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ORGANIC REACTIONS IN IONIC LIQUIDS: A SIMPLE HIGHLY REGIOSELECTIVE OR REGIOSPECIFIC SUBSTITUTIONS OF BENZOTRIAZOLE

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Abstract - In the absence of any added base in ionic liquids [Bmim][BF_4], benzotriazole replaces the halogen atom of an α-halogenated ketone or α-halogenated carboxylic ester to give the corresponding *N*-1-substituted benzotriazole as the only isomer, and 1-chloro-2,4-dinitrobenzene reacted similarly with benzotriazole to afford the *N*-1-substituted benzotriazole in a good yield. Alkyl halides reacted regioselectively to afford the *N*-1-alkylbenzotriazole in ratios of more than 15 to 1 over the *N*-2-isomer.

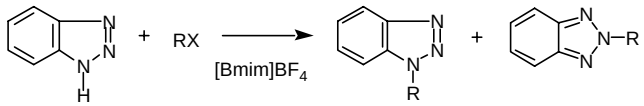
INTRODUCTION

Benzotrizole derivatives have been used as valuable intermediates and pharmaceutically important compounds.[1] It has been demonstrated that simple 1- and 2-alkylbenzotriazoles showed significantly different reactivity patterns towards lithium dissopropylamide (LAD) at –78°C in tetrahydrofuran.[2] They also have different biological activities as plant-growth regulators. 1-Alkylbenzotriaszoles are of wide interest as herbicides,[3] insecticides[4] and acaricides.[5] *N*-1-Substituted benzotriazoles (Bt-1) are usually prepared as a mixture with their *N*-2-substituted isomers (Bt-2) by reaction of benzotriazole with the corresponding alkylating reagents or halogen derivatives in the presence of a base and are subsequently separated. In these methods, most regioselectivity of 1-alkylated benzotriazoles are poor, the ratio of Bt-1/Bt-2 is about 1/1 to 3/1.[6,7] The development of highly regioselective or regiospecific synthetic method is a major challenge in modern organic synthesis. Recently Katritzky *et al.*[8] reported an improved method for *N*-substitution of benzotriazole with higher regioselectivity. But this method is limited by lengthy reaction time, using toxic, volatile solvent and sometime to give lower yield etc. Therefore, the development of a simple regiospecific or highly regioselective, environmentally more benign substitutions of benzotriazole is still urgent.

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.[9] To date some of the more important reactions have been carried out and investigated, and it has been demonstrated in some cases the reactions in ionic liquids show high selectivity or rate acceleration compared to conventional solvents.[10]

Our recent interest has been in the development of new synthetic method using ionic liquids as novel

environmentally benign reaction media and promoters.[11] As part of a program to investigate the range of organic reactions possible in ionic liquids, we examined the reaction of benzotriazole with alkylating reagents in the absence of any added base in ionic liquids (Scheme 1), which would provide a highly regioselective or regiospecific synthetic method for the preparation of 1-substituted benzotriazoles.



1 2 3 4

Scheme 1

RESULTS AND DISCUSSION

First, we found not only the reaction of benzotriazole with propyl bromide could proceed smoothly at 70 ^{o}C in ionic liquid 1-butyl-3-methylimidazolium tetraflouoraborate [Bmim][BF_4] for 30 h without an added base, but the yield and regioselectivity are dramatically high, the yield of 1-propylbenzotriazole is 83%, and the ratio of Bt-1/Bt-2 is 15:1 (Table 1, Entry 1). In similar fashion, the reaction of benzotriazole with a variety of halogen derivatives was investigated. We found that the reaction is general and applicable to primary and secondary bromides (Table 1, Entries1-3,5,7), allyl and benzyl bromide (Table 1, Entries 8,10), activated chloride (Table 1, Entry 9). But the reaction of butyl chloride with benzotriazole gave the lower yield of 1-*N*-butylbenzotriazole (Table 1, Entry 4). It is noteworthy that *tert*-butyl bromide could efficiently react, but its regioselectivity was poor (Table 1, Entry 6). 1-Chloro-2,4-dinitrobenzene reacted similarly with benzotriazole to afford the *N*-1-substituted benzotriazole in quantitative yield (Table 1, Entry 11). The reaction of benzotriazole with α-halogenated carbonyl compounds in ionic liquid [Bmim][BF_4] gave the *N*-1-substituted α-benzotriazol-1-ylcarbonyl derivatives as the only isomer (Table 1,Entries 12-13). Reaction of benzotriazole under the current conditions with α-tosyloxyacetophenone gave α-benzotriazol-1-ylacetophenone quantitatively (Table 1, Entry 14). α-Benzotriazol-1-ylacetic ester was obtained by the reaction of benzotriazole with ethyl α-bromoacetate without any hydrolysis side reation (Table 1, Entry 15).

