Tetrahedron Letters 50 (2009) 1007–1009

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient, rapid, and regioselective bromination of anilines and phenols with 1-butyl-3-methylpyridinium tribromide as a new reagent/solvent under mild conditions

Sanjay P. Borikar, Thomas Daniel, Vincent Paul *

Division of Organic Chemistry, National Chemical Laboratory, Homi Bhabha Road, Pune 411 008, India

ARTICLE INFO

Article history:
Received 3 October 2008
Revised 8 December 2008
Accepted 11 December 2008
Available online 24 December 2008

Keywords:
Ionic liquid
Bromination
Regioselective
[BMPy]Br_3

ABSTRACT

1-Butyl-3-methylpyridinium tribromide, [BMPy]Br_3 proves to be a highly efficient, regioselective reagent/solvent for nuclear bromination of various anilines and phenols. The synthesis and characterization of the room temperature ionic liquid [BMPy]Br_3 (**2**) is described. The bromination was carried out in the absence of organic solvents and in most cases the only extraction solvent needed was water. The spent 1-butyl-3-methylpyridinium bromide (**1**) was easily recycled.

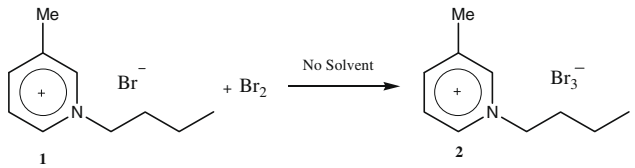
Bromo derivatives have wide utility both as products and as intermediates.[1,2] Many of these compounds are prepared using bromine. However, bromine is a hazardous chemical which is difficult to manipulate due to its toxicity and high vapor pressure. Pyridinium hydrobromide perbromide (PHP) salt was used as an alternative for selective ketone bromination.[3] PHP also proved useful as an alternative for bromination of alkenes,[4] aromatics,[5] as catalyst for aziridinations[6] and for stereoselective alkene bromination in water suspension.[7] There are many alkyl pyridinium salts, which are commercially available room temperature ionic liquids (RTILs). Bromination in classical RTIL media, such as [BMIm]PF_6, which replace environmentally problematic chlorinated solvents, has been demonstrated.[8] Bronsted acidic ionic liquids have been successfully applied to a variety of reactions including esterification of carboxylic acids,[9] protection of aldehyde and ketone,[10] and cleavage of ethers.[11] The combination of alkylpyridinium cation with the tribromide anion should, therefore, lead to a RTIL bromine analog. Trihalide-based ILs as reagents-solvents for iodochlorination and iodobromination of unsaturated compounds have been reported.[12]

Ionic liquids were introduced as alternative green reaction media because of their unique chemical and physical properties such as non-volatility, non-inflammability, thermal stability, and ease of recyclability. In recent years, there has been considerable interest in developing Green Chemistry[13] for organic synthesis due to environmental demand and sustainability. Today ILs have marched far beyond this border, showing their significant roles in controlling the reaction as new reagents.[14,15] For example, tribromide ILs based on imidazolium or pyridinium as non-volatile and regioselective bromination reagents have been developed by different groups.[16] Picolines are comparatively cheaper than imidazolium ionic liquids, especially in the production of low cost ILs for bulk application.

3-Picoline, on the other hand, an important intermediate in the synthesis of nicotinic acid and its derivatives, has been rarely used as a starting material for ILs.

We hereby disclose the synthesis, full characterization, and reactivity of 1-butyl-3-methylpyridinium tribromide, a proton-free RTIL bromine analog. This does not have any measurable vapor pressure and has been demonstrated for regioselective nuclear bromination reactions.

Addition of molecular bromine to 1-butyl-3-methylpyridinium bromide dropwise under stirring formed exothermally the red liquid 1-butyl-3-methylpyridinium tribromide that displayed a density of 1.75 g cm^{-3} and viscosity of 55.4 cP (Scheme 1).[17] Excess



Scheme 1. Preparation of 1-butyl-3-methylpyridinium tribromide.

