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**Review Article**

Maja Molnar*, Melita Lončarić, Martina Jakovljević, Mario Komar, and Mirjana Lončar

# Some applications of deep eutectic solvents in alkylation of heterocyclic compounds: A review of the past 10 years

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**Abstract:** This mini-review encapsulates the latest findings (past 10 years) in the field of the deep eutectic solvents (DESs) application in the alkylation/arylation of different heterocyclic compounds. These solvents have been developed to fulfill the green chemistry concept demands and have been proven excellent for the application in various fields. This review describes their application in different types of alkylation, *C*-, *N*-, *O*- and *S*-alkylation. *P*-alkylation has not yet been published within this scope. Not only have the authors in this study proven that DESs could be successfully applied for this specific type of reaction, but they have also offered an excellent insight into the mechanisms of their action.

**Keywords:** deep eutectic solvents, alkylation, heterocyclic compounds, green chemistry

## 1 Introduction

The application of deep eutectic solvents (DESs) in different fields of chemistry, pharmacology and medicine has been extensively investigated in the last 10 years, ever since they were introduced by Abbott et al. in 2003 [1]. As DESs fit the green chemistry concept and comply with most of its principles (set by Anastas and Werner in 1998 [2]), it is understandable why they have gained much attention. A sustainable concept in chemistry has been introduced through many different approaches, one of them being the decrease in the usage of toxic and environmentally adverse solvents in organic synthesis. So far, some approaches were suggested to overcome this problem, and lately the application of DESs has been extensively studied.

DESs are mixtures of hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs), which formed a eutectic mixture. The DES components interact with each other through the formation of the net of hydrogen bonding resulting in charge delocalization, which then results in the formation of a eutectic mixture, with a melting point lower than both the components, usually solids [3]. This depression of the melting temperature is a result of a low lattice energy of the mixture and is usually very high, so these mixtures are then referred to as DESs [3,4]. According to the literature, five different classes of DESs are described, depending on the type of HBD and HBA [5]. In general, Lewis or Brønsted acids and bases are used for their synthesis [3,6,7]. DESs are designated as “green” solvents, with the great perspective to replace conventional organic solvents in many applications, especially organic synthesis. DESs usually exhibit low vapor pressure, thermal stability, nonflammability, biodegradability, and the components for their synthesis are easily available and cheap, while their synthesis proceeds smoothly with 100% atom economy [4,8]. The properties of all DESs, both physical and chemical, are strongly dependent on the type and ratio of HBAs and HBDs. Therefore, their properties can be tailored and adjusted for a single use, the reason why they are usually referred to as “designer solvents.” According to Abbot et al. (2004), the freezing point of DES depends upon the salt and HBD lattice energies, entropy changes and ion-HBD interactions [6]. The density of DESs is often higher than that of water as well as viscosity; and in some chemical processes, it could be a limiting factor. Both density and viscosity are temperature dependent [7]. The stronger the interactions within the DES, hydrogen bonding, van der Waals and electrostatic interactions, the higher viscosity. The strong interactions, high ion volume and small void volume, lower the mobility of free species within the

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*** Corresponding author: Maja Molnar,** Department of Applied Chemistry and Ecology, Faculty of Food Technology Osijek, F. Kuhača 18, 31000 Osijek, Croatia, e-mail: maja.molnar@ptfos.hr
**Melita Lončarić, Martina Jakovljević, Mario Komar, Mirjana Lončar:** Department of Applied Chemistry and Ecology, Faculty of Food Technology Osijek, F. Kuhača 18, 31000 Osijek, Croatia

DES and increase the viscosity. Poor ionic conductivities are also associated with the high viscosity of the DESs, i.e., small void volume, as it was described by Abbot et al. (2012) that conductivity is controlled by the mobility of the charge carriers rather than by their number [6,7]. Acidity of the DESs is strongly dependent on the components of DES and is often evaluated using the Hammett function [7]. The type of the components also governs the toxicity of the DESs, which is not always low. Components forming DESs can be nontoxic themselves, but the final mixture may not be necessarily nontoxic [9].

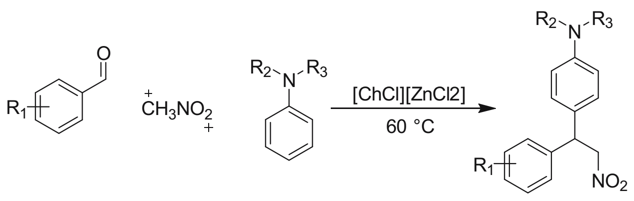
So far, DESs have been applied in many chemical processes, such as synthesis, extraction, electrodeposition and catalysis. They have been proven very efficient in these processes, with a high potential for recyclability. Separation processes, especially extractions, are among the most investigated processes applying DESs. Many bioactive compounds have been successfully extracted using DESs, rutin from *Sophora japonica* [10] and *Ruta graveolens* [11], different phenolic compounds [12–16], fatty acids [17,18] and many other applications in the extraction, extensively reviewed in some recent studies [19,20]. They have also been applied in the removal of the sulfur compounds from fuels [21–23]. Other authors have found them to be effective and selective in the extraction of different metals from waste waters, food samples and different soil samples [24–27]. The application of DESs has also been extensively investigated in the pretreatment of the food industry by-products, in order to maximize the utilization of the waste [28–30]. Procentese et al. [31–33] have been extensively working on the treatment of food industry waste by DESs. So far, they were successfully applied it in the pretreatment of a biomass in order to produce bio-butanol [32], in the pretreatment of coffee production by-products [33] and corncob [31]. Some of the mentioned processes include the removal of the lignin from the biomass in order to obtain a better utilization of the desired compounds [34], as was also investigated by other authors [35,36].

Their application in the synthesis is getting more prominent every day, while the authors have found them to be very effective for different organic transformations. Our group has successfully applied them in the synthesis of different heterocyclic compounds, coumarins [37,38], quinazolinones [39] and rhodanines [40]. Many other authors have proved DESs to be an excellent media for other synthetic procedures, both as solvents and as catalysts. There are some excellent reviews covering this topic, such as their application in the metal catalyzed reactions [41], for various synthetic paths in the formation of heterocyclic compounds [7,42,43], different biotransformations and their application in the metal electrodeposition and electropolishing [3]. Among all mentioned processes, hereby we focus on the alkylation of heterocyclic compounds performed in various DESs.

## 2 Alkylation of different heterocylces

### 2.1 *C*-alkylation/arylation

Friedel–Crafts alkylation is the most common reaction, which includes the C–C bond formation. In this manner, Hu et al. (2020) applied this reaction in the synthesis of some heterocyclic compounds (Scheme 1). They developed a one-pot multicomponent reaction, first on the model reaction, and then they applied it to widen the scope of the reaction. In their search for the optimal DES, they used choline chloride-based DES (combined with urea, glucose, glycerin, citric acid and $ZnCl_2$). The final product was not observed in the selected DES, except in choline chloride:$ZnCl_2$ (1:1) DES. The optimal conditions included a temperature of 60°C and molar ratio of the reactants of 1:1:1 (actually the ratio of 1:3:1 was better; but in order to keep the green character of the reaction, the aforementioned ratio was chosen). No catalyst was used for this reaction [44]. This research can be compared with the publication of Tang et al. (2018), where the same derivatives were synthesized but from different starting compounds [45]. The overall reaction was performed at room temperature, with the milder conditions than the one with DES; but they used hexafuoro-2-propanol, which has adverse effects on the human health and as such is to be avoided within the concepts of green chemistry. In another research, performed by Lang et al. (2011), they used two groups of catalysts, Rh/sulfoxide–phosphine and Rh/bis-sulfoxide-based ones, with the addition of KOH solution in dichloromethane (DCM), which took them up to 10 h to obtain the desired products [46].

