Chapter 1

General Introduction
1.1. INTRODUCTION

‘Green chemistry’ or ‘Sustainable technology’ is the widely accepted term to describe the movement in the direction of more environmentally suitable chemical processes and products. Green chemistry includes education, research and commercial applications across the entire supply chain for chemicals. Green chemistry can be achieved by applying environmental friendly technologies or processes; one of them is use of ionic liquids [1].

A simple definition of green chemistry can be expressed as follow: “Green chemistry efficiently utilizes renewable raw materials, eliminates waste and avoids the use of toxic or hazardous reagents and solvents in the manufacture and applications of chemical products”.

Chemistry plays an important role in our daily lives. Food and drink has been made safe to consume; the whole area of pharmaceuticals has allowed the development and synthesis of new medicines for illnesses and diseases; the development of cosmetics has empowered us to prettify; all as a result of chemistry. However, in the chemical industry, huge volumes of hazardous wastes are released to the air, water and land every hour. In particular, solvents are used in large quantities in chemical and pharmaceutical industries. Therefore, solvents define a major role in the environment pollution and also effect on safety and health problems. The constantly increasing air pollution has brought about changes in the global climate. The inspiration towards clean technology in the chemical industry is requirement of a high level of innovation and new technology in waste reduction. The idea of “green” solvents expresses the goal to minimize the environmental pollution resulting from the use of solvents in chemical production. To overcome these problems four directions towards the green solvents have been developed: (i) Replacement of hazardous solvents by ones that show better EHS (environmental, health and safety) properties, such as increased biodegradability or reduced ozone depletion potential [2-4]; (ii) Use of “bio-solvents” i.e. solvents produced from renewable resources such as ethanol produced by fermentation of sugar-containing feeds or starchy feed materials [5]. This replacement leads to an avoidance of fuel CO₂ emissions to the environment; (iii) Replacement of organic
solvents either with supercritical fluids that are environmentally friendly e.g. the use of supercritical CO$_2$ in polymer processing [6-9] to avoid the use of chlorofluorocarbons, and thus reduces ozone depletion; (iv) Use of non-volatile and thermally stable ionic liquids [10] as solvents in place of traditional solvents, most of which are volatile organic compounds (VOCs). Replacement of conventional solvents by ionic liquids would prevent the emission of VOCs which are major source of environmental pollution. Ionic liquids can be designed to be environmentally benign, with large potential benefits for sustainable chemistry. On the other hand, for many chemical processes a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome these problems it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, ultrasound irradiation and grinding techniques to promote chemical reactions.

Ionic liquids (ILs) have received considerable attention over the last decade due to their interesting chemical and physical properties, such as wide liquid range with low melting point, good stability in air and moisture, high solubility including inorganic, organic, and even polymeric materials, and negligible vapour pressure [11]. ILs are reported to be used in organic synthesis [12], catalysis [13], bio-catalysis [14], liquid-liquid separations [15], extraction [16] and dissolution processes (cellulose [17] and petroleum asphaltenes under microwave [18]), nanomaterials synthesis [19], polymerization reactions [20] and electrochemistry [21].

The present thesis describes the application of ionic liquid as the catalyst for synthesis of heterocyclic moieties under various energy sources. Therefore, it is thought proper to review the literature pertaining to various energy sources and ionic liquids in heterocyclic synthesis.

1.2. Various Energy Sources in Synthesis

Green chemistry is a very vast and multifacet field; it basically deals with the several principles, such as preventing the use of volatile and toxic solvents, reducing the quantity of catalyst and reagents required, using benign chemicals, employing atom-economy, optimizing reaction conditions, minimizing chemical
waste and minimizing energy usage [22]. Organic reactions and processes proceed on the addition of energy, mostly thermal energy. For most chemical reactions in solution, equilibrium is reached by working at reflux, i.e. part of the introduced thermal energy is constantly transferred to the cooling water by condensation of the boiling compound at the reflux condenser. Thus energy balances for such systems have to include the required cooling energy as well. The development of resources and environmentally friendly processes in terms of sustainable chemistry has become a focal point in chemical research in recent years. The thrust for finding alternative energy sources for enhanced chemical transformations under mild reaction conditions led to the discovery of the following prominent alternative energy systems.

- Microwave-assisted irradiation
- Sonochemistry-ultrasonic irradiation
- Mechanochemical mixing- Grinding

The present thesis describes synthesis of heterocycles by using various energy sources as applicable in particular reactions. Therefore it is appropriate to review all this energy sources one by one briefly.

1.2.1. Conventional

Usually, organic synthesis is carried out by conductive heating with an external heat source. Although fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the heating mantle, oil bath or hot plate as a source for applying heat to a chemical reaction. This is a comparatively slow and inefficient method for transferring energy into the system since it depends on convective currents and thermal conductivity of various materials that must be penetrated. As a result the temperature of the reaction vessel remains higher than that of the reaction mixture. In addition, a temperature gradient can get developed within the sample and local overheating can lead to product, substrate or reagent decomposition.
1.2.2. Microwave-assisted irradiation

