



Review

Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations



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ABSTRACT

The development of efficient and environmentally benign synthetic protocols has attracted increasing interest in modern organic syntheses in view of the growing concern over the environment. As part of this green concept, eutectic solvents (DESs) have emerged as an interesting type of ionic liquid and have shown their usefulness as environmentally benign sustainable alternative to the conventional organic solvents in synthetic chemistry to increase efficiency of organic transformations. The synthetic methodology with the use of DES as green solvent and inexpensive, biodegradable, recyclable catalyst and with its experimental simplicity and maximum synthetic efficiency will be attractive for academic and industrial research looking forward for simple catalytic organic transformations to synthesize drug like small molecules with structural diversity and molecular complexity. The present review focuses on the use of environmentally benign and inexpensive DES as solvent and catalyst in the field of organic chemistry.

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1. Introduction

With the growing awareness of environmental issues and increasing need to reduce use of harmful chemicals in chemical, medicinal and industrial research in view of their effects, and the consequent risk for the human health, in recent years green chemistry has been a fascinating area of chemical research. The green chemistry aims to design environmentally benign chemical processes and synthetic methodologies in order to eliminate or reduce the use of hazardous and toxic chemicals at any stage of production in the industry or laboratory [1,2].

In a typical chemical process, solvents are used extensively for dissolving reactants, affecting chemical reactivity, extracting and washing the products and for separating the mixtures. Traditional organic solvents, in spite of a large number of self-evident advantages, are generally volatile, flammable, explosive and toxic for human beings, animals and even plants. Conventional organic solvents are not only hazardous to the environment but also show acute and chronic toxicity, carcinogenicity, ecological toxicity and non-biodegradability. To improve the protection of human health and the environment from the risks associated with the use of hazardous organic volatile solvents, tremendous efforts have been devoted for the development of alternative green reaction media [3,4].

The precautions to minimize the effects of these solvents by improved recycling processes have limited success and cannot avoid some losses into the environment. Moreover, the risk connected to potential accidents is still present. For these reasons the replacement of

these hazardous solvents with green sustainable alternative solvents seems to be the only valid alternative for a sustainable use of solvents.

Two main routes towards green solvents have been developed: i) the substitution of petro-chemically fabricated solvents with “bio-solvents” from renewable resources [5], and ii) the substitution of hazardous solvents with ones that show better EHS (Environmental, Health and Safety) properties [6]. Although a variety of unconventional solvents, such as water [7a], ionic liquids [7b], fluorous media [7c], supercritical fluids [7d], and polyethylene glycol [7e] have been extensively used in chemical syntheses and fascinating results have been reported, and even though the last couple of decades has seen a considerable sustainable development in chemical research with green technology in organic syntheses and catalysis, it is also becoming increasingly clear that no single system will, in its own right, ever be able to replace completely all conventional reagents and solvents as a truly environmentally friendly alternative because the use of these solvents is still subject to strict limitations, such as the instability and solubility of some reactive reagents or substrates in water, high prices and lack of data about the toxicity and bio-compatibility for ionic liquids, including the demand of sophisticated equipments for supercritical fluids. It means that an ideal and universal “green” solvent for all situations does not exist because of the drawbacks associated with all of these systems, both from the point of views of applicability and sustainability. Therefore, the search of new reaction media is thus gaining prominence.

In the last decade, ionic liquids (ILs) have gained great attention in various areas such as organic syntheses, catalysis, biocatalysis and biomass pretreatment, due to their attractive properties such as biocompatibility, high viscosity, thermal and chemical stability, negligible volatility, high solubilization capacity for wide spectrum of solutes, high heat capacity, density and conductivity, in addition to their ability to act as catalysts [8,9]. ILs have been proposed as “fully green” alternative solvents because of their negligible vapor pressure and low flammability. The significance of ILs concerns not only to academia, but also to industry because their “green character” offers an interesting alternative to the use of toxic solvents [10].

Exploration of ionic liquids (ILs) as alternative sustainable solvents, can also be confirmed by the incredible amount of works in the literature [11]. However, it has been observed that commonly used imidazolium and pyridinium-based ILs are not as environmentally benign as previously thought in light of their syntheses from petrochemicals as starting materials and show a wide range of toxicities towards microorganism, vertebrates and invertebrates because of their relatively high solubilities in water and their poor biodegradability [12]. Although,

Table 1
List of some common DES with their important physicochemical properties.

Salt	HBD	Salt: HBD molar ratio	T _f /°C	Densities g/cm ³ at 25 °C	Viscosity(η) η/mPa s	Ref.
ChCl	urea	1:2	12	1.25	750 (25 °C)	[15a]
ChCl	glycerol	1:2	40	1.18	259 (25 °C)	[15b]
ChCl	glycerol	1:3	-*	1.20	450 (20 °C)	[15b]
ChCl	ethylene glycol	1:2	66	1.12	37 (25 °C)	[15b]
ChCl	malonic acid	1:2	-*	1.25	1124 (25 °C)	[15a]
		1:1	10	*	-*	
EtNH ₃ Cl	CF ₃ CONH ₂	1:1.5	-*	1.273	256 (40 °C)	[15c]
EtNH ₃ Cl	acetamide	1:1.5	-*	1.041	64 (40 °C)	[15c]
EtNH ₃ Cl	urea	1:1.5	29	1.140	128 (40 °C)	[15c]
ZnCl ₂	Urea	1:3.5	-*	1.63	11340 (25 °C)	[15d]
ZnCl ₂	acetamide	1:4	303.15	1.36	-*	[15d]

-* Data not available

in view of the low vapor pressure of ILs, these may reduce the air pollution with respect to the typical volatile organic solvents, the release of ILs from industrial processes into aquatic environments may lead to water pollution because of their high solubility in water. Moreover, due to their high stability in water, the ionic liquids could become as persistent pollutants in wastewaters and may have a toxic influence on the environment. But DESs seem to be a less toxic alternative to ionic liquids. Deep eutectic solvents show similar physicochemical properties to ionic liquids, but they are much cheaper and safer for their use as solvents as compared to ionic liquids in synthetic transformations. As compared to ILs, DESs have, however, notable advantages such as (i) their convenient synthesis (100% atom economy), (ii) their very low price since most of DESs can be prepared from readily accessible chemicals and (iii) their low toxicity, especially DESs derived from ChCl and renewable chemicals. Choline chloride is a commonly used organic salt for DESs, since it is biocompatible and most of the HBDs are cheap and environmentally benign such as urea, glycerol or carboxylic acids. Moreover, deep eutectic solvents do not produce toxic metabolites and are biodegradable. Additionally, the synthesis of ILs is not environmentally friendly and generally requires a large amount of salts and solvents in order to completely exchange the anions. These drawbacks together with the high price of common ILs unfortunately restrict their industrial emergence such as metal electroplating, electrodeposition and biocatalysts [13].

Deep eutectic solvents (DESs) have emerged as an interesting type of ionic liquid and have shown their usefulness as environmentally benign sustainable alternative to the conventional organic solvents in synthetic chemistry to increase efficiency of organic transformations. DESs are low melting mixtures based on a combination of readily available, biodegradable, recyclable and inexpensive components that are formed by mixing a quaternary ammonium or metal salt with a simple hydrogen bond donor (HBD), such as acids, amides, amines and alcohols and mostly exist as liquid at or below 100 °C because the melting point is drastically reduced after mixing two components as compared to the melting points of the original two components. The charge delocalization occurring through hydrogen bond formation between the halide anion and the hydrogen donor moiety is responsible for the decrease in the freezing point of the mixture relative to the melting points of its individual components (Fig. 1). Like ILs, one of the most promising advantages of DESs is their extremely low vapor pressure i.e. low volatility, which is very attractive for their use in greener catalytic technologies [14]. (Table 1)

Some of the physicochemical properties of DESs which are responsible for their use as greener solvents at room temperature are as follows.

1.1. Freezing points (T_f)

Deep eutectic solvents are generally characterized by their lower freezing points than the freezing points of individual constituents. The freezing points of DESs are also influenced by the ratio of salt and HBD. However, there is no clear correlation between the freezing point of DESs and melting points of the pure components (HBD or ChCl). According to Abbott et al. the freezing point depends on the lattice energy of DESs, interaction between couple anion-HBD and entropy changes arising from the formation of liquid phase.

1.2. Density

Most of DESs are denser than water for example ZnCl₂-HBD DESs have densities higher than 1.3 g/cm³. This notable difference of density might be attributed to a different molecular organization or packing of the DESs. This phenomenon may be explained by the hole theory. According to this theory the average hole radius is decreased and density is increased. Similar to imidazolium-based ILs, DESs are composed of holes or empty vacancies. When ZnCl₂ was mixed with urea for instance, the average hole radius was decreased, resulting in a slight increase of the DES density as compared to that of neat urea.

1.3. Viscosity

Most of the DESs are highly viscous at room temperature. But for their potential applications as green solvents, the DESs with low viscosities are highly desirable. Viscosity depends on the chemical nature of DES components, temperature and water content. Viscosity of binary eutectic mixture is essentially governed by hydrogen bonds, van der Waals and electrostatic interactions. The viscosity is also dependent on the nature of the HBD. The molar ratio of the components of DES also affect the viscosity. Viscosity of most eutectic mixtures changes significantly as a function of the temperature. As the temperature increases, the viscosity decreases. Water can be part of DES and plays an important role in overcoming the difficulty of high viscosity of DES. The dilution of DES with water allows the quantitative adjustment of physicochemical properties, such as their conductivity, polarity, viscosity and density, which facilitate their applications as solvents. The dilution also decreases their viscosity considerably and increases the solubility of some compounds. The optimal water content in DESs depends on the composition of DESs and also the polarity of the compounds.

1.4. Polarity, ionic conductivity and acidity/alkalinity

Extensive hydrogen bonding makes them polar in nature. DESs show poor ionic conductivity due to higher viscosity (the range 0.1 to 10 mS cm⁻¹) and changed with composition and temperature. Polar and protic DESs may be acidic and basic in nature. HBDs have strong effect on the acid or basic strength of the corresponding DESs.

DESs can be used without post-synthesis purification, making their industrial use economically viable and green, meaning that DESs can be used as sustainable, greener and safer alternative to many petroleum-based organic solvents in synthetic organic chemistry to increase the efficiency of organic transformations. DESs have been extensively explored in certain contexts, particularly, in the area of electroplating, however, they have not received as much attention for their potential in organic synthesis. If a solvent displays slightly acidic and basic nature, it can also act as catalyst for those reactions which are catalyzed in these conditions. The polar and protic DESs may be acidic and basic depending on the nature of hydrogen bond donor. Besides this, the acidity/coordination properties of deep eutectic solvents can be tuned according to requirements of different reactions or processes by changing the combination of their cations and anions. So theoretically, a large number of DESs are possible to have various

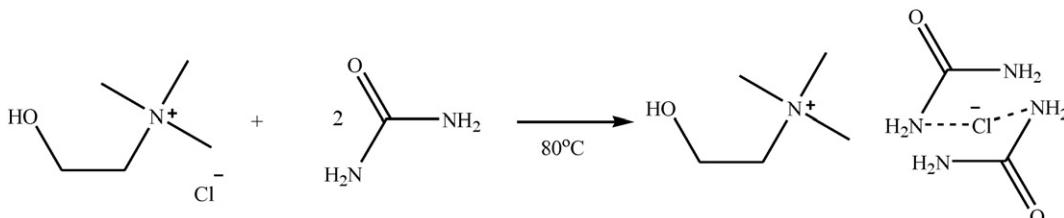


Fig. 1. Deep eutectic solvent with hydrogen bond interaction.

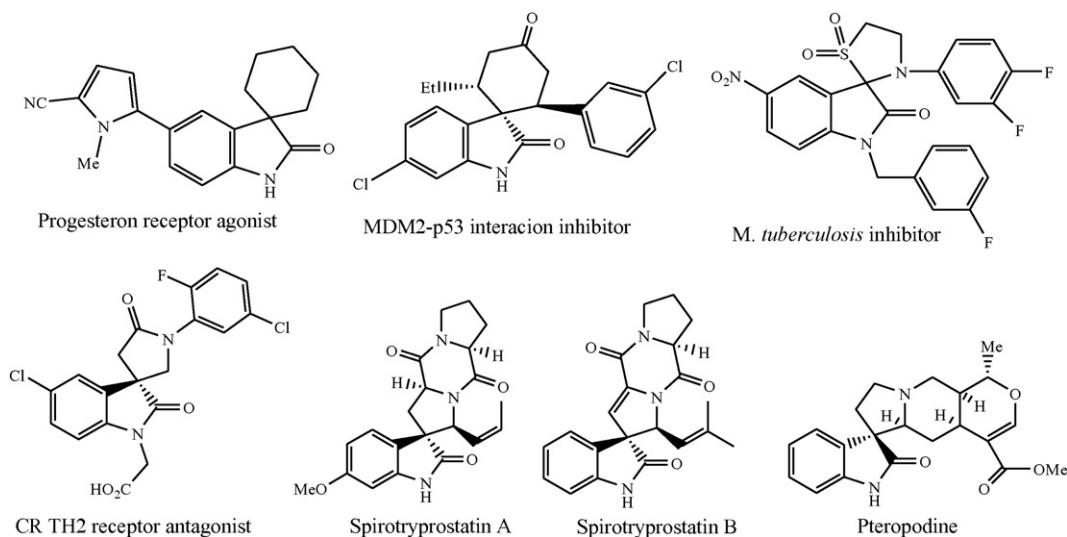


Fig. 2. Spirooxindole containing synthetic drugs and natural products.

combinations of cations and anions which provide great opportunity to design most suitable catalytic condition with green approach. Moreover, like ILs, ionic characters of DESs due to presence of hydrogen bond interaction between cation and anion show improved catalytic activities over those conducted in conventional organic solvents.

Therefore, DESs are able to function not only as a modest inexpensive and environmentally benign solvents but also recyclable and reusable organocatalysts and can play dual role in organic transformations. In the present review article, the critical account of synthetic methods involving dual role of deep eutectic solvents as environmentally benign sustainable solvents and catalysts along with the recent literature have been presented.

2. Organic transformation in deep eutectic solvents

2.1. Synthesis of heterocycles in DESs

2.1.1. Synthesis of spirooxindoles

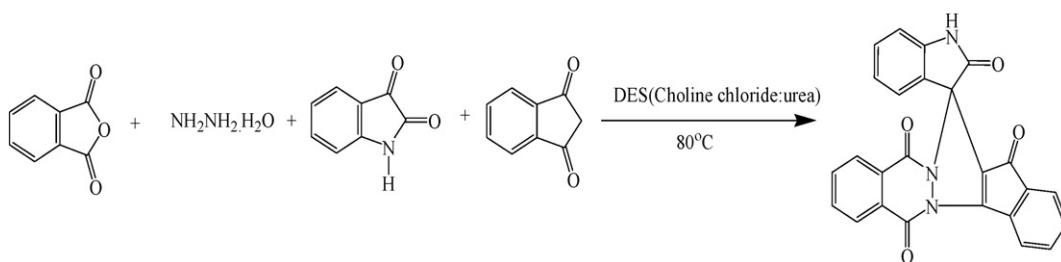
The heterocyclic spirooxindoles are very promising and attractive targets in organic and medicinal chemistry research because the spirooxindole heterosystem is the core structure of many pharmaceuticals and bioactive natural products (Fig. 2) [16].

An efficient and environmentally benign one-pot four-component domino protocol has been reported by Kumar et al. for the synthesis of structurally diverse spirooxindoles. Four series of spirooxindoles spiroannulated with pyrazolopyrimidophthalazines, indenopyrazolophthalazines, chromenopyrazolophthalazines and indazolophthalazines have been synthesized in deep eutectic solvent (choline chloride:urea: 1:2) by the reaction of phthalic anhydride, hydrazine hydrate, isatins and cyclic diketones/diamides. Two other solvent systems were also screened initially but deep eutectic solvent

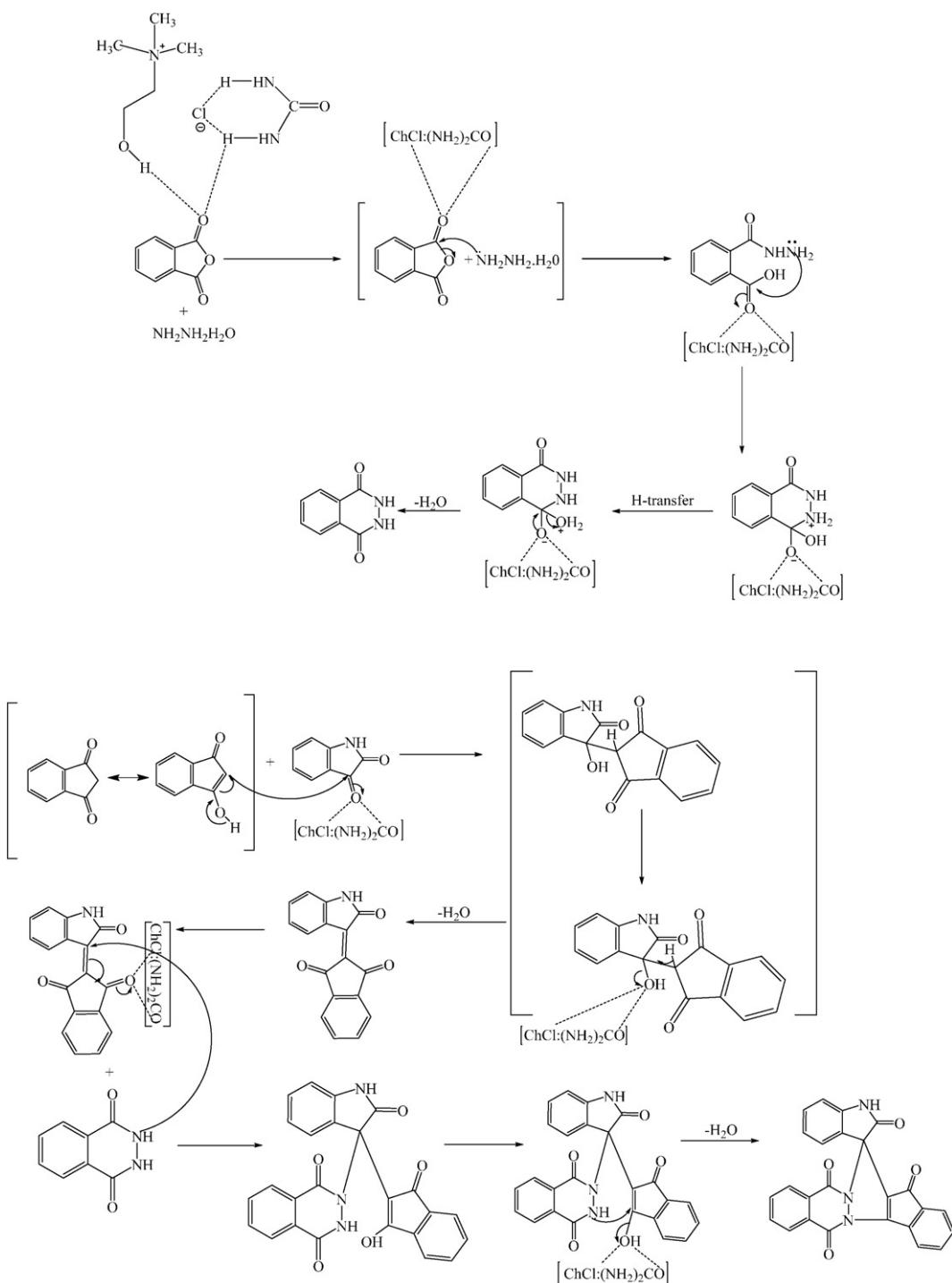
showed superiority over other solvent system with its dual role as catalyst and solvent for the synthesis of spirooxindoles and the desired products were obtained in excellent yields in shorter reaction time. Moreover, the deep eutectic solvent used as catalytic solvent system in the reaction was recycled up to four times and the heterocycles were obtained in comparable yields (Scheme 1) [17].

The reaction proceeds to involve the following reactions mechanism (Scheme 1a).

Structurally diverse spirooxindoles spiroannulated with pyranopyridopyrimidines, indenopyridopyrimidines, and chromenopyridopyrimidines were synthesized by Kumar et al. by an efficient and environmentally benign domino protocol which involves three-component reaction of aminouracils, isatins and cyclic carbonyl compounds in deep eutectic solvent (choline chloride–oxalic acid: 1:1) which acts as efficient catalyst and environmentally benign reaction medium. Initially, four deep eutectic solvents were screened to check feasibility of the reaction and to optimize reaction conditions. But it was observed that when the reaction was performed in DESs (ChCl:oxalic acid), the excellent yield of the desired product was obtained in shorter reaction time than that obtained with the use of other deep eutectic solvents. Thus, the results clearly indicate that DESs (ChCl:oxalic acid) shown superiority over the other systems as solvents and catalyzed the reaction efficiently to facilitate the synthesis of spiroheterocycles in excellent yields. The DES (ChCl:oxalic acid) catalyzed synthetic protocol was extended with 6-aminouracil using different isatines and carbonyl compounds and spirooxindoles were obtained in excellent yields. The present protocol offers several advantages such as operational simplicity with easy workup, shorter reaction times excellent yields with superior atom economy and environmentally benign reaction conditions with the use of cost-effective, recyclable, non-toxic and bio-degradable DESs as catalyst/solvent (Scheme 2) [18].



Scheme 1. Synthesis of spirooxindoles.

**Scheme 1a.** Plausible reaction mechanism.

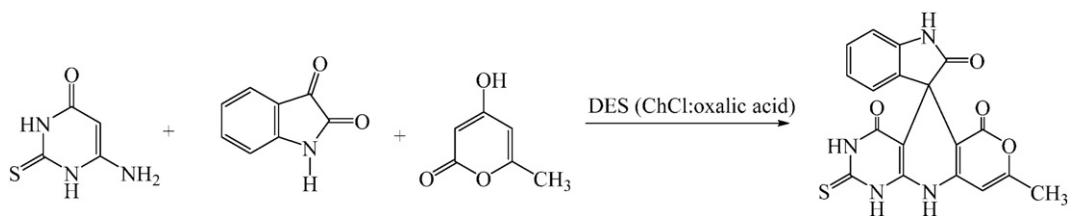
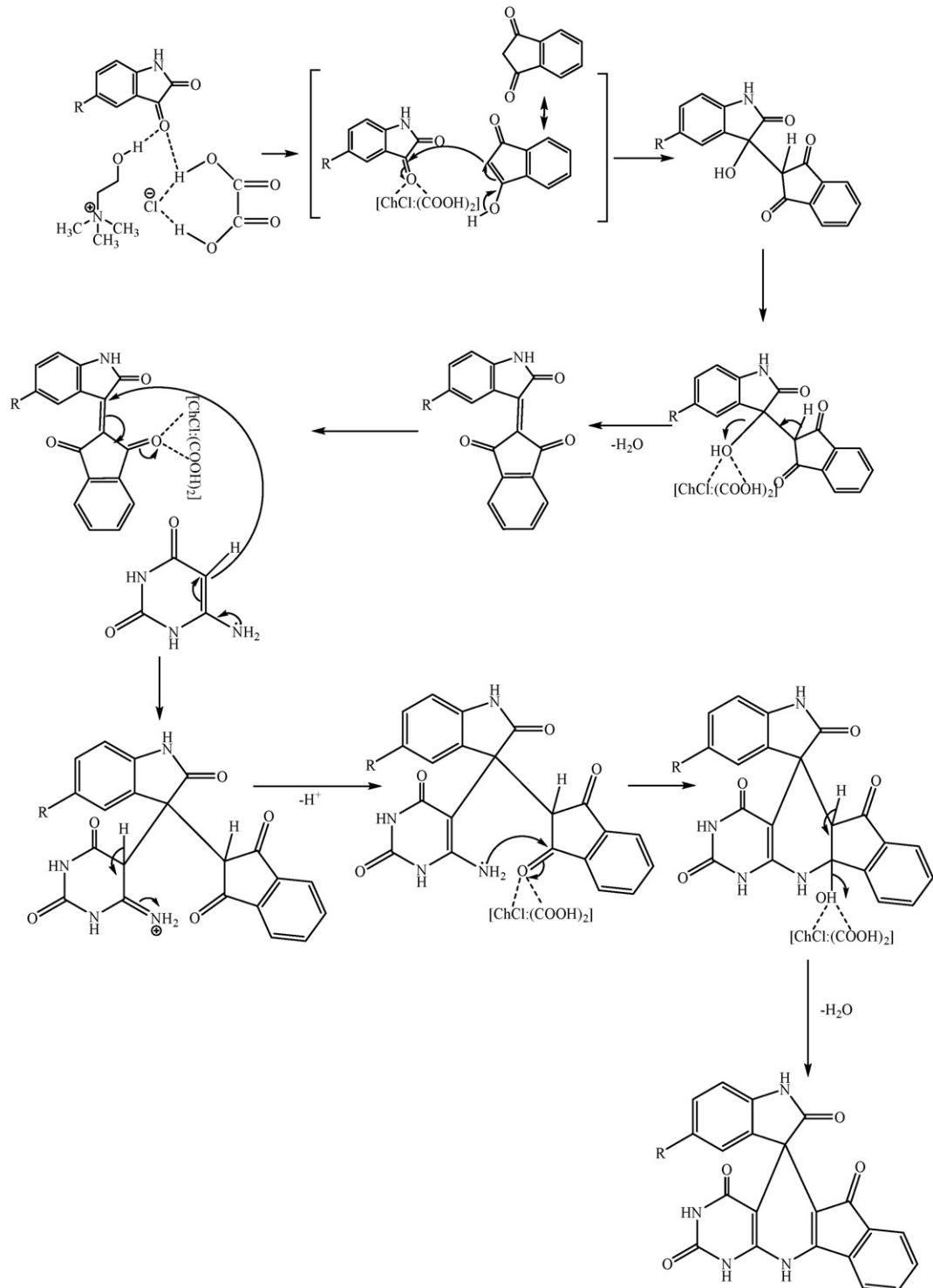
The plausible reaction mechanism proposed for the synthesized structurally diverse heterocycles is presented in **Scheme 2a**.

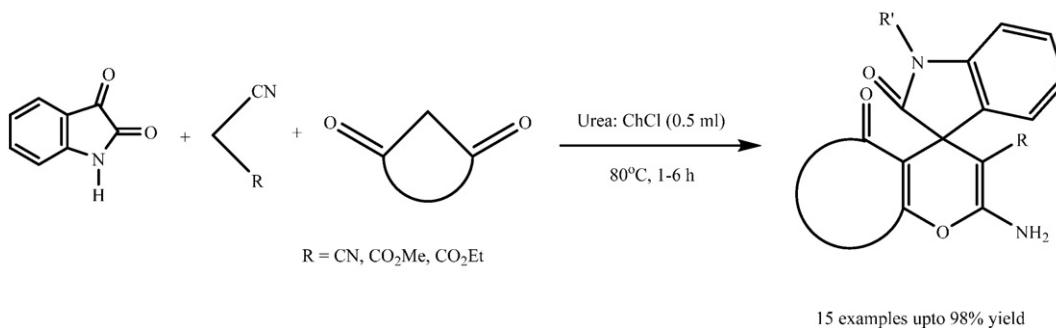
Azizi et al. also synthesized spirooxindole derivatives via multicomponent reaction of isatin, or acenaphthoquinone, and malononitrile or cyanoacetic ester with 1,3-dicarbonyl compounds, naphthol and 4-hydroxycumarin in biodegradable choline chloride based deep eutectic solvent. Initially, under optimized condition of temperature, various ChCl based DESs were applied on model reaction to check their efficiency to catalyze the reaction. It was observed that urea-choline chloride proved most effective reaction media and catalyst and provided excellent results (95%) while other DESs were less effective. The optimized synthetic protocol was further extended with a variety of 1,3-dicarbonyl

compounds, malononitrile or cyanoacetic ester and isatin using this new and green reaction media. The results clearly demonstrated that DES is an excellent catalyst and reaction media in terms of yields and time (**Scheme 3**) [19].

