# 1-Butyl-3-methylimidazolium Tetrafluoroborate ([Bmim]$BF_4$) Ionic Liquid: A Novel and Recyclable Reaction Medium for the Synthesis of *vic*-Diamines

J. S. Yadav,* B. V. S. Reddy, K. Premalatha

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax: +91-40-27160512, e-mail: yadav@iict.ap.nic.in

Received: January 30, 2003; Accepted: April 23, 2003

**Abstract:** Aziridines undergo ring opening smoothly with various arylamines in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]$BF_4$) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]$PF_6$) ionic liquids under mild and neutral conditions to afford the corresponding *vicinal*-diamines in excellent yields with high regioselectivity. The recovered activated ionic liquids are recycled for four to five runs with no loss of activity.

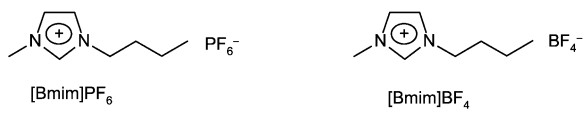
**Keywords:** arylamines; aziridines; *vic*-diamines; ionic liquids (ILs)

Aziridines are important intermediates for the synthesis of many biologically active molecules such as amino acids,[1] heterocycles[2] and alkaloids.[3,4] Particularly, *vic*-diamines are a biologically, medicinally and synthetically important class of compounds in the field of anti-HIV drugs[5] such as Zanamivir and Oseltamivir phosphate and other pharmaceuticals.[6] The simple and the most straightforward synthetic method for the preparation of *vic*-diamines is the ring opening of aziridines with amines. Especially, the cleavage of aziridines with amines has special interest because the resultant 1,2-diamines have widespread applications in asymmetric synthesis as chiral ligands.[7] The ring opening of activated aziridines with amines is generally carried out in the presence of Lewis acids.[8,9] However, many of these procedures involve the use of expensive reagents, extended reaction times and also require tedious aqueous work-up to isolate the products and thus produce a huge amount of toxic waste. These organic solvents are often harmful to the environment and as a result are frequently subject to government restrictions and high waste disposal costs. Consequently methods that successfully minimize their use are the focus of much attention. In this respect, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability.[10] Their high polarity and the ability to solubilize both organic and inorganic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. Accordingly they are emerging as novel replacements for volatile organic solvents in organic synthesis. They are particularly promising as solvents for catalysis.[11] Because of distinct advantages of ionic liquids as environmentally benign reaction media for catalytic processes, much attention has currently focused on organic reactions promoted by ionic liquids.

Since 1,2-diamines have become increasingly useful and important in drugs, pharmaceuticals and in asymmetric synthesis, the development of simple, convenient and environmentally benign processes for their synthesis is desirable.

In view of the emerging importance of the imidazolium-based ionic liquids as novel reaction media, we now report the use of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]$BF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]$PF_6$) ionic liquids (Figure 1) as environmentally friendly and recyclable solvents for the synthesis of 1,2-diamines under mild conditions (Scheme 1).

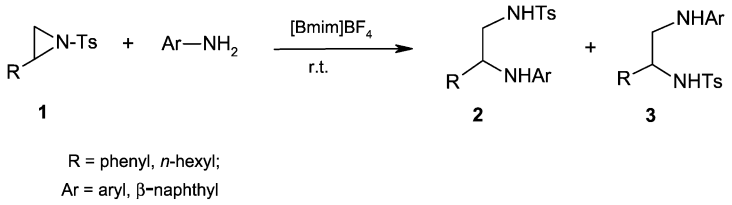
The treatment of the *N*-tosylaziridine from styrene with aniline in [bmim]$BF_4$ ionic liquid at room temperature gave the corresponding 2-anilino-2-phenylethylamine derivative **2** in 91% yield. Similarly, *p*-methyl- and *p*-chlorophenyl-*N*-tosylaziridines reacted smoothly with arylamines in [bmim]$BF_4$ ionic liquid to afford the corresponding 1,2-diamines **2** in excellent yields. Aryl-*N*-tosylaziridines underwent cleavage in a regioselective manner with preferential attack at the benzylic position (Table 1, entries a, b, c, d). The reactions proceeded smoothly at room temperature with high regioselectivity. Interestingly, alkyl-*N*-tosylaziridines also underwent