In the recent decades, microwave heating has taken an incontestable place in analytical and organic synthesis as a very effective and non-polluting method of activation. In electromagnetic radiation region, the microwave lies between radio-wave and infrared (IR) frequencies with relatively large wavelengths 1 mm-1 m (corresponding to frequencies between 0.3 and 300 GHz). Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. In general, in order to avoid interference, the wavelength for industrial and domestic microwave apparatus is regulated to 12.25 cm, corresponding to a frequency of 2.45 GHz. Microwaves, non-ionizing radiation, are a form of energy that manifest as heat through their interaction with the medium or materials wherein they can be reflected (metals), absorbed (decreasing the available microwave energy and rapidly heating the sample), or transmitted (good insulators that will not get heated). Microwave heating is more efficient in terms of the energy used, produces higher temperature homogeneity, and is considerably more rapid than conventional heat sources. This unconventional microwave (MW) energy source has been used for heating food materials for almost 50 years [23] and is now being utilized for a variety of chemical applications including organic synthesis [24–35]. All chemical reactions are accelerated because of selective absorption of MW radiation by polar molecules; non-polar molecules are inert to MW dielectric loss [34, 35]. The rate enhancements in such reactions are believed to be due to rapid superheating of the polar solvents and pressure effects [33]. However, in these liquid-phase reactions, the development of high pressures, and the use of specialized sealed vessels are some of the limitations, although they have been adequately addressed now by the introduction of commercial MW instruments with appropriate temperature and pressure controls. Among the alternative energy sources microwave irradiation occupies a prominent place as it not only reduces the reaction time and increases the reaction efficiency but also can replace many organic solvents with water or enables the reactions to proceed under solvent-free conditions with maximum efficiency [35, 36].
1.2.3. Sonochemistry-ultrasonic irradiation

The application of ultrasound in organic synthesis has gained considerable attention in recent years and several organic transformations are effected using ultrasound irradiation. It has been observed that ultrasound reduces the reaction temperature and higher reaction rates can be achieved under ambient conditions. The study of sonochemistry is concerned with understanding the effect of sonic waves and wave properties on chemical systems [37–41]. On the basis of the frequency, the sound waves are divided into three regions:

- Infrasound: frequencies below 20 Hz fall in the category of infrasound.
- Sonic: the human hearing range (20 Hz–20 kHz) and is termed sonic range.
- Ultrasonic: frequencies greater than 20 kHz are called ultrasonic waves.

Thus, ultrasound is the part of the Ultrasonic spectrum which ranges from about 20 kHz to 10 MHz and can be subdivided into three main regions: (1) low frequency, high power ultrasound (20–100 kHz), (2) high frequency, medium power ultrasound (100 kHz–1 MHz), and (3) high frequency, low power ultrasound (1–10 MHz). The range from 20 kHz to around 1 MHz is used in sonochemistry; whereas, frequencies above 1 MHz are used in medical and diagnostic applications. Ultrasonic waves can be focused, reflected and refracted, but they require a medium of elastic properties for propagation. When these waves propagate, particles in the elastic medium oscillate and transfer the energy through the medium in the direction of propagation. The effect of ultrasound actually arises from the way in which sound propagates through the medium. In solids, both longitudinal and transverse waves can be transmitted whereas in gases and liquids only longitudinal waves can be transmitted. In liquids, longitudinal vibrations of molecules generate compressions and rarefactions, i.e. an alternating zone of high pressure and low pressure. The low-pressure gives rise to the formation of cavities or bubbles which expand. Finally, the bubbles collapse violently during the compression phase generating shock waves. The phenomenon of bubble formation and collapse, referred to as cavitation, is responsible for most of the ultrasonic physical and chemical effects
A cavity or bubble is grown by reducing the ambient pressure by static or dynamic means. Cavitation is classified into various forms and is often based on the method of its generation namely:

- **Acoustic cavitation**
  
  ✓ In this cavitation the growth of the cavity is induced by the pressure variation in the passage of ultrasound.

- **Hydrodynamic cavitation**
  
  ✓ This type of cavitation is induced by pressure variation in the system by changing the geometry of the flow system. This can be achieved by passing the fluid through a reducing crosssection, like a venture or a cavity.

- **Optic cavitation**
  
  ✓ This cavitation is produced by passing photons of high intensity light (laser), rupturing the bonds.

- **Particle cavitation**
  
  ✓ This type of cavitation is produced by bombarding a liquid with high intensity particles, like protons.

Among the aforementioned cavitation processes only acoustic cavitation and hydrodynamic cavitation have great potential for commercial exploitation. In general, acoustic cavitation has been used to carry out organic reactions. Since liquids are not elastic, successive cycles of compression and rarefaction lead to non-uniform translational motion of individual molecules within the solution, which enhances the rate of the transport processes. As the power is increased, more efficient mixing is typically observed. This non-conventional energy source proved to be better in terms of selectivity, reaction time and operational simplicity.

### 1.2.4. Mechanochemical mixing- Grinding

Mechanochemistry was applied to the type of reactions accomplished by mechanical energy. A narrower field, tribochemistry, was used for reactions generated by friction during the grinding of solid reagents \[43\text{–}45\]. There are variety of changes that take place on mechanical grinding of solids such as:
Comminution of the particles to a very small size

- Production of large surfaces
- Formation of point defects and dislocations in the crystalline structure
- Phase transformations in polymorphic materials
- Chemical reactions: decomposition, oxidation-reduction, ionic exchange, complex and adduct formation, etc.

The occurrence of these reactions was credited to the heat generated in the grinding process. This is favoured by the large area of contact between the solids. However, towards the end of 19th century it was noticed that mechanochemical processes were different from thermal processes [43]. The role played by mechanical defects as high energy structures and their importance in chemical transformations were recognized later [45-50]. Grinding of two solid substances leads to a complex series of transformations, the mechanical energy breaking the order of the crystalline structure, producing new surfaces and cracks. At the point of collision of the edges, the solids deform and even melt, forming hot points where the molecules can reach very high vibrational excitation states leading to bond breakage. These stochastic processes occur in a period of $10^{-7}$ s in which thermal equilibrium does not exist. This time frame is called the plasma phase. This is followed by post-plasma duration of $10^{-6}$ s or more in which relaxation processes dissipate the energy reaching the Maxwell-Boltzmann distribution. These post-plasmatic reactions are responsible for many of the products formed; the energy accumulated in the defects of the crystalline structure can lead to slower chemical processes.

