Article

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One-pot Green Synthesis of Azides from Alcohols Using Brønsted Acidic Ionic Liquid [HMIM][BF_4] as Solvent and Catalyst

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Brønsted acidic ionic liquid, [HMIM][BF_4], has been used as a non-volatile, eco-friendly solvent, and catalytic medium for the one-pot green synthesis of azides from corresponding alcohols. The [HMIM][BF_4] showed high reactivity than [BMIM][BF_4] and [BMIM][PF_6], affording azides in up to 97% yield, which could be easily separated from the reaction mixture. The ease of recyclability of [HMIM][BF_4] makes the reaction economically and potentially viable for practical applications.

Keywords: [HMIM][BF_4]; Azide; Alcohol; Green chemistry; Ionic liquid.

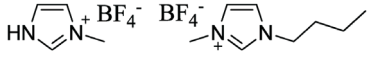
INTRODUCTION

Azides are probably one of the most important 1,3-dipoles in organic chemistry[1,2] and serve as important precursor for the amino groups, which are quite essential and versatile in the synthesis of natural products as well as N-containing heterocycles.[3] Owing to their remarkable stability under physiological conditions and inimitable reactivity, azides play a significant role in 'click' chemistry[4] and in bioconjugation.[5] Additionally, azides have also been employed for the synthesis of sugar triazole derivatives as antituberculosis agents[6] and azido pyrimidines/purines as anti HIV-1 biological agents.[7]

In spite of the availability of a range of indirect methods, direct access of azides from corresponding alcohols is relatively less studied. In this context, Mitsunobu displacement[8-11] employing hydrazoic acid as azide source for the aforementioned transformation is especially notable. However, considering the health hazards associated with hydrazoic acid, modified Mitsunobu conditions have also been surfaced from time to time.[12-17] Despite this noticeable improvement, most of these methods are inappropriate due to high cost, side reactions, excessive use of reagents, toxicity, and separation issues. In a bid to replace Mitsunobu conditions, the use of BF_3-Et_2O[18] and N-methyl-2-pyrrolidonium hydrogen sulphate [HNMP][HSO_4][19] have also been found to be effective for the direct synthesis of azides from alcohols. Nevertheless, the excessive use and non-recyclability of catalysts still possess serious shortcomings. Furthermore, the solubility associated with [HNMP][HSO_4] also makes it difficult to separate from the reaction mixture.[20] Accordingly, the search for alternative approaches employing highly efficient, eco-friendly, and recyclable catalysts is of colossal importance.

In recent years, ILs in particular based on imidazolium cations (Fig. 1) have gained considerable interest as green alternative to conventional acid catalysts.[21-23] Furthermore, owing to their non-volatility, heat resistance, non-corrosiveness, and negligible vapour pressure, they are highly advantageous in minimizing solvent consumption and addressing the problem of volatile organic solvents emission into the atmosphere, a key feature required to develop economical, efficient, and green chemical processes.[24-30]

Recently, we have explored the unique catalytic potential of Brønsted acidic ILs in the high yield synthesis of N-confused calix[4]pyrrole.[31] In yet other work, we have employed them in the rapid and sensitive determination of tertiaryalkyl amines.[32] In continuation of our high interest in green catalysis,[33,34] herein, we report a practical procedure for the efficient conversion of benzyl alcohols into azides using 1-methylimidazolium tetrafluoroborate



[HMIM][BF_4] [BMIM][BF_4]

Fig. 1. Imidazolium based ionic liquid.

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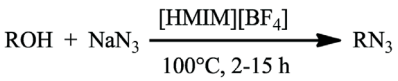
Abbreviations: [HNMP][HSO_4], N-methyl-2-pyrrolidonium hydrogen sulphate; IL, Ionic liquid; [HMIM][BF_4], 1-methylimidazolium tetrafluoroborate; [BMIM][BF_4], 1-butyl-3-methylimidazolium tetrafluoroborate; [BMIM][PF_6], 1-butyl-3-methylimidazolium hexafluorophosphate.

