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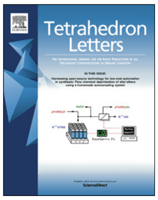

Recyclable zinc (II) ionic liquid catalyzed synthesis of azides by direct azidation of alcohols using trimethylsilylazide at room temperature

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ABSTRACT

A new efficient method has been reported for the synthesis of azides by direct azidation of alcohols with $TMSN_3$ in presence of recyclable task specific ionic liquid (TSIL) [bmim]$ZnCl_3$ as a catalyst in DCM at room temperature. Ionic liquid [bmim]$ZnCl_3$ was synthesized under solvent free conditions and characterized by IR, ^1H NMR, ^{13}C NMR and HRMS. The Lewis acidity of catalyst was also examined using IR spectroscopy. The main features of this new methodology are high yields of products, recyclability of catalyst, scalability of reaction to gram scale and short reaction time.

Organic azides are energy-rich, flexible nitrogenous compounds which have numerous applications in organic synthesis.[1,2] Azides are used as starting material for the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions for the synthesis of biologically and industrially important 1,2,3-triazoles[3,4] and in areas of material science.[5,6] The azide group itself can act as a pharamacophere and is a key component of the HIV/AIDS drug zidovudine.[7] Azides have been employed for the synthesis of tetrazoles,[8] isoquinolines,[9] benzylamines,[10] *N*-arylmethylarenes,[11] quinolines,[12] phenanthridines[13] for Schmidt reaction[14] and Schmidt–Mannich type rearrangement reaction.[15] They act as 1,3-dipoles and thus undergo 1,3-dipolar cycloaddition reactions to give a variety of nitrogenous heterocyclic compounds.

The synthesis of azides from alcohols is generally a two step reaction involving conversion of alcohol to the corresponding halide or sulfonate, followed by nucleophilic substitution by azide anion. One of the disadvantages of using sodium azide, besides its high toxicity, is its sensitivity to external factors such as heat, light or pressure, which can cause them to explode when handled in large quantity.[16] Therefore methods using safer azide substitutes such as diphenylazidophosphate[17] and di-4-nitrophenyl azidophosphate[18] have been reported. The conversion of alcohols directly to azides in one step reaction has been reported by a combination of a Lewis acid such as copper triflate,[19a] bismuth triflate,[19b] povidone-phophotungstic acid,[19c] silver triflate[19d] and trimethylsilylazide. The reported methods have few disadvantages such as long reaction time, poor yield, and use of toxic organic solvents and catalysts. [bmim]$ZnCl_3$ has found applications in synthetic organic chemistry as a catalyst[20] but is much less explored compared to other Lewis acid ionic liquids. Thus, in view of the importance of organic azides and limitations of their methods of synthesis, we decided to explore the application of environmentally benign [bmim]$ZnCl_3$ as a recyclable catalyst for the syntheses of various organic azides by direct azidation of alcohols using trimethylsilylazide.

In this paper, we have reported an efficient and simple protocol for the synthesis of organic azides directly from alcohols using stable, non-explosive azidotrimethylsilane ($TMSN_3$) in presence of 5 mol% of Lewis acid ionic liquid [bmim]$ZnCl_3$ as a catalyst in DCM at room temperature.

The Lewis acidic ionic liquid [bmim]$ZnCl_3$ was prepared according to Scheme 1. In the first step, ionic liquid 1-methyl-3-butylimidazolium chloride [bmim]Cl was obtained by the reaction of 1-methylimidazolium (1.0 mmol) and butyl chloride (1.0 mmol) at 80 °C for 72 h.[21] The desired Lewis acid catalyst was then prepared by reaction of equimolar amounts of [bmim]Cl and $ZnCl_2$ under solvent-free conditions at 80 °C for 10 h unlike the reported procedure in solution and subsequent removal of solvent and vacuum drying[20] (Scheme 1).

The formation of [bmim]$ZnCl_3$ was confirmed by spectroscopic studies *i.e.* IR, ^1H NMR, ^{13}C NMR and HRMS. The IR spectra of [bmim]$ZnCl_3$ showed peaks at 3106 cm^{-1}, 1567 cm^{-1}, 1460 cm^{-1},

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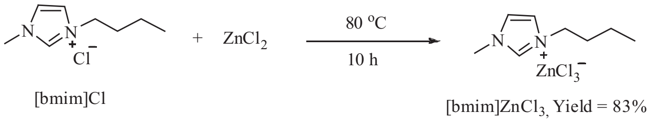


Scheme 1. Synthesis of Lewis acid ionic liquid [bmim]ZnCl$_3$.

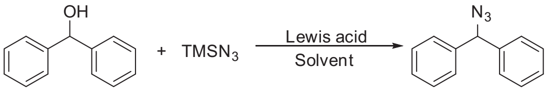
748 cm^{-1} and 651 cm^{-1}. ^{1}H NMR spectra of [bmim]ZnCl$_3$ showed a triplet at δ_H 0.83–0.86 ppm due to terminal methyl protons, two multiplets at δ_H 1.18–1.23 ppm and δ_H 1.68–1.75 ppm due to two methylene protons of *n*-butyl chain. The two methylene protons (NCH$_2$) of butyl chain appeared as triplet at δ_H 4.10–4.14 ppm, while three methyl protons (NCH$_3$) appeared as singlet at δ_H 3.80 ppm. Three aromatic protons of imidazole ring appeared in aromatic region at δ_H 9.06, 7.71, 7.64 ppm. The ^{13}C NMR spectra of [bmim]ZnCl$_3$ gave 8 peaks corresponding to eight non-equivalent carbon atoms. The composition of ionic liquid was further confirmed by recording ESI-HRMS in both positive mode as well as in negative mode. The positive mode HRMS showed a peak at m/z = 139.1224 corresponding to the [bmim]+H$^+$ (Calc. for [bmim]+H$^+$ m/e 139.1235) cation of the ionic liquid, while negative mode HRMS of [bmim]ZnCl$_3$ showed peak at m/e 168.8349 for ZnCl$_3$ anion (Calc. for ZnCl$_3$ m/e 168.8357) which confirms the composition as well as purity of ionic liquid [bmim]ZnCl$_3$.

