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Yassine Riadi, Oussama Ouerghi, Mohammed H. Geesi, Abdellah Kaiba, El Hassane Anouar, et al.. Efficient novel eutectic-mixture-mediated synthesis of benzoxazole-linked pyrrolidin-2-one heterocycles. *Journal of Molecular Liquids*, 2021, 323, 115011 (9 p.). 10.1016/j.molliq.2020.115011 . hal-03102378

**HAL Id: hal-03102378**

**<https://hal.science/hal-03102378v1>**

Submitted on 13 Jan 2021

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

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16

## 17 **Abstract**

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

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

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

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## 30 **1. Introduction**

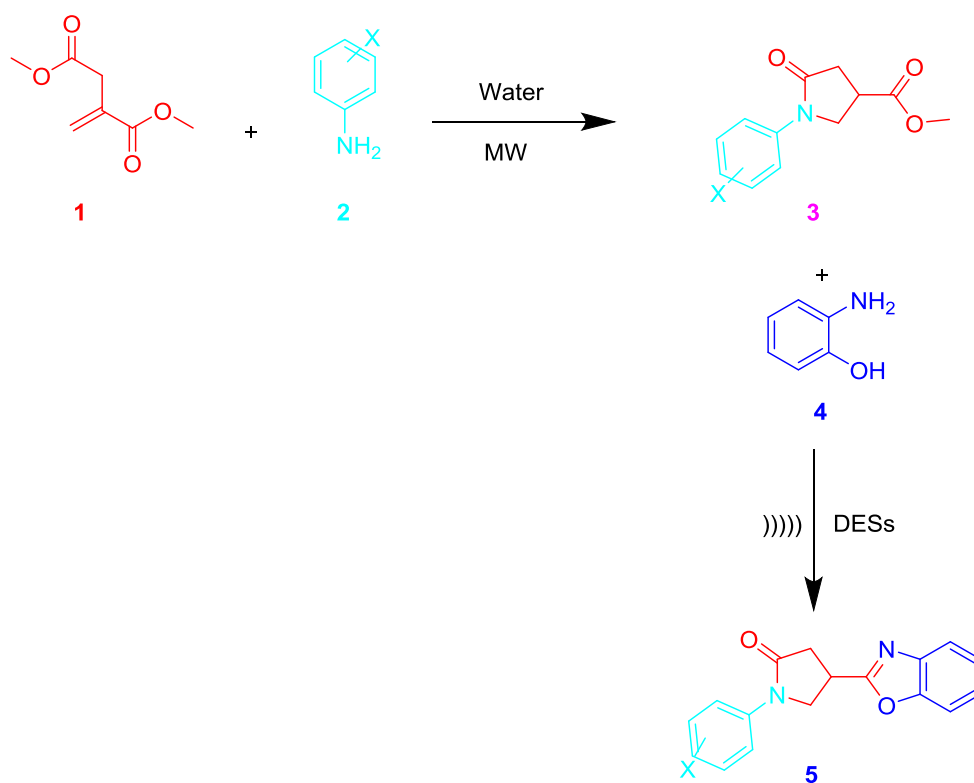
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31 The last two decades has witnessed a rapid increase in the applications of deep eutectic solvents  
32 (DESs) as a green alternative to standard organic solvents and ionic liquids (IL). Historically,  
33 DESs are prepared by the simple mixing of hydrogen bond acceptors (HBAs); generally, a  
34 quaternary ammonium salt, e.g., choline chloride (ChCl). ChCl is typically used, in addition to  
35 hydrogen-bond donor (HBD) molecules such as amines, amides, alcohols, carboxylic acids, and  
36 metal salts, etc. to form a eutectic mixture linked via hydrogen-bond interactions, which is  
37 characterized by a melting point less than those of its individual precursor components [1,2].  
38 Conceptually, the interactions between HBDs and salts disturb the electrostatic forces between  
39 anions and cations, leading to the decrease in the freezing point of the mixture [3].  
40 DESs are typically used as an environmentally-benign reaction medium in organic chemistry as  
41 an alternative to standard organic solvents or IL. In addition, they have been utilized in a wide  
42 range of applications, including polymer synthesis, metal electrodeposition and electropolishing  
43 [4,5], as well as for the growth of nanomaterials with well-controlled shapes and dimensions.  
44 Additional applications span the solubility of biomaterials such as chitin or cellulose as well as  
45 extraction and separation, such as the separation of phenol compounds from oils [6-12].  
46 Recently, diverse approaches based on the use of cost-effective, renewable and abundant raw  
47 precursor materials have been developed to synthesize new natural-based DESs with  
48 characteristics of biocompatibility, biodegradability and low toxicity, as well as facile  
49 preparation and purification. Among the DESs, urea-based DESs are attracting immense interest.  
50 The large-scale production of DESs was previously performed by mixing urea and ChCl  
51 [2,13,14].  
52 Versatile 2-pyrrolidinone derivatives are found in different bioactive natural products. Owing to  
53 their outstanding pharmaceutical features, they have aroused substantial importance due to their  
54 wide applications in medicinal chemistry [15]. These scaffolds exhibit antibacterial [16],  
55 antimicrobial [17], anti-inflammatory [18], analgesic [19], anticancer [20] and anticonvulsant  
56 activities [21], as well as HIV-1 inhibitors [22]. Therefore, numerous synthetic protocols and  
57 reactions have been reported for the preparation of pyrrolidinone derivatives [23-31].  
58 Similarly, benzoxazole derivatives also have aroused immense interest in the scientific  
59 community due to their biological and pharmacological activities [32,33]. In fact, they have been  
60 recognised to exhibit prominent antitumour [34], anticancer [35], antiviral [36] and antimicrobial