2.1.2. Synthesis of 1,4-dihydropyridines

1,4-Dihydropyridines (1,4-DHPs) constitute an important class of bioactive molecules. 1,4-Dihydropyridines are well known for their role as calcium channel modulators and used extensively for the treatment of hypertension [20]. The derivatives of 1,4-DHPs have shown their uses as vasodilators, bronchodilators, and antitumors, including their hepatoprotective and geroprotective activity [21,22]. Commercial

**Scheme 2.** Synthesis of spirooxindoles.**Scheme 2a.** Plausible reaction mechanism.

**Scheme 3.** Synthesis of spirooxindole derivatives.

drugs such as Nifedipine which is a prototype of the 1,4-DHP structure has been used extensively in both antianginal and antihypertensive treatment (Fig. 3) [23].

Pednekar et al. reported one-pot multicomponent synthesis of 1,4-dihydropyridines derivatives by the reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in biocompatible DESs. Initially to optimize the reaction conditions, water, various DESs and some polar and non-polar conventional organic solvent were screened. But results clearly indicate that DESs have more potential than conventional organic solvent for synthesis of 1,4-DHPs. The greener synthetic protocol provided excellent yields of the resultant products with the recyclability of deep eutectic solvents with very little loss in activity up to five recycles (Scheme 4) [24].

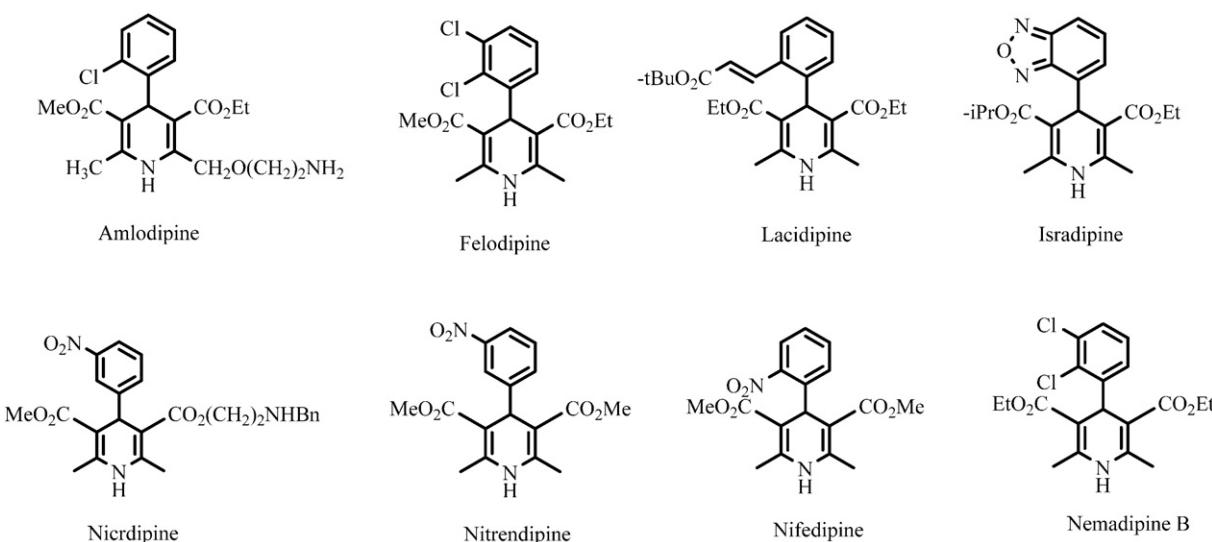
2.1.3. Synthesis of dihydropyrimidinones

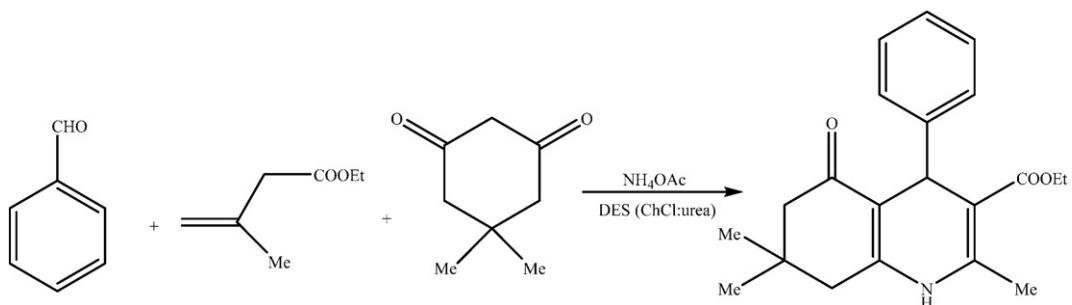
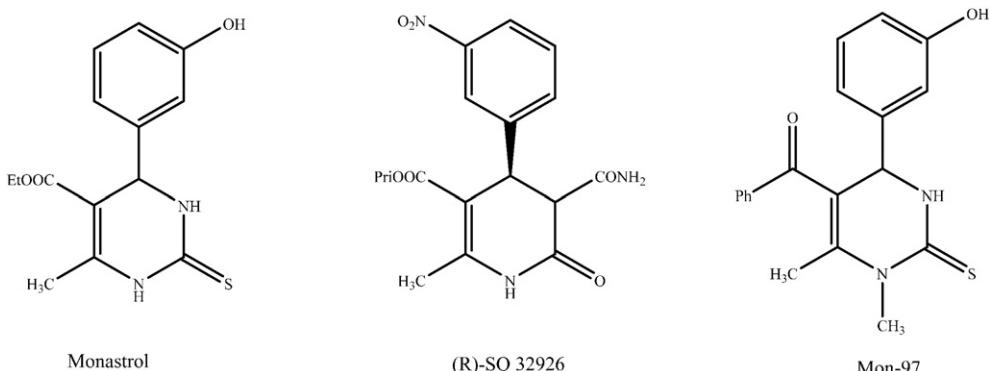
Dihydropyrimidinones occupy an important place in the realm of natural and synthetic organic chemistry (Fig. 4) [25]. In addition to their wide ranging pharmacological activities, dihydropyrimidinones have emerged as potent calcium channel blockers [26]. Numerous marine alkaloids containing the dihydropyrimidinone skeleton have shown interesting biological properties [27].

Azizi et al. reported synthesis of 3,4-dihydropyrimidin 2(1H)-one derivatives via Biginelli reaction involving the reaction of aromatic and aliphatic aldehydes, 1,3-dicarbonyl compounds, and urea using simple deep eutectic solvent based on tin (II) chloride as a dual catalyst and environmentally benign reaction medium. Initially to optimize the reaction conditions, five choline-based deep eutectic solvents at different reaction

conditions were screened and ChCl:SnCl_2 deep eutectic solvent was found to be the most appropriate with excellent yields of the products. Under optimized reaction conditions, a broad range of structurally diverse 1,3-dicarbonyl compounds, aromatic and aliphatic aldehydes, and urea were subjected to this green procedure to produce the corresponding dihydropyrimidinones not only in good to excellent yields but also with higher reaction rates and high purity of desired products. Deep eutectic solvent, synthesized from choline chloride and tin chloride, is relatively inexpensive and recyclable, thus making it applicable for industrial applications (Scheme 5) [28].

It was reported by Koenig et al. that these heterocycles can also be synthesized by one-pot multicomponent reaction of benzaldehyde, ethylacetacetate under mild reaction condition by using low melting mixtures of *L*-(+)-tartaric acid and urea derivatives as a novel reaction medium. The melt played a triple role: as solvent, as catalyst and as reactant, furnishing highly functionalized dihydropyrimidinones in good to excellent yields. Initially, five melt systems were screened for optimization for the model reaction of 4-nitrobenzaldehyde, ethylacetacetate and dimethylurea, as one of the melt components at different temperatures. It was observed that the reaction progressed fastest in *L*-(+)-tartaric acid-DMU melt and the corresponding DHPM was isolated in excellent yield (96%). The scope of the multicomponent reaction was investigated with different aldehydes and β -ketoesters to provide the library of highly functionalized DHPMs. It is important to note that the DHPM synthesis in a melt (an organic acid-DMU) requires neither tedious work-up procedure nor column chromatographic purification (Scheme 6) [29].

**Fig. 3.** Clinically used dihydropyridyl cardiovascular drugs.

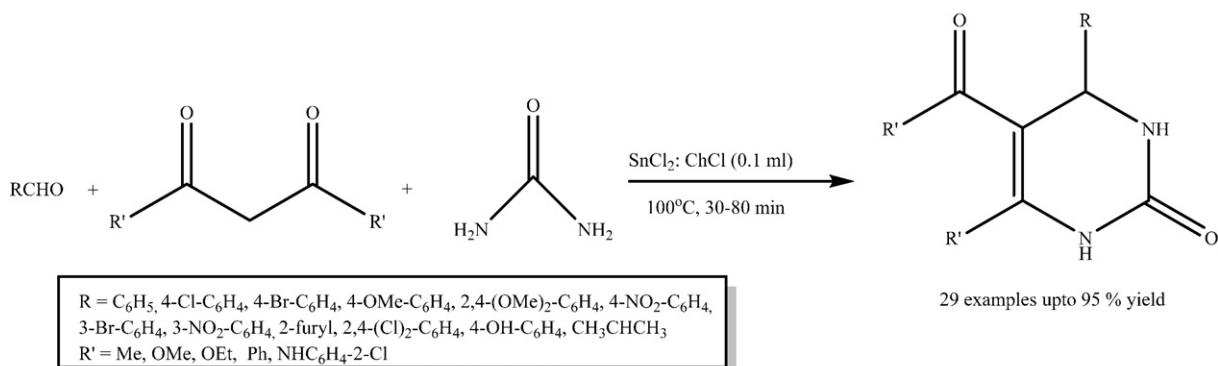
**Scheme 4.** Synthesis of 1,4-dihydropyridines derivatives.**Fig. 4.** Pharmacologically active DHPMs.

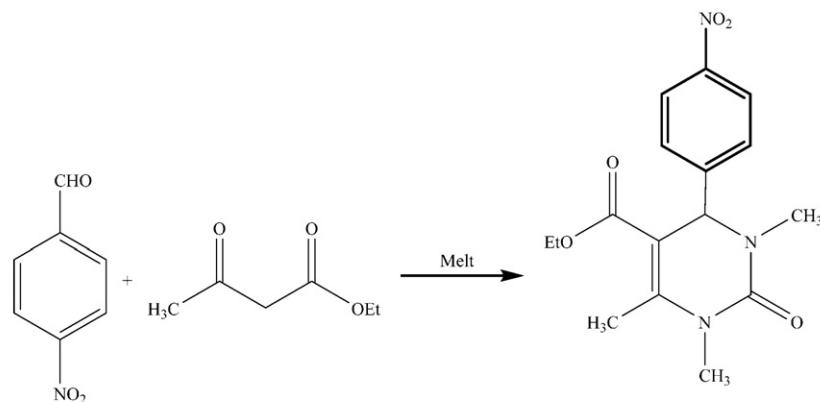
Biologically active dihydropyrimidin-2(1H)-ones were also synthesized via one pot three component reaction of active methylene group containing compounds, urea/thiourea and aldehyde using *Rhizopus oryzae* lipase biocatalyst in deep eutectic solvent by Shukla et al. To check the feasibility of reaction and to optimize reaction conditions, various conventional catalysts such as K₂CO₃ and t-BuOK and biocatalyst such as proline, L-histidine and lipase were used to afford the product but the catalytic activity of the lipase biocatalyst was found to be more effective than the other biocatalysts and conventional catalysts used in the reaction. Different organic solvents were also screened with lipase to observe their efficiency in the reaction. It was observed that the reaction progressed smoothly and in better way in DES solvents than progressed in water, methanol, dioxane, and DMF in terms of yield of desired product and reaction time. The quantity of the lipase was also optimized and 5% w/w of lipase was found to be optimal. Under the optimized conditions, various substituted aromatic aldehydes were reacted to obtain the corresponding products. The reported synthetic

protocol was characterized by high efficiency and selectivity, short reaction time, mild and environmentally friendly reaction conditions. The yields were found to be significantly higher and the reuse of both the lipase and deep eutectic solvent was possible up to four consecutive cycles. The products were found to exhibit appreciable *in vitro* antibacterial activity against *Escherichia coli*, *Pseudomonas pneumoniae* and *in vitro* antifungal activity against *Aspergillus niger* and *Candida albicans* (Scheme 7) [30].

2.1.4. Synthesis of pyrimidopyrimidinediones

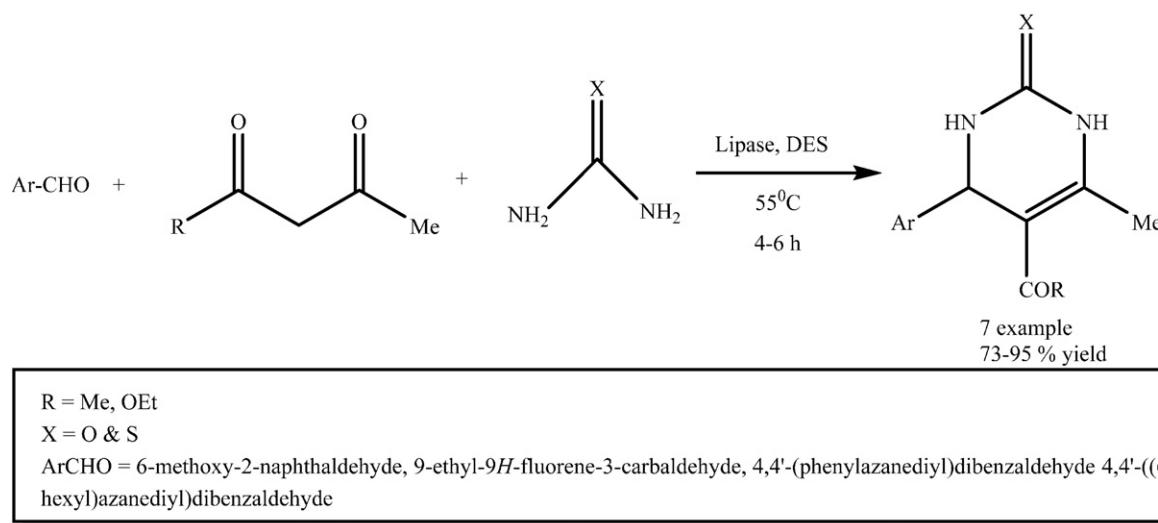
Fused pyrimidine systems, particularly, pyrimidopyrimidine (Fig. 5), have attracted increasing interest of synthetic and medicinal research and exhibit wide range of potential biological activities and inhibitory action regarding the tyrosine kinase domain of epidermal growth factor receptor [31a], 5-phosphoribosyl-1-pyrophosphate synthetase [31b] and dihydrofolate-reductase [31c].

**Scheme 5.** Synthesis of dihydropyrimidinones.



Melt: Citric acid-DMU, L-(+)-Tartaric acid-DMU, D-(-)-Fructose-DMU, Sorbitol-DMU-NH₄Cl, D-(+)-Mannose-DMU

Scheme 6. Synthesis of dihydropyrimidinones.



Scheme 7. Synthesis of DHPMs.

Koenig et al. developed an efficient synthesis of pyrimido-pyrimidinediones, the six-membered analogs of glycoluril by the reaction of acetophenone derivatives and paraformaldehyde using low melting L-(+)-tartaric acid-dimethylurea mixture as reaction medium. In the reaction, the melt acted not only as the solvent but at the same time acted also as catalyst and reactant. In order to improve

the efficiency of the synthesis, initially the reaction was carried out under various melt conditions. It was observed that in case of L-(+)-tartaric acid-DMU melt (tartaric acid: pKa = 2.95), the reaction provided the corresponding pyrimidopyrimidinedione derivative in excellent yield (90 °C, 7 h, 95%). This observation clearly indicates the catalytic role of acidic component in DESs. The reaction with optimal conditions

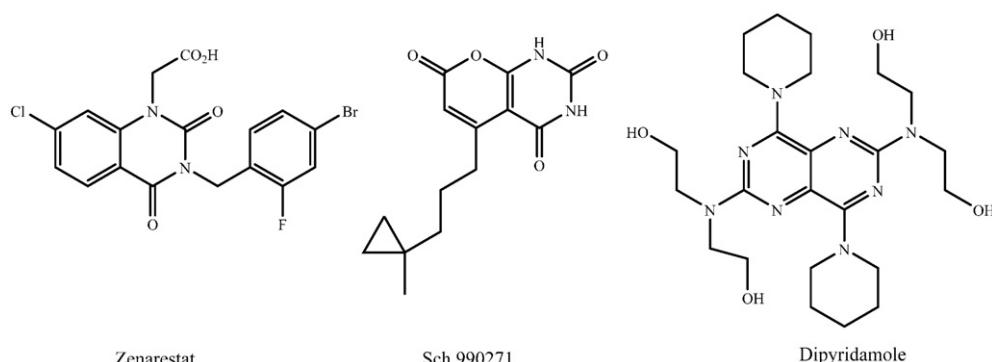
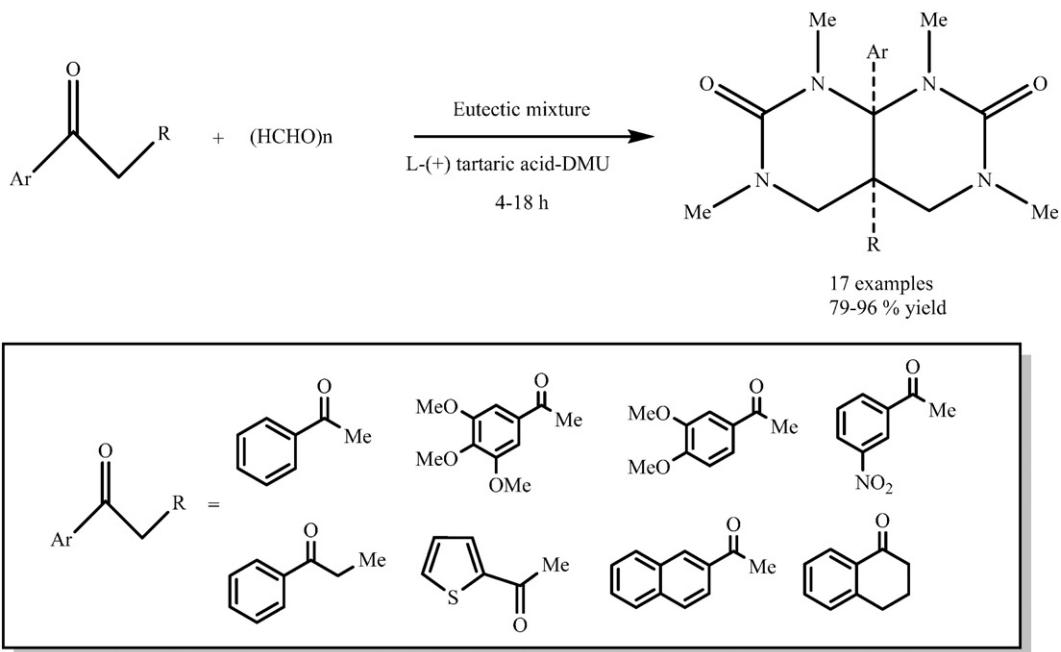


Fig. 5. Bioactive fused pyrimidine derivative.

**Scheme 8.** Synthesis of pyrimidopyrimidinedione derivatives.

were further extended with different aryl ketones and it was observed that desired products were obtained in good to excellent yields (79–96%) (**Scheme 8**) [32].

2.1.5. Synthesis of quinoline derivatives

The quinoline ring system is an important structural unit present in many naturally occurring alkaloids, therapeutics, and synthetic analogs with interesting biological activities (**Fig. 6**) [33,34].

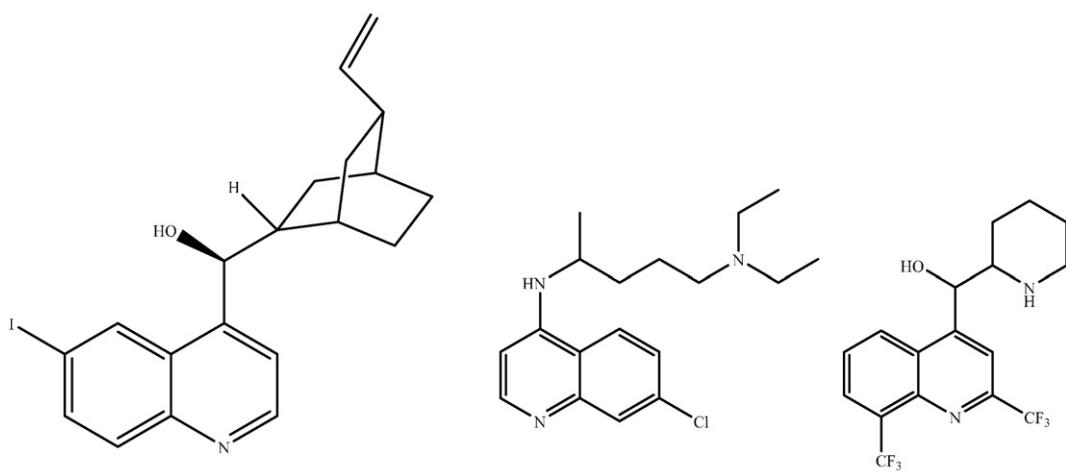
Biologically important quinoline derivatives were synthesized by Zhang et al. via the Friedländer heteroannulation reaction of 2-aminoaryl ketones and α -methylene ketones employing low melting mixtures of *L*-(+)-tartaric acid and urea derivatives as an inexpensive, non-toxic, easily biodegradable reaction medium. The melt acts as both the reaction medium and catalyst, providing quinolines in high to excellent yields (**Scheme 9**) [35].

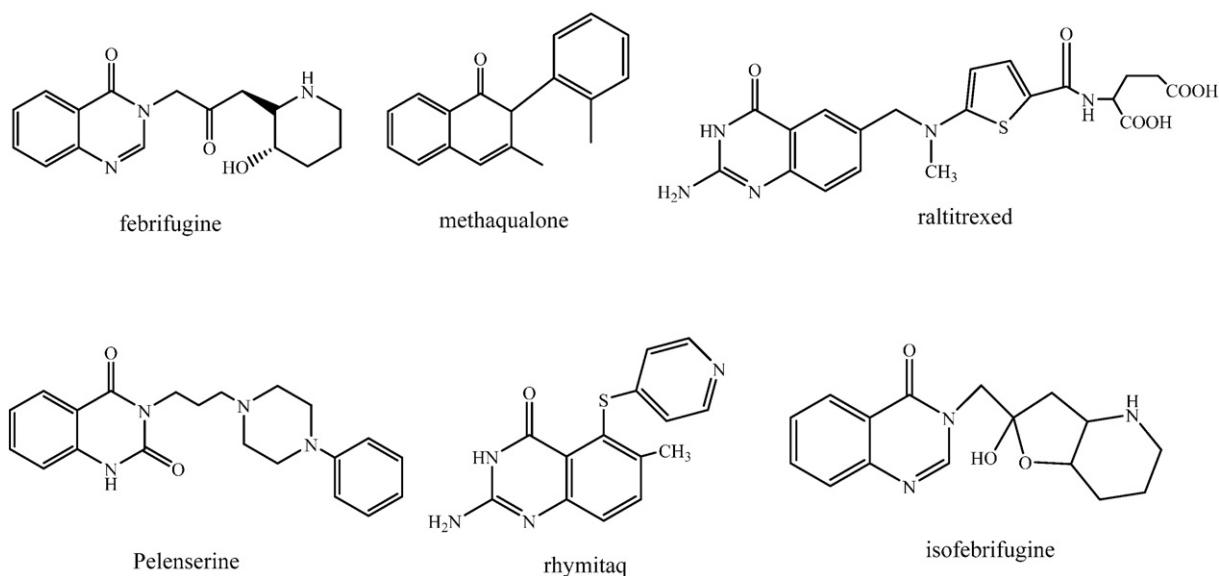
2.1.6. Synthesis of quinazoline derivatives

Quinazoline is one of the most important nitrogen heterocycles commonly found in a wide variety of natural products, pharmaceutical

molecules, and functional materials [36]. Quinazoline derivatives have been reported to possess diverse biological and therapeutic properties such as antibacterial, anti-inflammatory, antiplasmodial, antitumor, antimicrobial and antioxidant [37,38]. In addition, they have also been used as photochemotherapeutic agents, DNA-gyrase, JAK2, PDE5, and EGFR tyrosine kinase inhibitors, as well as CB2 receptor agonists [39, 40]. (**Fig. 7**).

In recent years, low melting mixtures consisting of carbohydrates, urea and inorganic salts have been introduced as new alternative sustainable solvents for organic transformations. Zhang et al. employed low melting mixture of maltose-dimethylurea (DMU)-NH₄Cl as an inexpensive, nontoxic, easily biodegradable and effective reaction medium in the catalyst-free synthesis of quinazoline derivatives. The screening of solvent was done by performing model reaction of 2-aminobenzophenone with 4-nitrobenzaldehyde and ammonium acetate in different (**Fig. 7**) solvents under aerobic oxidation conditions. Only a trace amount of product was detected when the reactions were carried out in EtOH or H₂O. Poor to low yields were observed when the reactions proceeded in CH₃CN, DMF, DMSO, toluene or in neat

**Fig. 6.** Natural product incorporating quinoline moiety.

**Fig. 7.** Bioactive quinazolinone derivatives.

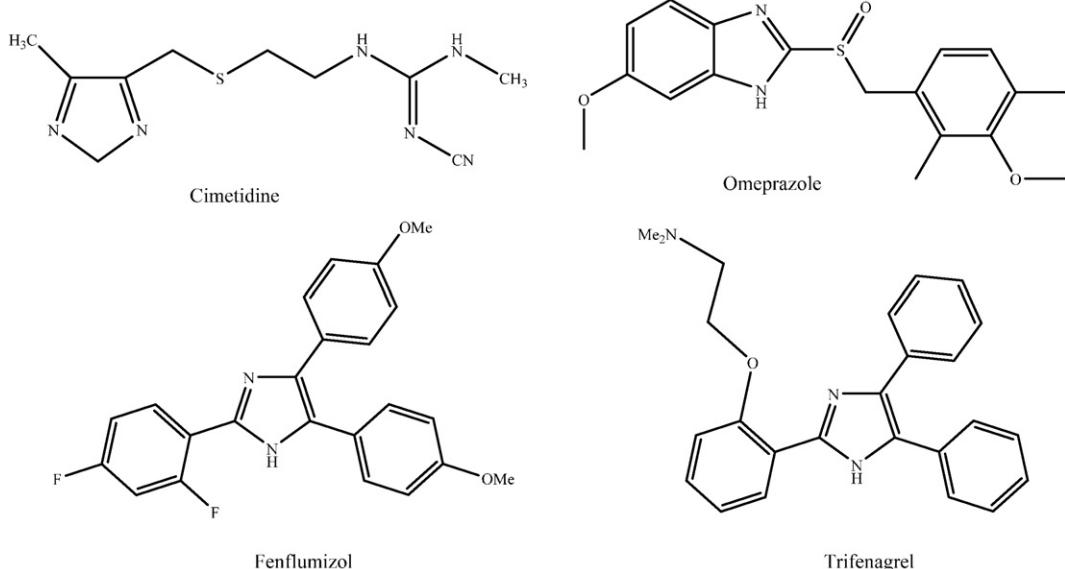
conditions. To meet the requirement of green chemistry, various deep eutectic solvents were also screened to check the feasibility of reaction such as citric acid–DMU, D-(–)-fructose–DMU, L-(+)-tartaric acid–DMU, L-(+)-tartaric acid–choline chloride, mannose–DMU–NH₄Cl, lactose–DMU–NH₄Cl, and maltose–DMU–NH₄Cl at their minimal melting temperature. The reaction preceded smoothly in these melt mixtures, and the corresponding product was obtained in 75–92% yields. Further investigation of this reaction was achieved by using these melt mixtures at 90 °C. At this temperature, maltose–DMU–NH₄Cl was found to be superior to other melts, which gave 93% yield of the product.

