[bmim]Br_3 as a New Reagent for Regioselective Monobromination of Arylamines under Solvent-Free Conditions

Zhang-Gao Le,[a,b,c] Zhen-Chu Chen,*[a,b] Yi Hu,[b] Qin-Guo Zheng[d]

[a] Ningbo Institute of Technology Zhejiang University, Ningbo, 315100, P. R. China

[b] Department of Chemistry, Zhejiang University (xi xi campus), Hangzhou, 310028, P. R. China
E-mail: lezhang_ecit@163.com

[c] Department of Applied Chemistry, East China Institute of Technology, Fuzhou, 344000, P. R. China

[d] Pharmaceutical Science Reseach Institute, Aston University, Aston Triangle, Birmingham B4 7ET, UK

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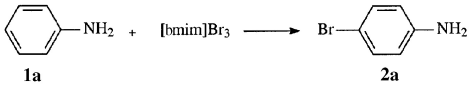
Abstract: Reaction of arylamines with 1-butyl-3-methylimidazolium tribromide ([bmim]Br_3) under solvent-free conditions, gave selectively the corresponding monobromination products with excellent yields.

Key words: ionic liquid, aniline, monobromination, [bmim]Br_3

Electrophilic aromatic bromination is an important and fundamental reaction known to organic chemists. Brominated aromatic compounds are of paramount importance as building blocks in organic synthesis. They are key intermediates in the preparation of organometallic reagents[1] and play vital roles in transition metal mediated coupling reactions.[2] They can be used as potent antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidising agents.[3] A variety of brominating reagents (capable of bromination) are available including Br_2,[4] *N*-bromosuccinimide (NBS),[5] tetrabutylammonium tribromide,[6] DBUH·Br_3,[7] cetyltrimethylammonium tribromide,[8] pyridinium tribromide,[9] LiBr/ceric ammonium nitrate,[10] and HBr/DMSO.[11] The bromination of activated aromatic compounds such as aniline derivatives remains a problem due to mixtures of *ortho* and *para* products and polybromination.[12] There are, however, a handful of selective bromination procedures. For example, Smith and coworkers[13] reported a selective one-pot, four-step sequence for arylamine bromination via tin amides formed in situ; Zhai et al.[14] developed an efficient arylamine bromination by a three-stage approach (lithiation, boron amide formation and bromination); and Roche et al.[15] demonstrated the oxidative bromination of anilines using KBr and sodium perborate. There are some disadvantages in these methods, such as multistep procedures, harsh reaction conditions, relatively low selectivity and yield, or the need for large amount of reagents, oxidants, and catalysts. Therefore, the development of an efficient, selective monobromination reaction for anilines is still a major challenge in organic synthesis.

Solvent-free chemical synthesis has recently received much attention.[16] The advantages of this method over conventional reaction conditions are that it provides greater selectivity, enhanced reaction rates and cleaner products. In addition, the method is operationally simple and environmentally friendly. In continuation of our ongoing program to develop environmentally benign and new synthetic methods using ionic liquids as novel promoters and selective reagents,[17] we report here a new and efficient method for the regioselective monobromination of anilines using 1-butyl-3-methylimidazolium tribromide ([bmim]Br_3). This tribromide is a stable liquid, readily prepared by reaction of equimolar amounts of 1-butyl-3-methylimidazolium bromide and bromine. The reagent, which can be stored for several months without loss of activity, has recently been used for the stereoselective bromination of alkynes.[18]



Scheme 1

1-Butyl-3-methylimidazolium tribromide ([bmim]Br_3), is an efficient and novel reagent for the regioselective monobromination of arylamines. We found that the reaction of aniline (**1a**) with [bmim]Br_3 (Scheme 1), occurred rapidly under solvent-free conditions at –10 °C and was complete within two minutes. The reaction leads to selective monobromination, preferentially in the *para* position (Table 1, entry 1), to produce *p*-bromoaniline (**2a**). In similar fashion, the reaction of [bmim]Br_3 with a variety of aromatic amines was investigated. We found that the reaction is general and applicable to several substituted anilines containing different groups, such as methyl, bromo, nitro, carboxyl groups. The results are summarized in Table 1 (entries 2–6). When the *para* position of the substituted anilines is occupied, the reaction leads to selective monobromination in the *ortho* position. In order to explore the generality of the method developed for the monobromination of activated aromatic substrates, we conducted the experiments with [Bmim]Br_3 and secondary or tertiary anilines or amides, which were also effective and gave the corresponding monobromination products in excellent yields (Table 1, entries 7–10). Furthermore, in a similar fashion we tried the reaction of [bmim]Br_3 with 1- and 2-