61 [37,38] activities. Moreover, they have been utilized in several fields, including the plastic [39],  
62 textile [40], and dye [41] industries.

63 Within the framework of our research program to access bio-active heterocyclic scaffolds  
64 [42,43], particularly by the development of new green strategies [44-47], new 2-pyrrolidinones  
65 linked to the benzoxazole moiety were synthesized using a urea-based DES under ultrasonic  
66 irradiation to access new derivatives in this study (Scheme 1). Despite this interest, to the best of  
67 our knowledge, this synthesized DES has never been examined.

68



69

70 **Scheme 1.** Synthesis of substituted pyrrolidinone linked to benzoxazole.

## 71 2. Experimental Section

### 72 2.1. General remarks

73 All chemicals purchased from Sigma-Aldrich were used without any further purification.

74 Melting points of the prepared derivatives were recorded in open capillaries using a melting

75 point apparatus (Sanyo Gallenkamp, South Borough, UK). Pre-coated silica gel TLC plates  
76 (0.25-mm silica gel, 60G F254, Merck, Germany) were employed for TLC experiments. The  
77 mobile-phase system used for developing TLC plates comprised a mixture of n-hexane:EtOAc  
78 (80:20 v/v). Fourier transform infrared (FTIR) spectra were recorded on a Thermo Scientific  
79 Nicolet iS50 FTIR spectrometer. Viscosity was measured using an Ostwald viscometer. The total  
80 number of protons and carbons as well the environment were elucidated by recording  $^1\text{H}$  NMR  
81 spectra on an NMR instrument BRUKER PLUS (400 MHz). A Biotage Initiator microwave  
82 reactor and an UP200Ht ultrasonic processor with a frequency of 20 kHz were used for the  
83 experiments.

## 84 **2.2. Synthesis of carboxymethanamonium chloride (CMAC)**

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

## 91 **2.3. General preparation procedure for DES**

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

## 95 **2.4. General synthetic procedure for derivatives 3 and 5**

### 96 *2.4.1. General methods to access derivative type 3*

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

#### 101 2.4.2. General synthetic procedure for derivatives type 5

102 First, a mixture of methyl-1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylate (1 mmol) and  
103 2-aminophenol (1 mmol) in DES (1 g) was irradiated for an appropriate time. Second, the  
104 reaction mixture was cooled to room temperature. Next, the mixture was poured in a beaker  
105 containing 50 mL of water and stirred for 10 min, and the crude product was filtered. Finally, the  
106 compounds were further purified over a chromatography column using n-hexane:EtOAc (80:20  
107 v/v) as the eluent