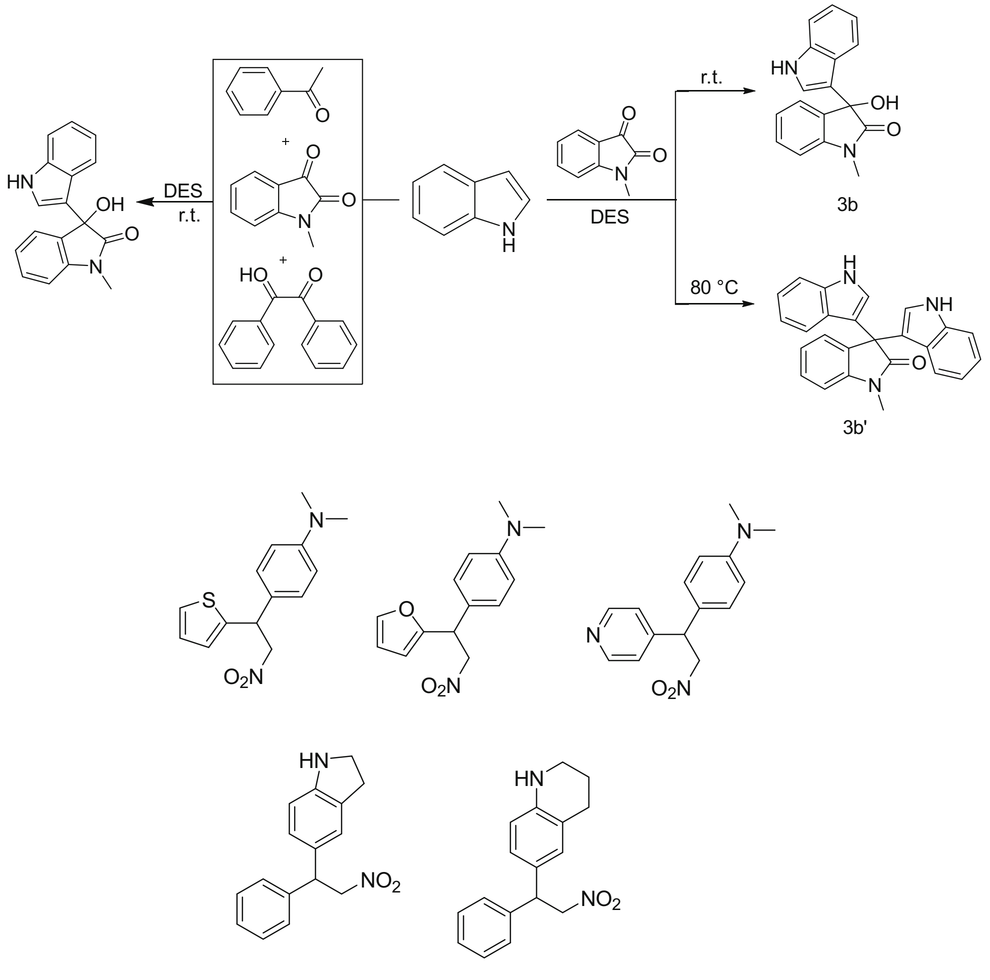


**Scheme 1:** Friedel–Crafts alkylation performed by Hu et al. (2020) [44].

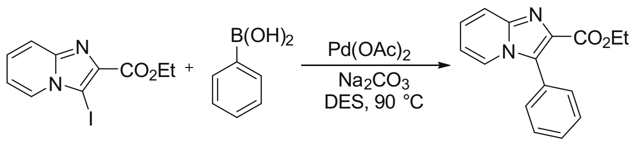
Therefore, the described DES, catalyst-free method with the easy workup, is much more environmentally acceptable to obtain high yields for most of the synthesized compounds.

Friedel–Crafts alkylation was also investigated by Kumar et al. (2015), where they tried to obtain indole derivatives using DESs (Scheme 2). Upon optimization process, they investigated different choline chloride-based DESs and found that the best results are obtained with choline chloride:urea (1:2) system. They obtained a desired product at room temperature. They also investigated a substrate selectivity in a competitive reaction of indole and different carbonyl compounds. The results revealed that this protocol was substrate selective, since only indole reacted in the aforementioned reaction. This reaction was also highly influenced by temperature, where the room temperature gave the desired product, while the temperature of 80°C resulted in the formation of diindolyl product 3b. Their investigation on the recyclability of the DES showed that it could be used up to five cycles with only a small loss of its activity. The DES can be recycled by the addition of either water, with the precipitation of the product and subsequent evaporation of water or 2-methyl THF to extract the product and separate DES. They also checked its cross reusability and found it suitable for three cycles [47]. Brahmachari and Banerjee also performed a similar synthesis, using sulfamic acid as a recyclable catalyst, at room temperature. They used an aqueous ethanol and obtained their products in 2–7 h [48]. Compared with the DES method, it can be seen that the methods adapted by Brahmachari and Banerjee had the characteristics of the green chemistry methods, with the exception that the DES method does not require the addition of catalyst.

In their effort to synthesize imidazo-fused heterocycles, Delaye et al. (2018) used different DESs in a Suzuki–Miyaura cross-coupling reactions, using $Pd(OAc)_2$ as a catalyst (Scheme 3). During optimization, among many tested