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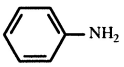
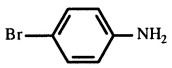
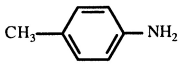
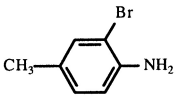
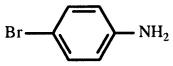
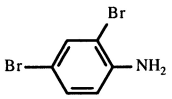
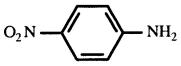
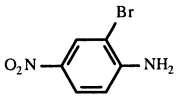
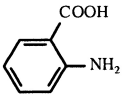
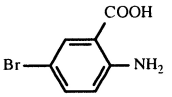
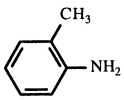
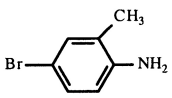
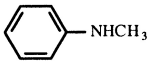
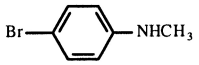
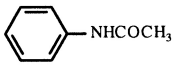
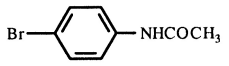
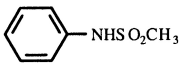
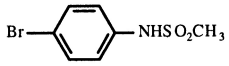
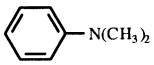
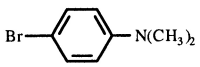
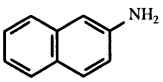
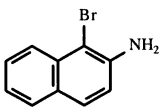
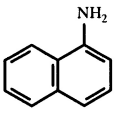
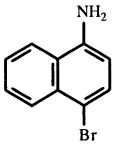
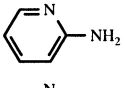
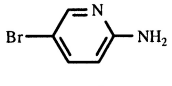
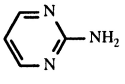
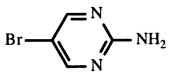
aminonaphthalene, 2-aminopyrimidine, and 2-aminopyridine. The corresponding monobromination products were also obtained with good yields (Table 1, entries 11–14).

All the products gave satisfactory melting point, IR, and ^{1}H NMR data, which were consistent with the literature data.

The present method has many obvious advantages, compared to those reported in the literature, including high selectivity, higher yield, shorter reaction time, and solvent-free conditions. For example, the reactions of *p*-chloroaniline, *o*-aminobenzoic acid, *p*-nitroaniline with pyridinium hydrobromide perbromide by recently reported method[12] under grinding or ultrasound for ten hours, gave

Table 1 Monobromination of Aromatic Amine with [bmim]Br_3

Entry	Aromatic amine **1**	Reaction conditions	Product **2**		Yield[a] (%)
1		2 min, –10 °C		**a**	90
2		2 min, –10 °C		**b**	85
3		10 min, 10 °C		**c**	95
4		40 min, 25 °C		**d**	99
5		40 min, 25 °C		**e**	98
6		10 min, 0 °C		**f**	90
7		2 min, –10 °C		**g**	94
8		50 min, 25 °C		**h**	96
9		120 min, 25 °C		**i**	88
10		2 min, –10 °C		**j**	97
11		2 min, –10 °C		**k**	96
12		2 min, –10 °C		**l**	95
13		5 min, –10 °C		**m**	91
14		5 min, –10 °C		**n**	96

[a] Isolated yield.

corresponding products with 56% dibromination of *p*-chloroaniline and 48% dibromination *o*-aminobenzoic acid and 62% monobromination of *p*-nitroaniline, respectively. But by using the present method, the same reaction completed smoothly and gave products with high monobromination, with isolated yields of 94%, 98%, 99% respectively. In Smith's reported method,[13] monobromination of arylamines needed (one-pot) four steps using a strong base (LDA), trialyklatin halide (R_3SnCl), Br_2, KF etc. at –78 °C, and gave 76% monobromination of aniline, 30% monobromination of *p*-toluidine, and 40% monobromination of 1-aminonaphthalene. The same reaction completed smoothly with the present method and gave higher yields of were 90%, 85%, 90%, respectively.