1.3. Ionic Liquids in Organic Reactions

Many studies have described the application of ionic liquids in different areas and their use in heterocyclic synthesis. Additionally, there are a few reports that provide a clear discussion on questions such as "how do ionic liquids act in organic reactions?" or "are ionic liquids solvents, catalysts, or both?" Conceivably for the synthetic organic chemist, these questions are secondary, in view of the noteworthy improvement in products yields, reaction times, reaction work-up, etc. On the other hand, the answer to these
questions will allow the synthetic organic chemist to better plan the synthesis and thus improve results and making ionic liquids a strong tool in the area of organic synthesis. The data on properties, such as dielectric constants, polarity, etc. are not sufficient to explain the solvent/catalyst effect of ionic liquids in organic transformations. Some have suggested that ionic liquids act as an organocatalyst [51]. One of the promising approaches to organocatalysis is through hydrogen bonding interactions, and the results obtained with some ionic liquids have confirmed this statement and demonstrated their potential to have a huge impact on organocatalysis. On the other hand, Welton [52] studied catalytic reactions in ionic liquids and postulated that the potentially most powerful way in which an ionic liquid can be used in catalysis was as a combination of solvent and catalyst. From this postulate, whenever changing solvent leads to a faster reaction, the new solvent can be considered as a catalyst. After all, the reaction has been accelerated, and the solvent has remained unchanged during the process.

1.3.1. Ionic Liquids as Solvent
The study of solvent effects on reactions is one of the longest established areas of chemical research [53] and organic reactions are just as sensitive to changes in solvents. Usually we think of solvents in terms of their polarity as expressed by the dielectric constant. However, it is not possible to measure the dielectric constant of an ionic liquid directly, so this cannot help us. In reactions, we are generally interested in two things: the solubilities of the reaction components (starting materials, products, catalyst, co-solvents) and any specific interaction that may take place between the solvent and solutes to enhance or reduce the reactivity of any of the solute species. Clearly, the miscibility of any given substance with an ionic liquid is dependent on the particular ions of which it is composed as well as the properties of the solute. The ionic liquids are interacting with solute via high dipolar and dispersion forces and also acting as strong hydrogen bond bases. The dipolar forces and hydrogen bond basicity vary with the different ionic liquids, whereas the dispersion forces remain nearly constant for all of the reported ionic liquids. The hydrogen bond basicity can be controlled by the
choice of anion. When hydrogen bond acidity is observed it arises from the
cation of the ionic liquid, although the anion also greatly influences this
property. Not surprisingly, ionic liquids with aromatic ions are more capable
of most type of interactions (e.g., dispersive, $\pi-\pi$, n-$\pi$, hydrogen bonding,
dipolar, and ionic or charge-charge). Ionic liquids exhibit multiple behaviors,
which explain why many ionic liquids act as polar solvents in organic
reactions containing polar molecules and as less polar solvents in the
presence of less polar molecules [54]. Ionic liquid possess several attractive
properties such as negligible vapour pressure, chemical and thermal
stability, non-flammability, high ionic conductivity, wide electrochemical
potential window and moreover the ability to act as catalysts. In addition,
many of their physicochemical properties can be changed substantially by
variation of the cation and the anion; thus, they are “tunable” to the desired
properties. For this reason, they have been referred to as “designer
solvents” [55].

1.3.2. Ionic Liquids as Catalyst
More than 60% of products and more than 90% of processes worldwide
depend on the rapidly expanding field of catalysis. High specificity and
efficiency are the most important features provided by “green” catalysis.
Two concepts frequently discussed in green chemistry are atom economy
and chemical specificity. Few of the many catalytic reactions can be atom
economic. Furthermore, even for such reactions, in most cases it is hard to
reach 100% conversion with 100% selectivity due to thermodynamic
obstacles and/or the competition of parallel reactions. In order to measure
the quality of a synthetic method, chemical specificity is more fundamental
and important. High specificity, for example by accelerating the target
reaction to reach equilibrium as fast as possible while eliminating or
minimizing side reactions (high selectivity), or via reducing long synthetic
routes to one or two steps (high efficiency), is usually our only choice. An
ionic liquid can be useful if the cation or anion of the ionic liquid can act as a
catalyst, catalyst activator, or co-catalyst for a reaction. In the literature
reviews, it is found that the ionic liquid is deliberately prepared so that one
of the ions serves as the catalyst for the reaction [56, 57]. Recently, the synthesis of functionalized ionic liquids (FIL) or task-specific ionic liquids (TSILs) with special functions according to the requirement of a specific reaction has become an attractive field. This is due to their tunable features for various targeted chemical tasks and the advantages as reusable homogenous supports, reagents, and catalysts with green credential. All these studies offered us the possibility of designing suitable catalysts for the appointed reaction. The tasks specific ionic liquids often serve the dual role of catalyst and reaction medium. Endowed with catalytically active groups, functional ionic liquids have been developed and successfully applied as catalyst in a number of chemical transformations. These kinds of ionic liquids still maintain the unique properties of ionic liquids, therefore can be easily recycled and reused as homogenous small molecular catalysts. Nowadays, functionalized ionic liquids catalysis has been mainly focused on exploring acid or base mediated reactions. Ionic liquids, containing the functional group \( \text{SO}_3\text{H} \), have recently been employed in the oligomerization of various alkenes to produce branched alkene derivatives with high conversions and excellent selectivity [58]. Brønsted-basic ionic liquids have also been described as catalysts to organic reactions, for example, Ranu and Banerjee demonstrated the use of a task-specific and stable ionic liquid [bmim]OH as basic catalyst for Michael addition [59]. Considering the ‘designer’ properties of ionic liquids, there remains incredible potential for functionalized ionic liquids catalysis [60-63].

