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1-Butyl-2,3-trimethyleneimidazolium bis(trifluoromethylsulfonyl)imide ([b-3C-im][NTf_2]): a new, stable ionic liquid

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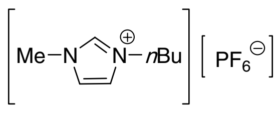
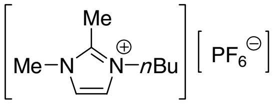
Abstract—Using imidazole as the starting material, the synthesis of a new bicyclic ionic liquid [b-3C-im][NTf_2] is described. Except for the alkylation reaction in the second step (40% yield) of this four-step synthesis of [b-3C-im][NTf_2], others were all high yielding reactions (85–94% isolated yields). We investigated intrinsic reactivity of this and other imidazolium-based ionic liquids and found that, under strongly basic conditions (KOD in CD_3OD/D_2O (1:1) solution), the new ionic liquid was stable to solvent deuterium isotope exchange while the previously reported [bdmim][NTf_2] and [bdmim][PF_6] ionic liquids were 50% deuterium exchanged at its C-2 methyl in 30 min at ambient temperature. At the same experimental condition, the most commonly employed [bmim][PF_6] ionic liquid was deuterium exchanged instantaneously at its C-2 hydrogen. In the absence of bases ($CD_3OD/D_2O = 1:1$), only [bmim][PF_6] was deuterium exchanged (50% within 1 h) and other ionic liquids gave no detectable exchanges even after one week at ambient temperature. It is therefore concluded that the new [b-3C-im][NTf_2] ionic liquid is far more chemically stable than previously reported [bmim][PF_6], [bdmim][NTf_2], and [bdmim][PF_6].

We recently demonstrated that [bdmim][PF_6][1] and [bdmim][NTf_2][2] ionic liquids are much more chemically stable than the popular [bmim]-based ionic liquids, and thus avoid some of the competing reactions such as nucleophilic additions[1] or substitutions[2] that are evident in [bmim] solvents. We now have extended our research to a new, more stable and bicyclic imidazolium ionic liquid, 1-butyl-2,3-trimethyleneimidazolium bis(trifluoromethylsulfonyl)imide ([b-3C-im][NTf_2]). Ionic liquids are a class of highly polar solvents that are entirely constituted of ions.[3] They are liquid at low temperature and are often considered as recyclable and environmentally friendly substitutes for conventional organic solvents, primarily because of their negligible vapor pressure, ability to dissolve a large array of compounds in relatively small volumes, good chemical and thermal stability, non-flammability, and high ionic conductivity that readily accelerates rates of reactions in, for example, microwave-mediated organic synthesis.[1b] Because of these intriguing properties, ionic liquids outperform conventional solvents in many organic reactions and applications such as separation technology and battery electrochemistry.[3]

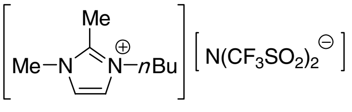
A large number of ionic liquids have been reported in the literature.[3] Up to now, the alkylimidazolium salts are still the most studied and best characterized ionic liquids. 1-*n*-Butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) ionic liquid, for example, has been widely studied in many areas of research for reasons of its ease of preparation, lack of vapor pressure, and, most significantly, hydrophobicity that presents an



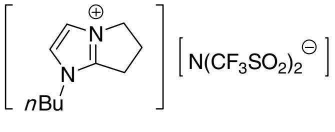
[bmim][PF_6]



[bdmim][PF_6]



[bdmim][Tf_2N]



[b-3C-im][NTf_2]

Keywords: Ionic liquid; Organic synthesis.

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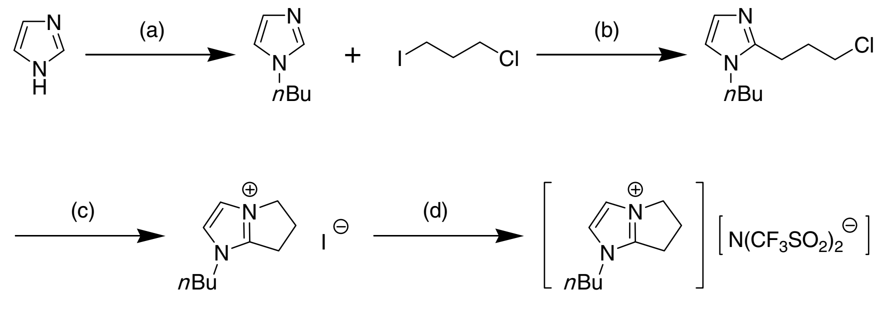
obvious advantage as a potential replacement for volatile organic solvents in developing green processes. However, it is known that the $[PF_6]$ anion in ionic liquids has the propensity to decompose to release HF and related species, and the [bmim] cation is not at all compatible with the highly basic reaction conditions.[1–3] These disadvantages obviously limited the application of ionic liquids to synthetic reactions. The development of ionic liquids with new formulation is therefore of an urgent need.

