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[Omim][BF_4], a green and recyclable ionic liquid medium for the one-pot chemoselective synthesis of benzoxazinones

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ABSTRACT

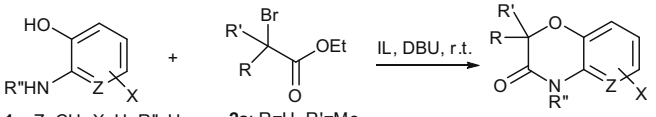
An efficient procedure for the one-pot chemoselective synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives from their corresponding *o*-aminophenols is developed using DBU in the ionic liquid [omim][BF_4]. Upon completion of the reaction and separation of the product, the ionic liquid is recovered and successfully reused over nine recycles without any noticeable loss of performance.

In line with increasing global environmental safety regulations, ionic liquids (ILs) have gained significant attention as appropriate media in various fields of chemistry.[1,2] In particular, by alteration of their cationic and anionic components, ILs with desired physical and chemical properties can be tailored to boost the selectivity and reactivity of various synthetic transformations.[3,4] As a result, ILs are very popular surrogates to the conventional organic solvents due to their ease of recovery, very low vapor pressure, increased thermal stability, ability to dissolve a wide range of organic compounds and long shelf lives.[5,6]

2*H*-Benzo[*b*][1,4]oxazin-3(4*H*)-ones (**3**) have been the subject of extensive research in synthetic[7,8] and medicinal organic chemistry.[9–15] Heterocycles **3** contribute to the structure of many important biologically active natural and synthetic compounds.[16–23] In the majority of methods, ring closure of *o*-aminophenols or *o*-nitrophenols with appropriately α-substituted carbonyl compounds or their synthetic equivalents have served as the main routes for the syntheses of **3**.[24] Typically, *o*-aminophenols are easier starting materials to work with and their reactions do not require the extra step of nitro group reduction associated with the use of *o*-nitrophenols.[25–28] A significant contribution towards the one-pot synthesis of products **3** was made by Dai et al. using microwave irradiation.[29,30] Nevertheless, many of the *o*-aminophenol annulation methods either require multi-step reactions, involve heating at high temperatures, lead to low or moderate yields of products, are limited to electron-rich reactants or demand the use of the commercially unavailable starting materials. On the basis of our studies on heterocyclic systems,[31–33] and in continuation of our previous investigations on the development of environmentally friendly procedures,[34–36] we report here our preliminary results obtained on the IL-mediated annulation of *o*-aminophenols **1** with 2-bromoalkanoates **2** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1). The procedure presents a one-pot reaction which is mild, involves a broad range of starting materials, takes place at room temperature and offers the possibility to recycle the IL efficiently.

The initial reactions of *o*-aminophenol (**1a**) with ethyl 2-bromopropionate (**2a**), conducted to optimize the conditions, are summarized in Table 1. Among various carbonate bases used in [omim][BF_4][37] as the IL (entries 1–3), Cs_2CO_3 showed the best performance (12 h reaction time) and selectively gave the desired product **3aa** in 80% yield (entry 3). $NaHCO_3$ (entry 4), KF (entry 5) and CsF (entry 6) were unable to induce significant formation of **3aa**. In the search for other mild bases to convert efficiently the starting materials to **3aa**, we next examined the effect of several amines in the reaction (entries 7–10), where DBU exhibited the best performance producing **3aa** in 93% yield after 2 h (entry 11). When the reaction was conducted in the absence of the IL (entry 12), no formation of **3aa** was noticed even after 24 h. Alternatively, omission of DBU also led to no detectable quantities of the product after the same time period (entry 13) illustrating the crucial roles of both the IL and DBU in the reaction. Other ILs were prepared[38,39] and used as the reaction medium (entries 14–21) leading to lower yields of **3aa** after 2 h.

Next, the optimized conditions ([omim][BF_4]/DBU) were employed to examine the generality of the procedure (Table 2).[40]



1a: Z=CH, X=H, R"=H
1b: Z=CH, X=4-Me, R"=H
1c: Z=CH, X=4-Cl, R"=H
1d: Z=CH, X=4-NO_2, R"=H
1e: Z=CH, X=H, R"=CH_2Ph
1f: Z=N, X=H, R"=H

2a: R=H, R'=Me
2b: R=H, R'=H
2c: R=Me, R'=Me

3

Scheme 1.

