Organic reactions in ionic liquids: an efficient method for the *N*-alkylation of benzotriazole

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The *N*-alkylation of benzotriazole with alkyl halides proceeds efficiently in the presence of potassium hydroxide in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]).

Keywords: ionic liquids, *N*-alkylation, benzotriazole

In recent years benzotriazole has been developed as a synthetic auxiliary.[1] 1-and 2-alkylbenzotriazoles are of wide interest due to their biological activities as herbicides, insecticides and acricides.[2,3] It has been reported that the *N*-alkylation of benzotriazole can be achieved by use sodium or potassium alkoxides[2,4] or sodium hydride[5] as base, or phase-transfer catalysis(PTC) with quaternary ammonium salt,[6] with crown ethers,[7] or with polyethylene glycols(PEG), or their dialkyl ether (PEG ether).[8] *N*-alkylatioin of benzotriazole can also be achieved without a solvent either in basic media or in the absence of base by conventional and microwave heating. However, some of these methods suffer from disadvantages such as the use of strong base and toxic solvent or catalysts, the lower yields of the products. An improved method for the *N*-alkylation of benzotriazole was reported by Katrittzky *et al.*,[10] which employs DMF as the solvent and NaOH as the base. In this method, although the yields are often superior to those previously reported, there are some disadvantages, in particular, connected to the use of DMF. DMF is toxic, and the product is isolated by aqueous work-up which generates a large amount of waste from which the solvent cannot be recovered.

In recent years, room temperature ionic liquids (RTIL) have attracted increasing interest as a 'green' recyclable alternative to classical molecular solvents for synthetic organic chemistry.[11] To date some of the more important reactions have been carried out and investigated, for example, Diels–Alder reactions, Friedel–Crafts reactions, Heck reactions, Suzuki reaction, Wittig reactions, hydrogenation, *etc*.[12]

We have investigated clean synthesis using ionic liquids as novel environmentally benign reaction media. We have already reported the use of ionic liquids in organic synthesis, such as α-tosyloxylation of ketones,[13] cyclocondensation of α-tosyloxyketones with 2-aminopyridine,[14] and the Knoevenagel condensation catalysed by ethylene-diammonium diacetate.[15] As part of a program to investigate the range of organic reactions possible in ionic liquids, we now report the use of ionic liquids for the *N*-alkylation of benzotriazole.

We found that the reaction of benzotriazole with methyl iodide could proceed smoothly at room temperature in ionic liquid 1-butyl-3-methylimidazolium tetraflouoroborate ([Bmim][BF_4]) in the presence of potassium hydroxide to

Table 1 The *N*-alkylation of benzotriazole in ionic liduids [Bmim][BF_4][a]

Entry	Alkylating agent	Product no.	Reaction time/h	Total yield /%[b]	Ratio of isomer (3:4)	Lit. yield/%
1	CH_3I	**3a**	2.0	95	72:28	70[4],70[7] ,95[10]
		4a	2.0	88[c]	71:29	
2	C_2H_5Br	**3b**	2.0	92	65:35	91[8]],79[10]
		4b				
3	*n*-C_3H_7Br	**3c**	2.0	86	63:37	76[9] ,80[10]
		4c				
4	*i*-C_3H_7Br	**3d**	3.0	92	66:33	
		4d				
5	*i*-C_3H_7I	**3d**	3.0	96	65:35	80[10]
		4d				
6	*n*-C_4H_9Cl	**3e**	3.0	83	63:37	
		4e	3.0	98[d]	64:36	
7	*n*-C_4H_9Br	**3e**	2.5	96	63:37	83[1],78[7],86[10], 61[9]
		4e				
8	$PhCH_2Cl$	**3f**	1.5	97	74:26	89[8],60[9] , 95[17]
		4f	1.5	89[c]	73:27[c]	
9	$PHCH_2Br$	**3f**	1.5	98	74:26	99[10]
		4f				
10	$ClCH_2COOC_2H_5$	**3g**	4.0	98	77:23	95[10] ,57[17]
		4g				
11	$BrCH_2COPh$	**3h**	2.0	94	74:26	98[10]
		4h				

[a]All reaction were run with benzotriazole (5mmol), KOH (15mmol), alkylating reagent (6mmol) in [Bmim][BF_4] (2ml) at room temperature.
[b]Isolated yield.
[c]Ionic liquid is [Bmim][PF_6].
[d]Reaction temperature is 60 °C.

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form the corresponding *N*-methylated benzotriazole in 86% yield (Scheme 1).

