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Ultrasound and deep eutectic solvent (DES): A novel blend of techniques for rapid and energy efficient synthesis of oxazoles

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ABSTRACT

The present work deals with the synthesis of novel oxazole compounds by using effective combination of ultrasound (US) and deep eutectic solvent (DES). The reaction was also conducted by thermal method (NUS) and the comparative studies are 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 DES as reaction medium is highlighted from the fact that it is bio-degradable, non-toxic, recyclable and could be easily prepared using inexpensive raw materials. The recyclability for DES was studied wherein it was found that ultrasound has no negative effects on DES even up to four runs. In addition, the present work is the first report on the combinative use of DES and US in organic synthesis.

1. Introduction

The synthesis of substituted oxazole derivatives has attracted much attention because of their versatile applications, including biological activity such as antibacterial, anti-fungal [1], anti-tubercular [2] and anti-inflammatory activities [3] as well as their utility as valuable precursors in many useful synthetic transformations [4–6]. Oxazoles also attract considerable attention in colorant chemistry especially as scintillating compounds and as fluorescent whitening agents for textiles [7,8].

Although significant progress has been made towards the synthesis of oxazoles, they are most commonly obtained by the reaction of α-haloketones with amides [9] or the cyclodehydration of β-ketoamides [10]. Other methods include dehydrogenation of oxazolines [11] and other processes such as aza-Wittig reactions [12], Schmidt rearrangements [13], use of isocyanides [14], TosMIC [15], intramolecular alkyne additions [16] and microwave [17]. Majority of the above stated methods suffer from many demerits that include use of toxic reagents, volatile solvents or expensive catalysts. The reaction conditions are also harsh for most of these reactions and some are even related with tedious work-up procedures. Therefore, there is an obvious need to develop an efficient synthetic method that would synthesize oxazoles under milder conditions and in an environmentally benign manner.

Application of ultrasound in organic transformation has proved to be an important tool in enhancing reaction rates and improving yields [18,19]. It promotes the reaction under milder conditions where drastic conditions are required conventionally. Ultrasound functions by cavitation process that involves sequential formation, growth and collapse of millions of microscopic vapor bubbles (voids) in the liquid. These rapid and violent implosions generate short-lived regions with temperatures of roughly 5000 °C, pressures of about 1000 atm as well as heating and cooling rates above 10 billion degree celsius per second [20]. Such localized hot spots can be visualized as a micro reactor in which the energy of sound is transformed into a useful chemical form [21,22]. It follows that ultrasound energy can activate reactant molecules that are capable of penetrating the atmosphere of the bubble [23]. To add to this, it has been shown that the rates of ultrasound-assisted reactions can be improved by lowering the vapor pressure of solvents [24,25]. In this context, non-volatile solvents like ionic liquids have been reported to be used in ultrasound promoted reactions that can force even less volatile substrates to undergo the cavitational activation [26,27].

Ionic liquids (ILs) are ionic compounds composed of discrete cations and anions mostly liquid at or below 100 °C. However, ionic liquids, especially those based on imidazole with fluorinated anions, not only suffer from the demerits of being non-biodegradable,

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toxic and commercially expensive, but their production is also related to the use of large amounts of unsafe and volatile organic solvents [28]. In addition, a large group of ILs is found to be combustible [29] and moisture-sensitive. Hence, with a view to explore other non-volatile solvents derived from bio-compatible resources, we present the first time use of deep eutectic solvents (DES) in sonochemical organic synthesis.

Deep eutectic solvents differ from ionic liquids since the former can be said to be ionic mixtures rather than ionic compounds, containing combination of organic halide salts (choline chloride) with hydrogen bond donating compounds (urea, glycerol, etc.) or Lewis acids (zinc chloride). The ability to form hydrogen bond with the halide ion gives rise to a eutectic combination. These hydrogen-bonding interactions lead to depression in freezing point since the formation of eutectic is more energetically favored relative to the lattice energies of the pure constituents [30]. Deep eutectic solvents retain many beneficial properties of ILs like non-volatililty and recyclability [30]. In addition, they also possess several merits over conventional ionic liquids like: (1) ease of preparation and storage; (2) cost-effectiveness due to inexpensive starting materials; (3) biodegradable nature; (4) non-toxicity; (5) no sensitivity towards moisture and (6) high scope of industrial applicability due to the above discussed merits. Some reports on the utility of DES in organic synthesis include acetylation of carbohydrates and cellulose [31], selective *N*-alkylation [32], phthalimide synthesis [33].

Owing to the similarity of ionic liquid to DES in terms of viscosity, it could be said that the application of ultrasound to DES might create difficulty in forming cavitation owing to larger cohesive forces due to high viscosity. However, if once formed, such a cavitation will have lesser solvent interferences due to almost negligible vapor entering the cavitation bubble. Hence less violent collapse of bubble due to cushioning effect will not be observed as seen in the case of more volatile solvents [34]. In addition, the reduction in solvent interference will minimize the possibility of DES itself participating in the reaction, thereby making them ideal as solvents for sonochemical synthesis.

