DOI: 10.1002/adsc.200600277

Ionic Liquid, 1-*n*-Butyl-3-methylimidazolium Bis(trifluoromethanesulfonyl)imide, Resulted in the First Catalyst-Free Aminohalogenation of Electron-Deficient Alkenes

Yi-Ning Wang,[a] Bukuo Ni,[b] Allan D. Headley,[b,*] and Guigen Li[a,*]

[a] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, USA
Fax: (+1)-505-277-2609; e-mail: Guigen.li@ttu.edu
[b] Department of Chemistry, Texas A&M University–Commerce, Commerce, Texas 75429-3011, USA

Received: June 12, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

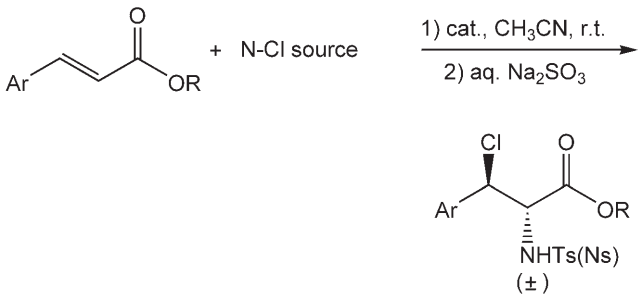
Abstract: The 2-Ns-based aminohalogenation of α,β-unsaturated ketones has been achieved in an ionic liquid, 1-*n*-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide {[bmim][$N(SO_2CF_3)_2$]}. [Bmim][$N(SO_2CF_3)_2$] was found to be superior not only to classical organic solvents but also to its counterpart, [bmim][BF_4], which was proven to be successful in the $TsNCl_2$-based aminohalogenation but failed to give any product for this reaction. The present process takes the advantage of 2-$NsNCl_2$ as the stable nitrogen/halogen source in a one-pot operation without the use of any metal catalysts, it is convenient to perform without special protection of inert gases. Eight examples were examined with good to excellent stereoselectivity (1:5 to one isomer) and modest to good chemical yields (53–72%).

Keywords: aminohalogenation; haloamines; ionic liquids; α,β-unsaturated ketones

The functionalization of unsaturated carbon-carbon bonds with haloamines has long been an important topic in modern organic and medicinal chemistry.[1–3] Although several synthetic approaches to the vicinal haloamine functionality have been developed,[4–7] the study of efficient and highly regio- and stereoselective methods still remains very interesting and challenging.

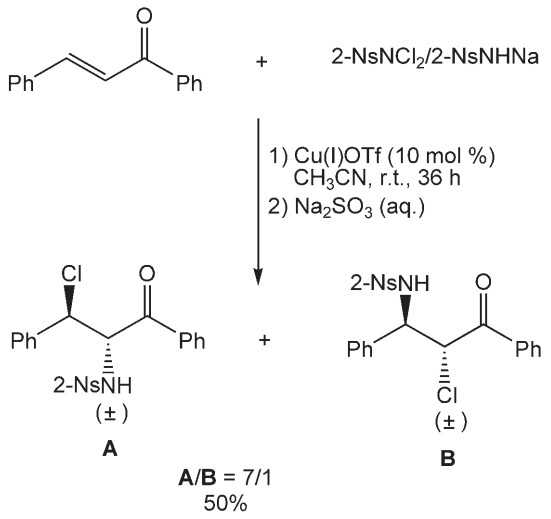
In the past several years, we have successfully developed the catalytic aminohalogenation of α,β-unsaturated esters using various nitrogen/halogen sources, such as 4-$TsNCl_2$,[6a] 2-NsNNaCl (2-Ns: 2-nitobenzenesulfonyl),[6b] or the combination of 2-$NsNCl_2$ and 2-NsNHNa[6c] in the presence of metal catalysts[6d–h] (Scheme 1). For the aminohalogenation of α,β-unsaturated ketones only 4-$TsNCl_2$ has been successfully employed as the nitrogen/halogen source.[7a] In the continuing study of this reaction, we turned our attention to the replacement of 4-$TsNCl_2$ with 2-$NsNCl_2$ which is much more stable and more convenient handled. In fact, 2-$NsNCl_2$ was found to be stable at room temperature for several months. More importantly, the resulting haloamine products with 2-Ns protecting group can be readily cleaved under mild conditions by treating with $PhSH/K_2CO_3$ in DMF at room temperature.[8] With the aminohalogenation of α,β-unsaturated cinnamic esters in hand,[6c] we utilized the combination of 2-$NsNCl_2$ and 2-NsNHNa as the nitrogen/halogen source, and the corresponding aminohalogenation products were successfully synthesized (Scheme 2).[7d] However, it turned out that an excess amount of nitrogen/halogen source and prolonged reaction periods were required for the complete consumption of α,β-unsaturated substrates. As a result, further improvement is necessary.