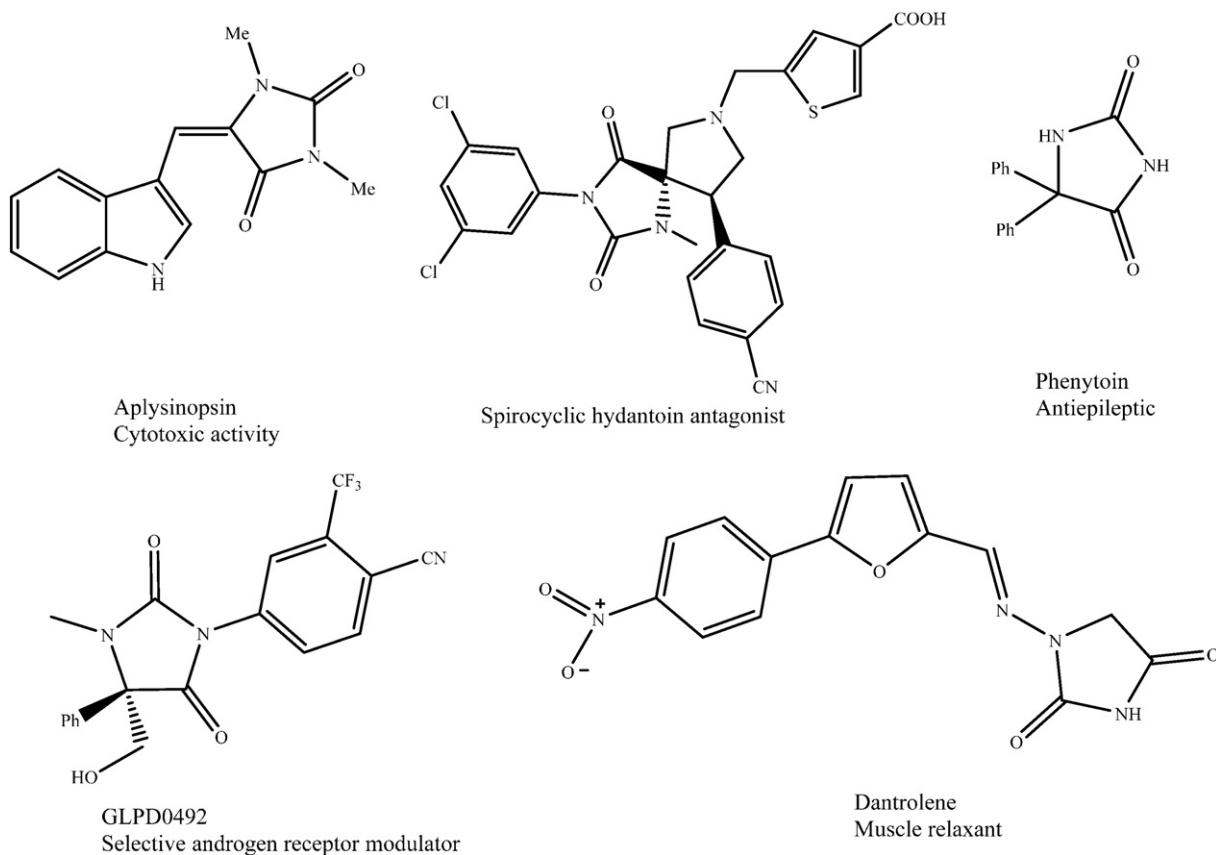
The optimized protocol was extended with a wide range of 2-aminoaryl ketones, aldehydes under aerobic oxidation conditions and products were obtained in good to excellent yields. The simple work-up, mild reaction conditions and high yields of the products make this new strategy attractive for the preparation of a wide variety of biologically relevant quinazolines (**Scheme 10**) [41].

2,3-Dihydroquinazolinones belong to an interesting class of heterocycles that possess a wide range of biological and pharmaceutical

activities [42]. Some examples of very significant quinazolinone molecules include medicinally approved drugs like metolazone, quinethazone, raltitrexed, fenquizone as well as bio-active natural products such as febrifugine and isofebrifugine [43]. (**Fig. 7**).

An efficient protocol has been developed for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones via one-pot multi-component reaction of isatoic anhydride, aldehyde and aromatic amines by Shankarling et al. using DESs (choline chloride: malonic acid) in methanol. Initially various deep eutectic mixtures were screened as catalyst in methanolic media to derive the best outcome. The deep eutectic solvents generated from glycerol or urea provided very poor yields due to their lower acidity than DESs made from acidic components. However, the eutectic mixture of choline chloride: malonic acid gave best results among all other eutectic mixtures. The optimization for quantity of catalyst suggested 20% (v/v) of DES catalyst in methanol was the optimum quantity for effective results. The catalyst, being a deep eutectic mixture of choline chloride and malonic acid, gave better results than several reported catalysts. Moreover, such eutectic mixtures are cost-effective,

**Fig. 8.** Examples of bioactive 2,5-diarylimidazoles.

**Fig. 9.** Biologically active hydantoins.

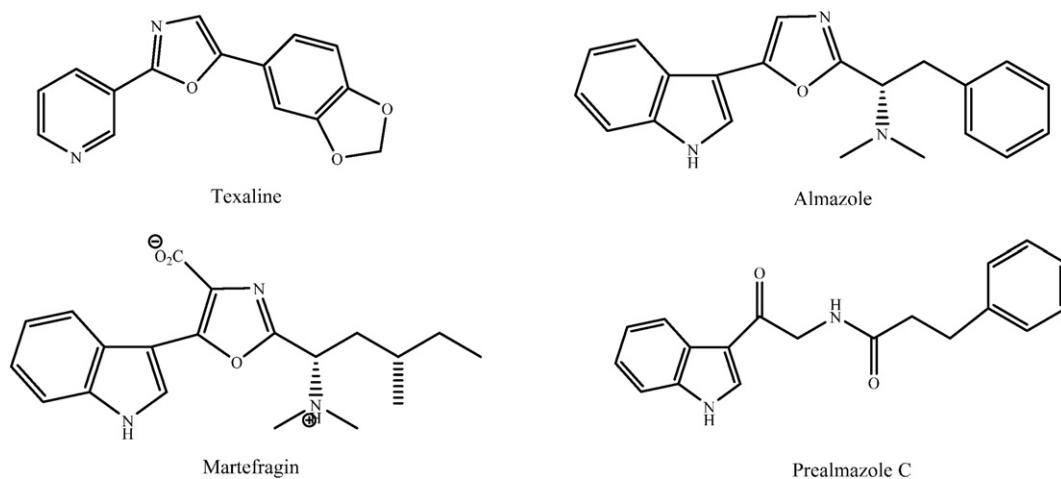
recyclable, non-toxic and bio-degradable. A variety of aromatic as well as heteroaromatic aldehydes and amines underwent three component condensation with isatoic anhydride by this procedure to provide several novel 2,3-dihydroquinazolin-4(1*H*)-one derivatives [44]. (*Scheme 11*).

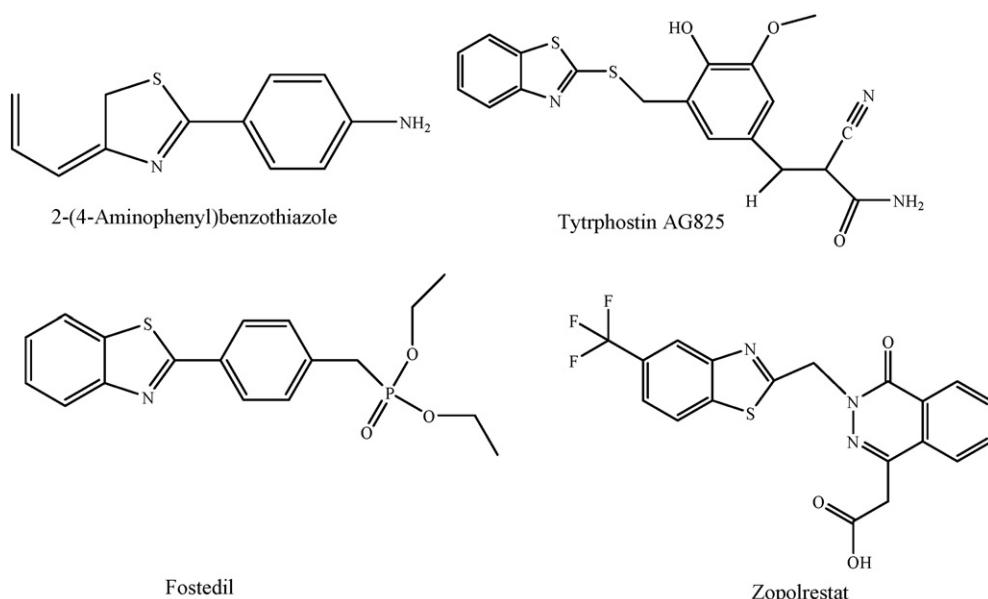
2.1.7. Synthesis of trisubstituted and tetrasubstituted imidazoles

Naturally occurring as well as synthetic derivatives of imidazoles play an important role in chemical and biological systems. Many of the substituted imidazoles are known as plant growth regulators and many of the substituted imidazoles are known as plant growth regulators and attractive targets in medicinal chemistry as the antiulcerative agent cimetidine, the proton pump inhibitor omeprazole, the fungicide

ketoconazole, the benzodiazepine antagonist flumazenil and anticancer agents (Fig. 8) [45,46].

Tetrasubstituted imidazoles were synthesized via a robust and simple one-pot four component reaction by Azzizi et al. The four-component reaction of aldehydes, amines, ammonium acetate, and 1,2-diphenylethane-1,2-dione progressed smoothly in the presence of eutectic mixture stabilized iron oxide nanoparticles at 60 °C to give a range of imidazole derivatives in moderate to good yields. Initially, solvent-free condition and a wide variety of solvents were also explored but yield of desired product in these systems was not satisfactory. Furthermore, it was also observed that when the reaction was carried out in DESs without ferrofluids, yield of the desired product reduced to 25%. In this synthetic protocol, DESs played triple role: as ionic

**Fig. 10.** Oxazole containing bioactive natural products.

**Fig. 11.** Synthetic drugs containing thiazole moiety.

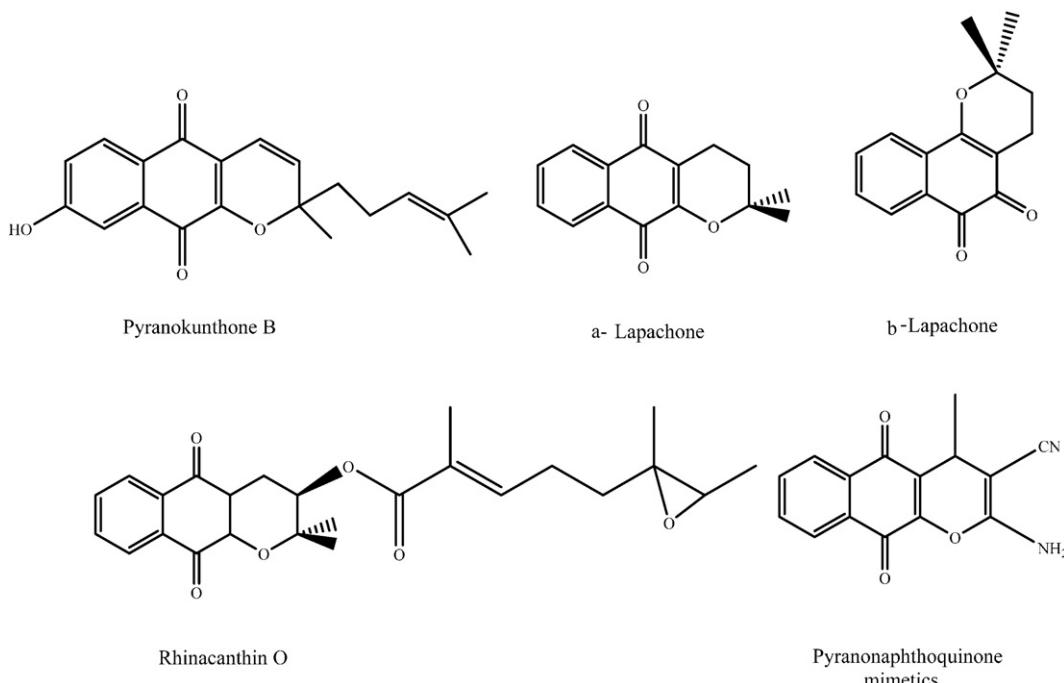
reaction media, as hydrogen bond catalyst and as stabilizer of Fe_3O_4 nanoparticle ([Scheme 12](#)) [47].

Wang et al. used a Brønsted acidic deep eutectic solvent based on choline chloride and *p*-toluenesulfonic acid for the one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles with high yields [48].

Amiri et al. also synthesized 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles by condensation reaction of benzil, aldehydes and ammonium acetate/aniline in the presence of deep eutectic solvents as eco-friendly ionic liquid catalysts under solvent-free conditions at 100 °C. Initially a series of experiments were carried out to optimize the reaction conditions. For this purpose, model reaction of benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (3 mmol) in the presence of five ionic liquids were studied. It was observed that ChCl.2ZnCl_2 ionic liquid shown superiority over

other ionic liquids as catalyst to produce 2,4,5-triphenyl imidazole ([Scheme 1](#)). The one-pot four-component condensation reaction of benzil (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1.5 mmol) and aniline (1 mmol) for the synthesis of tetra substituted imidazole was also examined and the results showed that ChCl.2ZnCl_2 ionic liquid again proved its superiority over other catalysts for this condensation. Three component and four-component reaction under optimized reaction conditions for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles were successfully extended with different aldehydes ([Scheme 13](#)) [49].

A plausible mechanism for the synthesis of 1,2,4,5-tetrasubstituted imidazoles was proposed. ChCl.2ZnCl_2 catalyst activates the carbonyl groups of benzaldehyde and benzil, then nucleophilic attack of the nitrogen of ammonia (obtained from ammonium acetate) and aniline to the activated carbonyl group of benzaldehyde produced diamine

**Fig. 12.** Biologically active pyrane derivatives.

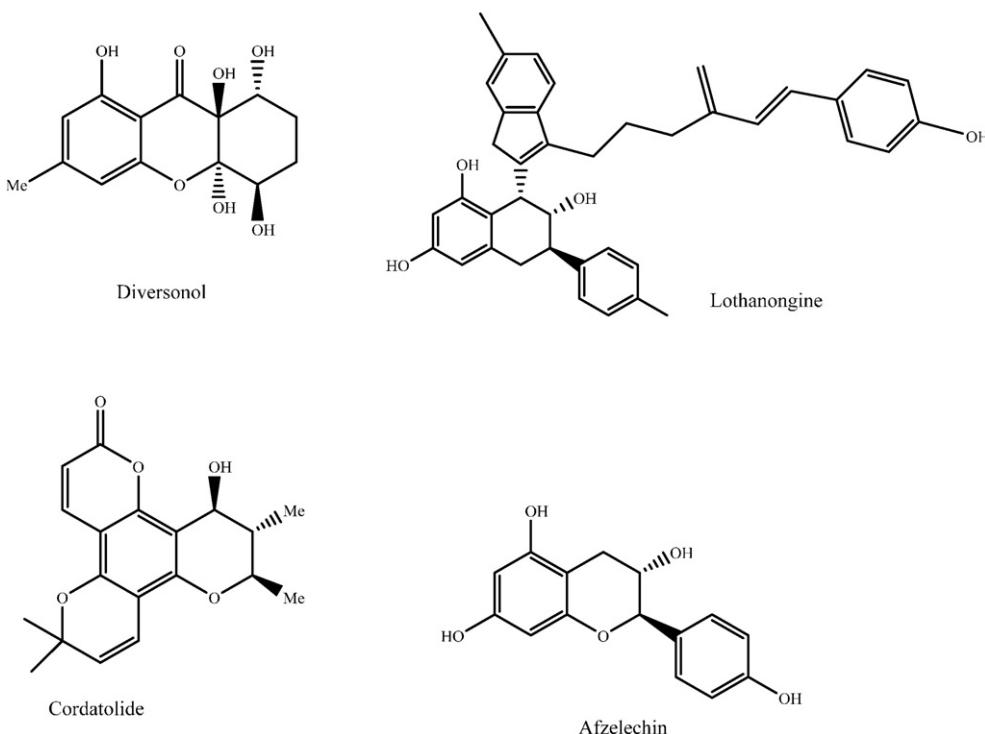


Fig. 13. Natural products with a chromene core.

intermediate 1. Benzil in the presence of $\text{CHCl}_2\text{ZnCl}_2$ condenses with diamine intermediate to form diamine intermediate which is rearranged by water elimination to the corresponding imidazole. Similarly, in the case of the CHCl_2 urea catalyst, the hydrogen of urea can activate the carbonyl group of benzaldehyde and benzil via formation of hydrogen bonding (Scheme 13a).

2.1.8. Synthesis of substituted hydantoins

The hydantoin moiety is an important structural scaffold present in a number of biologically active compounds [50]. Many hydantoin derivatives have been identified as anticonvulsant, antiulcer, antiarrhythmic, antimuscarinic, antiviral and antidiabetic agents [51]. Some hydantoin derivatives have also been used as antidepressants as well as platelet aggregation inhibitors (Fig. 9) [52].

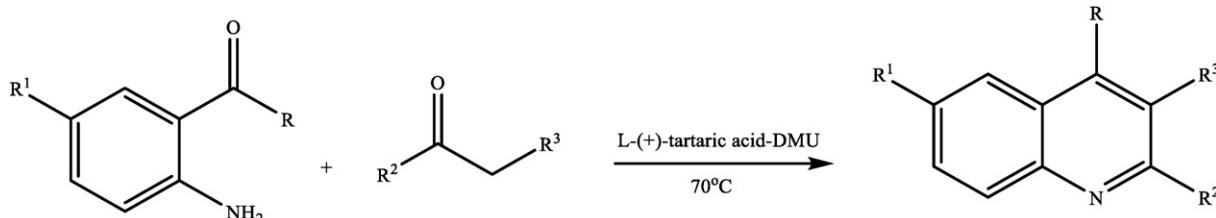
A number of synthetic methods have been reported in the literature for the preparation of hydantoins from diverse starting materials [53]. The classic methods for the synthesis of hydantoin include the Bucherer–Bergs synthesis and the reaction of urea with carbonyl compounds [54]. In particular, the synthesis of highly substituted hydantoins is accomplished by reacting N-substituted α -amino acids or their esters with isocyanates [55]. Alternative strategies for the synthesis of substituted hydantoins use transition metal catalyzed reactions [56], Ugi condensation [57a], reaction of α,β -unsaturated carboxylic acids with carbodiimide [57b], as well as the reaction of α -amino amides with phosgene [57c]. Among the numerous synthetic approaches, first mild and environmentally benign domino synthesis of 1,3,5-

trisubstituted hydantoin from a β,γ -unsaturated ketoacid in low melting mixtures was reported by Koenig et al. In this approach, β,γ -unsaturated ketoacid reacted in a surprising transformation, upon exposure to L-(+)-tartaric acid–dimethylurea (DMU) melt conditions, to 1,3,5-trisubstituted hydantoin derivative in excellent yield with good diastereoselectivity. The melt medium serves simultaneously as a solvent, a catalyst and a reactant in the reaction. The reaction was extended with various β,γ -unsaturated ketoacids derived from electron rich as well as electron deficient aldehydes under the melt conditions and synthesized the corresponding substituted hydantoin derivatives in good to excellent yields (84–92%) (Scheme 14) [58].

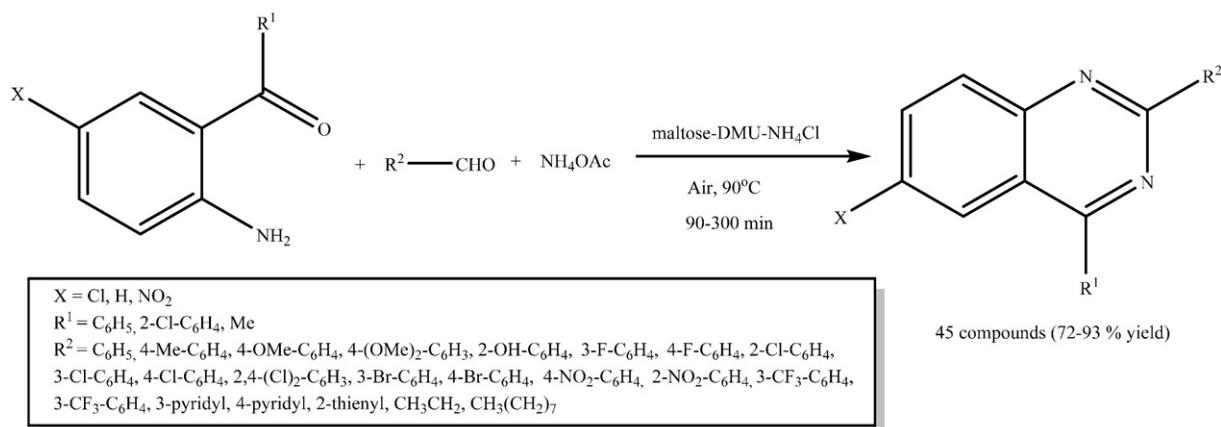
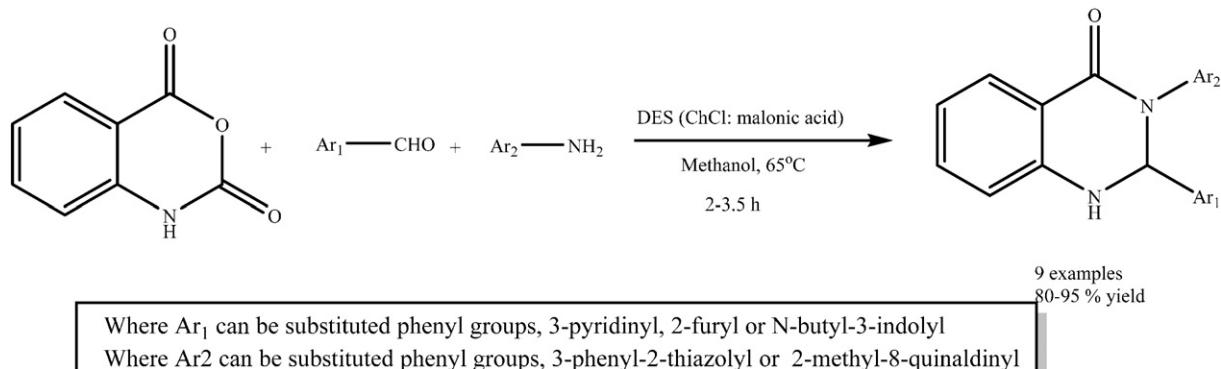
2.1.9. Synthesis of oxazoles

The synthesis of substituted oxazole derivatives has attracted much attention because of their versatile applications, including biological activity such as antibacterial, anti-fungal, anti-tubercular, anti-inflammatory [59] etc. as well as their utility as valuable precursors in many useful synthetic transformations [60]. Oxazoles also attract considerable attention in colorant chemistry especially as scintillating compounds and as fluorescent whitening agents for textiles (Fig. 10) [61].

Recently, Shankarling et al. reported synthesis of oxazole derivatives by the reaction of 4'-substituted phenacyl bromide and amide derivatives in deep eutectic solvent. In their work, the organic synthesis was performed using effective combination of deep eutectic solvents and ultrasound technique. This technique was proved to be a cutting edge technique for synthesis of novel oxazole derivatives. The reaction was



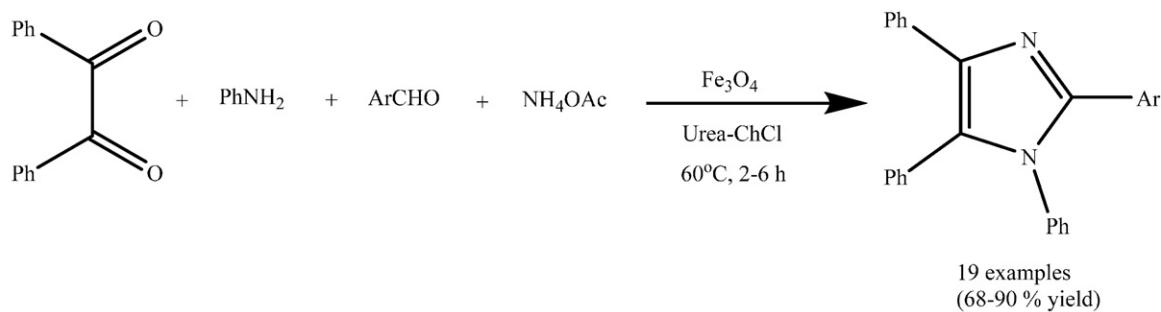
Scheme 9. Synthesis of quinoline derivatives.

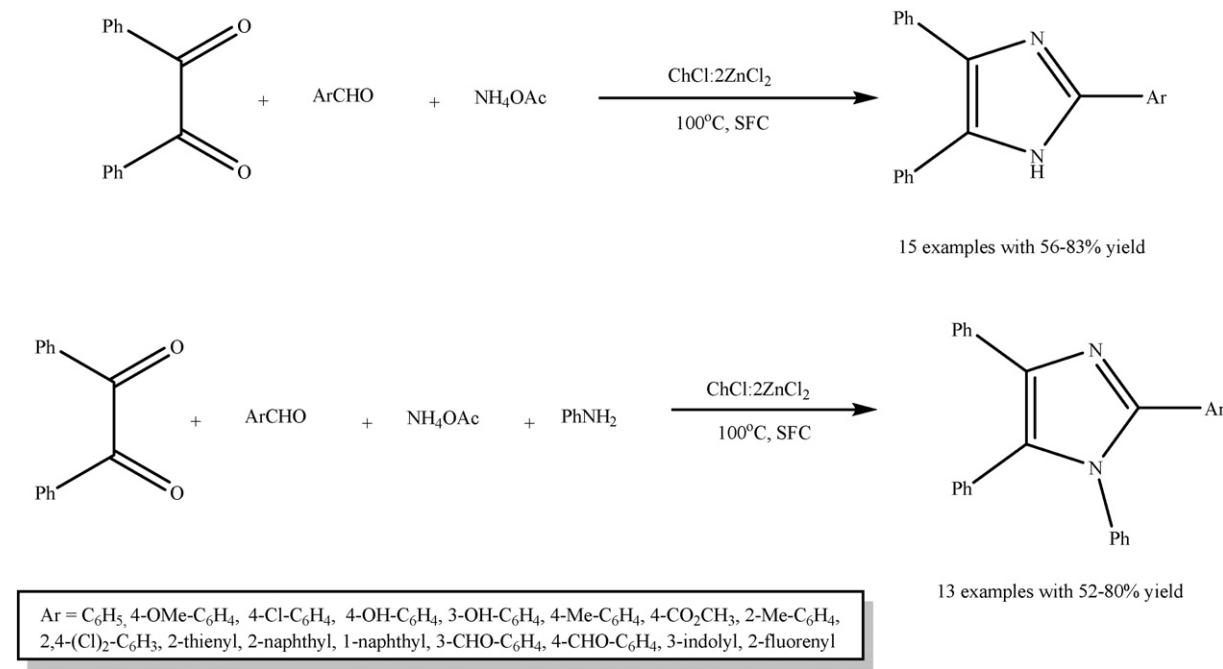
**Scheme 10.** Synthesis of quinazolines.**Scheme 11.** Synthesis of quinazolinone derivatives.

also conducted by thermal method (NUS) and the comparative studies were also provided. It was observed that applying ultrasound not only improved yields and reduced reaction times, but also saved more than 85% energy as shown by energy consumption calculations. The advantages of using DESs as reaction medium was highlighted from the fact that it is bio-degradable, non-toxic, recyclable and can be easily prepared using inexpensive raw materials. The recyclability for DESs was also studied wherein it was found that ultrasound has no negative effects on DESs even up to four runs. In addition (Fig. 7), the present work has been reported as the first report on the combinative use of DESs and US in organic synthesis (Scheme 15) [62].

