IOSR Journal of Multidisciplinary Research (IOSR -JMR)
ISSN: 3048-7439 (January 2026) PP 28-32
www.iosrjournals.org

Exploring the utility of ionic liquids in the synthesis of N-heterocycles

Pravin R. Kharade[1,2*], Dipak S. Gaikwad[3], Rohit R. Powar[4], Satish S. Kadam[5], Kiran N. Patil[6], Uttam A. Khot[7], Sandip D. Gorshettwar[8], Prakash S. Pawar[8], Vikram M. Desai[9], Savita S. Desai[2]
[1]*(Department of Chemistry, Karmaveer Hire Arts, Science, Commerce & Education College, Gargoti, Maharashtra – 416209, India)*
[2]*(Research Laboratory in Heterocyclic Chemistry, Devchand College, Arjunnagar, Maharashtra – 416216, India)*
[3]*(Department of Chemistry, Shikshanmaharshi Dr. Bapuji Salunkhe College, Miraj, Maharashtra – 416209, India)*
[4]*(Department of Chemistry, Doodhsakhar Mahavidyalaya, Bidri, Maharashtra – 416216, India)*
[5]*(Department of Chemistry, Vivekanand College, Kolhapur (An empowered autonomous institute), Maharashtra – 416004, India)*
[6]*(Department of Chemistry, Dr. Ghali College, Gadhinglaj, Maharashtra – 416209, India)*
[7]*(Department of Basic Sciences and Humanities, KIT's College of Engineering, Kolhapur, Maharashtra – 416216, India)*
[8]*(Department of Chemistry, Shri Yashawantrao Patil Science College, Solankur, Maharashtra – 416209, India)*
[2]*(Department of Chemistry, Smt. Kasturbai Walchand College, Sangli, Maharashtra – 416209, India)*

Abstract:
Background*: Nitrogen-containing heterocycles represent indispensable scaffolds in numerous pharmaceuticals, agrochemicals, dyes, and functional materials. Traditional synthetic approaches for N-heterocycles frequently involve volatile organic solvents, corrosive reagents, or non-reusable catalysts, leading to environmental concerns and limited sustainability. In response, the adoption of greener reaction media and catalytic systems has become major focus of contemporary synthetic chemistry. Ionic liquids (ILs) owing to their negligible vapor pressure, high thermal stability, tunable physicochemical properties, and ability to act as solvents and/or catalysts, have emerged as attractive alternatives for the sustainable synthesis of nitrogen heterocycles.*
Materials and Methods*: Various classes of ionic liquids, including imidazolinium-, pyridinium-, and ammonium-based ILs, were utilized as reaction media and catalytic promoters for the synthesis of diverse N-heterocyclic frameworks from readily available starting materials. The reactions were conducted under relatively mild conditions, where ionic liquids facilitated key bond-forming steps through enhanced solvation, hydrogen bonding, and ionic interactions. After completion, products were recovered and reused in subsequent cycles. Product structures and purity were confirmed using standard spectroscopic and analytical methods.*
Results*: The use of ionic liquids enabled efficient synthesis of a wide range of nitrogen heterocycles such as imidazoles, pyrimidines, quinazolines, indoles, pyrazoles, triazoles, quinolines, pyrazines, and pyrazolo-phthalazines, affording good to excellent yields with reduced reactions times. The ionic liquids demonstrated high stability and retained their activity over multiple reuse cycles without significant loss of efficiency. Enhanced selectivity, and cleaner reaction profiles were also observed compared to conventional solvent systems.*
Conclusion: *Ionic liquids serve as versatile, environmentally benign, and recyclable media for the synthesis of nitrogen heterocyclic compounds. Their dual role as solvents and catalysts, combined with operational simplicity and reusability, highlights their significant potential in green and sustainable heterocyclic synthesis scalable organic transformations.*
Key Word*: Ionic liquids, nitrogen heterocycles, green synthesis, recyclable media, sustainable catalysis.*

