https://doi.org/10.30799/jacs.S306.26120406 J. Adv. Chem. Sci. – Volume 12 Issue 4 (2026) 999–1004

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ISSN: 2394-5311

Ionic Liquid Mediated Synthesis of Some Heterocyclic Compounds: A Comprehensive Review

Yogesh B. Shinde*, Sandip S. Pathade

Dept. of Chemistry, M.G.V's M.S.G. Arts, Science and Commerce College, Malegaon Camp, Malegaon, Nashik – 423 105, Maharashtra, India.

ARTICLEDETAILS

Article history:
Received 24 February 2026
Accepted 11 March 2026
Available online 15 April 2026

Keywords:
Ionic Liquids
Heterocyclic Compounds
Catalysts

ABSTRACT

Ionic liquids (ILs) have emerged as versatile and environmentally benign alternatives to conventional organic solvents, offering unique physicochemical properties such as negligible vapour pressure, wide liquid-state temperature range, high thermal stability, and tunable polarity. These attributes have made ILs highly effective media and catalysts for the synthesis of structurally diverse heterocyclic compounds such as imidazole, thiazole, pyrazole, benzimidazole, etc. which continue to serve as fundamental scaffolds in pharmaceuticals, agrochemicals, dyes, and advanced functional materials. This comprehensive review critically examines recent developments in the ionic liquid–mediated synthesis of heterocyclic frameworks, emphasizing the versatile roles of ILs as solvents, catalysts, co-catalysts, and reaction modifiers. The special emphasis is placed on IL-assisted strategies for constructing nitrogen, oxygen, and sulphur-containing heterocyclic derivatives, along with comparisons to traditional synthetic approaches in terms of efficiency, selectivity, yield, and sustainability. The review also discusses mechanistic insights, the influence of IL structure on reactivity, and the integration of ILs with microwave, ultrasound, and metal-free methodologies. Furthermore, challenges such as recyclability, toxicity, cost, and scale-up limitations are critically evaluated. Overall, this work underscores the growing significance of ionic liquids as green and powerful platforms for advancing heterocyclic chemistry and outlines future research directions for their broader application in sustainable organic synthesis.

1. Introduction

Heterocycles represent one of the largest and most important branches of organic chemistry. They are extremely important not only in biology and industry but also in modern human society. Their role in many different fields is significant and cannot be overlooked.

Most pharmaceutical drugs that imitate natural biologically active compounds contain heterocyclic structures. Many major breakthroughs in disease treatment have come from designing and testing new molecules, which are often hetero aromatic compounds. In addition, many important natural products such as pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic compounds that are essential for human and animal health. For this reason, scientists continuously work to develop improved medicines, pesticides, insecticides, rodenticides, and herbicides, often inspired by natural structures. A large number of these biologically active substances contain heterocycles.

Heterocyclic compounds also play vital roles in biochemical processes and are present in key components of living cells. Beyond biological importance, they have many industrial applications. They are used as additives and modifiers in industries such as cosmetics, printing and imaging, data storage, plastics, solvents, antioxidants, and rubber processing. As a practical and applied science, heterocyclic chemistry offers endless possibilities for creating new compounds. By combining carbon, hydrogen, and different heteroatoms, chemists can design molecules with a wide variety of physical, chemical, and biological properties. Therefore, developing new methods—and improving existing ones—for synthesizing complex heterocyclic compounds remains a major focus in synthetic organic chemistry. Among these methods, cyclocondensation reactions are especially attractive for building heterocyclic Compound [1-5], and there is a continuing need to improve them.

Traditional methods for heterocycle synthesis often rely on volatile organic solvents, harsh reaction conditions, toxic catalysts, and multistep procedures that generate significant waste. In recent years, green chemistry principles have driven the search for sustainable alternatives that minimize environmental impact while maintaining high efficiency. Among these alternatives, ionic liquids have emerged as promising reaction media and catalysts due to their unique physicochemical properties [6-8].

In recent years, ionic liquids have gained considerable attention in green organic synthesis. They were first introduced as environmentally friendly alternatives to traditional solvents because of their special properties, such as low volatility, non-flammability, high thermal stability, and adjustable miscibility. However, their role has expanded beyond that. Today, ionic liquids are not only used as solvents but also as catalysts and reaction controllers. Another important advantage is that they can often be recycled and reused multiple times [9-13].

Many review articles have discussed ionic liquids, focusing on their role in catalysis (including homogeneous, heterogeneous, transition-metal, and organometallic catalysis), their use as solvents in organic and bio-organic reactions, and their chemical reactivity. However, only a few reviews have focused on specific reactions carried out in ionic liquids. However, despite the growing interest in ionic liquids and their versatile applications, no comprehensive review has yet focused specifically on their role in the synthesis of heterocyclic compounds.

While a number of publications have referred to condensation reactions, a comprehensive overview dedicated to the role of ionic liquids in heterocyclic synthesis through cyclocondensation processes is still lacking [14, 15].

