Organic Process Research & Development **2004**, *8*, 568–570

0Oxidative Bromination of Activated Aromatic Compounds Using Aqueous Nitric Acid as an Oxidant

Ashutosh V. Joshi,[†] Mubeen Baidossi,[†] Sudip Mukhopadhyay,*[,‡] and Yoel Sasson*[,†]

Casali Institute of Applied Chemistry, Hebrew University, Jerusalem, 91904, Israel, and Chemical Engineering Department, University of California, Berkeley, California 94720

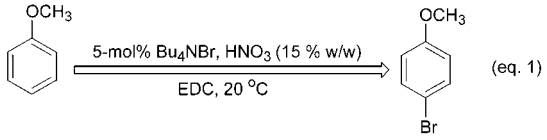
Abstract:

Oxidative bromination of activated aromatic compounds using alkali metal bromide salts and aqueous nitric acid to the corresponding bromo-derivatives is achieved in a liquid−liquid, two-phase system under ambient conditions. Nitric acid offers a dual function of an oxidant as well as a proton donor, which is essential for oxidative bromination using metal bromide salts. Bromination as well as chlorination could be accomplished with this simple system.

Introduction

Halogenation is usually used as a tool for providing complex functionality to achieve the desired structure and activity of the end compound. Aryl halides are intermediates for the preparation of organometallic reagents, numerous bulk and fine chemicals, and pharmaceuticals.[1] Classical direct halogenation of aromatic compounds using Cl_2 or Br_2 suffers from the major drawbacks that only half of the halogen is utilized and the other half ends up as a halogen acid.[2] A possible solution to this limitation is oxidative halogenation where a halogen acid or salts of acid are used in combination with an oxidant.[3] The commonly used oxidant is 30% H_2O_2. The reaction proceeds well without adding any catalyst particularly in liquid phase;[4] however, several reports on oxidative halogenation, using catalysts such as V_2O_5,[5a,b,c] NH_4VO_3, or Na_2MO_4,[5d,e] and heteropolyanion compounds[5f] have appeared. Chemoselective oxybromination of methoxy arenes in acidic media using oxone,[6a] alkali bromates,[6b] or sodium chlorite[6c] have been recently reported. On the other hand, there is evidence that the rate of reaction increases significantly in the presence of a phase-transfer catalyst in conjunction with H_2O_2[7a,b] or *tert*-butylhydroperoxide[7c,d] and alkali perborate.[7e] Oxidative halogenations using enzymes such as haloperoxidases were also described.[8] Yet, large-scale halogenations using enzymes have not been commercialized; one of the reasons is that such reactions need to be performed in dilute solutions, rendering it less attractive from the economic point of view.[9]

We have studied recently the nitration of phenolic compounds with dilute nitric acid using tetrabutylammonium bromide as a phase transfer catalyst.[10] Interestingly, when we extended the same protocol to the nitration of anisole, bromoanisoles were obtained as the major product. We attributed this phenomenon to the oxidative bromination of anisole where tetrabutylammonium bromide catalyst had provided the source of bromine in dilute nitric acid solution (eq 1).



(eq. 1)

Oxidative bromination of aromatic substrates utilizing a KBr−nitric acid mixture in the presence of phase transfer catalysts is performed in this study. Nitric acid offers a dual function of an oxidant as well as a proton donor, which is essential for oxidative halogenation using alkali metal halide salts. Using a metal halide−H_2O_2 system requires a stoichiometric amount of mineral acids.[5b] Bromination of aromatic compounds was studied using KNO_3/KBr/aq CF_3-COOH or KBr/O_2/CF_3COOH in the presence of a catalytic amount of $NaNO_2$ or NO_2Br/aq CF_3COOH, where it was suggested that the nitrite species formed is deoxidized.[11] Selective monobromination of arenes with KBr/$NaNO_3$/H_2-

* Corresponding author. E-mail: sudip.mukhopadhyay@honeywell.com.
† Hebrew University.
‡ University of California, Berkeley.