Table 1 The *N*-substitutions of benzotriazole in ionic liquid [Bmim][BF_4][a]

Entry	RX	Product No	Reaction condition	Bt-1 yield[b] (%)	Bt-1/Bt-2[d]
1	C_3H_7Br	**3a, 4a**	70 ^{o}C, 30 h	83 (80)[c]	15:1
2	*i*-C_3H_7Br	**3b, 4b**	60 ^{o}C, 30 h	70	11:1
3	*n*-C_4H_9Br	**3c, 4c**	80 ^{o}C, 30 h	85 (80)[c]	15:1
4	*n*-C_4H_9Cl	**3c, 4c**	70 ^{o}C, 30 h	10	15:1
5	*s*-C_4H_9Br	**3d, 4d**	80 ^{o}C, 30 h	65	11:1
6	*t*-C_4H_9Br	**3e, 4e**	80 ^{o}C, 48 h	38 (36)[c]	1:1
7	$C_5H_{11}Br$	**3f, 4f**	80 ^{o}C, 30 h	78	15:1
8	allyl bromide	**3g, 4g**	70 ^{o}C, 20 h	90	10:1
9	$PhCH_2Cl$	**3h, 4h**	80 ^{o}C, 20 h	91	14:1
10	$PhCH_2Br$	**3h, 4h**	80 ^{o}C, 20 h	93	14:1
11	1-chloro-2,4-dinitrobenzene	**3i**	100 ^{o}C, 50 h	99	∞
12	$PhCOCH_2Br$	**3j**	80 ^{o}C, 10 h	99	∞
13	*p*-$ClC_6H_4COCH_2Br$	**3k**	80 ^{o}C, 10 h	98 (98)[c]	∞
14	$PhCOCH_2OTs$	**3j**	80 ^{o}C, 10 h	100	∞
15	$BrCH_2COOC_2H_5$	**3l**	80 ^{o}C, 8 h	99	∞

[a]All reaction were run with benzotriazole (2 mmol), RX (4 mmol) in ionic liquid [Bmim][BF_4] (2 mL).

[b]Determined by GC analysis based on benzotriazole.

[c]Isolated yield based on benzotriazole.

[d]Determined by GC analysis.

The ionic liquid can be typically recovered by extracting out the product and followed by drying at vacuum. The recovered solvent can be reused with no appreciable decrease in yield. The representative results are summarized in Table 2.

Table 2 Recycling of [Bmim][BF_4] in *N*-butylation of benzotriazole[a]

Entry	Cycle	1-butylbenzotriazole Yield [b] (%)
1	1	80
2	2	81
3	3	79

[a]All reaction were run with benzotriazole (2 mmol), butyl bromide (4 mmol) in ionic liquid [Bmim][BF_4] (2 mL) at 80 ^oC .
[b]Determined by GC analysis based on benzotriazole .

The present method has many obvious advantages, compared to those reported in literature, including regiospecificity or higher regioselectivity, being environmentally more benign, the generality, simplicity of the methodology, the ease of product isolation, the higher yield and potential for recycling of ionic liquids. For example, in recent reported method,[9] the reaction of *N*-benzylation of benzotriazole needed reflux in benzene for 61 h to give 1-benzylbenzotriazole of 75%, ratio of 1-/2-benzylbenzotriazole is 11:1. But same reaction completed only within 20 h at 80^{o}C in ionic liquid [Bmim][BF_4] and gave excellent regioselective yield >90%, ratio of 1-/2-benzylbenzotriazole is 14:1. The reaction of benzotriazole with 1-chloro-2,4-dinitrobenzene needed reflux in toluene for 9 d, and the same reaction only needed 50 h in ionic liquid [Bmim][BF_4]. On the other hand, the synthesis of α-benzotriazol-1-ylacetophenone by traditional procedure,[6] yield of α-benzotriazol-1-ylacetophenone was 78%, however, the synthesis readily performed in ionic liquid [Bmim][BF_4] and gave 99% yield. Some representative date are summarized in Table 3.
In conclusion we have demonstrated that the *N*-substitution of benzotriazole can not only effectively be performed in the ionic liquids [Bmim][BF_4], but regiospecific or highly regioselectively, which provides a simple efficient method for the synthesis of the *N*-1-substituted benzotriazoles.

