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REVIEW ARTICLE

Synthesis of *N*-heterocyclic compounds: A green approach using deep eutectic solvents

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ABSTRACT

The synthesis of *N*-heterocyclic compounds is an important area of organic chemistry that provides tremendous potential for the development of new products with vital applications in our daily life, like- pharmaceuticals, dyes, agrochemicals, and more generally, engineered materials with inventive properties. As *N*-heterocyclic compounds are used in numerous industries and are produced in very large amounts, the development of sustainable methods for their synthesis has become a key goal for modern green chemistry, which aims to reduce the environmental impact of chemical processes. In this context, the current review is focused on new methodologies to synthesize *N*-heterocyclic compounds in deep eutectic solvents, a new category of ionic solvents that are non-toxic, non-volatile, easily prepare, easily recyclable, and can be derived from renewable sources. Focus has been put on those techniques that recycle the catalyst and solvent on prior basis, as they provide the dual benefit of promoting synthetic efficiency while exhibiting environmental responsibility.

KEY WORDS: Deep eutectic solvents, H-bond catalysis, *N*-heterocyclic compounds

INTRODUCTION

Nitrogen-containing heterocycles are extremely beneficial compounds that are used in a variety of areas, including the synthesis of chemicals and materials. Moreover, the presence of *N*- heterocyclic cores in the structure of various compounds is another characteristic that distinguishes the compounds with notable biological and pharmacological activity.[1] Over the years, as a result of extensive environmental problems, more focus has been placed on the development of new approaches for the synthesis of *N*-heterocyclic compounds, characterized by more eco-friendly and green settings, particularly to avoid the use of toxic and volatile organic solvents. Deep eutectic solvents (DESs) have drawn a lot of attention in recent years as a green and long-lasting substitute for conventional ionic liquids and volatile organic solvents in organic synthesis.[2,3] In reality, as one of the green chemistry principles,[4] the use of DESs in the synthesis of heterocyclic compounds is acquiring more and more attention. As shown in Figure 1, the molecular structures of *N*-heterocyclic cores are reviewed.

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DESs

First, DES were reported by Abbott *et al*. in the year 2003.[5] DESs are defined as a mixture of at least two components (cheap, renewable, and biodegradable), that are capable of forming a eutectic mixture with a melting point lower than each individual component. They are also known as low transition temperature mixtures since some of these mixtures could exhibit a glass transition temperature point rather than a strict melting point.[3,6] Based on their composition, DESs are now classified into five main types.[3,7] Among all five, type III DESs are a preferred choice due to their high degree of environmental

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sustainability, as they often utilize components obtained from natural sources. They are made up of different molar ratios of hydrogen bond acceptors, such as quaternary ammonium salts, and hydrogen bond donors (HBD). Urea or its derivatives, glycerol, various polyols, carboxylic acids, carbohydrates, etc. are commonly employed as HBDs.[6] The utilization of DESs as green media in the synthesis of organic compounds including heterocycles has increased significantly over the last few years due to their low toxicity, chemical stability, easy preparation, non-volatility, non-flammability, biodegradability, and recyclability.[3,6,8] In general, the eutectic mixture plays an important role in the chemical transformation as described in this review. Because of the strong connection of hydrogen bonds between reagents (or reaction intermediates) and DES components, DES not only acts as an eco-friendly solvent but also could be used as a catalyst. Additionally, DESs also provide a number of advantages that make them a desirable option for a variety of applications. These include easy work-up processes, speedy reactions, high yields of desired products, mild reaction conditions, availability, affordability, and the option for reusing the eutectic mixture, all of which impart to the effectiveness of reported methodologies. This Review, providing contributions on the synthesis of *N*-containing heterocyclic compounds in a variety of DESs, aims to deliver an overview of the developments made in the field of sustainable synthesis of *N*- containing heterocycles from the year 2019 to date. In Figure 2, the molecular structures of the deep eutectic mixtures are reported.

PREPARATION OF *N*-CONTAINING HETEROCYCLIC COMPOUNDS IN DES MIXTURES

Among the various kinds of heterocyclic compounds, imidazole-containing moieties are well known due to their wide range of chemical and biological functions. Different therapeutic activities such as anti-hypertensive, analgesics, anti-fungal, anti-obesity, anti-tumor,[9] antiviral, anti-tubercular, anthelmintic,[10] anti-histaminic, anti-ulcer,[11] anti-inflammatory, anti-depressant,[12] anti-diabetic,[13] anti-convulsant,[14] anti-allergic, anti-rheumatic,[15] alpha-blockers, anti-asthmatic,[16] anti-protozoal,[17] anti-aging, anti-malarial, anti-coagulant,[18] and anti-amoebic activity[19] have been shown by imidazole and its derivatives.