According to the suggested mechanism, the urea component in deep eutectic solvent (choline chloride: urea) catalyzed the reaction via hydrogen bond catalysis. Urea component in deep eutectic solvent might stabilize the oxygen atom of carbonyl group via hydrogen bonding that facilitated the attack of amide on phenacyl bromide derivative resulting in cyclization with the formation of oxazole (Scheme 15a).

The present synthetic protocol with the combined use of DESs and ultrasound radiation was extended for the synthesis of 2-aminooxazole derivatives involving the reaction of phenacyl bromide derivative with urea in deep eutectic solvent. It was observed that ultrasound-assisted method gave 90% yield in just 8 min as against

**Scheme 12.** Synthesis of 1,2,4,5-tetrasubstituted imidazoles.

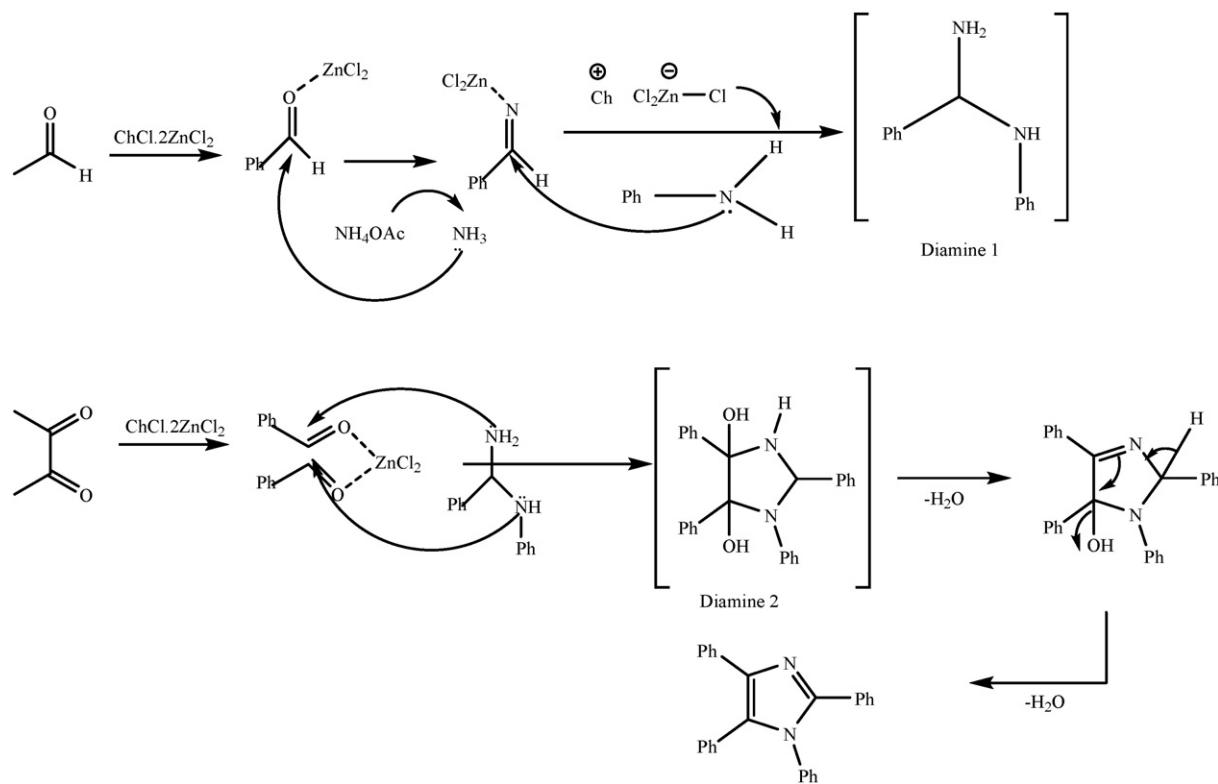
**Scheme 13.** Synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles.

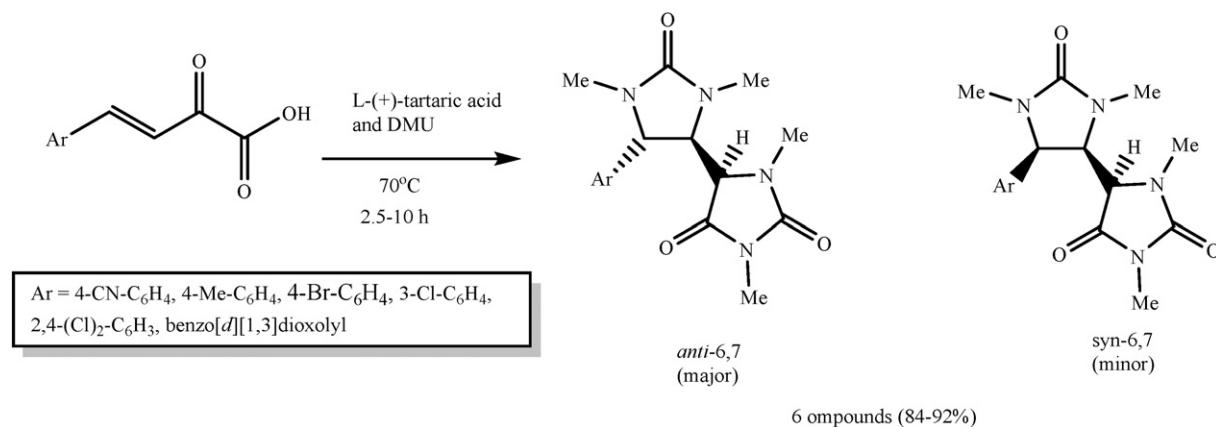
3.5 h required to obtain 69% yield by conventional method. It was observed that the use of ultrasound radiation not only increased the rate of reaction but also improved the quality of product obtained in terms of crystallinity. In addition, ultrasound assisted synthesis also saved more than 70% energy as reported by energy calculations. Moreover, the use of DESs in sonochemical organic synthesis is quite suitable owing to their negligible vapor pressure. Not only, deep eutectic solvent catalyzed the reaction since no reaction was observed with conventional organic solvents (**Scheme 16**) [63].

2.1.10. Synthesis of thiazoles

Thiazole derivatives have been reported to be associated with several biological activities which have made them extremely useful in the treatment of hypertension, schizophrenia, inflammation, and HIV infections [64,65]. Its derivatives like aminothiazoles are known to be ligands of estrogen receptors and also adenosine receptor antagonists (**Fig. 11**) [66].

In view of their extensive biological properties, many improved methods have been reported for the synthesis of thiazoles using various

**Scheme 13a.** Proposed reaction mechanism.

**Scheme 14.** Synthesis of a 1,3,5-trisubstituted hydantoin derivatives.

catalysts [67]. Although these methods are efficient in terms of yields and some even use greener methods, however, most of these methods suffer from some limitations. Synthesis of thiazoles has also been performed in ionic liquids, however, the ionic liquids based on imidazole and fluorinated anions suffer from the demerits of being toxic and commercially expensive [68]. In this context, Shankarling et al. used ammonium based deep eutectic mixture (choline chloride–urea) as efficient catalyst for aqueous phase synthesis of methylthiazole and aminothiazole derivatives involving the reaction of phenacyl bromide and thioamide derivatives. The deep eutectic catalyst, easily synthesized from choline chloride and urea, is inexpensive, recyclable and biodegradable, thus making it suitable for industrial applications (**Scheme 17**) [69].

2.1.11. Synthesis of thiazolidin-4-ones

Thiazolidin-4-one derivatives constitute an important class of heterocyclic compounds because of their applications in organic syntheses to prepare heterocyclic compounds with diverse biological and pharmaceutical activities [70,71]. Thiazolidinones were earlier prepared by two or three step procedures [72]. But Amiri et al. proposed one-step synthetic strategy involving the reaction of thioureas with chloroacetyl chloride and an aldehyde in natural deep eutectic solvent (urea/choline chloride) to synthesize thiazolidin-4-ones. The methodology is mild and rapid for green synthesis of various 4-thiazolidinones in good to excellent yields in natural deep eutectic solvent as a catalyst and reaction media (**Scheme 18**) [73].

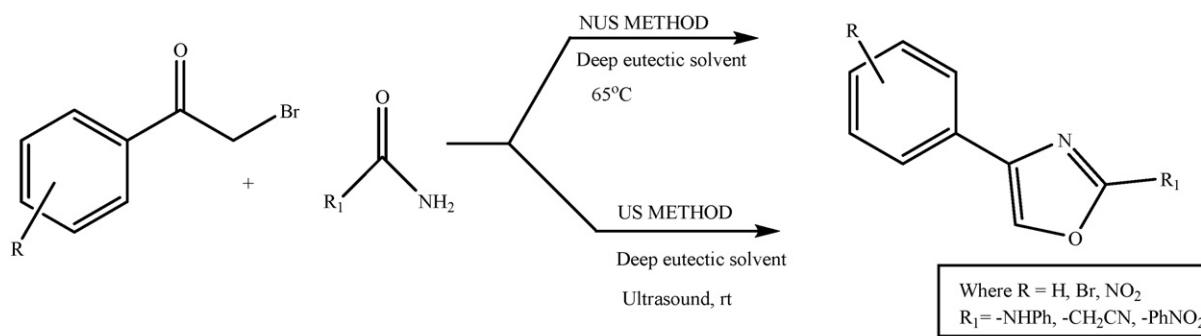
Mane et al. proposed an alternative synthetic route for an antidiabetic drug, rosiglitazone which is thiazolidine-2,4-dione derivative. The developed route has overall four steps. The first step involving Knoevenagel

condensation of 4-fluorobenzaldehyde and 2,4-thiazolidinedione, provides 5-(4-fluorobenzylidene) thiazolidine-2,4-dione. This condensation was carried out using a safer non-volatile solvent, freshly prepared deep eutectic solvent. Initially, attempts have been made to optimize the reaction conditions for the condensation of 4-fluorobenzaldehyde and 2,4-thiazolidinedione to synthesize 5-(4-fluorobenzylidene) thiazolidine-2,4-dione by carrying out the condensation using various reaction media and organic/inorganic bases. It was observed that freshly prepared deep eutectic solvent worked as better medium and catalyst. Optimized temperature required for the condensation was also checked. It was also noted that maximum conversion was obtained at 80 °C and deep eutectic solvent could be recovered and recycled for another batch of the condensation (**Scheme 19**) [74].

2.1.12. Synthesis of pyran derivatives

The pyran is an important pharmacophore and incorporated in the bioactive compounds with antitumor, antibiotic, antibacterial, antiallergic, hypolipidemic and immunomodulating activities [75]. Furthermore, substitution of hydrogen atom of pyran with amino or cyano makes these compounds as synthons for natural products (**Fig. 12**) [76].

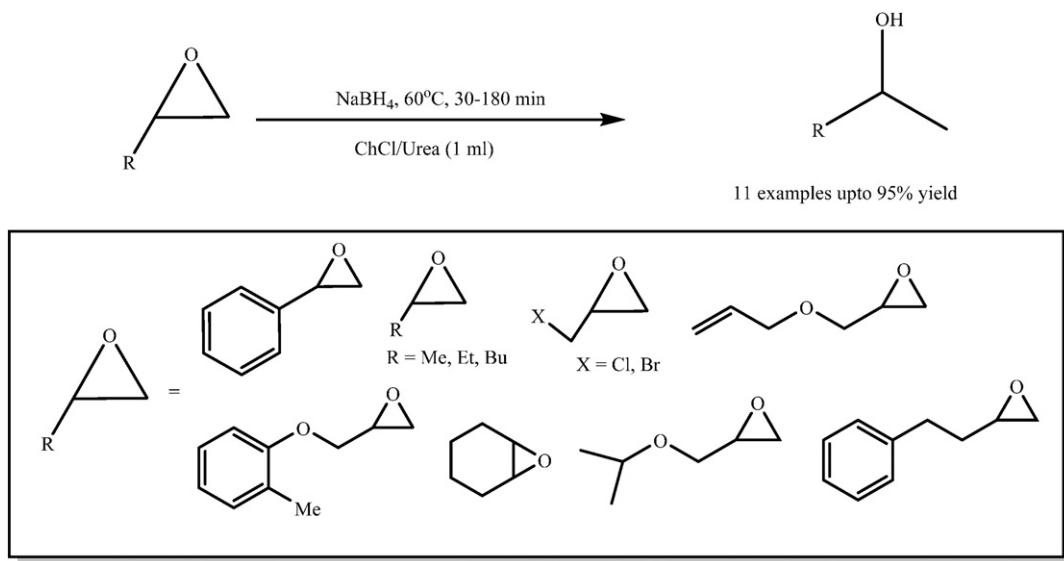
Azizi et al. developed an eco-friendly one-pot multicomponent synthetic protocol involving the reaction of 1,3-dicarbonyl compounds, aldehydes, and malononitrile in deep eutectic solvent (DES) based on choline chloride, to synthesize highly functionalized benzopyran and pyran derivatives under catalyst-free conditions. To check the feasibility of reaction and to optimize reaction conditions, various conventional solvents and ChCl based deep eutectic solvents were screened on model reaction of benzaldehyde, malononitrile, and dimedone. The



US method = 5 examples (82-90 % yield in 12-17 min)

NUS method = 5 examples (45-65 % yield in 3.5-5 h)

Scheme 15. Synthesis of oxazole derivatives.

**Scheme 15a.** Proposed reaction mechanism.

effect of temperature was also screened on efficiency of ChCl:urea deep eutectic solvent. After screening different solvents with reaction conditions, the deep eutectic solvent, ChCl:urea, at 80 °C showed superiority over other solvent systems as the desired product was obtained within 60 min with excellent yield (95%). The deep eutectic solvent, urea:choline chloride, was considered best solvent and applied successfully to a wide range of aldehydes, active methylene compounds. The products were obtained with high yields (75–95%) in short reaction times (1–4 h). The present method offers the advantages of catalyst-free reaction, easy purification, short reaction time, and high yield (**Scheme 20**) [77].

The proposed mechanism involves the catalytic role of DESs in the synthesis of pyrane derivatives. The reversible hydrogen bonding between urea and carbonyl groups giving substrate–solvent complex activated aldehydes. The initial condensation of carbonyl groups with activated malononitrile with urea in the DES leads to the formation of arylidene malononitrile with the loss of a water molecule. The nucleophilic addition of the enolizable ethylacetacetate to arylidene malononitrile followed by intramolecular cyclization results in the formation of 4H-pyran derivatives (**Scheme 20a**).

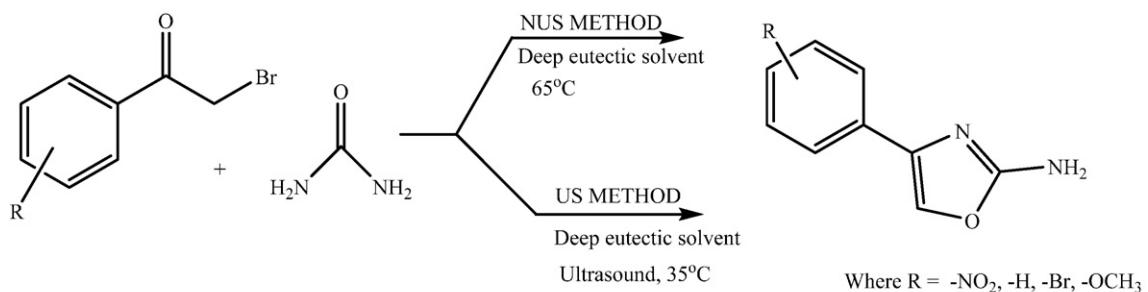
2.1.13. Synthesis of 4H-chromene based dyes

Chromenes or benzopyrans constitutes an important group of heterocyclic compounds with various biological and pharmacological activities such as spasmolytic, diuretic, antiviral, antitumoral and

antianaphylactic, among others [78,79]. Furthermore, the chromene skeleton is present in numerous natural products used as pigments, photoactive compounds and biodegradable agrochemicals (**Fig. 13**) [80]. Hence, the synthesis of chromens holds a special place and considerable efforts have been devoted to the development of efficient synthetic methods. The synthesis of chromene based dyes in green solvents at room temperature under catalyst-free conditions is a promising alternative to previously used procedures.

Azzizi et al. presented a facile, atom-economic and environmentally-benign one-pot reaction of salicylaldehyde and malononitrile with various nucleophiles, including indoles, thiols, secondary amines, cyanide and azide in choline chloride based deep eutectic solvent (DES). In this green protocol, the products formation depends on the nature of the nucleophile used in the reaction. The reaction of salicylaldehyde derivatives and malononitrile with thiols, indoles, and cyanide gave 2-amino-3-cyano-4H-chromene derivatives. But the use of secondary amines in the reaction result in the formation of benzopyrano[2,3-d]pyrimidines, due to the further reaction of salicylaldehyde with 4H-chromene under the reaction conditions. The DES was recycled without any reduction in activity or yield (**Scheme 21**) [81].

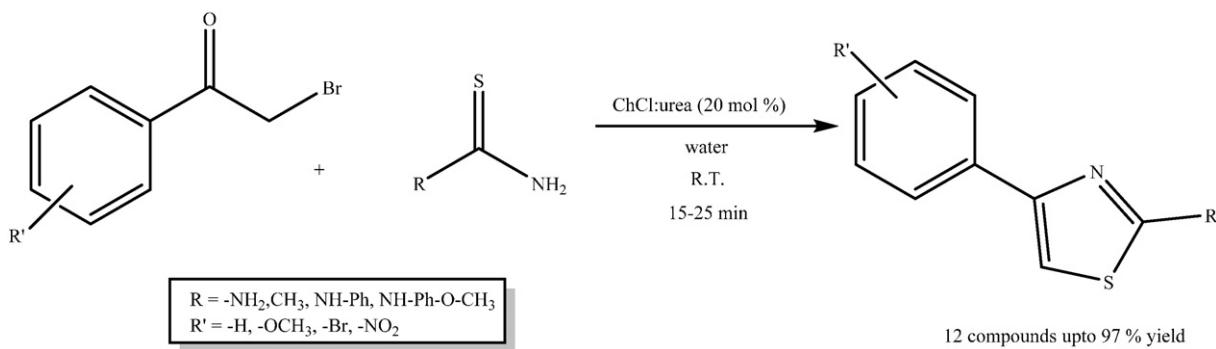
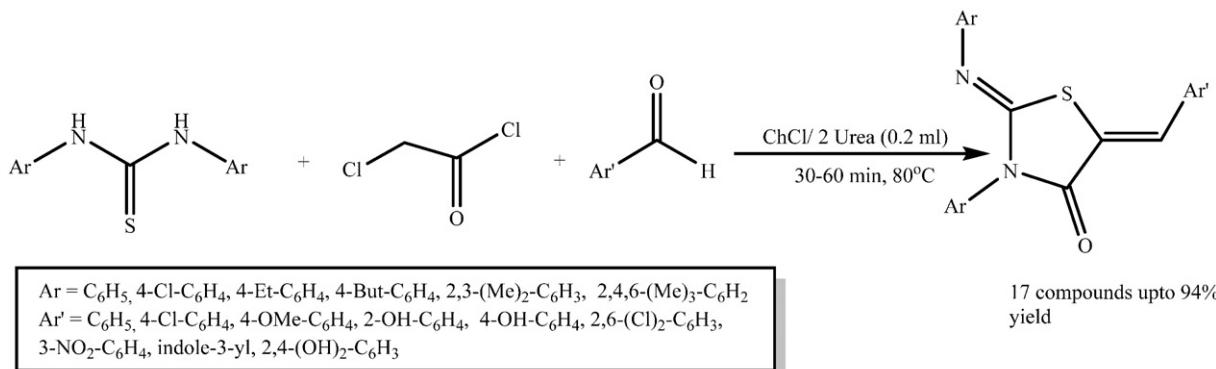
2-Aminochromenes constitute an important class of compounds and are present as the main components of many naturally occurring products employed as cosmetics and pigments [82] and utilized as potential biodegradable agrochemicals [83]. Multifunctional chromenes have been efficiently synthesized by Chaskar et al. in aqueous medium at



US method = 4 examples (79–90 % yield in 8–20 min)

NUS method = 4 examples (51–69 % yield in 3.5–5 h)

Scheme 16. Synthesis of 2-aminooxazole derivatives.

**Scheme 17.** Synthesis of thiazoles.**Scheme 18.** Synthesis of thiazolidin-4-one derivatives.

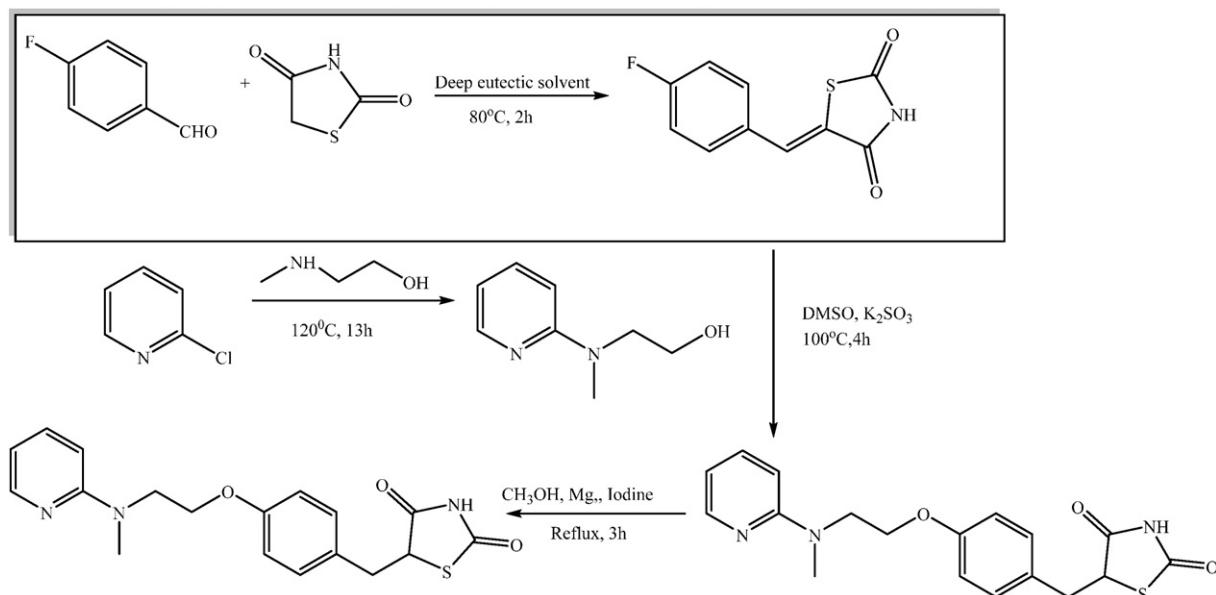
room temperature using deep eutectic mixture of choline chloride:urea. In this one-pot multicomponent synthesis, the benzylidene malononitrile firstly formed by Knoevenagel condensation of aldehyde and malononitrile eventually underwent Michael addition-cyclization with dimedone and provided the chromenes in good to excellent yields (**Scheme 22**) [84].

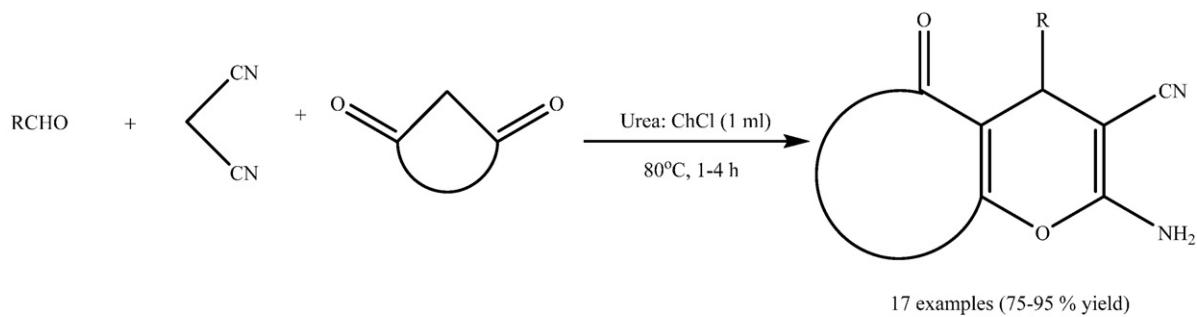
2.1.14. Synthesis of xanthenes and tetraketones

Tetraketones are important structural units in heterocycles with three-ring systems, such as xanthendione and acridindione. Meanwhile,

tetraketones are also interesting because their properties are similar to those of 1,4-dihydropyridines, and their structures are similar to those of biologically important compounds, such as NADH and NADPH [85]. Natural products incorporating xanthene heterocyclic system have a great deal of importance because of their diverse ubiquitous pharmacological properties, such as antibacterial, antiviral and antinociceptive activities [86]. In addition, they are also used as fluorescent compounds in laser technology and in the monitoring of biomolecules.

The tandem Knoevenagel condensations and Michael addition of aldehydes with active methylene compounds in the presence of acid

**Scheme 19.** Synthesis of rosiglitazone drug.



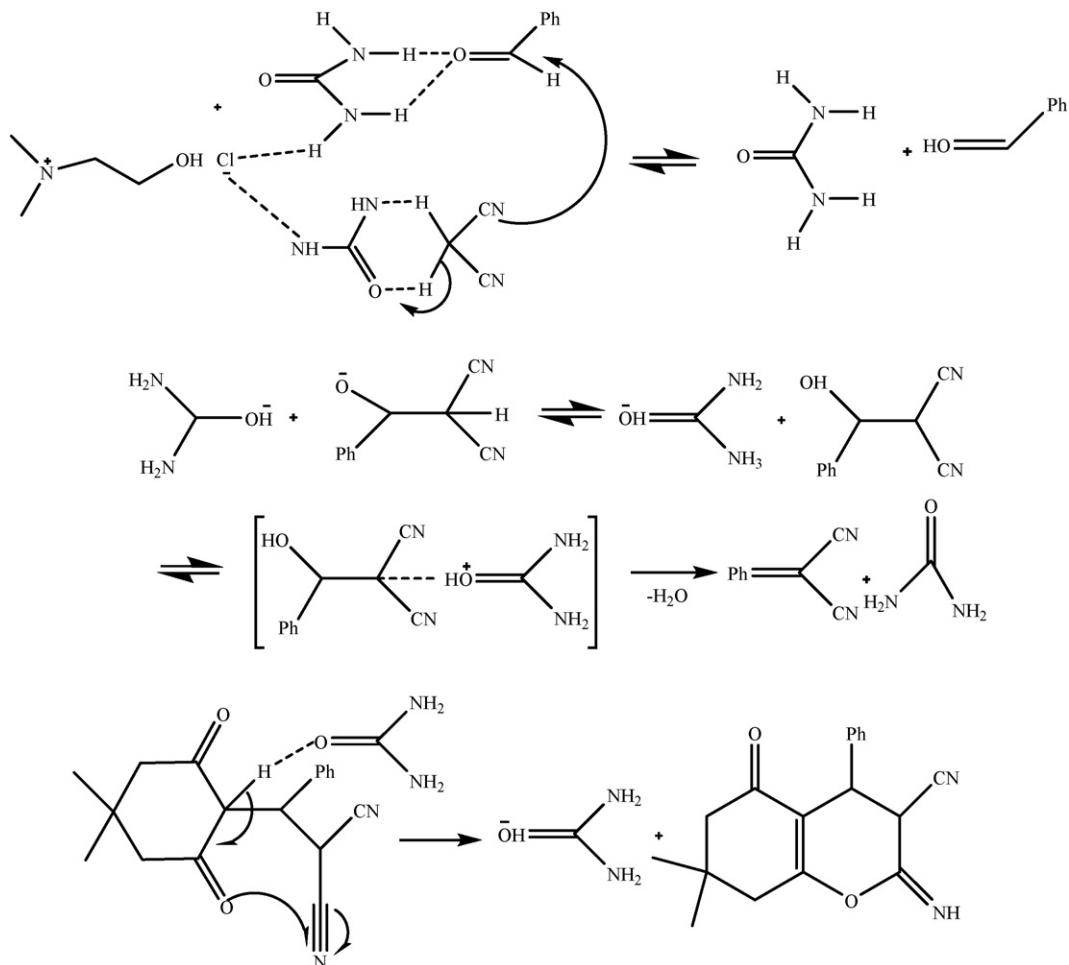
R = C₆H₅, 4-NO₂-C₆H₄, 3-NO₂-C₆H₄, 4-Cl-C₆H₄, 4-OMe-C₆H₄, 4-OH-C₆H₄, 4-F-C₆H₄, 2,4-(OMe)₂-C₆H₃, 2-furyl
1,3-dicarbonyl compounds = Acetyl acetone, Ethyl acetoacetate, Methyl acetoacetate, Dimedone

Scheme 20. Syntheses of pyran and benzopyran derivatives.

