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Sustainable and efficient synthesis of oxazolidinones using a unique deep eutectic solvent (DES)

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A quaternary diammonium salt and urea (1 : 2)-containing deep eutectic solvent (DES) is introduced as a simple and promising catalytic medium for the atom-economic synthesis of oxazolidinone compounds from epoxides and isocyanates. This DES is an economical, reclaimable, and environmentally gentle medium. In this protocol, no other supplementary catalyst or organic solvent is used since the DES plays the twofold roles of solvents and catalysts in the reaction. An extensive variety of oxazolidinone compounds were synthesized in good-to-excellent yields using this procedure. This protocol has a low *E*-factor (0.11), high atom economy (AE = 100%), excellent reaction mass efficiency (RME = 90.1%), and great process mass intensity (PMI = 1.11).

Sustainability spotlight

To develop more green and sustainable processes in organic synthesis, deep eutectic solvents (DESs) have gained increasing attention as alternatives to various metal-based catalysts and organic solvents due to their eco-friendly nature and customizable structure. In this work, we report the synthesis of a wide variety of oxazolidinone compounds using a novel deep eutectic solvent containing a quaternary diammonium salt (QDAS) and urea (1 : 2). This DES played the dual role of solvent and catalyst without using any other organic additives. Our work adheres to the UN Sustainable Development Goals, particularly SDG 9 (industry), SDG 12 (sustainable consumption and production), and SDG 13 (climate action) by reducing waste generation and implementing greener production processes.

Introduction

Developing green chemical processes has now become one of the major subjects in both academic and industrial research because it intends to protect the environment and reduce the negative impact of human involvement. Green technology promotes the minimum use of hazardous substances, some new environmentally benign techniques, and the development of novel green solvents.[1] Recently, deep eutectic solvents (DESs) have attracted increasing attention as versatile and eco-friendly alternatives to conventional toxic organic solvents.[2] DESs, first reported by Abbott and co-workers,[3] are eutectic mixtures formed by the combination of a hydrogen bond donor and acceptor. DESs offer numerous advantages, including low toxicity, biodegradability, ease of preparation, low vapor pressure, and low cost.[4–6] Due to the presence of a large hydrogen bonding network in DESs and their environmentally friendly solvent properties, interest in using DESs in various chemical synthetic processes has grown immensely among chemists. DESs have been reported to facilitate a wide range of electrochemical processes, biomass processing, polymerization and catalysis, acting as a medium/catalyst.[7–16] Specifically, a variety of DESs have been employed as reaction media/catalysts in several organic transformations, *e.g.*, Perkin reaction,[17] Mannich reaction,[18] Ugi reaction,[19] Knoevenagel condensation,[20] and many other related reactions.[21]

Oxazolidinones, an important class of heterocyclic motifs containing both nitrogen and oxygen, have great value in medicinal and pharmaceutical chemistry. Specifically, *N*-aryl-substituted oxazolidinones act as useful intermediates and protecting groups in many organic syntheses,[22,23] as chiral auxiliaries in asymmetric synthesis,[24,25] as building blocks for polymerization,[26] and as precursors for antibacterial and antimicrobial medicines.[27,28] Fig. 1 shows some representative

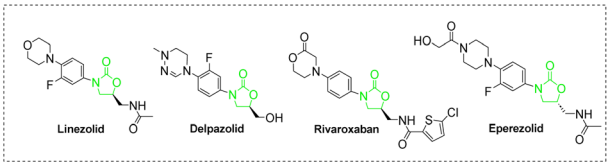

Fig. 1 Some representative examples of drugs containing the oxazolidinone scaffold.

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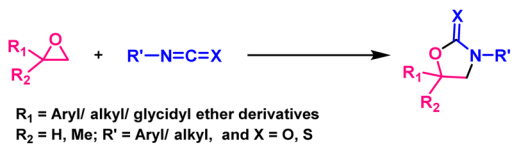
examples of drugs containing an oxazolidinone scaffold, such as linezolid and delpazolid (antibiotic agents),[29,30] rivaroxaban (blood clot treatment),[31] and eperezolid (antimicrobial agent).[32] Therefore, the synthesis of oxazolidinone compounds is significant for drug discovery.