Therefore, this review consolidates recent developments in the use of ionic liquids for the synthesis of heterocyclic frameworks, discussing their synthetic relevance, mechanistic features, and practical advantages. The insights provided are intended to offer a comprehensive perspective on the field and support further innovation in ionic-liquid-based synthetic chemistry.

2. Ionic Liquids: Properties and Classification

Ionic liquids are salts composed entirely of ions that remain liquid below 100 °C. Typically, they consist of bulky organic cations such as imidazolium, pyridinium, ammonium, or phosphonium paired with inorganic or organic anions like tetrafluoroborate, hexafluorophosphate, acetate, or bis(trifluoromethylsulfonyl)imide. Room-temperature ionic

*Corresponding Author:9890046074y@gmail.com(Yogesh B. Shinde)

https://doi.org/10.30799/jacs.S306.26120406

liquids (ILs) based on 1-alkyl-3-methylimidazolium salts were first reported in 1982 by Wilkes et al. as tetrachloroaluminates (first generation) [16].

Key properties of ionic liquids include negligible vapour pressure, high thermal and chemical stability, wide liquid-phase temperature range, non-flammability, and tunable polarity. By appropriate selection of cation–anion combinations, ILs can be designed to possess specific solvation abilities, acidity, basicity, or catalytic behaviour. These features make ionic liquids attractive as green solvents and multifunctional reaction media in organic synthesis [17].

3. Role of Ionic Liquids in Heterocyclic Synthesis

Ionic liquids have become increasingly important in modern organic synthesis, particularly in the construction of heterocyclic structures. Their unique physicochemical properties have encouraged extensive investigation into their application as reaction media. Many studies have reported that reactions carried out in ionic liquids often proceed with higher efficiency, improved product yields, and simplified isolation of products. Although these practical benefits are widely recognized, the fundamental role played by ionic liquids in such transformations is not always clearly understood. In particular, it remains uncertain whether ILs function mainly as solvents, as catalytic species, or through a combination of both effects. Gaining deeper insight into these roles is essential for the rational development of improved methodologies for heterocyclic synthesis.

The mechanistic contribution of ionic liquids in organic reactions continues to be an area of active investigation. Conventional solvent descriptors, such as polarity and dielectric constant, do not fully capture the complex interactions that occur in ionic liquid media. Increasing evidence suggests that ILs may participate directly in the reaction process rather than merely providing an inert solvent environment. For example, specific interactions such as hydrogen bonding between the ionic liquid components and reacting substrates can promote activation of functional groups, thereby influencing the course of heterocyclic ring formation [18, 19].

Welton [14] proposed that the effectiveness of ionic liquids may arise from their ability to perform dual functions within a reaction system. When a reaction proceeds more rapidly in the presence of an ionic liquid without any measurable consumption of the IL, this observation indicates that the ionic liquid not only acts as the reaction medium but may also contribute to catalytic activation of the reacting species [14].

A considerable number of investigations have focused on determining the physical and chemical properties of ionic liquids; however, the reported polarity values vary widely across different studies. Some researchers have suggested that the polarity of ionic liquids is comparable to that of short-chain alcohols or polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), placing them between water and chlorinated organic solvents on the polarity scale. Other reports indicate that certain ionic liquids exhibit solvent strengths approaching or even surpassing those of highly polar aprotic solvents such as acetonitrile. In contrast, some authors describe ionic liquids more generally as solvents of moderate polarity [19-24].

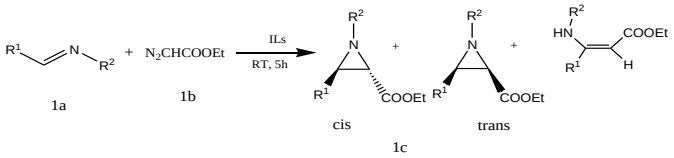
Despite these differing interpretations of their physicochemical properties, ionic liquids possess several distinctive advantages that make them attractive for heterocyclic synthesis. Their tunable polarity, excellent thermal stability, and potential for recyclability provide opportunities to design more sustainable and efficient synthetic protocols. Furthermore, their capacity to function simultaneously as solvent and catalytic medium can lead to enhanced reaction rates, improved selectivity, and overall better performance in heterocyclic transformations. As a result, ionic liquids are increasingly recognized as valuable tools in the advancement of modern heterocyclic chemistry.

4. Synthesis of Three- and Four- Membered Heterocycles

4.1 Aziridines

Aziridines, also known as azaethylene or ethylenimine compounds, are important three-membered nitrogen-containing heterocycles. They are widely used in organic synthesis because their strained ring structure makes them highly reactive. As a result, aziridines serve as valuable building blocks for making more complex molecules and for various functional group transformations. Many methods have been developed for their synthesis, including asymmetric approaches, and they are useful intermediates in several synthetic applications.