In the present work, for the first time, organic synthesis is performed using effective combination of deep eutectic solvents and ultrasound technique. Such combination has till now been used for electrochemical applications [35] and inorganic synthesis of metal organic frame-work [36]. This technique proved to be a cutting edge technique for synthesis of novel oxazole molecules in comparison to use of thermal methods. Moreover, the use of DES in sonochemical organic synthesis is quite suitable owing to their negligible vapor pressure.

2. Materials and methods

2.1. Materials

All the solvents and chemicals were procured from S D fine chemicals (India) and were used without further purification. The reactions were monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated plates, which were visualized with UV light. Key intermediates, 2-bromo-1-(4-methoxyphenyl) ethanone, 2-bromo-1-(4-nitrophenyl)ethanone and 2-bromo-1-(4-bromophenyl)ethanone were prepared by bromination of their respective acetophenone derivatives with *N*-bromosuccinimide (NBS) in accordance to the reported reference [37]. The deep eutectic solvent used in the present work was easily prepared from choline chloride (1 eq) and urea (2 eq) at 80 °C by a previously reported method [38] with 100% atom economy. The resulting viscous liquid was used directly without any purification.

2.2. Reaction scheme

The reaction scheme depicting synthesis of oxazoles from various derivatives of phenacyl bromide and amide in deep eutectic medium is shown in Scheme 1.

2.3. Ultrasound set-up

Ultrasound for sonochemical synthesis is generated with the help of ultrasonic instrument set-up (horn type). The animated representation of the set-up is given in Fig. 1. The specification and details of the set-up, processing parameters used during the experiments are:

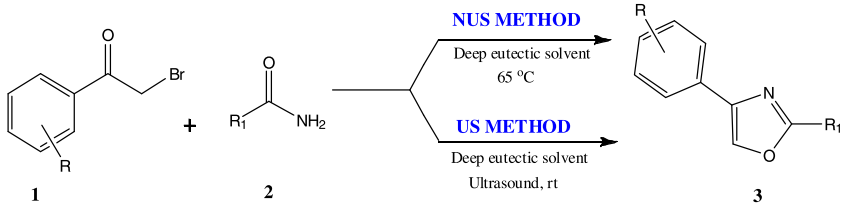
Make: ACE, USA.
Operating frequency: 22 kHz.
Rated output power: 750 W.
Diameter of stainless steel tip of horn: 1.3×10^{-2} m.
Surface area of ultrasound irradiating face: 1.32×10^{-4} m^2
Intensity: 3.4×10^5 W/m^2.

2.4. Synthesis of oxazole derivatives 3a-e by thermal heating in DES medium

A mixture of 4′-substituted phenacyl bromide (1.0 eq) and amide derivative (1.0 eq) was added to the deep eutectic solvent (7.0 g) with stirring. The reaction mixture was stirred at (65 ± 2 °C). After completion of the reaction, as monitored by thin layer chromatography (TLC), it was found that 3.5–5 h were required for the completion consumption of the reactant 4′-substituted phenacyl bromide. The reaction mass was extracted using dichloromethane (DCM). The DCM layer was subjected to evaporation under reduced vacuum to obtain the final product.

2.5. Synthesis of oxazole derivatives 3a-e by ultrasound method in DES medium

A mixture of 4′-substituted phenacyl bromide (1.0 eq) and amide derivative (1.0 eq) was added to the deep eutectic solvent (7.0 g) and the mixture was stirred initially for slight mixing of



where R = H, Br, NO_2
R_1 = -NHPh, -CH_2CN, -PhNO_2

Scheme 1. Thermal and ultrasound assisted synthesis of oxazole derivatives using deep eutectic solvent as reaction medium.

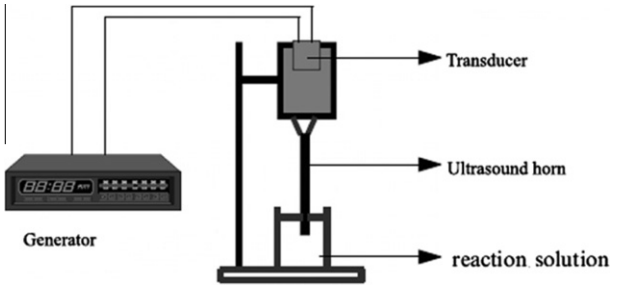


Fig. 1. Schematic of ultrasound horn set-up.

substrates. The reaction mixture was then placed under sonication using an ultrasonic horn (ACE horn, 22 kHz frequency) at 40% amplitude for required time with a 5 s ON and 5 s OFF cycle from time $t = 0$ h. The temperature of the process was maintained at 35 ± 2 °C by means of supply of water to the jacketed reactor, used for the synthesis. The reaction was monitored by thin layer chromatography (TLC) by observing completion consumption of the reactant 4′-substituted phenacyl bromide. The reaction mass was extracted using dichloromethane (DCM). The DCM layer was subjected to evaporation under reduced vacuum to obtain the final product. The reaction time was estimated by repeating the same reaction three times. The final compound was purified by column chromatography using toluene:ethyl acetate (8:2) as eluent.