I. Introduction

Nitrogen-containing heterocyclic compounds represent one of the most important classes of organic molecules due to their extensive presence in natural products, pharmaceuticals, agrochemicals, paints, dyes and polymeric materials. Statistical analyses reveal that more than half of all FDA-approved small-molecule drugs contain at least one nitrogen heterocycle, underscoring their indispensable role in the medicinal chemistry.[1-3] Structural motifs such as imidazoles, pyrimidines, quinazolines, pyrazoles, pyrazines, triazoles, indoles and phthalazines are frequently associated with diverse biological activities including anticancer, antimicrobial, antiviral and anti-inflammatory properties.[4-6] Beyond drug discovery, nitrogen heterocycles also serve as key components in dyes, ligands, catalysts and organic electronic materials.[7,8]

Traditional synthetic methodologies for N-heterocycles often suffer from significant drawbacks including the use of volatile organic solvents, toxic reagents, prolonged reaction times and non-recycled homogeneous catalysts. These processes typically generate large quantities of waste and rise serious environmental and safety concerns, conflicting with the fundamental principles of green and sustainable chemistry.[9-11] Consequently, the development of environmentally benign, efficient and reusable reaction systems has become a central objective in contemporary heterocyclic synthesis.

In recent years, ionic liquids (ILs) have emerged as promising alternatives to conventional solvents and catalysts. Ionic liquids are salts composed of entirely of ions that exist in the liquid state at or near room temperature. Their unique physicochemical properties-such as negligible vapor pressure, high thermal stability, wide electrochemical window and excellent solvating ability-make them attractive for sustainable chemical transformations.[12-14] importantly, the tunability of ionic liquids through rational selection of cations and anions enables the design of task-specific ILs for targeted reactions.[15]

The application of ILs in organic synthesis has expanded rapidly, particularly in heterocyclic chemistry. Ionic liquids can function simultaneously as solvents and catalysts, facilitating bond-forming reactions via hydrogen binding, electrostatic interactions and stabilization of charged intermediate.[16,17] these features often result in enhanced reaction rates, improved selectivity and higher product yields compared to traditional solvent systems.[18] Moreover, the ability of ILs to dissolve both organic substrates and inorganic catalysts enables their use in multicomponent and one-pot reactions, which are highly desirable from a green chemistry perspective.[19]

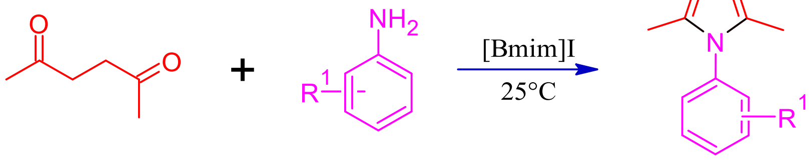
Another significant advantage of ILs is their recyclability. Due to their low volatility and thermal robustness, ILs can be recovered and reused multiple times with minimal loss of catalytic activity, thereby reducing waste generation and operational costs.[20] Numerous studies have demonstrated the successful synthesis of a wide variety of nitrogen heterocycles-including imidazoles, pyrimidines, quinazolines, pyrazoles, pyrazines, triazoles, indoles and phthalazines- using ILs under mild and sustainable conditions.[21-24] These attributes position ILs as versatile and powerful tools for advancing green synthetic methodologies in heterocyclic chemistry.

II. Synthesis of ionic liquids (ILs)

Ionic liquids are generally synthesized through straightforward and versatile procedures that allow precise control over their structural and physicochemical properties. Most ionic liquids are prepared via a two-step process involving the formation of an organic cation followed by anion exchange. In the first step, quaternization reactions are carried out by alkylating nitrogen-, phosphorous-, or sulfur-containing heterocycles or amines, such as imidazoles, pyridines or ammonium salts, using appropriate alkyl halides to generate the desired cationic framework. The resulting halide-based ionic liquids are then subjected to metathesis or acid-base neutralization reactions to replace the halide anion with more weakly coordinating or functional anions, including tetrafluoroborate, hexafluorophosphate, bis(trifluoromethylsulfonyl)imide or organic anions. These transformations are typically conducted under mild conditions and often proceed in high yields with minimal byproduct formation. Advances in synthetic strategies have also enabled one-pot solvent-free and microwave-assisted approaches, further improved the efficiency and sustainability of ionic liquid synthesis while allowed fine-tuning of properties such as polarity, viscosity and thermal stability for targeted applications.