1.3.3. Role of ionic liquids in Multi Component Reactions (MCRs)

As per above discussion, it is clear that the role of ionic liquids in organic reactions as solvent or catalyst or both has been investigated in a general manner. The most widely studied reaction in which ionic liquids can be used as solvent is the nucleophilic substitution reaction. Investigations of this reaction have used ionic liquids as solvents for a wide range of chemical processes, both stoichiometric and catalytic. It is well-known that the microenvironment generated by a solvent can change the outcome of a reaction, in terms of both equilibria and rates [64]. Since ionic liquids have
the potential to provide reaction media that are quite unlike to any other available at room temperature, it is possible that they will dramatically affect reactions carried out in them. Certainly, there have been many claims of great improvements in reaction yields and rates using ionic liquids [65]. From this perspective, combining synthetic potentialities of MCRs with the dual properties of ionic liquids as solvents and promoters results in the emergence of promising strategies for the development of valuable eco-compatible organic synthesis procedures [66]. There are several types of reactions in which the prominent effect of ILs has been observed. Therefore, it is proper to review the synthetic procedures of well-known heterocyclic compounds by using ionic liquids as a solvent or catalyst or both.

1.4. Ionic liquids in MCRs

Maishal et al. [67] described the synthesis of cyclobutenone 3 in ionic liquid [bmim]PF₆ via MCR involving alkyl and/or aryl carbene complexes 1 with tolane 2 (Scheme 1.1). The desired product was obtained in 98% yield in the reaction of in ionic liquid, while only a 27% yield of the cyclobutenone chromium tricarbonyl complex was isolated when the reaction was performed in di-n-butyl ether under similar reaction conditions.

![Scheme 1.1 Synthesis of cyclobutenone derivatives.](image)

Yavari et al. [68] used the [bmim]OH–H₂O system in the three-component condensation of acid chlorides 4 with aminoacids 5 and dialkyl acetylene dicarboxylates 6 affording a one pot access to highly functionalized pyrroles 7 (Scheme 1.2). The crucial role of the hydroxyl counter anion of the IL catalyst was confirmed by comparison with the activity of the tetrafluoroborate-containing IL analogue, which revealed to be a less effective catalyst. Thereby, this methodology constituted efficient eco-
friendly alternative to more classical methods for the synthesis of pyrroles, such as the Hantzsch or the Paal–Knorr procedures.

Yadav et al. [69] in 2004 reported isocyanide-based MCRs for the synthesis of poly substituted 2-aminofuran derivatives 11. Accordingly, the three-component reaction of cyclohexyl isocyanide 8 with dimethyl acetylenedicarboxylate (DMAD) 9 and various aromatic or aliphatic aldehydes 10 went to completion in less than 2 h when ran in ionic liquids, affording the expected heterocycles in high yields (Scheme 1.3). The hydrophilic [bmim]BF₄ was found to give the best results, whereas either hydrophobic [bmim]PF₆ or organic solvents gave poor yields, even under forced conditions.

Xia et al. [70] described the synthesis of 2,4,5-trisubstituted imidazoles 14 in ionic liquid via MCRs involving an alkyl and/or aryl aldehyde 10, ammonium acetate 12 as a source of ammonia and a 1,2-dicarbonyl reactant 13 (Scheme 1.4).
Hasaninejad et al. [71] recently described a catalyst-free one-pot four-component methodology for the synthesis of 1,2,4,5-substituted imidazoles 16 from benzil 13, aldehydes 10, amines 15 and ammonium acetate 12 under conventional heating and microwave irradiation using [bmim]Br as an efficient promoting reaction medium (Scheme 1.5).

Srinivasan et al. [72] reported a one-pot synthesis of 2-aryl benzimidazoles 19 initiated by imidazolium-based ionic liquids. The compounds were obtained in good yields (82-94%) by reacting 1,2-phenylenediamines 17 with benzoyl chlorides 18 for a short time (10-20 min), as shown in Scheme 1.6.
Siddiqui et al. [73] reported a synthesis of 1-pyridylimidazo[1,5-a]pyridines 21 through a one-pot condensation of 1,2-dipyridylketone 20, aromatic aldehydes 10 and ammonium acetate 12 in ionic liquid [Hbim]BF₄, in the absence of any added catalyst (Scheme 1.7).

![Scheme 1.7 Synthesis of 1-pyridylimidazo[1,5-a]pyridines](image)

Shaabani et al. [74] developed a synthesis for 3-aminoimidazo[1,2-a]pyridines 24 via a three-component condensation reaction of aldehydes 10, 2-amino-5-methyl-pyridines 22, and isocyanides 23 at room temperature in the presence of [bmim]Br (Scheme 1.8).

![Scheme 1.8 synthesis for 3-aminoimidazo[1,2-a]pyridines](image)

Shaabani et al. [75] reported Biginelli-type reaction for 4H-pyrimido[2,1-b]benzazoles 27 systems involving 2-aminobenzimidazole or 2-amino benzothiazole 25 as urea or thiourea synthetic equivalents with aromatic aldehydes 10 and β-ketoesters 26 (Scheme 1.9). The ionic liquid, tetramethylguanidinium trifluoroacetate (TMGT), acted as catalyst under solvent-free conditions rendering the reaction an environmentally benign
process where the use of volatile organic solvents was only required for the recrystallization of the crude product precipitated out from water.

