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Efficient Novel Eutectic-Mixture-Mediated Synthesis of Benzoxazole-linked Pyrrolidin-2-one Heterocycles

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Abstract

In this study, new benzoxazole-linked pyrrolidinone heterocyclic compounds were synthesized by an eco-efficient strategy using substituted benzylamines and 2-aminophenol under ultrasonic irradiation in the presence of a newly designed metal-free deep eutectic solvent (DES). This DES was prepared by using a eutectic mixture of urea and a synthesized glycine-derived ionic liquid. X-ray diffraction and infrared spectroscopy were employed to investigate the structure of the ionic liquid and characterize the DES, respectively.

This method exhibited key advantages of high productivity, a short reaction time, and simple processing. Moreover, this DES was easily separated from reaction mixtures and can be recycled for multiple reactions.

Keywords: pyrrolidinone, benzoxazole moiety, ionic liquid, eutectic mixture, glycine derivative.

1. Introduction

The last two decades has witnessed a rapid increase in the applications of deep eutectic solvents (DESs) as a green alternative to standard organic solvents and ionic liquids (IL). Historically, DESs are prepared by the simple mixing of hydrogen bond acceptors (HBAs); generally, a quaternary ammonium salt, e.g., choline chloride (ChCl). ChCl is typically used, in addition to hydrogen-bond donor (HBD) molecules such as amines, amides, alcohols, carboxylic acids, and metal salts, etc. to form a eutectic mixture linked via hydrogen-bond interactions, which is characterized by a melting point less than those of its individual precursor components [1,2]. Conceptually, the interactions between HBDs and salts disturb the electrostatic forces between anions and cations, leading to the decrease in the freezing point of the mixture [3].

DESs are typically used as an environmentally-benign reaction medium in organic chemistry as an alternative to standard organic solvents or IL. In addition, they have been utilized in a wide range of applications, including polymer synthesis, metal electrodeposition and electropolishing [4,5], as well as for the growth of nanomaterials with well-controlled shapes and dimensions. Additional applications span the solubility of biomaterials such as chitin or cellulose as well as extraction and separation, such as the separation of phenol compounds from oils [6-12].

Recently, diverse approaches based on the use of cost-effective, renewable and abundant raw precursor materials have been developed to synthesize new natural-based DESs with characteristics of biocompatibility, biodegradability and low toxicity, as well as facile preparation and purification. Among the DESs, urea-based DESs are attracting immense interest. The large-scale production of DESs was previously performed by mixing urea and ChCl [2,13,14].

Versatile 2-pyrrolidinone derivatives are found in different bioactive natural products. Owing to their outstanding pharmaceutical features, they have aroused substantial importance due to their wide applications in medicinal chemistry [15]. These scaffolds exhibit antibacterial [16], antimicrobial [17], anti-inflammatory [18], analgesic [19], anticancer [20] and anticonvulsant activities [21], as well as HIV-1 inhibitors [22]. Therefore, numerous synthetic protocols and reactions have been reported for the preparation of pyrrolidinone derivatives [23-31].

Similarly, benzoxazole derivatives also have aroused immense interest in the scientific community due to their biological and pharmacological activities [32,33]. In fact, they have been recognised to exhibit prominent antitumour [34], anticancer [35], antiviral [36] and antimicrobial

[37,38] activities. Moreover, they have been utilized in several fields, including the plastic [39], textile [40], and dye [41] industries.

Within the framework of our research program to access bio-active heterocyclic scaffolds [42,43], particularly by the development of new green strategies [44-47], new 2-pyrrolidinones linked to the benzoxazole moiety were synthesized using a urea-based DES under ultrasonic irradiation to access new derivatives in this study (Scheme 1). Despite this interest, to the best of our knowledge, this synthesized DES has never been examined.

Scheme 1. Synthesis of substituted pyrrolidinone linked to benzoxazole.