**Scheme 2:** Friedel–Crafts alkylation performed by Kumar et al. (2015) [47].

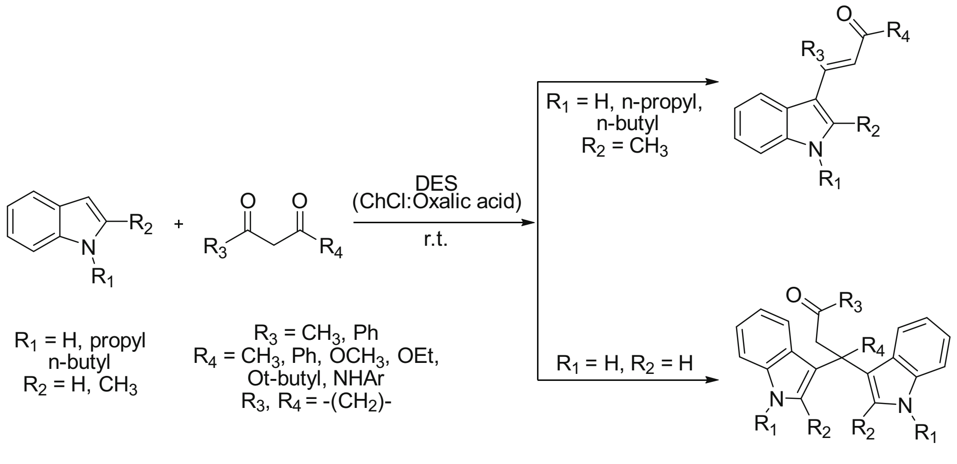


**Scheme 3:** Synthesis of imidazo-fused heterocycles in DES [49].

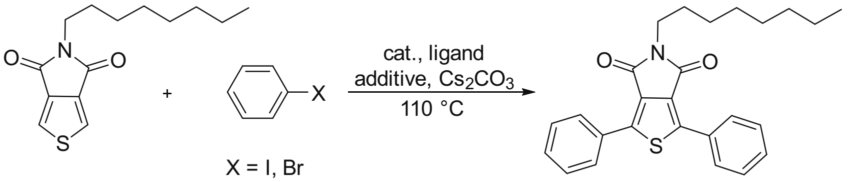
DESs, the mannose:dimethylurea (3:7) DES gave the best yield (93%, overnight) and choline chloride:glycerol gave the yield of 73% in 1 h. When authors investigated the scope of this reaction, using different halogenated heterocycles, choline chloride:glycerol DES was found to be better than choline chloride:dimethylurea in all reactions, providing better product yields in shorter times. The reaction was strongly dependent on the type and position of the halogen atom, where brominated compounds gave no or much lower yields compared with the iodinated ones [49]. If this method is compared with other methods using DESs, in this case, a catalyst was required. Furthermore, one of the disadvantages in this method was a long reaction time for some products (up to 48 h) as well as high temperature (90°C), while the isolation of the products was not as simple as expected; extraction and further column chromatography were required (using organic solvents), diminishing the green character of the protocol [49]. Similar compounds, with different substituents, were synthesized in a reaction of 2-aminopyridine, acetophenone and [Bmim]Br$_3$, using Na$_2$CO$_3$ without any solvent and in 40 min. The work-up demanded the use of organic solvents and column chromatography [50]. In general, both methods are aiming to fit within the green chemistry concept, but there are some limitations for both methods, as mentioned above. The use of DESs is a new approach in the synthesis; and for sure, there is much to be investigated in the application of DESs for Suzuki–Miyaura cross-coupling reactions in the synthesis of these compounds.

Sanap and Shankarling (2014) performed an investigation of the alkylation of indoles (Scheme 4). Undoubtedly, they have proved that DESs themselves act as promotors of the reaction, not the individual components of DESs as some may assume. Choline chloride:oxalic acid was excellent for this type of reaction with the final yields (61–88%) of the products, while the reactions were completed in 2.5–4.5 h at room temperature. The authors assumed that oxalic acid from the DES forms a hydrogen bond with carbonyl group, thus increasing its electrophilicity and enabling the attack of the indole molecule. The DES also facilitates the loss of water molecule in the final step of indole alkylation. Interestingly, the same reaction with 2-unsubstituted indole gave the bis-indolyl products [51]. Conventional reactions of this type usually require different synthetic approaches, using toxic organic catalysts or solvents [52–55], which makes this approach much more environmentally acceptable. The use of nontoxic solvents, mild reaction conditions and short reaction time are certainly the main advantages of the procedure, while the use of organic solvents in column chromatography for their purification could be emphasized as the disadvantage of this protocol.

Aside from alkylation, arylation as well could be successfully performed in DESs. Punzi et al. (2017) have successfully arylated thiophene derivatives with aryl iodides using Pd catalyst and DES as a solvent (Scheme 5). The authors compared hydrophobic (decanoic acid:tetraoctylammonium bromide 2:1) and hydrophilic (choline chloride combined with urea, glycerol or glycol) DESs for this synthetic path. Although the hydrophobic one showed better



**Scheme 4:** Alkylation of indoles in DES [51].

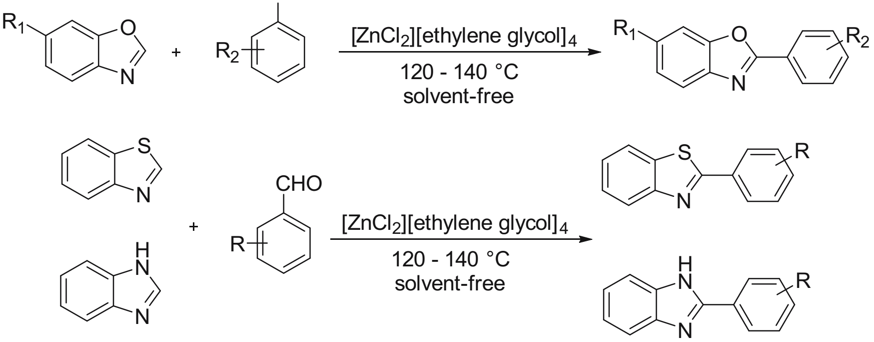


**Scheme 5:** Arylation of thiophene derivatives in DES [59].

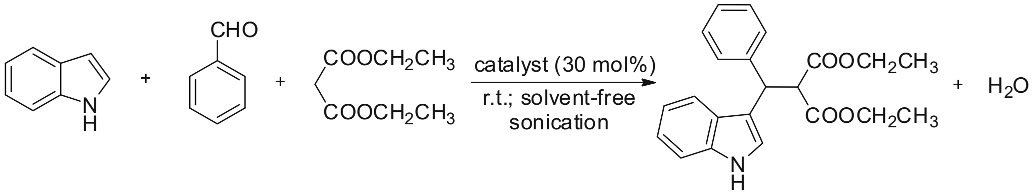
yield, the isolation and purification of the product were complex; while in hydrophilic DES, this final step was much easier. In their pursue for the best catalyst, $Pd_2(dba)_3$ 5 mol% was found to be the best. In order to increase the stability and electron density of the catalyst, P(*o*-MeOPh)$_3$ was also added to the reaction mixture. The final yield of the products was dependent on the functional group of the iodobenzene used as well. Steric hindrance or the presence of polar substituents on benzene ring lowers the final product yield. However, the yield could be increased if a small amount of organic solvents, like toluene or cyclopentyl methyl ether, is added to the DES. This reaction required an addition of the catalyst and not so mild conditions as well as the use of organic solvents in the purification step, which could be pointed out as the main disadvantage. Nevertheless, the use of green solvents compared with the conventional synthesis [56–58] is certainly one of the main advantages [59].

Benzoxazoles were efficiently arylated in position C-2 using benzaldehyde in $ZnCl_2$:ethylene glycol (1:4) DES (Scheme 6) [60]. The reaction required no other organic compounds, solvent or catalysts; and it was highly selective for C-2 arylation. All reactions were performed at 120°C and finished within 4–6 h. For the arylation of $NO_2$-substituted benzoxazole, a higher temperature of 140°C was required. The same conditions can be applied for both benzothiazole and benzimidazole arylation. The authors themselves compared their work with the published ones, whereas reactions were performed in organic solvents, and it is evident that their procedure is much less time-consuming, nontoxic biodegradable components are used and higher yields are obtained. Among aforementioned, the advantage of this method is certainly a reaction time (4–6 h) compared with the conventional methods where some approach took 20–30 h [61–63].