The deep eutectic solvent could be easily isolated after extraction of product as mentioned in procedure owing to its immiscibility in DCM. The recovered DES was further used for the next run wherein the reaction between phenacyl bromide and phenyl urea was considered as a standard reaction.

2.6. Characterization and spectral data

All oxazole compounds were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectrums were recorded on Varian 300 MHz mercury plus spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with micromass-Q-Tof (YA105) spectrometer.

2.6.1. N,4-diphenyl-1,3-oxazol-2-amine (3a)

UV λ_{max} (EtOAc)/nm 299; ν_{max}/cm^{-1} 3400 (N—H), 3128 (Ar. C—H), 1667 (C=N), 1567 (C=C), 1493 (C=C), 1447 (C=C), 1068 (C—O); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 7.63–7.20 (11H, m, CH), 5.20 (1H, s, NH); ^{13}C NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 160.7, 140.0, 131.5, 129.3, 128.9, 128.7, 127.8, 127.5, 125.2; EIMS m/z = 237.1, $C_{15}H_{12}N_2O$, calculated m/z: 236.0.

2.6.2. 4-(4-bromophenyl)-N-phenyl-1,3-oxazol-2-amine (3b)

UV λ_{max} (EtOAc)/nm 302 and 341; ν_{max}/cm^{-1} 3384 (N—H), 3101 (Ar. C—H), 1661 (C=N), 1585 (C=C), 1480 (C=C), 1071 (C—O), 823 (C—Br); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 7.50–7.25 (10H, m, CH), 4.90 (1H, s, NH); ^{13}C NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 160.7, 139.2, 131.8, 130.4, 127.8, 126.8, 121.5; EIMS m/z (-Ph)=238.9, 240.9, $C_{15}H_{11}BrN_2O$, calculated m/z: 315, m/z-Ph = 238.

2.6.3. 4-(4-nitrophenyl)-N-phenyl-1,3-oxazol-2-amine (3c)

UV λ_{max} (EtOAc)/nm 248 and 347; ν_{max}/cm^{-1} 3416 (N—H), 3146 (Ar. C—H), 1662 (C=N), 1606 (C=C), 1506 (—NO_2), 1419 (C=C), 1348 (—NO_2), 1082 (C—O); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 8.26–7.19 (10H, m, CH), 4.66 (1H, s, NH); ^{13}C NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 130.8, 129.8, 128.7, 125.5, 124.1; EIMS m/z = 238.0, 282.1, $C_{15}H_{11}N_3O_3$, calculated m/z: 281.3.

2.6.4. [4-(4-Nitrophenyl)-1,3-oxazol-2-yl]acetonitrile (3d)

UV λ_{max} (EtOAc)/nm 275 and 347; ν_{max}/cm^{-1} 3409 (N—H), 3143 (Ar. C—H), 1657 (C=N), 1571 (C=C), 1503 (—NO_2), 1418 (C=C), 1324 (—NO_2), 1081 (C—O); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 8.25–7.26 (5H, m, CH), 4.70 (2H, s, CH_2); ^{13}C NMR (300 MHz; $CDCl_3$; Me_4 Si) δ = 129.9, 125.7, 124.2; EIMS m/z = 228.2, $C_{11}H_7N_3O_3$, calculated m/z: 229.1.

2.6.5. 2,4-Bis(4-Nitrophenyl)-1,3-oxazole (3e)

UV λ_{max} (EtOAc)/nm 251 and 314; ν_{max}/cm^{-1} 3112 (N—H), 2932 (Ar. C—H), 1602 (C=N), 1518 (—NO_2), 1412 (C=C), 1343 (—NO_2), 1122 (C—O); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 8.40–8.10 (9H, m, CH); ^{13}C NMR (300 MHz; $CDCl_3$; Me_4Si) δ = 190.2, 164.2, 151.0, 138.4, 134.4, 131.2, 130.9, 129.1, 128.9, 124.3, 123.8; EIMS m/z = 313.1, $C_{15}H_9N_3O_5$, calculated m/z: 312.