(1) (a) *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: 2002. (b) Davis, S. G. *Organotransition Metal Chemistry: Application to organic synthesis*; Pergamon Press: Oxford, 1982.
(2) Sasson, Y. In *The chemistry of functional group Suppl. D2: The Chemistry of halides, pseudo-halides and azides Part 1;* Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: 1995.
(3) Bray, W. C.; Livinston, R. S. *J. Am. Chem. Soc.* **1928**, *50*, 1654.
(4) Mukhopadhyay, S.; Ananthakrishnan, S.; Chandalia, S. B. *Org. Process Res. Dev.* **1999**, *3*, 451.
(5) (a) Bhattacharjee, M. *Polyhedron* **1992**, *11*, 2817. (b) Rothenberg, G.; Clark, J. H.; *Green Chem.* **2000**, *2*, 248. (c) Bora, U.; Bose, G.; Chaudhari, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247. (d) Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1994**, *35*, 7249. (e) Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1996**, *37*, 8609. (f) Neumann, R.; Assael, I. *J. Chem. Soc., Chem. Commun.* **1988**, 1285.
(6) (a) Narender, N.; Srinivasu, P.; Prasad, M. R.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2313. (b) Groweiss, A. *Org. Process Res. Dev.* **2000**, *4*, 30. (c) Hirano, M.; Monobe, H.; Yakabe, S.; Morimoto, T. *Synth. Commun.* **1998**, *28*, 1463.
(7) (a) Dakka, J.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1421. (b) Mukhopadhyay, S.; Mukhopadhyaya, J. K.; Ponde, D. E.; Cohen, S.; Kurkalli, B. *Org. Process Res. Dev.* **2000**, *4*, 509. (c) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127. (d) Vyas, P. J.; Bhatt, A. K.; Ramchandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085. (e) Deshmukh, A. P.; Padiya, K. J.; Jadhav, V. K.; Salunkhe, M. M. *J. Chem. Res., Synop.* **1998**, 828.
(8) (a) Neidleman, S. L.; Geigert, J. *Biohalogenation*; Ellis Horwood: Chichester, 1986. (b) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937. (c) Martinez-Perez, J. A.; Pickel, M. A.; Caroff, E.; Woggon, W.-D. *Synlett* **1999**, 1875.
(9) Rothenberg, G.; Clark, J. H. *Org. Process Res. Dev.* **2000**, *4*, 270 and see ref 6 therein.
(10) Joshi, A. V.; Baidoosi, M.; Mukhopadhyay, S.; Sasson, Y. *Org. Process Res. Dev.* **2003**, *7*, 95.

Published on Web 05/25/2004

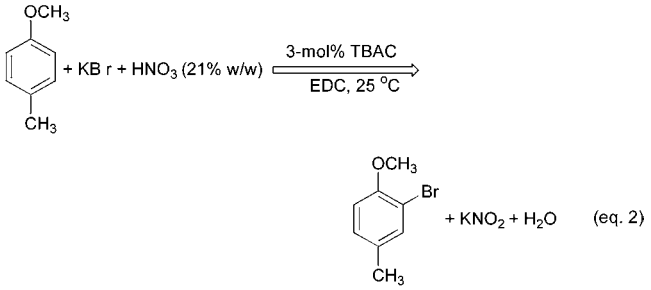
10.1021/op030055w CCC: $27.50

SO_4 (60%)[12a] or bromination of strongly deactivated compounds with NaBr/HNO_3 (65%)/H_2SO_4 (100%)[12b] have also been reported. There are some prior reports where concentrated nitric acid was used as an oxidant with halogen acids.[13] Lately, bromination using dilute nitric acid in microemulsion has also been reported,[14] utilizing stoichiometric amounts of the relatively expensive quaternary ammonium bromide (QBr) salts as a bromide source.

In this work, we report a simple method for the oxidative bromination of some activated aromatic substrates using dilute aqueous nitric acid and readily available potassium bromide in the presence of a phase transfer catalyst under ambient conditions. Active substrates such as substituted phenols, though, reacted under similar conditions to give nitro-brominated products. This is an interesting observation as one can use this protocol to make nitro-bromo substituted aromatic compounds in one step.

Results and Discussions

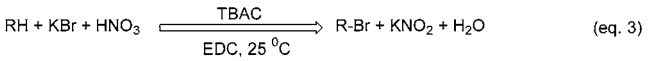
In a typical experiment, 5 mmol of 4-methylanisole (0.611 g) was stirred with 20 mmol of nitric acid (21% w/w; 1.80 g of 70%HNO_3 acid diluted with a desired amount of water to obtain a particular concentration of nitric acid), 10 mmol of potassium bromide (1.19 g), 3 mol % tetrabutylammonium chloride (0.15 mmol, 41 mg) (TBAC) as a phase transfer catalysts, and 10 mL of dichloroethane (EDC) at 25 °C for 3 h. GC analysis of the final mixture exhibited full conversion of the substrate to yield 2-bromomethylaniosle (eq 2) (see Experimental Section for isolation of the product).