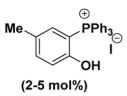
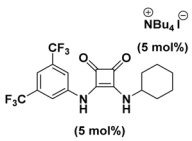
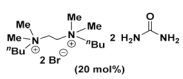
There are many reports on the synthesis of oxazolidinone compounds, such as the reaction of carbon dioxide with β-aminoalcohols or aziridines[33–36] and carbonylation of β-aminoalcohols with dialkyl carbonate.[37,38] Among these methods, one of the easiest and most atom-economic strategies is the [3 + 2] coupling reaction between epoxide and isocyanate. In 1958, Speranza and Peppel synthesized the oxazolidinone core for the first time using a tetraalkyl ammonium salt.[39] Later, several research groups prepared oxazolidinone compounds using different metal salts such as lanthanide salts,[40–42] lithium halides,[43] magnesium halides,[44] tetraphenylantimony iodide,[45,46] trialkyltin halides,[47,48] and metal complexes.[49–53] However, most of these approaches have various disadvantages such as high reaction temperature, excess catalyst loading, limited substrate scope, slow addition of isocyanates, and use of excess epoxides to reduce side reactions. Recently, numerous bifunctional organocatalysts have been employed for the synthesis of oxazolidinone derivatives (Table 1).[54–59] Rostami *et al.*[55] reported the synthesis of oxazolidinone using a binary catalytic system (squaramide/quaternary ammonium salt) at 70–100 °C for 24 h. However, the major difficulty with this protocol is the prolonged synthesis of the catalyst and harsh reaction conditions (Table 1). Further, D'Elia *et al.*[57] reported the synthesis of different oxazolidinone compounds using ascorbic acid as a hydrogen bond donor and a cocatalyst quaternary ammonium salt under reflux conditions in THF solvent for 24 h. Recently, Rostami *et al.*[59] demonstrated the synthesis of oxazolidinone under microwave irradiation using an organocatalyst; however, this process is environmentally benign, its major drawback is that the results cannot be reproduced due to the lack of exact temperature (Table 1). Therefore, it is highly desirable to design catalytic systems that are very efficient, easy to prepare, inexpensive, recyclable, and eco-friendly.

Recently, our research group demonstrated the efficient utility of choline chloride–urea (1 : 2)-based DESs playing a dual role of solvent and catalyst for the synthesis of different α-aminophosphorus derivatives and thioamide compounds.[60,61] Several analogous single-site quaternary ammonium salt-based DESs have been utilized in many chemical processes.[62,63] However, there have been no reports on the use of quaternary

Table 1 Summary of previous and current work



R_1 = Aryl/ alkyl/ glycidyl ether derivatives
R_2 = H, Me; R' = Aryl/ alkyl, and X = O, S

S. no.	X	Catalyst	Reaction conditions	Solvent	Avg. yield (%)	Ref.
1	O	 (2-5 mol%)	100 °C, 6–24 h	PhCl	49–97	54
2[a]	O	 (5 mol%)	70–100 °C, 24 h	Neat	44–95	55
3	O	Et_3N—H I (10 mol%)	100 °C, 1 h	Neat	56–99	56
4[a]	O	Ascorbic acid (4 mol%)/ NBu_4I (8 mol%)	Reflux, 24 h	THF	52–93	57
5	O	(5 mol%)	Microwave, 100 °C, 20–60 min	Neat	54–96	59
6	O, S	 (20 mol%)	85 °C, 4 h	Neat	81–90	[b]Current work

[a] Hydrogen donors such as squaramide and ascorbic acid were added separately, along with an organocatalyst *i.e.* tetrabutyl ammonium salt. [b] Novel and ecofriendly recyclable DES; DES in dual role (medium and catalyst); mild reaction conditions; metal and toxic organic solvent free; high yields; broad substrate scope.

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diammonium salt (QDAS)-based DESs to date. We anticipate that the presence of twofold ionic centers in diammonium salts can establish a cooperative environment where both sites can participate in hydrogen bond interactions with HBDs.[64] These enhanced interactions can stabilize the transition states and intermediates during catalytic reactions, potentially lowering the activation energies and increasing the reaction rates.[14,16] Consequently, we were keenly interested in developing a quaternary diammonium salt-based DES and investigating its catalytic efficiency in synthesizing pharmaceutically important oxazolidinone compounds *via* the 100% atom-economic [3 + 2] coupling reaction between epoxides and isocyanates.

Herein, we report the synthesis and spectroscopic characterization of a novel metal-free DES comprised of a quaternary diammonium salt [{$CH_2N(Me)_2$(*n*-Bu)}$_2Br_2$] (QDAS) and urea in 1 : 2 molar ratio (henceforth represented as QDAS–urea (1 : 2)) and its utilization in synthesizing different oxazolidinone compounds. Our approach provides sustainability given that no toxic solvent or cocatalyst is used for the reaction, reagents are used in stoichiometric amounts and the DES is recyclable and plays the dual role of medium and catalyst. We also described the wide substrate scope of this DES for different cyclic ethers and isocyanates/isothiocyanates (up to 22 examples) and investigated mechanistic insights into this reaction. Further, we evaluated the reusability of DES and calculated the green chemistry metrics to prove the greenness of this methodology. To the best of our knowledge, this is the first report on the synthesis and spectroscopic structural characterization of QDAS and urea-based DESs and their application in the synthesis of oxazolidinone compounds.