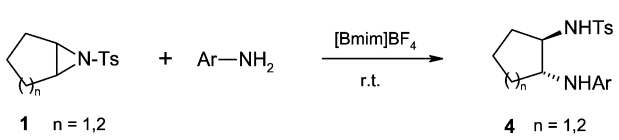

[Bmim]$PF_6$ [Bmim]$BF_4$

**Figure 1.**

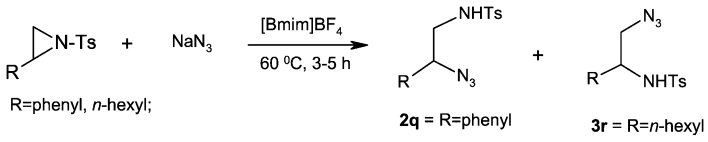
  DOI: 10.1002/adsc.200303029 




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

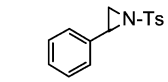
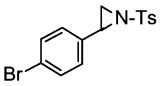
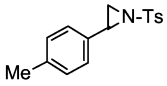
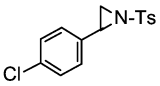
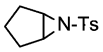
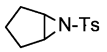
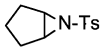
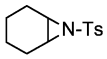
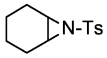
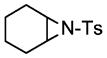
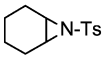
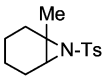
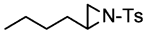
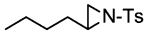
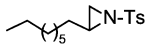
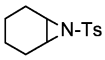
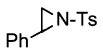
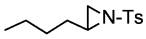
cleavage with arylamines under these reaction conditions to give the respective 1,2-diamines **3** in high yields. Alkylaziridines gave the ring opened products **3** resulting from the terminal attack of the amines. However, the treatment of cycloalkyl-*N*-tosylaziridines with aromatic amines afforded the corresponding 1,2-diamines in high yields (Scheme 2).

In the case of the cyclohexylaziridine, the stereochemistry of the ring product **4 h** was found to be *trans* from the coupling constants of the ring H-atoms at $\delta =$ 2.95 ppm (ddd, $J = 4.0, 10.0$, and 10.0 Hz, 1H) for (NCH) in the $^1$H NMR spectrum. Likewise, the peak at $\delta =$ 3.10 ppm for (CHN) showed a similar kind of splitting pattern (ddd, $J = 3.9, 10.0$, and 10.0 Hz, 1H). The method is clean and highly regioselective, affording 1,2-diamines in excellent yields. Furthermore, *N*-tosylaziridines also underwent cleavage with sodium azide in ionic liquids to produce β-azidoamines (Table 1, entries p, q, r, Scheme 3).

The cleavage of aziridines with sodium azide proceeded smoothly in ionic liquids at 60 °C with high regiosectivity. All the products were characterized by $^1$H NMR, IR and mass spectral analysis and also by comparison with authentic samples.[9] The reaction conditions are mild and no side products or decomposition of the products are observed. However, aliphatic amines such as *n*-butylamine, benzylamine and diethylamine failed to react with aziridines under these reaction conditions. In this reaction, the efficiency of the ionic liquid was strongly influenced by the nature of the anion. The reactions of various aziridines and arylamines were studied in hydrophilic [bmim]$BF_4$ and hydrophobic [bmim]$PF_6$ ionic liquids and the results are presented in Table 1. Among these ionic liquids, [bmim]$BF_4$ was found to be superior in terms of yields and reaction rates. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the oily ionic liquid was thoroughly washed with ether and recycled in subsequent reactions. Second and third reactions using recovered ionic liquid afforded similar yields to those obtained in the first run. In fourth and fifth runs, the yields were gradually decreased. For example, styrene-aziridine and aniline in [bmim]$BF_4$ ionic liquid afforded 90%, 90%, 89%, 86%, and 78% over five cycles. However, the activity of the ionic liquid was consistent in runs and no decrease in yield was obtained when the recycled ionic liquid was activated at 80 °C under vacuum in each cycle. Furthermore, the products obtained were of the same purity as in the first run. To compare the efficiency of ionic liquids, the cleavage of *N*-tosylaziridines with amines was carried out in conventional solvents in the presence of Lewis acids. For instance, treatment of styrene-*N*-tosylaziridine, cyclohexene-*N*-tosylaziridine and *n*-hexene-*N*-tosylaziridine with aniline in the presence of 20 mol % $InCl_3$ in acetonitrile at room temperature gave the desired 1,2-diamines in 85%, 72% and 78% yields, respectively, whereas the same experiments in [bmim]$BF_4$ ionic liquid in the absence of any catalyst at room temperature afforded the corresponding 1,2-diamines in 91%, 85%, and 90% yields (Table 1). These comparative results clearly show the effectiveness of ionic liquids in the cleavage of aziridines with arylamines. Both hydrophilic and hydrophobic ionic liquids were purchased from Fluka and used as such without any further purification. Ionic liquids have also been prepared in our laboratory from the readily available and inexpensive *N*-methylimidazole, 1-chlorobutane and hexafluorophosphoric acid or sodium tetrafluroborate.[13] The purity of the ionic liquids prepared in the laboratory was determined by comparing their $^1$H NMR spectra with those of commercial samples. The purity of [bmim]$BF_4$ ionic liquid is $\geq$ 97.0% (NMR). In further reactions, the efficiency of various quaternary ammonium salts was tested. The aziridine ring opening reactions were not successful at room temperature in other molten salts such as *n*-tetrabutylammonium chloride (*n*-$Bu_4NCl$) or 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl). These results clearly indicated that

