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Paper

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Green synthesis of 1,4-benzoxazin-3-one using a choline chloride based deep eutectic solvent

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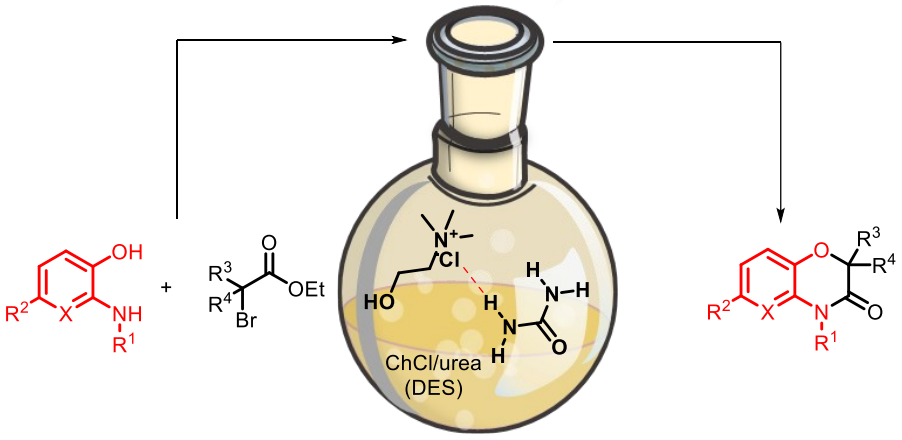
Abstract

An efficient method was devised for the synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one compounds through a one-pot chemoselective reaction between 2-aminophenols (or their corresponding *N*-alkylated derivatives) and 2-bromoalkanoates. This reaction was accomplished in a deep eutectic solvent (DES) consisted of choline chloride and urea at room temperature, using no additional catalyst or a base. The diversity scope of the reaction revealed that various reactants bearing functional groups with different electronic nature would be efficiently tolerated under DES conditions.

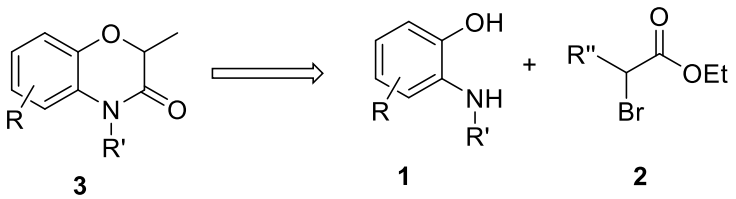


Keywords: Deep eutectic solvent, 1,4-benzoxazin-3-one, heterocycles, choline chloride

Introduction

Solvent is one of the most crucial factors on the progress of a chemical process. Due to its non-toxicity, inflammability, wide range of temperature applicability, and abundance, water has the potential to be one of the best solvents for chemical reactions.[1-3] However, many organic compounds and catalysts do not dissolve in water, and there is even the possibility of hydrolysis of starting materials and products in the presence of water.[4] Therefore, the majority of organic syntheses are performed in organic solvents, although many of these solvents have adverse effects on the environment. To have a solvent with properties resembling those of water and having the capacity to dissolve organic compounds as well, deep eutectic solvents (DES) have been developed, which commonly contain an eutectic mixture of a Lewis or Brønsted acid and a base, having non-ionic, anionic, or cationic species.[5-8] In this context, choline chloride (ChCl) is frequently employed as one of the components of DES along with a hydrogen donor species such as urea,[9,10] glycerol,[11,12] 1,3-dimethylurea,[13] carboxylic acids,[14] and so on.[15,16] The wide applicability of ChCl is due to its affordability, accessibility, non-toxic quaternary ammonium nature, safety, and biodegradability.[17-20]