Very recently, we reported that an ionic liquid (IL), [bmim][BF_4], can be employed as the reaction media for the Ts-based aminohalogenation of α,β-conjugated substrates, and the aminohalogenation reaction

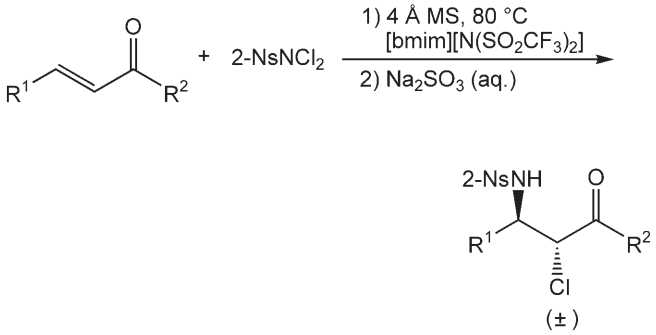


N-Cl source = 4-$TsNCl_2$, 2-$NsNCl_2$/2-NsNHNa, or 2-NsNClNa

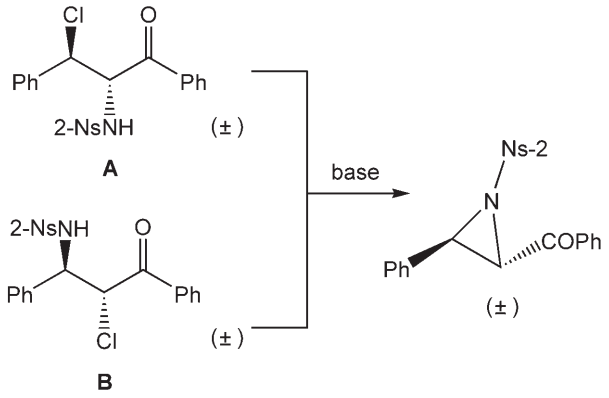
Scheme 1.



Scheme 2.



Scheme 3.



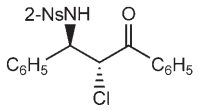
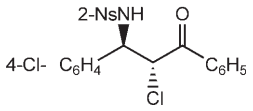
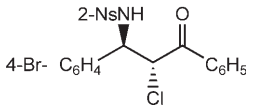
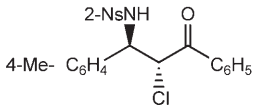
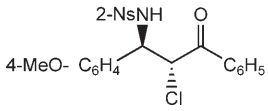
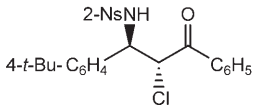
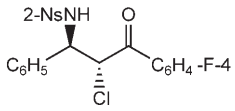
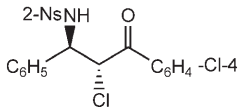
Scheme 4.

can be improved dramatically in terms of chemical yields and stereoselectivity.[7b,c] Since the aminohalogenation is believed to proceed through the formation of an ionic aziridinium intermediate, ionic liquid is believed to play an important role on stabilizing this intermediate through ionic solvation effect and on facilitating the chlorine atom's leaving the nitrogen source (2-$NsNCl_2$) for the formation of electrophilic species. In addition, as compared with normal organic solvents, the use of ionic liquids as reaction media has several other attractive properties for chemical transformations, including their nonvolatility, noncombustibility, and dissolvability of polar compounds.[10–12] Furthermore, ionic liquids can be easily recycled, and therefore, they are environmentally friendly. Surprisingly, when [bmim][BF_4] was utilized as the reaction media for this reaction under the similar condition as described before,[7b,c] the anticipated haloamine products were not observed even in the presence of metal catalysts. In this communication, we were pleased to report that in the ionic liquid of [bmim][$N(SO_2CF_3)_2$] the aminohalogenation reaction of α,β-unsaturated ketones can proceed smoothly in modest to good yields and excellent regio- and stereoselectivity (Scheme 3 and Table 1). More interestingly, this reaction can proceed without the use of metal catalysts. To our best knowledge, the present reaction could be the first aminohalogenation of electron-deficient olefins in the absence of metal catalysts (Scheme 3).