### 108 2.5. Theoretical study

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

## 115 3. Results and discussion

### 116 3.1. X-ray diffraction analysis of CMAC

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

#### 127 **Table 1**

128 Crystallographic data for CMAC

Empirical formula	C <sub>2</sub> H <sub>6</sub> Cl N O <sub>2</sub>	
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 <sup>3</sup>	
Z	4	
Density (calculated)	1.452 Mg/m <sup>3</sup>	
Absorption coefficient	0.619 mm <sup>-1</sup>	
F(000)	232	
Crystal size	0.12x0.05x0.05 mm <sup>3</sup>	
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 <sup>2</sup>	
Data / restraints / parameters	1021 / 0 / 55	
Goodness-of-fit on F <sup>2</sup>	1.075	
Final R indices [I>2sigma(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 <sup>-3</sup>	

### 129 3.2. Crystal structure

130 The compound crystallized in the monoclinic system with the P 21/c space group, with unit cell  
131 parameters a = 7.146(5) Å, b = 5.238(5) Å, c = 13.739(5) Å, β = 97.357(5)°, volume 510.0 (6) Å<sup>3</sup>  
132 and Z = 4 (**Table 1**). The asymmetric unit included one chloride anion and one protonated cation  
133 of 2-aminoacetic acid (Fig. 1A). Cohesion was ensured by hydrogen bonds between the <sup>+</sup>NH<sub>3</sub>-  
134 CH<sub>2</sub>-COOH cationic group and the chloride anion Cl<sup>-</sup> via N-H...Cl, OH...Cl and C=O...H-N  
135 hydrogen-bond interactions. Indeed, hydrogen-bond distances were d<sub>NH...Cl</sub> = 2.317 Å for N-  
136 H...Cl, d<sub>OH...Cl</sub> = 2.193 Å for OH...Cl and d<sub>C=O...HN</sub> = 3.003 Å for C=O...Cl. A three-dimensional  
137 framework was formed as a result of the H-bonding network. The structure also can be described  
138 as an alternation of anionic and cationic layers along the a axis (Fig. 1B).