2. Experimental Section

2.1. General remarks

All chemicals purchased from Sigma-Aldrich were used without any further purification. Melting points of the prepared derivatives were recorded in open capillaries using a melting

point apparatus (Sanyo Gallenkamp, South Borough, UK). Pre-coated silica gel TLC plates (0.25-mm silica gel, 60G F254, Merck, Germany) were employed for TLC experiments. The mobile-phase system used for developing TLC plates comprised a mixture of n-hexane:EtOAc (80:20 v/v). Fourier transform infrared (FTIR) spectra were recorded on a Thermo Scientific Nicolet iS50 FTIR spectrometer. Viscosity was measured using an Ostwald viscometer. The total number of protons and carbons as well the environment were elucidated by recording ^1H NMR spectra on an NMR instrument BRUKER PLUS (400 MHz). A Biotage Initiator microwave reactor and an UP200Ht ultrasonic processor with a frequency of 20 kHz were used for the experiments.

2.2. Synthesis of carboxymethanamonium chloride (CMAC)

The target compound was prepared as follows: 2-Aminoacetic acid (0.0133 mol, 1 g) was dissolved in distilled water and protonated by the dropwise addition of 1.14 mL of hydrochloric acid. The mixture was magnetically stirred at 80 °C for 60 min. The resulting solution was allowed to spontaneously evaporate at room temperature. Transparent rod-like structures with suitable dimensions for crystallographic investigation were formed. The structure of the as-prepared compound was theoretically solved, and its formula was estimated to be $\text{C}_2\text{NO}_2\text{H}_6\text{Cl}$.

2.3. General preparation procedure for DES

First, a mixture of CMAC (1 mmol) and urea (3.5 mmol) was ground in a mortar, followed by heating at 80 °C for 15 min. Finally, it was kept in an airtight container until further use. The mixture was visibly a fluid at room temperature.

2.4. General synthetic procedure for derivatives 3 and 5

2.4.1. General methods to access derivative type 3

First, a mixture of substituted arylamine (15 mmol) and an equimolar amount of dimethyl itaconate (15 mmol) was irradiated by microwaves in the presence of water as a solvent. Second, after 20 min of irradiation, ice was added to the mixture. The obtained solid was filtered and then washed with ethanol to obtain pure derivative type 3.

2.4.2. General synthetic procedure for derivatives type 5

First, a mixture of methyl-1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylate (1 mmol) and 2-aminophenol (1 mmol) in DES (1 g) was irradiated for an appropriate time. Second, the reaction mixture was cooled to room temperature. Next, the mixture was poured in a beaker containing 50 mL of water and stirred for 10 min, and the crude product was filtered. Finally, the compounds were further purified over a chromatography column using n-hexane:EtOAc (80:20 v/v) as the eluent

2.5. Theoretical study

Geometry optimization of the reactants **3** and **4** in the absence and presence of DES was performed by density functional theory (DFT) at the B3LYP/6-31++G(d,p) level of theory as implemented in the Gaussian 16 software [48]. Frequency calculations performed at the same level of theory confirmed that the optimized geometries are true minima. The effect of DES on the reactivity was investigated by determining the electronic energies and probable hydrogen bonds that may form between the reactants and DES.

3. Results and discussion

3.1. X-ray diffraction analysis of CMAC

Table 1 summarizes the collected crystal data processed at room temperature and structure refinement. Data were collected on a Nonius Kappa CCD diffractometer with a molybdenum anticathode. The ϕ and ω scan modes were adopted, with a crystal-detector distance of 35 mm. The value of its mosaicity degree was 1.48°. The DENZO-SMN program was utilized to reduce data. The SIR 97 program permitted the structural hypothesis [48], which was refined by full-matrix least-squares methods based on F^2 with the SHELX 97 program [49]. Hydrogen atoms were located theoretically and refined isotropically. All these programs were used within the WINGX package [50]. The MERCURY [51] software was used for all graphics. Crystallographic data were deposited in the Cambridge Crystallographic Data Centre CCDC No. CCDC2012265 and can also be acquired freely at www.ccdc.cam.ac.uk/data_request/cif.