Despite the growing interest in ionic liquids, only one method for the synthesis of aziridines using ionic liquids has been reported. In this study, Sun and co-workers [25] described the preparation of aziridines (1c) by reacting imines (1a) with ethyl diazoacetate (EDA) (1b) in an ionic liquid medium. The reaction was carried out using equal amounts of the imine and EDA in the ionic liquid [BMIM][PF_6] (Scheme 1).



Scheme 1 Synthesis of aziridine (1c)

Under these conditions, the reaction produced only the cis-aziridine isomer with a high yield of about 93%. When a small (catalytic) amount of the ionic liquid was used instead of a full solvent amount, the aziridine product was not formed. This shows that the ionic liquid plays an important role as a reaction medium rather than just as a catalyst.

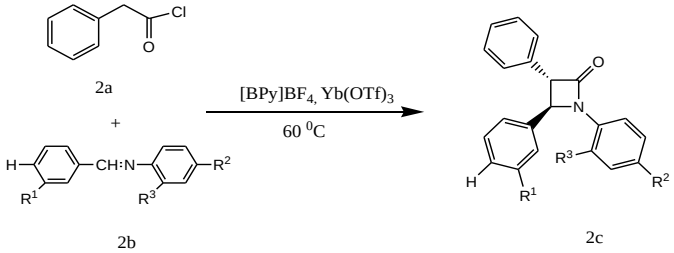
Both electron-donating and electron-withdrawing substituted aryl imines reacted smoothly in [BMIM][PF_6], giving the desired aziridines with excellent cis selectivity. An additional advantage of this method is that the ionic liquid could be recovered and reused up to five times, with only a slight decrease in yield.

The reaction in ionic liquids occurred faster than in conventional organic solvents. However, the reaction mechanism is believed to be similar to that observed when traditional Lewis acids, such as $BF_3{\cdot}OEt_2$, are used in solvents like hexane.

4.2 β-Lactams

β-Lactams are very important chemical compounds. They are found in many biologically active molecules, including antibiotics like Penicillin and Cephalosporin antibiotics [26]. Reacting acetyl chlorides with imines is one of the most useful and convenient approaches.

Chen et al. [27] prepared β-lactams (2c) in two main steps (Scheme 2): First, ketenes were formed inside the reaction mixture from acetyl chlorides (2a) using an ionic liquid (IL) and Yb(OTf)$_3$. And second, the ketenes reacted with imines (2b) in a [2+2] cycloaddition reaction to form the β-lactams.



Scheme 2 Synthesis of β-lactams (2c)

When both the ionic liquid [BPy]BF_4 and Yb(OTf)$_3$ were used, the yield (amount of product formed) was higher than when only the ionic liquid was used. The combination of [BPy][BF_4] and Yb(OTf)$_3$ gave better results than using Et_3N.

The reaction mainly produced the trans form of the β-lactam (stereoselective reaction). The reaction worked better when: R^1 groups were electron-withdrawing. However, the reaction was slow with some aliphatic imines. It also did not work when ketimines were used because bulky groups created too much steric hindrance (crowding effect).

The reactants were used in a 1:1 molar ratio, with 5 mol% of Yb(OTf)$_3$ in the ionic liquid solvent. The ionic liquid could be reused four times, and the yields remained almost the same (62%, 60%, 59%, and 59%).

5. Synthesis of Five-Membered Heterocycles

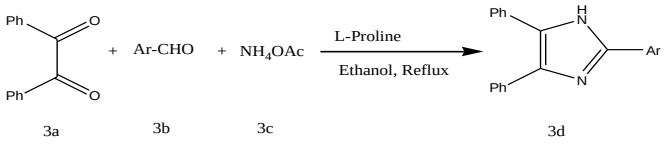
5.1 Imidazoles Derivatives

Imidazole derivatives are commonly synthesized via multicomponent condensation reactions involving aldehydes, diketones, and ammonia or amines. Ionic liquids such as imidazolium-based ILs have been extensively employed to promote these reactions, offering high yields, shorter reaction times, and excellent product purity. In many protocols, ILs function both as solvent and catalyst, eliminating the need for additional acidic or basic catalysts [28, 29].

Nana V. Shitole et al. [30] described an efficient L- Proline catalysed green protocol for synthesis of 2,4,5-Triaryl-1H-Imidazoles (3d) by mixture of aromatic aldehyde (3b), benzil (3a), ammonium acetate (3c) and L-Proline (10 mol%) in ethanol (20 mL) was stirred at reflux

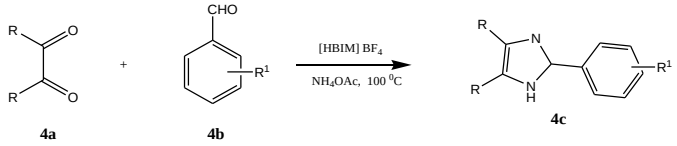
https://doi.org/10.30799/jacs.S306.26120406

temperature for 2~3 hr. The main advantages of this protocol are the excellent yield (93%) achieved, short reaction time and easy work -up procedure. Synthesized L- Proline catalysed imidazole derivatives (3d) by condensation of aromatic aldehyde (3b), benzil (3a), ammonium acetate (3c) (Scheme 3).