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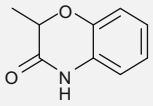
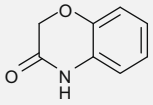
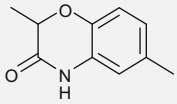
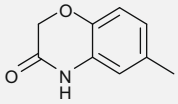
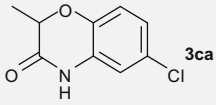
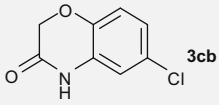
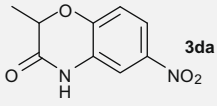
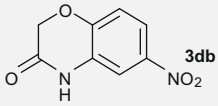
Table 1
Optimization of the reaction conditions for the synthesis of **3aa**

Entry	Conditions	Time (h)	Yield[a] (%)
1	[omim][BF_4]/Na_2CO_3	24	10
2	[omim][BF_4]/K_2CO_3	24	20
3	[omim][BF_4]/Cs_2CO_3	12	80
4	[omim][BF_4]/$NaHCO_3$	24	0
5	[omim][BF_4]/KF	24	0
6	[omim][BF_4]/CsF	24	10
7	[omim][BF_4]/Et_3N	24	18
8	[omim][BF_4]/pyridine	24	0
9	[omim][BF_4]/DABCO	24	0
10	[omim][BF_4]/DBN	2	85
11	[omim][BF_4]/DBU	2	93
12	DBU	24	0
13	[omim][BF_4]	24	0
14	[bmim][BF_4]/DBU	2	80
15	[opy][BF_4]/DBU	2	85
16	[bpy][BF_4]/DBU	2	81
17	[omim]Cl/DBU	2	80
18	[omim][NO_3]/DBU	2	82
19	[bmim]Cl/DBU	2	79[b]
20	[bmim][NO_3]/DBU	2	71
21	[omim][PF_6]/DBU	2	59

[a] Isolated yield.
[b] Reaction conducted at 50 °C.

Table 2
[Omim][BF_4] mediated synthesis of benzoxazinones

Entry	Product	Time (h)	Yield[a] (%)
1	 **3aa**	2	93
2	 **3ab**	1	86
3	 **3ba**	0.5	88
4	 **3bb**	1	87
5	 **3ca**	1.5	84
6	 **3cb**	2	83
7	 **3da**	2	78
8	 **3db**	2.5	73

[a] Isolated yield.

Reactions of unsubstituted *o*-aminophenol (**1a**) with 2-bromoalkanoates **2a** and **2b**, gave high yields of products within 1–2 h (entries 1 and 2). Electron-releasing *p*-methyl-substituted aminophenol **1b** also gave the expected products **3ba–bb** in short time periods (entries 3 and 4). Interestingly, aminophenols bearing electron-withdrawing groups, which in many cases are reported to undergo cyclization with much lower efficiency,[41,42] behaved equally well under the optimized conditions, giving high yields of the respective products in slightly longer times (entries 5–8).

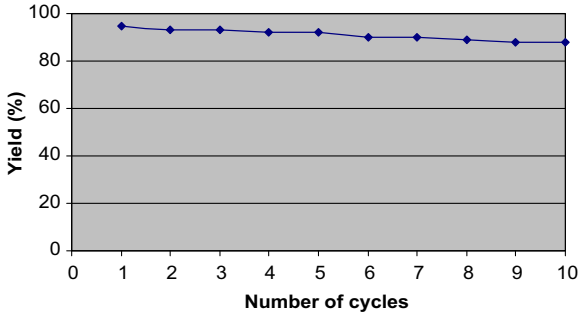
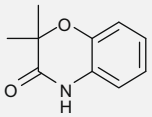
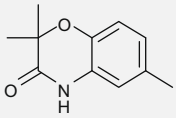
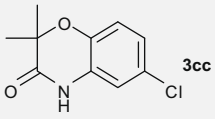
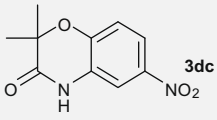


Figure 1. Efficient recycling of the catalyst.

In all cases, the reactions were completed rapidly at room temperature and the products were easily separated by extraction with Et_2O. The IL was recovered and reused in the subsequent reactions without significant loss of activity as shown in 10 consecutive reactions of **1a** with **2a** (Fig. 1).