Table 1

Crystallographic data for CMAC

Empirical formula	C ₂ H ₆ Cl N O ₂
Formula weight	111.53
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 7.146(5) Å b = 5.238(5) Å c = 13.739(5) Å β = 97.357(5)°.
Volume	510.0(6) Å ³
Z	4
Density (calculated)	1.452 Mg/m ³
Absorption coefficient	0.619 mm ⁻¹
F(000)	232
Crystal size	0.12x0.05x0.05 mm ³
Theta range for data collection	2.990 to 26.351°.
Index ranges	-8 ≤ h ≤ 8, -6 ≤ k ≤ 6, -17 ≤ l ≤ 17
Reflections collected	2626
Independent reflections	1021 [R(int) = 0.0326]
Completeness to theta = 25.240°	98.3 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1021 / 0 / 55
Goodness-of-fit on F ²	1.075
Final R indices [I > 2σ(I)]	R1 = 0.0369, wR2 = 0.1049
R indices (all data)	R1 = 0.0468, wR2 = 0.1095
Largest diff. peak and hole	0.219 and -0.252 e. Å ⁻³

3.2. Crystal structure

The compound crystallized in the monoclinic system with the P 21/c space group, with unit cell parameters $a = 7.146(5)$ Å, $b = 5.238(5)$ Å, $c = 13.739(5)$ Å, $\beta = 97.357(5)^\circ$, volume $510.0(6)$ Å³ and $Z = 4$ (**Table 1**). The asymmetric unit included one chloride anion and one protonated cation of 2-aminoacetic acid (Fig. 1A). Cohesion was ensured by hydrogen bonds between the ⁺NH₃-CH₂-COOH cationic group and the chloride anion Cl⁻ via N-H...Cl, OH...Cl and C=O...H-N hydrogen-bond interactions. Indeed, hydrogen-bond distances were $d_{\text{NH}\dots\text{Cl}} = 2.317$ Å for N-H...Cl, $d_{\text{OH}\dots\text{Cl}} = 2.193$ Å for OH...Cl and $d_{\text{C=O}\dots\text{HN}} = 3.003$ Å for C=O...Cl. A three-dimensional framework was formed as a result of the H-bonding network. The structure also can be described as an alternation of anionic and cationic layers along the a axis (Fig. 1B).

Fig. 1. (A) Asymmetric unit of CMAC (B) Crystal packing of the titled compound projected onto the b axis. Dashed lines represent N-H...Cl, C-OH...Cl and C=O...H-N hydrogen bonds.

3.3. Infrared analysis of CMAC/urea deep eutectic solvent

Fig. 2 shows the Fourier transform infrared (FTIR) spectra of the prepared CMAC, free urea and the CMAC/urea mixture. Table 2 lists the band positions of the major characteristic vibrations as well as their assignments.

In the FTIR spectrum of CMAC, a broad band was observed in the higher-energy region between 3500 and 2500 cm^{-1} comprising a series of weak peaks, corresponding to the NH_3^+ stretching vibrations. The characteristic C=O stretching peak for the carboxyl group in CMAC was observed at around 1743 cm^{-1} . Two neighbouring bands at ~1589 and 1491 cm^{-1} corresponded to the asymmetric and symmetric NH_3^+ deformation vibrations, respectively. IR bands at 1422

and 1339 cm^{-1} corresponded to the CH_2 bending and CH_2 wagging vibrations, respectively. Peaks at around 1220 , 1123 and 1043 cm^{-1} corresponded to CO stretching, NH_3^+ rocking and CN stretching, respectively. $\text{C}-\text{C}$ stretching vibrations were observed at 1031 and 894 cm^{-1} in the FTIR spectrum. The sharp band at 638 cm^{-1} corresponded to the CO deformation vibration. On the other hand, the FTIR spectrum relative to the CMAC/urea composite was characterized by a slight shift and enlarged peaks with respect to those of pure CMAC, in addition to the appearance of a new peak located at 1546 cm^{-1} , corresponding to the amine deformation vibration of urea. Considering the negligible shift of the peaks of CMAC in the CMAC/urea composite, the interaction of urea with CMAC was extremely weak apparently, which was ensured by the formation of a combination of hydrogen-bond interactions; this result was in agreement with an earlier reported study suggesting that urea interacts less often with polar or charged molecules [52]. Generally, the depression of the melting points of DESs compared to pure substances is explained in part by the presence of these hydrogen bonds in their structures [53].