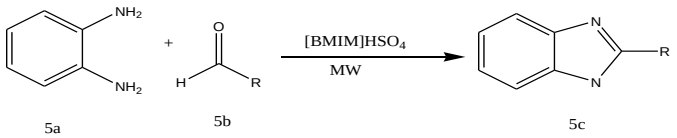
Scheme 3 Synthesis of imidazole derivatives (3d)

Siddiqui et. al. [31] The synthesis of imidazole derivatives using 1-butyl imidazolium tetrafluoroborate [HBIM]BF_4 ionic liquids. The various substituted 1,2-dione (4a) and benzaldehyde (4b) were reacted in the presence of ammonium acetate base to afford imidazole derivatives (4c) in high yield. The reaction proceeds via the condensation 1,2-dione (4a) and benzaldehyde (4b) were reacted in the presence of ammonium acetate base to afford imidazole derivatives (4c) (Scheme 4).



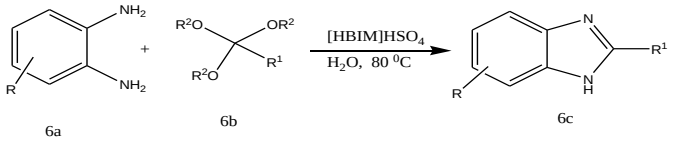
Scheme 4 Synthesis of imidazole derivatives (4c)

Sapkal S. B et al. [32] The synthesised of 2-substituted benzimidazoles derivatives (5c) with equimolar amounts of O-phenylenediamine (5a) and aromatic aldehydes (5b) under microwave irradiation is investigated using [BMIM]HSO_4 as ionic liquid and excellent yield (92%) achieved. The reaction proceeds in presence of microwave irradiation with equimolar amounts of O-phenylenediamine (5a) and aromatic aldehydes (5b) in the presence of a 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]) (Scheme 5).



Scheme 5 Synthesis of benzimidazoles (5c)

Devkate C. G. et al. [33] reported a green and efficient synthesised of benzimidazoles and its derivatives (6c) with 70-80 % yield, by the condensation of 1,2- phenylendiamine (6a) and 1,1,1-trimethoxyethane (6b) in presence of ionic liquid, 1-butylimidazolium bisulphate [Hbim][HSO_4] as a catalyst and water as solvent. The reaction proceeds via the condensation of 1,2-phenylendiamine (6a) and 1,1,1-trimethoxyethane (6b) in the presence of an 1-butylimidazolium bisulphate [Hbim][HSO_4] as ionic liquid (Scheme 6).

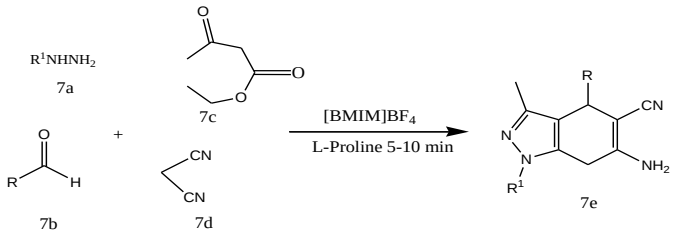


Scheme 6 Synthesis of benzimidazoles (6c)

5.2 Pyrazoles

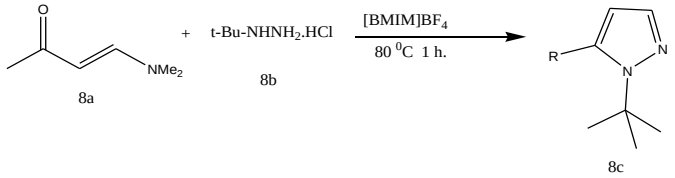
Pyrazole synthesis typically involves the cyclocondensation of hydrazines with β-dicarbonyl compounds or α,β-unsaturated carbonyl systems. Ionic liquids have been shown to enhance regioselectivity and facilitate reactions under solvent-free or low-temperature conditions. The use of ILs often results in cleaner reactions and easier product isolation.

Jitender M. Khurana et al. [34] developed a four-component cyclocondensation reaction for synthesizing of 4H-pyrano [2,3-c] pyrazoles (7e). The reaction makes the use of hydrazine monohydrate or phenyl hydrazine (7a), aldehydes (7b), ethyl acetoacetate (7c), and malononitrile (7d), facilitated by L-proline as a catalyst and conducted in room-temperature ionic liquids. This method highlights an environment-friendly and effective strategy for preparing these heterocycles. The reaction proceeds four-component cyclocondensation reaction for synthesizing of 4H-pyrano [2,3-c] pyrazoles (7e) in the presence of a 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF_4] as an ionic liquid (Scheme 7).