According to Vitale *et al*., functionalized imidazole derivatives (3/3') were synthesized using choline chloride (ChCl)/glycerol (gly) (1:2) as a DES in the year 2020. Notably, it was found that bromo- and chloromethyl ketones 1 when reacted with NaN_3 at 80°C for 4–16 h, could be simply changed into a mixture of two tautomeric forms of imidazole derivatives [2-aroyl-(4 or 5)-aryl-(1H)-imidazoles (3/3')] by forming arylacyl azide 2 as an intermediate step. This method enabled the synthesis of a variety of heterocyclic compounds (3/3') in yields varying from 32% to 98% [Scheme 1]. Hydrogen bond catalysis facilitated by DES entities could play a vital role in favor the process. It is remarkable how the researchers, using a similar procedure, were able to develop the synthesis of a regio-divergent. Indeed, the conversion of aryl acylazide intermediate 2 into pyrimidine derivatives was observed,

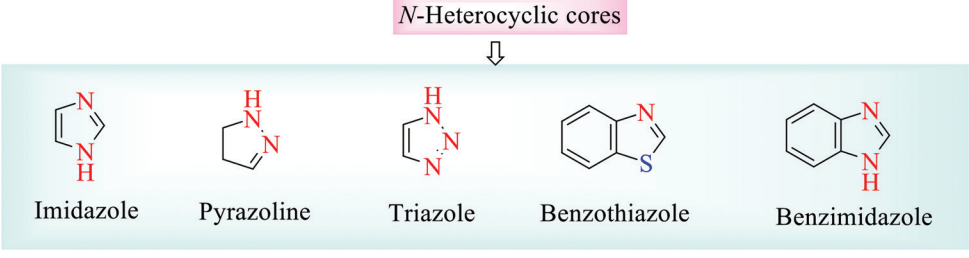


Figure 1: Molecular structures of *N*-heterocyclic cores

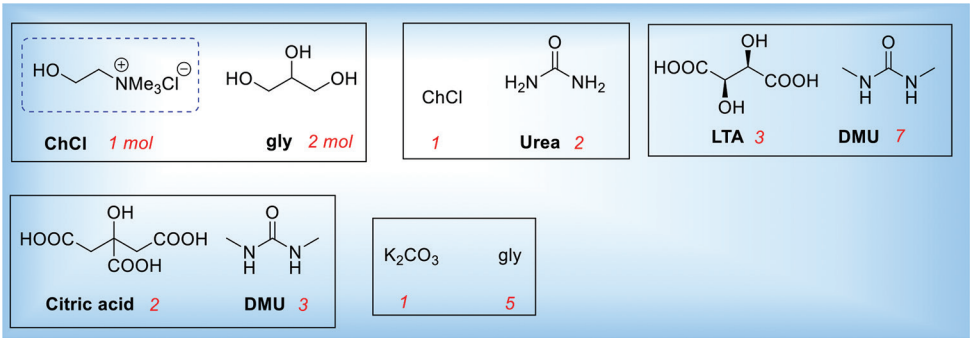


Figure 2: Molecular structures of heterocyclic moieties and deep eutectic solvents (with molar ratio) reviewed. ChCl: Choline chloride, gly: Glycerol, LTA: *L*-(+)-tartaric acid, DMU: *N, N'*-dimethylurea. The molar ratio of DES components is shown in red

which were achieved by using ChCl/urea (1:2 mol/mol) as a non-innocent reaction medium, and by changing the reaction temperature (25°C or 80°C) as well as the absence or presence of bases like Et_3N.[20]