In conclusion, we have demonstrated that the regioselective monobromination of arylamines with [bmim]Br_3 can efficiently be performed under solvent-free conditions. This will be a highly useful method because of its ease, simplicity, high selectivity, and excellent yield of product. [bmim]Br_3 plays double roles of reagent and solvent.

Melting points were determined on digital melting point apparatus and are not corrected. IR spectra were recorded on a VECTOR22 (Bruker) spectrometer. NMR spectra were recorded on AVANCE DMX 400 (Bruker) spectrometer. The ionic liquids were synthesized by reaction of equimolar amount of [bmim]Br and Br_2 at r.t. The other materials are commercially available and were used without further purification.

Synthesis of 2a–c,f,g,j–n; General Procedure

[bmim]Br_3 (1 mmol) was added very slowly (1 drop/5 s) to arylamine (1 mmol) with continuous stirring (see Table 1 for the reaction conditions). After the reaction completion, the solid crude product was extracted with Et_2O. The ethereal layer was concentrated by rotary evaporator. The crude product was purified by the preparative TLC on silica gel using a mixture of $CHCl_3$ and petroleum ether as developer to give the corresponding pure product of monobromination.

Synthesis of 2d,e,h,i; General Procedure

[bmim]Br_3 (1 mmol) was added to arylamine (1 mmol) with continuous stirring (see Table 1 for the reaction conditions). After the reaction completion, the reaction mixture was directly purified by recrystallization with EtOH (95%) to give the pure *p*-bromoacetanilide.

***p*-Bromoaniline (2a)**

Brown solid; mp 63–64 °C (lit.[19] 62–64 °C).

IR (KBr): 3472, 3382, 1612, 1489, 1285, 817, 603, 503 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.66(br s, 2 H), 6.57 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H).

***o*-Bromo-*p*-toluidine (2b)**

Oil.

IR (film): 3461, 3371, 3022, 2919, 1619, 1503, 1300, 1038, 810 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.22 (s, 3 H), 3.89 (br s, 2 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 7.22 (s, 1 H).

2,4-Dibromoaniline (2c)

Colorless solid; mp 79–80 °C (lit.[19] 78–80 °C).

IR (KBr): 3403, 3301, 3180, 1623, 1480, 1392, 1289, 1033, 866, 810 cm^{-1}.

^1H NMR ($CDCl_3$): d = 3.94 (br s, 2 H), 6.63 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.19 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.53 (d, *J* = 1.2 Hz, 1 H).

2-Bromo-4-nitroaniline (2d)

Yellow needles; mp 104–105 °C (lit.[19] 104.5 °C).

IR (KBr): 3488, 3372, 3097, 1623, 1586, 1488, 1317, 1121, 894, 822, 745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.10 (br s, 2 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 8.02 (dd, *J* = 2.5, 8.8 Hz, 1 H), 8.36 (d, *J* = 2.5 Hz, 1 H).

5-Bromo-2-aminobenzoic Acid (2e)

Yellow solid; mp 231 °C (lit.[20] 219–221 °C).

IR (KBr): 3468, 3363, 1680, 1536, 1224, 881 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.26 (br s, 2 H), 6.85 (br s, 1 H), 6.95 (d, *J* = 8.0Hz, 1 H), 7.01 (dd, *J* = 2.0, 8.0 Hz, 1 H), 8.00 (d, *J* = 2.0Hz, 1 H).

***p*-Bromo-*o*-toluidine (2f)**

Red solid; mp 55–57 °C (lit.[19] 152–156 °C).

IR (KBr): 3427, 3335, 3228, 2926, 1622, 1482, 1272, 870, 813, 679 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.09 (s, 3 H), 3.51 (br s, 2 H), 6.53 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.14 (s, 1 H).

***p*-Bromo-*N*-methylaniline (2g)**

Oil.

IR (film): 3423, 3050, 2983, 1600, 1504, 1317, 1261, 1178, 1075, 814 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.76 (s, 3 H), 3.27 (br s, 1 H), 6.45 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H).

***p*-Bromo-acetanilide (2h)**

White solid; mp 164–165 °C (lit.[19] 163–164 °C).

IR (KBr): 3439, 3305, 3262, 1670, 1604, 1536, 1489, 1393, 1315, 825, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.17 (s, 3 H), 7.40 (s, 4 H).

4-Bromo-*N*-methanesulfonylaniline (2i)

Colorless solid; mp 117 °C.

