slowly and has required a longer reaction time (2 h), while the reaction has not proceeded even after prolonged irradiation under microwave-mediated conditions. Similar to the conventional method, the progress of the reaction was very slow in ultrasound and afforded a lower product yield. It can be assumed that water facilitates the formation of acylimine intermediate generated by the reaction of urea and aldehyde through hydrogen bonding between NH hydrogen of urea and the carbonyl oxygen of aldehyde. From the mechanistic viewpoint, the generation of acylimine intermediate is the key step in Biginelli condensation, which subsequently reacts with the *β*-dicarbonyl compound followed by cyclodehydration to give corresponding 3,4-DHMPs (Singhal et al., 2010).

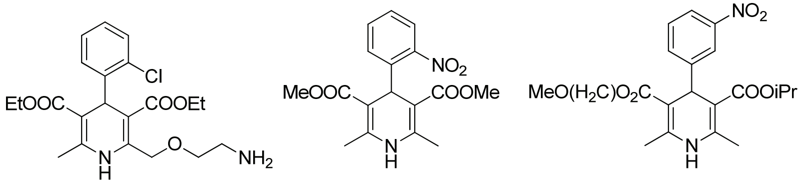


Ar= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, pyridin-2-yl, furan-2-yl, $CH{=}CHC_6H_4$; **R**= OEt, OMe, Me.

Scheme 154. MW or US supported Biginelli reaction.

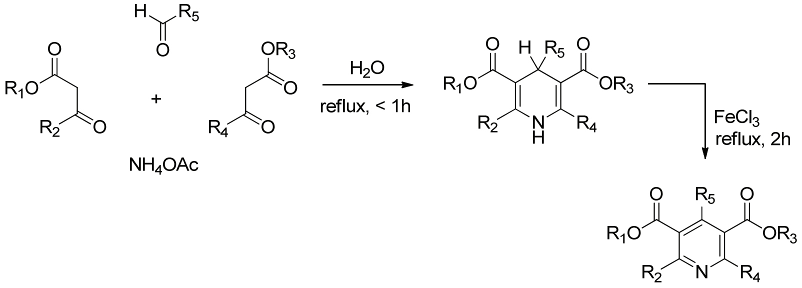
2.3.2. Hantzsch Reaction

The Hantzsch reaction, which was reported in 1881 by Arthur Rudolf Hantzsch, is a multicomponent reaction between an aldehyde, 2 equivalents of a *β*-keto ester, and a nitrogen donor such as ammonium acetate or ammonia leading to the formation of dihydropyridine as the initial product, which can be oxidized to a pyridine, subsequently. Aromatization is the driving force for the second step. The 1,4-dihydropyridine dicarboxylates have also been named 1,4-DHP compounds or Hantzsch esters. These compounds are among the most important classes of calcium channel blockers and some of them involving nifedipine, amlodipine, or nimodipine have been commercialized (Figure 14). The latter step has been shown to proceed in water with direct aromatization by manganese dioxide, ferric chloride, or potassium permanganate in a one-pot procedure (Li and Corey, 2004; Xia and Wang, 2005).



Amlodipine **Nifedipine** **Nimodipine**

Figure 14. Some commercial 1,4-DHP based calcium channel blockers.



Scheme 155. General representation of Hantzsch reaction.

Further, Hantzsch products have been considered useful electron donors and proton sources in photoredox catalyzed processes, as well. In addition, alkyl-1,4-dihydropyridines behave as versatile alkylation reagents via oxidative fragmentation under photoredox catalytic conditions. Oxidation of 1,4-DHPs renders one of the most straightforward ways of yielding pyridine derivatives. Common oxidation agents used to support the aromatization are CrO_3, $KMnO_4$, and HNO_3. However, generally, some adverse conditions such as strong oxidative conditions, the need for the excess amount of oxidant, burdensome workups, tiresome work-up procedures, or low chemical yields accompany aromatization (Sabir, 1998; Yadav, 2000; Ko, 1999).

Therefore, particular attention has been devoted to the development of aromatization methods to afford pyridine derivatives under milder and efficient conditions. Such approaches include, but are not limited to, using iodine in methanol, sodium chlorite, chromium dioxide, and metal-free photochemical conditions such as UV- and visible light. In metabolism, 1,4-DHP based antihypertensive drugs are converted to their pyridine derivatives by undergoing oxidation by cytochrome P-450 in the liver (Liao, Lin, Lu and Wang, 2010).

In recent years, researchers have investigated greener reaction conditions to make the Hantzsch dihydropyridine synthesis an even more environmentally friendly strategy. In several studies, ionic liquids, replacing traditional catalysts due to their being easy to handle and having non-toxic properties, have been tested in some room temperature reactions as the catalyst. These reactions have been reported to result in high yields at room temperature, reducing the impact of long-time heating on the reaction. In another study, ceric ammonium nitrate (CAN) has been used as an alternative catalyst, and the reaction was achieved at room temperature under solvent-free conditions (Majeed, Abdul Kareem, Qasim and Abdal Samad, 2020; Sharma, Rajani and Patel, 2017).

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