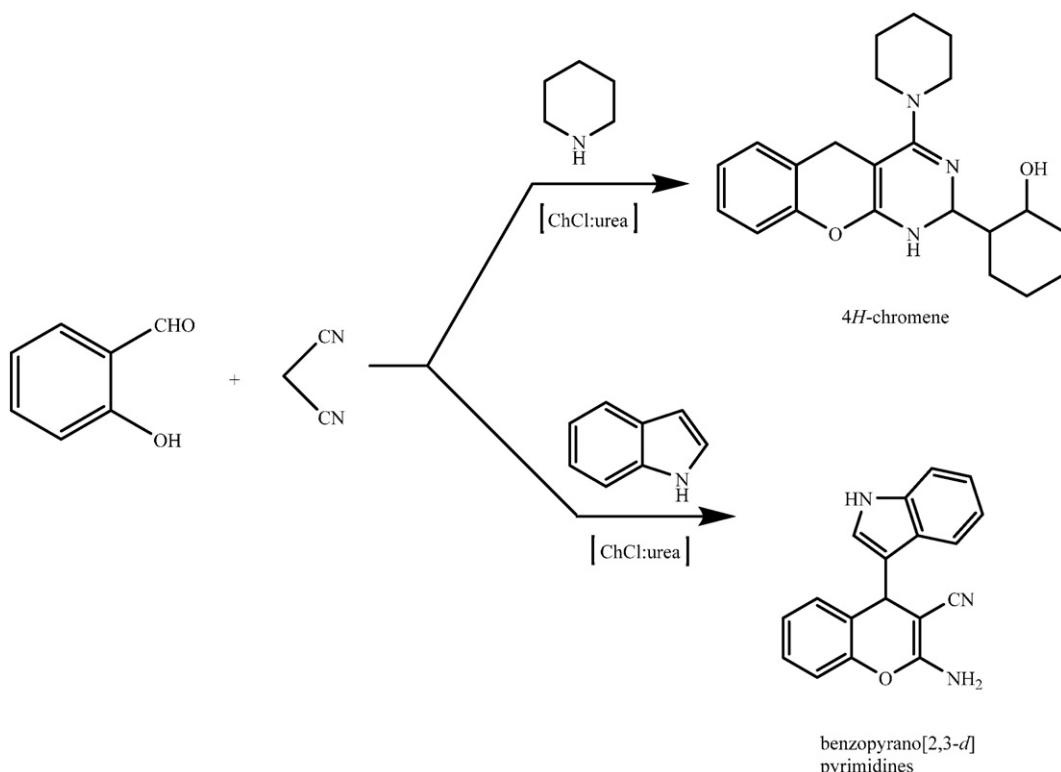
or alkaline catalysts are widely used as important versatile methods for the synthesis of tetraketones [87]. Because of their practical importance, several methods have been proposed, employing different catalysts and promoters, such as NaOH [88], KOH [89], piperidine [90], proline [91], and *p*-dodecylbenzenesulfonic acid [92]. Furthermore, catalyst-free reactions in pure water [93], in the solid state, and in melts have been reported [94]. Similarly, the numerous methods involving the condensation of aldehydes with active methylene compounds in the presence of an acidic catalyst or a promoter have been reported for

the synthesis of xanthene in the literature [95,96]. Some of these methods suffer from prolonged reaction times, high cost, or the catalysts' sensitivity to moisture. Therefore, the development of simple and efficient procedures for the synthesis of xanthenes in the novel reaction media is a challenging task.

Azizi et al. proposed three-component tandem synthesis of xanthenes and tetraketones from aldehydes and active methylene compounds in choline chloride-based deep eutectic solvents (DESs). In the optimization experiment on model reaction of benzaldehyde and



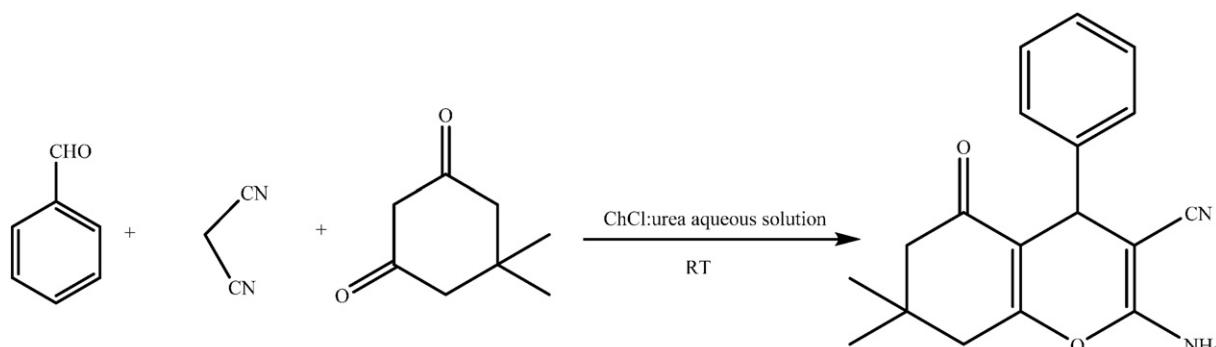
Scheme 20a. Proposed reaction mechanism.

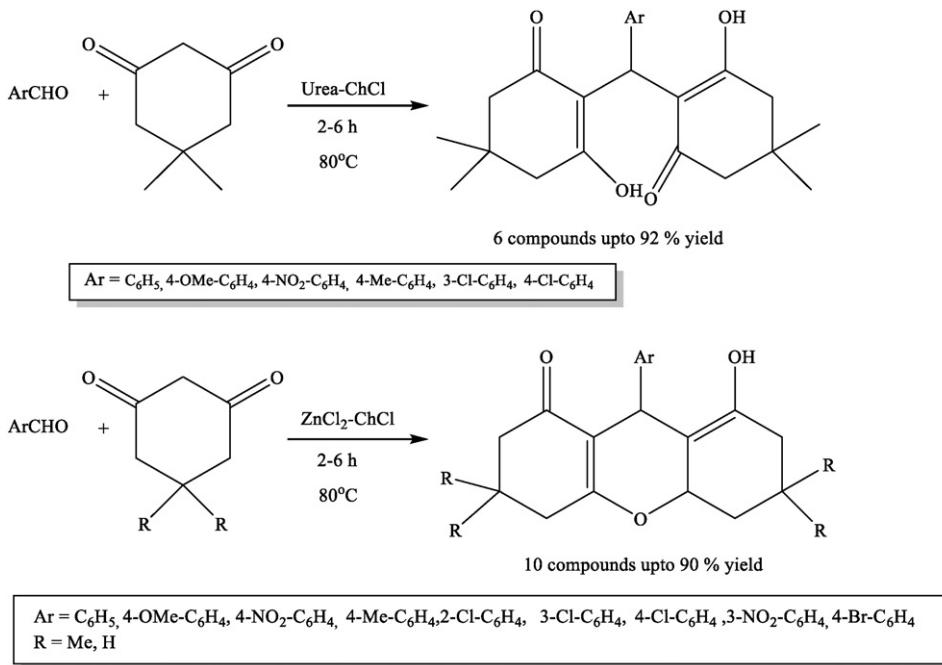
**Scheme 21.** Synthesis of 4*H*-chromene derivatives and benzopyrano[2,3-*d*]pyrimidines.

dimedone, it was observed that the DES-based choline chloride–urea and choline chloride– SnCl_2 provided tetraketones in higher yields and shorter reaction times than methods using other DESs. On the other hand, in choline chloride– ZnCl_2 and choline chloride–malonic acid mixtures, the reaction proceeded selectively to generate xanthene derivatives. The synthetic protocol was extended with a range of functionalized aromatic aldehydes and dimedone to examine the substrate scope of the reaction in choline chloride–urea for tetraketones and choline chloride– ZnCl_2 for xanthene derivatives. The reaction scope is quite broad with respect to a wide range of structurally varied aldehydes, and the electronic variation on the aryl aldehydes caused no appreciable changes in the efficiency of the condensations. Electron-rich, electron-poor, aromatic, heterocyclic, and sterically encumbered aldehydes were all well tolerated in these reaction conditions. The procedure has been reported to be simple with mild reaction conditions and operational simplicity as compared to the other reported methods (**Scheme 23**) [97].

2.1.15. Synthesis of pyrroles and furans

The Paal–Knorr synthesis of pyrroles and furans is a versatile method for the synthesis of these valuable heteroaromatics [98]. Numerous different reaction conditions have been developed over the years, including Lewis acid catalysis [99], heterogeneous catalysis [100], microwaves [101], different solvent variations (RTIL and solvent-free) [102], and ultrasound or microflow conditions [103]. Handy et al. described a synthesis of pyrroles and furans via the Paal–Knorr synthesis in DES. Deep eutectic solvents (the combination of either urea or glycerol with choline chloride) are effective solvents/catalysts for Paal–Knorr reactions to form pyrroles or furans. Initially, equimolar mixture of the dione and the amine as a 1 M solution were stirred in choline chloride/urea at 80 °C and pyrrole derivatives were obtained (**Scheme 24**). The synthetic strategy was also extended successfully with less nucleophilic anilines, but required longer reaction times and the pyrrole products were obtained in nearly quantitative yields. In this method, the diones were found to be less reactive but the yield of the product could be

**Scheme 22.** Synthesis of 2-aminochromene derivatives.

**Scheme 23.** Synthesis of xanthenes and tetraketones.

increased by allowing the reaction to proceed for 24 h. Overall, in this method the reaction conditions are quite mild and do not require the addition of an additional Bronsted or Lewis acid catalyst. These reaction conditions are simple and highly environmentally friendly in view of non-toxic, and recyclable nature of the DES. During pyrrole synthesis, furan formation was observed as a side reaction with less nucleophilic amines, so in the absence of any amine, the furan products obtained in good yield (**Scheme 25**) [104].

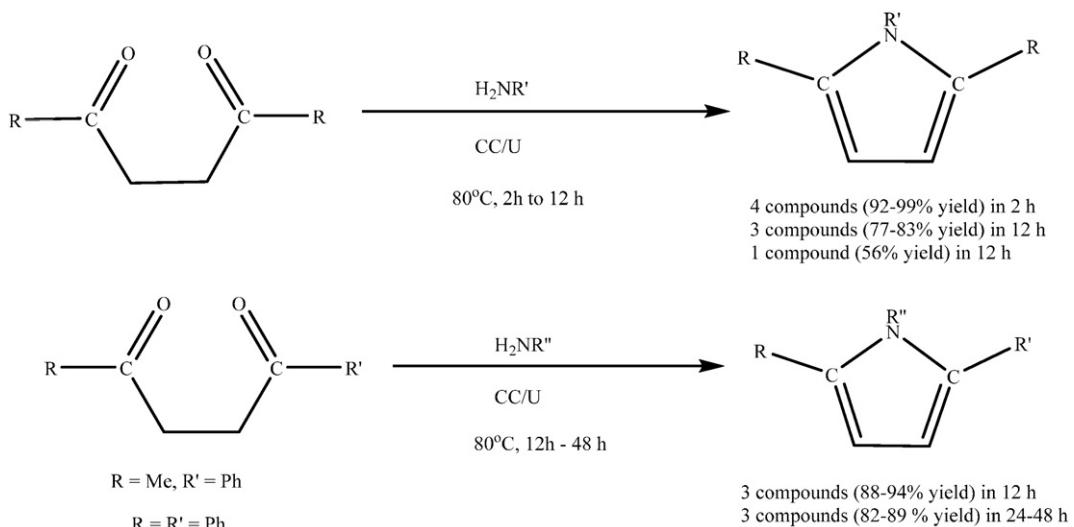
2.1.16. Synthesis of cyclic carbonates

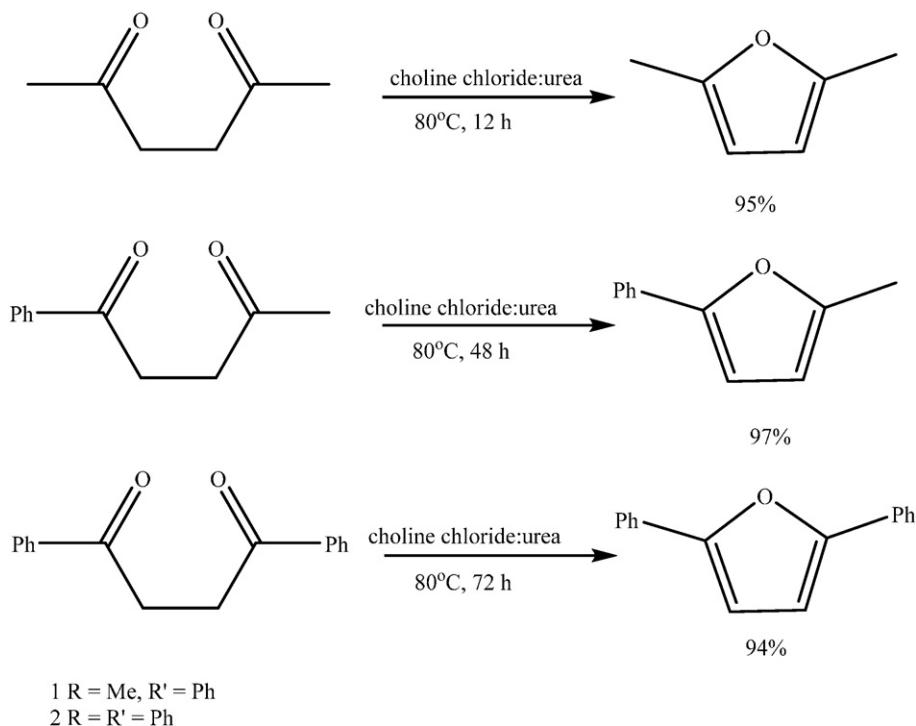
Chemical fixation of CO_2 is of great importance in connection with the development of environmentally benign processes, and there are many possibilities for using CO_2 as a safe and cheap Cl source in organic syntheses. The formation of cyclic carbonates via cycloaddition of CO_2 with epoxides is one of the attractive routes for chemical fixation of

CO_2 because the cyclic carbonates have shown interesting applications as polar aprotic solvents, precursors for polycarbonate materials, and intermediates in organic synthesis [105].

Numerous catalysts have been developed to catalyze these reactions. However, in most cases, organic solvents are used in the reactions or work-up procedures and the products are commonly isolated from the reaction systems by distillation [106–108]. Recently, supported ILs (SILs) were reported to be effective catalysts for cyclic carbonate synthesis, but the procedure to prepare catalyst is relatively complicated [109]. Therefore, it is still desirable to explore a highly efficient, easily separating and recyclable catalyst system for this transformation.

In the work reported by Zhu et al. the catalytic efficiency of ionic liquid (IL) choline chloride/urea supported on molecular sieves for the reactions of CO_2 and epoxides was studied under different conditions. It was demonstrated that this biodegradable and green catalyst is very

**Scheme 24.** Paal-Knorr pyrrole synthesis.

**Scheme 25.** Paal–Knorr furan synthesis.

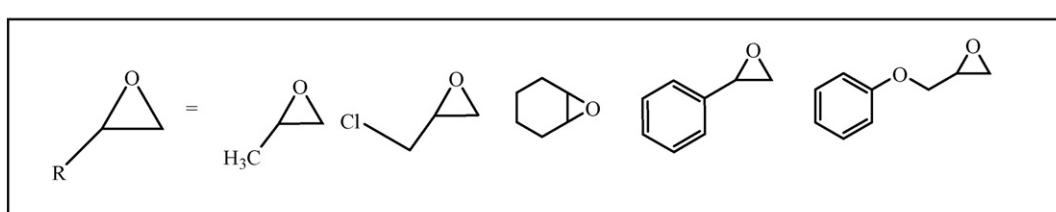
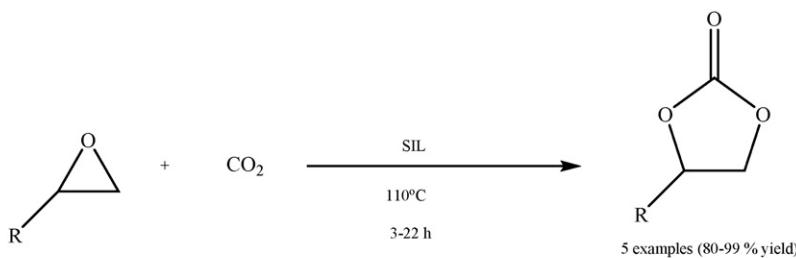
active and selective, and choline chloride and urea showed a synergistic effect in promoting these reactions. After the reaction, the solid catalyst and the products could be separated easily because the IL was insoluble in the products, and the catalyst was reusable. The origin of the high catalytic efficiency and the reaction mechanism were also discussed (**Scheme 26**) [110].

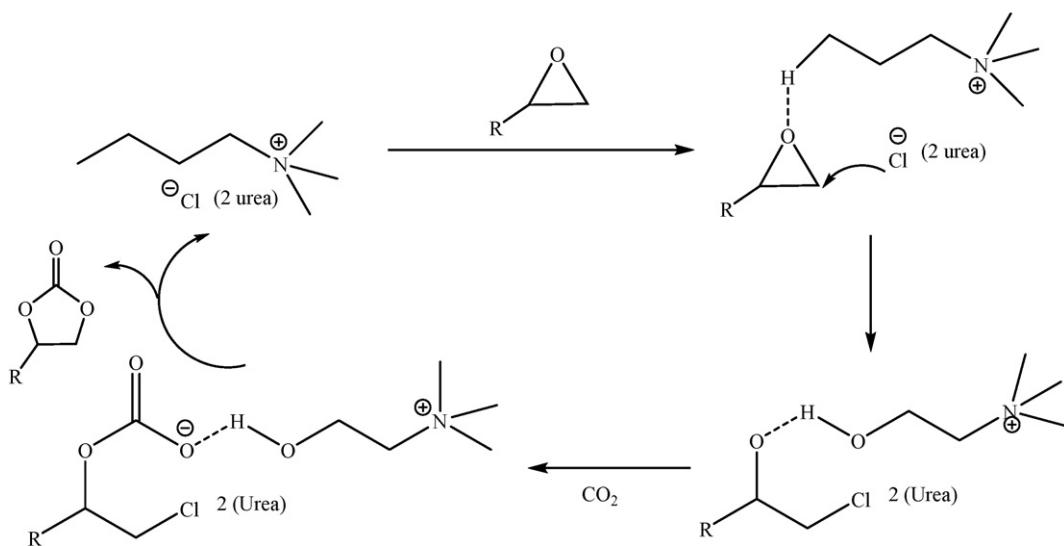
According to proposed mechanism the chlorine anion (combining with two urea molecules) of the IL facilitates the opening of the epoxy ring, which is activated by the choline cation through hydrogen bonding to give the intermediate. The intermediate thus formed reacts with CO₂ to provide the corresponding cyclic carbonate with the regeneration of catalyst (**Scheme 26a**).

2.2. Other organic transformations

2.2.1. Esterification

2.2.1.1. Esterification of acid. Synthesis of organic esters has a main role in organic synthesis from its infancy, due to the utility of esters as products or intermediates in diverse fields, both in the laboratory and in industry [111]. Most of the recent research work dealing with esterification has been associated with green chemistry for example, condensation between carboxylic acids and alcohols has been achieved in ILs as dual solvent-catalysts [112]. However, high temperature (110 °C) required in the process and the use of halogen atom containing ionic liquids

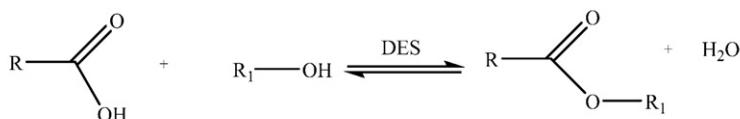
**Scheme 26.** Synthesis of cyclic carbonates.

**Scheme 26a.** Plausible reaction mechanism.

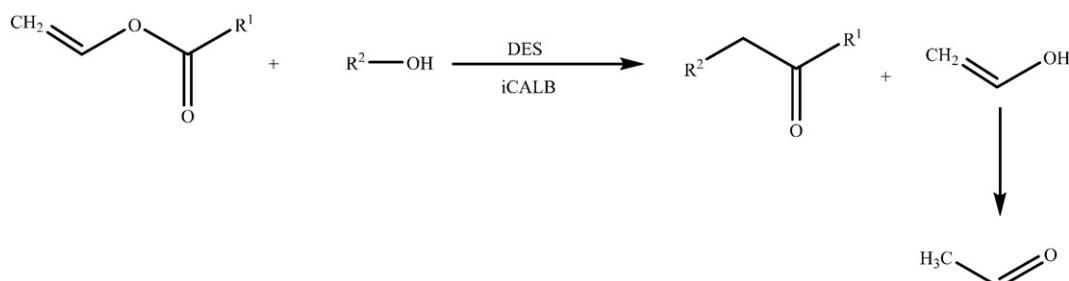
may cause serious concerns [113,114]. Germani et al. prepared halogen-free Brønsted acidic deep eutectic solvents (DESs) by mixing quaternary ammonium methanesulfonate salts (*i.e.* TCyAMsO, TBnAMsO, TOAMsO or TCyATos) with *p*-toluenesulfonic acid and used these DESs as dual solvent-catalyst for esterification of several carboxylic acids with different alcohols. When the reaction of lauric acid with methanol was selected as model reaction, the ester methyl laurate was obtained as desired product with maximum yield (97% by g.c.) in shorter reaction time (2 h at 60 °C) using the ionic eutectic solvent, TCyAMsO-*p*-TSA. The Fischer esterification was performed involving the reaction of benzoic acid with methanol and n-octanol, but the reaction rate was found to be lower than that observed in the reaction with aliphatic acid due to electronic effects. Optimum reaction time with methanol has been reported 4 h with yield 69% because for both shorter and longer reaction times the yield of the product decreased. On the other hand, for n-octanol the yield of the product monotonically increased

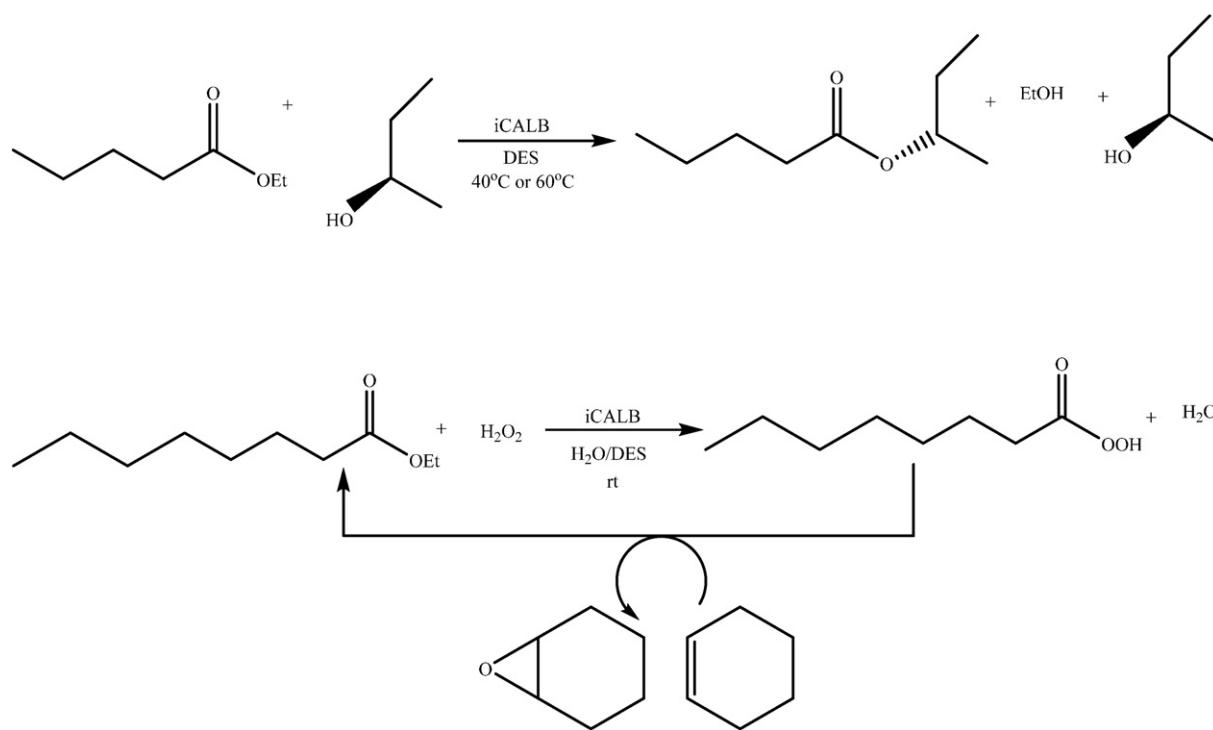
with reaction time, and the best yield (86%) was obtained in 17 h. This is mild, safe, and simple method and recovery and reusability of DESs with high activity makes this method efficient and eco-friendly (**Scheme 27**) [115].

2.2.1.2. Transesterification. Lipases (triacylglycerol hydrolases) are serine hydrolases that are able to act on long-chain carboxylic ester bonds. Not only, they are used for their natural hydrolyzing function but also catalyze ester synthesis, interesterification and transesterification reactions in non-aqueous media. Most lipases preserve a good activity in organic solvents and their ability to catalyze alcoholysis reactions in organic media is well known and documented [116]. However, most organic solvents can be damaging or toxic for the environment. Therefore, in context of green chemistry a number of studies have attempted to reduce environmental impact and tried to carry out lipase-catalyzed reactions in green solvents. Villeneuve et al. evaluated deep eutectic



Acids = Benzoic acid, Phenylacetic acid, Lauric acid, Octanoic acid, Palmitic acid, Stearic acid, Acetic acid, Isobutyric acid, Trimethylacetic
Alcohol = MeOH, n-OctOH, 2-(4-Hydroxyphenyl)-ethanol, n-BuOH, EtOH, Cyclohexanol, Isopropanol

Scheme 27. Esterification of acid.**Scheme 28.** Transesterification between a vinyl ester and an alcohol.

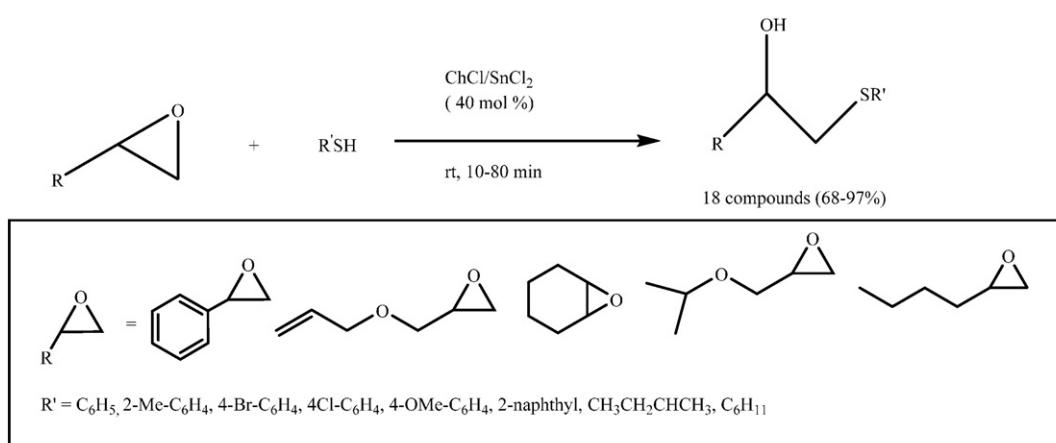
**Scheme 29.** Perhydrolysis, and transesterification.

