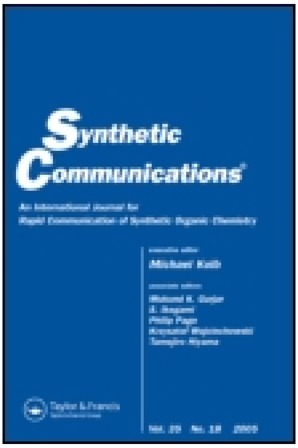

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Green and Efficient Protocol for N-Alkylation of Benzotriazole Using Basic Ionic Liquid [Bmim]OH as Catalyst Under Solvent-Free Conditions

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GREEN AND EFFICIENT PROTOCOL FOR N-ALKYLATION OF BENZOTRIAZOLE USING BASIC IONIC LIQUID [Bmim]OH AS CATALYST UNDER SOLVENT-FREE CONDITIONS

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N-Alkylation of benzotriazole bearing an acidic hydrogen atom attached to nitrogen with alkyl halides is accomplished in basic ionic liquid [Bmim]OH (1-butyl-3-methylimidazolium hydroxide) under solvent-free conditions. The procedure is convenient and efficient and generally affords the N-alkylated product.

Keywords: N-Alkylation; basic ionic liquid; benzotriazole; catalyst; solvent-free conditions

INTRODUCTION

N-Alkylation of benzotriazole has been a subject of considerable research interest over the past few years in view of its significance in the pharmaceutical, biological, and chemical industries. Benzotriazole derivatives exhibit a good degree of analgesic, anti-inflammatory, diuretic, antiviral, and antihypertensive activities.[1]

It has been reported that the N-alkylation of benzotriazole can be achieved by use different bases, such as potassium alkoxide,[2] sodium hydride,[3] potassium hydroxide,[4–6] sodium hydroxide,[7] potassium carbonate,[1,8,9] or phase-transfer catalysis (PTC) with quaternary ammonium salt,[8,10] crown ethers,[2,4] or polyethylene glycols (PEG) and their dialkyl ether (PEG ether).[5] N-Alkylation of benzotriazole can also be achieved without a solvent either in basic media or in the absence of base by conventional and microwave heating.[8,9] However, some of these methods suffer from several drawbacks, including the use of hazardous and carcinogenic organic solvents such as dimethylsulfoxide (DMSO), dimethylformamide

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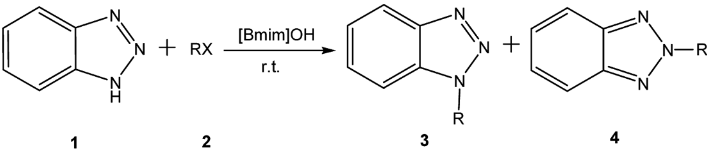

Scheme 1.

(DMF), benzene, or toluene; expensive reagents or catalysts; harsh reaction conditions; difficulty in product separation; and/or long reaction times. Moreover, the use of these strong bases may limit the processes because the experimental work can be laborious and time-consuming, requiring special care to avoid hydrolysis. So, the development of an efficient, convenient, and environmentally more benign method of the N-alkylation of benzotriazole is still a major challenge.

Ionic liquids have attracted extensive research interest in recent years as environmentally benign solvents because of their favorable properties such as nonflammability, negligible vapor pressure, reusability, and high thermal stability,[11] and a variety of catalytic reactions also have been successful using ionic liquids.[12] Increasingly, research activities have focused on the design of ionic liquids to produce task-specific ionic liquids for specific functions, for example, acidic or basic ionic liquids.[13] The acidic ionic liquids have been successfully applied in many organic reactions.[14] However, to the best of our knowledge, reports about the basic ionic liquids were relatively rare. Recently, basic functionalized ionic liquids have aroused unprecedented interest because they showed more advantages, such as convenient recycling and greater catalytic efficiency, than the mixtures of inorganic bases and ionic liquids for some base-catalyzed processes.[15] A basic functionalized ionic liquid, [Bmim]OH, has been successfully applied to catalyze the Knoevenagel condensation,[16,17] Markovnikov addition,[18] Michael addition,[19] Mannich reaction,[15] Perkin reaction,[17] interrupted Feist–Benary reaction,[20] and Henry reaction.[21]

The versatility of this basic ionic liquid encouraged us to study its utility for N-alkylation of N-heterocycles. Our group previously introduced [Bmim]OH as a catalyst and green solvent for the N-substitution of pyrrole and indole and the corresponding N-substituted pyrrole and indole in excellent yield.[22] This interesting observation prompted us to explore the potential of this ionic liquid for N-alkylation of benzotriazole (Scheme 1).