![Scheme 1.9 Biginelli-type reaction for 4H-pyrimido[2,1-b]benzazoles](image)

In another study, Shaabani and Maleki [76] reported the synthesis of 3-aminoimidazo[1,2-α]azines 30, using ionic liquids ([bmim]Br) as a promoter under classical heating conditions, as shown in Scheme 1.10. This synthesis proceeded through a multicomponent reaction involving the condensation of aldehydes 10, 2-aminoazines 28 and Trimethylsilyl cyanide (TMSCN) 29.

![Scheme 1.10 Synthesis of 3-aminoimidazo[1,2-α]azines](image)

Chen et al. [77] reported the use of ionic liquids as solvent in a molar ratio of 1:10 (reactant/IL) in the cyclocondensation reaction of α-tosyloxyketones 31 with 1-amino isoquinoline 32 in [BPy][BF₄] at room temperature and in the presence of sodium carbonate (Scheme 1.11). The mixture was stirred for about 1 h and gave the desired imidazo[2,1-α]isoquinolines 33 in good yields.
Wu et al. [78] introduced the use of ionic liquid in the synthesis of oxazoles 36 via the van Leusen reaction involving the condensation of aldehydes 10, tosylisocyanide 34 and alkyl halides 35 (Scheme 1.12).

Yadav et al. [79] published the synthesis of substituted thiazolidinones 40 or benzimidazoles 41 using ionic liquid in three-component reaction involving heteroaromatic amine 37 or 1,2-phenylenediamine 39 with 2-mercaptoacetic acid 38 and aromatic aldehydes 10 (Scheme 1.13-1.14).
Another well-established MCR is the Hantzsch reaction involving β-ketoesters 26, aldehydes 10 and primary amines 12, leading to dihydropyridines (DHPs) 42. Shaabani et al. [80] introduced ionic liquids and presented a modified method of the original Hantzsch dihydropyridines synthesis. The synthesis was performed from a three-component condensation in combination with TMGT as the ionic liquid using ultrasound irradiation at room temperature (Scheme 1.15).

Perumal and Karthikeyan [81] designed a methodology using ionic liquid for the synthesis of pyridines 44 by generating the enaminone from the β-ketoester 26 for an in situ heteroannulation in the Bohlmann-Rahtz reaction. The one-pot, three-component reaction of β-ketoester 26, ammonium acetate 12, and alkynones 43 in [Hmim]TFA as solvent gave good results (Scheme 1.16).
Ranu et al. [82] reported the use of [bmim]OH in a protocol to synthesize polyfunctionalized pyridines. The conventional method for this reaction involves the condensation of aldehydes 10, malononitrile 45, and thiols 46 to afford highly substituted pyridines 47 (Scheme 1.17).

Similarly Heravi et al. [83] described a ZrOCl$_2$·8H$_2$O/NaNH$_2$-catalyzed a pseudo-four-component condensation of aldehydes 10, thiophenols 48, and malononitrile 45 in [bmim]BF$_4$ under ultrasound irradiation at room temperature, which generated 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives 49 in high yields (Scheme 1.18).
Ionic liquid [bmim]PF$_6$ has been demonstrated by Xu et al. [84] to be an efficient and recyclable medium for highly chemoselective synthesis of 2,2-dimethyl-6-substituted 4-piperidones 52 via a L-proline catalyzed four-component tandem Mannich reaction of ammonia 50, aldehydes 10 and acetone 51 (Scheme 1.19).

Transition-metal-complex-catalysed MCRs may also be conducted in ionic liquids, with enhanced efficiency compared to classical organic solvents. Ye and Alper [85] reported [bmim]PF$_6$-promoted palladium-catalyzed cyclocarbonylation of o-iodoanilines 53 and allenes 54 to afford the corresponding 3-methylene-2,3-dihydro-1H-quinolin-4-ones 56 in moderate to excellent yields under a low pressure of CO 55 (Scheme 1.20).

Ji et al. [86] reported the use of catalytic amount of [hmim]BF$_4$ without solvent in the four-component Hantzsch reaction for the synthesis of polyhydroquinoline derivatives 58 involving β-ketoesters 26, aldehydes 10, dimedone 57 and ammonium acetate 12. The protocol shortened the reaction times to a few minutes at 90 °C, increasing the yields up to 96%, the effect being already marked at room temperature (Scheme 1.21).
Wu et al. [87] described four-component, one-pot reaction of aromatic aldehyde 10, cyclohexanone 59, malononitrile 45, and amines 60 in a basic ionic liquid [bmim]OH, providing N-methyl- or N-aryl-substituted 2-amino-4-aryl-5,6,7,8-tetrahydroquinoline-3-carbonitriles 61 in good to excellent yields (Scheme 1.22).

Yadav et al. [88] described the use of ionic liquids for a highly diastereoselective Biginelli-type synthesis of isoquinolic acid derivatives 63. The condensation of aldehydes 10 with amines 15 and homophthalic anhydride 62 in [bmim]BF₄ at room temperature afforded the desired heterocycles in excellent yields and high cis-selectivity (Scheme 1.23). Interestingly enough, when the same reactions were conducted in refluxing methanol, they afforded in longer reaction times and in lower yields the corresponding products as 3:1 mixtures of cis- and trans-isomers.
Yadav et al. [89] described a two-step synthesis of 4(1H)-quinolones 67 in ionic liquids. First, a three-component condensation of amines 15, Meldrum’s acid 64 and trimethylorthoformate 65 was carried out in [bmim]Br under nitrogen atmosphere at 40 °C, which generated compounds 66 in excellent yields. Then, the resulting compounds 66 were treated in [bmim]OTf at 80 °C, providing the desired 4(1H)-quinolones 67 in excellent yields after 2 hours (Scheme 1.24).