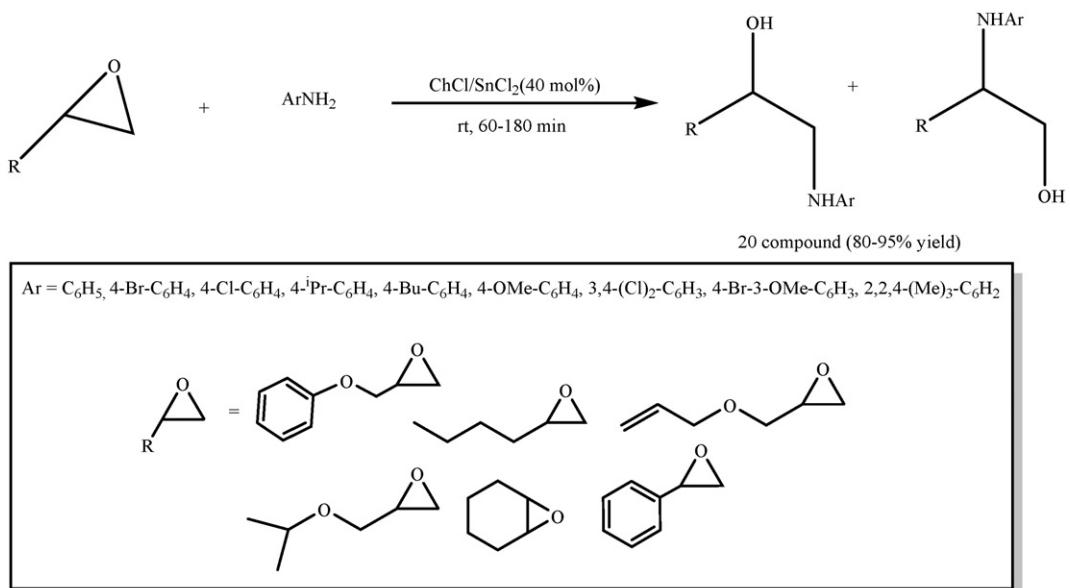
solvents as new media for *Candida antarctica* B lipase catalyzed reactions. Initially, in order to determine whether DESs could be a suitable medium for *C. antarctica* B lipase-catalyzed reactions, a model reaction was used for the alcoholysis of vinyl laurate with alcohols of different chain lengths (butanol, octanol, octadecanol). The effect of water was also included as a content in deep eutectic solvent on enzyme activity because water can decrease the viscosity and change the activity and selectivity of the enzyme. So, the activity and selectivity of enzyme is affected by water content of the DESs. On the other hand, water is the simplest hydrogen-bond donor, thus its content should be as low as possible in order to avoid any possible change of the initial eutectic composition and to prevent competitive hydrolysis reaction (Scheme 28) [117].

Kazlauskas et al. also applied DESs as alternative solvents for hydrolase-catalyzed reactions and found DESs as suitable solvents for a variety of reactions, including perhydrolysis, and transesterification (Scheme 29) [118].

2.2.2. Epoxide ring opening

2.2.2.1. Hydrolysis of epoxides. Epoxide hydrolases (EH) catalyze hydrolysis of epoxides to the corresponding vicinal diols. Both diols and epoxides are important prochiral and chiral intermediate molecules in chemical and pharmaceutical industry [119]. Widerstena et al. showed that deep eutectic solvents (DESs) are viable cosolvents for enzyme-catalyzed epoxide hydrolysis. Three different commercially available DESs: ethaline (ET) (ChCl:ethanediol), glyciline (GLY) (ChCl:glycerol), and reline (REL) (ChCl:urea), all in 1:2 stoichiometric ratios, were investigated with epoxide and the potato epoxide hydrolase StEH1 for the effect of DESs on enzyme stability and activity. The effect of the DESs on enzyme function was primarily elevations of K_M (up to 20-fold) and with lesser effects on turnover numbers (twofold variation). The regioselectivity in hydrolysis of the (1R,2R)-2-trans-methylstyrene oxide was altered in the presence of GLY or ET to favor epoxide ring opening at the benzylic carbon ($R = 2.33$), enhancing the regioselectivity observed

**Scheme 30.** Ring opening of epoxide with thiols.

**Scheme 31.** Reaction between various epoxides and aromatic amines.

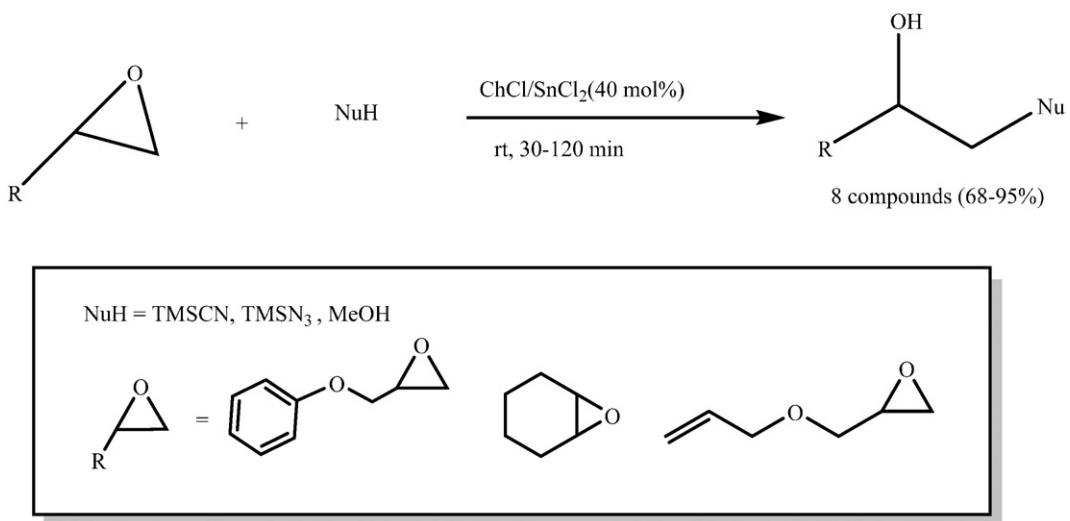
in buffer-only systems ($R = 1.35$). The DES solutions dissolved 1.5-fold higher epoxide concentrations as compared to phosphate buffer. The total conversion of high concentration (40 g/l) of (1*S*,2*S*)-MeSO was not negatively affected by addition of 40% GLY [120].

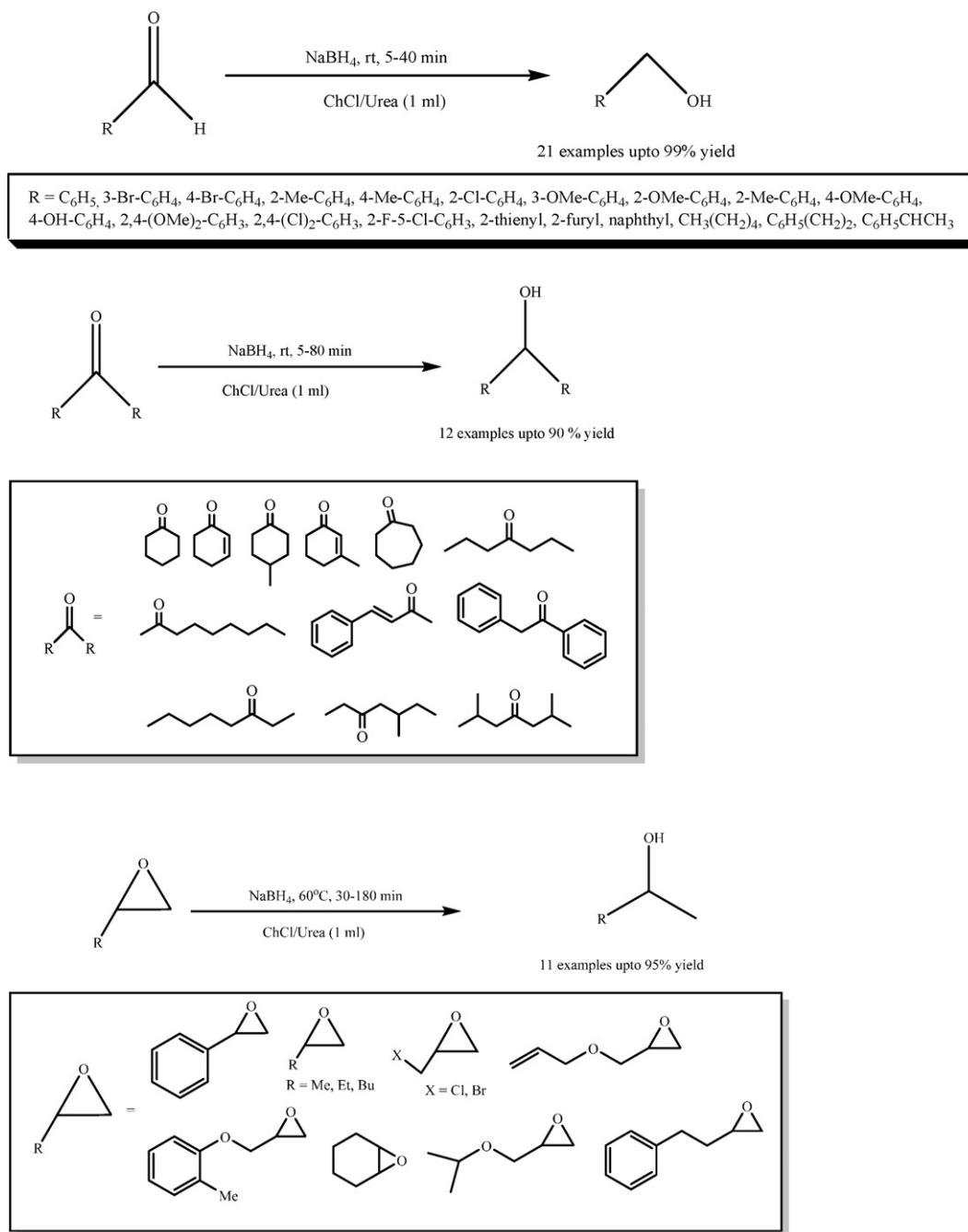
2.2.2.2. Epoxide ring opening using DES as catalyst. Epoxides have been recognized among the most versatile intermediates and starting materials in organic syntheses due to their ease of formation and wide reactivity with a broad range of nucleophiles with high or often complete stereo- and regioselectivity [121]. 1,2-Bifunctional ring-opened compounds represent the key step for synthesis of novel therapeutic agents, biologically active compounds and chiral auxiliaries [122]. As a result of their importance, extensive studies have been pursued to achieve clean, selective ring opening of epoxides to convert readily available, inexpensive bulk chemicals into 1,2-difunctionalized fine chemicals [123]. However, classical procedures had some limitations such as the requirement for an excess of amine and harsh reaction conditions, often working with poorly and sterically hindered nucleophiles, and undesirable side reactions due to the rearrangement or polymerization of sensitive epoxides. A choline-based deep eutectic solvent was found to be an

effective catalyst and reaction media for the chemoselective ring opening of the epoxides through the reaction of epoxides with aromatic amines, thiols, alcohols, azide and cyanide. Initially, the model reaction between glycidyl phenyl ether with thiophenol was conducted using tin chloride/choline chloride as deep eutectic solvent (40 mol%). As a result of the reaction, the corresponding 1,2-mercapto alcohol was only detectable product and isolated in 97% yield at room temperature after 10 min. The reaction was extended with functionally diverse epoxides and thiols under the same reaction conditions (Scheme 30) [124].

The potential of this procedure was further explored for the direct ring opening reactions of various epoxides with aromatic amines and corresponding β-amino alcohols with trans-stereochemistry obtained in good to excellent yields (Scheme 31).

In addition, TMSCN, TMSN₃ and methanol were also successfully used as nucleophiles in this procedure, and the corresponding β-hydroxy azides, β-hydroxy nitriles and β-alkoxy alcohols were obtained respectively with good region- and stereoselectivity in moderate to good yields and short reaction times. Finally, recycling of deep eutectic solvent from reaction mixtures was also examined for the preparation of 1,2-mercapto alcohols under the optimized reaction conditions. It

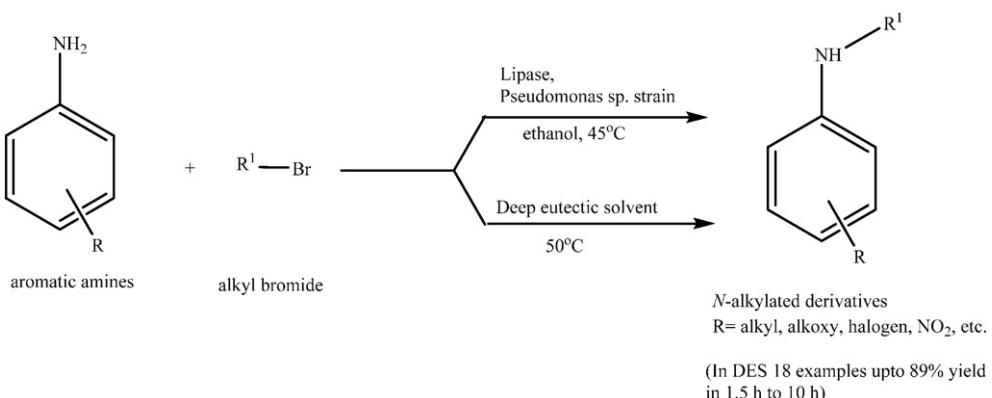
**Scheme 32.** Reaction between epoxide and different nucleophiles.

**Scheme 33.** Reduction of carbonyl compounds and epoxides.

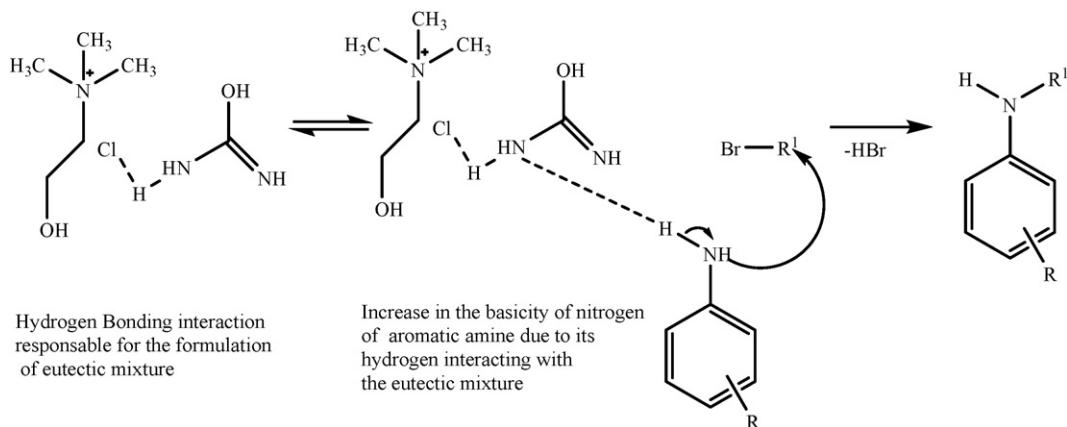
was found that at the end of the reactions, the DES easily recovered (by precipitation) by addition of diethyl ether to the reaction mixture and could be recyclable at least four successive operations without loss of its catalytic activity ([Scheme 32](#)).

2.2.2.3. Reductive cleavage of epoxides. The reduction of carbonyl compounds and reductive cleavage of epoxides to the corresponding alcohols are important transformations in organic syntheses [125] and the total synthesis of biologically active compounds [126]. Azizi et al. developed chemoselective reduction of functionalized carbonyl compounds and epoxides using commercially available NaBH₄ as reducing agent in urea/choline chloride eutectic mixture as a novel and green catalyst and reaction media. First the reaction conditions were optimized and then optimized reaction conditions were explored with variety of structurally diverse aldehydes and ketones, including saturated, unsaturated,

aromatic and heteroaryl aldehydes to afford the corresponding alcohols in excellent to quantitative yields. The potential of this procedure was further explored for the synthesis of alcohol derivatives from epoxides. When glycidyl phenylether was treated with NaBH₄ (2 mmol) in urea/choline chloride eutectic salt (1 mL), reductive cleavage of epoxides provided corresponding alcohols in excellent yields. This high yielding, simple and environmentally friendly green process was further explored with sterically, electronically and functionally diverse epoxides under the same reaction conditions. The reactions proceeded smoothly with the almost all commercially available epoxides such as glycidyl phenyl ether, allyl glycidyl ether, isopropyl glycidyl ether, propylene oxide, butane oxide, cyclohexene oxide and styrene oxide. It was also observed that when reduction of aldehyde/imine and aldehyde/epoxide was done in competitive reactions using DES as solvent/catalyst, only aldehyde reduction product was obtained in this reaction media,



Scheme 34. Selective N-alkylation of aromatic amines.



Scheme 34a. Plausible reaction mechanism.

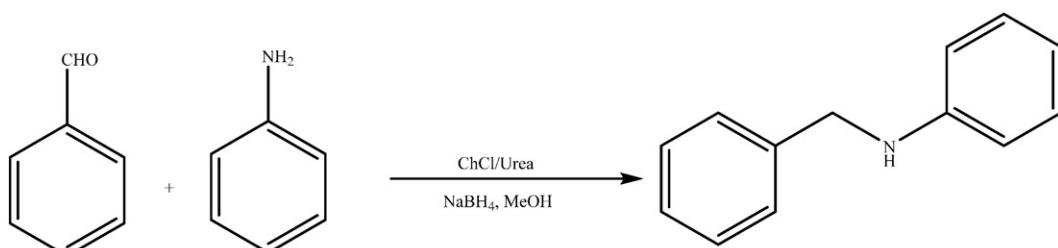
which demonstrated that the reaction in deep eutectic solvent had a good chemoselectivity (Scheme 33) [127].

2.2.3. Synthesis of amines derivatives

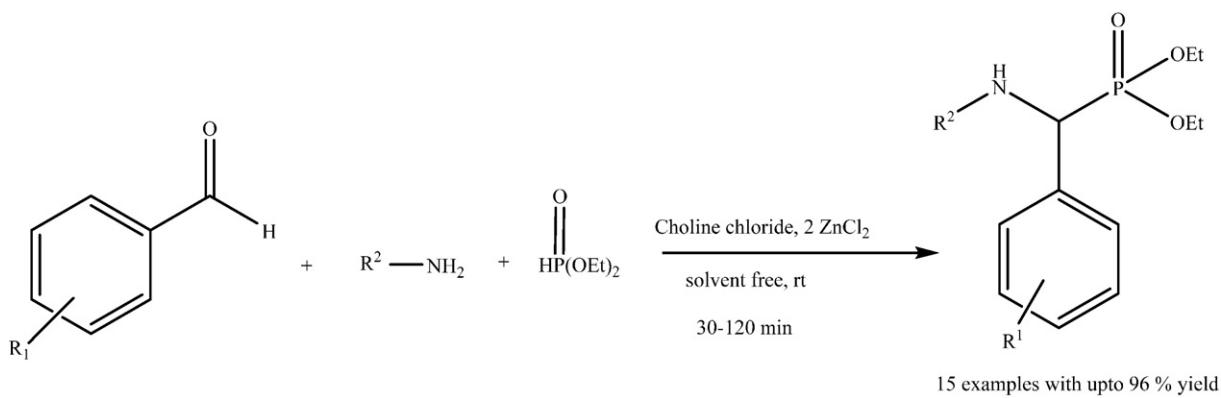
2.2.3.1. Synthesis of aromatic secondary amines. Amines and their derivatives find their applications as fine chemicals, agrochemicals, dye intermediates, pharmaceuticals and also as catalysts for polymerization [128]. Aromatic and aliphatic secondary amines are also used as antioxidants in petrochemicals, polymers, and rubber [129]. Due to their unique biological properties, substituted amines are widely used in antihypertensive, antihistamine, and anti-inflammatory drugs [130]. However, most of the traditional methods for the synthesis of aromatic secondary amines require polar organic solvents, high reaction temperature and lack selectivity, thus resulting in multiple alkylations, even with the use of limited amounts of the alkylating agent [131]. Hence, these factors greatly limit the scope of selective procedures for mono N-alkylation of aromatic primary amines. Shankarling et al. developed

selective mono N-alkylation of aromatic primary amines using deep eutectic solvent of choline chloride and urea that plays a dual role as efficient catalyst as well as a recyclable solvent. The method involving the use of lipase as biocatalyst in ethanolic medium was also developed for N-alkylation. Both methods of N-alkylation required mild reaction conditions, avoiding the use of a strong base or highly polar organic solvents. To optimize the reaction conditions, various organic solvents using lipase as biocatalyst and three biodegradable solvent with dual role as solvent and catalyst were screened but comparatively better results were obtained with the use of deep eutectic solvent as solvent and catalysts and also with ethanolic solution of lipase. The lipase and DES-catalyzed reactions were further exploited for their use in mono N-alkylation reactions of different aromatic amines (Scheme 34) [132].

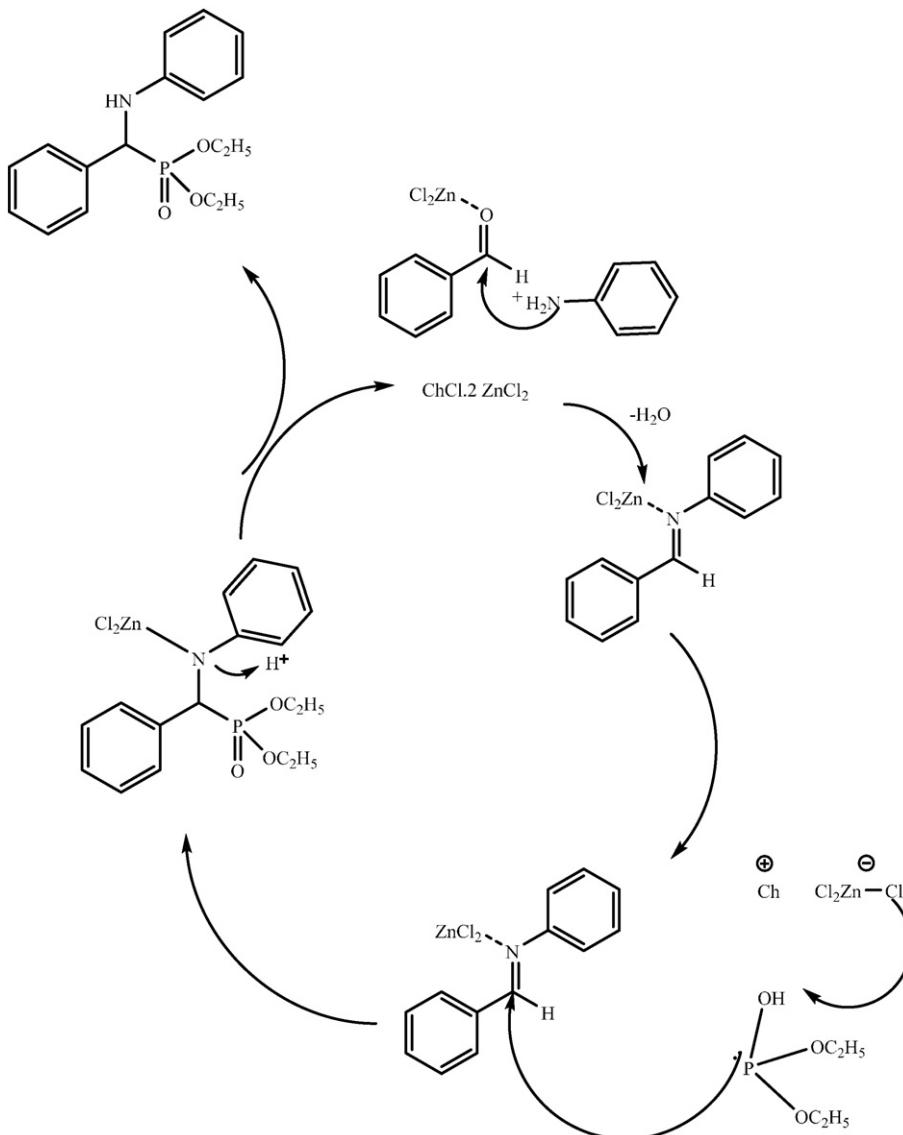
According to the proposed mechanism, the hydrogen bonding interactions between DES and aromatic amino group could be possibly responsible for increasing the nucleophilicity of the aromatic amine thus leading to its faster attack on alkyl bromide (Scheme 34a).



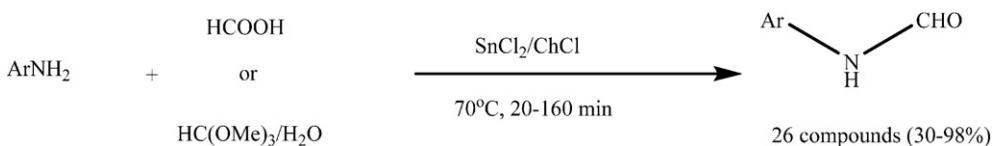
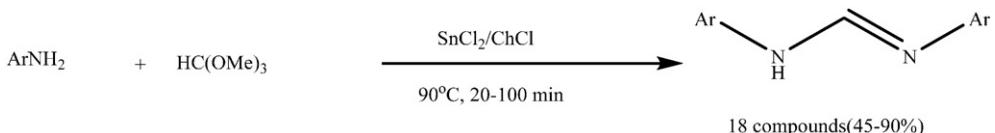
Scheme 35. Synthesis of N-benzylniline.



$R_1 = C_6H_5, 3\text{-Br-C}_6H_4, 4\text{-NO}_2\text{-C}_6H_4, 3\text{-Cl-C}_6H_4, 4\text{-OMe-C}_6H_4, 4\text{-OH-C}_6H_4, 4\text{-Br-C}_6H_4, 2\text{-Cl-C}_6H_4, 3\text{-OMe-C}_6H_4$
 $R_2 = C_6H_5, C_6H_5CH_2, 4\text{-F-C}_6H_4, 4\text{-Cl-C}_6H_4, 4\text{-Br-C}_6H_4$

Scheme 36. Synthesis of α -aminophosphonates.

Scheme 36a. Plausible reaction mechanism.

**Scheme 37.** Synthesis of formamides.**Scheme 38.** Synthesis of symmetric formamidines.

2.2.3.2. Synthesis of *N*-benzylaniline by reductive amination. Amine derivatives can also synthesize by direct reductive amination of carbonyl compounds. Several reducing methods for these conversions such as have been developed [133–135]. However, most of them may have one or more of the following drawbacks: the harsh reaction conditions, the generally poor yields, the low chemical selectivities, the use of toxic metals, and the generation of toxic by-products. Heydari et al. reported efficient and green synthesis of secondary amines by reductive amination of aldehydes/ketones in the presence of DES (ChCl/urea) as catalyst and NaBH₄ as a reducing agent in MeOH. Initially, it was observed that when the reaction was carried out in ChCl/urea (2 ml) as catalytic solvent and in the presence of NaBH₄ as a reducing agent, the yield of final product was very low (20%), which was probably due to the low solubility of NaBH₄ in ChCl/urea. After addition of methanol (2 mL) to the reaction mixture which is a suitable solvent for dissolving of NaBH₄, the yield of final product increased to 92%. In MeOH and in the absence of ChCl/Urea, the reaction yield was low, and this indicates that the reaction was catalyzed by DES. It was also observed that 50 mg of DES was optimum amount to catalyze the reaction efficiently. The optimized synthetic protocol was extended with variety of aldehyde/ketone and amine to synthesis of secondary amines with excellent yield (10 compounds with 89–98% yield in 30–60 min) (**Scheme 35**) [136].