139

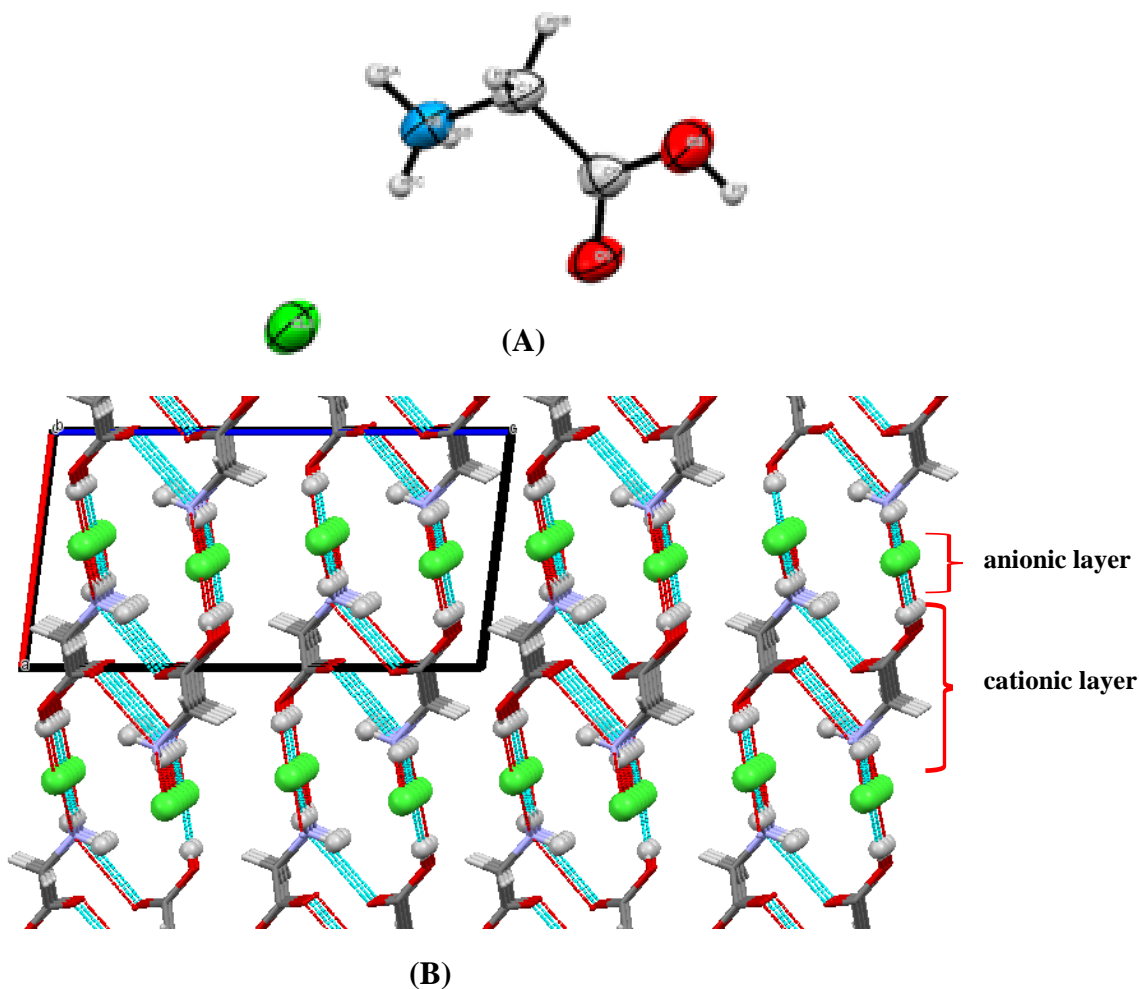
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162 **Fig. 1.** (A) Asymmetric unit of CMAC (B) Crystal packing of the titled compound projected  
163 onto the b axis. Dashed lines represent N–H...Cl, C–OH...Cl and C=O...H–N hydrogen bonds.

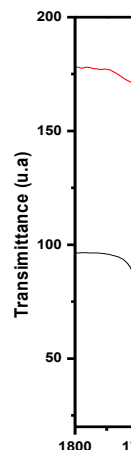
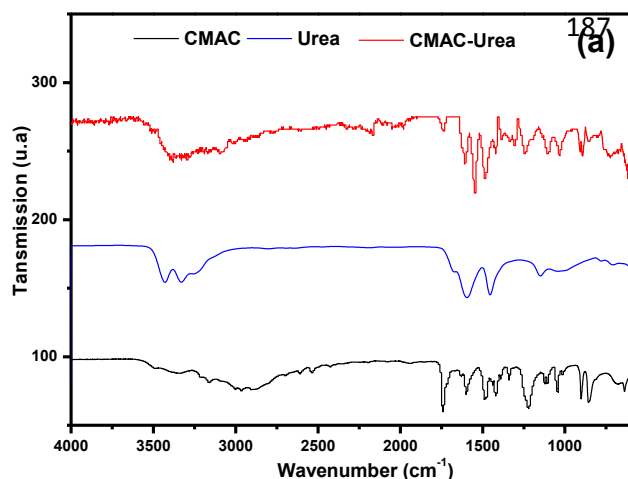
### 164 3.3. Infrared analysis of CMAC/urea deep eutectic solvent

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

168 In the FTIR spectrum of CMAC, a broad band was observed in the higher-energy region between  
169 3500 and 2500  $\text{cm}^{-1}$  comprising a series of weak peaks, corresponding to the  $\text{NH}_3^+$  stretching  
170 vibrations. The characteristic C=O stretching peak for the carboxyl group in CMAC was  
171 observed at around 1743  $\text{cm}^{-1}$ . Two neighbouring bands at ~1589 and 1491  $\text{cm}^{-1}$  corresponded  
172 to the asymmetric and symmetric  $\text{NH}_3^+$  deformation vibrations, respectively. IR bands at 1422