* Corresponding author. Tel.: +91 20 25902286; fax: +91 20 25902629.
E-mail address: vp.swamy@ncl.res.in (V. Paul).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.053

Table 1
Solvent-free bromination using 1-butyl-3-methylpyridinium tribromide **2** at room temperature[a]

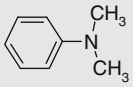
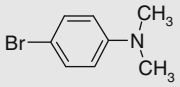
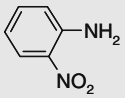
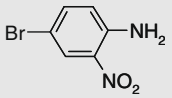
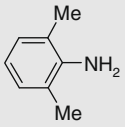
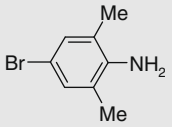
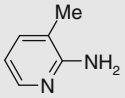
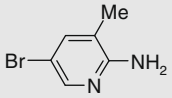
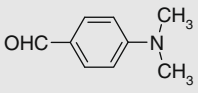
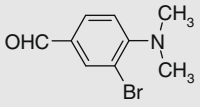
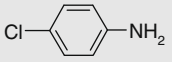
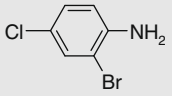
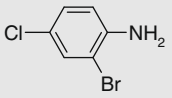
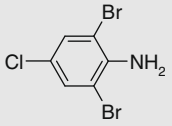
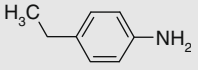
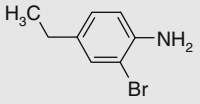
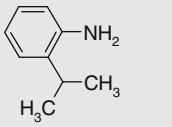
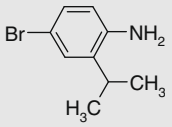
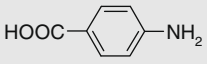
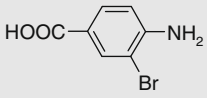
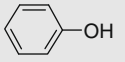
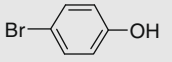
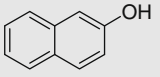
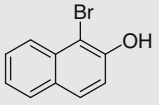
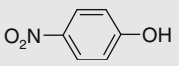
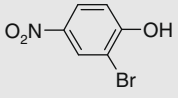
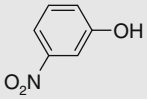
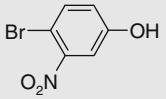
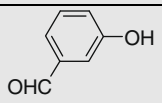
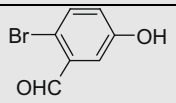
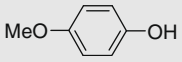
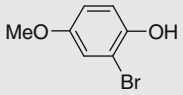
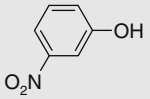
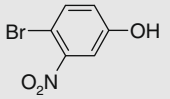
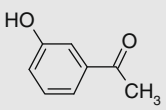
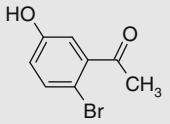
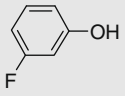
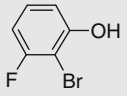
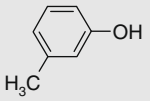
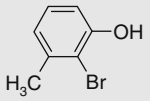
Entry	Substrate	Product	Time	Yield[b] (%)
1			6 min	92
2			Immediately	98
3			Immediately	98
4			Immediately	97
5			4 min	85
6			Immediately	97
7			2 min	98
8			60 min	87
9			4 min	75
10			10 min	93
11			Immediately	96
12			45 min	97
13			15 min	85
14			Immediately	98

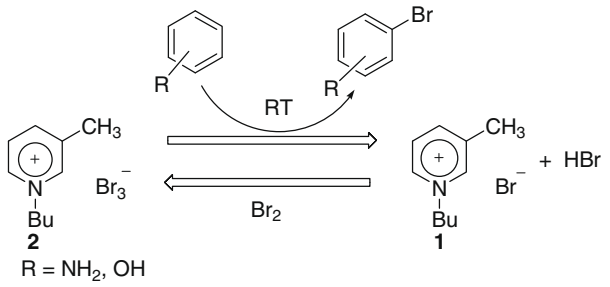
Table 1 (*continued*)