3. Results and discussions

3.1. Study of significance of DES in oxazole synthesis by thermal method

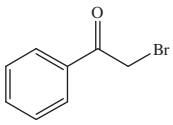
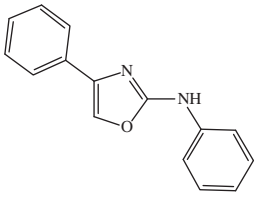
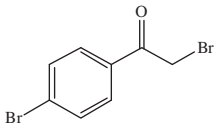
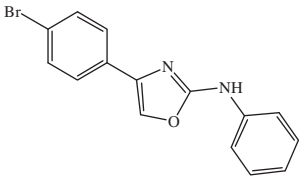
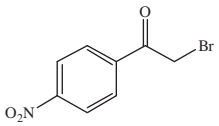
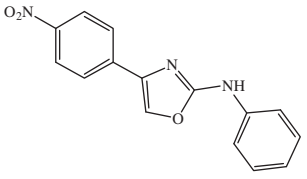
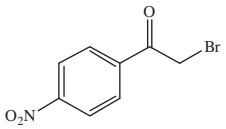
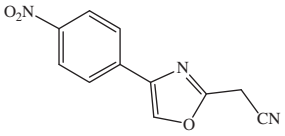
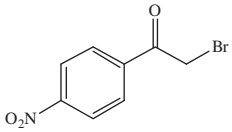
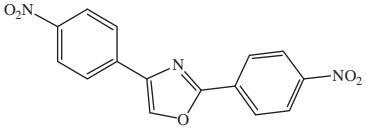
The reaction parameters were optimized by synthesis of a reported derivative **3a** by the reaction of phenacyl bromide with phenyl urea. Deep eutectic solvent and conventional organic solvents were chosen as reaction medium. Very low yields were obtained even after heating and refluxing the reaction mixture for several hours in organic solvents like ethanol, chloroform, toluene and hexane (Table 1). The yield in deep eutectic medium (choline choride and urea) was much improved in comparison to organic solvents that prompted us to explore the scope for further improvement in results using ultrasound method. This method fetched us an improvement of yield to 86% in just 17 min. We also tried other sonochemical synthesis of oxazoles in other deep

Table 1
Effect of organic solvents or deep eutectic solvent (DES) in the synthesis of oxazole derivatives by NUS or US methods.

Entry	Reaction medium	Reaction conditions	Temperature (°C)	Yield (%)[d]
1	Ethanol	NUS[a]	60	–
2	Chloroform	NUS[a]	60	–
3	Toluene	NUS[a]	110	10
4	Hexane	NUS[a]	70	–
5	DES (ChCl:urea)[c]	NUS[a]	65	60
6	DES (ChCl:urea)[c]	US[b]	R.T.	86
7	DES (ChCl:glycerol)[c]	US[b]	R.T.	15
8	DES (ChCl: malonic acid)[c]	US[b]	R.T.	Traces

[a] Reaction conditions: NUS (thermal method); phenacyl bromide (1.0 g, 5.0 mmol), phenylurea (0.76 g, 5 mmol), solvent (10 vol), reaction time = 5 h.
[b] Reaction conditions: US (ultrasound method), phenacyl bromide (1.0 g, 5.0 mmol), phenylurea (0.76 g, 5 mmol), solvent (10 vol), reaction time = 17 min.
[c] DES – deep eutectic solvent; ChCl – choline chloride.
[d] Isolated yields.

Table 2
Synthesis of novel oxazole derivatives from phenacyl bromide derivatives with substituted amides by application of DES-US (deep eutectic solvent-ultrasound) blend.

Entry	Acyl bromide	Product	Reaction Time		Yield (%)		Energy utilized	
			NUS[d] (h)	US[e] (min)	NUS[d]	US[e]	Thermal method (kJ/g)	Ultrasound method (kJ/g)
3a.[a]			5	17	60	86	8.24	1.05
3b.[a]			3.5	15	45	89	6.31	0.95
3c.[a]			3.5	12	65	90	6.25	0.75
3d.[b]			4	16	62	83	7.19	1.04
3e.[c]			4	15	60	82	6.92	0.94

[a] All reactions were carried out with acyl bromide (1 eq), phenyl urea 2a (1 eq), DES (10 vol).
[b] All reactions were carried out with acyl bromide (1 eq), cyanoacetamide 2b (1 eq), DES (10 vol).
[c] All reactions were carried out with acyl bromide (1 eq), 4-nitrobenzamide 2c (1 eq), DES (10 vol).
[d] Isolated yields of oxazoles by thermal method, reaction temperature = 65 °C.
[e] Isolated yields of oxazoles by ultrasonic method at room temperature.

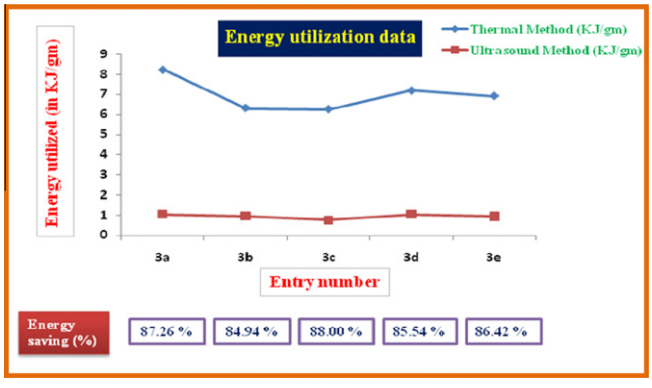


Fig. 2. Energy utilization by thermal and ultrasound methods in the synthesis of oxazoles.