Benzotriazole reacts with electrophiles to give mixtures of 1-substituted (**3**) and 2-substituted (**4**) products.[10] In the methylation of benzotriazole, the isomer ratio 3:4 is 72:28. Although the related ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim] [PF_6]) is similarly effective, although there is a small decrease in yield (Entries 1, 8).

In a similar fashion, a variety of alkylating reagents reacted smoothly with benzotriazole under these reaction conditions to give the corresponding *N*-alkylated benzotriazoles. The results are summarised in Table 1. All the products gave satisfactory m.p., IR and ^{1}H NMR data which are consistent with the literature data. As can be seen from Table 1, the reaction is general and applicable to primary and secondary halides and which involve iodised, bromide and chloride and the yield of *N*-alkylated benzotriazoles are higher (83–98%) than that of literature. In order to compare with previous methods, some literature data are also summarised in Table 1.

The ionic liquid can be typically recovered, the solvent can be reused by drying in vacuum first and filtering the suspension to remove the residual salt. The recovered solvent can be reused with no appreciable decrease in yield. The results are summarised in Table 2.

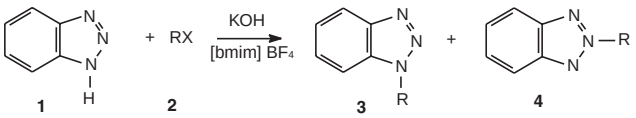
In conclusion, we have demonstrated that the *N*-alkylation of benzotriazole with alkyl halides can effectively be performed at room temperature in the presence of potassium hydroxide in ionic liquid [Bmim][BF_4], which provides a simple efficient method for the synthesis of *N*-alkylated benzotriazoles. The present method has many obvious advantages compared to those reported in the literature, including avoiding the use of toxic solvent or catalyst, being environmentally more benign, the simplicity of the methodology, the ease of product isolation, the higher yield and the potential for recycling of ionic liquids.

Experimental

Melting points were determined on digital melting point apparatus and were not corrected. IR spectra were recorded on a VECTOR22 (Bruker). NMR spectra were recorded on a AVANCE DMX400 (Bruker) spectrometer. Gas chromatographic analyses were performed on a Beckman model GC-2A gas chromatograph. The ionic liquids [Bmim][BF_4] and [Bmim][PF_6] were synthesised according to reported procedures.[16] All materials are commercially available and were used without further purification.

General procedure for the *N*-Alkylation of benzotriazole

KOH 0.84g (15mmol) was added to [Bmim][BF_4] (2ml), the mixture was stirred while the benzotriazole (5mmol) and alkylating reagent (6mmol) were introduced as a single portion, stirring was continued for 1.0–4.0h (reaction times given in Table 1) at room temperature (*ca* 20 °C). The reaction mixture was extracted with ether (4 × 5ml). The combined ethereal phase was evaporated under reduced pressure to give a crude product. Isomers were separated by the preparative TLC (silina gel; ethyl acetate / cyclohexane = 3:7). After isolation of the product, the remainder of the ionic liquid can be typically recovered by drying in vacuum first and filtering the suspension to remove the residual potassium salt.



Scheme 1

Table 2 Recycling of [Bmim][BF_4] in the methylation of benzotriazole

Entry	Cycle	Yield [a] (%)
1	1	88
2	2	86
3	3	87

[a] Isolated yield

Spectroscopic data: **3a:** m.p. 63–64°C.[lit.[10a] m.p. 64–66 °C]. ^{1}H NMR ($CDCl_3$): δ 4.29 (s, 3H), 7.36 (m, 1H), 7.49 (m, 2H), 8.04 (d, 1H). IR (KBr): 3049, 2924, 1615, 1497, 1451, 1384, 1299, 780, 739.

4a: ^{1}H NMR($CDCl_3$): δ 4.51 (s, 3H), 7.36 (m, 2H), 7.85 (m, 2H). IR (KBr): 3060, 2953, 1568, 1498, 1451, 1347, 1327, 1314, 845, 747.

3b: ^{1}H NMR ($CDCl_3$): δ 1.63 (q, 3H), 4.70 (t, 2H), 7.37 (m, 1H), 7.50 (m, 2H), 8.06 (m, 1H). IR (KBr): 3066, 2937, 1677, 1615, 1496, 1456, 1384, 1318, 1173,772, 746.

4b: ^{1}H NMR($CDCl_3$): δ 1.73 (q, 3H), 4.80 (t, 2H), 7.39 (m, 2H), 7.88 (m, 2H). IR (KBr): 3066, 2985, 2941, 1567, 1446, 1370, 1328, 1280, 826, 747.