Entry	Substrate	Product	Time	Yield[b] (%)
15			15 min	92
16			12 min	98
17			12 min	98
18			15 min	90
19			10 min	95
20			30 min	88
21			60 min	89
22			10 min	98
23			5 min	91

[a] All reactions were carried out with 1.0 equiv of [BMPy]Br_3 at room temperature.
[b] All compounds showed satisfactory ^{1}H NMR and mass spectral data.

bromine absorbed by **2** was removed completely under a high vacuum. The ionic nature of **2** thus effectively eliminates any noxious residual bromine vapor pressure.[18] RTIL **2** is hydrophobic forming two phases with water, while IL **1** is highly hydrophilic and hygroscopic. IL **2** can be stored for several months without change of structure and loss of activity. Even after prolonged heating at 60 °C under vacuum (<5 mm Hg), **2** was recovered unaltered without loss of bromine. IL **2** was miscible with MeOH/EtOH, acetone, DMSO, and with other strong polar organic solvents and immiscible with water, ether, $CHCl_3$, and with other weakly polar organic solvents.

RTIL **2** was used as an alternative brominating agent, and the results are summarized in Table 1. Various anilines and phenols were monobrominated with complete selectivity and in excellent yields (Scheme 2).[19] Phenol was cleanly monobrominated in the absence of any solvent at room temperature by RTIL **2**, affording exclusively *p*-bromophenol (entry 11). *p*-Nitrophenol underwent mono-bromination in 15 min, whereas *m*-Nitrophenol was brominated immediately (entries 13 and 14). α-Naphthol, being a bulky mole-



Scheme 2. Regioselective bromination of anilines and phenols with [BMPy]Br_3 under mild conditions.

cule, took 45 min for monobromination (entry 12). Similarly, a variety of substituted anilines underwent regioselective monobromination (entries 1–10). Imidazole underwent monobromination to afford 2-bromoimidazole in 5 min (entry 22).

All the reactions were quenched by adding water. This caused precipitation of the products as solids or oils, which were readily separated and washed with fresh portions of water, and then dried (either with sodium sulfate or in vacuo). The aqueous phase containing highly water soluble **1** was easily concentrated in vacuo to recycle **1**, which then could be used to regenerate RTIL **2** with bromine (Scheme 2).

All the reactions were carried out in air at room temperature, adding 1.0 equiv of IL **2** to an equimolar amount of substrate without any solvent. Although the reactions were slightly exothermic, no special precautions were taken for cooling. They were monitored by TLC and were stopped after the disappearance of the substrate.

In summary, a new room temperature ionic liquid bromine analog, which is safer and easier to use, was synthesized and characterized. It displayed improved selectivity and better reaction conditions, as compared to current bromination techniques. This new functional RTIL **2** may be classified as 'green' for the following reasons: (1) it eliminates toxic bromine vapors, (2) the bromine carrier **1** can be easily recovered and recycled, and (3) it avoids the use of organic solvents. Furthermore, **2** afforded good-to-excellent yields for a wide variety of anilines and phenols at room temperature.

Acknowledgments

The financial support from the DST, New Delhi (GAP264126) is gratefully acknowledged. We are grateful to Dr. Ganesh Pandey for his support and encouragement.