**Table 1.** Cleavage of aziridines with aryl amines and sodium azide in ionic liquids.

| Entry | Aziridine | Aryl amine | Product[a] | [bmim]$BF_4$ | | [bmim]$PF_6$ | |
|---|---|---|---|---|---|---|---|
| | | | | Time [h] | Yield [%][b] | Time [h] | Yield [%][b] |
| a) |  | $C_6H_5NH_2$ | **2a** | 4.5 | (91) | 6.0 | (87) |
| b) |  | *p*-$MeC_6H_4NH_2$ | **2b** | 5.0 | (89) | 6.5 | (85) |
| c) |  | $C_6H_5NH_2$ | **2c** | 4.0 | (92) | 7.0 | (83) |
| d) |  | $C_6H_5NH_2$ | **2d** | 5.5 | (90) | 6.5 | (80) |
| e) |  | $C_6H_5NH_2$ | **4e** | 6.0 | (85) | 8.0 | (78) |
| f) |  | *p*-$MeC_6H_4NH_2$ | **4f** | 6.5 | (89) | 9.0 | (82) |
| g) |  | *p*-$ClC_6H_4NH_2$ | **4g** | 6.0 | (90) | 9.0 | (75) |
| h) |  | $C_6H_5NH_2$ | **4h** | 5.5 | (85) | 9.5 | (78) |
| i) |  | *p*-$ClC_6H_4NH_2$ | **4i** | 6.0 | (91) | 8.0 | (87) |
| j) |  | *p*-$MeOC_6H_4NH_2$ | **4j** | 5.5 | (90) | 7.5 | (83) |
| k) |  | *p*-$FC_6H_4NH_2$ | **4k** | 5.0 | (85) | 9.5 | (79) |
| l) |  | $C_6H_5NH_2$ | **4l** | 7.0 | (82)[c] | 8.0 | (75)[c] |
| m) |  | $C_6H_5NH_2$ | **3m** | 6.0 | (90) | 8.0 | (82) |
| n) |  | *p*-$ClC_6H_4NH_2$ | **3n** | 5.5 | (87) | 9.0 | (75) |
| o) |  | *p*-$MeC_6H_4NH_2$ | **3o** | 6.0 | (91) | 8.0 | (77) |
| p) |  | $NaN_3$ | **4p** | 7.5 | (83) | 9.0 | (75) |
| q) |  | $NaN_3$ | **2q** | 5.5 | (89) | 6.0 | (85) |
| r) |  | $NaN_3$ | **3r** | 6.5 | (81) | 8.0 | (78) |

[a] All products were characterized by $^1H$ NMR, IR and mass spectroscopy.
[b] Yield refers pure products after chromatography.
[c] Aniline attack at less hindered side of aziridine

both cation and anion play an important role as the reaction media. The scope and generality of this process is illustrated with respect to various aziridines and arylamines and the results are presented in Table 1. The use of [bmim]$BF_4$ ionic liquid as reaction media for this transformation avoids the use of heavy metal Lewis acids or acidic promoters and also avoids aqueous work-up to isolate the products. The simple experimental and product isolation procedures combined with the ease of recovery and reuse of the novel reaction medium is expected to contribute to the development of a green strategy for the synthesis of 1,2-diamines.