III. Applications of ionic liquids in the synthesis of N-heterocycles

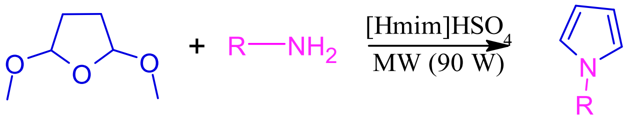
Wang *et. al.*[25] have described a synthesis of *N*-substituted-2,5-dimethylpyrrole with an aid of 1-butyl-3-methylimidazolium iodide [BMIM]I (**Scheme 1**). The reaction between 2,5-hexandione with substituted amines easily afforded desired pyrrole derivatives. The reaction was carried out at room temperature and the yields of the products obtained were about 95%. Simple product isolation, short reaction time, high yields are few key features of this method.



R = *n*-propyl, *n*-butyl, cyclohexyl, benzyl, phenyl, tolyl, *p*-nitrophenyl

Scheme 1

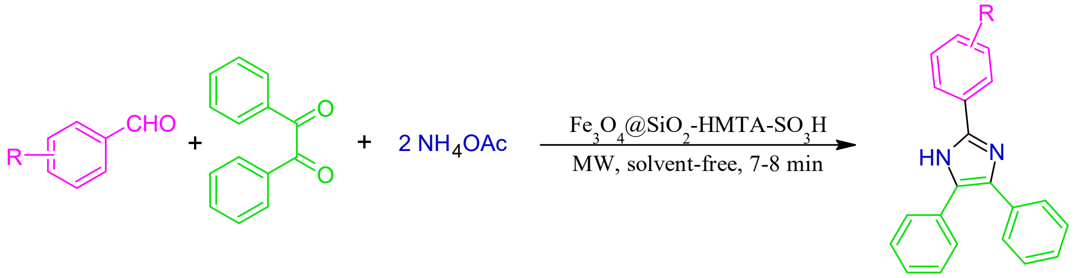
Yolacan and his research[26] group reported acidic ionic liquid [Hmim}HSO_4 mediated synthesis of N-substituted pyrrole from 2,5-dimethoxytetrahydrofuran and substituted amines under microwave irradiation (**Scheme 2**).



10 examples, Yield – 85-95%, Time – 3-5 min

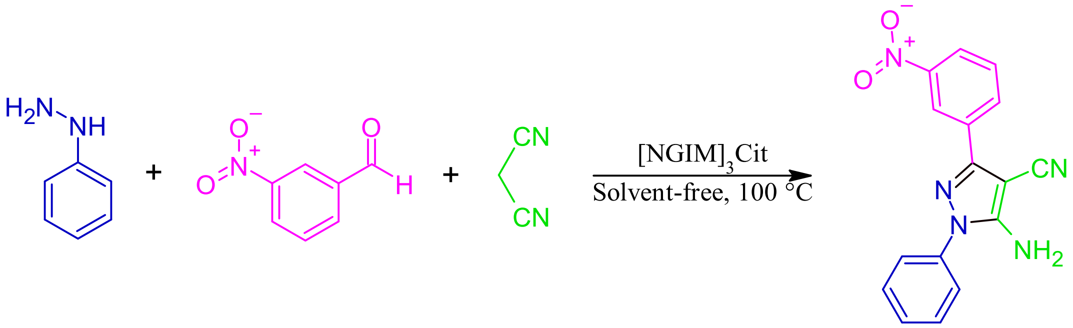
Scheme 2

Naemi and research group[27] explored a microwave assisted synthesis of 2,4,5-trisubstituted imidazoles from a three component one pot cyclocondensation of substituted aldehydes, benzil and ammonium acetate under solvent free conditions (**Scheme 3**). In this method, an immobilized HMTA-based IL functionalized with silica coated magnetite magnetic nanocatalyst viz. Fe_3O_4@SiO_2-HMTA-SO_3H which was recycled for 6 times.



