Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1815–1817

TETRAHEDRON LETTERS

Ionic liquid promoted regioselective monobromination of aromatic substrates with *N*-bromosuccinimide

R. Rajagopal, D. V. Jarikote, R. J. Lahoti, Thomas Daniel and K. V. Srinivasan*

Division of Organic Chemistry; Technology, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

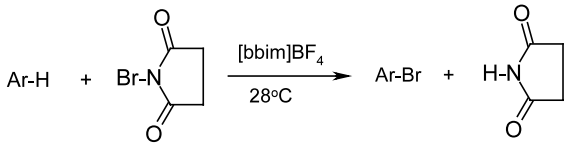
Received 27 November 2002; revised 31 December 2002; accepted 10 January 2003

Abstract—Aromatic substrates were monobrominated regioselectively with NBS in the ionic liquid 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 in 5 min at 28°C in excellent isolated yields (80–98%) in the absence of a catalyst.

Brominated arenes are versatile intermediates in the synthesis of a wide variety of biologically active compounds.[1] They are widely used for the preparation of products of commercial importance such as pharmaceuticals, agrochemicals, synthetic colorants and performance chemicals. A popular and inexpensive reagent often used for aromatic bromination is *N*-bromosuccinimide (NBS) in CCl_4.[2] A variety of methods for the bromination of aromatics with NBS have been reported in literature ranging from NBS–H_2SO_4,[3] NBS–SiO_2,[4] NBS–*p*TSA,[5] NBS–Amberlyst,[6] NBS–NaOH,[7] NBS–HZSM-5[8] and NBS–HBF_4/Et_2O.[9]

In particular, the nuclear bromination of activated aromatic compounds (alkyl benzenes, phenols, anisoles) with NBS has been reported to be clearly favoured by polar solvents such as propylene carbonate,[10] DMF[11] and CH_3CN.[12] Since this methodology is a unit process of commercial significance, the recovery and recycling of such volatile, polar and water miscible solvents both from the point of view of environmental hazards and economic viability assumes great importance. It is from this point of view in recent times, that the use of room temperature ionic liquids (ILs) as solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapour pressures, easy recoverability and reusability.[13] Very recently, we have reported the use of the newer room temperature ILs 1,3-*n*-dibutylimidazolium salts as solvents promoting the sonochemical Heck and Suzuki reactions at ambient conditions.[14] As a part of our ongoing investigations on the use of ILs both as solvents as well as promoters for organic transformations, this communication reports, for the first time, the regioselective monobromination of aromatic substrates with NBS in the IL [bbim]BF_4 with considerably enhanced reaction rates in excellent isolated yields without the need for any catalyst (Scheme 1).

A variety of aromatic substrates such as phenols, anisoles, toluene, xylenes, aniline, acetanilide, 2-naphthol and 2-methoxynaphthalene (nerolin) were subjected to bromination.[15] As soon as the reactants were mixed in the IL, the substrates were converted to the corresponding mono bromo derivatives in just 5 min with high regioselectivity and excellent isolated yields. The reaction is exothermic leading to a rise in temperature of ~7°C. The results are summarized in Table 1. All the bromoarenes isolated are known compounds reported in literature. Their identities were confirmed by IR, ^1H NMR and mass spectral analyses. Their melting points agreed with those reported in literature. The purities of liquid bromoarenes were further confirmed by GC analysis. The bromoarenes could be selectively extracted with ether leaving the IL and succinimide behind as residue. This residue was diluted with an equal volume of ethyl acetate, the insoluble succinimide filtered off and the IL recovered from the



Scheme 1.

Keywords: ionic liquid; bromination; NBS; ^{13}C NMR.

* Corresponding author. Fax: +91-20-5893614; e-mail: kvsri@dalton.ncl.res.in

0040-4039/03/$ - see front matter
PII: S0040-4039(03)00092-3

Table 1. Bromination of aromatic substrates with NBS in [bbim]BF_4

Entry	Substrate	Isolated product[a]	Yield (%)
1	Catechol	4-Bromocatechol	86
2	Resorcinol	4-Bromoresorcinol	95
3	2-Nitrophenol	4-Bromo-2-nitrophenol	82
4	Salicylaldehyde	5-Bromosalicylaldehyde	84
5	Anisole	4-Bromoanisole[b]	98
6	1,4-Dimethoxybenzene	2-Bromo-1,4-dimethoxybenzene	96
7	2-Methoxytoluene	5-Bromo-2-methoxy toluene	92
8	3-Methoxytoluene	2-Bromo-5-methoxytoluene	94
9	2,6-Dimethylanisole	4-Bromo-2,6-dimethylanisole	82
10	Acetanilide	4-Bromoacetanilide	96
11	Toluene	Benzyl bromide	35[c]
12	*o*-Xylene	4-Bromo-*o*-xylene	36[d]
		2-Bromo-*o*-xylene	14[d]
13	*m*-Xylene	4-Bromo-*m*-xylene	90
14	*p*-Xylene	2-Bromo-*p*-xylene	90
15	2-Naphthol	1-Bromo-2-naphthol	80
16	2-Methoxynaphthalene	1-Bromo-2-methoxynaphthalene	81
17	Cyclohexene	3-Bromocyclohexene	85