Table 3 *N*-Subtitution of benzotriazole under different reaction conditions

RX	Bt-1 Yield %(Bt-1/Bt-2)			
	This work	Literature method		
		A [a]	B [b]	C [c]
2- C_4H_9Br	65 (11:1)		29 (45:55)	37
n-$C_5H_{11}Br$	78 (15:1)	55 (11:1)		
$PhCH_2Cl$	91 (14:1)	75 (11:1)		
$PhCOCH_2Br$	99		78 (4:1)	
$BrCH_2COOC_2H_5$	99	73		

[a]Lit.,[8]: yields for reaction of benzotriazole with alkyl halides, reflux in benzene or toluene for 18 h-9 d.
[b]Lit.,[6]: yields for reaction of benzotriazole with alkyl halides using NaOH as base, stirring in DMF for 0.5 h-1 h.
[c]Lit.,[12]: yields for reaction of *N*-tributylstannylbenzotriazole with *sec*-butyl bromide, stirring at 110 ^{o}C for 18 h.

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 DMX 400 (Bruker) spectrometer. Gas chromatographic analyses were performed on a Beckman model GC-2A gas chromatograph. The ionic liquid [Bmim][BF_4] was synthesized according to the reported procedures.[13] All materials are commercially available and were used without further purification.

General procedure

A mixture of benzotriazole (2 mmol), alkyl halide (4 mmol) and ionic liquid (2 mL) was stirred for 5-30 h at 40-100 ^{o}C. (reaction condition given in Table 1), the reaction mixture was extracted with ether (3 × 5 mL). The combined ether extracts were evaporated under reduced pressure and the resulting crude product was determined by GC (HP-5, 5%phenyl methyl siloxane) or separated by the preparative thin layer chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (1:3) as developer. After isolation of the product, the remainder of the ionic liquid was further washed with ether, followed by drying at vacuum and recycled in subsequent runs.

*Spectroscopic data for new compounds***:**

1-*N*-*t*-Butylbenzotriazole (3e): oily compound. ^{1}HNMR ($CDCl_3$): 1.87 (s, 9 H, -CH_3×3), 7.33 (m, 1 H, 5-H), 7.44 (t, *J* = 7.2 Hz, 1H, 6-H), 7.70 (d, *J* = 8.4 Hz, 1H, 7-H), 8.08 (d, *J* = 8.4 Hz, 1 H, 4-H). IR (neat): 3062, 2984, 1458, 1372, 1201, 1099, 747 cm^{-1}. EI-MS: 175, 160, 146, 132, 117, 91 (base), 77, 57, 41. Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.21; H, 7.89; N, 23.78.

2-*N*-*t*-Butylbenzotriazole (4e): oily compound. ^{1}HNMR ($CDCl_3$): 1.84 (s, 9 H, -CH_3×3), 7.36 (dd, J= 6.6, 3.2 Hz, 2 H, 5-H, 6-H), 7.88 (dd, *J* = 6.5, 3.0 Hz, 2H, 4-H, 7-H), IR (neat): 3064, 2984, 1567, 1454, 1370, 1266, 1212, 747 cm^{-1}. EI-MS: 175, 119 (base), 91, 77, 64, 41 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.83; H, 7.12; N, 23.79.

4-Chloro-α-benzotriazol-1-ylacetophenone (3k): mp 154-155^{O}C. ^{1}HNMR ($CDCl_3$): δ 6.58 (s, 2 H, N-CH_2-CO), 7.43 (t, *J* = 7.2 Hz, 1H, 5-H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H, 7-H, 6'-H), 7.81 (d, *J* = 9.2 Hz, 1H, 2'-H), 8.09 (d, *J* = 8.8 Hz, 1H, 4-H), 8.15 (d, *J* = 8.4 Hz, 2H, 3'-H, 5'-H). IR (KBr): 2958, 1694, 1590, 1487, 1401, 1231, 1092, 993, 784, 741cm^{-1}. EI-MS: 272, 208, 180, 139, 132, 125, 111, 99, 89, 77 (base), 63, 51. Anal. Calcd for $C_{14}H_{10}N_3OCl$: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.54; H, 4.05; N, 15.69.

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