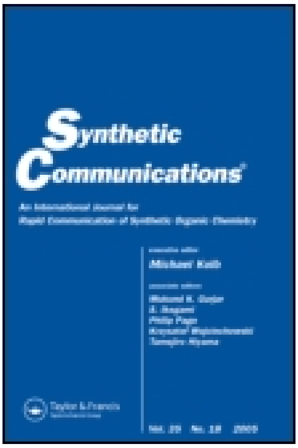

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NOVEL BASIC IONIC LIQUID BASED ON ALKYLAMMONIUM AS EFFICIENT CATALYST FOR KNOEVENAGEL REACTION

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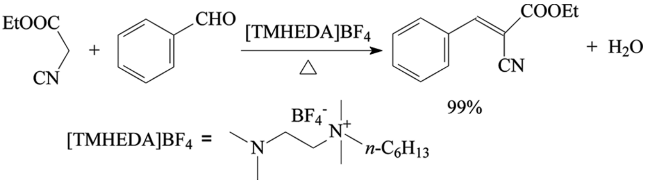
GRAPHICAL ABSTRACT



Abstract *The typical Knoevenagel condensation was carried out smoothly in the presence of a basic ionic liquid of N,N,N′,N′-tetramethyl-N′-hexyl-ethylenediammonium tetrafluoroborate ([TMHEDA]BF$_4$), and 99% of yield was obtained using ethyl cyanoacetate and benzaldehyde as substrates at 60 °C for 1 h. Four reuses of the ionic liquid without dramatic decrease in catalytic activity for Knoevenagel condensation demonstrated the good stability and operability of the ionic liquid. Moreover, the typical nucleophilic addition reactions were also accomplished by the same ionic liquid to check its feasibility. The dual function of the basic ionic liquid both as solvent and catalyst, combined with simple product separation and recycling, is expected to contribute to the development of a green and environmentally friendly strategy.*

Keywords Basic ionic liquid; dual function; Knoevenagel condensation; tetramethylethylenediamine

INTRODUCTION

Over the past few years, room-temperature ionic liquids (salts with a melting point at or below ambient temperature) have attracted renewed attention for a variety of reactions in the area of green chemistry because of their adjustable physical

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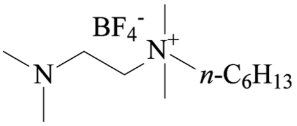
and chemical properties.[1] Although ionic liquids were initially introduced as alternative green reaction media, today they have gone far beyond, showing significant roles in controlling reactions as catalysts.[2] The designability gave us more opportunities to achieve ionic liquids with special properties. For instance, a series of acid-functionalized ionic liquids offered a new possibility for developing environmentally friendly acid catalysts because they could integrate the superiority of both liquid acids and solid acids, such as uniformly distributed acid sites, water and air stability, easy separation, and reusability.[3] Similarly, basic ionic liquids also have aroused unprecedented interest[4,5] because they have more advantages such as excellent catalytic efficiency and reusability over the immobilized inorganic bases in ionic liquids for some base-catalyzed processes.[6–9]

Knoevenagel condensation of carbonyl compounds on compounds containing an active methylene group is one of the most important preparation methods for substituted alkenes. Reactions are generally catalyzed using bases or Lewis acids.[10] Recently, use of ionic liquid as catalysts, resulting in great selectivity, milder conditions, and easier workup, has rapidly increased and has been reported as a useful condition for Knoevenagel condensation.[11,12] For example, cyclic guanidinium lactate ionic liquid,[13] $[H_3N^+–CH_2–CH_2–OH][CH_3COO^-]$ ionic liquid,[14] and $[MMIm][MSO_4]$ ionic liquid[15] have been reported mainly under solvent-free and aqueous conditions.