[HMIM][BF_4] (Scheme 1). The present protocol overcomes the problems encountered with classical Lewis acids and offers the recoverability and reusability of the catalyst.

Scheme 1 [HMIM][BF_4] catalyzed conversion of alcohols into azides



EXPERIMENTAL

Materials and methods: All the chemicals and reagents were commercially available and used without further purification. Most of the alcohols were purchased from Lancaster. 1-chlorobutane, potassium tetrafluoroborate and N-methyl imidazole were purchased from Sigma-Aldrich. The Fourier transform infrared spectroscopy was carried out on a Perkin-Elmer system 2000. The ^{1}H NMR (600, 400 MHz) and ^{13}C NMR (150 MHz) were recorded on a nuclear magnetic resonance spectrometer (Bruker Cryomagnet, Oxford) using $CDCl_3$ as solvent and TMS as an internal standard, unless otherwise mentioned. The splitting patterns are designed as s (singlet), d (doublet), t (triplet), bs (broad singlet), and m (multiplet). The column chromatography was carried out using Merck silica gel (60-120 mesh). ILs, [HMIM][BF_4] and 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4], were prepared according to an earlier reported procedures[21,35] while [BMIM][PF_6] were prepared by modification of known procedure.[35]

Synthesis of 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6]: To a freshly prepared [BMIM][Cl] (37.5 g) in DI water (225 mL), hexafluorophosphoric acid (66 mL) was added drop wise at 0 °C under vigorous stirring. After addition, two immiscible phases were formed and the stirring was continued for 2 h. The aqueous phase was separated and organic phase was washed repeatedly with ice cold DI water (5 × 100 mL). The crude was then dissolved in DCM (250 mL) and treated with activated charcoal (5 mg) for 30 min. The solution was filtered and dried over anhydrous magnesium sulfate. The solvent was evaporated and [BMIM][PF_6] was obtained as a colorless liquid. The product was dried under high vacuum at 80 °C for 24 h. The as-obtained [BMIM][PF_6] was kept in polypropylene bottle and stored in a dry box prior to use. ^{1}H NMR (600 MHz, DMSO-d_6, 298K): δ = 9.12 (s, 1H, Imidazole), 7.79 (s, 1H, Imidazole), 7.72 (s, 1H, Imidazole), 4.27 (t, 2H, -CH_2), 3.94 (s, 3H, -CH_3), 1.97-2.15 (m, 2H, -CH_2), 1.64-1.68 (m, 2H, -CH_2), 0.94 (t, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6, 298K): δ = 137.72, 124.79, 123.46, 49.73, 40.69, 36.97, 29.58, 13.22; Anal Calc. for $C_8H_{15}N_2PF_6$: C; 33.81, H; 5.32, N; 9.86. Found C; 33.83, H; 5.36, N; 9.84.

Typical procedure for the one-pot synthesis of azides catalyzed by [HMIM][BF_4]: In a 25 mL round bottomed flask containing [HMIM][BF_4] (5.0 mL) was added a mixture of alcohol (2 mmol) and sodium azide (2.1 mmol). The reaction mixture was stirred at 100 °C for appropriate time. After every 1 h interval, the progress of the reaction was monitored by TLC (hexane: ethyl acetate, 8:2, v/v). After completion of the reaction, the reaction mixture was extracted with hexane-ethyl acetate (2 × 10 mL, 9:1, v/v) and filtered off the solid. The organic layer was washed with water (2 × 10 mL). The combined organic layer was dried over anhydrous magnesium sulfate and solvent was evaporated under reduced pressure. The crude was column chromatographed over silica gel using hexane-ethyl acetate as an eluent to afford desired azides.