IR (KBr): 3414, 3299, 3073, 2924, 1616, 1455, 860 cm^{-1}.

^1H NMR (DMSO): δ = 3.34 (s, 3 H), 7.40 (s, 4 H).

4-Bromo-*N*,*N*-Dimethylaniline (2j)

White solid; mp 50–52 °C (lit.[19] 51.5–53.0 °C).

IR (KBr): 3090, 1592, 1500, 1355, 1223, 1063, 805 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.90 (s, 6 H), 6.57 (d, *J* = 8.8 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H).

1-Bromo-2-aminonaphthalene (2k)

Needles; mp 62–64 °C (lit.[19] 63 °C).

IR (KBr): 3407, 3295, 3181, 1626, 1500, 1347, 1241, 809, 740 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.37 (br s, 2 H), 7.01 (d, *J* = 8.6 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 8.6 Hz, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H).

4-Bromo-1-aminonaphthalene (2l)

Needles; mp 102–103 °C (lit.[19] 102.5 °C).

IR (KBr): 3418, 3316, 3207, 1627, 1512, 1451, 1373, 1273, 810, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.14 (br s, 2 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 8.2 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 8.18 (d, *J* = 8.0Hz, 1 H).

5-Bromo-2-aminopyridine (2m)
Colorless solid; mp 138 °C (lit.[20] 137 °C).

IR (KBr): 3453, 3293, 3148, 1627, 1589, 1486, 1389, 1141, 825, 515 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.28 (br s, 2 H), 6.42 (d, *J* = 8.8 Hz, 1 H), 7.50 (dd, *J* = 2.2, 8.8 Hz, 1 H), 8.01 (d, *J* = 2.2, 8.8 Hz, 1 H).

5-Bromo-2-aminopyrimidine (2n)
Colorless solid; mp 240–242 °C.

IR (KBr): 3327, 3186, 1652, 1575, 1545, 1489, 1357, 792 cm^{-1}.

^1H NMR (DMSO): δ = 6.87 (br s, 2 H), 8.32 (s, 2 H).

References

(1) (a) Cannon, K. C.; Krow, G. R. *Handbook of Grignard Reagents*; Dekker: New York, **1996**. (b) Davis, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon Press: Oxford, **1982**.
(2) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
(3) (a) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937. (b) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141. (c) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335.
(4) Onaka, M.; Izumi, Y. *Chem. Lett.* **1984**, 2007.
(5) Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055.
(6) (a) Buckles, R. E.; Popov, A. I.; Zelezny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* **1951**, *73*, 4525. (b) Berthelot, J.; Guette, C.; Essayegh, M.; Desbene, P. L.; Basselier, J. J. *Synth. Commun.* **1986**, *16*, 1641.
(7) Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740.
(8) Cerichelli, G.; Luchetti, L.; Mancini, G. *Tetrahedron Lett.* **1989**, *30*, 6209.
(9) Reeves, W. P.; King, R. M. *Synth. Commun.* **1993**, *23*, 855.
(10) Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941.
(11) Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *Chem. Commun.* **1996**, 2679.
(12) Toda, F.; Schmeyers, J. *Green Chem.* **2003**, *5*, 701.
(13) Smith, M. B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; Lachapelle, E. *Org. Lett.* **2002**, *4*, 2321.
(14) Zhao, J. G.; Jia, X. H.; Zhai, H. B. *Tetrahedron Lett.* **2003**, *44*, 9371.
(15) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083.
(16) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
(17) (a) Liu, Z.; Chen, Z. C.; Zheng, Q. G. *Org. Lett.* **2003**, *5*, 3321. (b) Xie, Y. Y.; Chen, Z. C.; Zheng, Q. G. *Synthesis* **2002**, 1505. (c) Su, C.; Chen, Z. C.; Zheng, Q. G. *Synthesis* **2003**, 555. (d) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 208. (e) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 995. (f) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Heterocycles* **2004**, *63*, 1077.
(18) Chiappe, C.; Conte, V.; Pieraccini, D. *Eur. J. Org. Chem.* **2002**, 2831.
(19) Buckingham, J. *Dictionary of Organic Compounds*, Vol. 1, 5th ed.; Chapman and Hall: New York, **1982**.
(20) *Lange's Handbook of Chemistry*, 13th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, **1985**.