173 and  $1339\text{ cm}^{-1}$  corresponded to the  $\text{CH}_2$  bending and  $\text{CH}_2$  wagging vibrations, respectively.  
 174 Peaks at around  $1220$ ,  $1123$  and  $1043\text{ cm}^{-1}$  corresponded to  $\text{CO}$  stretching,  $\text{NH}_3^+$  rocking and  $\text{CN}$   
 175 stretching, respectively.  $\text{C-C}$  stretching vibrations were observed at  $1031$  and  $894\text{ cm}^{-1}$  in the  
 176 FTIR spectrum. The sharp band at  $638\text{ cm}^{-1}$  corresponded to the  $\text{CO}$  deformation vibration.  
 177 On the other hand, the FTIR spectrum relative to the CMAC/urea composite was characterized  
 178 by a slight shift and enlarged peaks with respect to those of pure CMAC, in addition to the  
 179 appearance of a new peak located at  $1546\text{ cm}^{-1}$ , corresponding to the amine deformation  
 180 vibration of urea. Considering the negligible shift of the peaks of CMAC in the CMAC/urea  
 181 composite, the interaction of urea with CMAC was extremely weak apparently, which was  
 182 ensured by the formation of a combination of hydrogen-bond interactions; this result was in  
 183 agreement with an earlier reported study suggesting that urea interacts less often with polar or  
 184 charged molecules [52]. Generally, the depression of the melting points of DESs compared to  
 185 pure substances is explained in part by the presence of these hydrogen bonds in their structures  
 186 [53].



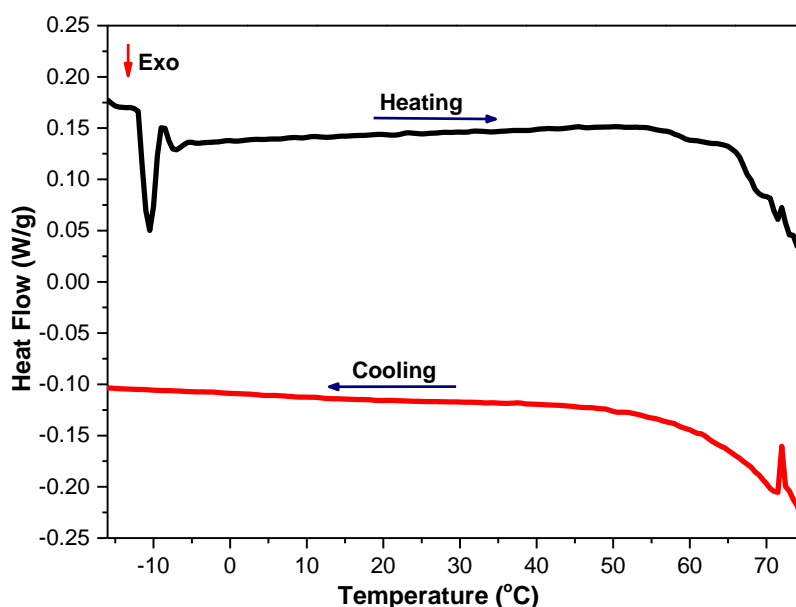
188  
 189 **Fig. 2.** Fourier transform infrared (FTIR) spectra of CMAC, free urea and CMAC/urea (a),  
 190 Magnified FTIR spectra showing the fingerprint regions for  $\text{C=O}$  and  $\text{NH}_2$  stretching vibrations  
 191 (b).

