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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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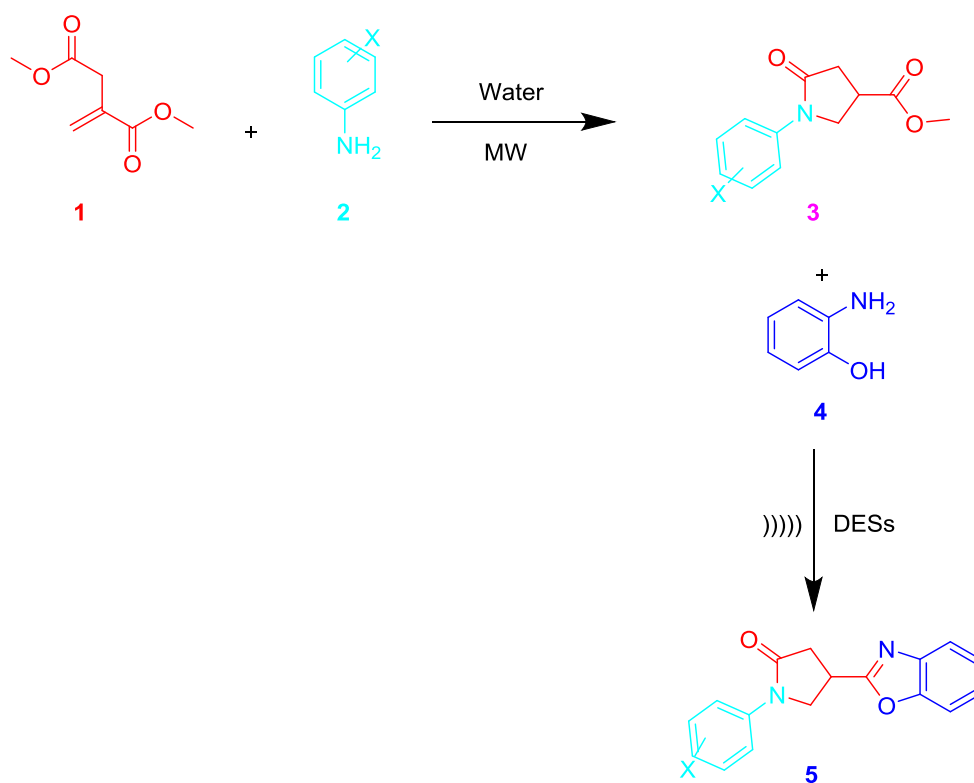
30 **1. Introduction**

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 ^1H 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 ϕ and ω 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.

127 **Table 1**

128 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>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 ⁻³	

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) Å³
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 ⁺NH₃-
134 CH₂-COOH cationic group and the chloride anion Cl⁻ via N-H...Cl, OH...Cl and C=O...H-N
135 hydrogen-bond interactions. Indeed, hydrogen-bond distances were d_{NH...Cl} = 2.317 Å for N-
136 H...Cl, d_{OH...Cl} = 2.193 Å for OH...Cl and d_{C=O...HN} = 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).