(eq. 2)

The above procedure was extended for the oxidative bromination of several other substrates, and the reaction products were confirmed by GC−MS. The results are enlisted in Table 1.

When a 100% molar excess of KBr was employed, a full conversion to the corresponding bromo derivatives was achieved using anisole, mesitylene, and 4-methylanisole as the substrate (eq 3). With a 20% molar excess of KBr,



(eq. 3)

where RH = anisole, 4-methylanisole, toluene, o-xylene, mesitylene and naphthalene

Table 1. **Oxidative bromination of various activated aromatic bubstrates**[a]

entry	substrate	molar ratio of bromide salt/ substrate	time, h	% conversion
1	anisole	2	1.5	99
		1.2	4	
2	4-methylanisole	2	3	99
		1.2	6	85
		1.2	22	98
3	toluene	2	2	25
		2	20	40
		1.2	22	33
4	mesitylene	2	3	99
		1.2	6	70
		1.2	22	89
5	*o*-xylene	2	5	35
		2	20	51
		1.2	6	32
		1.2	22	42
6	naphthalene	2	2	52

[a] Reaction conditions: substrate 5 mmol; KBr 6 or 10 mmol (0.714 or 1.19 g); HNO_3 20 mmol (21% w/w; 1.80 g of 70% HNO_3 diluted with calculated amount of water to obtain the particular concentration of nitric acid); TBAC 3-mol % of the substrate; EDC 10 mL; temperature, 25 °C.

reasonable conversions were obtained with these substrates (Table 1). Reaction was executed in the absence of light (covered vessel) with substrates such as toluene, *o*-xylene, and mesitylene to curb side chain bromination. In the case of toluene, *o*-xylene, and naphthalene, only moderate conversions were obtained even when a 100% molar excess of KBr was utilized in the reaction. In each of the cases, the yield of the corresponding mono-bromo derivative exceeded 95%.

High regioselectivity was observed during the oxidative bromination of 4-methylanisole, mesitylene, and *o*-xylene. 4-Bromoanisole was formed in high regioselectivity. In the case of naphthalene, 1-bromonaphthalene was the only isomer detected by GC−MS and confirmation by its comparison with the standard. However, toluene gave a mixture of isomers, *o*/*p* 34:66.

The presence of nitrite anion, namely potassium nitrite in the aqueous phase of the reaction mixture (eq 3) was qualitatively assayed with potassium permanganate solution.[15] To ascertain the in situ formation of Br_2 species, a blank reaction was conducted with KBr−HNO_3 using dichloroethane in the absence of substrate. The layers were separated, and styrene was added to the dark brown organic layer. GC analysis of the organic phase revealed formation of dibromostyrene, indicating the presence of Br_2.

We also attempted to chlorinate aromatic substrates such as anisole employing a similar protocol using a 100% molar excess of NaCl as a chloride source and 30% HNO_3. The reaction was executed at 45 °C. Complete conversion of the substrate was achieved. *Ortho*- and *para*-chloroanisoles were obtained in the ratio of 3:1 with more than 97% selectivity.

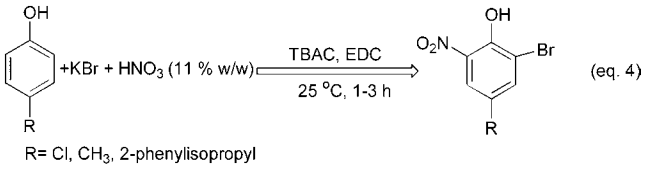
In another set of experiments, we employed a modified KNO_3−HBr system to brominate a substrate such as anisole.