Shaabani et al. [90] reported Biginelli-type scaffold for quinazolin-2,5-dione derivatives 69 via three component condensation reaction between dimedone 57, aldehydes 10 and urea or thiourea 68 using a combination of [bmim]Br and silica sulfuric acid (SSA) as a solid acid catalyst (Scheme 1.25).
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The use of additional acid catalyst for activation of the Biginelli reaction is obviated when the MCR was conducted in a Brønsted acidic ionic liquid. Srinivasan et al. [91] carried out a one pot synthesis of 3,4-dihydropyrimidine-2-(1H)-ones 70 by using ionic liquid [Hbim]BF₄ under ultrasound irradiation with excellent yields and short reaction times at ambient temperature (Scheme 1.26).

Recently, Yu et al. [92] synthesised a series of 1H-pyran[2,3-d]pyrimidin-2(8aH)-one derivatives 72 via one-pot three-component reaction of aromatic aldehydes 10, urea or thiourea 68, and 3,4-dihydro-2H-pyran 71 using a Brønsted acidic ionic liquid, 1-methyl-2-pyrrolidinone hydrosulfate ([HNMP]HSO₄), as catalyst under solvent-free conditions (Scheme 1.27).
Pend and Deng [93] were the first to report the use of ionic liquids as catalyst for the development of the Biginelli reaction under solvent-free and neutral conditions.

Recently Chakraborti et al. [94] reexamined the organocatalytic potential of [bmim]-based ionic liquids in Biginelli reaction of aldehydes, β-keto ester or β-diketone, and urea or thiourea.

Chavan and Degani [95] developed one-pot synthesis of 6-aminouracils 78 via *in situ* generated ureas 75 and cyanoacetylureas 77 (Scheme 1.28) using an ionic liquid, 1,1,3,3-tetramethylguanidine acetate ([TMG]Ac), as a recyclable solvent and catalyst.
Shaabani et al. [96] developed an efficient multicomponent sequence in ionic liquids for the synthesis of new 2,3-dihydroquinazolin-4(1H)-ones. These quinazolinones derivatives 81 resulted from the multicomponent coupling of isatoic anhydride 79, 2-aminobenzothiazole 80 and various aldehydes 10 in [bmim]Br at 130 °C within 30 min. (Scheme 1.29).

![Scheme 1.29 Synthesis of new 2,3-dihydroquinazolin-4(1H)-ones](image)

Dabiri et al. [97] reported one-pot condensation of isatoic anhydride 79 with triethyl orthoacetate 82 and various primary amines 15 in 1-methylimidazolium trifluoroacetate ([Hmim]TFA) led to the formation of the corresponding 2-methylquinazolinones. Subsequent addition of one equivalent of an aromatic aldehyde resulted in the one-pot formation of 2-styryl substituted products 83 in good overall yields (Scheme 1.30).

![Scheme 1.30 Synthesis of 2-styrylquinazolinones](image)

The method developed by Khosropour et al. [98] includes immobilization of Lewis acids on ionic liquids to obtain 4-(3H)-quinazolinone 85 by the condensation reaction of anthranilic acid 84, trimethyl orthoformate 65 and primary amines 15 in the presence of a catalytic amount of Bi(Tfa)3 in [NBP][FeCl4] as a room-temperature ionic liquid (Scheme 1.31).
Dabiri et al. [99] reported synthesis of 4-Substituted-spiro-1,2-dihydroquinazolines 88 and 89 by direct reaction of 2-aminobenzophenones 86, isatin 87 or 1,2-diketone derivatives 13 and ammonium acetate 12 in the presence of ionic liquid, 1-methylimidazolium trifluoroacetate [Hmim]TFA playing dual role catalyst and solvent (Scheme 1.32-1.33). In the presence of the same ionic liquid, [Hmim]TFA, a three-component condensation reaction between 2-aminobenzophenone derivatives 86, aromatic aldehydes 10, and ammonium acetate 12 efficiently provided substituted quinazolines 90 in a one-pot reaction in conjunction with aerobic oxidation (Scheme 1.34).
Shi et al. [100] reported the reaction between 6-aminopyrimidine-2,4-dione 91, dimedone 57 and various aromatic aldehydes 10 in [bmim]Br to deliver corresponding high yields pyrimido-[4,5-b]quinolones 92 in less than 5 h (Scheme 1.35). Interestingly enough, when phenylacetaldehyde 93 was used in this sequence, the corresponding oxidized product was isolated after elimination of toluene and formation of the pyridine moiety 94 (Scheme 1.36).
Alternatively, under similar reaction conditions, Shi et al. [100, 101] published the condensation of 1,3-indanedione 95 with aromatic aldehydes 10 and either 6-aminopyrimidine-2,4-dione 91 and 5-amino-3-methyl-1-phenylpyrazole 97 leading to the efficient formation of indeno[2',1':5,6]pyrido[2,3-d]pyrimidine 96 (Scheme 1.37) and indeno[2,1-e]-pyrazolo[3,4-b]pyridine-5(1H)-one derivatives 98 (Scheme 1.38), respectively. Compared with other classical methods, this environmentally benign procedure had the advantages of higher yields and easier work-up.