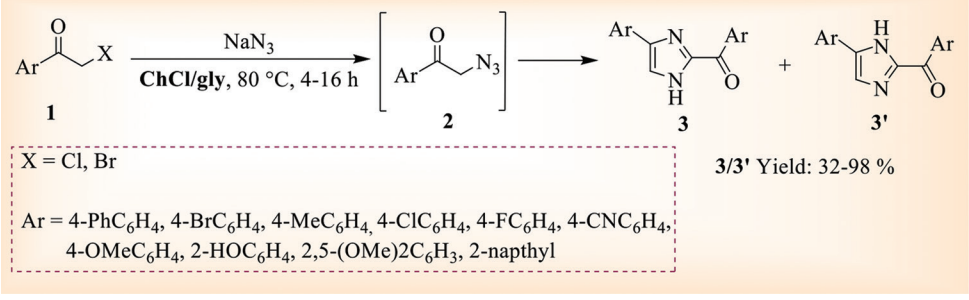
Furthermore, the application of heterogeneous catalysts in the C-H activation field, particularly C-H arylation processes, has drawn a lot of attention in recent years.[21] In this instance, direct C-H arylation reactions of heteroarenes with aryl halides, catalyzed by palladium, are now the most effective way to synthesize biaryl or aryl-heteroaryl compounds.

In 2019, Shariatipour *et al*. described a regioselective synthesis of C5-arylated imidazole derivatives, in K_2CO_3/gly (1:5) mixture as an alkaline DES under aerobic conditions. Particularly, in the presence of a modified magnetic reduced graphene oxide supported palladium catalyst (MRGO@ DAP-AO-Pd^{II}), a magnetically separable and recyclable heterogeneous catalyst, the direct regioselective C−H arylation reactions via C−H bond activation pathway were achieved in environmentally safe conditions between substituted imidazoles 4 and substituted aryl bromides 5, at 130°C, for 17 h, and synthesized a range of imidazole derivatives 6 in moderate-to-excellent yields [45–95%, Scheme 2]. This catalytic arylation protocol was performed under sustainable reaction conditions using green solvent and, showed a broad substrate scope. The catalyst was also recycled at least 7 times without significantly lowering the yield of reaction and the heterogeneous character of catalyst was demonstrated by hot filtration and Hg (0) poisoning.[22]

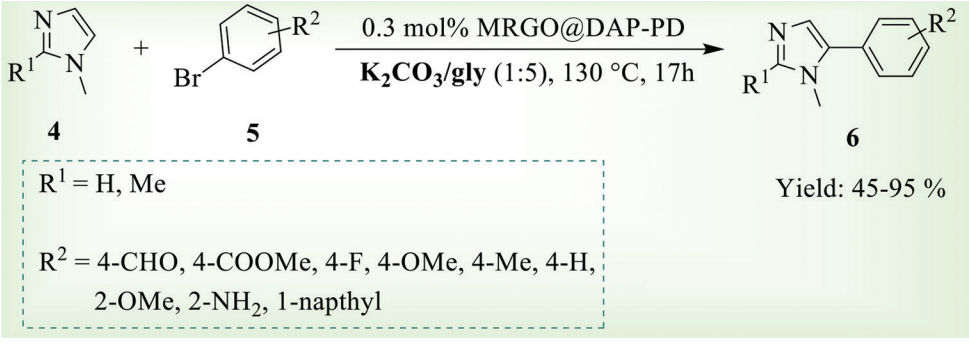
Pyrazolines are a class of bioactive nitrogen-containing heterocycles that exist in a wide range of chemical and biological agents and increase their therapeutic activities such as anti-viral, anti-bacterial, anti-fungal, anti-tubercular, anti-parasitic, anti-inflammatory, analgesic, anti-cancer, etc.[23]

In 2020, Sebest *et al*. described the synthesis of substituted 2-pyrazolines 10, through a (3+2) cycloaddition reaction between electron-deficient azides 7 and alkenes 8 by forming a transient 1, 4-disubstituted triazoline 9 intermediate in various DESs [Scheme 3]. Out of all DESs, ChCl/urea (1:2) was found to be the best reaction medium that reduced the amount of volatile organic solvents used in the reaction and substituted the base which promotes the preparation of 2-pyrazolines. Among all DESs, the eutectic mixture, ChCl/urea was found to be the most suitable reaction medium that significantly reduced the amount of volatile organic solvents used in the reaction and also substituted the base which promotes the preparation of substituted 2-pyrazolines. Further, the low vapor pressure of DES allowed the reaction to proceed at greater temperatures compared to previously reported solvents (typically methanol or toluene), greatly decreasing the reaction time. Depending on the electron-deficient alkene derivatives used in the chemical reaction, it should be pointed out that a variety of heterocycles, including triazoles, aziridines, or triazolines, could be prepared as reaction products.[24]

Among the various heterocyclic systems, benzothiazoles and benzimidazoles are two of the most significant