Scheme 3

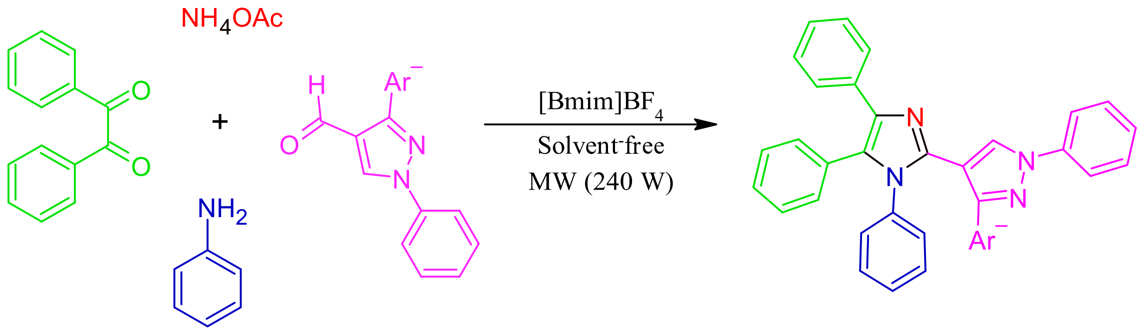
Naura *et.al.*[28] used nano gelatoric ionic liquids [NGIM]3Cit in the synthesis of pyrazole derivatives from a reaction between phenyl hydrazine, malononitrile and substituted aldehydes under solvent-free conditions (**Scheme 4**). The reaction proceeded within 10 minutes yielding 93% pyrazole.



Time – 10 min, Yield – 93%

Scheme 4

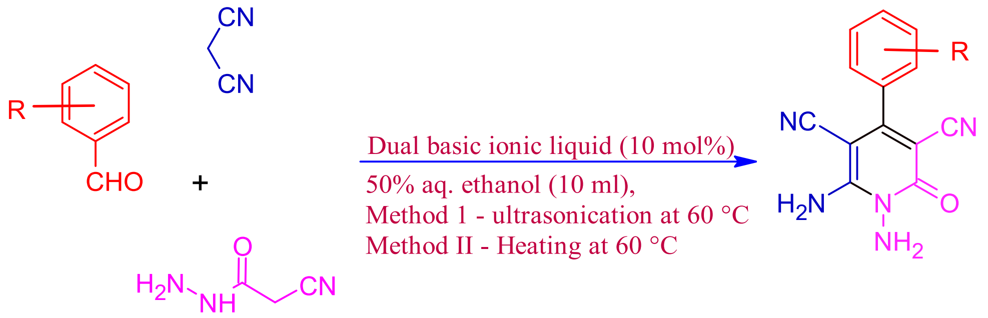
G. D. Shirole and coworkers[29] have reported the synthesis of imidazole derivatives via a multicomponent condensation reaction between 1,2-dione, aromatic amines, pyrazole aldehydes and ammonium acetate using 1-butyl-3-methyl-1-imidazolium tetrafluoroborate [BMIM][BF4] ionic liquid (**Scheme 5**). The reaction was carried out under microwave irradiation and conventional heating.