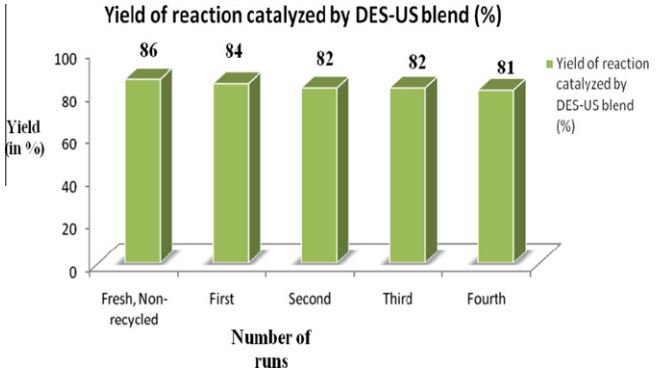
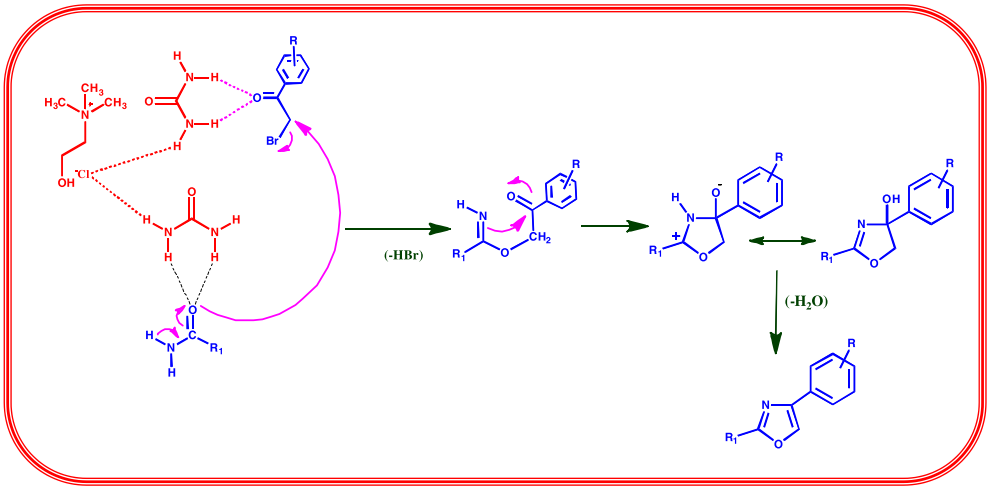


Fig. 3. Recyclability data of reaction between phenacyl bromide and phenylurea catalyzed by combination of DES and US.

eutectic mixtures to check the room for further improvement. However, the deep eutectic solvent of choline chloride and urea was found to be the most effective amongst them. Thus the results obtained, comprehend the effectiveness of the combinative technique of using ultrasound and DES rather than their individual usage.

3.2. Synthesis of novel oxazole derivatives and energy efficiency calculations

Novel oxazole derivatives were synthesized in DES medium by both conventional heating and ultrasound technique to understand



Scheme 2. Mechanism proposing the role of DES in synthesis of oxazole derivatives.

the merits of ultrasonication. The combination of DES and US showed marked improvements both in terms of reaction times and yields as depicted in Table 2. The reactions worked within just 12–16 min by use of ultrasound as against 3–5 h by thermal method (Table 2). The impact of acoustic energy results in rapid micromixing thus reducing the processing time. In order to exhibit the flexibility of this methodology for other derivatives as well, phenacyl bromide was derivatized and reacted with phenyl urea (entry 3b, 3c, Table 2). Novel derivatives of 2-methyl cyano oxazole (entry 3d, Table 2) and 2-phenyl oxazole (entry 3e, Table 2) were also synthesized using this methodology.

We also performed energy requirement estimation for both the methods to evaluate the energy efficiency of the processes. The reported methods for energy calculation have been pioneered by Pandit et al. [23]. However, such calculations are reported for the first time in DES-US blended technique. The data for energy utilization in kJ/g during reaction for all the derivatives is depicted in Table 2 as per the energy calculations stated in Appendix A. It was observed that ultrasound method saved more than 85% energy with much reduced reaction time as diagrammatically represented in Fig. 2.

3.3. Recyclability of deep eutectic solvent

The deep eutectic solvent medium was recycled and re-used up to four times. Reaction of phenacyl bromide with phenyl urea was selected as the model reaction. Deep eutectic solvent recycled from the previous run was re-used for the next run without further purification. No significant decrease in yields was obtained as shown in Fig. 3. This indicates the fact that ultrasound does not have any negative effect on the eutectic combination even after four runs thus endorsing the potential of this process towards industrial applicability.

3.4. Proposed mechanism for oxazole synthesis

Although the mechanism illustrating the role of such deep eutectic solvents in oxazole synthesis is yet to be confirmed, we suggest a mechanism predicting their probable role in synthesis (Scheme 2). It is well known that the urea component in deep eutectic solvent (choline chloride:urea) can catalyze reactions via hydrogen bond catalysis [39]. Many past reports have also investigated urea [40] based catalysts due to their effective hydrogen bonding ability. Based on these assumptions, we suggest that the urea component in deep eutectic solvent might stabilize the oxygen atom of carbonyl group via hydrogen bonding that encourages the attack of amide on phenacyl bromide derivative as well as promotes cyclization. At the same time, it is equally important to highlight the probable role of ultrasound in the mechanism. It is obvious that the use of ultrasound leads to generation of microscopic internal pressure within the cavitation bubbles. Due to this, extreme microscopic conditions are created within these bubbles such that substrates entering them are converted to highly reactive species, thereby assisting in faster cyclization and dehydration steps. Such an assumption has also been done in earlier reports wherein ultrasound is used to accelerate reactions in ionic liquids [26].