A couple of years later, the same authors published their work on the synthesis of 3-substituted indoles, in a reaction of indoles, aldehydes and activated methylene compounds (Scheme 7). They found that 30% addition of choline chloride:$ZnCl_2$ (1:3) DES was the optimal amount to obtain the best product yields. The influence of the substituents on both benzaldehyde and indole was observed. In this reaction, malononitrile was much more efficient than diethyl malonate. The authors assumed that DES increases the acidity of α-hydrogen in dimethyl malonate in order to induce the formation of the intermediate, which then attacks benzaldehyde followed by the final step, where product is formed. The reaction conditions were mild and the catalyst could be recycled several times, but aside from these advantages, the obtained yields were not high [64]. A similar reaction was performed by Singh et al. (2013), also starting from indole, aromatic aldehydes and active methylene compounds, under solvent-free conditions. This procedure brought much higher yields than the DES one, using a nontoxic catalyst tetrabutylammonium fluoride, but its limitation is certainly the



**Scheme 6:** Arylation of benzoxazoles in position C-2 [60].

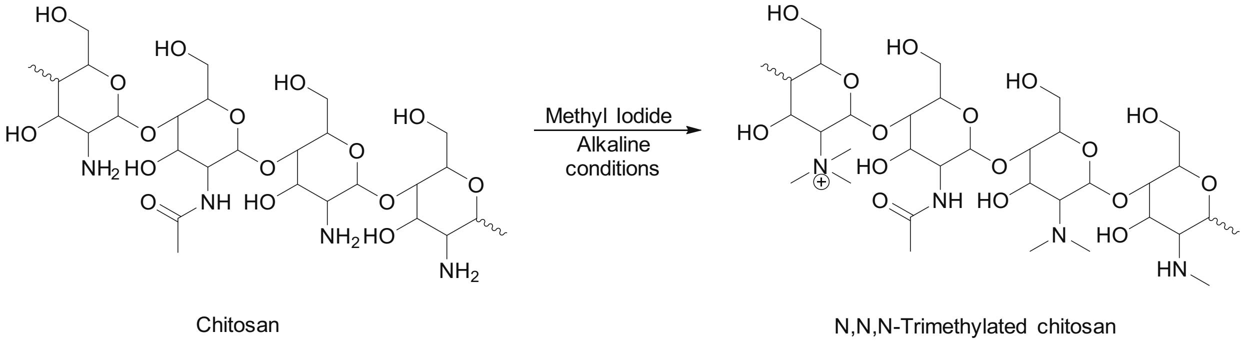


**Scheme 7:** Synthesis of 3-substituted indoles in DES [64].

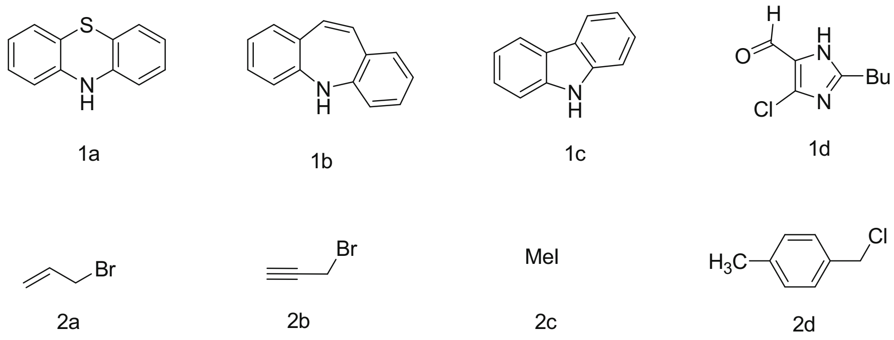
product work-up which requires different organic solvents for the extraction and the subsequent column chromatography [65].

## 2.2 *N*-Alkylation

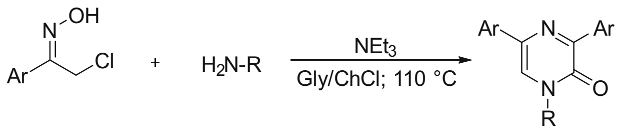
In order to synthesize methylated chitosan, a polycationic polymer, using methyl iodide, Bangde et al. (2016) employed various DESs and their combinations with water or other solvents (Scheme 8). They evaluated the success of the method based on the degree of quaternization, di-methylation and mono-methylation; while in some cases, *O*-methylation occurred as well, especially when multiple methylation steps were performed. Without NaOH, choline chloride:urea DES (and its combinations with water and/or DMF) was found to be better for methylation than choline chloride:glycerol. Furthermore, *O*-methylated products were observed in choline chloride:glycerol DES and its combinations. The authors assume that the mild alkaline conditions in choline chloride:urea DES eliminate the need for NaOH, which is often used in this kind of reaction. They also combined the utilization of enzyme derived from *Burkholderia* genus and DES for chitosan methylation of. The enzyme activity diminished in choline chloride:glycerol DES, while in choline chloride:urea, it was retained. A lipase from *Burkholderia cepacia* in a combination with dimethyl carbonate as an alkylating agent was found to be suitable for di-alkylation of chitosan, but it is worth mentioning that *O*-alkylated products were also observed [66]. A group of other authors was investigating the same subject few



**Scheme 8:** Synthesis of methylated chitosan in DES [67].



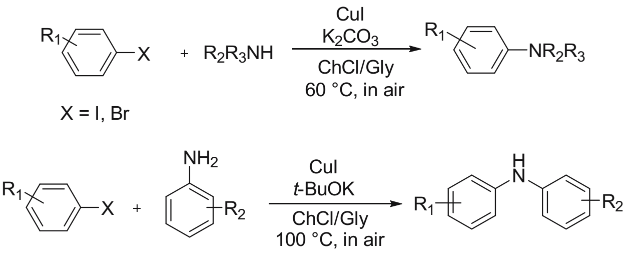
**Scheme 9:** Alkylation of secondary amines in DES [70].



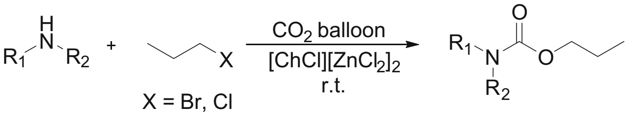
**Scheme 10:** Synthesis of 2(1*H*)-pyrazinones in DES [71].

years later [67]. For this purpose, they used dimethyl carbonate as a methylating agent and lipase as a biocatalyst, while the solvent was a ternary DES, choline chloride: urea:glycerol (1:2:1). *N*,*N*,*N*-Trimethylated chitosan was successfully formed using this method, with an excellent selectivity, without the production of *O*-methylated [67]. When these two methods are compared, it can be concluded that DESs are suitable for chitosan alkylation using different alkylating agents, although the one using dimethyl carbonate is more desirable, due to the toxicity of methyl iodide. Both methods are suitable for chitosan alkylation, with a good degree of quaternization and no formation of *O*-alkylated products, eliminating the need for the harmful basic catalysts and organic solvents, which are often used in this kind of reaction [68,69].

Alkylation of secondary amines was performed using alkyl halides in sugar:urea:salt mixture (Scheme 9). Two mixtures were used for this reaction, namely, glucose:urea: NaCl (6:3:1) and glucose:urea:$NH_4Cl$ (6:3:1), both showing excellent results. Various amines and alkyl halides were used, all giving excellent yields [70]. The authors themselves compared their results to other reported procedures where different solvents, water, benzene, toluene, DMF and different catalysts, such as $Pd(OAc)_2$, $K_2CO_3$, were used and found that their method was more efficient. The advantage of this method is the use of nontoxic solvents with no need for catalyst as well as short reaction time (up to 90 min). However, the work-up procedure was not simple, since it included the use of organic solvents, both for the extraction and for column chromatography purification. The reported conventional methods are usually more time-consuming.



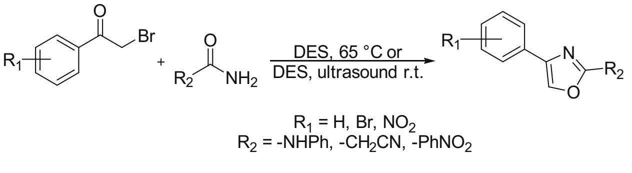
**Scheme 11:** *N*-alkylation in DES [72].