2.2.3.3. Synthesis of α -aminophosphonates. α -Aminophosphonates are the structural analogs of amino acids and attracted much attention due to their wide range of applications in biological and medicinal chemistry as enzyme inhibitors, antibiotics, herbicides, fungicides, plant growth regulators, pharmacological agents, and peptide mimics [137–139]. Several synthetic methodologies have been developed for the synthesis of α -aminophosphonates [140]. The Kabachnik–Fields reaction which involves a three-component reaction between an aldehyde, amine, and dialkyl or trialkyl phosphate promoted by Lewis or Bronsted acids is one of the most direct and appealing approach.

However, these methods suffer from drawbacks such as longer reaction time, use of hazardous and expensive catalysts, low yield of products, use of organic solvents, and harsh reaction conditions. Therefore, these methods do not comply with green chemistry protocols. To overcome these drawbacks, recent methodologies based on microwave, ultrasound, and use of ionic liquids have been reported [141].

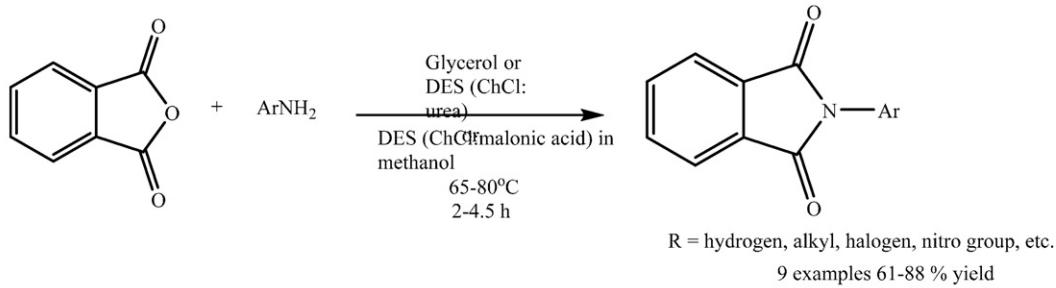
Recently, Jayaram et al. synthesized α -aminophosphonates via multicomponent reaction between aryl aldehyde, aniline, and diethyl phosphite in the presence of ChCl:2ZnCl₂ as a catalyst. Effect of catalyst loading was also studied and it was observed that quantitative conversion of the starting material was obtained using 15 mol% of the catalyst (**Scheme 36**) [142].

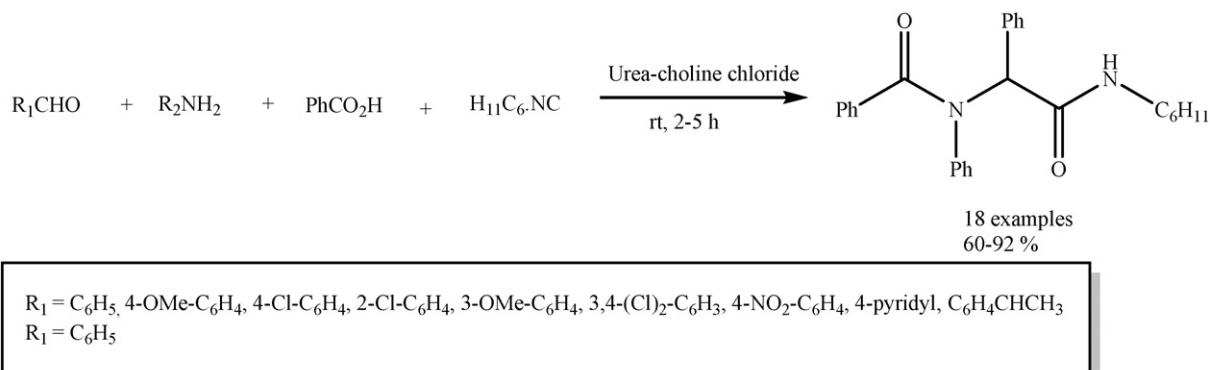
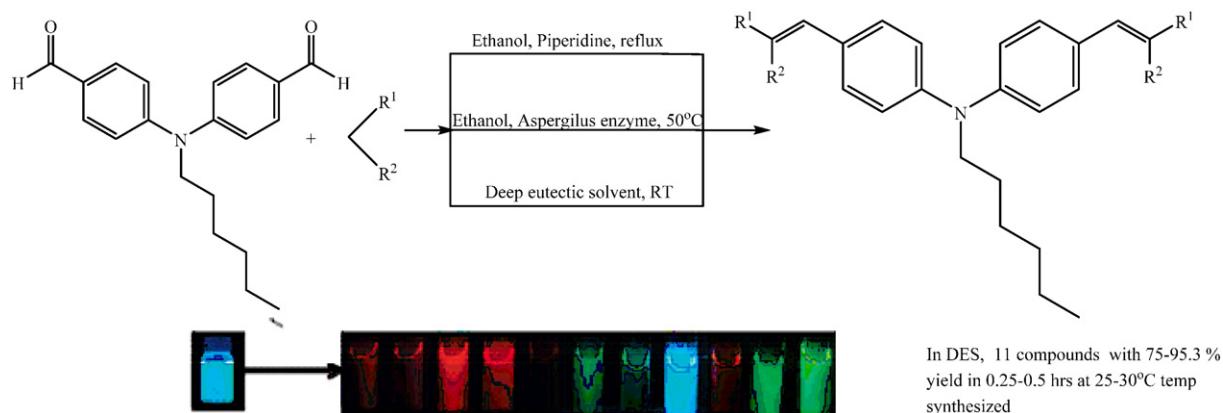
The reaction is considered to proceed with the complexation of ChCl:2ZnCl₂ catalyst with the aldehyde as presented (**Scheme 36a**).

2.2.4. Synthesis of *N,N*-diarylamide and formamide derivatives

Protection of amines as formamides is an important reaction in synthetic organic chemistry [143]. Formamides have wide applications as intermediates in the preparation of pharmaceuticals and as important reagents for Vilsmeier formylation [144]. They also use as Lewis base catalysts in organic transformations of carbonyl compounds [145]. In the literature, various approaches with some of the useful formylating reagents have been reported for N-formylation of amines [146–147]. However, many of the N-formylation methods have disadvantages such as expensive reagents, formation of side products, thermal instability and difficult accessibility to reagents.

Azizi et al. developed an environmentally benign method for efficient N-formylation of aromatic amines using deep eutectic solvent (ChCl:2SnCl₂) as a dual catalyst and reaction medium by the reaction of aniline and formic acid or trimethyl orthoformate. In the initial study, five deep eutectic solvents were screened under different reaction conditions but the best yield (98%) of N-formylaniline was obtained in choline chloride:2SnCl₂ (30 mol%) at 70 °C by simply mixing aniline

**Scheme 39.** Synthesis of N-phenylphthalimide.

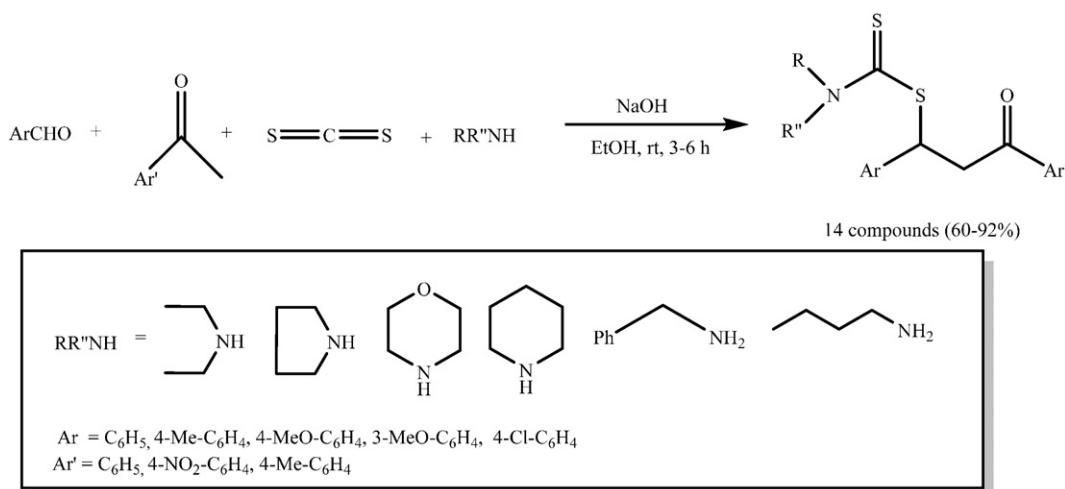
**Scheme 40.** Synthesis of peptide derivatives.**Scheme 41.** Synthesis of diphenylamine-based novel fluorescent styryl colorants.

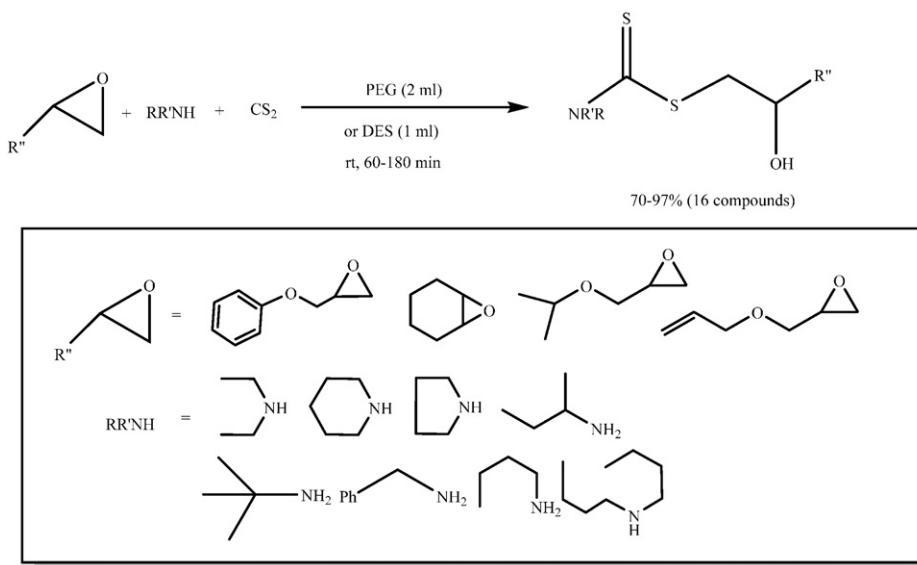
and formic acid within 20 min ([Scheme 37](#)). When the reaction of aniline with trimethyl orthoformate was carried out at 90 °C under anhydrous conditions, N,N'-diarylamidine was obtained as product in 90% yields within 20 min ([Scheme 38](#)). When the same reaction with same condition was carried out in the presence of water (0.5 mL), formamide was obtained in 80% yields [[148](#)].

2.2.5. Synthesis of *N*-phenylphthalimide

N-Phenylphthalimide and its derivatives have been reported to exhibit pharmacological properties that include anticonvulsant and

anti-inflammatory activities [[149](#)]. Imide derivatives have also been used in tuberculosis therapy, including use of some of their derivatives as growth stimulant for plants [[150](#)]. Phthalimide derivatives are also widely used in polymer and synthetic chemistry [[151](#)]. Previously N-phenylphthalimide derivatives were synthesized by many methods, including condensation of an anhydride with an amine in acetic anhydride medium catalyzed by acids [[152](#)], N-alkylation of phthaloyl dichloride with azide in the presence of triphenylphosphine [[153](#)], and N-alkylation of imides in alcohol media [[154](#)]. However, these methods have obvious disadvantages, like longer reaction times, use of acids,

**Scheme 42.** Synthesis of dithiocarbamates.

**Scheme 43a.** Synthesis of 2-hydroxydithiocarbamates.

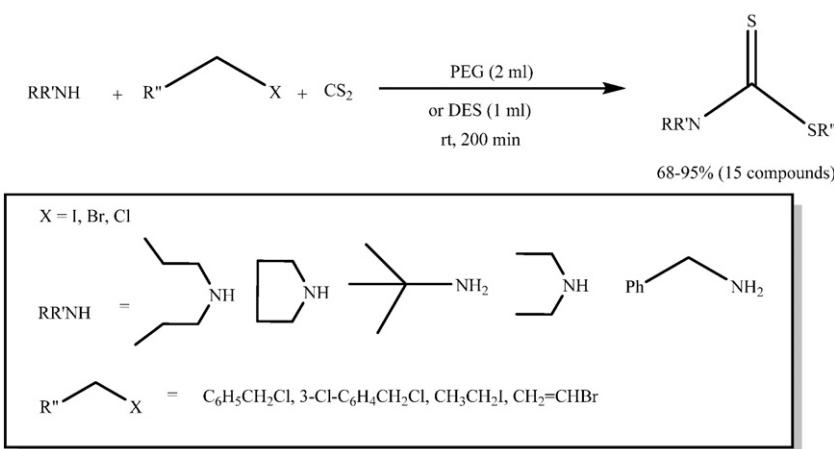
volatile organic solvents and toxic catalysts at stoichiometric levels, and recovery in small quantities. Apart from conventional methods, phthalimide synthesis has also been reported in ionic liquids like [bmim][PF6] [155] and [bmim][BF4] [156] or nonionic liquid solvents like polyethylene glycol [157]. Although these methods showed improved yields and environmentally benign in nature, however, they still suffers from some limitations such as longer reactions times, use of organic solvents during work-up, difficulty in recovery of reaction media or higher reaction temperatures. In addition, ionic liquids especially based on imidazole with fluorinated anions also suffer from the demerits of being non-biodegradable, toxic, commercially expensive and their production is also related to the use of large amounts of unsafe and volatile organic solvents. Shankarling et al. proposed efficient and green synthesis of N-aryl phthalimide derivatives by the reaction of phthalic anhydride and primary aromatic amines in efficient, biodegradable, and economical alternatives such as deep eutectic solvents (DESs) and glycerol. The efficiency of the method was compared with conventional routes by conducting N-phenylphthalamide synthesis in different organic solvents. It was observed that the reaction gave poor yields in organic solvents. However, the use of DES (ChCl:urea) as a reaction media at 80 °C provided excellent yields that could be owing to lesser viscosity of DES or greater solubility of phthalic anhydride at higher temperatures. On the contrary, the DES of choline chloride and malonic acid also provided excellent yields when used in catalytic amounts in methanol as solvent.

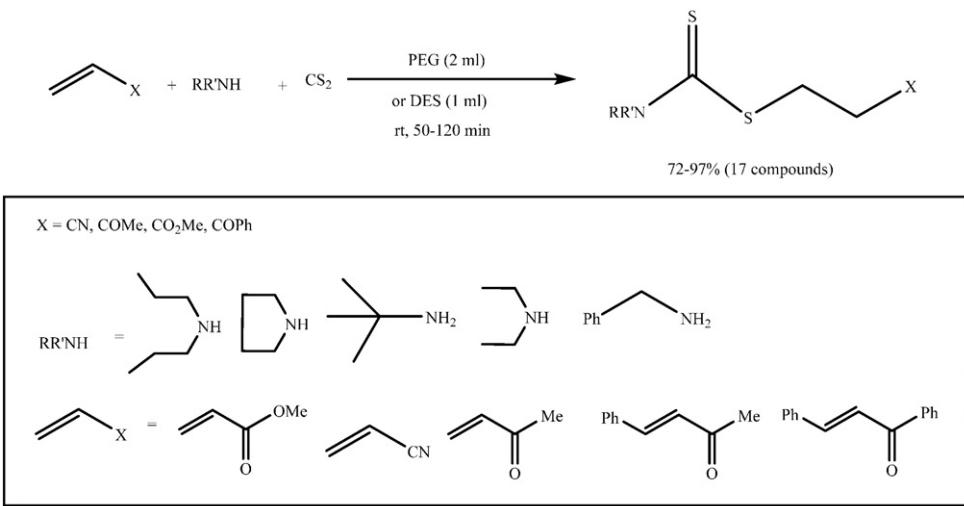
The results clearly indicated that the DES prepared from choline chloride and malonic acid proved to be an efficient catalyst, whereas glycerol and the DES of choline chloride and urea played a dual role of catalyst and solvent. These deep eutectic mixtures are biodegradable, nontoxic, and cost-effective thereby providing a good industrial alternative to conventional methods. These methods gave products in moderate to high yields with good recyclability of catalyst/solvent at least up to five times (Scheme 39) [158].

2.2.6. Synthesis of peptides

A large and important class of MCRs is constituted by the isocyanide-based Passerini and Ugi four-component reactions [159–161]. These reactions have become one of the most investigated transformations during the last decade, in conjunction with the enabling technologies, such as high-throughput screening, combinatorial and assembling complex pharmacologically important structures. The classical Ugi reaction is carried out in solvents, such as methanol and dichloromethane under stirring at room temperature overnight [162]. In order to further comply with the green chemistry, alternative green solvents, such as water and trifluoroethanol or ionic liquids, were used in an isocyanide-based multicomponent reaction [163–164].

Azizi et al. reported the first example of an efficient and green procedure for a one-pot multicomponent Ugi reaction in DES based on choline chloride and urea. The synthetic method involved four-component Ugi

**Scheme 43b.** Synthesis of dithiocarbamates.

**Scheme 43c.** Synthesis of dithiocarbamates.

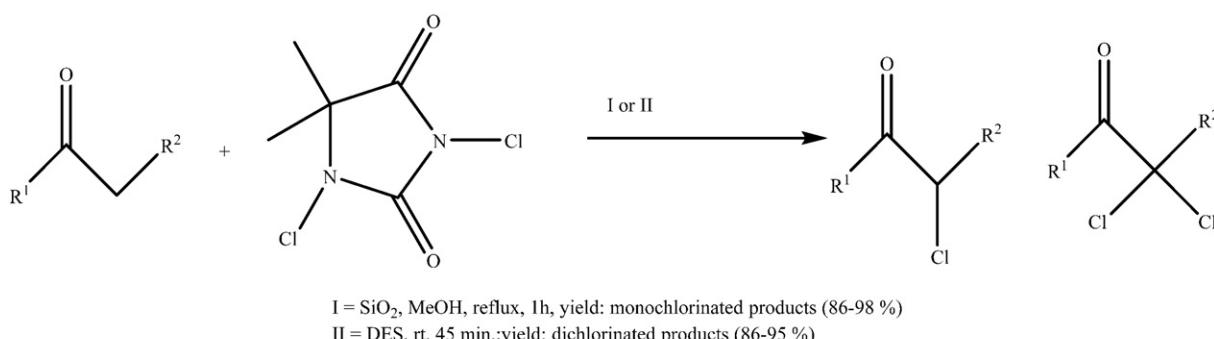
reaction of benzaldehyde, aniline, benzoic acid, cyclohexyl-isocyanide, in deep eutectic solvent at room temperature. To compare the efficiency of DES relative to conventional organic solvents, some protic and aprotic solvents were also used with the optimized conditions of DES and the results clearly indicated the superiority of DES over conventional solvents. Under these reaction conditions, the evaluation of DESs as solvents was tested for a wide range of carbonyl compounds. A variety of structurally diverse aldehydes and ketones, including saturated, unsaturated, aromatic and heteroaryl aldehydes underwent green reaction smoothly, without using any catalyst to afford the corresponding Ugi products in good to excellent yields. So the results confirmed that DES is the best solvent and catalyst for the one-pot multicomponent Ugi reaction. The reaction was also extended for various aromatic amines, isocyanides, and carboxylic acid and provided good to excellent yields of desired products. The experimental procedure is easy and the reactions went to completion at room temperature, within 2–5 h, depending on the reactivity of the aldehydes and carboxylic acids. The products were easily separated by easy extraction of the deep eutectic solvent with water, and were usually obtained in high purity. The recyclability of DES was also examined using the Ugi reaction under optimized conditions. The recovered DES was then reused for three runs without significant loss of activity (**Scheme 40**) [165].

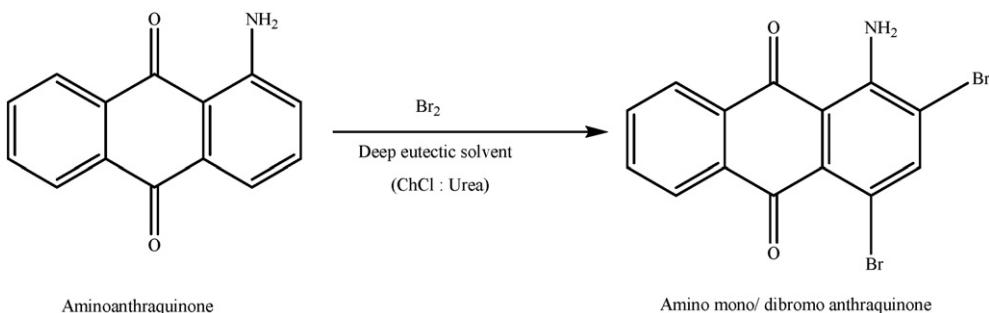
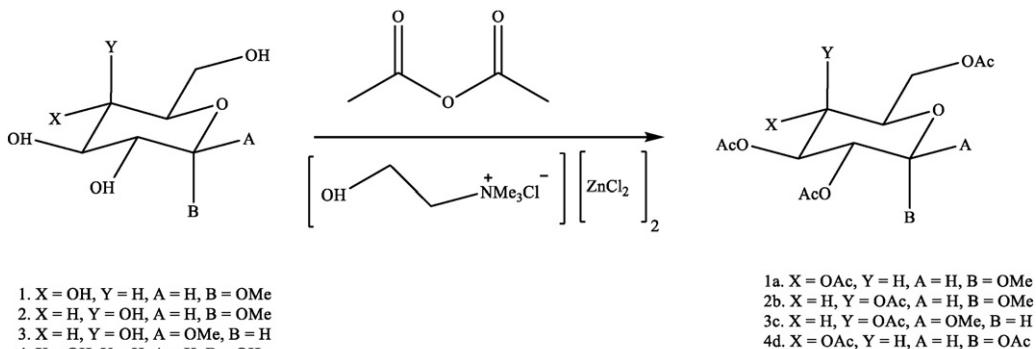
2.2.7. Synthesis of diphenylamine-based novel fluorescent styryl colorants

Organic fluorescent heterocyclic chromophores have a wide range of applications in biochemistry, for example, in traditional textile

coloration, molecular probes [166], organic light emitting diodes [167], photovoltaic cells [168], and mass coloration of polymers [169]. Electron acceptor isophorone derivatives, substituted phenyl acetonitrile compounds, and aliphatic active methylene compounds are used for the synthesis of chromophores. Traditional catalysts such as alkali metal hydroxides (e.g., NaOH and KOH), pyridine, and piperidine are used in condensation reactions. Basic zeolites, such as Cs-exchanged NaX (CsNaX) and GeX, Cs, Cs-lanthanum impregnated mesoporous MCM-41 [170–171] and alkali-exchanged zeolites, however, are also used [172]. To minimize environmental hazards as performance criteria, Shankarling et al. synthesized diphenylamine-based novel fluorescent styryl colorants by Knoevenagel condensation using a conventional method, biocatalyst lipase, and deep eutectic solvent by the reaction of 4,4'-hexyliminobisbenzaldehyde with active methylene compounds. These three methods were also compared in terms of yield, reaction time and reaction temperature. It was observed that better results were obtained with the use of lipase as biocatalyst than conventional method but use of deep eutectic solvent provided best results with excellent yield in shorter reaction time under mild reaction conditions (**Scheme 41**).

This method produced no byproducts; therefore, there was no loss during isolation of the solvent. Recycling of the deep eutectic solvent was also effectively achieved and recycled des could be reused five times without a significant decrease in the product yield. There was no need for further purification of the deep eutectic solvent before its reuse for the same transformation [173].

**Scheme 44.** Synthesis of α -mono or α,α -dichloroketones.

**Scheme 45.** Bromination of 1-aminoanthra-9,10-quinone.**Scheme 46.** O-acetylation of monosaccharides.

2.2.8. Synthesis of dithiocarbamates derivatives

Dithiocarbamates are found in many biologically important compounds, and have a variety of applications such as in the rubber industry as vulcanization accelerators, as animal repellants, and as biocides in many household products [174]. Because they have strong metal binding capacity, they can act as inhibitors of enzymes and have a profound effect in biological systems. Dithiocarbamates have also shown their importance in cancer treatment. Dithiocarbamates were used as efficient ligands in surface science and nanomaterial chemistry. Furthermore, they are useful building blocks in the synthesis of biologically active heterocyclic compounds [175].

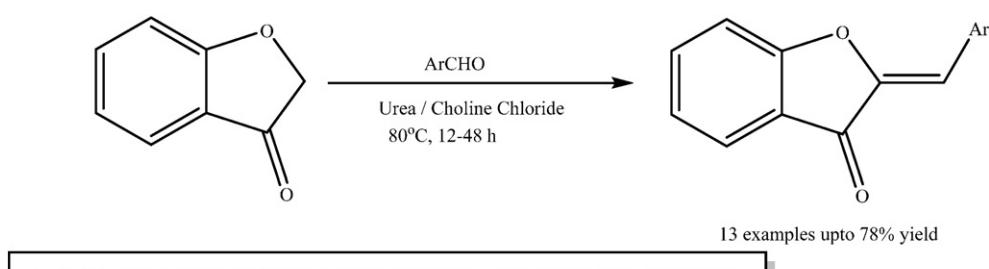
Azizi et al. developed an environmentally benign, mild, reliable, efficient, and scalable, catalyst free four-component synthesis of chemically and pharmaceutically interesting dithiocarbamate derivatives via one-pot reaction of various aromatic aldehydes, ketones, aliphatic amines, and carbon disulfide, in the presence of sodium hydroxide as additive in urea-choline chloride deep eutectic solvent or ethanol. To optimize the reaction condition, initially various solvents and additives were examined on the model reaction of benzaldehyde, acetophenone,

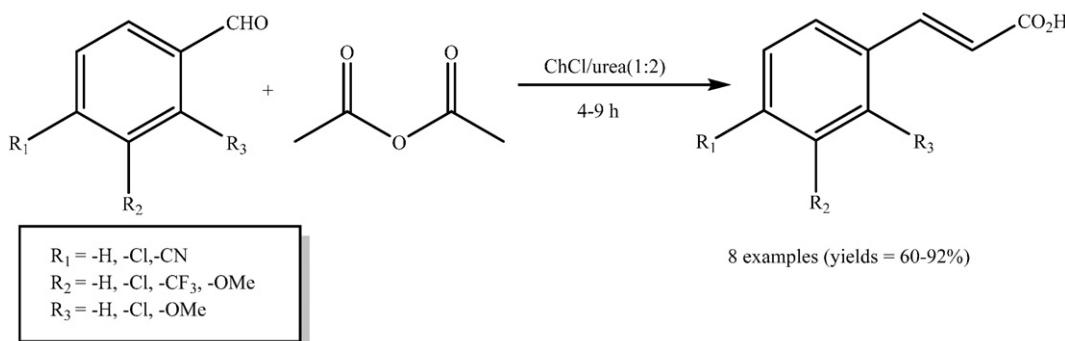
carbon disulfide, and pyrrolidine. It was observed that ethanol and DES as solvents and NaOH as additive are the best choice with excellent yield for the synthesis of dithiocarbamate (**Scheme 42**) [176].

Dithiocarbamate derivatives were also synthesized by Azizi et al. in high yields by environmentally benign catalyst free synthesis involving one-pot, three-component condensation of an amine, carbon disulfide, and a variety of electrophilic reagents using deep eutectic solvent (DES) and polyethylene glycol (PEG). These green solvents can be recovered and recycled for subsequent reactions (**Schemes 43a, 43b, 43c**) [177].

2.2.9. Halogenation

2.2.9.1. Chlorination of ketones. Chlorinated organic compounds constitute an important class of intermediates as they can be converted into other functional molecules by simple chemical transformations [178]. α -Chlorinated ketones and β -ketoesters are among the most versatile intermediates used in medicine and agriculture, and their high reactivity makes them to react with a large number of nucleophiles to provide

**Scheme 47.** Synthesis of aurones.

**Scheme 48.** Synthesis of cinnamic acid derivatives.

a variety of useful compounds [179]. The novel methods of halogenation with high selectivity that satisfy the requirements of green chemistry have attracted a lot of attention [180]. However, developing selective monochlorination reactions or selective dichlorination reactions remains a challenge [181]. There are some excellent methods that have been reported to solve this challenge [182]. Among the reported methods, DCDMH was found to be the best reagent for selective chlorination, but it produced acid sewage [183].