4. Conclusion

In conclusion, we have explored for the first time, a unique combination of deep eutectic solvent and ultrasonic radiation for clean and efficient synthesis of oxazole derivatives. Four novel derivatives of oxazole were synthesized in just 12–17 min by the use of ultrasound and DES as compared to conventional heating in DES that took 3–5 h. Ultrasonic irradiation also showed a significant improvement in parameters like reaction yield and percentage of conversion. Deep eutectic solvent was found to promote the reaction since no reaction was observed with conventional organic solvents. They also provide a good alternative for conventional ionic liquids owing to their simple and cost-effective preparation, bio-degradability, recyclable nature, non-toxicity. Ultrasonic synthesis (US) method also saved considerable energy (more than 85%) in the synthesis of oxazoles. To sum up, the method is convenient, economical, time and energy-saving, eco-friendly and extremely efficient.

Acknowledgements

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Appendix A.1. Energy calculations

Following sample calculation is done on the basis of data taken from Table 2 for the synthesis of **compound 3a**.

1. Energy delivered during sonication
   1a. Energy delivered during sonication = Energy required to synthesize oxazole material.
   1b. Electrical energy delivered during sonication using horn for 17 min (indicated by the power meter) = 30.70 kJ
   1c. Efficiency of Horn taken for the calculation = 30% (estimated independently using calorimetric studies)
   1d. Actual energy delivered by horn during sonication = Energy delivered during sonication using horn in 17 min × efficiency of Horn

$$= 30.70 \times 30/100$$
$$= 9.21 \text{ kJ}$$

   1e. Quantity of material processed = Quantity of phenacyl bromide + quantity of phenyl urea + quantity of DES

$$= 1(\text{g}) + 0.77(\text{g}) + 7(\text{g})$$
$$= 8.77(\text{g})$$

   1f. Net energy supplied for processing of material using sonochemical method = Actual energy delivered by horn during sonication/Total reaction mass processed

$$= 9.21(\text{kJ})/8.77(\text{g})$$
$$= 1.05(\text{kJ/g})$$

2. Energy delivered during conventional method.
   2a. Voltage input in overhead stirrer (Model REMI Motors RQ-129/D Rajendra Electrical Industries Ltd., Vasai, India.
   2b. Current measured using digital multimeter (KUSAM-MECO Model 2718, Kusam Electrical Industries Ltd., Mumbai, India) = 37 mA = 37×10^{-3} A
   2c. Power input in magnetic stirrer = Voltage input × current measured

$$= 230(\text{V}) \times 37 \times 10^{-3}(\text{A})$$
$$= 8.51 \text{ W(J/s)}$$

   2d. Efficiency of magnetic stirrer taken for the calculation = 40% (estimated independently using calorimetric studies)
   2e. Actual power input in overhead stirrer = Power input in magnetic stirrer (W) × 40/100

$$= 8.51(\text{W}) \times 40/100$$
$$= 3.404 \text{ W(J/s)}$$

   2f. Time required for completion of reaction = 5 h (18,000 s)
   2g. Energy delivered during conventional method for stirring = Power input in magnetic stirrer × time required for completion of reaction

$$= 3.404 \text{ J/s} \times 5 \text{ h} \times 3600 \text{ s/h}$$
$$= 61272 \text{ J} = 61.27 \text{ kJ}$$

   2h. Quantity of material processed = Quantity of phenacyl bromide + quantity of phenyl urea + quantity of DES

$$= 1(\text{g}) + 0.77(\text{g}) + 7(\text{g})$$
$$= 8.77(\text{g})$$

   2i. Energy supplied for heating reaction mixture to 65 °C from room temperature (35 °C)

$$= \text{Mass} \times C_P \times \Delta T$$
$$= 8.77 \times 1 \times (65 - 35) \quad (C_P \approx 1)$$
$$= 263.1 \text{ cal}$$
$$= 1096 \text{ J} \quad (1 \text{ cal} = 4.18 \text{ J})$$

   2j. Total energy supplied for heating reaction mixture to 65 °C from room temperature (35 °C)
   2k. Energy supplied for heating reaction mixture to 65 °C from room temperature

$$(35\ ^\circ\text{C}) \times 5 \text{ h} \times (1/30) \text{ h} \quad (30 \text{ min are required for cooling})$$
$$= 1096 \text{ J} \times 10$$
$$= 10960 \text{ J} = 10.96 \text{ kJ}$$