In our continuous quest aimed toward developing chemically stable and hydrophobic ionic liquids with utilities as green solvents for organic synthesis, we describe in this report the facile synthesis of a new bicyclic ionic liquid [b-3C-im]$[NTf_2]$. The bicyclic [b-3C-im] cation was employed in this new formulation for reasons that the proton at the C-2 in [bmim] as well as the C-2 methyl in [bdmim] cations are known to be relatively acidic and can be readily exchanged with D_2O,[4] and under basic conditions the [bmim] cation, in particular, readily reacts with various electrophiles such as aldehydes.[1] In addition, because of its electron richness at C-2 (C2–CH_2R in [b-3C-im] vs C2–CH_3 in [bdmim] and C2–H in [bmim]) of this constrained dihydropyrrol[1,2-*a*]imidazolium ring, it is expected that the resulting higher pK_a at C-2 makes [b-3C-im] cation more chemically stable. The hydrophobic $[NTf_2]$ anion was chosen in our new ionic liquid formulation not only because it is known to be hydrolytically stable, but also due to the fact that the strong delocalization of the negative charge in the fluoroanion weakens its interaction with the cation, therefore leading to lower melting points of ionic liquids.[3] Furthermore, the organofluoro compounds often possess unique resistance to extremes of temperature and pressure, to corrosive acids and bases, and to oxidizing agents.[3]

Our synthesis of [b-3C-im]$[NTf_2]$ is outlined in Scheme 1.[5,6] In the first step, the needed 1-butylimidazole was prepared from inexpensive imidazole and 1-butylbromide following a modified literature procedure.[5,7] Under refluxed condition (KOH in acetonitrile), this N-alkylation reaction was readily achieved with high isolated yield (85%). For the second step, substituents could be introduced via in situ lithiation by *n*-butyllithium at the most acidic C-2 of 1-butylimidazole to produce 1,2-disubstituted imidazoles.[8] Initially, we investigated the C-2 substitution using excessive 1,3-dibromopropane with a hope to prepare the expected 1-butyl-2-(3-bromopropyl)imidazole, but soon encountered problems of side products such as the dialkylated 2:1 adduct as well as the unwanted quaternized ionic liquids of various forms contaminated with the desired 1:1 product. During the course of synthesis of this new ionic liquid, we became aware that the nature of the halo group to be displaced in alkyl halides can dramatically determine the nature of the product.[8b] Although simple alkyl iodides such as *n*-butyl iodide behaved as anticipated for lithiation–alkylations, there was no guarantee that other alkyl iodides such as 3-chloro-1-iodopropane would follow suit. After several trials, we were pleased to find that, though the reaction was low-yielding (40%) and its experimental condition remained preliminary, the reaction of the lithiated *N*-butyllimidazole with 3-chloro-1-iodopropane cleanly furnished the 1-butyl-2-(3-chloropropyl)imidazole (Scheme 1).[5] Upon standing at ambient temperature for 8 days, this 1-butyl-2-(3-chloropropyl)imidazole slowly but smoothly cyclized to afford the ionic liquid [b-3C-im][Cl] with quantitative yield. If the condition of the Finkelstein cyclization (NaI in refluxed methanol) was employed, we found that the reaction was accelerated to completion in 5 h with excellent 94% isolated yield. The [b-3C-im][Cl] could readily be converted to the final [b-3C-im]$[NTf_2]$ ionic liquid via a simple ion exchange in water (Scheme 1).