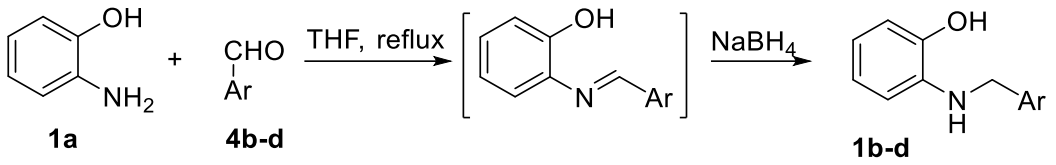
1,4-Benzoxazin-3-one derivatives constitute an important scaffold in phytochemistry,[21] agriculture,[22,23] and drug discovery,[24] because they possess various desirable biological properties including phytotoxicity, antibacterial, and antifungal activities.[25-27] Reduction of 2-nitrophenols to 2-aminophenols and ring-closure of the latter with α-substituted carbonyl compounds is a conventional method for the preparation of benzoxazinones.[28,29] However, many reported methodologies for the synthesis of benzoxazinones suffer from drawbacks, such as requiring high temperatures or harsh reaction conditions,[30] using strong basic reagents,[31] or involving multistep approaches.[32,33] Therefore, development of new green synthetic procedures for the preparation of 1,4-benzoxazin-3-one structures is in demand. In continuation of our studies on the development of green protocols for the synthesis of various heterocyclic scaffolds,[34-38] we were encouraged to design a new procedure for convenient base-free preparation of 1,4-benzoxazin-3-ones using a DES, as illustrated in Scheme 1 for the combination of 2-aminophenol derivatives **1** with ethyl 2-bromoalkanoates **2** in the presence of ChCl.



Scheme 1. Retrosynthetic pathway to 1,4-benzoxazin-3-ones.

Results and Discussion

As a part of our ongoing studies on the synthesis of various heterocycles under green conditions, current research is focused on the exploring of a selective ring-closing reaction to form benzoxazin-3-ones in a DES. At first, it was necessary to prepare the required derivatives of 2-aminophenol. For this purpose, 2-aminophenol **1a** was reacted with benzaldehyde derivatives at refluxing THF, while the intermediate imines were instantly reduced to amine **1b**-**d** using sodium borohydride (Scheme 2). The employed conditions were too mild to form directly the respective benzoxazole compounds.[39]

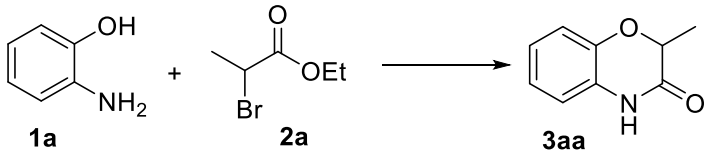


1a **4b-d** **1b-d**

b: Ar = 4-MeC_6H_4; **c**: 3-BrC_6H_4; **d**: 4-*i*-PrC_6H_4

Scheme 2. Synthesis of *N*-alkyl derivatives of 2-aminophenol.

Table 1. Optimization of the reaction conditions for the synthesis of benzoxazine



1a **2a** **3aa**

Entry	Solvent (ratio)	Additive	T (°C)	Time (h)	Yield (%)[a]
1	H_2O	-	reflux	24	0
2	H_2O	K_2CO_3 (2 mmol)	reflux	24	5
3	H_2O	NaOH (2 mmol)	reflux	24	5
4	ChCl/urea (1:2)	-	rt	1.5	85
5	ChCl/thiourea (1:2)	-	70 °C	24	20
6	ChCl/1,1-DMU (1:2)	-	80 °C	24	5
7	ChCl/1,3-DMU (1:2)	-	80 °C	24	5
8	ChCl/acetamide (1:2)	-	60 °C	24	8
9	ChCl/imidazole (3:7)	-	60 °C	24	10
10	ChCl/glycerol (1:2)	-	rt	24	3
11	ChCl/ethylene glycol (1:2)	-	rt	24	3
12	ChCl/$ZnCl_2$ (1:2)	-	80 °C	24	0
13	ChCl/tartaric acid (1:0.5)	-	50 °C	24	0
14	ChCl/ethanolamine (1:6)	-	80 °C	24	5
15	$ZnCl_2$/urea (1:3.5)	-	rt	24	10
16	ChCl/urea (1:2)	DBU[b]	r.t.	1.5	55
17	ChCl/urea (1:2)	DABCO[c]	r.t.	1.5	55
18	ChCl/urea (1:2)	NaOH	r.t.	1.5	40
19	ChCl/urea (1:2)	K_2CO_3	r.t.	1.5	75
20	ChCl/thiourea (1:2)	DBU	70 °C	24	25
21	ChCl/thiourea (1:2)	K_2CO_3	70 °C	24	25
22	ChCl/1,1-DMU (1:2)	DBU	80 °C	24	5
23	ChCl/1,1-DMU (1:2)	K_2CO_3	80 °C	24	10
24	Ch.Cl/$ZnCl_2$ (1:2)	DBU	80 °C	24	5
25	$ZnCl_2$/urea (1:3.5)	DBU	80 °C	24	5
26	$ZnCl_2$/urea (1:3.5)	K_2CO_3	80 °C	24	15

[a] Isolated yields.

