Pergamon

Tetrahedron Letters 42 (2001) 6941–6942

TETRAHEDRON LETTERS

An efficient chemo and regioselective oxidative nuclear bromination of activated aromatic compounds using lithium bromide and ceric ammonium nitrate

Subhas Chandra Roy,[a,*] Chandrani Guin,[a] Kalyan Kumar Rana[a] and Gourhari Maiti[b]

[a]*Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India*
[b]*Department of Chemistry, Jadavpur University, Jadavpur, Calcutta 700 032, India*

Received 25 June 2001; accepted 27 July 2001

Abstract—A mild, efficient and highly chemo- and regioselective method for the bromination of electron rich aromatic molecules has been developed by electrophilic substitution of Br^+, which was generated in situ from LiBr using ceric ammonium nitrate as the oxidant. Free aromatic amines remained unaffected under the reaction conditions.

Brominated arenes[1] are versatile intermediates for the synthesis of a wide variety of biologically active compounds. The direct bromination[2] of activated aromatic systems using Br_2 generates toxic and corrosive hydrogen bromide, which causes serious environmental pollution. To overcome this problem, various methods of oxidative nuclear bromination of aromatic molecules have been developed including NBS–HZMS-5,[3] NBS–amberlyst[4] and KBr–H_2O_2 using metal-oxo catalysts.[5] Very recently, bromination using KBr–$NaBO_3{\cdot}4H_2O$,[6] and ^{t}BuOBr–zeolite[7] has also been reported. Some of these methods suffer from harsh reaction conditions or cumbersome extraction procedures, hence a milder and better method is desirable. In addition to carbon–carbon bond forming reactions, ceric ammonium nitrate (CAN) has also been found to be a readily available reagent for various valuable transformations in organic synthesis. In addition to our continued interest[8] in exploring CAN as a powerful one-electron oxidant, we report here a mild and efficient method for the bromination of activated aromatic compounds by using LiBr as the bromine source and CAN as the oxidant. Thus, a series of aromatic compounds was subjected to bromination in the presence of CAN and LiBr in acetonitrile at room temperature to furnish the corresponding bromo-arenes and the results are summarized in Table 1.

In a typical reaction, a solution of CAN (2.8 g, 5.1 mmol) in CH_3CN (10 ml) was added dropwise to a stirred mixture of anisole (500 mg, 4.63 mmol) and anhydrous LiBr (443 mg, 5.1 mmol) in CH_3CN (10 ml) at room temperature under N_2. The reaction mixture was stirred for 1 h. It was decomposed with water (10 ml) and was extracted with ether (3×25 ml). The combined ether extract was washed successively with aqueous $NaHCO_3$ (2×10 ml), water (2×10 ml) and brine (1×10 ml), and was dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography over neutral alumina (petroleum ether) to furnish pure *p*-bromoanisole (860 mg, 99%).

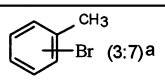
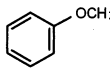
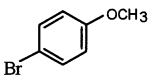
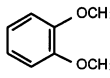
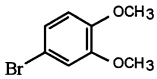
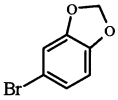
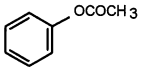
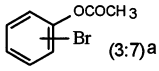
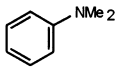
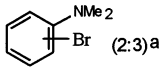
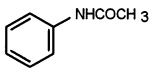
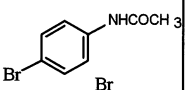
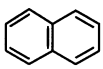
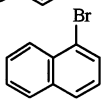
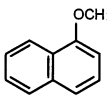
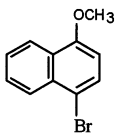
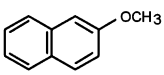
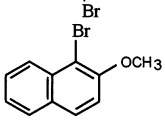
The electrophile Br^+ is generated in situ by the reaction of LiBr and CAN and attacks the electron-rich aromatic rings. While electron-rich arenes were brominated smoothly, electron deficient aromatic compounds such as anthranilic acid and methyl anthranilate remained unaffected under the reaction conditions. Surprisingly, free aromatic amines such as aniline and *p*-toluidine did not respond at all. This is probably due to the formation of a salt of the free amine with the acidic CAN which makes the aromatic ring electron deficient. Although the protected aromatic amine (Table 1, entry 6) could be brominated in satisfactory yield, the reaction was very slow with only 50% conversion even on prolonged stirring. Some of the substrates (Table 1, entry 1, 5 and 6) furnished a mixture of *ortho* and *para* brominated compounds, the *para* isomer always predominated. In most of the substrates the bromination was highly regioselective.

Keywords: chemo and regioselective; oxidative nuclear bromination; lithium bromide; ceric ammonium nitrate.

* Corresponding author. E-mail: ocscr@mahendra.iacs.res.in

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01412-5

Table 1. Bromination of aromatic compounds by using CAN and LiBr

Entry	Substrate	Product	Reaction time (h)	Yield(%)[b]
1		 (3:7)[a]	6	70
2			1	99
3			1.5	98
4			2	99
5		 (3:7)[a]	5	74
6		 (2:3)[a]	5	70[c]
7			7	99
8			6	98
9			1.5	98
10			2	98

[a]Ratio of *ortho*/*para* brominated compounds. [b]Yields refer to pure isolated products. [c]Only 50% conversion; the yield is calculated on the basis of recovered starting material.

In conclusion, we have developed a mild, efficient and ecofriendly regioselective method for the nuclear bromination of electron-rich aromatic compounds by using lithium bromide and ceric ammonium nitrate.

Acknowledgements

We are thankful to the Department of Science & Technology, New Delhi for financial assistance. C.G. thanks to CSIR, New Delhi for the award of a Junior Research Fellowship.

References

1. Christophersen, C. *Acta. Chem. Scand.* **1985**, *39B*, 515.
2. De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976; Chapter 5.
3. Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055.
4. Goldberg, Y.; Alper, H. *J. Mol. Cat.* **1994**, *88*, 377.
5. (a) Chaudary, B. M.; Sudha, Y.; Reddy, P. N. *Synlett* **1994**, 450; (b) Hanson, J. R.; Harpel, S.; Rodriguez Medina, I. C.; Rose, D. *J. Chem. Res. (S)* **1997**, 432; (c) Clague, M. H.; Butler, A. *J. Am. Chem. Soc.* **1995**, *117*, 3475.
6. Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083.
7. Smith, K.; El-Hiti, G. A.; Hammond, M. E. W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2745.
8. (a) Roy, S. C.; Mandal, P. K. *Tetrahedron* **1996**, *52*, 2193; (b) Roy, S. C.; Mandal, P. K. *Tetrahedron* **1996**, *52*, 12495; (c) Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Synlett* **2001**, 226.