Results and discussion

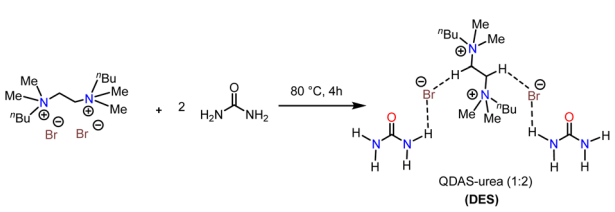
In this study, we describe a convenient and green methodology for the synthesis of oxazolidinone compounds *via* a one-pot multicomponent approach by utilizing a newly synthesized DES in a dual role (as a medium and catalyst) without the addition of any further catalyst or organic solvent.

Synthesis and characterization of DESs

The DES, QDAS–urea (1 : 2), was synthesized by heating a mixture of quaternary diammonium salt [{$CH_2N(Me)_2$(*n*-Bu)}$_2Br_2$][65] and urea in a 1 : 2 molar ratio at 80 °C for 4 h (Scheme 1). The synthesized DES is a brownish solid at room temperature, while becoming a liquid at 79.8 °C. Two other basic eutectic solvents were also prepared using QDAS and urea in 1 : 1 and 1 : 4 molar ratios following a similar methodology.

A comparative ATR-FTIR study of the synthesized DESs and pure urea established the hydrogen-bonded structural features of the DESs. The FTIR spectra of three DESs and pure urea are shown in Fig. 2, and the characteristic absorption frequencies (cm^{-1}) observed for pure urea and deep eutectic solvents of QDAS–urea in various molar ratios are summarized in Table 2. The ATR-FTIR spectrum of the QDAS–urea (1 : 2) DES exhibits a shift in its absorption peaks due to the N–H bond stretching (both out of phase and in phase) vibrations towards a lower frequency region compared to that of pure urea. Also, the absorption peaks due to C=O stretching, N–H bending, and C–N stretching vibrations shifted towards higher frequencies compared to that of pure urea (Table 2).[62,63,66,67] These considerable changes in the above-mentioned absorption frequencies for DES compared to urea support the presence of hydrogen bonding interactions between the bromide ion of QDAS and the N–H proton of urea in DES. Similar features were also observed in the FTIR of two other eutectic solvents of QDAS and urea in 1 : 1 and 1 : 4 molar ratios.

To further confirm the interactions between QDAS and urea in the DESs, their structures were characterized using ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The ^1H NMR spectrum of each DES (Fig. 3a–c) shows seven unique resonance signals, among which the characteristic peak in the range of 5.48–5.55 (s, 4H for QDAS : urea (1 : 1); 8H for QDAS : urea (1 : 2); 16H for QDAS : urea (1 : 4)) corresponds to the $-NH_2$ protons of the urea component and the six characteristic resonance signals in the range of 3.99–4.01 (s, 4H, $-N(CH_2)_2N-$), 3.39–3.43 (t, 4H, $-NCH_2(CH_2)_2CH_3$), 3.18–3.19 (s, 12H, $-NCH_3$), 1.75–1.67 (m, 4H, $-NCH_2CH_2CH_2CH_3$), 1.32–1.26 (m, 4H, $-N(CH_2)_2CH_2CH_3$) and 0.94–0.93 (t, 6H, $-N(CH_2)_3CH_3$) ppm correspond to the QDAS component of DES.[57] The $^{13}C\{^1H\}$ NMR data and spectra (Fig. S1–S3) are provided in the SI. The formation of eutectic



Scheme 1 Synthesis of the DES using QDAS salt and urea in a 1 : 2 molar ratio.

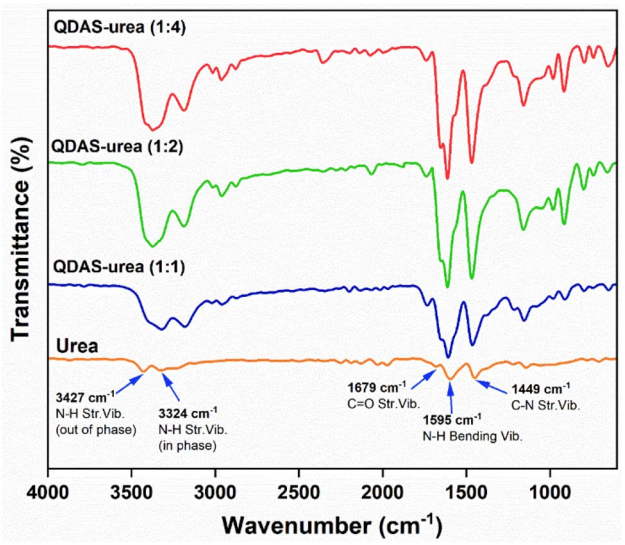


Fig. 2 ATR-FTIR spectra of the DESs composed of QADS and urea in different molar ratios and pure urea.