Khurana and Magoo [102] reported the synthesis of tetrahydrobenzoxanthenone derivatives 100 from β-naphthol 99, aldehydes 10, and dimedone 57 in ionic liquid [bmim]BF₄. The electronic character of the substituents showed no impact on the reaction giving access to tetrahydrobenzoxanthenone derivatives with high yields in less than 4 h (Scheme 1.39).
Shen et al. [103] developed the transformation with anilines 101 in place of ammonium acetate, involving two equivalents of dimedone 57 and aldehydes 10 under aqueous conditions for the synthesis of acridines 102. The catalytic system is a Brønsted acidic ionic liquid containing perfluoroalkyl tails either in monomeric or dimeric version (Scheme 1.40).

Zhang et al. [104] proved ionic liquid to be an efficient medium for the three-component reaction between cyanothioacetamide 103, malononitrile 45 and various aldehydes 104 leading to the one-pot, catalyst-free synthesis of thiopyran derivatives 105. The potentiality of this methodology was illustrated by the synthesis of a bioactive pyrimidine nucleoside-thiopyran hybrid (Scheme 1.41).
Esmaeili et al. [105] described an efficient one-pot three-component reaction of arylalkyl ketone 106, malononitrile 45 and carbon disulfide 107 in an ionic liquid, [bmim]Br, which generated a variety of 2-thioxo-2H-thiopyran derivatives 108 in fairly good yields (Scheme 1.42).

Shekouhy and Hasaninejad [106] described one-pot four-component reaction of aldehyde 10, phthalic anhydride 109, hydrazine 110 and dimesdone 57 under ultrasonic irradiation in ionic liquid [bmim]Br, which generated various 2H-indazolo[2,1-b]phthalazinetriones 111 in good yields under neutral and catalyst-free conditions (Scheme 1.43).
Similarly Shaterian and Mohammadnia [107] reported a new four-component synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives 112 using three weak basic ionic liquids such as [DBU][Ac] or [Pyrr][HCOO] or [Pyrr][Ac] as efficient catalysts for condensation reaction of hydrazine 110, phthalic anhydride 109, malononitrile 45, and aromatic aldehydes 10 under ambient and solvent-free conditions (Scheme 1.44).

Shi et al. [108] described condensation of 6-Methyl-4-hydroxypyran-2-one 113 with aldehyde 10 and a primary amine 15 in ionic liquid [bmim]Br. The sequence evolved through an intermolecular condensation with concomitant transamidation of the lactone ring to form bislactam systems 114 (Scheme 1.45).

A. Bazgir et al [109] reported green and efficient four-component synthesis of α-carboline derivatives 118 in presence of [bmim]Br and p-TSA using aldehydes 10, indolin-2-one 115, various hydrazines 116 and 3-oxo-3-phenyl propanenitrile 117 (Scheme 1.46). Among the different advantages related to the use of ionic liquids, it is important to note that a similar reaction conducted in organic solvents only afforded traces of the desired products.
Yong and Teo [110] demonstrated three-component Mannich reaction of aromatic aldehyde 10, aniline 101 and ketone 119 proceeded well in the presence of a siloxy-L-serine organocatalyst in ionic liquid [bmim]PF$_6$ to furnish the β-amino carbonyl scaffold 120 in high enantio- and diastereoselectivities (Scheme 1.47).

1.4.1. Supported ionic liquids in MCRs
Zhang et al. [111] developed a simple and efficient chitosan (CS) supported ionic liquid catalyst for the synthesis of cyclic carbonates 123 from epoxides 121 and CO$_2$ 122 without metal co-catalyst and co-solvent (Scheme 1.48).
Cheng et al. [112] also applied supported ionic liquids, Polystyrene-bound diethanolamine based ionic liquids (PS-DHEEAB and PS-THEAB), for the chemical fixation of CO$_2$ into cyclic carbonates without any additional co-catalyst.

Yang et al. [113] developed a series of polyethylene glycol (PEG)-functionalized basic ionic liquids (ILs) for efficient CO$_2$ conversion into organic carbonates under mild conditions.

Similarly Bhanage et al. [114] investigated Polymer supported diol functionalized ionic liquids, PS-DHPIMBr, as an efficient, heterogeneous and recyclable catalyst for coupling of carbon dioxide (CO$_2$) to aziridines providing high conversion with excellent regioselectivity towards 5-aryl-2-oxazolidinones under mild and solvent free conditions (Scheme 1.49).

Luo et al. [115] developed a facile, efficient and eco-friendly procedure for the one-pot synthesis of amidoalkyl naphthols via a three-component condensation reaction of aldehydes with 2-naphthol and amides using a silica gel supported dual acidic IL as a powerful and recyclable catalyst under solvent-free conditions (Scheme 1.50).
Luo and Zhang [116] developed a mild and efficient method for preparation of amidoalkyl naphthols via one-pot three component condensation of aldehydes with amides and 2-naphthol in the presence of polyethylene glycol (PEG)-based dicationic acidic ionic liquid as a powerful catalyst under solvent-free conditions.

Recently Kotadia and Soni [117] also reported an efficient procedure for the synthesis of amidoalkyl naphthols using benzimidazolium based ionic liquid immobilized on silica based solid support. Abdollahi-Alibeik and Pouriayevali [118] found that (BSPY)HSO₄ as protic ionic liquid could be highly dispersed on the surface of MCM-41 nanoparticles. The obtained material ([BSPY]HSO₄/MCM-41) can be used as solid acid catalyst for the Friedlander synthesis of quinolines 130 (Scheme 1.51).