The Lewis acidity of [bmim]ZnCl$_3$ was examined by FT-IR spectroscopy using pyridine as a probe molecule and examining IR bands in the range of 1400–1700 cm^{-1} arising from its ring vibration modes. Pyridine showed a single absorption band at 1437 cm^{-1} while in presence of [bmim]ZnCl$_3$ this absorption band shifts to 1449 cm^{-1} which indicates that pyridine is coordinated to Lewis acid sites and thus [bmim]ZnCl$_3$ showed Lewis acidity and hence can act as a acid catalyst. The solubility of [bmim]ZnCl$_3$ was also examined. The ionic liquid is soluble in water, methanol, acetone, chloroform and acetonitrile and insoluble in ethyl acetate, toluene and petroleum ether.

The application of [bmim]ZnCl$_3$ as Lewis acid catalyst was investigated for the synthesis of azides by direct azidation of alcohols. The optimum reaction conditions were identified by attempting model reaction of diphenylmethanol (1a, 1.0 mmol) and trimethylsilylazide (1.1 mmol) (Eq. 1) under different reaction conditions by varying catalyst, catalyst loading, solvent and temperatures as summarized in Table 1 (entries 1–12). However, the best results were obtained when the reaction was attempted using DCM as solvent in presence of [bmim]ZnCl$_3$ (5 mol%) at room temperature as desired product (azidomethylene)dibenzene (**2a**) was obtained in 94% yield in 20 min (Table 1, entry 3). The structure of (azidomethylene)dibenzene (**2a**) was confirmed by IR ^{1}H NMR and ^{13}C NMR spectra. Reaction attempted under other reaction conditions gave inferior yields of product **2a** and also required longer reaction time as shown in Table 1 (entries 1–2, 4–12). Thus, the reaction of diphenylmethanol and trimethylsilylazide (1.1 mmol) using 5 mol% of [bmim]ZnCl$_3$ in DCM at room temperature was chosen as the optimum reaction condition to further explore this reaction.

The scope of this reaction was further explored by attempting reactions of different alcohols with trimethylsilylazide under optimized conditions. All the reactions were complete in less than 30 min and gave the corresponding azides in high yields. The results have been summarized in Table 2. The reaction can be generalized as in Eq. 2.

All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra. It can be inferred from the results in Table 2 that only secondary and tertiary benzylic alcohols could be converted to corresponding azides (entries 1 to 12). Secondary alcohols attached to heteroaryl group could also be converted to corresponding azides (entries 13, 14). However, primary benzylic alcohol (entry 15), aliphatic secondary alcohol (entry 16), allylic secondary alcohol (entry 17) and α-keto secondary benzylic alcohol (entry 18) did not undergo any reaction under these conditions. Phenol gave trimethylsilyloxy benzene under these conditions (entry 19).



1a **2a** ... (1)

A plausible reaction mechanism for the synthesis of organic azides from alcohols is shown in Scheme 2. The first step involves the interaction of Lewis acidic ionic liquid [bmim]ZnCl$_3$ with alcohol to give complex **A**, which undergoes nucleophilic substitution with TMSN$_3$ to give the desired organic azides.

In order to determine the type of nucleophilic substitution (S$_N$1 or S$_N$2) mechanism, we performed a reaction of optically pure S-(−)-1-phenylethanol with trimethylsilylazide using [bmim]ZnCl$_3$ in DCM at room temperature. The corresponding product was obtained in low optical purity of 24% ee[22] and the remaining 76% product was consisted of racemic mixture. Therefore, the reaction is taking place predominantly via (S$_N$1) pathway.

$$\underset{1}{\mathrm{RR'R''COH}} + \mathrm{TMSN_3} \xrightarrow[\mathrm{DCM,\ RT}]{[\mathrm{bmim}]\mathrm{ZnCl_3}\ (5\ \mathrm{mol\%})} \underset{2}{\mathrm{RR'R''CN_3}} \qquad ...(2)$$

R = Aryl; R' = alkyl, aryl; R'' = H, aryl, alkyl

Table 1
Optimization of reaction conditions for synthesis of organic azides using [bmim]ZnCl$_3$.

Entry	Lewis acid catalyst	Solvent	Temperature	Time (min)	Yield (%)
1.	[bmim]ZnCl$_3$ (5 mol%)	MeCN	RT	360	20[a]
2.	[bmim]ZnCl$_3$ (5 mol%)	DMSO	RT	360	35[a]
3.	[bmim]ZnCl$_3$ (5 mol%)	DCM	RT	20	94
4.	[bmim]ZnCl$_3$ (5 mol%)	–	RT	240	72
5.	–	DCM	RT	240	–
6.	[bmim]ZnCl$_3$ (5 mol%)	DCM	50 °C	20	93
7.	[bmim]ZnCl$_3$ (10 mol%)	DCM	RT	20	92
8.	ZnCl$_2$ (10 mol%)	DCM	RT	60	81
9.	InBr$_3$ (10 mol%)	DCM	RT	40	72
10.	CuCl (10 mol%)	DCM	RT	200	70
11.	Bi(OTf)$_3$ (10 mol%)	DCM	RT	60	83
12.	*p*-TSA	DCM	RT	360	–[b]

[a] Incomplete reaction.
[b] No reaction.