(11) Cheprakov A. V.; Makhonkov, D. I.; Rodkin, M. A.; Beletskaya, I. P. *Zh. Org. Khim.* **1988**, *24*, 248.
(12) (a) Iqbal, S.; Anwar, M.; Munawar, M. A.; Siddiq, M. *J. Chem. Soc. Pak.* **1992**, *14*, 212. (b) Marterer, W.; Prikoszovich, W.; Wiss, J.; Prashad, M. *Org. Process Res. Dev.* **2003**, *7*, 318 and references therein.
(13) (a) Hashem, A. I. *J. Appl. Chem. Biotechnol.* **1972**, *22*, 1223. (b) Datta, R. L.; Chatterjee, N. R. *J. Am. Chem. Soc.* **1916**, *38*, 2545.
(14) Currie, F.; Holmberg, K.; Westman, G. *Colloid Surf., A* **2003**, *215*, 51.
(15) Vogel A. I. *A Text-Book of Quantitative Inorganic Analysis including Elementary Instrumental Analysis*, 3rd ed.; Longmans: 1961.

Anisole was successfully brominated as well as chlorinated ($NaNO_3$−HCl) to the corresponding haloanisoles.

Different behavior was observed when substituted phenols were exposed to the above reagents. Reaction of substituted phenols such as 4-chlorophenol, *p*-cresol, and 4-cumylphenol was carried out using 5 mmol of the substrate, 20 mmol of 11% nitric acid, 6 mmol of KBr, and 5-mol % TBAC. In all these instances, 100% conversion of the substrate was achieved.

We expected to obtain bromophenols in high yields, but surprisingly we observed a different route of the consecutive nitration and bromination process (eq 4). Yields of bromo−nitro derivatives of these substrates were in the range of 30−45%.



R= Cl, CH_3, 2-phenylisopropyl

The presence of 100% molar excess of KBr and higher concentration of nitric acid (21% HNO_3) resulted in almost similar yields of bromo−nitro derivatives of these substrates. GC analysis of the samples drawn at periodic intervals indicated that the rate of nitration is 2 orders of magnitude faster than that of the bromination, and consequently nitro intermediates, which are instantly formed, are finally oxybrominated to the end product.

Conclusion

We have demonstrated a simple reaction protocol that could be utilized for oxidative bromination of activated aromatic substrates using a readily available source of an oxidant (aqueous nitric acid) and halide source such as a metal halide.

Experimental Section

Materials and Instrumentation. All the chemicals were purchased from a commercial firm (of high purity) and used without further purification. GC analyses were performed using a HP-5890 gas chromatography with a RTX-5 capillary column (25 m). Reaction products were characterized by GC−MS or comparison of their GC spectra with standard samples.

General Procedure for Oxidative Bromination: A. Preparation of 2-Bromomethylaniosle. In a typical procedure, KBr (40 mmol, 4.76 g) was added to 80 mmol of nitric acid (21% w/w, 7.2 g of 70% nitric acid diluted with a calculated amount of water to obtain the particular concentration of nitric acid), to which were added 40 mL of dichloroethane, 20 mmol of 4-methylanisole (2.44 g), and TBAC 3-mol % of the substrate (166 mg) and stirred together in a 100-mL closed glass reactor at 25 °C. The progress of the reaction was monitored by GC. After the completion of the reaction, the organic layer was separated from the aqueous layer. It was then washed with 3 × 30 mL water and finally with 30 mL of 2% K_2CO_3, and the organic layer was separated and dried over magnesium sulfate. The dried organic layer was concentrated under reduced pressure to obtain an oil (3.57 g, 89% yield) of 2-bromomethylanisole of 97% purity (GC and GC−MS analysis).

B. Preparation of Bromo−Nitro Phenols. In a typical procedure, KBr (6 mmol, 0.74 g) was dissolved in 20 mmol of nitric acid (11% w/w, 1.8 g of 70% nitric acid diluted with a calculated amount of water to obtain the particular concentration of nitric acid), to which was added 10 mL of dichloroethane, 5 mmol of 4-chlorophenol (0.643 g), and TBAC 5 mol % of the substrate (69 mg). The mixture was stirred together in a 50-mL closed glass reactor at 25 °C for 2 h. GC analysis revealed that the yield to bromo−nitro product was around 40%.

Acknowledgment

We thank Mrs. Marcela Haimberg and Mr. Michael Mogilnitsky from the MS laboratory at Makhteshim Chemical Works, Beer Sheva, for GC−MS analysis and interpretation of several products in this study. A.V.J. acknowledges the Israeli Ministry of Science and Technology for financial support.

Received for review December 11, 2003.

OP030055W