[b] 1,8-Diazabicyclo(5.4.0)undec-7-ene.

[c] 1,4-Diazabicyclo[2.2.2]octane.

In our initial experiments to optimize the conditions for the synthesis of benzoxazin-3-ones, 2-aminophenol **1a** was reacted with ethyl 2-bromopropanoate **2a** as the model reaction. In refluxing water and in the absence of any catalyst, no change in the reactants was noticed (entry 1). Not much better results were obtained in the presence of a base, such as potassium carbonate (entry 2) or sodium hydroxide (entry 3). In contrast, when choline chloride (ChCl) was used in combination with urea as the medium, high yields of **3aa** were obtained (entry 4). Replacement of urea with either thiourea (entry 5), 1,1-DMU (entry 6), 1,3-DMU (entry 7), or acetamide (entry 8) did not improve the results even at higher temperatures and longer reaction times. This was also the case when ChCl was liquefied using other various reagents (entries 9-14). A DES mixture of zinc chloride and urea did not end up with desirable results (entry 15). Further experiments showed that addition of organocatalysts (entries 16-17) or inorganic bases (entries 18-19) to the optimum conditions would not improve the outcome. This was also the case when these bases were used in combination with other sets of conditions (entries 20-26).

With the optimized conditions in hand, we next explored the scope of the reaction by using various reactants having different electronic and steric nature (Figure 1). By the use of ChCl/urea (DES medium), various simple and *N*-alkylated 2-aminophenols were reacted with **2a**-**e** at room temperature to afford their respective derivatives of **3** within 1-2 h. No significant differences in the rate and yields of the reactions of various starting materials were observed, except in the case of 2-bromoalkanoate bearing longer alkyl groups, a slight decrease in the efficiency of the reaction was noticed, presumably due to higher steric hindrance.

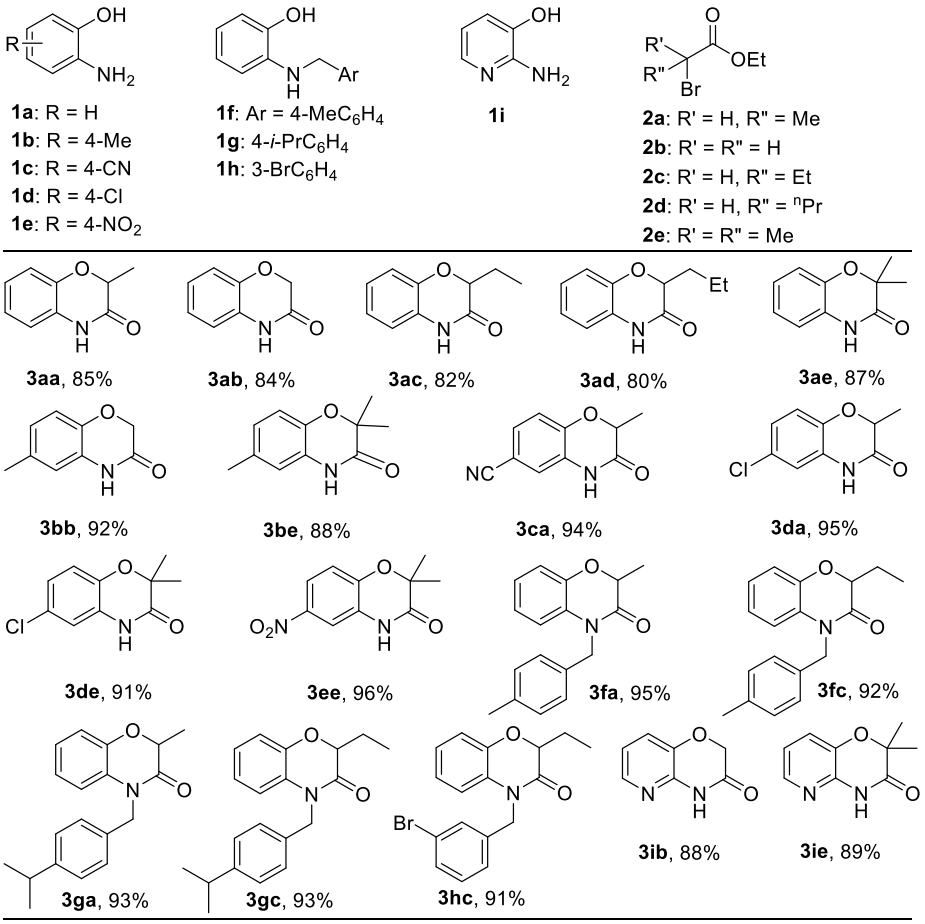


Figure 1. Diversity of the reactants and the products for ChCl-urea mediated synthesis of 1,4-benzoxazin-3-one.