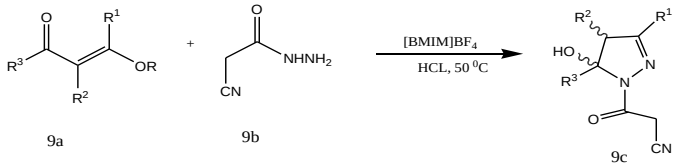
Scheme 7 Synthesis of pyrazole derivatives (7e)

Frizzo C. P. et al. [35] Synthesised of pyrazole derivatives (8c) from the reaction of butanone (8a) and amine (8b). 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF_4] facilitated cyclocondensation reactions and yielded the best result up to 96% pyrazole derivatives. The reaction proceeds via the condensation of butanone (8a) and amine (8b) in the presence of an 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF_4] ionic liquid (Scheme 8).



Scheme 8 Synthesis of pyrazole derivatives (8c)

Moreira et al. [36] used ionic liquids (ILs) to prepare 4,5-dihydropyrazoles (9c). These compounds were made by reacting enones (9a) with cyanoacetohydrazide (9b) in a cyclocondensation reaction (Scheme 9).



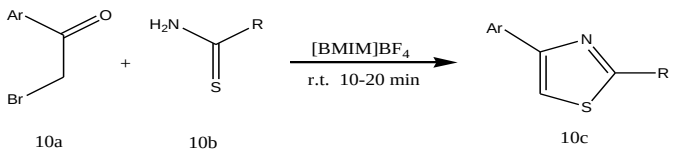
Scheme 9 Synthesis of pyrazole derivatives (9c)

The reaction was carried out in the ionic liquid [BMIM][BF_4], with a small amount of concentrated HCl as a catalyst. The reaction was heated at 50 ℃ and took 10 to 180 minutes. The products were obtained in moderate to good yields. The molar ratio of reactant to ionic liquid was 1:1. The authors suggested that the faster reaction happened because the ionic liquid lowers the activation energy of the slow step in the reaction. Ionic liquids are especially helpful for condensation reactions because they can better stabilize charged or highly polar intermediate species. This makes the reaction proceed more easily. As a result, the reaction in [BMIM][BF_4] was faster than in normal molecular solvents, even though a Brønsted acid catalyst (HCl) was used.

5.3 Thiazole

One of the earliest and well-explored approaches to thiazoles is the Hantzsch reaction, involving condensation between α-halocarbonyls and thioureas or thioamides [37-39]. In IL media, imidazolium-based salts like 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]) not only solvate reactants but also activate carbonyl groups via hydrogen bonding or Lewis interactions, thereby enhancing electrophilicity and facilitating cyclization.

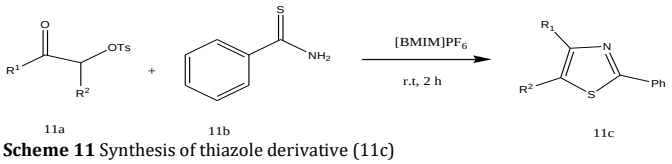
In the year 2007, Potewar et al. [40] The synthesizing a process of 2,4-disubstituted thiazoles (10c) by reacting phenacyl bromide (10a) with substituted thiourea (10b) in 1-butyl-3-methylimidazolium tetra-fuoroborate [BMIM]BF_4, an ionic liquid. The current approach enabled the instantaneous development of amino- and methyl-substituted 4-arylthiazole scaffolds, delivering high yields (87–96%) within 10–20 minutes. The reaction proceeds via the condensation of phenacyl bromide (10a) with substituted thiourea (10b) in the presence of an imidazolium-based ionic liquid (Scheme 10).



Scheme 10 Synthesis of thiazole derivative (10c)

https://doi.org/10.30799/jacs.S306.26120406

Hou et al. [41] reported a method for preparing substituted 2-thiazoles (11c) using ionic liquids. In their study, α-tosyloxyketones (11a) were reacted with thiobenzamide (11b) in the ionic liquid [BMIM][PF_6] at room temperature, and the cyclocondensation was completed in about 2 hours (Scheme 11).

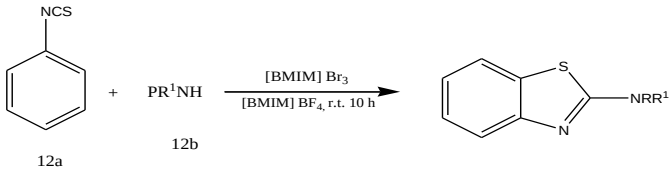


11a 11b 11c

Scheme 11 Synthesis of thiazole derivative (11c)

The ionic liquid was used in a 1:10 molar ratio of reactant to ionic liquid. Importantly, it could be recovered and reused up to three times without a significant loss in product yield (78%, 77%, and 79%). In contrast, when the same reaction was performed in the conventional solvent dichloromethane, the synthesis of 2,4-diphenylthiazoles required heating under reflux for 7 hours [41].