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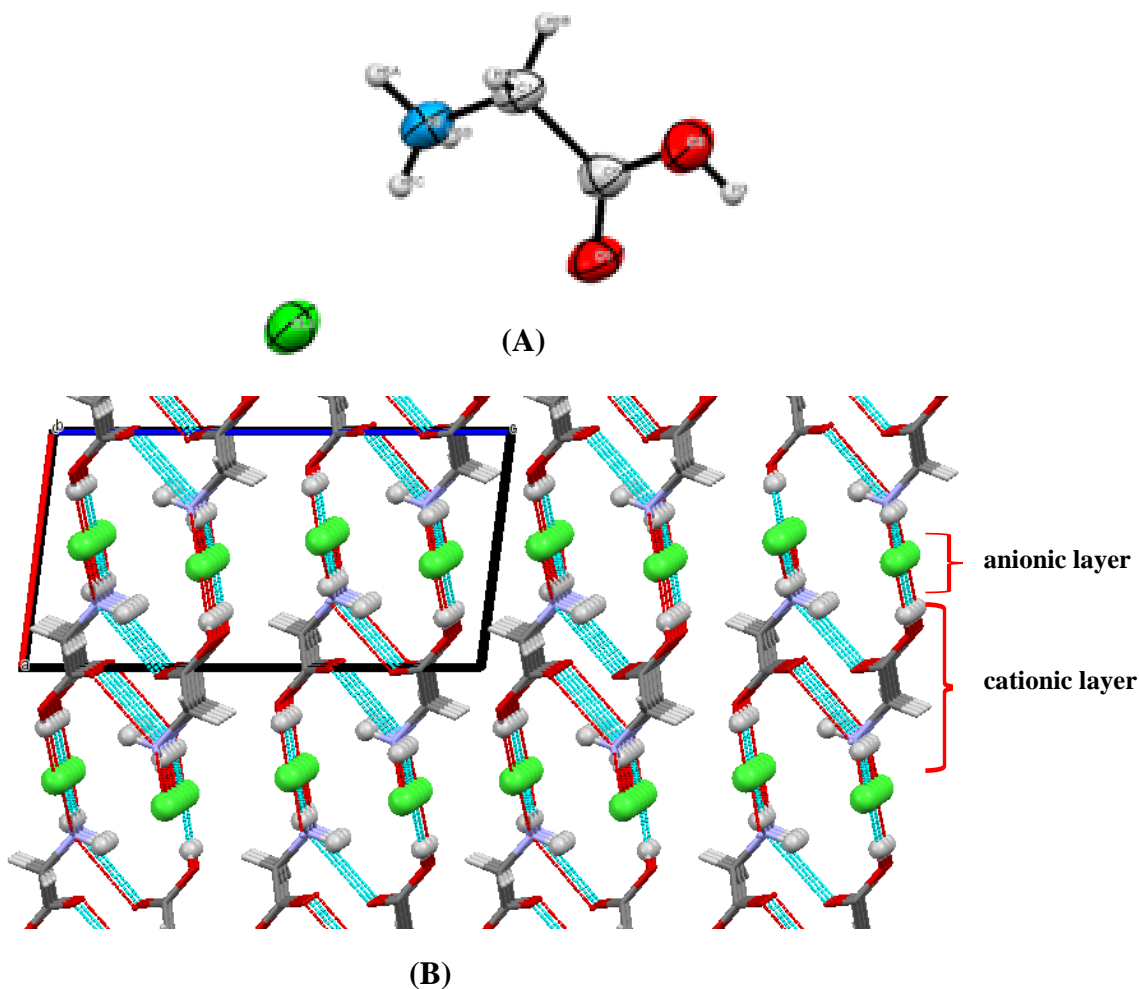
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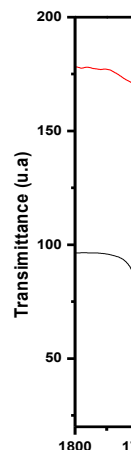
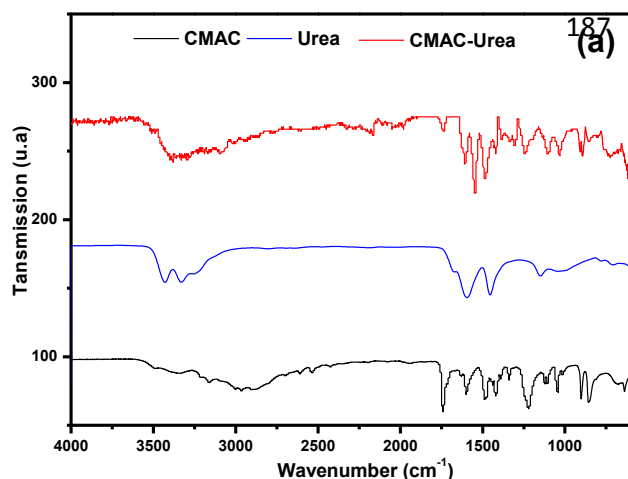
162 **Fig. 1.** (A) Asymmetric unit of CMAC (B) Crystal packing of the titled compound projected
163 onto the b axis. Dashed lines represent N–H...Cl, C–OH...Cl and C=O...H–N hydrogen bonds.

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 cm^{-1} comprising a series of weak peaks, corresponding to the NH_3^+ stretching
170 vibrations. The characteristic C=O stretching peak for the carboxyl group in CMAC was
171 observed at around 1743 cm^{-1} . Two neighbouring bands at ~1589 and 1491 cm^{-1} corresponded
172 to the asymmetric and symmetric NH_3^+ deformation vibrations, respectively. IR bands at 1422

173 and 1339 cm^{-1} corresponded to the CH_2 bending and CH_2 wagging vibrations, respectively.
 174 Peaks at around 1220 , 1123 and 1043 cm^{-1} corresponded to CO stretching, NH_3^+ rocking and CN
 175 stretching, respectively. C-C stretching vibrations were observed at 1031 and 894 cm^{-1} in the
 176 FTIR spectrum. The sharp band at 638 cm^{-1} corresponded to the 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 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].