Scheme 1: Synthesis of 2-aroyl-(4 or 5)-aryl-(1*H*)-imidazoles 3/3' in choline chloride/glycerol deep eutectic solvents



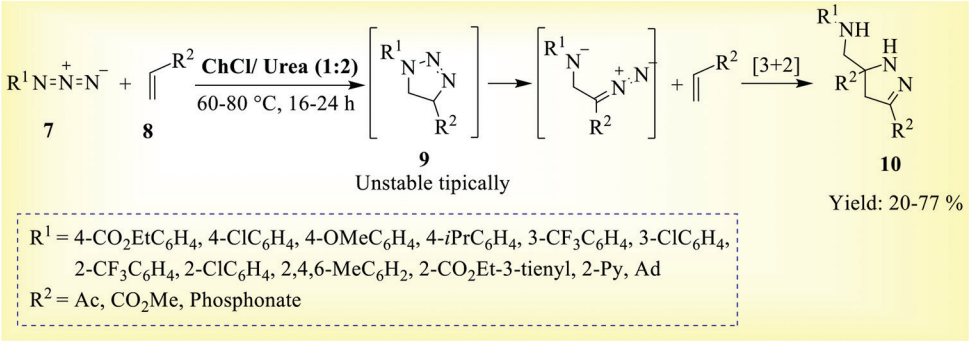
Scheme 2: Synthesis of C5 arylated imidazole derivatives 6 in K_2CO_3/glycerol deep eutectic solvents

heterocyclic systems, with privileged biological and optical features that make them useful in drug discovery, material science, medicine, polymer chemistry, fluorescent probes, sensors, photosensitizers, calcium channel antagonists, and organocatalysis, etc.

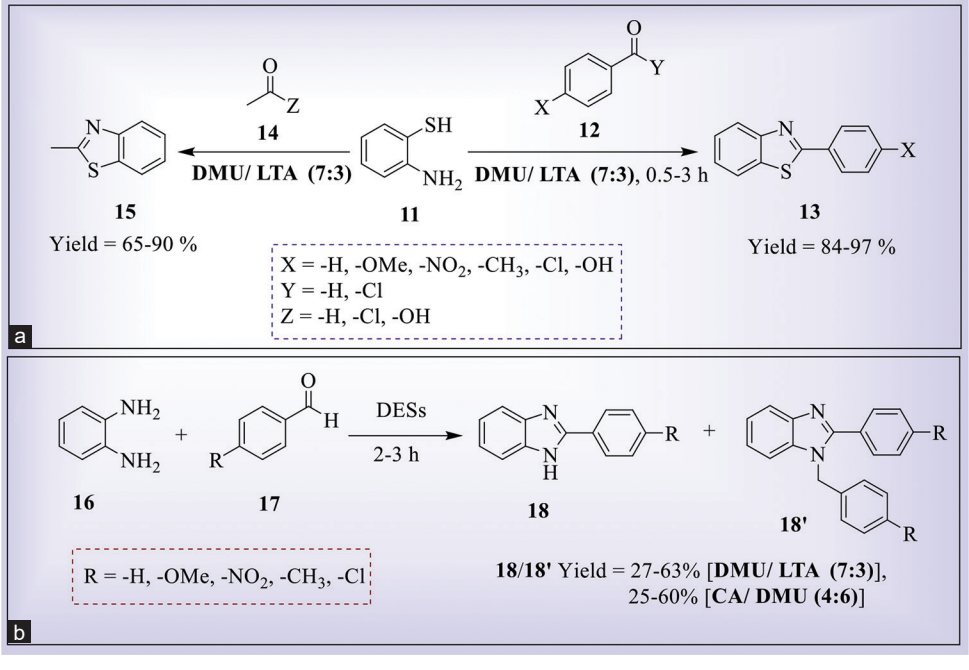
In 2022, Wagay *et al*. reported the synthesis of a variety of 2-substituted benzothiazole and benzimidazole derivatives, in environmentally benign *N, N'*-dimethylurea (DMU)-based eutectic mixtures (DMU/*L*-(+)-tartaric acid [LTA] and citric acid/DMU), [Scheme 4]. Only 2-substituted benzothiazoles 13/15 (mono-condensed products) were obtained by reacting aromatic aldehydes 12 and/or aliphatic aldehydes 14 with 2-aminobenzenethiol 11 which have good to excellent yield 84–97%[13] and 65–90%[15] in DMU: LTA mixture) [Scheme 4a**]**, while mono-substituted and/or di-substituted benzimidazoles 18/18' with moderate to good yield (27–63% in DMU: LTA and 25–60% in CA: DMU mixtures), were formed by condensing *o*-phenylenediamine 16 with substituted aromatic aldehydes 17 [Scheme 4b]. Moreover, the eutectic mixtures used in these reactions were found to play a dual role both as catalyst and reaction medium, and they could be recycled up to four consecutive runs without lowering their efficiency. These metal-free protocols were performed under mild reaction conditions and showed a broad substrate scope with easy preparation of DESs.[25]