As compared with the results previously obtained in our laboratories, it was surprised to find that in the ^{1}H NMR spectra of resulting new compounds, the splitting patterns are more complicated than we anticipated in $CDCl_3$ as the solvent. In order to determine the regio- and stereoselectivity, product **1** was chosen as an example, and was converted into the corresponding aziridine. As a result, the same aziridine was obtained exclusively compared with that derived from compound **A**, which indicated that isomer **B** was mainly formed in the present aminohalogenation mediated by [bmim][$N(SO_2CF_3)_2$] (Scheme 4). The regioselectivity was further confirmed by mass spectroscopy analysis, which showed prominent peak corresponding to $[PhCHNHNs]^+$ ($m/z = 291$). We believe that the hydrogen bonding existing between the hydrogen of nitrobenzensulfonyl amine and carbonyl groups to form a stable six-membered ring could be responsible (Figure 1) for the complex ^{1}H NMR spectra. The equilibrium of major conformers can coexist in in $CDCl_3$ solution. Then some hydrogens of nitrobenzensulfonyl amine conformers can be shifted to the lower field in their ^{1}H NMR spectra.

The aminohalogenation reaction can be carried out simply by mixing reactants in a one-pot operation system. Since there are no sensitive catalysts involved, the reaction can be performed without the special protection by inert gases. To optimize the yields, 4 Å molecular sieves were also added, which is similar to the situation of the previous systems. Meanwhile, in order to improve the chemical yield, it is necessary to increase the reaction temperature to 80 °C. The ionic liquid employed in this reaction was readily prepared by reacting 1-methylimidazole with 1-butyl bromide,[10] followed by the anion metathesis using *N*-lithiotrifluoromethanesulfonimide in acetone solution. The resulting ionic liquid, [bmim][$N(SO_2CF_3)_2$], was

Table 1. Results of aminohalogenation of enones in [bmim][$N(SO_2CF_3)_2$].

Entry	R^1	R^2	Product (±)	Yield[a] [%]	Regioselectivity[b] (**A**:**B**)
1[13]	C_6H_5	C_6H_5	**1** 	66	1:8
2	4-Cl-C_6H_4	C_6H_5	**2** 	62	1:7
3	4-Br-C_6H_4	C_6H_5	**3** 	53	1:5
4	4-Me-C_6H_4	C_6H_5	**4** 	60	1:15
5	4-MeO-C_6H_4	C_6H_5	**5** 	72	1:7
6	4-*t*-Bu-C_6H_4	C_6H_5	**6** 	68	only **B**
7	C_6H_5	4-F-C_6H_4	**7** 	68	1:10
8	C_6H_5	4-Cl-C_6H_4	**8** 	66	1:8

[a] The combined yields of two isomers which were difficult to separate by column chromatography.
[b] Yields after column chromatography.

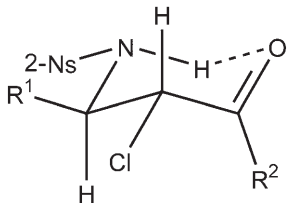


Figure 1. Possible hydrogen bonding conformation.

carefully dried by heating at 60 °C in vacuum, then confirmed by ^{1}H NMR anlysis.[13]

In summary, the ionic liquid, [bmim][$N(SO_2CF_3)_2$], makes the *2*-Ns-based aminohalogenation of α,β-unsaturated ketones to occur smoothly. The reaction can be conducted under convenient conditions without the special protection of inert gases. The present new method represents the first aminohalogenation of electron-deficient olefins in the absence of metal catalysts.

Experimental Section

General Remarks

All reactions were performed in oven-dried vials. Flash chromatography was performed using silica gel (Merck 60, 230–400 mesh).

Aminohalogenation of α,β-Unsaturated Ketones in [bmim][$N(SO_2CF_3)_2$]; Typical Procedure:

Into an oven-dried vial was loaded chalcone (104 mg, 0.5 mmol, 1.0 equiv.), 4 Å molecular sieves (100 mg), 2-$NsNCl_2$ (163 mg, 0.6 mmol, 1.2 equivs.), [bmim][$N(SO_2CF_3)_2$] (500 mg). The resulting mixture was stirred at 80 °C for 24 h. The reaction was finally quenched with saturated aqueous solution of Na_2SO_3. The product was extracted with diethyl ether (5 mL × 3) and the combined ether extracts were washed with brine and dried over anhydrous Na_2SO_4. The crude product was subjected to flash chromatography (EtOAc and hexane, v/v = 1:3) to afford the product as a white solid; yield: 146 mg (66 %).

Acknowledgements

We gratefully acknowledge the Robert A. Welch foundation (D-1361 to GL, T-1460 to AH) for generous support of this work. We thank Mr. David W. Purkiss for his assistance in NMR determination.

References

[1] J. E. G. Kemp, in: *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 3, pp. 471–513, and references cited therein.