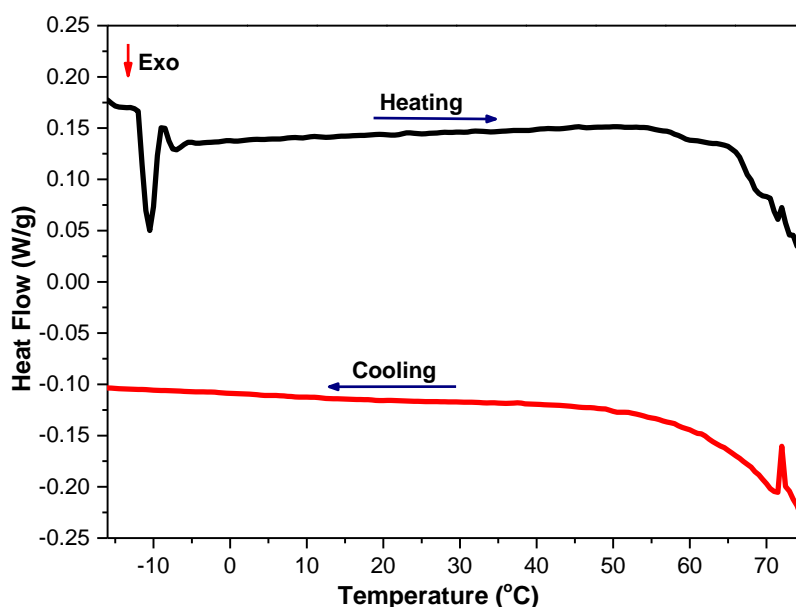
188
 189 **Fig. 2.** Fourier transform infrared (FTIR) spectra of CMAC, free urea and CMAC/urea (a),
 190 Magnified FTIR spectra showing the fingerprint regions for C=O and NH_2 stretching vibrations
 191 (b).

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

CMAC		CMAC/Urea	
Wavenumber (cm ⁻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

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).

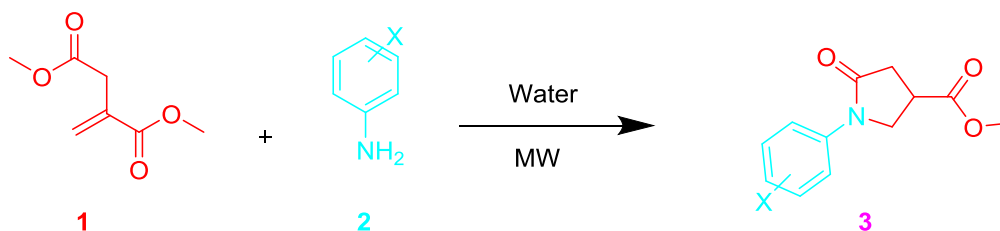


214

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).



220

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

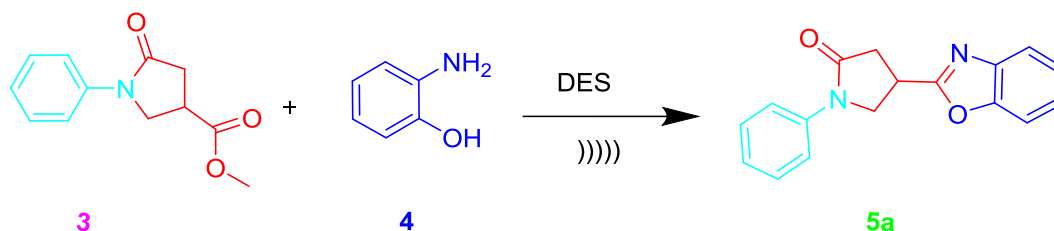
223 Synthesis conditions were optimized by using 5-oxo-1-phenylpyrrolidine-3-carboxylate **3a** and
224 2-aminophenol **4** as a model reaction. Table 3 lists the effect of different DESs.

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.