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Table 2 Characteristic FTIR frequencies (cm^{-1}) observed for pure urea and the DESs composed of QDAS and urea in different molar ratios

Mode (cm^{-1})	Urea	QDAS–urea (1 : 1)	QDAS–urea (1 : 2)	QDAS–urea (1 : 4)
N–H stretch (out of phase)	3427	3373	3373	3318
N–H stretch (in phase)	3324	3187	3186	3180
C=O stretch	1679	1733	1734	1738
N–H bending	1595	1608	1608	1612
C–N stretching	1449	1463	1463	1467

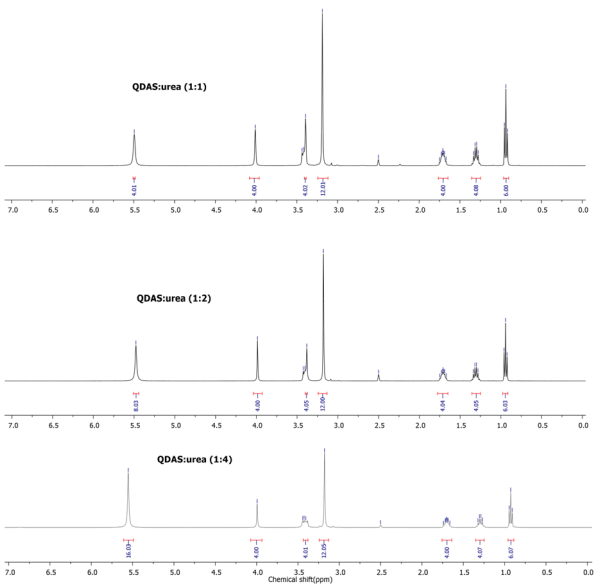

Fig. 3 ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) spectra of the DESs composed of QADS and urea in different molar ratios.

solvents was also supported by differential scanning calorimetry (DSC). It was observed that the melting temperature of the QDAS–urea (1 : 2) DES is much lower (T_m = 79.83 °C) than that of its individual components, *i.e.* quaternary diammonium salt (T_m = 103.98 °C) and urea (T_m = 135.21 °C) (see SI, Fig. S5). The decrease in the melting temperature of DES may be due to the charge delocalization occurring through the hydrogen bond interaction between the bromide ion of QDAS and the N–H proton of urea.[63,68] The melting points of two other eutectic mixtures of QDAS and urea in 1 : 1 and 1 : 4 molar ratios were found to be 100.94 °C and 77.34 °C (see the SI, Fig. S4 and S6), respectively. The deep eutectic mixtures were used for the catalytic reaction without any further purification. This method is 100% atom-economic given that the formation of side products was not observed.

Catalytic study

Initially, we selected epichlorohydrin and 4-methoxyphenyl isocyanate as model reactants for the screening of the [3 + 2] coupling reaction. Firstly, the coupling reaction between epichlorohydrin and 4-methoxyphenyl isocyanate in a 1 : 1 molar ratio was performed in 20 mol% of QDAS–urea (1 : 2) DES with constant stirring at 85 °C for four hours. The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature, and then diluted with water and ethyl acetate. The corresponding oxazolidinone compound was isolated in 90% yield (Table 3, entry 3). The DES was recovered easily by evaporating the water under vacuum.

To determine the role of the DES, the same reaction was performed with no DES at room temperature and 85 °C for 24 h. No product formation was observed in both cases (Table 3, entries 1 and 2), respectively. These results justify the role of the DES as a catalyst as well as the medium in the given reaction. The unique hydrogen-bonding network and high polarity of DES accelerate the reactivity of the reactants and stabilize the reactive intermediates or transition states in the catalytic reactions.[16] We further investigated the influence of the DES of QDAS and urea in different molar ratios (1 : 1 and 1 : 4) on the yield of the products under similar reaction conditions.

The corresponding product was obtained in a yield of 40% and 90% in the presence of the DES containing QDAS–urea in 1 : 1 and 1 : 4 molar ratios (Table 3, entries 4 and 5), respectively. Given that the QDAS–urea (1 : 1) DES remained solid even at 85 °C, the mass transfer of reactants was difficult, thereby affording a low yield. The catalytic activity of the other DESs such as ChCl–urea (1 : 2), ChCl–oxalic acid (1 : 1), and ChCl-pTSA (1 : 1) towards the same coupling reaction was also tested. It was observed that the ChCl–urea (1 : 2) DES gave the product in the yield of only 10% (Table 3, entry 6), which may be due to the lower nucleophilicity of the chloride ion.[55] Alternatively, no product formation was noted in the presence of the ChCl–oxalic acid (1 : 1) and ChCl-*p*TSA (1 : 1) DESs (Table 3, entries 7 and 8),[4,69] respectively, which is probably because isocyanate could not react with epoxide in an acidic medium. Thus, these results confirmed that this reaction is favored in a basic medium.