[2] a) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1991**, *113*, 5863; b) D. H. R. Barton, M. R. Britten-Kelly, D. Ferreira, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1090; c) H. Driguez, J.-P. Vermes, J. Lessard, *Can. J. Chem.* **1978**, *56*, 119; d) J. Lessard, H. Driguez, J.-P. Vermes, *Tetrohedron Lett.* **1970**, *11*, 4887.

[3] a) F. A. Daniher, P. E. Butler, *J. Org. Chem.* **1968**, *33*, 4336; b) F. A. Daniher, P. E. Butler, *J. Org. Chem.* **1968**, *33*, 2637; c) F. A. Daniher, M. T. Melchior, P. E. Butler, *Chem. Commun.* **1968**, 931; d) T. P. Seden, R. W. Tuner, *J. Chem. Soc.* (*C*) **1968**, 876; e) A. Klepacz, A. Zwierzak, *Tetrahedron Lett.* **2001**, 4539.

[4] a) B. S. Orlek, G. Stemp, *Tetrahedron Lett.* **1991**, *32*, 4045; b) T. Bach, B. Schlummer, K. Harms, *Eur. J. Org. Chem.* **2001**, 2581.

[5] S. Karur, S. R. S. S. Kotti, X. Xu, J. F. Cannon, A. D. Headley, G. Li, *J. Am. Chem. Soc.* **2003**, *125*, 13340.

[6] a) G. Li, H.-X. Wei, S. H. Kim, M. Nerghbors, *Org. Lett.* **1999**, *1*, 395; b) H.-X. Wei, S. H. Kim, G. Li, *Tetrahedron* **2001**, *57*, 3869; c) G. Li, H.-X. Wei, S. H. Kim, *Org. Lett.* **2000**, *2*, 2249; for the recent excellent work on aminohalogenation by several other groups see: d) S. Minakata, Y. Yoneda, Y. Oderaotoshi, M. Komatsu, *Org. Lett.* **2006**, *8*, 967; e) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618; f) X. Qi, S. H. Lee, J. Y. Kwon, Y. Kim, S. J. Kim, Y. S. Lee, J. Yoon, *J. Org. Chem.* **2003**, *68*, 9140; g) V. V. Thakur, S. K. Talluri, A. Sudalai, *Org. Lett.* **2003**, *5*, 861; h) H. Danielec, J. Klugge, B. Schlummer, T. Bach, *Synthesis* **2006**, 551.

[7] a) D. Chen, C. Timmons, S. Chao, G. Li, *Eur. J. Org. Chem.* **2004**, 3097; b) X. Xu, S. R. S. S. Kotti, J. Liu, J. F. Cannon, A. D. Headley, G. Li, *Org. Lett.* **2004**, *6*, 4881; c) S. R. S. S. Kotti, X. Xu, Y.-N. Wang, A. D. Headley, G. Li, *Tetrahedron Lett.* **2004**, *45*, 7209; d) J. Liu, Y.-N. Wang, G. Li, *Eur. J. Org. Chem.* in press.

[8] a) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373; b) S. G. Nelson, K. L. Spencer, *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1323; c) P. Wipf, T. C. Henninger, *J. Org. Chem.* **1997**, *62*, 1586; d) S. C. Miller, T. S. Scanlan, *J. Am. Chem. Soc.* **1997**, *119*, 2301.

[9] W. Pei, H.-X. Wei, D. Chen, A. D. Headley, G. Li, *J. Org. Chem.* **2003**, *68*, 8404.

[10] a) R. Sheldon, *J. Chem. Soc., Chem. Commun.* **2001**, 2399; b) M. J. Earle, P. B. McCormac, K. R. Seddon, *Green Chem.* **1999**, 23; c) D. A. Jaeger, C. E. Tucker, *Tetrahedron Lett.* **1989**, *30*, 1785; d) J. Howarth, K. Hanlon, D. Fayne, P. McCormac, *Tetrahedron Lett.* **1997**, *38*, 3097; e) S. Park, R. Kazlauskas, *J. Org. Chem.* **2001**, *66*, 8395; f) J. X. Wu, B. Beck, R. X. Ren, *Tetrahedron Lett.* **2002**, *43*, 387.

[11] a) G. W. Kabalka, B. Venkataiah, G. Dong, *Tetrahedron Lett.* **2003**, *44*, 4673; b) S. R. S. S. Kotti, X. Xu, G. Li, A. D. Headley, *Tetrahedron Lett.* **2004**, *45*, 1427.

[12] a) A. D. Headley, N. M. Jackson, *J. Phys. Org. Chem.* **2002**, *15*, 52; b) A. D. Headley, J. Nam, *J. Phys. Org. Chem.* **2002**, *15*, 62.

[13] P. Lucas, N. El Mehdi, H. Anh Ho, D. Bélanger, L. Breau, *Synthesis* **2000**, *9*, 1253.