3c: ^{1}H NMR($CDCl_3$): δ 0.96 (t, 3H), 2.16 (m, 2H), 4.67 (t, 2H), 7.36 (m, 1H), 7.50 (m, 2H), 8.09 (d, 1H). IR (KBr): 3065, 2968, 2936, 2878, 1615, 1590, 1495, 1455, 1385, 1305, 1269, 1231, 802, 746.

4c: ^{1}H NMR($CDCl_3$): δ 1.00 (t, 3H), 2.18(m, 2H), 4.72(m, 2H), 7.39(m, 2H), 7.88(m, 2H). IR (KBr): 3067, 2969, 2878, 1567, 1497, 1459, 1444,1386,1327, 1283, 1202, 1104, 939, 747.

3d: ^{1}H NMR($CDCl_3$): δ 1.71 (d, 6H), 5.06 (m, 1H), 7.33 (m, 1H), 7.44 (m, 1H), 7.56 (d, 1H), 8.04 (d, 1H). IR (KBr): 3067, 2984, 1674, 1431, 1241,746.

4d: ^{1}H NMR($CDCl_3$): δ 1.75 (d, 6H), 5.17 (m, 1H), 7.38 (m, 2H), 7.88 (m, 2H). IR (KBr): 3066, 2985, 2935, 1567, 1447, 1370, 1273, 1323, 747.

3e: ^{1}H NMR($CDCl_3$): δ 0.83 (t, 3H), 1.23 (m, 2H), 1.87 (m, 2H), 4.51 (t, 2H), 7.22 (m, 1H), 7.34 (m, 1H), 7.42 (d,2H), 7.93 (d,1H). IR (KBrfilm): 3065, 2960, 2874, 1678, 1615, 1495, 1455, 1295, 1160, 778, 746.

4e: ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H), 1.33 (m, 2H), 4.67 (t, 2H), 7.31 (m, 2H), 7.82 (m, 2H). IR (KBr): 3067, 2961, 2874, 1567, 1465, 1380, 1327, 1281, 1105, 746.

3f: m.p.114–115°C. [lit.[10a] m.p. 115–117°C]. ^{1}H NMR ($CDCl_3$): δ 5.85 (s, 2H), 7.29–7.41 (m, 8H), 8.07 (d, 1H). IR (KBr film): 3066, 3030, 1615, 1588, 1496, 1456, 1365, 1325, 1262, 1225, 747, 721, 695.

4f: m.p.30–31°C. [lit.[10a] m.p. 30–32 °C]. ^{1}H NMR ($CDCl_3$): δ 5.95 (s, 2H), 7.43 (m, 7H), 7.92 (m, 2H). IR (KBr): 3065, 3031, 1614, 1588, 1454, 1322, 747, 720, 694.

3g: m.p.81–82°C. [lit.[10a] m.p. 81–82°C]. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H), 4.28 (q, 2H), 5.45 (s, 2H), 7.43 (m, 1H), 7.53 (m, 2H), 8.11(d, 1H). IR (KBr): 2979, 2942,1755, 1617, 1499, 1472, 1456, 1377, 1320, 1213, 1104, 790, 745.

4g: m.p. 119–120°C. [lit.[10a] m.p. 120–121 °C]. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H), 4.29 (q, 2H), 5.54 (s, 2H), 7.43 (m, 2H), 7.94 (m, 2H). IR (KBr): 3055, 3001, 2987, 2959, 1749, 1637, 1618, 1566, 1396, 1375, 1337, 1209, 755.

3h: m.p. 116–117°C. [lit.[10a] m.p. 116–117 °C]. ^{1}H NMR ($CDCl_3$): δ 6.07 (s, 2H), 7.32 (m, 3H), 7.51 (m, 2H), 7.59 (m, 1H), 8.02 (m, 3H). IR (KBr): 3066, 2927, 1690, 1638, 1617, 1501, 748, 621.

4h: m.p. 157–158°C. [lit.[10a] m.p. 156–158 °C]. ^{1}H NMR ($CDCl_3$): δ 6.22 (s, 2H), 7.40 (m, 2H), 7.59 (m, 2H), 7.67 (m, 1H), 7.92 (m, 2H), 8.15 (d, 2H). IR (KBr): 3065, 2940, 1700, 1636, 1617, 1452, 1228, 753, 691.

Received 1 August 2003; accepted 20 November 2003
Paper 03/2046

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