In summary, this paper describes a novel and efficient method for the synthesis of 1,2-diamines by regioselective ring opening of aziridines with arylamines using imidazolium-based ionic liquids as novel reaction media as well as promoters. This method is also useful for the preparation of β-azidoamines from aziridines and sodium azide. The notable features of this procedure are mild reaction conditions, simplicity in operation, improved yields and reaction rates, cleaner reaction profiles and recyclability of ionic liquids which make it a simple, convenient and user-friendly process for the synthesis of 1,2-diamines.

## Experimental Section

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1H$ and $^{13}C$ NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. [Bmim]$BF_4$ and [bmim]$PF_6$ ionic liquids were prepared according to the procedures reported in the literature.[13]

### General Procedure

A mixture of aziridine (1 mmol), arylamine (1 mmol), in [bmim]$BF_4$ or [bmim]$PF_6$ (2 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated under vacuum and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:9) to afford the pure 1,2-diamine. The remaining ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs. In the case of solids, the products were purified by recrystallization in an appropriate solvent.

**2a**: solid, mp 150–152 °C; $^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.0 Hz), 7.58–7.63 (m, 1H), 7.20–7.38 (m, 6H), 7.05 (t, 2H, *J* = 7.8 Hz), 6.60 (t, 1H, *J* = 7.8 Hz), 6.40 (d, 2H, *J* = 8.0 Hz), 5.25 (brd, 1H, *J* = 6.5 Hz), 4.30 (dd, 1H, *J* = 4.0, 9.8 Hz), 3.18 (ddd, 1H, *J* = 4.0, 9.8, 10.0 Hz), 3.0 (ddd, 1H, *J* = 3.7, 9.8, 10.0 Hz), 2.40 (s, 3H); EIMS: *m/z* = 366 [$M^+$], 180, 155, 104, 91, 77, 65; IR (KBr): ν = 3368, 2942, 1619, 1518, 1448, 1328, 1257, 1158, 1085, 808 $cm^{-1}$; anal. calcd. for $C_{21}H_{22}N_2O_2S$ (366.47): C 68.82, H 6.05, N 7.64, S 8.74; found: C 68.87, H 6.09, N 7.69, S, 8.79.

**4e**: solid, mp 98–100 °C; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.2 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.07 (t, 2H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 8.0 Hz), 6.43 (d, 2H, *J* = 8.2 Hz), 5.38 (brd, *J* = 5.7 Hz, 1H), 3.30–3.45 (m, 2H), 2.38 (s, 3H), 2.08–2.25 (m, 2H), 1.60–1.85 (m, 2H), 1.20–1.35 (m, 2H); EIMS: *m/z* = 330 [$M^+$], 175, 132, 120, 91, 56; IR (neat): ν = 3378, 2967, 1621, 1538, 1448, 1332, 1156, 1098, 824, 677 $cm^{-1}$; anal. calcd. for $C_{18}H_{22}N_2O_2S$ (330.44): C 65.42, H 6.70, N 8.47, S 9.70; found: C 65.47, H 6.73, N 8.51, S 9.75.

**4 h**: solid, mp 152–154 °C; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.3 Hz), 7.08 (t, 2H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 8.0 Hz), 6.40 (d, 2H, *J* = 8.3 Hz), 4.84 (brd, *J* = 5.5 Hz, 1H), 3.40 (brs, 1H), 3.10 (ddd, *J* = 3.9, 10.0, 10.0 Hz, NCH, 1H), 2.95 (ddd, *J* = 4.0, 10.0, 10.0 Hz, NCH, 1H), 2.45 (s, 3H), 2.03-2-20 (m, 2H), 1.65–1.70 (m, 2H), 1.23–1.38 (m, 3H), 0.99–1.05 (m, 1H); EIMS: *m/z* = 344 [$M^+$], 189, 172, 141, 96, 91, 65; IR (neat): ν = 3400, 2958, 1620, 1528, 1423, 1324, 1092, 824, 732 $cm^{-1}$; anal. calcd. for $C_{19}H_{24}N_2O_2S$ (344.47): C 66.24, H 7.01, N 8.12, S 9.30; found: C 66.29, H 7.05, N 8.16, S 9.35.