   2l. Net energy delivered during conventional method = Energy delivered during conventional method for stirring + total energy supplied for heating reaction mixture to 65 °C from room temperature (35 °C)

$$= 61.27 + 10.96$$
$$= 72.23 \text{ kJ}$$

   2m. Net energy supplied for processing of material using conventional method = Net energy delivered during conventional method/quantity of material processed

$$= 72.23(\text{kJ})/8.77(\text{g})$$
$$= 8.24(\text{kJ/g})$$

3. Percentage of energy saved (%)
   3a. Net energy saved = (Net energy supplied for processing of material using conventional method (B)) − (net energy supplied for processing of material using sonochemical method (A))/(net energy supplied for processing of material using conventional method (B)) × 100

$$= (8.24 - 1.05)/8.24 \times 100$$
$$= 87.26$$

Similarly energy efficacy calculations have been carried out for compounds **3b** – **3e** and tabulated in Table 2.

References

[1] C. George, N. Martin, R. Ray, Thiourea derivatives of 2-aminooxazoles showing antibacterial and antifungal activity, J. Med. Chem. 16 (1973) 1402–1405.
[2] C.G. Anna, I.M.B. Helena, G.F. Scott, E.B. Clifton, R.C. Brent, Antimycobacterial natural products: synthesis and preliminary biological evaluation of the oxazole-containing alkaloid texaline, Tetrahedron Lett. 46 (2005) 7355–7357.
[3] C. George, J.F. Michael, Derivatives of 2-aminooxazoles showing antiinflammatory activity, J. Med. Chem. 14 (1971) 1075–1077.
[4] I.J. Turchi, M.J.S. Dewar, Chemistry of oxazoles, Chem. Rev. 75 (1975) 389–437.
[5] H.H. Wasserman, R.J. Gambale, Synthesis of (+)-antimycin A3. Use of the oxazole ring in protecting and activating functions, J. Am. Chem. Soc. 107 (1985) 1423–1424.
[6] A. Floersheimer, M.R. Kula, The application of *N*-α-formyl amino acid esters in the enzyme-catalyzed peptide synthesis, Monatsh. Chem. 119 (1988) 1323–1331.
[7] D.C. Palmer, S. Venkatraman, Oxazoles: synthesis, reactions and spectroscopy, Part A, J. Wiley & Sons, Hoboken, NJ, 2004.
[8] I.H. Leaver, B. Milligam, Fluorescent whitening agents – a survey (1974–82), Dyes Pigm. 5 (1984) 109–144.
[9] T.R. Kelly, F. Lang, Total synthesis of dimethyl sulfomycinamate, J. Org. Chem. 61 (1996) 4623–4633.
[10] P. Wipf, J.L. Methot, Synthetic studies toward diazonamide A. A novel approach for polyoxazole synthesis, Org. Lett. 3 (2001) 1261–1264.
[11] P. Wipf, T.H. Graham, Total synthesis of (−)-disorazole C_1, J. Am. Chem. Soc. 126 (2004) 15346–15347.
[12] A. Tarraga, P. Molina, D. Curiel, M.D. Velasco, Synthesis and electrochemical study of novel oxazolo-ferrocene derivatives displaying redox-switchable character, Tetrahedron 57 (2001) 6765–6774.