After the selection of the DES, we optimized the coupling reaction conditions by changing several other parameters such as temperature, reaction time, and loading of DES. Firstly, to examine the effect of temperature on this reaction, the coupling reaction was performed for four hours at room temperature, and then at elevated temperatures, *i.e.* 70 °C, 85 °C, and 100 °C, respectively. We observed no product formation at room temperature and low yield (only 55%) of product at a reaction time from 4 h to 2 h, where a considerable decrease in the product yield was observed. However, when the reaction time was increased from 4 h to 10 h, no appreciable change in the product yield was detected (Table 3, entries 3, 11, and 12),

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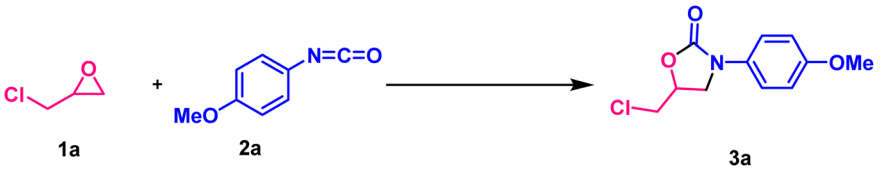
Table 3 Optimization of the reaction conditions for the coupling reaction between epichlorohydrin and 4-methoxyphenyl isocyanate[a]



S. no.	1a (equiv.)	2a (equiv.)	DES	DES (mol%)	t (h)	T (°C)	Yield[a] (%)
1	1	1	—	—	24	rt	—
2	1	1	—	—	24	85	—
3	1	1	QDAS–urea (1 : 2)	20	4	85	90
4	1	1	QDAS–urea (1 : 1)	20	4	85	40
5	1	1	QDAS–urea (1 : 4)	20	4	85	90
6	1	1	ChCl–urea (1 : 2)	20	4	85	10
7	1	1	ChCl–OA* (1 : 1)	20	4	85	—
8	1	1	ChCl–*p*TSA* (1 : 1)	20	4	85	—
9	1	1	QDAS–urea (1 : 2)	20	24	70	55
10	1	1	QDAS–urea (1 : 2)	20	4	100	90
11	1	1	QDAS–urea (1 : 2)	20	2	85	72
12	1	1	QDAS–urea (1 : 2)	20	10	85	90
13	1	1	QDAS–urea (1 : 2)	15	4	85	69
14	1	1	QDAS–urea (1 : 2)	25	4	85	90
15	1	1	QDAS only	20	24	85	—

[a] Isolated yield. *OA-oxalic acid; and *p*TSA-*p*-toluene sulfonic acid.

respectively. The loading of DES was also varied, and it was found that 20 mol% of DES gave the best result (Table 3, entries 13 and 14). Further, the coupling reaction was also performed in the presence of only QDAS salt under similar conditions, and no product formation was noted (Table 3, entry 15). These results prove the role of the hydrogen-bonding network of DES in the catalytic coupling reaction of epoxides and isocyanates.

After the optimization of the reaction conditions, the substrate scope of this QDAS–urea (1 : 2) DES-catalyzed protocol was explored using a variety of epoxides and isocyanates as substrates. All the reactions were performed with an epoxide or glycidyl ether (1.08 mmol) and isocyanate or isothiocyanate (1.08 mmol) in 20 mol% of QDAS–urea (1 : 2) DES at a temperature of 85 °C for four hours without using any toxic organic solvent. After completion of each reaction, the targeted oxazolidinone compounds were isolated and characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy (see Fig. S7–S51 in the SI). The substrate scope is summarized in Table 2.

We observed that aliphatic epoxide containing both electron-donating and electron-withdrawing groups worked well and was converted to the corresponding products in good yields (Table 4, **3a–3i**). Next, we examined the reaction by reacting different aromatic epoxides with isocyanate compounds and isolated the corresponding 3,5-oxazolidinone products in good to excellent yields (~82–89%) (Table 4, **3j–3o**).

Similarly, various aryl isocyanates such as *o*/*p*-phenyl, *p*-methoxyphenyl, and *p*-chlorophenyl isocyanates were also screened to check the generality of this protocol and it was observed that all the isocyanates worked efficiently and afforded the corresponding products in high yield (82–89%). Also, when isothiocyanate was employed, the corresponding products were obtained in good yield (81–85%) (Table 4, **3p–3r**). In addition, we achieved a good yield of products for epoxides and isocyanates substituted with an electron-withdrawing group, chlorophenyl (Table 4, **3c** and **3o**), respectively. These results demonstrate that our protocol provided a highly efficient, easy, and green method for the synthesis of a wide variety of corresponding oxazolidinone compounds.

Motivated by the above-mentioned results, we set to examine the scope of the QDAS–urea (1 : 2) DES catalyzed oxazolidinones synthesis using a variety of glycidyl derivatives given that these glycidyl compounds are readily available from renewable resources.

Under the given optimized conditions, various glycidyl derivatives were treated with several aryl isocyanates such as *p*-chlorophenyl, *p*-methoxyphenyl, and *p*-tolyl isocyanates and the respective oxazolidinones (Table 5, **4a–4d**) were obtain in good yield (85–87%).