192 **Table 2**  
 193 FTIR **band** assignments of both CMAC and CMAC/urea  
 194

CMAC		CMAC/Urea	
Wavenumber (cm <sup>-1</sup> )	Assignments [54]	Wavenumber(cm <sup>-1</sup> )	Assignments
2300-3500	NH <sub>3</sub> <sup>+</sup> stretching and deformation	2700-3400	NH stretching
1741	C=O str of COOH	1739	C=O
1599	Assym NH <sub>3</sub> <sup>+</sup> def vib	1606	Assym NH <sub>3</sub> <sup>+</sup> def vib
1486	Sym NH <sub>3</sub> <sup>+</sup> def vib	1546	NH <sub>2</sub> def
1422	CH <sub>2</sub> binding vib	1483	Sym NH <sub>3</sub> <sup>+</sup> def vib
1339	CH <sub>2</sub> wagging	1419	CH <sub>2</sub> binding vib
1220	CO str	1304	Assym N-C-N
1123	NH <sub>3</sub> <sup>+</sup> 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

### 195 3.4. Thermal analysis (DSC)

196 The thermal stability of CMAC was investigated on a differential scanning calorimetry (DSC)  
 197 214 Polyma instrument. The experiment was conducted using a 31-mg sample between -16 °C  
 198 and 75 °C at a ramp rate of 5 °C/min under a static atmosphere of nitrogen. On heating, an  
 199 exothermic transition was observed at approximately -10°C, with an enthalpy of -2.03 (J/g),  
 200 corresponding to the crystallization of this compound. In the temperature range of -5 °C to 55  
 201 °C, this compound was stable, while at a temperature greater than 55 °C, it underwent  
 202 degradation (Fig. 3).

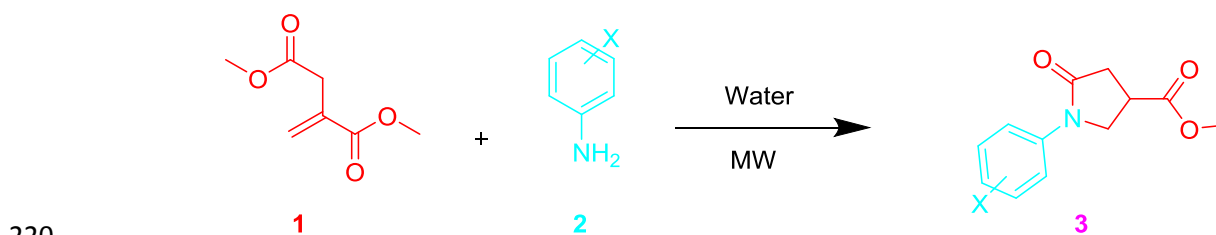


214

**Fig. 3.** Differential scanning calorimetry thermogram of CMAC

### 215 3.5. Catalyst optimization

216 To synthesize the target derivatives, intermediates methyl 5-oxo-1-arylpyrrolidine-3-carboxylate  
 217 type **3** were prepared by the reaction of different arylamines with an equimolar amount of  
 218 dimethyl itaconate under microwave irradiation in the presence of water as the solvent (Scheme  
 219 2).



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

### 222 3.6. Optimization of the reaction conditions to synthesize the target derivative type 5

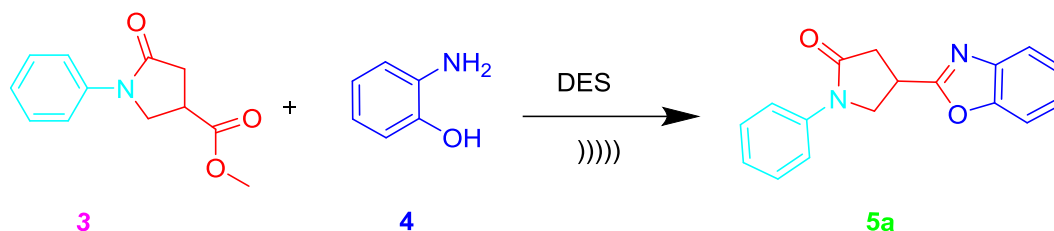
223 Synthesis conditions were optimized by using 5-oxo-1-phenylpyrrolidine-3-carboxylate **3a** and  
 224 2-aminophenol **4** as a model reaction. Table 3 lists the effect of different DESs.