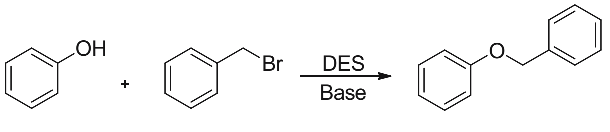
**Scheme 12:** Synthesis of carbamates from amines, carbon dioxide and alkyl halides [73].

Synthesis of 2(1*H*)-pyrazinones from aliphatic amines and $\alpha$-chloro oximes was reported by Perrone et al. (2017) (Scheme 10) [71]. They used choline chloride-based DES (combined with urea and glycerol) and compared their efficiency with conventional organic solvents, THF, toluene and DMF. DESs gave the best results, the reaction was performed under air and no by-product formation was observed. The yields of the products formed in the conventional solvents were from very low (traces) to 58%; while in DESs, it was 43–70%, depending on the amount of the starting compounds used. The final yield could be increased if the corresponding amine is added in excess. The authors point out that this procedure is not effective with aromatic amines. In some cases, DESs act as both the solvents and the catalysts; but in this method, an addition of $Et_3N$ was required. The reaction temperature was also a bit high, 110°C, while the reaction time was 10 h. All of these conditions actually diminish the green character of the procedure [71].

*N*-alkylation of heterocyclic compounds was investigated in terms of their reaction with various aromatic halides having different aromatic amines (Scheme 11). In this reaction, CuI was used as a catalyst and $K_2CO_3$ as a base. Various DESs were tested, L-proline:L-lactic acid (1:2), choline chloride:urea (1:2), L-proline:glycerol (2:5) and choline chloride:glycerol (1:2), with the best results achieved in choline chloride:glycerol. The same protocol could also be used for the synthesis of diarylamines; but instead of $K_2CO_3$, t-BuOK was more efficient for this kind of reaction. The use of DES and mild temperature are the main advantages of this method. However, a long reaction time and the work-up which requires a volatile organic solvents are the main disadvantages [72].



**Scheme 13:** Synthesis of oxazole derivatives from phenacyl bromides and different amides in DES [78].

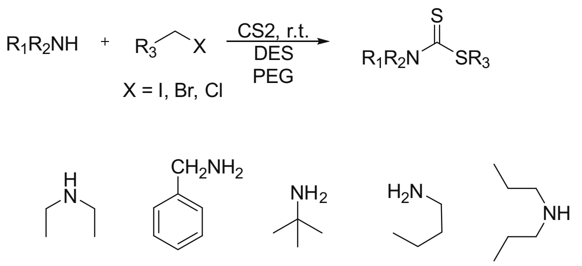


**Scheme 14:** *O*-Alkylation in DESs [79].

## 2.3 *O*-Alkylation

An efficient synthesis of carbamates was developed by Inaloo and Majnooni (2019) [73], starting from amines, carbon dioxide and alkyl halides (Scheme 12). They examined a wide variety of choline chloride-based DESs, where choline chloride was combined with different metal halides. For the optimization purposes, choline chloride:$ZnCl_2$ (1:2) gave the best product yields, whose presence was crucial for the formation of carbamates. This reaction gave the best results for primary amines, but it can also be applied for secondary and tertiary amines. In this case, lower yields are achieved. Although both showed excellent results, alkyl chlorides produced lower yields than alkyl bromides [73]. This method is simple, short, proceeds at room temperature and the final work-up is simple, but the DES could be recycled for several times. A literature survey reveals that the synthesis of carbamates using $CO_2$ and amines usually requires a long reaction time, high temperatures and different organic solvents [74–77], so this method is more preferable in a context of its environmentally benign character.

DES as green solvents can be combined with other green techniques, such as ultrasound. This combination was applied by Singh et al. (2013) in the synthesis of oxazole derivatives (Scheme 13). They performed the synthesis starting from phenacyl bromides and different amides in DES and subjected to ultrasound in ultrasonic horn. The recovery of the product was obtained by the addition of DCM. The DES itself was easily recovered due to its immiscibility with this organic solvent. When organic solvents, such as ethanol, chloroform, toluene or hexane, were used, it resulted in low yields. The authors examined a combination of choline chloride with urea, glycerol and malonic acid, and ChCl:urea was found to be the best, with 86% yield. When the same reaction was performed in the same DES, but without ultrasound, lower yield was obtained. An ultrasound-assisted reaction was less time-consuming compared to the thermal reaction (65°C), and it was finished in 12–16 min, against 3–5 h which were needed for thermal reaction. The proposed mechanism suggests the stabilization of oxygen on carbonyl group, which is achieved through the hydrogen bonding with urea from DES, attacking the amide and subsequent cyclization into oxazole [78].

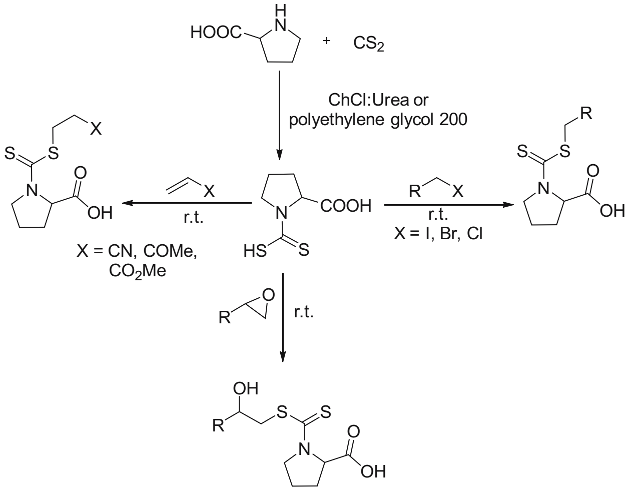


**Scheme 15:** Electrophilic alkylation of aromatic amines in DESs [80].

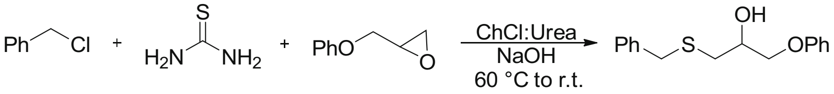
Other authors, Singh et al. (2014), also investigated *O*-alkylation in DESs (Scheme 14). Choline chloride:urea DES was the most convenient for this reaction, which was performed using benzyl bromide and different phenols at 80°C, and the reaction took only 2 h to complete. Different bases were also investigated for this purpose, with the most effective one being KOH. The authors themselves compared their results with other methods. In other methods, organic solvents were used. The yields as well as reaction times were similar, but the DES required no catalyst [79].

## 2.4 *S*-Alkylation

Azizi and Gholibeglo (2012) performed a research on the synthesis of dithiocarbamates in choline chloride:urea DES, but their initial experiment starting from ether, $CS_2$ and aliphatic amine was expanded to the electrophilic alkylation of aromatic amines (Scheme 15). They



**Scheme 16:** Synthesis of dithiocarbamates in choline chloride:urea DES at room temperature [82].



**Scheme 17:** Thiolysis of 1,2-epoxides in choline chloride:urea DES [83].

used aliphatic amines, carbon disulfide and alkyl halides and performed the reaction at room temperature. Desired dithiocarbamates were formed in satisfactory yields in relatively short times, with the fact that the halide ions (chloride, bromide and iodide) had no effect on the reaction time or yield. Primary, secondary and tertiary amines all gave the excellent results. The reactions were performed at room temperature in short times (up to 200 min). The DES was recycled and used for at least three more cycles [80]. The same authors developed another green method for the synthesis of these derivatives. They used water as a solvent and the reaction time was up to 18 h, which was much longer then the previously described DES method [81].