**3 m**: solid, mp 68–70 °C; $^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.3 Hz), 7.05 (t, 2H, *J* = 7.8 Hz), 6.70 (t, 1H, *J* = 7.8 Hz), 6.40 (d, 2H, *J* = 8.0 Hz), 5.15 (m, 1H, NH), 4.20 (dd, 1H, *J* = 4.0, 9.8 Hz), 3.15 (ddd, 1H, *J* = 4.0, 9.8, 10.0 Hz), 3.0 (ddd, 1H, *J* = 3.5, 9.8, 10.0 Hz), 2.43 (s, 3H), 1.38–1.50 (m, 2H), 1.08–1.20 (m, 4H), 0.80 (t, 3H, *J* = 6.8 Hz); EIMS: *m/z* = 346 [$M^+$], 162, 106, 91, 65; IR (KBr): ν = 3268, 2930, 1602, 1508, 1433, 1318, 1158, 1089, 966, 815, 751 $cm^{-1}$; anal. calcd. for $C_{19}H_{26}N_2O_2S$ (346.48): C 65.85, H 7.56, N 8.09, S 9.25; found: C 65.89, H 7.59, N 8.11, S 9.29.

## Acknowledgements

*BVS and KP thank CSIR New Delhi, for the award of fellowships.*

## References and Notes

[1] a) D. Tanner, *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 599; b) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.

[2] a) A. Dureault, I. Tranchepain, J. C. Depezay, *J. Org. Chem*. **1989**, *54*, 5324; b) D. Tanner, H. M. He, *Tetrahedron* **1992**, *48*, 6079.

[3] T. Hudlicky, H. Luna, J. D. Price, F. Rulin, *J. Org. Chem*. **1990**, *55*, 4683.

[4] a) A. R. Katritzky, C. W. Rees, *Comprehensive Heterocylic Chemistry*, Pergamon Press, Oxford, **1984**, Vol. 7, pp. 47; b) J. E .G. Kump, *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 7, pp. 469.

[5] a) *Drugs of the Future* **1999**, *24*, 1175; b) P. W. Smith, S. L. Sollis, P. D. Howes, P. C. Cherry, I. D. Starkey, K. N. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, N. Taylor, D. Green, R. C. Bethell, S. Madar, R. J. Fenton, P. J. Morley, T. Patemann, A.

Beresford, *J. Med. Chem*. **1998**, *41*, 787; c) P. W. Smith, J. E. Robinson, D. N. Evans, S. L. Sollis, P. D. Howes, N. Trivedi, R. C. Bethell, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 601.

[6] M. T. Reetz, R. Jaeger, R. Drewlies, M. Hubel, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103 and references cited therein.

[7] S. G. Davies, A. A. Mortlock, *Tetrahedron* **1993**, *49*, 4419.

[8] M. Meguro, N. Asao, Y. Yamamoto, *Tetrahedron Lett*. **1994**, *35*, 7395; b) G. Sekar, V. K. Singh, *J. Org. Chem*. **1999**, *64*, 2537; c) J. S. Yadav, B. V. S. Reddy, B. Jyothirmai, M. S. R. Murthy, *Synlett* **2002**, 53.

[9] a) M. Meguro, Y. Yamamoto, *Heterocycles* **1996**, *43*, 2473; b) J. Wu, X. L. Hou, L. X. Dai, *J. Org. Chem*. **2000**, *65*, 1344.

[10] Recent reviews on ionic liquids: a) T. Welton, *Chem. Rev*. **1999**, *99*, 2071; b) P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed*. **2000**, *39*, 3772.

[11] Catalytic reactions in ionic liquids: a) R. Sheldon, *Chem. Commun*. **2001**, 2399; b) C. M. Gordon, *Applied Catalysis A*: *General* **2001**, *222*, 101.