[13] M. Lautens, A. Roy, Synthetic studies of the formation of oxazoles and isoxazoles from *N*-acetoacetyl derivatives: scope and limitations, Org. Lett. 2 (2000) 555–557.
[14] M. Ohba, H. Kubo, T. Fujii, H. Ishibashi, M.V. Sargent, D. Arbain, Synthesis and absolute configuration of (−)-normalindine, Tetrahedron Lett. 38 (1997) 6697–6700.
[15] J. Sisko, A.J. Kassick, M. Mellinger, J.J. Filan, A. Allen, M.A. Olsen, An investigation of imidazole and oxazole syntheses using aryl-substituted TosMIC reagents, J. Org. Chem. 65 (2000) 1516–1524.
[16] M.D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, Ruthenium- and gold-catalysed sequential reactions: a straightforward synthesis of substituted oxazoles from propargylic alcohols and amides, Chem. Commun. (2004) 2712–2713.
[17] J.C. Lee, In-Goul Song, Mercury(II) *p*-toluenesulfonate mediated synthesis of oxazoles under microwave irradiation, Tetrahedron Lett. 41 (2000) 5891–5894.
[18] H. Zang, Y. Zhang, Y. Zang, B.W. Cheng, An efficient ultrasound-promoted method for the one-pot synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives, Ultrason. Sonochem. 17 (2010) 495–499.
[19] M.R.P. Heravi, An efficient synthesis of quinolines derivatives promoted by a room temperature ionic liquid at ambient conditions under ultrasound irradiation via the tandem addition/annulation reaction of *o*-aminoaryl ketones with α-methylene ketones, Ultrason. Sonochem. 16 (2009) 361–366.
[20] K. Prasad, D.V. Pinjari, A.B. Pandit, S.T. Mhaske, Phase transformation of nanostructured titanium dioxide from anatase-to-rutile via combined ultrasound assisted sol-gel technique, Ultrason. Sonochem. 17 (2010) 409–415.
[21] R.M. Srivastava, R.A. Filho Neves, C.A. da Silva, A.J. Bortoluzzi, First ultrasound-mediated one-pot synthesis of *N*-substituted amides, Ultrason. Sonochem. 16 (2009) 737–742.
[22] A. Duarte, W. Cunico, C.M.P. Pereira, A.F.C. Flores, R.A. Freitag, G.M. Siqueira, Ultrasound promoted synthesis of thioesters from 2-mercaptobenzoxa(thia)zoles, Ultrason. Sonochem. 17 (2010) 281–283.
[23] K.J. Jarag, D.V. Pinjari, A.B. Pandit, G.S. Shankarling, Synthesis of chalcone (3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one): advantage of sonochemical method over conventional method, Ultrason. Sonochem. 18 (2011) 617–623.
[24] C. Petrier, J.-L. Luche, Synthetic Organic Sonochemistry, in: J.-L. Luche (Ed.), Plenum Press, New York, 1998, pp. 53–56. Chapter 2.
[25] B. Toukoniitty, E. Toukoniitty, P. Maki-Arvela, J.-P. Mikkola, T. Salmi, D. Murzim, P. Yu, J. Kooyman, Effect of ultrasound in enantioselective hydrogenation of 1-phenyl-1,2-propanedione: comparison of catalyst activation, solvents and supports, Ultrason. Sonochem. 13 (2006) 68–75.
[26] E. Kowsari, M. Mallakmohammadi, Ultrasound promoted synthesis of quinolines using basic ionic liquids in aqueous media as a green procedure, Ultrason. Sonochem. 18 (2011) 447–454.
[27] Atul.R. Gholap, K. Venkatesan, T. Daniel, R.J. Lahoti, K.V. Srinivasan, Ionic liquid promoted novel and efficient one pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones at ambient temperature under ultrasound irradiation, Green Chem. 6 (2004) 147–150.
[28] D. Zhao, Y. Liao, Z. Zhang, Toxicity of ionic liquids, Clean 35 (2007) 42–48.
[29] M. Smiglak, W.M. Reichert, J.D. Holbrey, J.S. Wilkes, L. Sun, J.T. Thrasher, K. Kirichenko, S. Singh, A.R. Katritzky, R.D. Rogers, Combustible ionic liquids by design: is laboratory safety another ionic liquid myth?, Chem Commun. (2006) 2554–2556.
[30] Andrew P. Abbott, Glen Capper, David L. Davies, Raymond K. Rasheed, Vasuki Tambyrajah, Novel solvent properties of choline chloride/urea mixtures, Chem. Commun. (2003) 70.
[31] A.P. Abbott, T.J. Bell, S. Handa, B. Stoddart, *O*-acetylation of cellulose and monosaccharides using a zinc based ionic liquid, Green Chem. 7 (2005) 705–707.
[32] B. Singh, H. Lobo, G. Shankarling, Selective N-alkylation of Aromatic Primary Amines Catalyzed by Bio-catalyst or deep eutectic solvent, Catal. Lett. 141 (2011) 178–182.
[33] H.R. Lobo, B.S. Singh, G.S. Shankarling, Deep eutectic mixtures and glycerol: a simple, environmentally benign and efficient catalyst/reaction media for synthesis of *N*-aryl phthalimide derivatives, Green Chem. Lett. Rev. (2012), http://dx.doi.org/10.1080/17518253.2012.669500.
[34] T.J. Mason, Practical Sonochemistry. User's Guide to Applications in Chemistry and Chemical Engineering, Ellis Horwood, Chichester, 1991.
[35] B.G. Pollet, J.Y. Hihn, T.J. Mason, Sono-electrodeposition (20 and 850 kHz) of copper in aqueous and deep eutectic solvents, Electrochimica Acta 53 (2008) 4248–4256.
[36] S.H. Kim, S.T. Yang, J. Kim, W.S. Ahn, Sonochemical synthesis of $Cu_3(BTC)_2$ in a deep eutectic mixture of choline chloride/dimethylurea bull, Korean Chem. Soc. 32 (2011) 2783–2786.
[37] J.C. Lee, Y.H. Bae, S.K. Chang, Effect of alpha-halogenation of carbonyl compounds by *N*-bromosuccinimide and *N*-chlorosuccinimide, Bull. Korean Chem. Soc. 24 (2003) 407–408.
[38] A.P. Abbott, G. Capper, D.L. Davies, H.L. Munro, R.K. Rasheed, V. Tambyrajah, Preparation of novel, moisture-stable, Lewis-acidic ionic liquids containing quaternary ammonium salts with functional side chains, Chem. Commun. (2001) 2010–2011.
[39] B.S. Singh, H.R. Lobo, G.S. Shankarling, Choline chloride based eutectic solvents: magical catalytic system for carbon–carbon bond formation in the rapid synthesis of β-hydroxy functionalized derivatives, Catal. Comm. 24 (2012) 70–74.
[40] S.J. Connon, Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts, Chem. Commun. (2008) 2499–2510.