Spectroscopic data of selected azides: 1-(azidomethyl)-4-hydroxybenzene (**2b**): ^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ = 7.70 (d, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 8.4 Hz), 5.62 (bs, 1H, Ar-OH) and 4.15 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 298K): δ = 158.05 (C), 127.05 (CH), 124.80 (C), 115.29 (CH) and 54.81 (CH_2); 1-(1-azidoethyl)-4-methoxybenzene (**2g**): ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.57 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 4.49-4.53 (q, 1H), 3.70 (s, 3H) and 1.90 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 298K): δ = 158.01, 137.04, 128.44, 113.05, 58.36, 55.22 and 18.31; 2-(azidomethyl)thiophene (**2q**): ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.69-7.71 (m, 1H), 7.60-7.62 (m, 2H) and 4.00 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 298K): δ = 151.75 (C), 138.44 (CH), 124.52 (CH), 122.23 (CH) and 54.01 (CH_2); 1-(azidomethyl)-4-nitrobenzene (**2r**): ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.84 (d, 2H, *J* = 8.2 Hz), 7.62 (d, 2H, *J* = 8.2 Hz) and 4.60 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 298K): δ = 151.85 (C), 146.04 (C), 126.02 (CH), 122.86 (CH) and 55.11 (CH_2); 1-(azidomethyl)-4-fluorobenzene (**2s**): ^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.83 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz) and 4.30 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 298K): δ = 162.28 (C), 160.64 (C), 128.83 (CH), 114.67 (CH) and 55.52 (CH_2).

RESULTS AND DISCUSSION

In order to demonstrate the practical (dual) utility of [HMIM][BF_4] as a reaction media as well as catalyst, bulk synthesis of [HMIM][BF_4], [BMIM][BF_4], and [BMIM][PF_6] was carried out by following the reported procedures.[21,35] The identity and purity of all derivatives was unambiguously confirmed by different spectroscopic techniques and elemental analysis. The spectral data and ele-

mental analysis results were in good agreement as reported previously.

To optimize the product distribution at room temperature, the conversion of 4-methylbenzyl alcohol **1a** into 1-(azidomethyl)-4-methyl benzene **2a** was primarily screened as a model reaction under a variety of experimental conditions. Nevertheless, either the variations in reactants molar ratio or amount of [HMIM][BF_4] were all found unproductive to afford the desired azide. The qualitative TLC and ^{1}H NMR of recovered mixture showed only the presence of starting alcohol. Later on, the reaction was examined under varying temperature (50-100 °C) conditions. To our delight, after 4 h, the reaction of **1a** and NaN_3 (1: 1.1 mmol) at 100 °C in [HMIM][BF_4] gave > 90% conversion of **1a** as determined by ^{1}H NMR spectroscopy. After completion of the reaction, the product was extracted with an ethyl acetate-hexane mixture and subsequently washed with water. The purification of crude by column chromatography afforded analytically pure **2a** in 85% yield (Table 1, entry 1). It has to be stressed that minimal changes in the isolated yield were observed upon increasing the reaction time, temperature, and molar ratio of reactants.

To determine whether the ionic liquid [HMIM][BF_4] was an essential factor to realize the conversion of aforementioned reaction, the same reaction was performed in dichloromethane, acetonitrile and dimethyl sulfoxide in the absence of [HMIM][BF_4]. As expected, the reaction did not proceed at all in the absence of [HMIM][BF_4]. To further verify the influence of [HMIM][BF_4] in this reaction, the reaction was carried out in [BMIM][BF_4] and under optimized conditions (4 h), the qualitative TLC showed only < 20% conversion of **1a**. However, on prolonging the reaction for 12 h, **2a** could be isolated in 30% yield. Likewise, though a bit improved yield, **2a** was obtained in 35% yield in the presence of more hydrophobic IL, [BMIM][PF_6]. These findings are in fair agreement with that made in the synthesis of isoxazolyl-1,3-benzoxazines.[23] It is noteworthy that both the [BMIM][BF_4] and [BMIM][PF_6] are neutral ILs while [HMIM][BF_4] greatly influences the azidation reaction, probably, by acting as proton donor as well as effective solvent media.