11 examples, Time – 10-12 minutes, Yield – 85-86 %

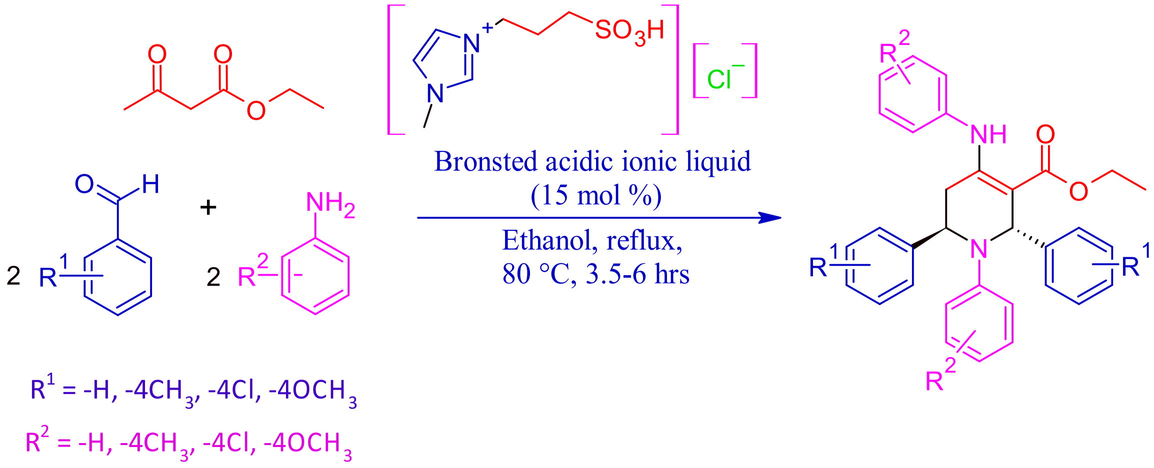
Scheme 5

P. Kharade *et. al.*[30] reported a synthesis of N-amino-3-cyano-2-pyridone derivatives using a basic ionic liquid (**Scheme 6**). The reaction of substituted aromatic/heteroaromatic aldehydes with malononitrile followed by subsequent condensation with cyanoacetohydrazide easily afforded the products in 30-45 minutes with 95-98% yield under ultrasound irradiation. This approach offered numerous advantages such as an ecofriendly and robust catalyst, mild reaction conditions, avoidance of corrosive, toxic, expensive catalysts and solvents, easy workup method, high yields of products in short reaction time.



Scheme 6

P. Kharade and his coworkers[31] have synthesized tetrahydropyridines derivatives using sulfonic acid functionalized Bronsted acidic ionic liquid (**Scheme 7**). The reaction between two moles of aldehydes, two moles of aromatic amines and one mole of ethyl acetoacetate in ethanol-water (1:1) solvent easily afforded the products with 89-95% yield. This protocol possesses several advantages such as operational simplicity, easy workup, high yield of product, less reaction times.



Scheme 7

IV. Conclusion

The present study highlights the effectiveness of ionic liquids as green and sustainable alternatives to conventional solvents and catalysts in the synthesis of nitrogen-containing heterocycles. By virtue of their unique physicochemical properties, ionic liquids enable efficient bond-forming processes under mild reaction conditions, leading to improved reaction rates, high product yields, and enhanced selectivity. Their ability to function simultaneously as reaction media and catalytic promoters, coupled with excellent thermal stability and recyclability, significantly reduces waste generation and environmental impact. The successful synthesis of a broad spectrum of biologically and industrially relevant N-heterocyclic frameworks demonstrates the versatility and robustness of ionic liquid-based systems. Overall, these findings underscore the considerable potential of ionic liquids in advancing environmentally benign and scalable synthetic methodologies, thereby contributing meaningfully to the development of sustainable heterocyclic chemistry and green organic synthesis.

References

[1]. Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem. 2014;57(24):10257–10274.

[2]. Eicher T, Hauptmann S, Speicher A. The Chemistry of Heterocycles. 3rd ed. Weinheim: Wiley-VCH; 2013.

[3]. Joule JA, Mills K. Heterocyclic Chemistry. 5th ed. Chichester: Wiley; 2010.

[4]. Katritzky AR, Rees CW, Scriven EFV. Comprehensive Heterocyclic Chemistry II. Oxford: Pergamon Press; 1996.

[5]. Michael JP. Quinoline, quinazoline and acridone alkaloids. Nat Prod Rep. 2008;25(1):166–187.

[6]. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules. 2020;25(8):1909.

[7]. Fabian J, Nakazumi H, Matsuoka M. Near-infrared absorbing dyes. Chem Rev. 1992;92(6):1197–1226.

[8]. Roncali J. Molecular engineering of the band gap of π-conjugated systems: facing technological applications. Chem Rev. 1997;97(1):173–206.

[9]. Sheldon RA. Green solvents for sustainable organic synthesis: state of the art. Green Chem. 2005;7(5):267–278.

[10]. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. Oxford: Oxford University Press; 1998.

[11]. Clark JH, Macquarrie DJ. Handbook of Green Chemistry and Technology. Oxford: Blackwell Science; 2002.