Le et al. [42] developed an effective one-pot method for synthesizing substituted 2-benzothiazoles (12c) using ionic liquids. In this approach, [BMIM][Br_3] was employed as a novel reagent, while [BMIM][BF_4] was used as the reaction medium in a 1:5 molar ratio of reactant to ionic liquid. The reaction involved phenyl isothiocyanate (12a) and various amines (12b) as starting materials (Scheme 12).



12a 12b 12c

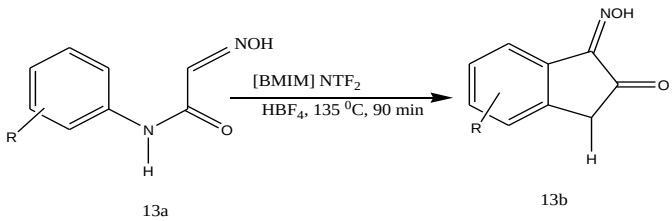
Scheme 12 Synthesis of thiazole derivative (12c)

According to the authors, this procedure offers several clear advantages over previously reported methods, such as better yields and shorter reaction times. In earlier methods, the preparation of compounds like 2-(propylamino) benzothiazole, 2-(N-piperidino) benzothiazole, and pyrrolidinobenzothiazole required overnight reactions and gave only moderate to low yields (73%, 69%, and 7%, respectively) [42].

5.4 Indoles

The indole heterocyclic framework is found in numerous naturally occurring alkaloids known for their medicinal and biological activities. This scaffold has played a significant role in the advancement of natural, chemical, and pharmaceutical sciences, serving as a key structural unit in the synthesis of many complex molecules. Among indole derivatives, isatins are particularly valuable as versatile synthetic intermediates with a wide range of biological and pharmacological properties [43]. Derivatives of these compounds function as potassium channel openers and are used in the treatment of respiratory disorders, seizures, kidney diseases, urinary incontinence, and diarrhea [44].

The most widely used method for synthesizing isatins is the Sandmeyer procedure, which entails reacting anilines with chloral hydrate and hydroxylamine hydrochloride in the presence of a sodium sulfate solution. The resulting isonitrosoacetanilides are then treated with concentrated sulfuric acid to yield isatin derivatives. Over time, several modifications to this original method have been developed to improve the synthesis of these biologically active compounds. Typically, isatin-3-oxime derivatives are obtained from the corresponding isatins by reacting them with hydroxylamine hydrochloride in ethanol under basic conditions [44].



13a 13b

Scheme 13 Synthesis of indoles derivative (13b)

Pinto et al. [45] reported the application of a range of ionic liquids (ILs), namely [BMIM][X] (X = $InCl_4$, PF_6, BF_4, Cl, $AlCl_4$, NTf_2), as reaction media for Lewis and Brønsted acids such as CF_3CO_2H, CH_3SO_3H, p-TSA, $PhB(OH)_2$, HBF_4, $BF_3{\cdot}OEt_2$, and $InCl_3$. These systems were employed to facilitate the direct synthesis of isatin-3-oxime derivatives (13b) from substituted isonitrosoacetanilides (13a). Among the catalysts examined, the combination of [BMIM][NTf_2] and HBF_4 proved to be the most effective for this cyclization process. In the optimized procedure, isonitrosoacetanilide (13a) and HBF_4 were used in a 1:0.05 mmol in the presence of 0.5 mL of [BMIM][NTf_2] (Scheme 13).

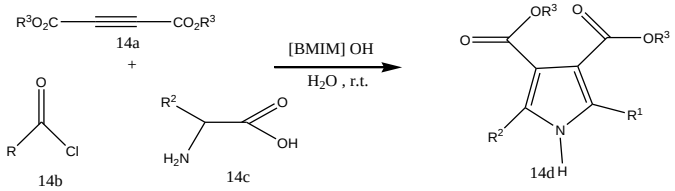
After 90 minutes, unsatisfactory yields were observed only when R = Cl. This outcome was attributed to the strong electron-withdrawing nature of chlorine, which reduces the electron density of the aromatic ring and diminishes its nucleophilicity compared to other substituents. However, when a CF_3 group was present, the negative electronic effect was less significant, and the corresponding isatin-3-oxime was obtained in 73% yield.Notably, substrates bearing a methoxy substituent afforded improved results. The electron-donating character of the methoxy group enhances the nucleophilicity of the aromatic ring, promoting more efficient attack on the electrophilic carbon of the oxime and thereby facilitating formation of the desired isatin-3-oxime product. The study did not report on the recyclability or reuse of the ionic liquid.

5.5 Pyrroles

Pyrroles are an important group of heterocyclic compounds that are widely used in organic synthesis and materials science. Because of their unique chemical properties, many researchers have worked on developing efficient methods to prepare substituted pyrroles.