[b-3C-im]$[NTf_2]$ is a liquid at ambient temperature.[9] We were interested in the $[NTf_2]$-based ionic liquids because of their reported minimal water association with the liquid and unusual low melting points.[10,11] In addition, the conformationally constrained and non-planar structure of this new ionic liquid may somewhat contribute to low melting point. For physical properties, [b-3C-im]$[NTf_2]$ is miscible with polar organic solvents—methanol, acetone, dichloromethane, ethyl acetate, and acetonitrile—and insoluble in less polar solvents such as diethyl ether, *n*-hexane, and toluene. Like ionic liquids



[b-3C-im]$[NTf_2]$

Scheme 1. Preparation of a new bicyclic room temperature ionic liquid, [b-3C-im]$[NTf_2]$. Reagents and conditions: (step a) imidazole (1 equiv), 1-bromobutane (1 equiv), KOH (2 equiv), acetonitrile, refluxed, 4 h, 85%; (step b) 1-butylimidazole (1 equiv), BuLi (1.2 equiv), 1-chloro-3-iodopropane (1 equiv), THF, −50 to 60 °C (1 h) → rt (7 h), 40%; (step c) 1-butyl-2-(3-chloropropyl)imidazole (1 equiv), NaI (1.1 equiv), MeOH, refluxed, 5 h, 94%; (step d) [b-3C-im][I] (1 equiv), $LiNTf_2$ (1 equiv), H_2O, 12 h, rt, 92%.

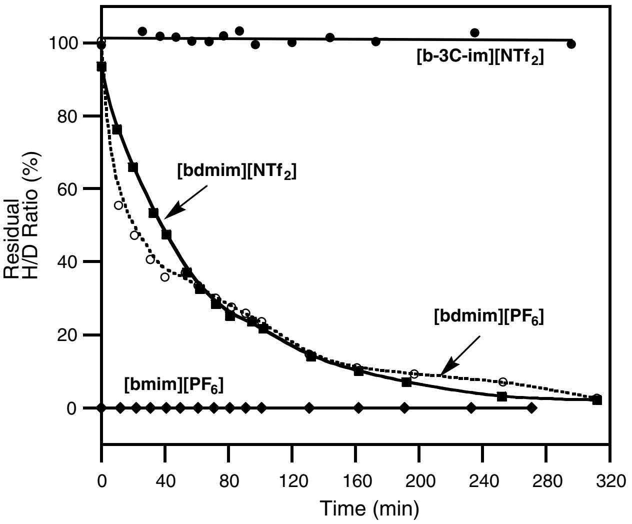


Figure 1. Solvent deuterium isotope exchanges at C-2 of [b-3C-im][NTf_2], [bdmim][NTf_2], [bdmim][PF_6], and [bmim][PF_6] room temperature ionic liquids (0.1 M each) in CD_3OD/D_2O (1:1, v/v; 0.5 mL) containing 0.1 M KOD. The progress of deuterium exchange could be readily monitored by ^1H NMR.

incorporating PF_6, the new ionic liquid is immiscible with water.

Handy et al. recently investigated chemical reactivities of C2-unsubstituted as well as C2-methyl-substituted fructose-derived imidazolium ionic liquids and found that, in the absence of base, only C2-unsubstituted ionic liquid underwent deuterium isotope exchange rapidly.[4a] They further established that the C2-methyl-substituted ionic liquid was not totally inert and could proceed deuterium exchange under basic conditions.[4a] Their results prompted us to investigate the intrinsic chemical reactivity of our new [b-3C-im][NTf_2]. Also, we envisaged that the constrained ring system and high pK_a at C-2 of [b-3C-im][NTf_2] may exhibit resistance to solvent deuterium exchanges. For these reasons, we decided to set up deuterium isotope exchange experiments at ambient temperature for the new [b-3C-im][NTf_2] and three previously reported ionic liquids ([bmim][PF_6], [bdmim][PF_6], and [bdmim][NTf_2]).