225 First, by using benzalkonium chloride or ChCl with glycerol or ethylene glycerol as the mixture,  
 226 the product was obtained in low yields (Table 3, entries 1, 2, 6, and 7). On the other hand, by  
 227 using a mixture of benzalkonium chloride/urea, derivative **5a** was obtained in 58% yield (Table  
 228 3, entry 3). By using a mixture of ChCl/urea, **5a** was obtained in 55% yield (Table 3, entry 5).  
 229 Moreover, by using a mixture oxalic acid and benzalkonium chloride or ChCl, the product was  
 230 obtained in a better yield (Table 3, entries 4 and 8). The use of CMAC alone afforded a moderate  
 231 product yield of 41% (Table 3, entry 9). Remarkably, by using a mixture of CMAC/urea, the  
 232 product was obtained in an excellent yield in an extremely short time (Table 3, entry 10). This  
 233 increased yield implied that the developed DES serves not only as a solvent but also as a catalyst  
 234 for the reaction. Such dual solvent/catalyst characteristics of DESs have been reported previously  
 235 by several authors [55-57]. By heating the reaction at 50°C or subjecting the reaction to  
 236 microwave irradiation, the product was successively isolated in 22% or 83% yield, respectively.  
 237 The use of urea alone afforded a trace amount of the product (Table 3, entry 13). In the presence

238 of water or in the absence of any additive, no compound was generated (Table 3, entry 14 and  
 239 15, respectively).

240 **Table 3**

241 Optimization of the heterocycle construction.

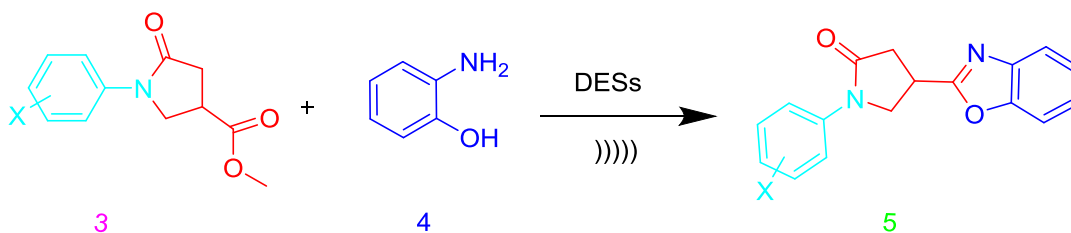


Entry	Mixture of deep eutectic solvent	Conditions	Time (min)	Yield (%) <sup>a</sup>
1	Benzalkonium chloride/glycerol	)))))	20	36
2	Benzalkonium chloride/ethylene glycol	)))))	20	42
3	Benzalkonium chloride/urea	)))))	20	58
4	Benzalkonium chloride/oxalic acid	)))))	20	79
5	Choline chloride/urea	)))))	20	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	-

243 <sup>a</sup>Yields in pure isolated products.

244 **3.7. Extension of the methodology**

245 First, a mixture of methyl-1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylate **3** (1 mmol) and  
246 2-aminophenol **4** (1 mmol) in DES (1 g) (3.5:1 molar ratio) was subjected to microwave  
247 irradiation for an appropriate time. Second, the reaction mixture was irradiated till the starting  
248 materials were completely converted (monitored by TLC using 80:20 v/v of hexane:AcOEt)  
249 (Scheme 3). Third, the reaction mixture was cooled to room temperature. Next, the mixture was  
250 poured into a beaker containing 50 mL of water and stirred for 10 min, followed by the filtration  
251 of the crude product. The compounds were further purified by column chromatography using n-  
252 hexane:AcOEt (80:20 v/v) as the eluent.



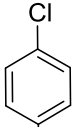
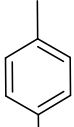
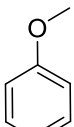
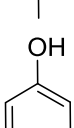
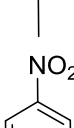
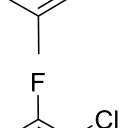
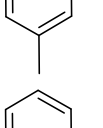
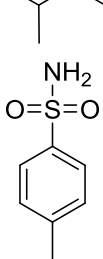
254 **Scheme 3.** Investigation of synthesis of benzoxazole-linked pyrrolidinone type **5**.