Luo et al. [119] developed a novel magnetic nanoparticle supported acidic IL catalyst for the first time and used it in one-pot three component condensation of dimedone 57 with aldehyde 10 and 2-naphthol 99 to prepare benzoxanthenes 131 in excellent yields (Scheme 1.52).
Liu et al. [120] synthesized new N-heterocyclic carbene (NHC) precursors bearing PEG moieties, which were readily accessible from inexpensive and commercial materials. The in situ-generated catalysts from palladium acetate and water-soluble imidazolium salts demonstrated excellent catalytic activities towards the Suzuki reaction between aryl halides and aryl boronic acids bearing a wide range of functional groups (Scheme 1.53).

\[
\begin{align*}
R_1 \overset{\text{X}}{\bigodot} \bigodot R_2 & + (\text{HO})_2 \overset{\text{B}}{\bigodot} \overset{\text{R}_2}{\bigodot} & \overset{\text{pd(OAc)}_2/i \text{Et}_3\text{N}, \text{H}_2\text{O}}{\rightarrow} & R_1 \overset{\text{Y}}{\bigodot} \overset{\text{X}}{\bigodot} \overset{\text{R}_2}{\bigodot} \\
\text{X} = \text{Br, Cl} & & \text{Y} = \text{C, N} & \\
\text{i} = \text{PEG functionalized imidazolium salts}
\end{align*}
\]

Scheme 1.53 Suzuki reaction using supported ionic liquid

Wang et al. [121] synthesized PEG-supported IL [PEGmim][Cl] and found Pd(OAc)$_2$ in [PEGmim][Cl] as a highly efficient and recyclable catalytic system for the Heck reaction of aryl bromides 135 with olefin 136 in the absence of ligands (Scheme 1.54).

\[
\begin{align*}
\text{R}_1 \overset{\text{Br}}{\bigodot} & + \overset{\text{R}_2}{\bigodot} & \overset{\text{pd(OAc)}_2 [\text{PEGmim}][\text{Cl}] \text{K}_2\text{CO}_3, 140 \, \text{°C}}{\rightarrow} & \text{R}_1 \overset{\text{R}_2}{\bigodot} \\
\text{135} & & \text{136} & \text{137}
\end{align*}
\]

Scheme 1.54 Heck reaction using supported ionic liquid

Fang et al. [122] developed a novel recyclable temperature-dependant phase-separation catalytic system comprised of PEG$_{1000}$-based functional dicationic acidic ionic liquid and propylene glycol monomethyl ether. This catalytic system could be used for the synthesis of 2,4,5-trisubstituted imidazoles 14 via one-pot three-component condensation with various aldehydes 10, benzil 13 and ammonium acetate 12 in reasonable to good yield of 81–95% (Scheme 1.55).
The perusal of literature revealed that ionic liquids are continuously being attempted by the chemists in search of green protocols for organic synthesis. ILs have certain properties which can be explored to find the better alternative for molecular solvents and hazardous catalyst.

One pot multicomponent reactions are particularly useful to synthesize heterocyclic scaffolds having enormous pharmaceutical importance. It becomes the prime necessity to develop library of bioactive compounds out of which some can be employed as the new generation pharmaceutical agents for following reasons:

1. More potent drug molecules can be applied for quicker and safer therapy at low cost.
2. Bacteria, Viruses and fungi may develop drug resistance and hence new highly potent and task specific drugs are required.
3. Drug molecule should be designed to be used for targeted delivery.
4. New compounds should be synthesized utilizing minimum energy and producing no waste.

Thus in search of green protocols for synthesizing heterocyclic compounds of pharmaceutical interest, an attempt has been made to perform organic synthesis in ILs. To reduce the energy consumption in obtaining the heterocyclic moieties, we have also tried different energy sources to perform the reactions.

The present thesis describes the synthesis of imidazo[1,2-a]quinolines, chromenes and substituted quinolones by using ionic liquid as a catalyst or solvent or both under the various energy sources as applicable in particular reactions. The reviews on the synthetic procedures of these three
heterocycles by using ionic liquids are discussed in their respective chapters.

1.5. OBJECTIVE

The key objectives of the present work are as under

- To design a chemical transformation in such a way that satisfies two key principles of Green Chemistry namely safer solvents and design for energy efficiency.
- To modify synthesis of ionic liquid by using non-conventional energy sources.
- To carry out synthesis of desired heterocycles by using ionic liquid as a catalyst or reaction media or both.
- To apply non-conventional energy sources for the activation of reaction mixture.

1.6. Outline of the Present Work

Keeping in mind the above objectives, the work has been carried out during the tenure of research. This doctoral thesis comprises five chapters as under.

- **CHAPTER 1** deals with the introduction to green chemistry, brief introduction to various energy sources employed for chemical reactions and literature review on applications of ionic liquids in heterocyclic synthesis.
- **CHAPTER 2** deals with ultrasound assisted modified synthesis of ionic liquid [DBU][Ac] and synthesis of PEG-DIL by conventional method and their characterization by $^1$H NMR and $^{13}$C NMR.
- **CHAPTER 3** deals with ionic liquid [DBU][Ac] catalyzed one pot synthesis of imidazo[1,2-a]quinolines under various energy sources (conventional and ultrasound) and spectroscopic characterization of the synthesized compounds.
- **CHAPTER 4** deals with ionic liquid [DBU][Ac] catalyzed one pot synthesis of chromenes under various energy sources (conventional and grinding) and spectroscopic characterization of the synthesized compounds.
CHAPTER 5 deals with ionic liquid PEG-DIL catalyzed one pot synthesis of substituted quinolones under various energy sources (conventional and microwave) and spectroscopic characterization of the synthesized compounds.
1.7. REFERENCES


Chapter 1

General Introduction


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