The reusability of any solvent or catalyst is an important aspect in organic transformations given that it not only makes them useful for commercial applications but also from a green chemistry point of view.[70] In the DES reusability test, we performed the coupling reaction between epichlorohydrin and 4-methoxyphenyl isocyanate in DES under the optimized conditions (at 85 °C temperature for four hours). After completion of the reaction, DES was recovered from the water phase by evaporation at 85 °C under reduced pressure. The recovered DES was dried for three hours at 70 °C under reduced pressure

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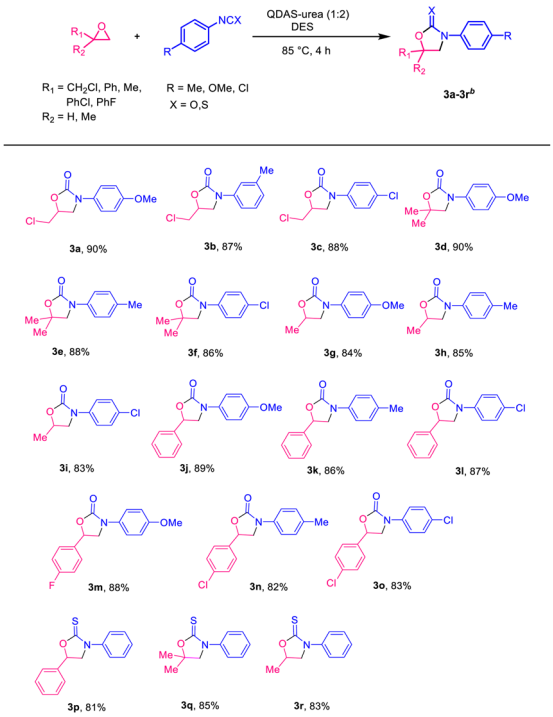
Table 4 Substrate scope of the DES with different epoxides and isocyanates for the synthesis of oxazolidinone compounds[a,b]



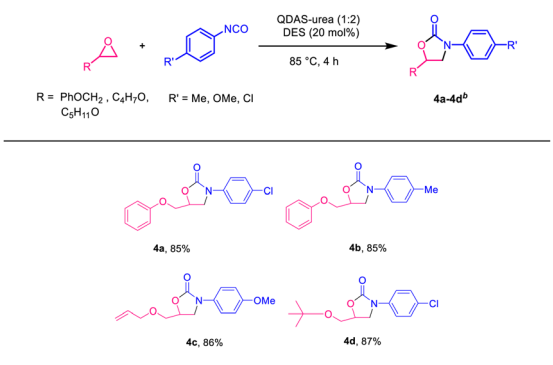
[a] Reaction conditions: epoxide (1.08 mmol) and isocyanate (1.08 mmol) in 20 mol% DES QDAS–urea (1 : 2) at 85 °C for 4 h. [b] Isolated yields.

to remove any traces of water and subjected to the next run with the same reactants without adding further DES. Delightfully, we could reuse the DES for four successive reactions with negligible loss in the product yield (Fig. 4).

We also examined the industrial applicability of this methodology by performing a gram-scale reaction between 5 g of epichlorohydrin and 8.1 g of 4-methoxyphenyl isocyanate in QDAS–urea (1 : 2) DES (20 mol%) under solvent-free conditions with constant stirring at 85 °C for four hours, and the corresponding oxazolidinone compound was obtained with a yield of 88% (11.5 g). These results exhibit the efficacy of the QDAS–urea (1 : 2) DES for the industrially scalable, eco-friendly synthesis of a variety of medicinally important oxazolidinone derivatives.

For an ideal green reaction, high atom economy, low *E*-factor value, and high process mass intensity are very important.[71] Therefore, we also assessed green chemistry metrics for our protocol to illustrate its environment-friendly nature under the optimized reaction conditions and found that our reaction has a small *E*-factor value (0.11), high atom economy (AE = 100%), high reaction mass efficiency value (RME = 90.1%), and high process mass intensity (PMI = 1.11) (see the SI for the calculation of the green metrics). Further, this reaction does not use

Table 5 Substrate scope of the DES with different glycidyl ethers and aryl isocyanates for the synthesis of oxazolidinone compounds[a,b]



[a] Reaction conditions: glycidyl ether (1.08 mmol) and isocyanate (1.08 mmol) in 20 mol% DES QDAS–urea (1 : 2) at 85 °C for 4 h. [b] Isolated yields.