Exchange rates of the C-2 hydrogens of imidazolium ions were measured in two (neutral and strongly basic) experimental conditions by observing the change in area of the signal due to the C-2 hydrogens in the ^1H NMR spectra. We found that, under strongly basic conditions (0.1 M KOD in the 1:1 mixture of CD_3OD and D_2O), the new [b-3C-im][NTf_2] ionic liquid (0.1 M) underwent essentially no deuterium isotope exchanges at C-2 methylene even after 1 day while the [bdmim][NTf_2] ionic liquid was 50% deuterium exchanged at C-2 methyl position in 20 min at ambient temperature (Fig. 1). Rates of exchange were based on the decrease in ^1H NMR signals relative to those for the non-exchanging groups. We were totally surprised to find that, under the strongly basic condition, the widely used [bmim][PF_6] ionic liquid was deuterium exchanged instantaneously at C-2 (Fig. 1). This 1-butyl-3-methylimidazolium cation likely undergoes base-catalyzed abstraction of the C-2 proton to form the ylide intermediate stabilized by a carbene-like resonance structure.[12]

In neutral conditions ($CD_3OD/D_2O = 1:1$), only [bmim][PF_6] was found to be deuterium exchanged rapidly (50% in 1 h) and [b-3C-im][NTf_2] gave no detectable exchanges even after one week at ambient temperature.[13] Another two ionic liquids, [bdmim][NTf_2] and [bdmim][PF_6], produced less than 10% deuterium exchange at C-2 methyl group at room temperature for one week time. From the results of solvent deuterium exchange experiments, we therefore concluded that the new [b-3C-im][NTf_2] ionic liquid is far more chemically stable than previously reported [bmim][PF_6], [bdmim][NTf_2], and [bdmim][PF_6] (i.e., [b-3C-im][NTf_2] $\gg$ [bdmim][NTf_2] $\approx$ [bmim][PF_6] $\gg$ [bdmim][PF_6]).

The results presented in this research clearly indicate that C2-unsubstituted ionic liquids such as [bmim][PF_6] are chemically reactive; the replacement of the C-2 hydrogen with a methyl group to produce 2-methyl-substituted ionic liquids (e.g., [bdmim][NTf_2]) adds additional stability but is not totally inert under basic reaction conditions. Our new [b-3C-im][NTf_2] ionic liquid appears to provide sufficient chemical tolerance to bases so that many potential side reactions that are common in imidazolium-based ionic liquids may therefore be avoided.

In summary, we report a new ionic liquid [b-3C-im][NTf_2] that fulfills the requirement as an inert solvent and this ionic liquid opens exciting perspectives of use for synthetic applications of many natural and non-natural products of biological significance. In addition, this conformationally constrained [b-3C-im][NTf_2] ionic liquid may enable new applications that are not possible with conventional solvents.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.125.

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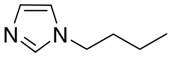
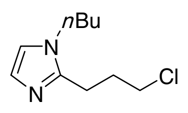
5. *Synthesis and characterization of 1-butyl-2,3-trimethyleneimidazolium bis(trifluoromethylsulfonyl)imide, [b-3C-im][NTf$_2$], ionic liquid:*



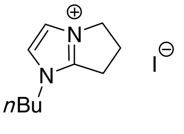
1-butylimidazole

To a round-bottomed flask containing imidazole (6.0 g, 88 mmol) in acetonitrile (50 mL) were added potassium hydroxide (9.9 g, 177 mmol) and 1-bromobutane (9.9 mL, 90 mmol). The reaction mixture was refluxed for 4 h and then cooled to room temperature. After a flash column chromatography (ethyl acetate/methanol = 25:1), the purified product 1-butylimidazole was isolated as an oil (9.5 g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz, CH_3), 1.32 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 3.92 (t, 2H, J = 7.2 Hz, NCH_2), 6.89 (s, 1H, C=CH), 7.04 (s, 1H, C=CH), 7.44 (s, 1H, N=CH).



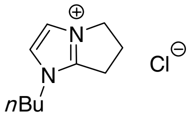
1-butyl-2-(3-chloropropyl)imidazole

Under dry nitrogen, a solution of butyllithium in hexanes (2.5 M, 16 mL, 40 mmol) was added dropwise in 10 min time to a cold (−50 to 60 °C) solution of 1-butylimidazole (3.96 mL, 30 mmol) in anhydrous tetrahydrofuran (60 mL). The yellow solution was stirred at −50 to 60 °C for 1 h, and 1-chloro-3-iodopropane (3.22 mL, 30 mmol) was added dropwise, and the mixture was allowed to slowly warm to room temperature (for a total of 7 h). Ethyl acetate (100 mL) and brine (60 mL) were added and the organic layer was separated and dried (Na_2SO_4). After evaporation, the ^{1}H NMR spectrum of the reaction mixture indicated the presence of about 50% starting 1-butylimidazole and the crude 1-butyl-2-(3-chloropropyl)imidazole was then purified by column chromatography of silica gel (ethyl acetate/methanol = 25:1) to afford an amber oil (2.4 g, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.4 Hz, CH_3), 1.36 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.83 (t, 2H, J = 7.4 Hz, $N{=}CCH_2$), 3.67 (t, 2H, J = 6.1 Hz, CH_2Cl), 3.86 (t, 2H, J = 7.3 Hz, NCH_2), 6.83 (s, 1H, C=CH), 6.94 (s, 1H, C=CH).