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

260 **Table 4**

261 Synthesis of derivatives **5a-i**.

Entry	ArNH <sub>2</sub>	Compound	Yield (%) <sup>b</sup>
1		<b>5a</b>	88

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

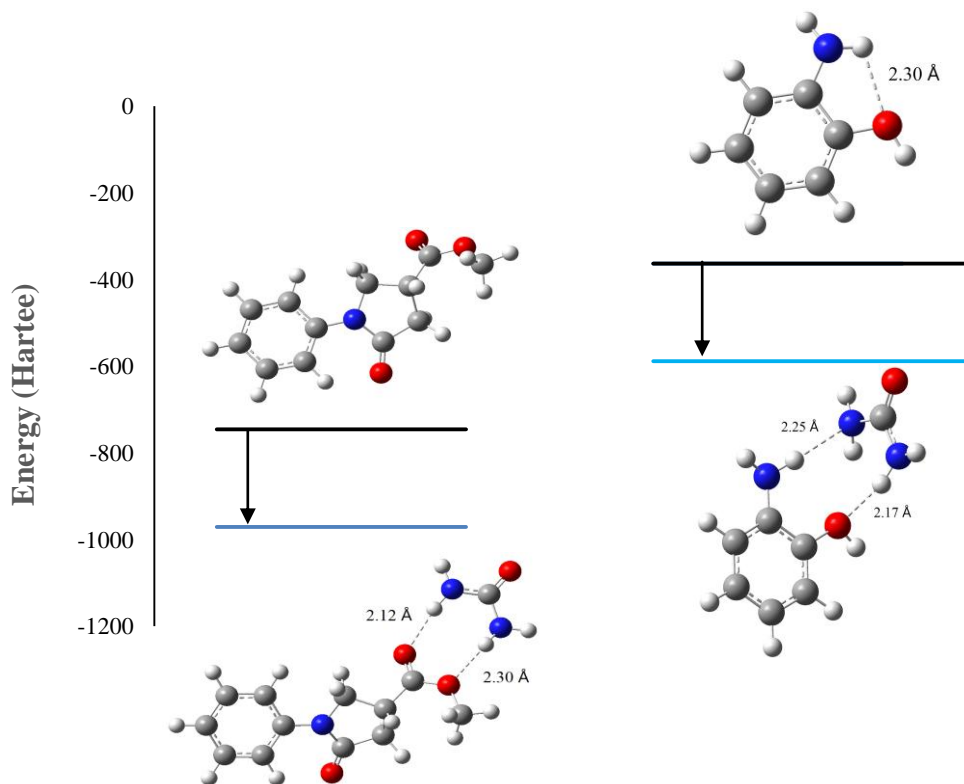
262 <sup>a</sup>Yield of pure isolated products. Reaction conditions: *o*-aminophenol (1 mmol), intermediate **3** (1 mmol),  
 263 1 g of DES, 20 min. <sup>b</sup> Isolated yield.

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

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

### 268 3.8. Plausible Mechanism Involved in the Formation of Product 5

269 The reactivity of reactants might be improved by the presence of catalysts or a specific type of  
270 solvent. Herein, the effect of DES on the stability of reactants **3** and **4** was determined by the  
271 calculation of electronic energies in the absence and presence of DES (Fig. 4). Indeed, the DES  
272 stabilized **3** and **4** by 225 Hartree. The stability of the starting material in the presence of DES  
273 was mainly related to the formation of strong intermolecular hydrogen bonds between DES and  
274 the starting reagents (Fig.4). Indeed, the amine group of urea (DES part) formed (i) two  
275 hydrogen bonds with keto and methoxyl groups of **3**, with distances 2.12 Å and 2.30 Å,  
276 respectively, and (ii) two hydrogen bonds with amine and hydroxyl groups of **4**, with distances  
277 2.25 Å and 2.17 Å, respectively.



278  
279 **Fig. 4.** Energetic diagram of reactants in the presence and absence of the deep eutectic solvent.

### 280 4. Conclusion

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

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