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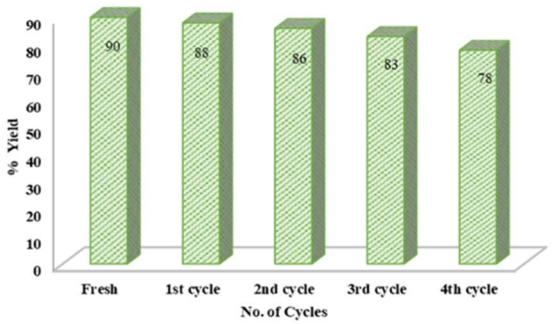


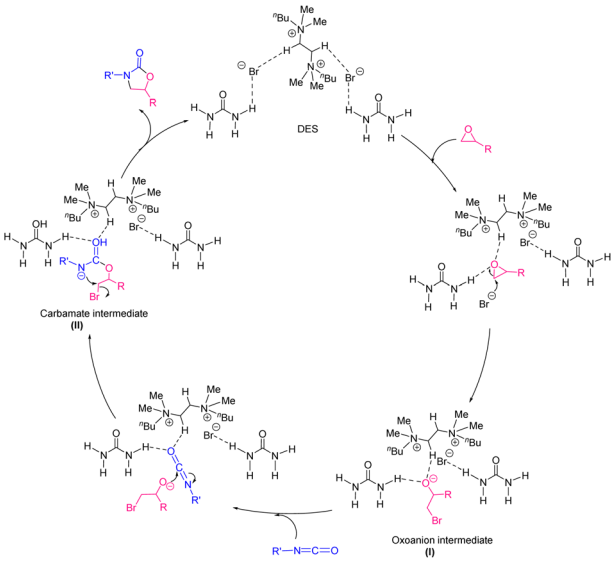
Fig. 4 Recyclability test of the DES.

any toxic solvents or expensive reagents, and no byproduct formation occurs. Thus, the green chemistry metric values demonstrate the eco-friendly nature of the present protocol. We also compared our green chemistry metric parameters with reported protocols. For this purpose, we calculated the green metric parameters for previously reported procedures[49–52,54] by following the procedure previously reported in the literature.[66] All the results are summarized in Table 6 (please see the SI for detailed calculation). It can be observed that green chemistry metrics such as the *E*-factor and PMI values are better in our case than the reported methods. Although in the case of ref. 54, its green metric values are very good, the main problem with its methodology is the use of microwave irradiation, and consequently the results are not reproducible.

To gain insights into the mechanism of this [3 + 2] cycloaddition reaction, we performed one control experiment with the optimized reaction. At first, epichlorohydrin was mixed with DES in a stoichiometric ratio and kept stirring at 85 °C for four hours. The mixture was analyzed by ^{1}H NMR spectroscopy (see SI, Fig. S52). We observed a slight downfield shift in the NMR signals due to NH protons (δ_H 5.77 ppm) and ethylene protons (δ_H 4.04 ppm) compared to that of pure DES (δ_H 5.48 ppm for NH proton and δ_H 3.99 ppm for N–CH_2 protons), respectively. This may be due to the hydrogen bonding interactions of the NH proton (from urea) and N–CH_2 protons (from salt) of DES with the oxygen atom of epoxide. Upon the addition of epoxide, the hydrogen bonds between Br^- and urea in DES were weakened, and new hydrogen bonds were formed between epoxide and DES. These hydrogen bond interactions enhanced the nucleophilic attack ability of Br^- to the epoxide and promoted the ring opening of the epoxide.

Based on our investigation and previous reports,[54,59,72] we proposed the plausible reaction mechanism for the [3 + 2] cycloaddition reaction catalyzed by the QDAS–urea DES (Scheme 2). Initially, the epoxide is activated *via* the hydrogen bond interactions of the NH (from urea) and N–CH_2 (from QDAS) the protons of DES with the oxygen atom of epoxide, and then simultaneous nucleophilic attack of Br^- occurs at the less sterically hindered β-C atom of the epoxide, which results in the ring opening of epoxide and the formation of an oxoanion intermediate (I). Subsequently, the inclusion of isocyanate occurs in the system and a carbamate intermediate (II) is formed by nucleophilic attack of oxoanion on the electrophilic carbon of isocyanate. The electrophilicity of the carbonyl carbon of isocyanate is increased through the hydrogen bond interaction of its carbonyl oxygen with DES. Finally, the oxazolidinone compound is formed *via* intramolecular ring closure of the carbamate intermediate (II) and the DES is regenerated.

To exhibit the further applicability of this cycloaddition reaction, we synthesized toloxatone from **3b** in a two-step process according to the previous literature, as shown in Scheme 3.[54] Toloxatone is an antidepressant drug that acts as a selective and reversible inhibitor of the depressant monoamine oxidase-A (MOA).[73] In the first step, oxazolidinone compound **3b** was treated with KOAc in DMF at 90 °C for 24 h.



Scheme 2 Plausible mechanism for the QDAS–urea (1 : 2) DES-catalyzed cycloaddition of the epoxide and isocyanate.

Table 6 Comparison of green chemistry metric parameters of the current study with previous studies

No.	*E*-factor	Atom economy (AE)	Atom efficiency	Carbon efficiency	PMI	RME
Ref. 49	493.9	100%	94%	100%	494.9	83.3%
Ref. 50	0.14	100%	88%	100%	1.14	88%
Ref. 51	0.2	100%	86%	100%	1.2	82.3%
Ref. 52	7.1	100%	90%	100%	8.1	90%
Ref. 54	0.05	100%	95%	100%	1.05	95%

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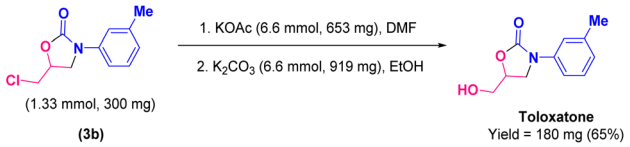

Scheme 3 Synthesis of toloxatone from the oxazolidinone **3b**.