[b-3C-im][I]

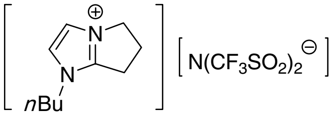
or



[b-3C-im][Cl]

[b-3C-im][I]: To a solution of 1-butyl-2-(3-chloropropyl)imidazole (2.4 g, 12 mmol) in methanol (20 mL) was added sodium iodide (1.98 g, 13.2 mmol). The mixture was refluxed for 5 h, cooled to room temperature and was filtered to remove sodium chloride. The filtrate was concentrated in vacuo to give a slight yellow solid, which was dissolved with dichloromethane (4 × 4 mL) and filtered again. After removal of the solvent, the [b-3C-im][I] was isolated as a brownish oil (3.3 g, 94%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, J = 7.4 Hz, CH_3), 1.28 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 3.16 (t, 2H, J = 7.8 Hz, $N{=}CCH_2$), 4.06 (t, 2H, J = 7.2 Hz, $C{=}NCH_2$), 4.20 (t, 2H, J = 7.4 Hz, $C{=}NCH_2$), 7.64 (d, 1H, J = 2.0 Hz, C=CH), 7.67 (d, 1H, J = 2.0 Hz, C=CH).

[b-3C-im][Cl]: To a round-bottomed flask containing-1-butyl-2-(3-chloropropyl)imidazole (0.94 g, 4.7 mmol) was placed at ambient temperature for 8 days. The spontaneously cyclized product was washed by ethyl acetate and the resulting amber oil proved to be 1-butyl-2,3-trimethyleneimidazolium chloride [b-3C-im][Cl] (0.95 g, 100%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, J = 7.4 Hz, CH_3), 1.28 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 3.14 (t, 2H, J = 7.6 Hz, $N{=}CCH_2$), 4.05 (t, 2H, J = 7.2 Hz, $C{=}NCH_2$), 4.19 (t, 2H, J = 7.2 Hz, $C{=}NCH_2$), 7.64 (d, 1H, J = 1.8 Hz, C=CH), 7.67 (d, 1H, J = 1.8 Hz, C=CH).



[b-3C-im][NTf$_2$]

To a solution containing 1-butyl-2,3-trimethyleneimidazolium iodide (3.32 g, 11.3 mmol) and water (30 mL) was added the bistrifluoromethanesulfonimide lithium salt (3.24 g, 11.3 mmol). The mixture was allowed to proceed the ion exchange for 12 h at room temperature. Two phases were formed in the mixture solution. The resulting solution was diluted with dichloromethane (20 mL) and then washed with water (3 × 10 mL). Removal of the solvent under reduced pressure afforded 1-butyl-2,3-trimethyleneimidazolium bis(trifluoromethylsulfonyl)imide [b-3C-im][NTf$_2$] as a slightly brownish liquid (4.63 g, 92%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, J = 7.4 Hz, CH_3), 1.28 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.13 (t, 2H, J = 7.6 Hz, $N{=}CCH_2$), 4.04 (t, 2H, J = 7.2 Hz, $C{=}NCH_2$), 4.18 (t, 2H, J = 7.3 Hz, $C{=}NCH_2$), 7.62 (d, 1H, J = 2.0 Hz, C=CH), 7.64 (d, 1H, J = 2.0 Hz, C=CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.6, 19.2, 22.8, 25.9, 31.3, 48.1, 48.2, 118.2, 119.8 (q, J_{CF} = 320 Hz, CF_3), 126.0, 152.6; FAB-HRMS m/z $[M]^+$ calcd = 165.1392, obsd = 165.1392.
6. Using the same protocol, 1-methyl-2,3-trimethyleneimidazolium bis(trifluoromethylsulfonyl)imide [m-3C-im][NTf$_2$] was also prepared. This ionic liquid is however a solid (mp 83–85 °C) at room temperature.
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