Having established the essential nature of [HMIM][BF_4], the conversion of a variety of benzylic alcohols into their corresponding azide analogues were examined under virtually identical conditions and the results are summarized in Table 1. As demonstrated in Table 1, after reaction with NaN_3, various structurally diverse alcohols (**1b-1q**), regardless of the presence of electron donating, heterocyclic or branched chain functionalities could be directly converted into their respective azides in 81-97% yields (Table 1, entries 2-17). Nevertheless, in comparison to primary alcohols (Table 1, entries 1-2, 4) except **1c** (Table 1, entry 3), secondary alcohols (Table 1, entries 5, 8) reacted faster and azides were formed in shorter reaction time. Furthermore, the reactivity of secondary alcohols having electron donating substituents appeared much higher and azides were isolated in > 93% yields (Table 1, entries 6-7, 9, 15). On the other hand, the reactivity of alcohols containing electron withdrawing substituents, in particular, -NO_2 and -F was very low and consequently poorer yield of azides were obtained even after prolonging the reaction time (Table 1, entries 18-21). On the contrary, secondary alcohols appended with halogen-substituents afforded corresponding azides in appreciable yields in 3-5 h (Table 1, entries 11-13). Likewise, the catalyst was found equally effective for the conversion of 2-hydroxymethyl thiophene **1q** and afforded **2q** in 94% yield.

To study the reusability, the recovered [HMIM][BF_4] was reused for the conversion of 1-(2,4-dimethylphenyl)-ethanol **1g**. In particular, after extraction of respective azide from the IL with an ethyl acetate – hexane mixture (9:1, v/v), the IL was solubilized in acetonitrile and filtered to separate any remaining NaOH. The organic layer was evaporated and the IL was dried under vacuum for 1 h. To this dried IL, NaN_3 and **1g** were added and mixture was stirred at 100 °C for 2 h. After the reaction, the reaction mixture was extracted by the ethyl acetate – hexane mixture, washed with water and combined organic layers were evaporated. Subsequently, **2g** was isolated by column chromatography as mentioned before. This procedure was repeated at least five times. Interestingly, even after four con-

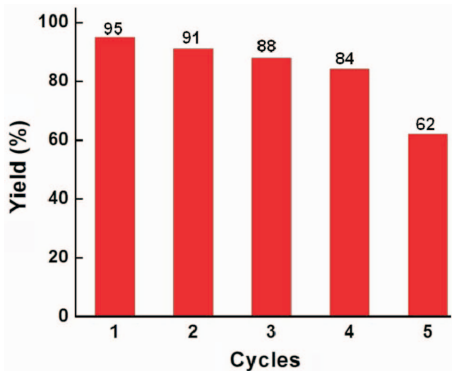
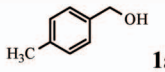
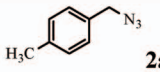
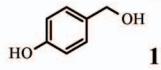
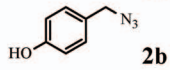
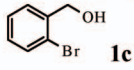
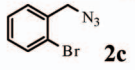
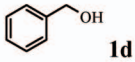
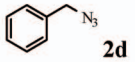
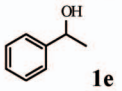
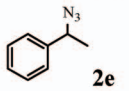
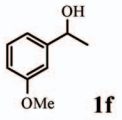
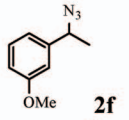
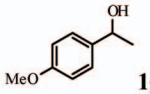
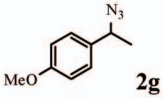
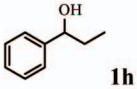
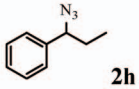
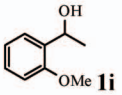
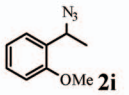
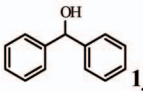
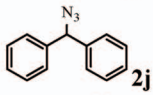
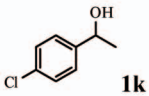
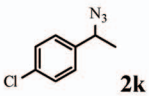
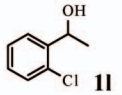
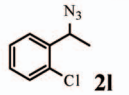
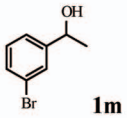
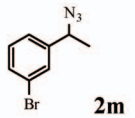
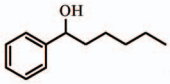
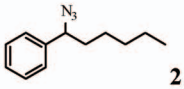
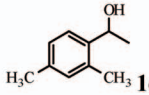
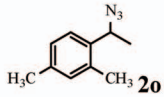
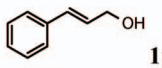
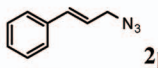
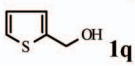
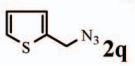
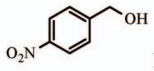
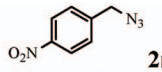
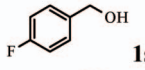
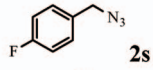
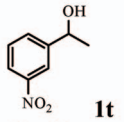
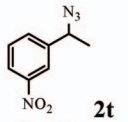