Similarly, a basic ionic liquid paired with 1-butyl-3-methylimidazolium cation and imidazolide anion ([bmim]Im) catalyzing Knoevenagel condensation under aqueous conditions has been reported.[16] In addition, a series of basic ionic liquids with OH^- anion functionalized hydroxyapatite-encapsulated γ-Fe_2O_3 magnetic nanoparticles were also used as efficient heterogeneous catalysts for the same condensation, and 86–95% yield and 100% selectivity for ylidenemalononitriles were obtained.[17,18] Moreover, a series of Hünig's-base tethered ammonium ionic liquids have been used to catalyze Knoevenagel condensation. By adjusting the distance between the ammonium head group and Hünig's base, the activity of the catalyst was changed.[19] Furthermore, it has been reported that *N*-(3-aminopropyl),*N*(3)-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium bromide hydrobromide was successively grafted onto mesoporous silicas of MCM-41 and SBA-15, and then they were neutralized by treatment with potassium bicarbonate, leading to the immobilized basic amino-containing task-specific ionic liquids, which showed great efficiency (particularly reusability) than that of similar pure basic task-specific ionic liquid (TSIL) of *N*-(3-aminopropyl),*N*(3)-(methyl)-imidazolium tetrafluoroborate or amino-functionalized mesoporous silicas in aqueous media.[20] All the features of milder conditions, greater selectivity, simpler workup, and easier recycling of catalyst and product make this process environmentally friendly.

As part of a program aimed at expanding the chemically modified ionic liquids, we have prepared a novel basic *N,N,N′,N′*-tetramethyl-*N′*-hexyl-ethylenediammonium tetrafluoroborate ($[TMHEDA]BF_4$) ionic liquid, depicted in Scheme 1. Evidently, the alkylamine group attached to the cation of ionic liquid may promote organic reactions, which stems from the inherent feature of the organic base. In this study, we report our findings on this ionic liquid, by which the considerable efficiency was displayed in several base-catalyzed reactions including Knoevenagel condensation, Micheal addition, aldol condensation, Claisen–Schmidt, and epoxidation of α,β-unsaturated carbonyl compounds under solvent-free conditions.



Scheme 1. Structure of [TMHEDA]BF_4 ionic liquid.

EXPERIMENTAL

Materials and Reagents

All solvents and chemicals used were commercially available and used without further purification unless otherwise stated. They are chemical pure or analytical pure. Tetramethylethylenediamine (99.0%), 1-bromohexane (99.5%), *n*-octanal, and mesityl oxide were purchased from Aldrich. Sodium tetrafluoroborate, benzaldehyde, furfural, acetophenone, cyclohexanone, hydrogen peroxide, and acetone were obtained from Shanghai Chemicals. Butyraldehyde, acrylonitrile, ethyl cyanoacetate, and 2-butanone were obtained from Sinopharm Chemical Reagent Beijing.

Analysis and Characterization

The qualitative analysis of products was carried out on a Hewlett-Packard 6890/5793 gas chromatograph/mass spectrometer (GC/MS) equipped with a HP 5MS column (30 m) and a FID detector, with helium as carrier gas. The column temperature was raised from 60 to 260 °C at a heating rate of 10 °C min^{-1}. The concentration of reactant and product was directly given by the analysis of GC chemstation according to the area of each chromatograph peak. NMR spectra were recorded on a Mercury-Plus 400 NMR spectrometer.

[TMHEDA]BF_4 Ionic Liquid

[TMHEDA]BF_4 ionic liquid was prepared by the following procedure: (1) *N,N,N′,N′*-Tetramethylethylenediamine (14.9 mL, 0.1 mol) and a stoichiometric amount of 1-bromohexane (14.2 mL, 0.1 mol) were transferred in succession to 50 mL toluene in a 250-mL round-bottom flask equipped with a reflux condenser under magnetic stirring at room temperature. Then, the mixture was heated to 80 °C and stirred for 12 h. During this period, the content changed from a colorless homogenous solution to a biphasic system. The lower amber phase was separated and washed with toluene twice (10 mL × 2) followed by treatment under vacuum at 80 °C to get *N,N,N′,N′*-tetramethyl-*N*-hexyl-ethylenediammonium bromide ([TMHEDA]Br) (98.2% of yield), (2) [TMHEDA]Br was dissolved to 50 mL acetone, and sodium tetrafluoroborate (22.0 g, 0.2 mol) was added under vigorous stirring. Stirring for 48 h at room temperature was done to ensure the completion of ion exchange: (3) The white solid in the mixture was filtered out, and the filtrate was evaporated under vacuum to get a sticky liquid, which was diluted with 50 mL CH_2Cl_2. The solution was washed with water twice (20 mL × 2), followed by the vacuum treatment at 80 °C to get the amber and viscous ionic liquid (96.7% of yield).

However, the NMR characterization had illustrated that the ionic liquid was not pure; it is a mixture attributed to the nearly 20% of dialkylated ammonium compound *(N,N,N′,N′*-tetramethyl-*N,N′*-dihexyl-ethylenediammonium tetrafluoroborate).