[a] All the products were isolated by column chromatography unless otherwise indicated.
[b] Isolated by fractional distillation under reduced pressure.
[c] Yield estimated by GC analysis.
[d] Yields calculated from the ratio of isomers estimated from ^{1}H NMR analysis.

filtrate by distilling off the ethyl acetate under reduced pressure. The recovered IL could be reused four times for bromination of anisole, affording the same isolated yields of bromoanisole.

In the case of substituted phenols, the methodology gave equivalent high yields of the *p*-isomer for both electron-donating and electron-withdrawing substituents (entries 1–4). Anisole, *o*- and *m*-substituted anisoles afforded exclusively the *para* bromo compound with no trace of the *ortho* isomer as established by GC analysis (entries 5, 7, and 8). All xylenes (entries 12–14) and methyl anisoles (entries 7 and 8) gave the ring brominated mono bromo compounds in excellent yields. In these cases, the identity of the products was confirmed by ^{1}H NMR spectra, which indicated no side-chain bromination. Whereas *m*- and *p*-xylenes afforded the 4-bromo and 2-bromo isomers, respectively, as the only products in excellent isolated yields, it was found that *o*-xylene gave rise to a mixture (^{1}H NMR) of isomeric ring brominated products which was difficult to resolve by TLC or isolate by chromatography. In this case the conversion of *o*-xylene was stopped at 50% and the selectivities for the 4-bromo- (72%) and 3-bromo- (28%) derivatives were estimated from ^{1}H NMR. 2-Naphthol and nerolin afforded 1-bromo derivatives exclusively to an extent of 65 and 81%, respectively. Cyclohexene was regioselectively brominated at the C3 allylic carbon with the olefinic bond remaining intact. Benzene, naphthalene, nitrobenzene and chlorobenzene did not react under these conditions.

With a view to control the exothermicity of the reaction, a larger scale (25 g) reaction was performed with anisole.[16] The temperature of the reaction mixture could be easily maintained at 30±2°C by the slow addition of NBS to a solution of the substrate over 30 min. The 4-bromoanisole could be isolated in excellent yield (98%) by distillation under reduced pressure showing thereby that the methodology has a distinct advantage when the bromoarene can be isolated by distillation under reduced pressure from the non-volatile IL.

The nuclear bromination observed in almost all the cases (with the exception of toluene) strongly indicates that an electrophilic aromatic substitution mechanism operates predominantly in this bromination methodology using the IL [bbim]BF_4. The remarkable enhancement in reaction rates could possibly be explained by the enhancement of the reactivity of NBS as a result of increased polarization of the -N–Br bond in the polar IL medium. Support for this idea was found by recording the ^{13}C NMR spectrum of NBS in the IL, acetonitrile and DMF as solvents, respectively. The ^{13}C chemical shifts for the carbonyl group of NBS in the various solvents are recorded in Table 2. As is evident, the polarization of the carbonyl group increases progressively from the non-polar CCl_4 through the dipolar aprotic CH_3CN and DMF, and reaches a maximum in the IL [bbim]BF_4, as indicated by an increase in the chemical shift by 10.68 and 3.34–3.71 ppm, respectively, in comparison to those of non-polar and dipolar

Table 2. ^{13}C NMR study of NBS in different solvents

No.	System	C=O[a] (δ ppm)
1	NBS–[bbim]BF_4	183.09
2	NBS–DMF	179.75
3	NBS–acetonitrile	179.38
4	NBS–CCl_4	172.41

[a] ^{13}C NMR spectra were recorded using DMSO-d_6 as internal standard at 50 MHz.

aprotic solvents commonly used in NBS bromination. This results in greater polarization of the N–Br bond in the IL to generate the bromo cation leading to the observed enhanced reactivity. The inherent Brønsted and Lewis acidities of ring protons H2, H4 and H5 in the imidazolium cation in [bbim]BF_4 may have contributed to the observed enhanced polarization of NBS in the IL. Previous studies involving multi-nuclear NMR spectroscopy and conductivity measurements for imidazolium ions correlating their acidity characteristics substantiate the above observations.[17–19] Further evidence came when we conducted the bromination of anisole with NBS in the IL, *N*-*n*-octylpyridinium tetrafluoroborate which does not exhibit such acidity characteristics. Indeed this reaction was quite sluggish taking 5 h at 30°C as compared to 5 min in [bbim]BF_4 for complete conversion.