Their research on the synthesis of dithiocarbamates in DESs was continued in 2013, when Azizi and Marimi prepared dithiocarbamates in choline chloride:urea DES at room temperature (Scheme 16). They used different electrophiles for this reaction, such as epoxides, alkyl halides and enones, to obtain final products in good yields and the possibility to reuse the solvent for several times [82].

Their investigation on the application of DESs was also applied on the thiolysis of 1,2-epoxides in choline chloride:urea DES (Scheme 17). Their proposed mechanism includes an electrophilic attack of benzyl halide on thiourea, where *S*-alkylisothiouronium salt was formed. Its formation proceeds smoothly when DES is used as a solvent. At the same time, DES captures the urea formed in hydrolysis of the salt and activates the ring opening of the epoxide. Subsequently, thiolate generated during hydrolysis is added to the epoxide and the final product is formed. The authors claim that the order in which the reactants are added plays a crucial role in achieving high yields [83].

Tang et al. (2015) investigated an alkylation of thiophenic compounds and olefins in oil and gasoline. DESs were prepared from $AlCl_3$ and urea or acetamide. The temperature had a high impact on the alkylation process, and the performance of the DES could be enhanced by adding 1% toluene and benzene. The addition of toluene not only increases the alkylation but also decreases the conversion of olefin. This reaction occurs on the interface of two systems, namely oil and DES [84]. The alkylation of thiophenic compounds was also investigated by other authors who used modified zeolite [85,86], but this DES method seems much simpler and environmentally benign.

## 3 Conclusion

This short review on the application of DES in a specific synthetic path focused on a specific type of organic reactions. Although not many authors have been working on this type of reactions, it is evident that recently it is getting more prominent. They have proven that DESs, as a new generation of green solvents, can be successfully applied in various fields of organic synthesis and for sure their application will grow with time. Moreover, DESs can replace the volatile organic solvents, and they can successfully be used as catalysts and successfully recycled and reused. When the DES methods are compared with the conventional synthesis, it is evident that they possess many advantages over the conventional ones. A benign DES components, mild reaction conditions, short reaction times and simple work-up are their main advantages. Nevertheless, some of the procedures mentioned in this review still show some disadvantages, such as the need for external catalysts, long reaction times or the need for utilization of organic solvents in the purification of the final products; but these methods are yet to be improved in order to enhance their greenness. Therefore, in the next few years, their potential will rise and, undoubtedly, they will find their application in everyday use in many laboratories.

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## References

[1] Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V. Novel solvent properties of choline chloride/urea mixtures. Chem Commun. 2003;2003:70–1.

[2] Anastas PT, Warner JC. Green chemistry: theory and practice. New York: Oxford University Press; 2000.

[3] Smith EL, Abbott AP, Ryder KS. Deep eutectic solvents (DESs) and their applications. Chem Rev. 2014;114:11060–82.

[4] Alonso DA, Baeza A, Chinchilla R, Guillena G, Pastor IM, Ramón DJ. Deep eutectic solvents: the organic reaction medium of the century. Eur J Org Chem. 2016;2016:612–32.

[5] Hansen BB, Spittle S, Chen B, Poe D, Zhang Y, Klein JM, et al. Deep eutectic solvents: a review of fundamentals and applications. Chem Rev. 2020;121(3):1232–85.

[6] Abbott AP, Boothby D, Capper G, Davies DL, Rasheed RK. Deep eutectic solvents formed between choline chloride and carboxylic acids: versatile alternatives to ionic liquids. J Am Chem Soc. 2004;126:9142–7.

[7] Zhang Q, Vigier KDO, Royer S, Jérôme F. Deep eutectic solvents: syntheses, properties and applications. Chem Soc Rev. 2012;41:7108–46.

[8] Clarke CJ, Tu W-C, Levers O, Bröhl A, Hallett JP. Green and sustainable solvents in chemical processes. Chem Rev. 2018;118:747–800.

[9] Hayyan M, Hashim MA, Hayyan A, Al-Saadi MA, AlNashef IM, Mirghani MES, et al. Are deep eutectic solvents benign or toxic? Chemosphere. 2013;90:2193–5.

[10] Zhao B-Y, Xu P, Yang F-X, Wu H, Zong M-H, Lou W-Y. Biocompatible deep eutectic solvents based on choline chloride: characterization and application to the extraction of rutin from *Sophora japonica*. ACS Sust Chem Eng. 2015;3:2746–55.

[11] Molnar M, Jakovljević M, Jokić S. Optimization of the process conditions for the extraction of rutin from *Ruta graveolens* L. by choline chloride based deep eutectic solvents. Solv Extr Res Dev Jpn. 2018;25:109–16.

[12] García A, Rodríguez-Juan E, Rodríguez-Gutiérrez G, Rios JJ, Fernández-Bolaños J. Extraction of phenolic compounds from virgin olive oil by deep eutectic solvents (DESs). Food Chem. 2016;197:554–61.

[13] Fraige K, Arrua RD, Sutton AT, Funari CS, Cavalheiro AJ, Hilder EF, et al. Using natural deep eutectic solvents for the extraction of metabolites in Byrsonima intermedia leaves. J Sep Sci. 2019;42:591–7.

[14] Dai Y, van Spronsen J, Witkamp G-J, Verpoorte R, Choi YH. Natural deep eutectic solvents as new potential media for green technology. Anal Chim Acta. 2013;766:61–8.

[15] Nam MW, Zhao J, Lee MS, Jeong JH, Lee J. Enhanced extraction of bioactive natural products using tailor-made deep eutectic solvents: application to flavonoid extraction from Flos sophorae. Green Chem. 2015;17:1718–27.

[16] Ozturk B, Parkinson C, Gonzalez-Miquel M. Extraction of polyphenolic antioxidants from orange peel waste using deep eutectic solvents. Sep Pur Techn. 2018;206:1–13.

[17] Tommasi E, Cravotto G, Galleti P, Grillo G, Mazzotti M, Sacchetti G, et al. Enhanced and selective lipid extraction from the microalga p. tricornutum by dimethyl carbonate and supercritical $CO_2$ using deep eutectic solvents and microwaves as pretreatment. ACS Sust Chem Eng. 2017;5:8316–22.

[18] Le Thi TX, Tran HL, Cu TS, Ho SL. Separation and enrichment of omega 3, 6, and 9 fatty acids from the by-products of vietnamese basa fish processing using deep eutectic solvent. J Chem. 2018;2018:e6276832.

[19] Cunha SC, Fernandes JO. Extraction techniques with deep eutectic solvents. TrAC. 2018;105:225–39.

[20] Li X, Row KH. Development of deep eutectic solvents applied in extraction and separation. J Sep Sci. 2016;39:3505–20.

[21] Li J, Xiao H, Tang X, Zhou M. Green carboxylic acid-based deep eutectic solvents as solvents for extractive desulfurization. Energy Fuels. 2016;30:5411–8.

[22] Li C, Li D, Zou S, Li Z, Yin J, Wang A, et al. Extraction desulfurization process of fuels with ammonium-based deep eutectic solvents. Green Chem. 2013;15:2793–9.