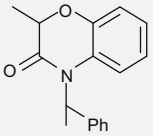
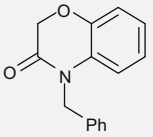
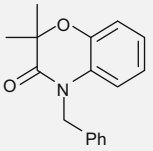
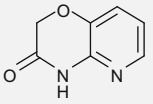
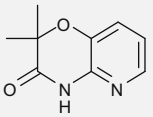
A comparison of the results with previous related investigations[24–30] clearly verifies the superiority of the current method, where both primary and secondary 2-bromoalkanoates react to give high yields of benzoxazinones in short time periods. This encouraged us to further investigate the applicability of the procedure in engaging less reactive substrates. For example, there is very limited precedence for one-pot annulations of *o*-aminophenols with 2-bromoalkanoates bearing tertiary carbons at their α position (i.e., **2c**). Such substrates usually give moderate to low yields of products using either high temperature reactions[43] or step-wise procedures.[24,44] Another less reactive group of substrates are *N*-alkyl substituted *o*-aminophenols which require high temperatures (conventional or microwave) and mixtures of solvents to give good or moderate quantities of products.[29] As shown in Table 3, both types of the starting materials underwent cyclization reactions. Reactions of sterically hindered **2c** with **1a–d** rapidly gave benzoxazinones **3ac–dc** in high yields (entries 1–4). Similar results were

Table 3
[Omim][BF_4] mediated reactions of less reactive substrates

Entry	Product	Time (h)	Yield[a] (%)
1	 **3ac**	2	94
2	 **3bc**	1	94
3	 **3cc**	2.5	95
4	 **3dc**	3	91

(*continued on next page*)

Table 3 (*continued*)

Entry	Product		Time (h)	Yield[a] (%)
5		**3ea**	8	93[b]
6		**3eb**	7	95[b]
7		**3ec**	12	92[b]
8		**3fb**	1.5	80
9		**3fc**	2	94

[a] Isolated yield.
[b] Reaction conducted at 80 °C.

observed for the reactions of (benzylamino)phenol **1e** with **2a–c** (entries 5–7). The generality of the procedure was shown further by subjecting the heterocyclic 2-aminopyridin-3-ol **1f**, to annulation with 2-bromoalkanotes **2b** and **2c** (entries 8 and 9).

Based on the observed results, a mechanistic pathway can be suggested for the procedure where initial deprotonation of the hydroxy group of the *o*-aminophenol provides the phenolate required to attack **2**. This is then followed by in situ annulation of the ethyl aminophenoxyalkanoate intermediate to give the product (Fig. 2).

In summary, a very convenient procedure is developed for the room temperature, one-pot annulation of *o*-aminophenols with 2-bromoalkanoates of different steric demand. The reactions are chemoselective and give high yields of products in short times. The IL is used in minimum quantity and, upon completion of the reactions, is recovered and reused efficiently without any noticeable loss of activity. The generality of the reaction and its efficient engagement of electron-deficient *o*-aminophenols and sterically hindered 2-bromoalkanotes make it an interesting and useful addition to the present methods. Similar annulation of *o*-aminothiophenols and phenylenediamines with various acceptors is currently under investigation in our laboratory.

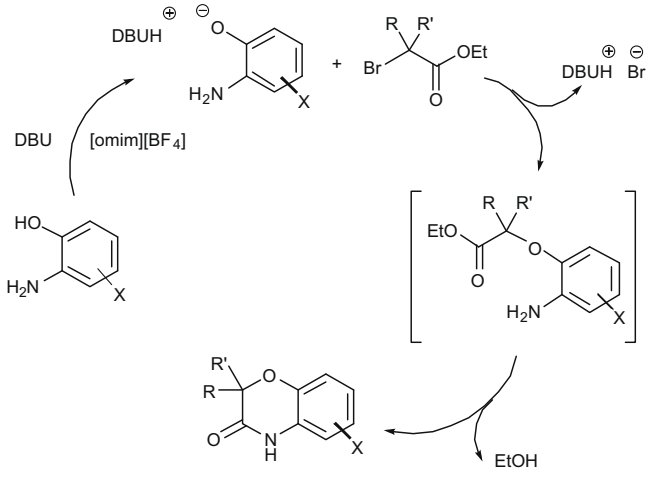


Figure 2. Suggested mechanism of the reaction.

Acknowledgements

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Supplementary data

Supplementary data (Spectra of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.122.

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40. *Typical procedure:* A mixture of **1** (1 mmol), **2** (1.1 mmol) and DBU (172 μL, 1.2 mmol) in [omim][BF_4] (780 μL, 3 mmol) was stirred at room temperature for the appropriate length of time. After completion of the reaction, based on TLC monitoring, the reaction mixture was extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel and EtOAc/hexanes as eluent, if necessary. The IL was recovered by removing its ether content (under reduced pressure at 50 °C for 1 h using a rotary evaporator) and reused in subsequent reactions. Products **3aa**, **3ab**, **3ba**, **3ca**, **3cb**, **3cc**, **3da**, **3db** and **3dc** are known and their identity was confirmed by comparison of their spectroscopic data with those available in the literature. New products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectra (available in Supplementary data) and their purity was confirmed by elemental analysis.
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