It is known that choline chloride (decomposition point of 302 °C) and urea (melting point of 133 °C) make a deep eutectic solvent (freezing point of 12 °C) through ionic bonding between chloride and choline moieties, and hydrogen bonding interactions between chloride and urea, as shown in.[40] In the present study, the (ChCl)-based DES not only performs as the solvent in the synthesis of benzoxazines, but also it apparently acts as the catalyst through hydrogen exchange to promote the process. Such dual performance of ChCl/urea system in organic transformations has precedence in the literature.[41-43]

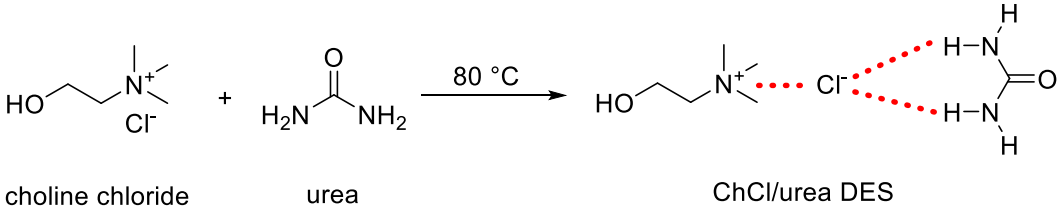


Figure 2. Interactions between choline chloride and urea.

Based on the results, a mechanism would be proposed for the reaction, as illustrated in. The medium may act as a hydrogen bond acceptor through interaction with the 2-aminophenol moiety to activate the hydroxyl group to attack the C-Br bond of the starting 2-bromoalkanoate reactant to form the respective intermediate. Further activation of the carbonyl group of the intermediate causes the ring closure step, furnishing the synthesis of **3**.

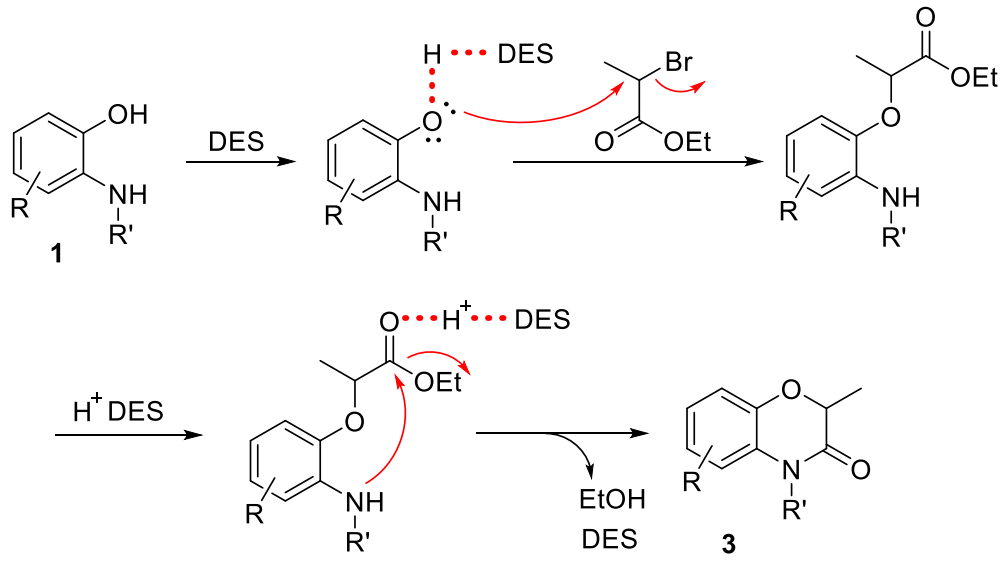


Figure 3. The proposed mechanism for the synthesis of benzoxazines using (ChCl/urea)-based DES.

Conclusions

In summary, a very convenient process was developed for the green, catalyst-free, and base-free synthesis of several benzoxazine compounds through the annulation of 2-aminophenol derivatives with 2-bromoalkanoate derivatives. The chemoselectivity and efficiency of this reaction depend on the use of choline chloride/urea

(DES), whose ionic character and proton exchange with the reactants led to the progression of the process. High product yields, short reaction times, independent from the electronic nature of the reactants, and economic efficiency of the process are advantages of this method.