Fig. 2. Fourier transform infrared (FTIR) spectra of CMAC, free urea and CMAC/urea (a), Magnified FTIR spectra showing the fingerprint regions for $\text{C}=\text{O}$ and NH_2 stretching vibrations (b).

Table 2

FTIR **band** assignments of both CMAC and CMAC/urea

CMAC		CMAC/Urea	
Wavenumber (cm ⁻¹)	Assignments [54]	Wavenumber(cm ⁻¹)	Assignments
2300-3500	NH ₃ ⁺ stretching and deformation	2700-3400	NH stretching
1741	C=O str of COOH	1739	C=O
1599	Assym NH ₃ ⁺ def vib	1606	Assym NH ₃ ⁺ def vib
1486	Sym NH ₃ ⁺ def vib	1546	NH ₂ def
1422	CH ₂ binding vib	1483	Sym NH ₃ ⁺ def vib
1339	CH ₂ wagging	1419	CH ₂ binding vib
1220	CO str	1304	Assym N-C-N
1123	NH ₃ ⁺ rokking vib	1243	C-C binding/C-N str
1043	CN str vib	1104	CN str vib
901	C-C Str	1032	CN str vib
857	C-C Str	894	C-C Str
638	CO def vib	725	N-H binding vib

3.4. Thermal analysis (DSC)

The thermal stability of CMAC was investigated on a differential scanning calorimetry (DSC) 214 Polyma instrument. The experiment was conducted using a 31-mg sample between $-16\text{ }^{\circ}\text{C}$ and $75\text{ }^{\circ}\text{C}$ at a ramp rate of $5\text{ }^{\circ}\text{C}/\text{min}$ under a static atmosphere of nitrogen. On heating, an exothermic transition was observed at approximately -10°C , with an enthalpy of -2.03 (J/g) , corresponding to the crystallization of this compound. In the temperature range of $-5\text{ }^{\circ}\text{C}$ to $55\text{ }^{\circ}\text{C}$, this compound was stable, while at a temperature greater than $55\text{ }^{\circ}\text{C}$, it underwent degradation (Fig. 3).

Fig. 3. Differential scanning calorimetry thermogram of CMAC

3.5. Catalyst optimization

To synthesize the target derivatives, intermediates methyl 5-oxo-1-arylpyrrolidine-3-carboxylate type **3** were prepared by the reaction of different arylamines with an equimolar amount of dimethyl itaconate under microwave irradiation in the presence of water as the solvent (Scheme 2).

Scheme 2. Synthetic route of 5-oxo-1-arylpyrrolidine-3-carboxylates.

3.6. Optimization of the reaction conditions to synthesize the target derivative type 5

Synthesis conditions were optimized by using 5-oxo-1-phenylpyrrolidine-3-carboxylate **3a** and 2-aminophenol **4** as a model reaction. Table 3 lists the effect of different DESs.

First, by using benzalkonium chloride or ChCl with glycerol or ethylene glycerol as the mixture, the product was obtained in low yields (Table 3, entries 1, 2, 6, and 7). On the other hand, by using a mixture of benzalkonium chloride/urea, derivative **5a** was obtained in 58% yield (Table 3, entry 3). By using a mixture of ChCl/urea, **5a** was obtained in 55% yield (Table 3, entry 5). Moreover, by using a mixture oxalic acid and benzalkonium chloride or ChCl, the product was obtained in a better yield (Table 3, entries 4 and 8). The use of CMAC alone afforded a moderate product yield of 41% (Table 3, entry 9). Remarkably, by using a mixture of CMAC/urea, the product was obtained in an excellent yield in an extremely short time (Table 3, entry 10). This increased yield implied that the developed DES serves not only as a solvent but also as a catalyst for the reaction. Such dual solvent/catalyst characteristics of DESs have been reported previously by several authors [55-57]. By heating the reaction at 50°C or subjecting the reaction to microwave irradiation, the product was successively isolated in 22% or 83% yield, respectively. The use of urea alone afforded a trace amount of the product (Table 3, entry 13). In the presence

of water or in the absence of any additive, no compound was generated (Table 3, entry 14 and 15, respectively).

Table 3

Optimization of the heterocycle construction.

