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Organic Reactions in Ionic Liquids: Ionic Liquid-promoted Three-component Condensation of Benzotriazole with Aldehyde and Alcohol

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Abstract: 1-(α-Alkoxyalkyl)benzotriazoles are readily synthesized from three-component condensation of benzotriazole with aldehyde and alcohol in ionic liquid [Bmim]PF_6.

Keywords: Ionic liquid, benzotriazole, condensation.

Combinatorial chemistry has gained importance as a tool for the synthesis of a wide variety of useful compounds including pharmaceuticals[1]. In this context, the multiple component condensation (MCC) approach is especially appealing due to its simplicity and environmentally benign. 1-(α-Alkoxyalkyl)benzotriazoles are of great importance for biochemistry and antitumor activity[2]. Generally, 1-(α-alkoxyalkyl)benzotriazoles were prepared by condensation of benzotriazole with aldehyde and alcohol[3]; reaction of 1-(α-chloroalkyl)benzotriazole with alkoxide[4]; acetal or ketal with benzotriazole[5]; or reaction of benzotriazolylmethyl methyl ether with lithiation and halide[6]. Among these methods, the three-component condensation of benzotriazole, aldehyde and alcohol is most satisfactory. However, the reaction needed special Soxhlet apparatus[3,4b] and long refluxing times[7]. In addition, the use of harmful organic solvents is undesirable from the view of environmental consciousness. Therefore, to develope a mild efficient, environmentally more benign method for synthesis of 1-(α-alkoxyalkyl) benzotriazoles is still needed.

Scheme 1

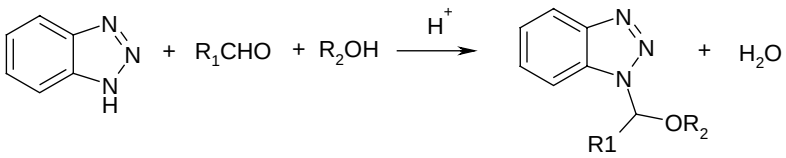

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Table1 Condensation of benzotriazole, butyric aldehyde and methanol in different ionic liquids

Entry[a]	Ionic liquid	Yield[b] (%)
1	$[Bmim]PF_6$	97
2	$[Bmim]BF_4$	90
3	$[BuPy]BF_4$	88

[a] All reaction were run with benzotriazole (2 mmol), butyric aldehyde (3 mmol), methanol (4 mmol), and sulphuric acid (1 drop) in ionic liquid (2 mL) at 80 ^oC for 0.5 h.
[b] Isotated yield base on benzotriazole.

In recent years, the room temperature ionic liquids are attracting increasing interest as a 'green' recyclable alternative to classical molecular solvents for synthetic organic chemistry[8]. To date, some important reactions have been carried out and investigated, and it has been demonstrated that some reactions in ionic liquids show rate acceleration[9]. Our recent interest is in the development of new synthetic method using ionic liquids as novel environmentally benign reaction media and promoters[10]. As a part of program to investigate the range of organic reactions possible in ionic liquids, we tried the convenient and rapid synthesis of 1-(α-alkoxyalkyl)benzotriazoles by ionic liquid-accelerated three-component reaction.

First, we examined the efficacy of different ionic liquids in the three-component condensation of benzotriazole with butyric aldehyde and methanol. We found that in the presence of catalytic amount of sulphuric acid, the reaction occurred easily at 80 ^0C in ionic liquids and completed within 0.5 hr to give 1-(α-methoxybutyl)benzotriazoles in high yields. The results are summarized in **Table1**. The results show that $[Bmim]PF_6$ gives the best results in terms of yield.

Then the scope of the condensation of benzotriazole with various aldehydes and alcohols in ionic liquid $[Bmim]PF_6$ was investigated. The results showed that the condensation of benzotriazole with aldehyde and alcohol occurred easily in ionic liquid $[Bmim]PF_6$ at 80 ^oC in the presence of catalytic amount of sulphuric acid, the reaction completed within 0.5h to form the corresponding 1-(α-alkoxyalkyl)benzotriazoles with high yields. The results are summarized in **Table 2**. In order to compare with the traditional procedure, some literature data are also summarized in **Table 2**.

The m.p., IR and ^{1}HNMR data of all the products were consistent with the literature data. As can be seen from **Table 2**, this reaction condition is applicable to various alphatic aldehydes and alcohols.

The ionic liquid can be recovered after extracting the product with ether and drying at vacuum. The recovered ionic liquid can be reused. The results are summarized in **Table 3**.

The present method has many obvious advantages compared to the conventional method, including rate acceleration, environmentally more benign, the simplicity of isolation of the product, higher yield, and possibility of recycling of the ionic liquid.