Generally, 1,2,3,4-tetrasubstituted pyrroles are synthesized using well-known methods such as the Knorr reaction, the Hantzsch pyrrole synthesis [46], or through 1,3-dipolar cycloaddition reactions [47] involving azomethine ylides and alkynes. Traditional approaches to prepare pyrrole derivatives also include condensation reactions of 1,4-dicarbonyl compounds [48].

Yavari et al. [49] reported an efficient method for synthesizing pyrrole derivatives through the reaction of acid chlorides (14b), amino acids (14c), and dialkyl acetylenedicarboxylates (14a) in water using the ionic liquid [BMIM][OH] (Scheme 14).



14a 14b 14c 14d

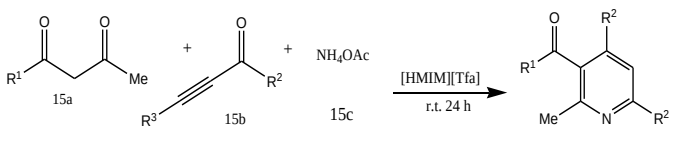
Scheme 14 Synthesis of pyrrole derivative (14d)

6. Synthesis of Six-Membered Heterocycles

6.1 Pyridines

It is widely recognized that 1,4-dihydropyridines possess diverse biological activities [50]. The synthesis of 1,4-dihydropyridines is commonly carried out using the Hantzsch method [51]. The classical Hantzsch synthesis involves a cyclocondensation reaction between two equivalents of ethyl acetoacetate, an aldehyde, and ammonia. This reaction is typically performed in acetic acid or under reflux in alcohol for extended periods, and it generally results in relatively low yields [52].

Karthikeyan and Perumal [53] developed a synthetic approach employing an ionic liquid for the preparation of pyridines(15d). In this method, the corresponding β-ketoesters (15a) were first converted into enaminones, which subsequently underwent in situ heteroannulation via the Bohlmann–Rahtz reaction. The process involves a one-pot, three-component reaction between 1,3-dicarbonyl compounds(15a), ammonium acetate (15c), and alkynones (15b), using [HMIM][Tfa] as the reaction medium, affording the desired products in 80-94% yields (Scheme 15).



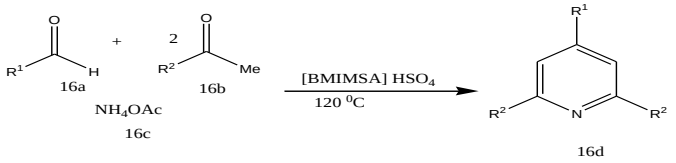
15a 15b 15c 15d

Scheme 15 Synthesis of pyridine derivative (15d)

Davoodnia et al. [54] reported the use of [BMIMSA][HSO_4] as an efficient catalyst for synthesizing a range of 2,4,6-triarylpyridines (16d) through a one-pot, three-component reaction involving acetophenones (16b), aryl aldehydes (16a), and ammonium acetate (16c) (Scheme 16).

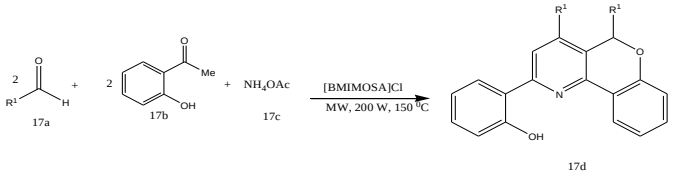
https://doi.org/10.30799/jacs.S306.26120406

Cite this Article as: Yogesh B. Shinde, Sandip S. Pathade, Ionic liquid mediated synthesis of some heterocyclic compounds: A comprehensive review, J. Adv. Chem. Sci. 12(4) (2026) 999–1004.



Scheme 16 Synthesis of Pyridine derivative (16d)

The reaction was carried out using 20 mol % of the ionic liquid, with a molar ratio of 2:1:1.3 for compounds (16b), (16a), and (16c), respectively. Notably, when the ionic liquid was omitted, only trace amounts of the desired product (16d, R^1 = R^2 = Ph) were obtained, even after 4 hours. Various aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents participated effectively in the reaction, affording the corresponding products (16d) in high yields ranging from 82% to 93%. It was observed that aldehydes containing electron-withdrawing groups reacted more rapidly than those with electron-donating groups, which aligns with expected electronic effects. The recyclability of the ionic liquid was evaluated using the model reaction (R^1 = R^2 = Ph). The results showed that the catalyst could be reused at least three times with only a slight decrease in yield (88%, 86%, and 83% over successive runs). Additionally, when the reaction was performed in refluxing acetonitrile with 20 mol % of the ionic liquid, a longer reaction time of 4 hours was required, and the product was obtained in a reduced yield of 60%. Wu et al. [55] reported the application of [BMIMOSA][Cl] as a reaction medium for synthesizing chromeno[4,3-b]pyridines (17d). These compounds were prepared via a cyclocondensation reaction involving aromatic aldehydes (17a), ammonium acetate (17c), and 2′-hydroxyacetophenone (17b) (Scheme 17). using a reactant-to-ionic liquid molar ratio of 1:4.