[23] Hadj-Kali MK, Mulyono S, Hizaddin HF, Wazeer I, El-Blidi L, Ali E, et al. Removal of thiophene from mixtures with *n*-heptane by selective extraction using deep eutectic solvents. Ind Eng Chem Res. 2016;55:8415–23.

[24] Osch DJGP van, Parmentier D, Dietz CHJT, Bruinhorst A van den, Tuinier R, Kroon MC. Removal of alkali and transition metal ions from water with hydrophobic deep eutectic solvents. Chem Commun. 2016;52:11987–90.

[25] Bagda E, Altundag H, Tuzen M, Soylak M. A novel selective deep eutectic solvent extraction method for versatile determination of copper in sediment samples by ICP-OES. Bull Envir Contam Tox. 2017;99:264–9.

[26] Matong JM, Nyaba L, Nomngongo PN. Determination of As, Cr, Mo, Sb, Se and V in agricultural soil samples by inductively coupled plasma optical emission spectrometry after simple and rapid solvent extraction using choline chloride-oxalic acid deep eutectic solvent. Ecotoxicol Env Saf. 2017;135:152–7.

[27] Panhwar AH, Tuzen M, Kazi TG. Deep eutectic solvent based advance microextraction method for determination of aluminum in water and food samples: multivariate study. Talanta. 2018;178:588–93.

[28] Fanali C, Della Posta S, Dugo L, Gentili A, Mondello L, De Gara L. Choline-chloride and betaine-based deep eutectic solvents for green extraction of nutraceutical compounds from spent coffee ground. J Pharm Biomed Anal. 2020;189:113421.

[29] Yoo DE, Jeong KM, Han SY, Kim EM, Jin Y, Lee J. Deep eutectic solvent-based valorization of spent coffee grounds. Food Chem. 2018;255:357–64.

[30] Sander A, Petračić A, Parlov Vuković J, Husinec L. From coffee to biodiesel – deep eutectic solvents for feedstock and biodiesel purification. Separations. 2020;7:22.

[31] Procentese A, Johnson E, Orr V, Garruto Campanile A, Wood JA, Marzocchella A, et al. Deep eutectic solvent pretreatment and subsequent saccharification of corncob. Biores Techn. 2015;192:31–6.

[32] Procentese A, Raganati F, Olivieri G, Russo ME, Rehmann L, Marzocchella A. Low-energy biomass pretreatment with deep eutectic solvents for bio-butanol production. Biores Technol. 2017;243:464–73.

[33] Procentese A, Rehmann L. Fermentable sugar production from a coffee processing by-product after deep eutectic solvent pretreatment. Biores Techn Rep. 2018;4:174–80.

[34] Kalhor P, Ghandi K. Deep eutectic solvents for pretreatment, extraction, and catalysis of biomass and food waste. Molecules. 2019;24:4012–49.
[35] Zhang C-W, Xia S-Q, Ma P-S. Facile pretreatment of lignocellulosic biomass using deep eutectic solvents. Biores Technol. 2016;219:1–5.
[36] Kumar AK, Parikh BS, Pravakar M. Natural deep eutectic solvent mediated pretreatment of rice straw: bioanalytical characterization of lignin extract and enzymatic hydrolysis of pretreated biomass residue. Env Sci Pollut Res. 2016;23:9265–75.
[37] Molnar M, Komar M, Brahmbhatt H, Babić J, Jokić S, Rastija V. Deep eutectic solvents as convenient media for synthesis of novel coumarinyl schiff bases and their QSAR studies. Molecules. 2017;22:1482–97.
[38] Molnar M, Periš I, Komar M. Choline chloride based deep eutectic solvents as a tuneable medium for synthesis of coumarinyl 1,2,4-triazoles: effect of solvent type and temperature. Eur J Org Chem. 2019;2019:2688–94.
[39] Molnar M, Klenkar J, Tarnai T. Eco-friendly rapid synthesis of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones in choline chloride based deep eutectic solvent. Synt Comm. 2017;47:1040–5.
[40] Molnar M, Brahmbhatt H, Rastija V, Pavić V, Komar M, Karnaš M, et al. Environmentally friendly approach to knoevenagel condensation of rhodanine in choline chloride: urea deep eutectic solvent and qsar studies on their antioxidant activity. Molecules. 2018;23:1897–912.
[41] García-Álvarez J. Deep eutectic mixtures: promising sustainable solvents for metal-catalysed and metal-mediated organic reactions. Eur J Inorg Chem. 2015;2015:5147–57.
[42] Khandelwal S, Tailor YK, Kumar M. Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations. J Mol Liq. 2016;215:345–86.
[43] Liu P, Hao J-W, Mo L-P, Zhang Z-H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. RSC Adv. 2015;5:48675–704.
[44] Hu Z, Jiang G, Zhu Z, Gong B, Xie Z, Le Z. One-pot domino Henry–Friedel–Crafts alkylation reaction in deep eutectic solvent. Chin J Org Chem. 2021;41(1):325–32.
[45] Tang R-J, Milcent T, Crousse B. Friedel–Crafts alkylation reaction with fluorinated alcohols as hydrogen-bond donors and solvents. RSC Adv. 2018;8:10314–7.
[46] Lang F, Chen G, Li L, Xing J, Han F, Cun L, et al. Rhodium-catalyzed highly enantioselective addition of arylboronic acids to 2-nitrostyrenes by *tert*-butanesulfinylphosphine ligand. Chem Eur J. 2011;17:5242–5.
[47] Kumar A, Shukla RD, Yadav D, Gupta LP. Friedel–Crafts alkylation of indoles in deep eutectic solvent. RSC Adv. 2015;5:52062–5.
[48] Brahmachari G, Banerjee B. Facile and one-pot access of 3,3-bis(indol-3-yl)indolin-2-ones and 2,2-bis(indol-3-yl)acenaphthylen-1(2h)-one derivatives via an eco-friendly pseudo-multicomponent reaction at room temperature using sulfamic acid as an organo-catalyst. ACS Sust Chem Eng. 2014;2:2802–12.
[49] Delaye P-O, Pénichon M, Boudesocque-Delaye L, Enguehard-Gueiffier C, Gueiffier A. Natural deep eutectic solvents as sustainable solvents for suzukimiyaura cross-coupling reactions applied to imidazo-fused heterocycles. SynOpen. 2018;2:0306–11.
[50] Le Z-G, Xie Z-B, Xu J-P. One-pot synthesis of 2-phenylimidazo [1,2-α]pyridines from acetophenone, [Bmim]$Br_3$ and 2-aminopyridine under solvent-free conditions. Molecules. 2012;17:13368–75.
[51] Sanap AK, Shankarling GS. Choline chloride based eutectic solvents: direct C-3 alkenylation/alkylation of indoles with 1,3-dicarbonyl compounds. RSC Adv. 2014;4:34938–43.
[52] Cadierno V, Francos J, Gimeno J. Ruthenium/TFA-catalyzed regioselective C-3-alkylation of indoles with terminal alkynes in water: efficient and unprecedented access to 3-(1-methylalkyl)-1H-indoles. Chem Commun. 2010;46:4175–7.
[53] Basak S, Alvarez-Montoya A, Winfrey L, Melen RL, Morrill LC, Pulis AP. B(C6F5)3-catalyzed direct C3 alkylation of indoles and oxindoles. ACS Catal. 2020;10:4835–40.
[54] Cano R, Yus M, Ramón DJ. Environmentally friendly and regioselective C3-alkylation of indoles with alcohols through a hydrogen autotransfer strategy. Tetrahedron Lett. 2013;54:3394–7.
[55] Jana U, Maiti S, Biswas S. An $FeCl_3$-catalyzed highly C3-selective Friedel–Crafts alkylation of indoles with alcohols. Tetrahedron Lett. 2007;48:7160–3.
[56] Hayashi S, Kojima Y, Koizumi T. Highly regioselective Pd/C-catalyzed direct arylation toward thiophene-based π-conjugated polymers. Polym Chem. 2015;6:881–5.
[57] Song Y-T, Lin P-H, Liu C-Y. Copper-catalyzed direct C–H Arylation of Thieno[3,4-c]pyrrole-4,6-dione (TPD): toward efficient and low-cost synthesis of π-functional small molecules. Adv Synth Catal. 2014;356:3761–8.
[58] Kuwabara J, Yamazaki K, Yamagata T, Tsuchida W, Kanbara T. The effect of a solvent on direct arylation polycondensation of substituted thiophenes. Polym Chem. 2015;6:891–5.
[59] Punzi A, Coppi DI, Matera S, Capozzi MAM, Operamolla A, Ragni R, et al. Pd-catalyzed thiophene–aryl coupling reaction via C–H bond activation in deep eutectic solvents. Org Lett. 2017;19:4754–7.
[60] Tran PH, Hang A-HT. Deep eutectic solvent-catalyzed arylation of benzoxazoles with aromatic aldehydes. RSC Adv. 2018;8:11127–33.
[61] Teo YC, Riduan SN, Zhang Y. Iodine-mediated arylation of benzoxazoles with aldehydes. Green Chem. 2013;15:2365–8.
[62] Liu S, Chen R, Guo X, Yang H, Deng G, Li C-J. Iron-catalyzed arylation of benzoazoles with aromatic aldehydes using oxygen as oxidant. Green Chem. 2012;14:1577–80.
[63] Kim D, Yoo K, Kim SE, Cho HJ, Lee J, Kim Y, et al. Copper-catalyzed selective arylations of benzoxazoles with aryl iodides. J Org Chem. 2015;80:3670–6.
[64] Tran M-NT, Nguyen X-TT, Nguyen HT, Chau D-KN, Tran PH. Deep eutectic solvent: an efficient and green catalyst for the three-component condensation of indoles, aromatic aldehydes, and activated methylene compounds. Tetrahedron Lett. 2020;61:151481.
[65] Singh N, Allam BK, Raghuvanshi DS, Singh KN. An efficient tetrabutylammonium fluoride (TBAF)-catalyzed three-component synthesis of 3-substituted indole derivatives under solvent-free conditions. Adv Synth Catal. 2013;355:1840–8.
[66] Bangde PS, Jain R, Dandekar P. alternative approach to synthesize methylated chitosan using deep eutectic solvents, biocatalyst and “green” methylating agents. ACS Sust Chem Eng. 2016;4:3552–7.