In conclusion we have demonstrated that the three-component condensation of benzotriazole with aldehyde and alcohol, can effectively be performed in ionic liquid $[Bmim]PF_6$ at 80 ^oC. The ionic liquid plays the dual role of solvent and promoter.

Table 2 Condensation of benzotriazole with aldehyde and alcohol in ionic liquid [Bmim]PF_6

Entry[a]	R_1	R_2	Yield[b] (%)	Lit. yield (%) (Reaction time)
1	Me	Me	80	75[3] (3h)
2	Pr	Me	97	59[7] (3h)
3	Pr	Et	94	65[7] (3h)
4	Pr	*i*-Pr	92	76[7] (4h)
5	Pr	Bu	87	76[7] (4h)
6	Pr	*i*-Bu	90	76[7] (5h)
7	Pr	*c*-hexyl	91	
8	*i*-Pr	Me	98	99[3] (3h)
9	*i*-Pr	*i*-Bu	95	
10	*i*-Pr	*i*-Pr	96	96[3] (3h), 97[4b] (4h)

[a] All reaction were run with benzotriazole (2 mmol), aldehyde (3 mmol), alcoholl (4 mmol),and sulphuric acid (1 drop) in ionic liquid [Bmim]PF_6 (2 mL) at 80 ^oC for 0.5 h.
[b] Isotated yield base on benzotriazole.

Table 3 The yield of the product with recycled [Bmim]PF_6 [a]

Entry	Cycle	Yield [b] (%)
1	1	98
2	2	96
3	3	97
4	4	95
5	5	95

[a] All reaction were run with benzotriazole (2 mmol), butyric aldehyde (3 mmol), methanol (4 mmol),and sulphuric acid (1 drop) in ionic liquid [Bmim]PF_6 (2 mL) at 80 ^oC for 0.5 h.
[b] Isotated yield base on benzotriazole.

Experimental

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on a VECTOR22 (Bruker). Nuclear magnetic resonance spectra were recorded on a AVANCE DMX400 (Bruker) spectrometer. Gas chromatographic analysis was performed on a Beckman model GC-2A gas chromatograph. The ionic liquids [Bmim][BF_4] and [Bmim][PF_6] were synthesized according to reported procedures[11]. All materials are commercially available and were used without further purification.

Benzotriazole (2 mmol), aldehyde (3 mmol), alcohol (4 mmol), sulphuric acid (1 drop) and [Bmim][PF_6] (2 mL) were stirred for 0.5 h at 80 ^oC. The reaction mixture was extracted with ether (3 ×5 mL). The combined ethereal phase was evaporated under reduced pressure to give crude product, which was separated by the preparative thin-layer chromatography (silica gel). After isolation of the product, the ionic liquid can be recovered simply by drying at vacuum.

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12. 1-(α-Cyclohexoxybutyl)benzotriazoles: oily compound, ^{1}HNMR($CDCl_3$, δ ppm): 8.09(dd, 1H, *J*=8.4, 1.0Hz), 7.84(dd, 1H, *J* = 8.4, 1.2Hz), 7.48(m, 1H), 7.40(m, 1H), 6.23(t, 1H, *J*=6.8Hz), 3.26(m, 1H), 2.20-1.10(m, 14H), 0.97(t, 3H, *J* = 7.2Hz). MS (EI): *m/z* 274 (M+1), 155, 120, 104, 91, 83, 73, 55 (base), 43. IR (neat): 3062, 2934, 1614, 1451, 1113, 1086, 748cm^{-1}. 1-(α-*i*-Butoxy-*i*-butyl)benzotriazoles: oily compound, ^{1}HNMR($CDCl_3$, δ ppm): 8.09(dd, 1H, *J* = 8.4, 0.8Hz), 7.78(dd, 1H, *J* = 8.4, 1.2Hz), 7.48(m, 1H), 7.39(m, 1H), 5.65(d, 1H, *J* =8.8Hz), 3.22(d, 1H, *J* = 7.2Hz), 2.98(m, 1H), 2.57(m, 1H), 1.84(m, 1H), 1.22(d, 3H, *J* = 7.0Hz), 0.92 (d, 3H, *J* = 6.8Hz), 0.85(d, 3H, *J* = 6.8Hz), 0.65(d, 3H, *J* = 7.2Hz). MS (EI): *m/z* 248 (M+1), 220, 204, 176, 129, 120 (base), 104, 91, 77, 73, 57, 43. IR (neat): 3063, 2965, 1614, 1492, 1471, 1098, 803, 748 cm^{-1}.

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