In order to reduce the acid sewage while retaining high selectivity, initially Xinzhuo Zou et al. tried various catalysts and found that when silica gel was added to the mixture of acetophenone, methanol and DCDMH, the α -chlorination occurred quickly and easily under reflux. Effect of amount of silica on yield of the product was also studied but it was observed that the larger amount of silica gel added to the reaction mixture was not so helpful to the process.

The same method was also used to prepare dichlorinated acetophenones but a mixture of α -monochloroacetophenone and α,α -dichloroacetophenone was obtained. So a convenient method of preparing α,α -dichlorinated ketones needed to be developed. In this context, it was found that deep eutectic solvents (DES) derived from choline chloride and *p*-TsOH provided α,α -dichlorinated products in 86–95% yield more efficiently by simple stirring for 45 min at room temperature (**Scheme 44**) [184].

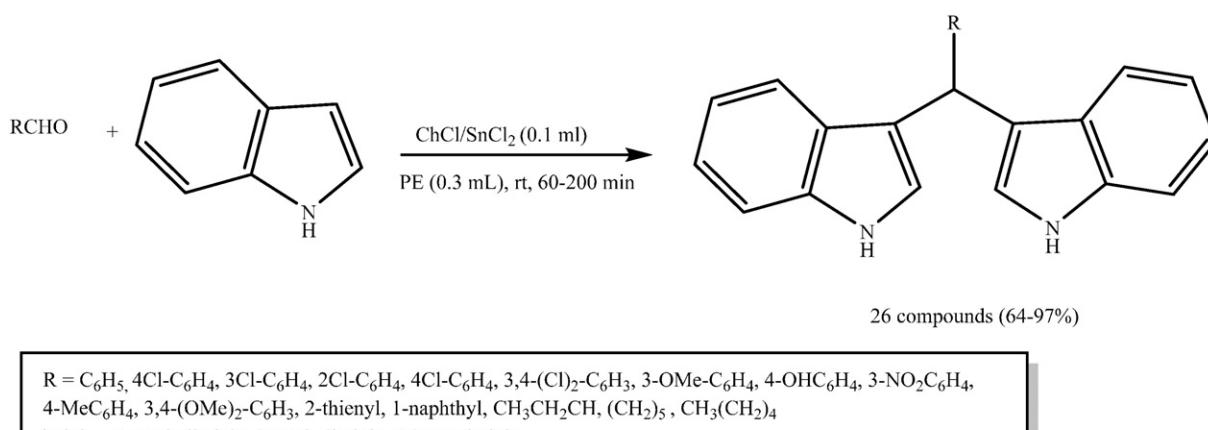
2.2.9.2. Bromination of 1-aminoanthra-9,10-quinones. Halogenated 1-aminoanthra-9,10-quinones are important intermediates in the dye-stuff industry [185]. The halogenation of 1-aminoanthra-9,10-quinone is difficult as anthra-9,10-quinone contains two carbonyl groups that deactivate the ring towards any electrophilic substitution. Several methods were used to brominate 1-aminoanthra-9,10-quinone, however, all reported methods required drastic conditions involving strong

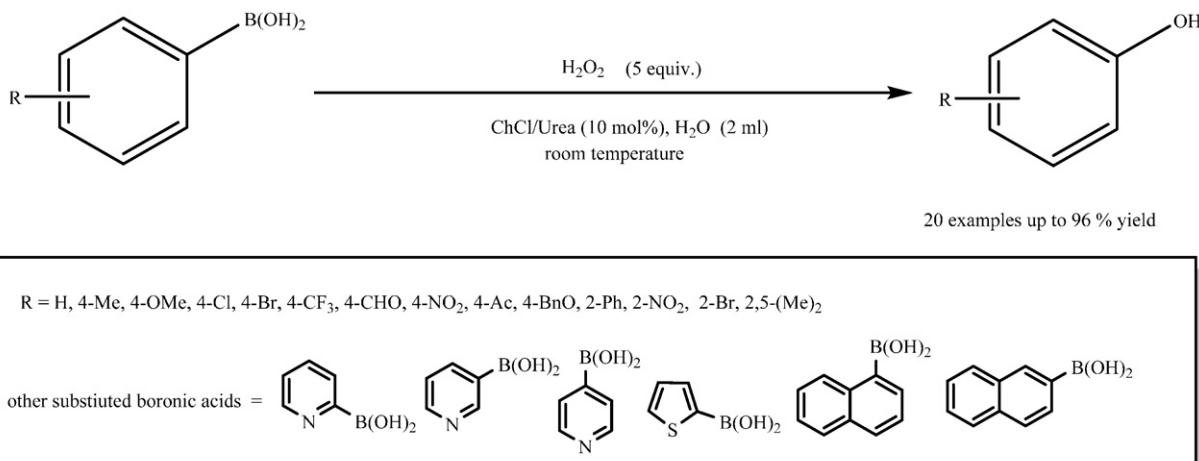
acids, high temperature, and environmentally toxic chlorinated solvents [186]. Stavber et al. reviewed halogenations of organic compounds in ionic liquids such as (BMIM)PF₆ and [BMIM][Br₃]. But the toxicity and the presence of impurities limited the use of ionic liquids as solvent in halogenation of organic compounds [187].

Shankarling et al. used simple ammonium deep eutectic solvent as a catalyst and environmentally benign reaction medium for the bromination of 1-aminoanthra-9,10-quinone, eliminating the need for volatile organic solvents and concentrated acids like H₂SO₄ as solvents or catalysts. The results obtained using the deep eutectic solvent were also compared with two conventional organic solvents (methanol and chloroform) and it was observed that the reaction using the deep eutectic solvent was much faster and required only 2 to 3 h for completion. Both yield and purity of the brominated product were greater in the reaction using the deep eutectic solvent as compared with the reaction using organic solvents such as methanol and chloroform. The deep eutectic solvent was also recycled five times and reused without purification. The reactions using recycled deep eutectic solvent continued to provide excellent results without any significant decrease in the yield (**Scheme 45**) [188].

2.2.10. O-acetylation of carbohydrates

The O-acetylation of carbohydrates is widely employed not only for the protection of hydroxy groups but also for the purification and structural elucidation of natural products. Abbott et al. proposed O-acetylation of cellulose and monosaccharides using zinc based ionic liquid. It can be seen (entries 1–4) that the [ChCl][ZnCl₂] ionic liquid can be successfully employed as both solvent and catalyst for the acetylation of simple monosaccharides. Solvent recycling was also examined and it was observed that recovered DES could be used for subsequent reactions up to four run without any appreciable loss in the reaction yield

**Scheme 49.** Synthesis of the bis(indolyl)alkanes.

**Scheme 50.** Synthesis of phenol.

and for different reactions with very low levels of cross contamination ([Scheme 46](#)) [189].

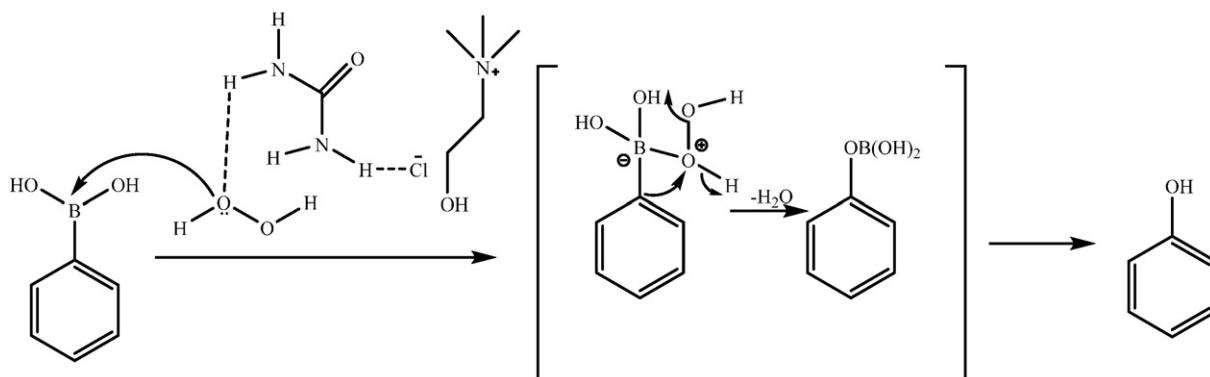
2.2.11. Synthesis of aurones

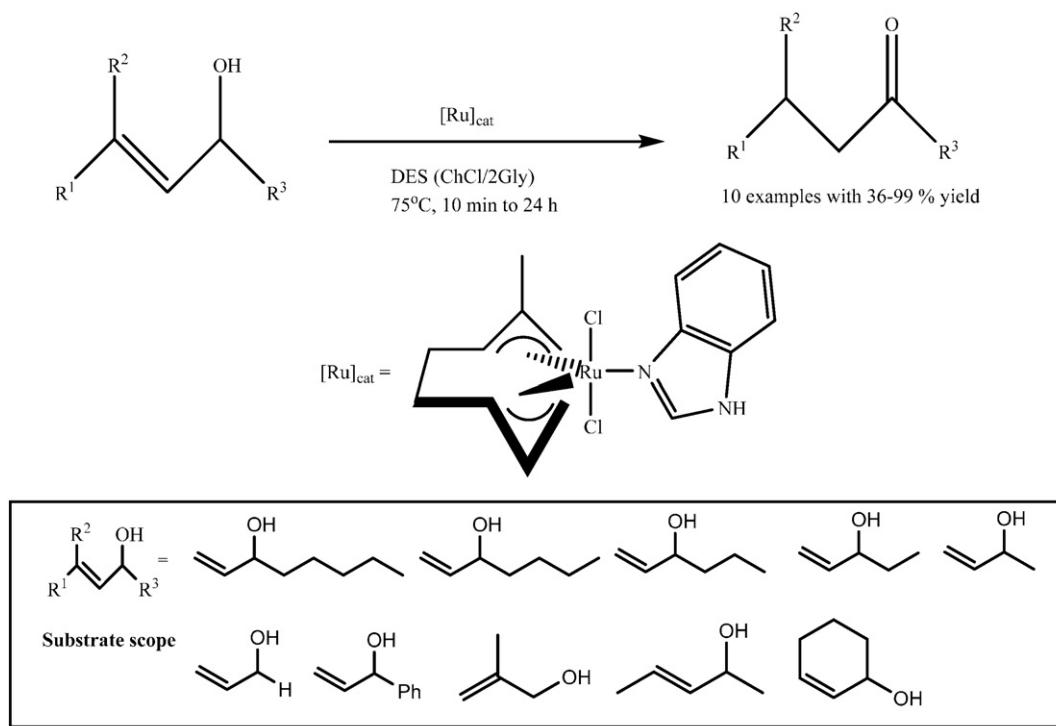
Aurones, constitute a part of a larger family of natural products known as flavonoids [190]. This family consists of flavones, isoflavones, chalcones, and aurones and are mainly secondary metabolites of plants found in fruits and flowers. Aurones have been found to be possibly beneficial in anti-cancer therapies [191], in the treatment of malaria [192], and in microbial infections [193]. Handy et al. reported acid- and base-free approach for the synthesis of aurones by the condensation of coumaranone with aryl aldehydes using DES derived from choline chloride and urea. When this reaction was attempted using even the mild neutral alumina conditions, a very low 16% yield of the aurone was obtained, while in CC/U a modest 66% yield was isolated. By this procedure, numerous aurones can be synthesized in shorter reaction time under mild reaction conditions with good yield ([Scheme 47](#)) [194].

2.2.12. Synthesis of cinnamic acid and its derivatives

Cinnamic acid and its derivatives are used in various fields including, medicines, perfumery, polymers, cosmetics and agriculture [195]. They are also used as matrices for ultraviolet laser desorption mass spectrometry of protein, and as useful intermediates for the synthesis of heterocyclic compounds [196]. Conventionally, cinnamic acid and its derivatives are prepared by base catalyzed Perkin reaction using benzaldehyde and acetic anhydride in presence of a base [197]. The effects of various bases such as fused sodium acetate, sodium formate, sodium tartrate, sodium borate, sodium sulfite, sodium carbonate, and

potassium carbonate on yield of Perkin reaction have been extensively studied [198]. Cinnamic acid and its derivatives are also prepared by Knoevenagel condensation using pyridine as catalyst [199]. Microwave irradiation method is also used for Perkin reaction [200]. In spite of great variety of well known and established methods for cinnamic acid and its derivatives, organic solvents and bases used in these transformations are high on the list of hazardous and harmful chemicals because of their volatile nature, considerable toxicity and their use in large quantities for the reaction. To overcome these drawbacks Weng et al. used quaternary ammonium ionic liquids for synthesis of cinnamic acid. The process developed by Weng et al. is environmentally benign, but higher reaction temperature (120 °C) and longer reaction time (8 h) make this process more energy intensive [201]. Recently, Shankarling et al. use biodegradable deep eutectic solvent (DES) based on choline chloride and urea as reaction medium and catalyst, for the synthesis of cinnamic acid and its derivatives *via* Perkin reaction. The reaction proceeded efficiently under mild reaction condition without use of additional catalyst with better yields. Ease of recovery and reusability of solvent with consistent activity make this method efficient and environmentally benign. This method is also energy efficient with operational simplicity. The synthetic protocol involving the use of DES was also compared with conventional protocol in terms of energy efficiency for synthesizing cinnamic acid. The reaction time required to synthesize cinnamic acid was 4 h for DES method while 9 h for conventional method. Total energy required per unit weight of the material processed to synthesize cinnamic acid is 14.15 (kJ g⁻¹) for DES synthetic method while 37.85 (kJ g⁻¹) energy required for conventional synthetic method ([Scheme 48](#)).

**Scheme 50a.** Reaction mechanism.

**Scheme 51.** Redox isomerization of allylic alcohols into carbonyl compounds.

Thus, DES assisted method is proved to be energy efficient which saved more than 62% of energy utilized by conventional synthesis method and also a reduction in the reaction time.

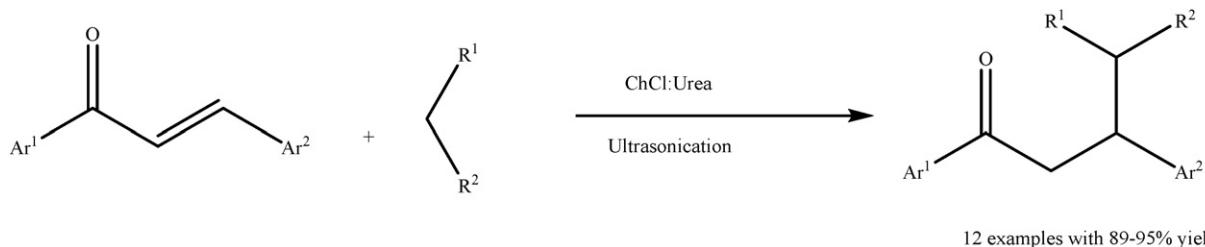
2.2.13. Synthesis of the bis(indolyl)alkanes

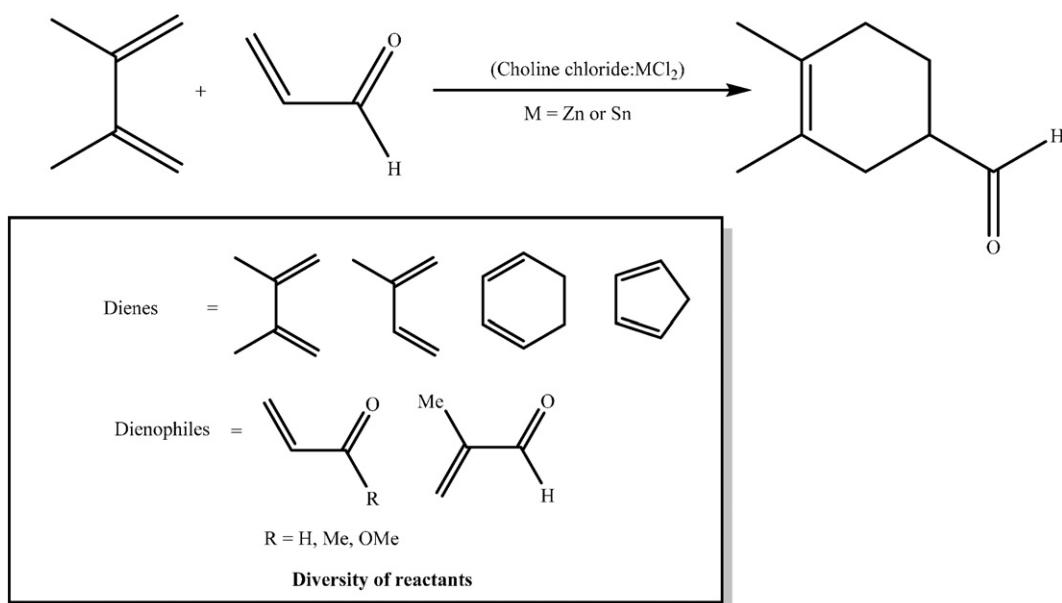
The bis(indolyl)alkane moiety is incorporated in various natural products possessing important biological activities [202]. A number of synthetic methods have been reported in the literature for the synthesis of bis(indolyl)alkane derivatives. The synthetic methods mainly involve the reaction of indole with various aldehydes and ketones in the presence of either a Lewis acid or a protic acid [203–206]. Azizi et al. developed a method involving electrophilic substitution reaction of indoles with carbonyl compounds using deep eutectic solvent as green and reusable catalysts to afford the corresponding bis(indolyl) methanes in excellent yields at room temperature. Initially, five deep eutectic solvents were screened at different reaction conditions on the model reaction of equimolar amounts of indole and benzaldehyde. The results of screening clearly indicates superiority of choline chloride:2SnCl₂ as catalyst over other DES because the desired product obtained in shorter reaction time (20 min) with excellent the yield (80%). Further optimization of the reaction temperature and solvent for the condensation reaction was also examined to improve the yield of the product. By increasing the reaction temperature, the viscosities of the mixture were improved greatly and the yield of the product increased to 90% yield. It was found that the amount of green solvent also affected the

yields of the reaction, and a better result was obtained by carrying out the reaction at room temperature in the presence of 0.3 mL of polyethylene glycol. The synthetic protocol was extended with a variety of aromatic aldehydes, including with electron-withdrawing and electron-donating groups, and indoles using optimized reaction conditions. A comparative study of the catalytic efficiency of various catalysts reported in the literature has also been reported in the literature (**Scheme 49**) [207].

2.2.14. Synthesis of phenols in DES

The derivatives of phenol are incorporated in numerous natural products and they frequently serve as key synthetic intermediates for the construction of more complex structures [208]. Consequently, the synthesis of phenols is of great importance and continues to attract the attention of organic chemists. Among the previously reported synthetic methods, the methods involving nucleophilic substitution of activated aryl halides or metal-catalyzed transformations of diazoarenes are dominant [209]. However, these methods suffer from drawbacks such as harsh reaction conditions or the incompatibility of the substrates. Recent investigations have also clearly showed that aromatic boronic acids can be transformed into phenols by copper catalyzed hydroxylation or oxidative hydroxylation in the presence of a wide variety of catalysts or reagents [210]. Metal free oxidative hydroxylation of aromatic boronic acids have also been achieved in various reaction systems, including aqueous H₂O₂ [211], H₂O₂–I₂ [212], H₂O₂–poly(N-

**Scheme 52.** Synthesis of β-functionalized ketonic derivatives.



Scheme 53. Diels–Alder reactions.

vinylpyrrolidone) [213], H_2O_2 –Amberlite IR-120 resin [214], and N-oxides [215]. However, these methods have some disadvantages, such as long reaction times, a large amount of oxidants or reagents, or the use of toxic chlorinated organic solvents. He et al. developed a sustainable, and gram-scale synthesis of phenols from aryl/heteroarylboronic acids and their derivatives in deep eutectic solvent (DES), derived from choline chloride and urea, in the presence of 30% aqueous H_2O_2 as oxidant and water as solvent (For model reaction, 5 min, 92% yield). Other oxidants such as oxone and tert-butyl hydroperoxide (TBHP) were also used but provided poor yields of the products. The reaction parameters were also examined in detail and it was observed that the reactions proceed smoothly at room temperature to give the desired products selectively in a few minutes and in good to excellent yield (5–15 min, 81–96% yield) and the catalyst is recyclable up to five times without any appreciable difference in its catalytic activity (Scheme 50) [216].

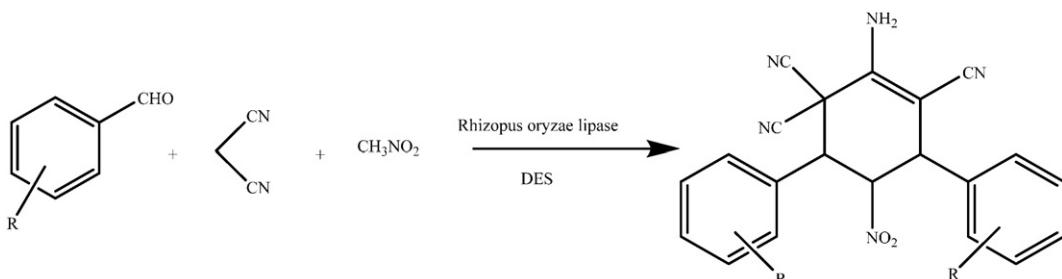
The suggested mechanism involves the activation of hydrogen peroxide effectively by DES with the polarization of peroxide bond through hydrogen bonding. The activated peroxide then attacks the boronic acid, and subsequent phenyl migration and hydrolysis result in the formation of final product (Scheme 50a).

2.2.15. Synthesis of ketones derivatives

2.2.15.1. By isomerization of allylic alcohols. Isomerization reactions are typical examples of atom economic processes as no by-products are generated during isomerisation. The redox isomerization of readily accessible allylic alcohols is a useful and straightforward synthetic route

to saturated carbonyl compounds, which are very valuable raw materials in organic chemistry [217]. García-Álvarez et al. utilized, for the first time, the catalytic activity of the ruthenium(IV) complex [$\text{Ru}(\eta^3:\eta^3\text{-C}_10\text{H}_{16})\text{Cl}_2(\text{benzimidazole})$] in the selective isomerization of both primary and secondary allylic alcohols into carbonyl compounds using DES as green and bio-renewable solvents. For the isomerization of monosubstituted aliphatic allylic alcohols, the catalytic process displays: i) high efficiency for the isomerization reaction in DES [mixtures of non-toxic quaternary ammonium salt (ChCl) with a safe and renewable hydrogens donor, ii) high activity under mild reaction conditions and low catalyst loadings, iii) high yields in the absence of base, and iv) recyclability for four consecutive runs. Thus, a series of primary and secondary allylic alcohols could be isomerized into the corresponding carbonyl compounds in the absence of base (Scheme 51) [218].

2.2.15.2. Synthesis of β -functionalized ketonic derivatives by Michael addition. Carbon–carbon bond forming reactions show great importance in organic chemistry for the synthesis of complex organic molecules [219]. The addition of active methylenes such as ethyl cyanoacetate, malononitrile and nitromethane to α,β -unsaturated ketones results in the synthesis of ketonic nitriles and ketonic nitro derivatives which can be transformed into functionally important hydroxypyridine derivatives [220]. These addition reactions are usually catalyzed by inorganic bases and organic bases but possibilities of various side reactions such as auto-condensation, retro-Michael addition and bis-addition reduce the yield of desired product. Remarkable efforts have been made by researchers to obtain purer products. Various catalysts have been developed such as transition metal catalyst [221], organocatalysts [222],



Scheme 54. Synthesis of poly substituted cyclohexene derivatives.

and phase transfer catalyst [223] for this purpose. However, these reactions are complicated by drawbacks related to the use of expensive catalysts and their efficiency after reuse, high reaction temperature, tedious multi-step synthesis of a catalyst, stability and storage of a catalyst, and use of organic solvents. Shankarling et al. proposed efficient synthesis of β -functionalized ketonic derivatives by the combination of ultrasound and the deep eutectic solvent derived by choline chloride–urea. To optimize the reaction condition, the model reaction of nitromethane and 4-fluorobenzylideneacetophenone was carried out in varying equivalents of CHCl :urea (1:2) and in different sets of reaction conditions. Among the various tested solvents such as methanol, ethanol, tetrahydrofuran (THF), diethylamine, solvent free conditions, ionic liquid [$\text{C}4\text{mim}][\text{C}_2\text{H}_5\text{SO}_4]$ and various catalysts (K_2CO_3 , KF , SmI_3 , LiNO_3 , diethylamine), the best result was observed with 5 equiv. of CHCl :urea (1:2) as catalyst (89% yield, 2 h). The results obtained with conventional heating was also compared with ultrasound condition and it was also observed that rate of reaction was faster with better yield under ultrasound compared to conventional heating. The optimized reaction conditions were applied on nucleophilic attack of active methylene on α,β -unsaturated ketones and conjugate addition products were obtained in the short span of 40–50 min with excellent yield of 89–95% (Scheme 52) [224].

2.2.16. Diels–Alder reactions in DES

Diels–Alder reactions are some of the most useful carbon–carbon bond forming reactions in organic chemistry being used in the synthesis of many natural products and physiologically active molecules [225]. The effects of the solvent on the rate and selectivity of Diels–Alder reactions are well established. Notably the use of water as a solvent leads to dramatic enhancements of rate and stereoselectivity [226]. Ionic liquids have also been used as solvents and as Lewis acid catalysts for Diels–Alder reactions. Diels–Alder reactions between cyclopentadiene and ethyl or methyl acrylate have been studied in a number of 1-alkyl-3-methylimidazolium salts [227]. Choroaluminate ionic liquids have also been reported both as solvent and Lewis acid catalyst for Diels–Alder reactions [228], but choroaluminate ionic liquids are extremely sensitive to water and are corrosive to many materials because of the presence of aluminum chloride. Davies et al. employed combination of MCl_2 ($\text{M} = \text{Zn}$ or Sn) with choline chloride, or related ammonium salts in a 2:1 ratio as both solvent and catalyst in Diels–Alder reactions of a number of dienes and dienophiles. In all cases, it was observed that the isolated yields of desired product was about 90% or greater in shorter reaction time than that reported for uncatalyzed reaction. This indicates that the ionic liquid derived from choline chloride is used not only as polar solvent but also as catalyst in Diels–Alder reactions. These are water insensitive, non-corrosive to steel, and have a wide range of applications. In addition, they are relatively inexpensive compared with the imidazolium based ionic liquids (Scheme 53) [229].

2.2.17. Synthesis of polysubstituted cyclohexene derivatives

Shukla et al. synthesized polysubstituted cyclohexene derivatives by multicomponent reactions (MCRs) between aromatic aldehydes, malononitrile and nitromethane by using *R. oryzae* lipase as a biocatalyst in a biodegradable deep eutectic solvent (DES) derived from choline chloride and urea. This method provides access to pharmaceutically relevant products in excellent yields using environment friendly mild reaction conditions. The remarkable catalytic activity and reusability of lipase and DES widened their applicability in MCRs for the synthesis of polysubstituted alkenes (Scheme 54) [230].

3. Conclusion

Recently, deep eutectic solvents (DESs) have emerged as interesting and inexpensive types of ionic liquids and have shown their usefulness as environmentally benign sustainable alternative to the conventional organic solvents in organic syntheses. The synthesis of deep eutectic

mixtures is more energy efficient and can be synthesized simply by mixing and heating the components without the need of ion-exchange chromatography and purification. The DESs are efficiently able to function not only as modest, inexpensive and environmentally benign solvents but also recyclable and reusable organocatalysts to facilitate the organic transformations. Thus, the DES can play dual role in organic transformations. We believe that the use of deep eutectic solvents with their tailor-made properties will be able to develop environmentally benign and economically viable synthetic protocols with their experimental simplicity and maximum synthetic efficiency. The organic transformations involving the use of DES will be attractive not only for academic and medicinal research but also for industrial research looking forward for simple catalytic organic transformations to synthesize drug-like small molecules with structural diversity and molecular complexity.

Acknowledgments

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