[67] Mahajan T, Bangde P, Dandekar P, Jain R. Greener approach for synthesis of *N*,*N*,*N*-trimethyl chitosan (TMC) using ternary deep eutectic solvents (TDESs). Carbohydr Res. 2020;493:108033.

[68] Curti E, Britto D, de, Campana-Filho SP. Methylation of chitosan with iodomethane: effect of reaction conditions on chemoselectivity and degree of substitution. Macromol Biosci. 2003;3:571–6.

[69] Polnok A, Borchard G, Verhoef JC, Sarisuta N, Junginger HE. Influence of methylation process on the degree of quaternization of *N*-trimethyl chitosan chloride. Eur J Pharm Biopharm. 2004;57:77–83.

[70] Kumar KSV, Swaroop TR, Ravi Singh K, Rangappa KS, Sadashiva MP. Sugar-urea-salt eutectic mixture as an efficient green solvent for *N*-alkylation of heterocyclic secondary amines. Chem Data Coll. 2020;29:100536.

[71] Perrone S, Capua M, Messa F, Salomone A, Troisi L. Green synthesis of 2-pyrazinones in deep eutectic solvents: from α-chloro oximes to peptidomimetic scaffolds. Tetrahedron. 2017;73:6193–8.

[72] Quivelli AF, Vitale P, Perna FM, Capriati V. Reshaping ullmann amine synthesis in deep eutectic solvents: a mild approach for Cu-catalyzed C–N coupling reactions with no additional ligands. Front Chem. 2019;7:723.

[73] Inaloo ID, Majnooni S. Carbon dioxide utilization in the efficient synthesis of carbamates by deep eutectic solvents (DES) as green and attractive solvent/catalyst systems. N J Chem. 2019;43:11275–81.

[74] Riemer D, Hirapara P, Das S. Chemoselective synthesis of carbamates using $CO_2$ as carbon source. ChemSusChem. 2016;9:1916–20.

[75] Germain N, Hermsen M, Schaub T, Trapp O. Synthesis of carbamates from carbon dioxide promoted by organostannanes and alkoxysilanes. App Organomet Chem. 2017;31:e3733.

[76] Ion A, Doorslaer CV, Parvulescu V, Jacobs P, Vos DD. Green synthesis of carbamates from $CO_2$, amines and alcohols. Green Chem. 2008;10:111–6.

[77] Zhang Q, Yuan H-Y, Fukaya N, Yasuda H, Choi J-C. Direct synthesis of carbamate from $CO_2$ using a task-specific ionic liquid catalyst. Green Chem. 2017;19:5614–24.

[78] Singh BS, Lobo HR, Pinjari DV, Jarag KJ, Pandit AB, Shankarling GS. Ultrasound and deep eutectic solvent (DES): a novel blend of techniques for rapid and energy efficient synthesis of oxazoles. Ultrason Sonochem. 2013;20:287–93.

[79] Singh AS, Shendage SS, Nagarkar JM. Choline chloride based deep eutectic solvent as an efficient solvent for the benzylation of phenols. Tetrahedron Lett. 2014;55:7243–6.

[80] Azizi N, Gholibeglo E. A highly efficient synthesis of dithiocarbamates in green reaction media. RSC Adv. 2012;2:7413–6.

[81] Azizi N, Aryanasab F, Torkiyan L, Ziyaei A, Saidi MR. One-pot synthesis of dithiocarbamates accelerated in water. J Org Chem. 2006;71:3634–5.

[82] Azizi N, Marimi M. Fast 62–92% yield preparation of amino acid dithiocarbamates in green solvent at room temperature. Envir Chem Lett. 2013;11:371–6.

[83] Azizi N, Yadollahy Z, Rahimzadeh-oskooee A. Odourless strategy for deep eutectic solvent-mediated ring opening of epoxides with *in situ* generated S-alkylisothiouronium salts. Synlett. 2014;25:1085–8.

[84] Tang X, Zhang Y, Li J. Alkylation of thiophenic compounds catalyzed by deep eutectic solvents. Catal Comm. 2015;70:40–3.

[85] Zheng X-D, Dong H-J, Wang X, Shi L. Study on olefin alkylation of thiophenic sulfur in FCC gasoline using $La_2O_3$ modified HY zeolite. Catal Lett. 2009;127:70–4.

[86] Hu L, Zhang Z, Xie S, Liu S, Xu L. Effect of grain size of zeolite Y on its catalytic performance in olefin alkylation thiophenic sulfur process. Catal Comm. 2009;10:900–4.