[12]. Welton T. Room-temperature ionic liquids: solvents for synthesis and catalysis. Chem Rev. 1999;99(8):2071–2084.

[13]. Plechkova NV, Seddon KR. Applications of ionic liquids in the chemical industry. Chem Soc Rev. 2008;37(1):123–150.

[14]. Hallett JP, Welton T. Room-temperature ionic liquids: solvents for synthesis and catalysis. 2. Chem Rev. 2011;111(5):3508–3576.

[15]. Wasserscheid P, Keim W. Ionic liquids—new "solutions" for transition metal catalysis. Angew Chem Int Ed. 2000;39(21):3772–3789.

[16]. Dupont J, de Souza RF, Suarez PAZ. Ionic liquid (molten salt) phase organometallic catalysis. Chem Rev. 2002;102(10):3667–3692.

[17]. Olivier-Bourbigou H, Magna L, Morvan D. Ionic liquids and catalysis: recent progress from knowledge to applications. Appl Catal A Gen. 2010;373(1–2):1–56.

[18]. Parvulescu VI, Hardacre C. Catalysis in ionic liquids. Chem Rev. 2007;107(6):2615–2665.

[19]. Zhao D, Wu M, Kou Y, Min E. Ionic liquids: applications in catalysis. Catal Today. 2002;74(1–2):157–189.

[20]. Wasserscheid P, Welton T, editors. Ionic Liquids in Synthesis. 2nd ed. Weinheim: Wiley-VCH; 2008.

[21]. Jain N, Kumar A, Chauhan S, Chauhan SMS. Chemical and biochemical transformations in ionic liquids. Tetrahedron. 2005;61(5):1015–1060.

[22]. Zolfigol MA, Khazaei A, Mokhlesi M, Vahedi H. Ionic liquids as recyclable catalysts in heterocyclic synthesis. J Mol Liq. 2017;248:934–954.

[23]. Kappe CO, Dallinger D. The impact of microwave synthesis on drug discovery. Nat Rev Drug Discov. 2006;5(1):51–63.

[24]. Polshettiwar V, Varma RS. Green chemistry by nano-catalysis. Green Chem. 2010;12(5):743–754.

[25]. Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. Pyrrole synthesis in ionic liquids by Paal–Knorr condensation under mild conditions. Tetrahedron Lett. 2004, 45:3417–3419.

[26]. Li, D.; Zang, H.; Wu, C.; Yu, N. 1-Methylimidazolium hydrogen sulfate catalyzed convenient synthesis of 2,5-dimethyl-Nsubstituted pyrroles under ultrasonic irradiation. Ultrason. Sonochem. 2013, 20:1144–1148.

[27]. Naeimi H., Aghaseyedkarimi D., Ionophore silica-coated magnetite nanoparticles as a recyclable heterogeneous catalyst for one-pot green synthesis of 2,4,5-trisubstituted imidazole, Dalt. Trans. 2016, 45:1243-1253.

[28]. Noura, S.; Ghorbani, M.; Zolfigol, M.A.; Narimani, M.; Yarie, M.; Oftadeh, M. Biological based (nano) gelatoric ionic liquids (NGILs): Application as catalysts in the synthesis of a substituted pyrazole via vinylogous anomeric based oxidation. J. Mol. Liq. 2019, 271:778–785.

[29]. Shirole, G.D.; Kadnor, V.A.; Tambe, A.S.; Shelke, S.N. Brønsted-acidic ionic liquid: Green protocol for synthesis of novel tetrasubstituted imidazole derivatives under microwave irradiation via multicomponent strategy. Res. Chem. Intermed. 2017, 43:1089–1098.

[30]. Kharade P et.al. [DMAP-DABCO]AcO as a basic ionic liquid for ultrasound assisted domino synthesis of *N*-amino-2-pyridone derivatives and their molecular docking study, Res. Chem. Intermed., 2025.

[31]. Kharade PR, Chougale UB, Gaikwad DS, Kadam SS, Patil KN, Rathod SS, Choudhari PB, Desai SS. Synthesis and in vitro evaluation of tetrahydropyridines as potential CDK2 and DprE1 inhibitors, Res. Chem. Intermed., 2024, 50:1777-1808.