[TMHEDA]BF$_4$. ^{1}H NMR (400 MHz, DMSO TMS) $\delta = 0.88$ (m, CH$_2$*CH$_3$*, 3H), 1.30 (m, (*CH$_2$*)$_3$, 6H), 1.61–1.67 (m, *CH$_2$*, 2H), 2.22 (s, N*CH$_3$*, 6H), 2.64 (t, N*CH$_2$*, J = 5.64 Hz, 2H), 3.05 (s, N$^+$*CH$_3$*, 6H), 3.29 (m, N$^+$*CH$_2$*, 2H), 3.38 (t, N$^+$*CH$_2$*, J = 6.28 Hz, 2H). ^{13}C NMR (400 MHz, DMSO TMS) $\delta = 13.82$ (1C, CH$_2$*CH$_3$*), 21.69 (1C, *CH$_2$*), 21.85 (1C, *CH$_2$*), 25.41 (1C, *CH$_2$*), 30.65 (1C, *CH$_2$*), 44.95 (2C, N*CH$_3$*), 50.36 (2C, N$^+$*CH$_3$*), 52.21 (1C, N*CH$_2$*), 59.68 (1C, N$^+$*CH$_2$*), 63.67 (1C, N$^+$*CH$_2$*).

N,N,N′,N′-Tetramethyl-N,N′-dihexyl-ethylenediammonium tetrafluoroborate. ^{1}H NMR (400 MHz, DMSO TMS) $\delta = 0.89$ (m, CH$_2$*CH$_3$*, 6H), 1.32 [m, (*CH$_2$*)$_3$, 12H], 1.64–1.69 (m, *CH$_2$*, 4H), 3.10 (s, N$^+$*CH$_3$*, 12H), 3.34 (m, N$^+$*CH$_2$*, 4H), 3.79 (s, N$^+$*CH$_2$*, 4H). ^{13}C NMR (400 MHz, DMSO TMS) $\delta = 13.82$ (2C, CH$_2$*CH$_3$*), 21.65 (2C, *CH$_2$*), 21.91 (2C, *CH$_2$*), 25.34 (2C, *CH$_2$*), 30.65 (2C, *CH$_2$*), 50.44 (4C, N$^+$*CH$_3$*), 54.91 (2C, N$^+$*CH$_2$*), 64.41 (2C, N$^+$*CH$_2$*).

A Representative Procedure for Knoevenagel Condensation in [TMHEDA]BF$_4$

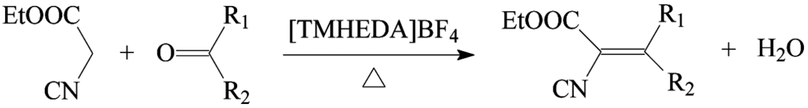
All the reactions were performed in a 50-mL round-bottomed flask equipped with a condenser under magnetic stirring for the desired time. The basic ionic liquid [TMHEDA]BF$_4$ (2.0 g) was put into the flask, and then benzaldehyde (0.1 mol) and ethyl cyanoacetate (0.1 mol) were added sequentially with stirring. The mixture was heated to 60 °C and stirred for 1 h. After the mixture cooled to room temperature, diethyl ether (20 mL) was poured into it. The upper ether phase was separated, and the lower phase was extracted with diethyl ether (10 mL × 2). By combining the ether, the product was obtained by removing the volatile ether. [TMHEDA]BF$_4$ ionic liquid can be recovered, purified under vacuum, and directly used in the next run.

RESULTS AND DISCUSSION

It is evident that the basicity of [TMHEDA]BF$_4$ ionic liquid originated from the alkyl amino group. That is to say, the cation of this basic ionic liquid probably predominated the catalytic efficiency. Because the base-catalyzed reactions in [BMim][BF$_4$] have been described by the pioneering work, low conversion and less-efficient activity were still inextricable.[21] Thus, it is very suitable to check the reactivity of [TMHEDA]BF$_4$ using Knoevenagel condensation as a test reaction.