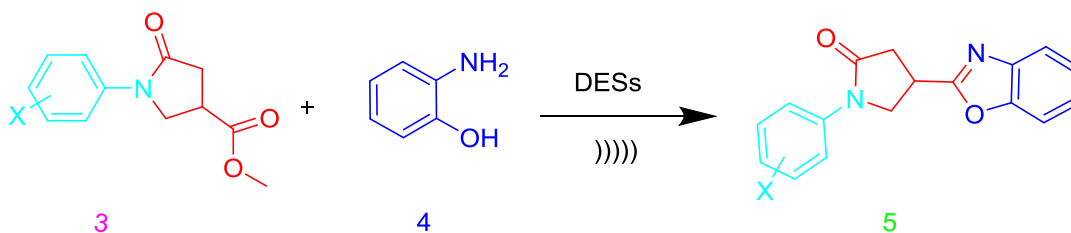


Entry	Mixture of deep eutectic solvent	Conditions	Time (min)	Yield (%) ^a
1	Benzalkonium chloride/glycerol)))))	20	36
2	Benzalkonium chloride/ethylene glycol)))))	20	42
3	Benzalkonium chloride/urea)))))	20	58
4	Benzalkonium chloride/oxalic acid)))))	20	79
5	Choline chloride/urea)))))	20	55
6	Choline 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	-

243 ^aYields 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.



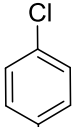
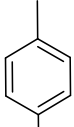
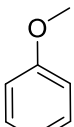
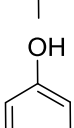
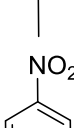
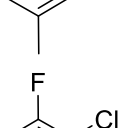
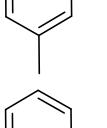
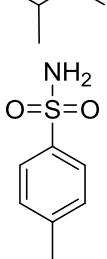
254 **Scheme 3.** Investigation of synthesis of benzoxazole-linked pyrrolidinone type **5**.

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., ¹H NMR and IR).

260 **Table 4**

261 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

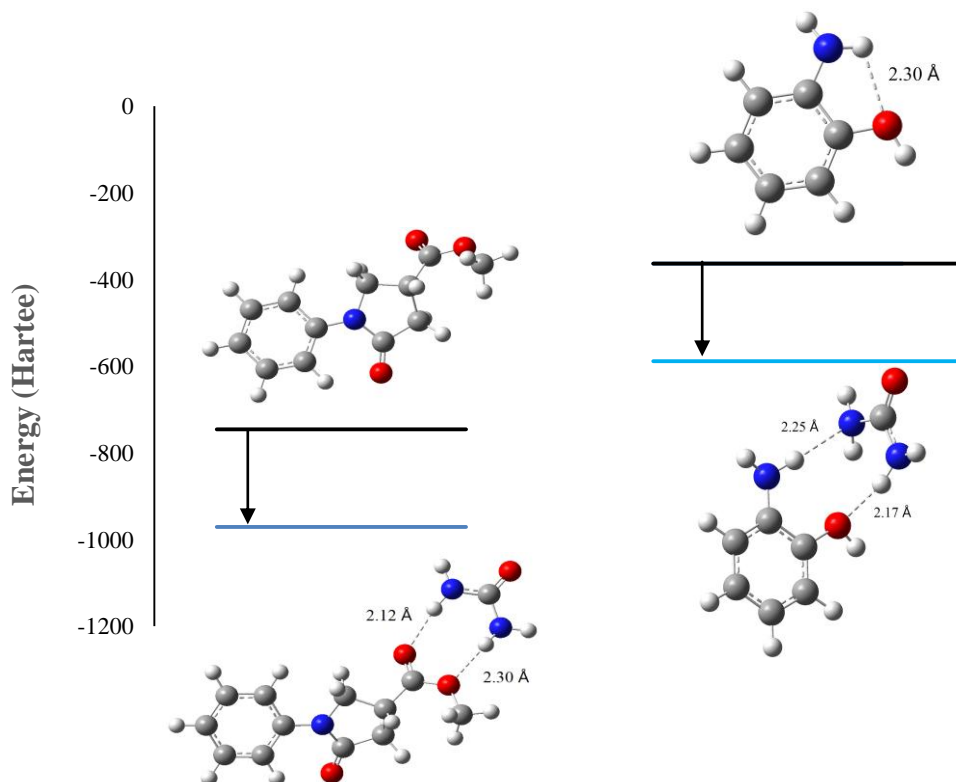
262 ^aYield of pure isolated products. Reaction conditions: *o*-aminophenol (1 mmol), intermediate **3** (1 mmol),
 263 1 g of DES, 20 min. ^b Isolated yield.

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

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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