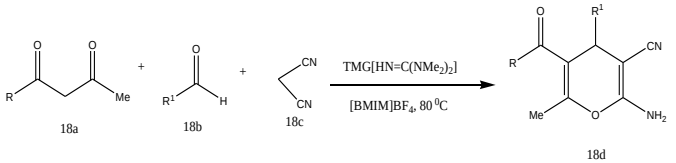
Scheme 17 Synthesis of pyridine derivative (17d)

It was found that aldehydes bearing electron-donating substituents provided higher yields. Moreover, both the electronic properties and steric effects of substituents on the aromatic aldehyde significantly affected the reaction outcome. When the reaction was carried out in the absence of the ionic liquid, the target product was not formed.

6.2 Pyrans

Polyfunctionalized 4H-pyrans are considered an important class of heterocyclic compounds, as numerous derivatives exhibit significant pharmacological activities [56]. Furthermore, the intrinsic reactivity of the pyran ring makes these compounds valuable intermediates in organic synthesis. In particular, 2-amino-4H-pyrans are commonly synthesized through the reaction of arylidenemalonitriles with activated methylene compounds, typically in the presence of organic bases [57]. Additionally, a wide range of studies have reported the use of ionic liquids as efficient media or catalysts for pyran-forming reactions.

Peng et al. [58] reported the preparation of 2-amino-4H-pyrans (18d) through a multicomponent reaction involving malononitrile (18c), aryl aldehydes (18b), and 1,3-dicarbonyl compounds (18a), employing ionic liquids as a soluble support. In their work, a TMG–[BMIM][BF_4] system was used in a 1:3 molar ratio (reactants to ionic liquid). The ionic liquid could be recovered and reused up to five times without any significant loss in product yield, as illustrated in Scheme 18.



Scheme 18 Synthesis of pyran derivatives (18d)

The study also examined the influence of substituents on the phenyl ring. Results indicated that electron-donating groups reduced product formation, whereas electron-withdrawing groups enhanced the yield. Moreover, when compared to ethanol as a solvent (which afforded yields of 60–80%), the ionic liquid system proved more efficient, providing higher isolated yields and faster reaction rates.

7. Integration of Ionic Liquids with Advanced Techniques

The combination of ionic liquids with modern activation techniques such as microwave irradiation and ultrasound has further expanded their applicability. Microwave-assisted IL-mediated reactions often exhibit dramatically reduced reaction times and enhanced yields due to efficient energy transfer [59]. Similarly, ultrasound promotes improved mass transfer and reaction kinetics in ionic liquid media [60]. Additionally, ILs have been successfully integrated with metal-free methodologies, offering environmentally friendly alternatives to metal-catalyzed processes. These strategies are particularly attractive for pharmaceutical synthesis, where metal contamination is a major concern [61].

8. Conclusion

Ionic liquids have emerged as highly versatile and environmentally friendly media for the synthesis of heterocyclic compounds, offering unique advantages such as negligible vapour pressure, tunable polarity, high thermal stability, and recyclability. Their dual role as solvents and catalysts has enabled more efficient, selective, and sustainable synthetic routes for a wide range of heterocycles, including aziridines, β-lactams, imidazoles, pyrazoles, thiazoles, indoles, and pyrroles. The use of ILs has improved reaction rates, yields, and product purities, while facilitating milder reaction conditions and simplified workup procedures. Integration with advanced techniques such as microwave irradiation, ultrasound, and metal-free protocols has further enhanced their practical applicability. Mechanistic studies highlight the critical influence of IL structure on reactivity and selectivity, enabling rational design of task-specific ILs for targeted transformations. Despite challenges related to cost, toxicity, and large-scale application, ILs represent a powerful and sustainable platform for green heterocyclic synthesis. Future research should focus on developing biodegradable, low-cost ILs and expanding their use in industrial and continuous-flow processes, reinforcing their role in advancing environmentally responsible and efficient organic synthesis.

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Special Issue Publication Statement

This article is included in the Special Issue of the journal comprising peer-reviewed papers selected from the International Conference on "Frontiers in Chemical and Material Sciences (ICFCMS-2026)", held on 3rd and 4th February 2026 at MGV's Maharaja Sayajirao Gaikwad Arts, Science and Commerce College, Malegaon Camp, Malegaon, Nashik – 423 105, Maharashtra, India.

https://doi.org/10.30799/jacs.S306.26120406

Cite this Article as: Yogesh B. Shinde, Sandip S. Pathade, Ionic liquid mediated synthesis of some heterocyclic compounds: A comprehensive review, J. Adv. Chem. Sci. 12(4) (2026) 999–1004.