In conclusion, we have developed an efficient new method for the regioselective monobromination of aromatic substrates using NBS in a room temperature ionic liquid [bbim]BF_4 in very short reaction times. The considerably enhanced reactivity even in the absence of an acid catalyst has been explained on the basis of increased polarization of NBS in the IL based on the evidence of ^{13}C NMR chemical shifts. The high reaction rates with excellent regioselectivities makes this methodology a valuable tool for combinatorial chemistry to generate dynamic combinatorial libraries of bromo compounds of importance. It has also been demonstrated that the process is amenable to scale up.

Acknowledgements

R.R. thanks CSIR, New Delhi for a research associateship. The authors acknowledge financial assistance from Department of Science and Technology, New Delhi, vide Project No. SP/S5/OC-23/02.

References

1. Chrisophersen, C. *Acta Chem. Scand.* **1985**, *39B*, 517–529.
2. (a) Buu-Hoi, N. P. *Justus Liebigs Ann. Chem.* **1944**, *556*, 1–9; (b) Roberts, J. C.; Roffey, P. *J. Chem. Soc. (C)* **1966**, 160–163.
3. Lambert, F. L.; Ellis, W. D.; Parry, R. J. *J. Org. Chem.* **1965**, *30*, 304–306.
4. Konishi, H.; Aritomi, K.; Okano, T.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 591–593.
5. Bovonsombat, P.; McNelis, E. *Synthesis* **1993**, 237–241.
6. Goldberg, Y.; Alper, H. *J. Mol. Cat.* **1994**, *88*, 377–383.
7. Auerbach, J.; Weissmann, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931–934.
8. Vincent Paul; Sudalai, A.; Thomas Daniel; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055–7056.
9. Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504–4506.
10. Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1958**, *80*, 4327–4330.
11. (a) Mitchell, R. H.; Lai, Y. H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733–4735; (b) Dijkstra, P. J.; den Hertog, H. J.; van Erden, J.; Harkema, S.; Reinboudt, D. N. *J. Org. Chem.* **1988**, *53*, 374–382; (c) Gnaim, J. M.; Keehn, P. M.; Green, B. S. *Tetrahedron Lett.* **1992**, *33*, 2883–2886.
12. Carreno, M. C.; Garcia Ruano, J. L.; Sans, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331.
13. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3772–3789; (c) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391–1398; (d) Charles, G. *M. Appl. Catal. A: Gen.* **2001**, *222*, 101–117; (e) Sheldon, R. *Chem. Commun.* **2001**, 2399–2407.
14. (a) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544–1545; (b) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616–617.
15. **Bromination of aromatics**: To a stirred solution of the aromatic substrate (0.018 mol) in [bbim]BF_4 (4 g) [the IL prepared as per the method reported by us[14]] at 28°C, NBS (0.018 mol) was added in one portion when the temperature rose to ~35°C. A clear solution resulted immediately. The reaction was monitored by TLC and complete conversions were achieved after 5 min for most of the substrates. At this stage, the reaction mixture turned turbid due to the precipitation of succinimide. The mixture was extracted with ether (3×10 ml) when all the products were extracted into it leaving behind a slurry of succinimide in IL. The ether layer was separated, washed with water, brine, dried over sodium sulphate and solvent evaporated to furnish the products which were further purified by chromatography through a column of silica gel (60–120 mesh) or by distillation under reduced pressure.
The remaining mixture of IL with succinimide was diluted with ethyl acetate and filtered to recover succinimide. The filtrate consisting of the IL in ethyl acetate was subjected to distillation under reduced pressure to remove ethyl acetate. The recovered IL was pure enough for at least two recycles.
16. **Scaled up batch operation with controlled addition of NBS**: To a stirred solution of anisole (25 g, 0.23 mol) in [bbim]BF_4 (50 g) at 28°C, NBS (41.25 g, 0.23 mol) was introduced in small portions slowly over 30 min in such a way as to maintain the temperature of the reaction at 30±2°C. After the complete addition, the mixture was stirred further for 15 min at 30°C. The completion of the reaction was monitored by GC. The reaction mixture was subjected to distillation under reduced pressure when 4-bromoanisole distilled out at 90°C/8 mmHg in 98% yield. The distillation residue was diluted with ethyl acetate (100 ml) and the thin slurry was filtered to remove succinimide. The filtrate was subjected to distillation under reduced pressure to remove ethyl acetate and to recover the IL completely. The recovered IL could be recycled four times for the bromination of anisole successfully.
17. Avent, A. G.; Chaloner, P. A.; Day, M. P.; Seddon, K. R.; Welton, T. *J. Chem. Soc., Dalton Trans.* **1994**, 3405–3413.
18. Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097–3100.
19. (a) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363; (b) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.