References and notes

1. (a) Kuroboshi, M.; Waki, Y.; Tanaka, H. *J. Org. Chem.* **2003**, *68*, 3938; (b) Qingwei, Y.; Elizabeth, P. K.; Zhi, Y. *J. Org. Chem.* **2003**, *68*, 7528.
2. (a) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Chem. Commun.* **2003**, 1444; (b) Euzenat, L.; Horhant, D.; Ribourdouille, Y.; Duriez, C.; Alcaraz, G.; Vaultier, M. *Chem. Commun.* **2003**, 2280.
3. Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417.
4. Arcus, C. L.; Strauss, H. E. *J. Chem. Soc.* **1952**, 2669.
5. (a) Reeves, W. P.; Lu, C. V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* **1998**, *28*, 499; (b) Banks, R. E.; Hasszeldine, R. N.; Latham, J. V.; Young, I. M. *J. Chem. Soc.* **1965**, 594.
6. Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* **1999**, *1*, 705.
7. (a) Tanaka, K.; Shiraishi, R.; Toda, F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3069; (b) Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740; (c) Kajigaeshi, S.; Moriwaki, M.; Tanaka, T.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 897; (d) Avramoff, M.; Weiss, J.; Schaechter, O. J. *J. Org. Chem.* **1963**, *28*, 3256; (e) Buckles, R. E.; Popov, A. I.; Zelezny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* **1951**, *73*, 4525.
8. Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett.* **2001**, *3*, 1061.
9. Zhu, H.-P.; Yang, F.; Tang, J.; He, M.-Y. *Green Chem.* **2003**, *5*, 38.
10. Wu, H.-H.; Yang, F.; Pg, C.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* **2004**, *45*, 4963.
11. Driver, G.; Johnson, K. E. *Green Chem.* **2003**, *5*, 163.
12. Bortolini, O.; Bottai, M.; Chiappe, C.; Conte, V.; Pieraccini, D. *Green Chem.* **2002**, *4*, 621.
13. Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169.
14. (a) Ranu, B. C.; Banerjee, S. J. *J. Org. Chem.* **2005**, *70*, 4517; (b) Noguera, G.; Mostany, J.; Agrifoglio, G.; Dorta, R. *Adv. Synth. Catal.* **2005**, *347*, 231; (c) Davis, J. H. *Chem. Lett.* **2004**, *33*, 1072; (d) Earle, M. J.; Katdare, S. P.; Seddon, K. R. *Org. Lett.* **2004**, *6*, 707.
15. Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 952.
16. (a) Chang-chun, L. *Huaxue Shijie* **2008**, *49*, 481; (b) Kaushik, M. P.; Polshttiwar, V. *Indian J. Chem., Sect. B Org. Med. Chem.* **2006**, *45*, 2542; (c) Iranpoor, N.; Firouzabadi, H.; Azadi, R. *Tetrahedron Lett.* **2006**, *47*, 5531; (d) Zhang-Gao, L.; Zhen-Chu, C.; Yi, H. *Chin. J. Chem.* **2005**, *23*, 1537; (e) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 2809; (f) Salazar, J.; Dorta, R. *Synlett* **2004**, 1318; (g) Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536.
17. *Preparation of 1-butyl-3-methylpyridinium tribromide* **2**: In a fume cupboard, molecular bromine (0.22 mL, 0.436 mmol) was added dropwise over 10 min to 1-butyl-3-methylpyridinium bromide (**1**, 1.0 g, 0.436 mmol) under stirring and cooling in a ice-bath affording a deep red liquid IL **2,** and stirring was continued for 2 h. Under reduced pressure over 5 h at 60 °C, 1.62 g (95.4%) of the pure IL **2** was obtained as a red oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.72 (t, 3H, J = 7.33 Hz), 1.14 (m, 2H), 1.76 (m, 2H), 2.38 (s, 3H), 4.41 (t, 2H, J = 7.58 Hz), 7.74 (t, 1H, J = 7.83 Hz), 8.07 (d, 1H, J = 8.09 Hz), 8.62 (d, 1H, J = 6.07 Hz), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 12.86, 18.23, 18.76, 32.81, 61.36, 127.34, 139.41, 141.10, 143.35, 145.47; MS (ESI): 150 ($M-X_3$); Anal. Calcd for $C_{10}H_{16}Br_3N$: C, 30.80; H, 4.14; N, 3.59. Found: C, 31.01; H, 4.13; N, 3.40.
18. Similar examples that demonstrate the complete elimination of residual vapor pressure of strong acids in functional RTIL are: (a) Susan, M. A. B. H.; Noda, A.; Mitsushima, S.; Watanabe, M. *Chem. Commun.* **2003**, 938; (b) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5962.
19. *Typical experimental procedure*: To a stirred mixture of anilines or phenols (3.3 mmol) was added 1-butyl-3-methylpyridinium tribromide (3.3 mmol) at room temperature. After completion of the reaction as indicated by TLC, water was added into the reaction mixture to quench the IL. The resulting reaction mixture was extracted with diethyl ether, separated from the organic layer, dried over sodium sulfate, and concentrated to afford pure monobromo anilines or monobromo phenols.