Experimental Section

General. All reagents and solvents were commercially available and used as received. Progress of the reactions was monitored by TLC using silica gel coated plates and EtOAc/petroleum ether mixture as the eluent. NMR spectra were obtained on a FT-NMR Bruker 500 Ultra Shield™ instrument as $CDCl_3$ solutions and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. FT-IR spectra were recorded using a Perkin-Elmer 400 spectrometer. An Agilent Mass Spectrometer in the range of 10-800 daltons, having adjustable electron impact ionization with 20-70 eV power and a quadrupole analyzer was employed to obtain the mass spectra. The eutectic solvents were prepared using known procedures.[8] The identity of the known products was confirmed by the comparison of their melting points with those of authentic compounds available in the literature.[44-50] New products were fully characterized based on their spectral data.

General procedure for the synthesis of *N*-methylaryl 2-aminophenol compounds (1b-d). A mixture of 2-aminophenol **1a**, (1.0 mmol, 0.11 g), aldehyde **1b**-**d** (1.0 mmol), and THF (3 mL) was stirred in a round bottom flask at refluxing temperature. After the formation of the imine, traced by TLC, $NaBH_4$ (0.5 mmol, 0.02 g) was added to the mixture, and the mixture was continued to star at room temperature. When the completion of imine reduction to amine was detected by TLC, distilled water (3 mL) and EtOAc (3×3 mL) were added to the mixture to extract the product. Next, the organic layer was washed with saline and dried over Na_2SO_4. Finally, the volatiles were evaporated under reduced pressure, and the crude product was purified by column chromatography using silica gel and EtOAc/hexanes as the eluent.[26]

General procedure for the synthesis of benzoxazine compounds (3). In a round bottom flask, a mixture of one of the 2-aminophenol derivatives (**1a-i**, 1.0 mmol) and DES (1 mL, choline chloride/urea, 1.0:2.0 ratio) was stirred at room temperature for 5 minutes. 2-Bromoalkanoate (**2a**-**e**, 1.2 mmol) was added to this mixture and the mixture was continued to stir for another 1-2 h. When completion of the reaction was confirmed by TLC, the crude product was extracted with EtOAc (3×3 mL), washed with saline, and dried over Na_2SO_4. The product was obtained through the evaporation of the volatiles of the mixture and the residue was purified using column chromatography using silica gel and EtOAc/hexanes as the eluent, if needed.

2-Methyl-4-(4-methylbenzyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3fa). 95% (253 mg); Oil, FTIR *v* = 3050, 2986, 1684, 1500, 1112 cm^{-1}; ^1H NMR ($CDCl_3$), δ = 1.66 (d, 3H, CH_3, *J* 5.0 Hz), 2.34 (s, 3H, Ar-CH_3), 4.78 (q, 1H, CH, *J* 5.0, 10.0 Hz), 5.15 (AB quartet, 2H, -NCH_2, *J* 15.0, 30.0 Hz), 6.93 (d, 2H, Ar-H, *J* 5.0 Hz), 6.97 (m, 1H, Ar-H), 7.02 (d, 1H, Ar-H, *J* 5.0 Hz), 7.17 (m, 4H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$) = 16.9, 20.6, 45.0, 73.6, 115.5, 117.2, 122.6, 123.9, 126.6, 129.1, 129.5, 132.2, 136.9, 144.9, 167.0 ppm; MS (70 eV) *m/z* 267 [M^+], 120, 105, 77; Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.55; H, 6.69; N, 5.05.

2-Ethyl-4-(4-methylbenzyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3fc). 92% (258 mg); Oil, FTIR *v* = 3047, 2971, 1684, 1501, 1119 cm^{-1}. ^1H NMR ($CDCl_3$), δ = 1.15 (t, 3H, CH_2CH_3, *J* 7.5 Hz), 2.0 (m, 2H, CH_2Me), 2.34 (s, 3H, Ar-CH_3), 4.63 (q, 1H, CH, *J* 5.0, 10.0 Hz), 5.15 (AB quartet, NCH_2, *J* 15.0, 85.0 Hhz), 6.98 (td, 2H, Ar-H, *J* 5.0, 5.0 Hz), 7.02 (d, 2H, d, *J* 5.0 Hz), 7.16 (m, 4H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$) = 8.9, 18.9, 23.4, 44.9, 78.3, 115.4, 117.3, 122.4, 123.9, 126.5, 128.9, 129.5, 133.2, 137.0, 143.6, 166.6 ppm; MS (70 eV) *m/z* 281 [M^+], 120, 105, 77; Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.10; H, 6.52; N, 5.15.