RESULTS AND DISCUSSION

Initially, we examined the reaction of benzotriazole with ethyl bromide in the presence of [Bmim]OH, which proceeded smoothly at room temperature and afforded the corresponding N-ethylated benzotriazole in 90% yield (Table 1, entry 1). Benzotriazole reacts with electrophiles to give mixtures of 1-substituted **3** and 2-substituted **4** products.[6] Thus, the reaction produced **3a** along with **4a** (ratio of isomer, 66:34).

To recognize the generality and scope of the method, various alkyl halides were tested with benzotriazole to give the corresponding N-alkylated benzotriazoles. The

Table 1. N-Alkylation of benzotriazole in basic ionic liquid [Bmim]OH[a]

Entry	Alkyl halide	Product	Time (h)	Yield (%)[b]	Ratio of isomer (3:4)
1	EtBr	**3a** **4a**	3	90	74:26
2	n-PrBr	**3b** **4b**	3	87	62:38
3	*i*-PrBr	**3c** **4c**	4	89	76:24
4	$ClCH_2CH{=}CH_2$	**3d** **4d**	2	92	90:10
5	n-BuBr	**3e** **4e**	3	87	68:32
6	n-BuCl	**3e** **4e**	4	91	66:34
7	n-$C_8H_{17}Br$	**3f** **4f**	4	88	65:35
8	BnCl	**3g** **4g**	2	95	86:14
9	BnBr	**3g** **4g**	2	93	74:26
10	$BrCH_2COPh$	**3h** **4h**	3	90	70:30

[a] All reactions were run with benzotriazole (5 mmol) and alkyl halide (7.5 mmol) in basic ionic liquid [Bmim]OH (10 mmol).

[b] Isolated yield based on benzotriazole.

results are summarized in Table 1. We found that the reaction is general and applicable to alkyl halides containing bromide and chloride, and the desired products were obtained in good to excellent yields and moderate regioselectivity. The products were characterized by ^{1}H NMR, infrared (IR) spectra, and melting points, which were consistent with the literature data.

The basic ionic liquid [Bmim]OH can be typically recovered by extracting the product, adding KOH, and drying at vacuum. The recovered ionic liquids can be reused with no appreciable decrease in yield. The representative results are summarized in Table 2. The yields did not obviously decrease over four runs, which shows that [Bmim]OH is an efficient catalyst.

The present method has many obvious advantages compared to those reported in the literature, including being environmentally more benign, general and simple

Table 2. Recycling of [Bmim]OH in the butylation of benzotriazole

Entry	Run	Yield[a] (%)
1	1	90
2	2	88
3	3	89
4	4	88

[a] Isolated yield.

operation, good yield, and potential for recycling the basic ionic liquid. For example, the synthesis of N-butylbenzotriazole by the traditional procedure not only used the strong base sodium hydroxide but also needed the hazardous and carcinogenic organic solvent DMF to give N-butylbenzotriazole in 86%; the ratio of 1-/2-butylbenzotriazole is 53:47.[7] The same synthesis was performed in 3 h in basic ionic liquid [Bmim]OH and gave 87% yield; the ratio of 1-/2-butylbenzotriazole is 68:32 (Table 1, entry 5). The reaction of N-benzylation of benzotriazole by a recently reported method using K_2CO_3 as base needed high temperature (90 °C) to give N-benzylbenzotriazole in 53% yield.[8] The same reaction was completed within only 2 h at room temperature and gave an excellent yield (95%) (Table 1, entry 8).

In summary, we have demonstrated that the basic ionic liquid [Bmim]OH could efficiently catalyze N-alkylation of benzotriazole with alkyl halides at room temperature under solvent-free conditions. The present procedure is more environmentally benign and has mild reaction conditions, relative short reaction times, wide applicability, and easy recovery of the catalyst.

EXPERIMENTAL

Melting points were determined on a digital melting-point apparatus and were not corrected. Infrared (IR) spectra were recorded on a Vector 22 instrument (Bruker). Nuclear magnetic resonance (NMR) spectra were recorded on an Avance DMX 200 spectrometer (Bruker). The ionic liquids, 1-methyl-3-butylimidazolium hydroxide ([Bmim]OH), was synthesized according to reported procedures.[23] The other materials are commercially available and were used without further purification.

General Procedure for N-Alkylation of Benzotriazole Catalyzed by [Bmim]OH

A mixture of benzotriazole (5 mmol), [Bmim]OH (10 mmol), and alkyl halide (7.5 mmol) was stirred at room temperature (30 °C) for 2–4 h (reaction condition given in Table 1). The course of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was extracted with ethyl ether. The combined ether extracts were evaporated under reduced pressure, and the resulting crude product was separated by the preparative TLC on silica gel using a mixture of ethyl acetate and petroleum ether as developer to give the corresponding pure product. The residual ionic liquid was washed with small amount of ethyl ether, dried under vacuum at 80 °C for 2 h, and reused after KOH (5 mmol) was added.

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