Entry	Mixture of deep eutectic solvent	Conditions	Time (min)	Yield (%) ^a
1	Benzalkonium chloride/glycerol	))))	20	36
2	Benzalkonium chloride/ethylene glycol	))))	20	42
3	Benzalkonium chloride/urea	))))	20	58
4	Benzalkonium chloride/oxalic acid	))))	20	79
5	Choline chloride/urea	))))	20	55
6	Choline chloride /glycerol	))))	20	48
7	Choline chloride /ethylene glycol	))))	20	51
8	Choline chloride / oxalic acid	))))	20	71
9	CMAC	))))	30	41
10	CMAC/urea	))))	20	88
11	CMAC/urea	50 °C	20	22
12	CMAC/urea	MW	20	83
13	Urea		20	Traces
14	Water		20	-
15	-		20	-

^aYields in pure isolated products.

3.7. Extension of the methodology

First, a mixture of methyl-1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylate **3** (1 mmol) and 2-aminophenol **4** (1 mmol) in DES (1 g) (3.5:1 molar ratio) was subjected to microwave irradiation for an appropriate time. Second, the reaction mixture was irradiated till the starting materials were completely converted (monitored by TLC using 80:20 v/v of hexane:AcOEt) (Scheme 3). Third, the reaction mixture was cooled to room temperature. Next, the mixture was poured into a beaker containing 50 mL of water and stirred for 10 min, followed by the filtration of the crude product. The compounds were further purified by column chromatography using n-hexane:AcOEt (80:20 v/v) as the eluent.

Scheme 3. Investigation of synthesis of benzoxazole-linked pyrrolidinone type **5**.

Pyrrolidinone derivatives **5a–i** were obtained in 10 min in excellent yields. All reactions were performed using reactant type **3** and **4**. The substituents linked to derivative **3** did not affect the reaction, and the corresponding products were obtained in an extremely short time (10 min) in high yields (Table 4). Derivatives structures of **5a–i** were confirmed by spectral characterization (m.p., ^1H NMR and IR).

Table 4

Synthesis of derivatives **5a–i**.

Entry	ArNH ₂	Compound	Yield (%) ^b
1		5a	88

2		5b	91
3		5c	82
4		5d	84
5		5e	81
6		5f	79
7		5g	80
8		5h	85
9		5i	89

262 ^aYield of pure isolated products. Reaction conditions: *o*-aminophenol (1 mmol), intermediate **3** (1 mmol),
263 1 g of DES, 20 min. ^b Isolated yield.

264 Reusability of DESs is one of its performance criteria. Therefore, to evaluate the recycling ability
265 of the synthesized DES, the reaction is performed for four consecutive cycles. Notably, the

product was obtained in excellent yield after each cycle, indicative of its possible recovery till the fourth cycle.

3.8. Plausible Mechanism Involved in the Formation of Product 5

The reactivity of reactants might be improved by the presence of catalysts or a specific type of solvent. Herein, the effect of DES on the stability of reactants **3** and **4** was determined by the calculation of electronic energies in the absence and presence of DES (Fig. 4). Indeed, the DES stabilized **3** and **4** by 225 Hartree. The stability of the starting material in the presence of DES was mainly related to the formation of strong intermolecular hydrogen bonds between DES and the starting reagents (Fig.4). Indeed, the amine group of urea (DES part) formed (i) two hydrogen bonds with keto and methoxyl groups of **3**, with distances 2.12 Å and 2.30 Å, respectively, and (ii) two hydrogen bonds with amine and hydroxyl groups of **4**, with distances 2.25 Å and 2.17 Å, respectively.

Fig. 4. Energetic diagram of reactants in the presence and absence of the deep eutectic solvent.

4. Conclusion

In summary, a green strategy for the preparation of new benzoxazole-linked pyrrolidinone heterocycles was developed by using arylamines and 2-aminophenol under ultrasonic irradiation in the presence of a newly prepared deep eutectic solvent (DES). X-ray diffraction and infrared spectroscopy were employed to investigate the structure of the ionic liquid and characterize the DES, respectively. This strategy exhibited main advantages of a short reaction time and high productivity, in addition to the simple separation of DES from reaction mixtures.

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