Thereafter, the corresponding intermediate product was extracted with diethyl ether and treated with K_2CO_3 in EtOH at 0 °C for four hours with constant stirring. Finally, the respective toloxatone compound was isolated in a yield of 65% and characterized using ^{1}H and ^{13}C{^{1}H} NMR spectroscopy (see SI, Fig. S53 and S54), respectively.

Comparison with previously reported organocatalysts

Various organocatalysts have been reported in the literature for the synthesis of oxazolidinone compounds from epoxide/ether and isocyanate. Toda *et al.*[54] demonstrated the use of tetra-arylphosphonium salt as a catalyst to perform the [3 + 2] coupling reaction for the synthesis of oxazolidinone in the presence of chlorobenzene as a base, which has a TOF value of 2 h^{-1} in 24 h at 100 °C. However, both the catalyst tetra-arylphosphonium salts and co-catalyst chlorobenzene are well known to have a high toxicity profile. Rostami *et al.*[55] described the synthesis of oxazolidinone using a binary catalyst (squaramide/quaternary ammonium salt), which had a TOF value of 0.4 h^{-1} in 24 h at 70 °C. However, the synthesis of the binary catalyst (squaramide/quaternary ammonium salt) used involves a multistep procedure and is quite tedious. An ionic liquid triethylamine hydroiodide was also reported by Shirakawa and coworkers as an efficient catalyst for the cycloaddition reaction between ether and isocyanate with a TOF value of 9 h^{-1} in 1 h at 100 °C.[56] D'Elia *et al.* employed an ascorbic acid-containing organocatalyst for the synthesis of oxazolidinone using THF as the solvent, which had a TOF of 0.3 h^{-1} in 24 h at 67 °C.[57] This methodology involves the use of a toxic organic solvent and long reaction time, which can contribute to environmental pollution, increased costs associated with waste disposal, and higher energy consumption. The catalytic efficiency of a hydroxy group-containing bifunctional organocatalyst was also examined under microwave irradiation by Rostami *et al.*[59] However, in this case, although a higher TOF value of 58 h^{-1} was achieved within 20 min, the results might not be reproducible due to the lack of exact temperature. Additionally, none of the above-mentioned studies showed the reusability of the organocatalysts, which is one of the important features in the context of sustainability. Alternatively, in the present study, we achieved a TOF value of 1 h^{-1} at 85 °C in four hours without using any toxic volatile organic solvent in a deep eutectic solvent containing QDAS and urea (1 : 2) as the catalyst/medium, which is easy to prepare, recyclable, and inexpensive. It demonstrates excellent efficiency with a wide substrate scope and contributes to the sustainable advancement of the oxazolidinone synthesis methodology.

Conclusions

In this study, we demonstrated the synthesis and characterization of a novel DES, QDAS–urea (1 : 2), and its utility as a green, efficient, and reusable catalyst/medium for the synthesis of different oxazolidinone derivatives *via* the cycloaddition reaction of epoxide and isocyanate. In this reaction, DES played the dual role of solvent and catalyst. This metal and toxic organic solvent-free medium helped in halide nucleophilic-induced ring-opening of epoxide, followed by isocyanate insertion in a cooperative manner to produce oxazolidinone compounds without the slow addition of isocyanates or excess amount of epoxides. In addition, simple operational methods, short reaction time, broad substrate scope, high yield of products, and low cost make this process an important addition to the existing methods of oxazolidinone synthesis. The green metric parameters such as high atom economy and small *E*-factor values for the optimized cycloaddition reaction further support its eco-friendly nature. A gram-scale reaction was also performed to show the industrial applicability of this DES. The importance of oxazolidinone compounds was also emphasized by synthesizing an antidepressant drug molecule. To the best of our knowledge, this is the first report on the synthesis of oxazolidinone using a recyclable and quaternary diammonium salt-based DES.

Author contributions

Susmita Mandal: conceptualization, data curation, formal analysis, methodology, software, validation, and writing (original draft). Shiva Lall Sunar: conceptualization and investigation. Archana Jain: conceptualization, data curation, project administration, writing – review and editing. Tarun K. Panda: conceptualization, funding acquisition, investigation, project administration, resources, supervision, and writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the findings of this study are available in the SI.

General procedure for synthesis of DESs, General procedure for [3 + 2] coupling reactions, ^{1}H NMR, and ^{13}C{^{1}H} NMR spectra of oxazolidinone compounds (**3a–3r**) and (**4a–4d**), toloxatone compounds, DSC curves of DESs are given in SI. See DOI: **https://doi.org/10.1039/d5su00147a**.

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