Fig. 2. Bar diagram: recyclable activity of [HMIM][BF_4].

Table 1. Conversion of various alcohol with sodium azide into corresponding azides using $[HMIM][BF_4]$[a]

Entry	Substrate (1) + NaN_3	Product (2)	Time (h)	% Yield[b]
1	 **1a**	 **2a**	4.5	85
2	 **1b**	 **2b**	4.5	84
3	 **1c**	 **2c**	3	96
4	 **1d**	 **2d**	4.5	83
5	 **1e**	 **2e**	3	87
6	 **1f**	 **2f**	2	94
7	 **1g**	 **2g**	2	95
8	 **1h**	 **2h**	3	92
9	 **1i**	 **2i**	3	93
10	 **1j**	 **2j**	6	81
11	 **1k**	 **2k**	4	90
12	 **1l**	 **2l**	5	83
13	 **1m**	 **2m**	2.5	89
14	 **1 n**	 **2 n**	4	82
15	 **1o**	 **2o**	2	97
16	 **1p**	 **2p**	4	87
17	 **1q**	 **2q**	4	94
18	 **1r**	 **2r**	15	9
19	 **1s**	 **2s**	15	13
20	 **1t**	 **2t**	8	49
21	**1u**	**2u**	10	45

[a] All reactions were performed at 100 °C with 5 mL $[HMIM][BF_4]$ using 2 mmol alcohol, 2.1 mmol NaN_3 for the indicated reaction time. $[HMIM][BF_4]$ was kept under vacuum for 1 h prior to use. [b] Isolated yield.

secutive uses, $[HMIM][BF_4]$ showed good catalytic activity with little deterioration in product yield (Fig. 2). Nevertheless, the yield was significantly decreased during the fifth run which may be attributed to the decomposition or decreased activity of IL due to release of moisture sensitive NaOH in the reaction.

CONCLUSIONS

In summary, we have developed a simple and efficient method for direct conversion of alcohol into azide. Avoiding expensive starting materials, the use of $[HMIM][BF_4]$ as green solvent and catalytic system has proven to be very effective for this conversion. The protocol showed good selectivity in favor of benzylic hydroxyls. Furthermore, secondary –OH group at benzylic position could easily be substituted in relatively shorter reaction time. This simple experimental set-up, remarkable reactivity towards primary and secondary alcohols, good to excellent yields, one-pot synthesis combined with easy recovery and recyclability of IL contribute to the development of a green strategy to synthetic chemists.

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