Initially, the feasibility of [TMHEDA]BF$_4$ used as the catalyst for Knoevenagel condensation was investigated using benzaldehyde and ethyl cyanoacetate as substrates as shown in Table 1, and only 43% of yield was achieved at room temperature after 1 h (entry 1). As the temperature was raised to 40 °C, a better result was obtained (88% yield, entry 2). Then, subsequential experiments revealed that 60 °C is necessary to complete the reaction to the maximum yield (entry 3). However, when changing benzaldehyde to aliphatic aldehyde and ketones, more effort for Knoevenagel condensation has to be made to improve the yields. As can be seen

Table 1. Knoevenagel condensation of some aldehydes/ketones with ethyl cyanoacetate in the [TMHEDA][BF_4] ionic liquid[a]



Entry	R_1	R_2	Temp. (°C)	Time (h)	Yield (%)[b]
1	Ph	H	r.t.	1.0	43
2	Ph	H	40	1.0	88
3	Ph	H	60	1.0	99 (95)[c]
4	Ph	H	60	0.5	75
5	Ph	Me	80	4.0	67
6	Cyclohexanone		60	2.5	95
7	n-C_7H_{15}	H	60	2.0	98
8	Et	Me	60	2.5	89

[a] [TMHEDA]BF_4 (2.0 g), aldehyde or ketone (0.1 mol), and ethyl cyanoacetate (0.1 mol).

[b] GC yield, conversion based on ethyl cyanoacetate.

[c] Ionic liquid reused for the fourth time.

from entries 5–8, extended reaction time and even greater reaction temperature (entry 5) afforded the product in 67–98% yields. It should be pointed out that these results are generally high and compare favorably with those catalyzed by solid basic catalyst in conventional organic solvents.[22]

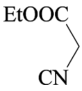
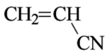
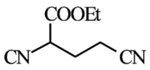
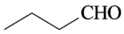
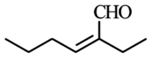
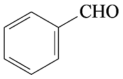
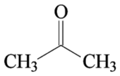
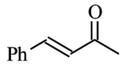
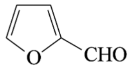
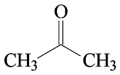
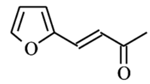
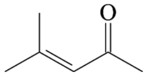
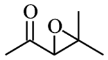
It is well-known that the usual ethyl cyanoacetate-benzaldehyde test reaction is much more facile with most base catalysts. Clearly this method would be substantially improved if the ionic liquid could be efficient in other reactions. With this in mind, we have investigated some organic reactions catalyzed by [TMHEDA]BF_4 ionic liquid, and the results are summarized in Table 2.

Reactions of 1–4, are typical nucleophilic addition reactions, usually carried out in the presence of a base catalyst. Herein, [TMHEDA]BF_4 ionic liquid could exhibit potential catalytic activity for these reactions with moderate to good yields. Importantly, no by-product was detected in these nucleophilic addition reactions except for the unreacted substrates. However, in the epoxidation of mesityl oxide, the inescapable ring-opening reaction contributed to the poor yield. Interestingly, the ionic liquids mostly used for Claisen-Schmidt reactions are reported to be acidic.[23,24] However, the ionic liquid-supported pyrrolidine amide catalyst has been developed to perform Claisen–Schmidt reaction, and the (*E*)-α,β-unsaturated ketone products were obtained in good yields,[25] which also evidenced the wide applications of the ionic liquids based on the alkylamino groups.

CONCLUSION

A novel basic ionic liquid of *N,N,N′,N′*-tetramethyl-*N*-hexyl-ethylenediammonium tetrafluoroborate was synthesized and applied to Knoevenagel condensation as basic catalyst. Moderate to excellent yields were obtained using cyanoacetate and benzaldehyde as substrates. Four reuses without dramatic decrease in yield of

Table 2. Organic reactions carried out in [TMHEDA]BF_4 ionic liquid[a]

Reaction	Reactants		Product	Time (h)	Yield (%)[b]
1. Micheal addition				8	53.7
2. Aldol				4	77.4
3. Claisen–Schmidt				4	60.5
4. Claisen–Schmidt				14	46.0
5. Epoxidation[c]		H_2O_2		2	7.9

[a]Reaction conditions: [TMHEDA]BF_4, 20 wt%; equivalent amount of two substrates; room temperature.

[b]GC yield.

[c]Five times excess of H_2O_2 to mesityl oxide.

Knoevenagel condensation demonstrated the good stability and operability of the ionic liquid. In addition, the catalytic activity of this ionic liquid was further tested through some other nucleophilic addition reactions including Michael condensation, Claisen-Schmidt reaction, and epoxidation. The dual function of the basic ionic liquid both as solvent and catalyst, combined with simple recycling and product separation, is expected to contribute to the development of green and environmentally friendly strategies.

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