Triazole scaffold has grown to be one of the most desirable five-membered *N*-heterocycles due to its broad range of biological activities.[26,27]

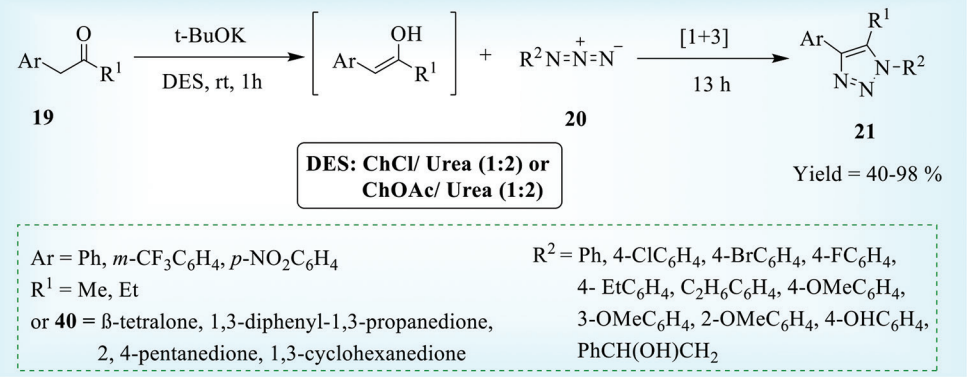
In 2022, the environmentally friendly urea-based eutectic mixtures (ChCl/urea and choline acetate [ChOAc]/urea) were used to synthesize a regioselective functionalized 1,2,3-triazole derivatives 21 by Cicco *et al*. [Scheme 5]. This reaction was carried out between enolates of alkanones 19 and azides 20 up to 13 h, via a 1,3-dipolar cyclo-addition reaction to obtain desired triazole derivatives having yields from 40% to 98%. Moreover, this metal-free process was



Scheme 3: Synthesis of substituted 2-pyrazolines 10 in choline chloride/urea (1:2) deep eutectic solvents



Scheme 4: (a and b) Synthesis of 2-substituted benzothiazole and benzimidazole derivatives in *N, N'*-dimethylurea (DMU)-based eutectic mixtures (DMU/*L*-(+)-tartaric acid and citric acid/DMU)



Scheme 5: Synthesis of functionalized 1,2,3-triazole derivatives 21 in deep eutectic mixtures

established under mild conditions like- room temperature and aerobic conditions and exhibited a broad substrate scope. The yield of the product decreased from 98% (first cycle) to 66% (fourth cycle) in the eutectic mixture ChOAc/ urea throughout four recycling runs. In addition, one-pot cycloaddition/reduction procedures in ChCl/urea DES were successfully performed to produce functionalized triazoles having a variety of pharmacological properties.[28]

CONCLUSION

After reviewing the synthesis of *N*-heterocyclic compounds in deep eutectic mixtures, various general observations can be drawn. The described conditions in the experiment are generally mild and many authors described the use of neutral reactants. In addition, the non-volatile characteristics of DESs and their compatibility with water allow the recycling of both the solvent and the metal catalysts, consequently reducing expenditures and waste generation. While the usefulness of these synthetic techniques is undeniable, the role of DES, which is believed to encourage H-bond catalysis, needs more investigation to validate its supposed unique activities that cannot be explained. In the future, the successful synthesis of *N*-heterocyclic compounds using DESs opens up new avenues for drug discovery, agrochemical development, and materials science. The potential to expand the scope of accessible *N*-heterocycles with improved yields and reduced waste offers opportunities for novel applications and functional materials. The innovative use of DESs as environmentally friendly alternatives to conventional solvents holds immense promise for reducing the ecological footprint of *N*-heterocyclic compound synthesis. This green approach addresses the growing concerns about environmental impact and aligns with global efforts towards sustainable practices.

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