4-(4-*iso*Propylbenzyl)-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3ga). 93% (274 mg); Oil FTIR *v* = 3051, 2961, 1685 1500, 1111 cm^{-1}. ^1H NMR ($CDCl_3$), δ = 1.24 (d, 6H, CH**(**CH_3**)2**, *J* 10.0 Hz), 1.65 (d, 3H, $CHCH_3$, *J* 10.0 Hz), 2.9 (septet, 1H, $CHMe_2$), 4.78 (AB quartet, 1H, $CHCH_3$, *J* 5.0, 10.0 Hz), 5.14 (AB quartet, 2H, CH_2Ar, *J* 15.0, 32.5 Hz), 6.94 (m, 2H, ArH), 6.99 (m, 1H, ArH), 7.04 (d, 1H, ArH, *J* 10.0 Hz), 7.21 (bs, 4H, ArH) ppm. ^{13}C NMR ($CDCl_3$) = 16.5, 24.0, 33.8, 45.1, 73.6, 115.5, 117.2, 122.6, 123.9, 126.5, 126.9, 129.2, 133.5, 144.5, 148.0, 167.0 ppm; MS (70 eV) *m/z* 295 [M^+], 133, 117, 91; Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.45; H, 7.36; N, 5.02.

2-Ethyl-4-(4-*iso*propylbenzyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3gc). 93% (287 mg); Oil FTIR *v* = 3051, 2961, 1686, 1501, 1119 cm^{-1}. ^1H NMR ($CDCl_3$), δ = 1.14 (t, 3H, CH_2CH_3, *J* 7.5 Hz), 1.23 (d, 6H, $CH(CH_3)_2$, *J* 10.0 Hz), 1.98 (m, 2H, CH_2CH_3), 2.89 (septet, 1H, $CHMe_2$), 4.62 (AB quartet, 1H, $CHCH_2$, *J* 5.0, 10.0 Hz), 5.10 (AB quartet, 2H, CH_2Ar, *J* 15.0, 90.0 Hz), 6.90 (m, 2H, ArH), 6.98 (td, 1H, ArH, *J* 5.0, 10.0 Hz), 7.02 (d, 1H, ArH, *J* 10.0 Hz), 7.19 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$) = 9.5, 23.8, 23.9, 33.7, 44.9, 78.3, 115.4, 117.3, 122.4, 123.8, 126.5, 126.9, 129.0, 133.5, 144.0, 148.0, 166.6 ppm; MS (70 eV) *m/z* 309 [M^+], 133, 105; Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.87; H, 7.68; N, 4.69.

4-(3-Bromobenzyl)-2-ethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3hc). 91% (313 mg); Oil FTIR, *v* = 3050, 2971, 1685, 1500, 1119 cm^{-1}. ^1H NMR ($CDCl_3$), δ = 1.15 (t, 3H, CH_2CH_3, *J* 7.5 Hz), 2.0 (m, 2H, CH_2), 4.63 (AB quartet, 1H, CH, *J* 5.0, 10.0 Hz), 5.12 (AB quartet, 2H, $ArCH_2$, *J* 15.5, 62.5 Hz), 6.82 (d, 1H, ArH, *J* 10.0 Hz), 6.93 (t, 1H, ArH, *J* 7.5 Hz), 7.02 (m, 2H, ArH), 7.19 (m, 2H, ArH), 7.40 (bs, 2H, ArH)ppm. ^{13}C NMR ($CDCl_3$) = 9.5, 23.4, 43.9, 78.3, 115.1, 117.5, 122.6, 123.0, 124.2, 125.1, 128.7, 129.6, 130.4, 130.6, 138.6, 144.1, 166.6 ppm; MS (70 eV) *m/z* 345 [M^+], 169, 90; Anal. Calcd for $C_{17}H_{16}BrNO_2$: C, 58.98; H, 4.66; N, 4.05. Found: C, 58.74; H, 4.79; N, 4.27.

Acknowledgements

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Supplementary Material

Copies of ^1H and ^{13}C NMR spectra of new compounds are given in the Supplementary Material file associated with this article.

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