SHORT PAPER

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Mild and regioselective oxidative bromination of aromatic compounds using ammonium bromide and oxone®†

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The selective mono-bromination of various activated aromatic compounds is reported using *in situ* generated bromine from NH_4Br as a bromine source and oxone® as an oxidant for the first time.

Keywords: oxidative bromination, aromatic compounds, ammonium bromide, oxone

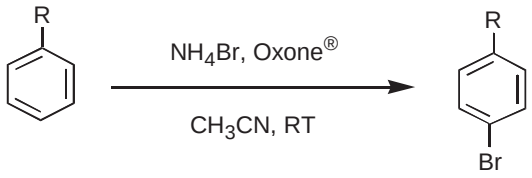
Halogenated organic compounds form an important class of intermediates as they can be converted efficiently into other functionality by simple chemical transformations. The manufacture of a range of bulk and fine chemicals including flame retardants, disinfectants and antibacterial and antiviral drugs, involve bromination. Bromoaromatics are widely used as intermediates in the manufacture of pharmaceuticals, agrochemicals and other speciality chemical products. Selective bromination of aromatic compounds is investigated in view of the importance of the brominated compounds in organic synthesis. Consequently, a variety of methods for the bromination of aromatics have been reported in the literature.[1–10]

Classical nuclear bromination[11] of aromatic compounds involves the use of: (a) bromine; (b) a catalyst like $FeCl_3$, $FeBr_3$, iodine, thallium(III)acetate; and (c) absence of light, often yielding undesired co-products. The direct bromination[12] of an aromatic system presents an environmental problem in large-scale operations. Besides, the bromination is wasteful as one half ends up as hydrogen bromide and this renders the process more expensive. Oxybromination using HBr as a bromine source and H_2O_2 as an oxidant[13–16] which was thought to be a possible solution to overcome these difficulties met with partial success, since the HBr is highly toxic and corrosive and is as harmful as molecular bromine to the environment.

More recently Roy *et al*. reported bromination using $LiBr–Ce(NH_4)_2(NO_3)_6$[17] which is a more expensive reagent combination and involves a tedious work-up procedure. Herein we report a new method for the regioselective oxybromination of aromatic compounds using oxone as an oxidant and NH_4Br as a bromine source without catalyst.

Potassium peroxymonosulfate is an inexpensive and readily accessible oxidising agent. It is commonly used as oxone ($2KHSO_5.KHSO_4.K_2SO_4$) and is a versatile oxidant for the transformation of a wide range of functional groups.[18]

A number of different aromatic substrates were subjected to bromination to test the generality of this method and the results are summerised in Table 1. Efficient bromination of aromatic substrates with good yields and regioselectivity with oxone and ammonium bromide is presented in Table 1. As Table 1 shows that the reaction gives high yields and *para*-selectivity for a range of substituted benzenes with high activity. In cases where the substrates have a para-substituent, such as *p*-cresol, *p*-methylanisole, 2-methoxynaphthalene, *ortho* bromination occurred, but reaction is slow compared to *para* bromination.



Scheme 1

Introduction of an electron-withdrawing group on the aromatic ring substantially decreases the rate of ring bromination (Table 1, entries 6 and 11) and less reactive aromatics such as bromobenzene, nitrobenzene, benzoic acid failed to undergo bromination under the same reaction conditions. We also report the bromination of several methyl phenols and methylanisole with this system. The absence of bromination of the ring methyl group is indicative of the electrophilic mechanism of the reaction rather than a radical pathway.

Initially, several solvents were tested in order to access the best solvent for the reaction. The results obtained suggest that acetonitrile is a good solvent for selective production of *p*-bromoanisole from anisole.

A typical oxybromination of an aromatic compounds in the presence of oxone proceeds according to the stoichiometry of Eqn (1). It is believed that the bromination proceeds via the formation of hypobromous acid. The hypobromous acid has higher instability due to its pronounced ionic nature and is thus more reactive towards the aromatic nucleus.

$$ArH + NH_4Br + 2\ KHSO_5.KHSO_4.K_2SO_4 \rightarrow$$

$$ArBr + NH_4OH + K_2S_2O_8.KHSO_4.K_2SO_4 + H_2O \quad (1)$$

Oxone, in direct comparison, has a higher onset of decomposition than hydrogen peroxide and liberates less energy. This reaction is performed at lower temperature, which provides a larger margin of safety. Additionally oxone is a solid, allowing for the addition of precisely weighed amounts of reagent to be used in the reaction.

In conclusion, we developed an efficient new method for the selective monobromination of aromatic compounds using NH_4Br/oxone in CH_3CN. The method is attractive as each of the reagents is commercially available and cheap, reactions are easy to effect, there is no evolution of hydrogen bromide and reactions are clean, high yielding and easy to work-up

General procedure for the bromination of aromatic compounds

Oxone (2.2 mmol) was added to a well stirred solution of NH_4Br (2.2 mmol) and substrate (2 mmol) in acetonitrile (10 ml) and the reaction mixture was stirred at room temperature. The reaction was monitored

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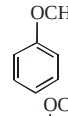
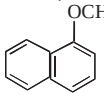
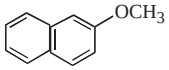
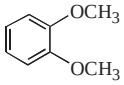
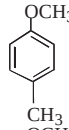
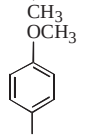
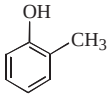
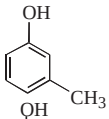
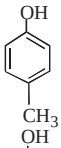
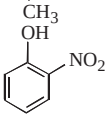
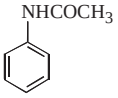
Table 1 Regioselective oxybromination of aromatics with NH_4Br and oxone

Entry	Substrate	T/h	Conversion (%)	Selectivity (%)[b] *Ortho*	*Para*	Di
1		5	99	2	98	--
2		7	99	--	99	--
3		5	99	99	--	--
4		5	97	--	99	--
5		8	99	99	--	--
6		8	--	--	--	--
7		5	99	12	88	--
8		6	99	5	95	--
9		5	91	--	99	--
10		6	99	94	--	6
11		61/2	53	48	52	--
12		5	89	10	90	--
13		5	99	2	98	--

[a]Substrate (2 mmol), NH_4Br (2.2 mmol), oxone (2.2 mmol), acetonitrile (10 ml), rt.
[b]The products were characterised by NMR, mass spectra and quantified by gas chromatography.

by thin layer chromatography (TLC). After the completion of the reaction, the mixture was filtered and the solvent evaporated under reduced pressure. The products were purified by column chromatography over silica gel (finer than 200 mesh) with 5–50% ethyl acetate in hexane as eluent. All the products were confirmed by NMR and mass spectra which are reported in the literature.[2, 7, 19–23]

4-Bromoanisole:[2] the compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:19).

4-Bromo-1-methoxynaphthalene:[2] the compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:19).

1-bromo-2-methoxynaphthalene:[2] m.p. 83–85°C (lit[24]. 85°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:19).

4-bromo-1,2-dimethoxybenzene:[2] the compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:9).

2-bromo-4-methylanisole:[19] the compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:19).

4-bromophenol:[7] m.p. 63–64°C (lit[25]. 63°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:9).

4-bromo-2-methylphenol:[7] m.p. 61–63°C (lit[24]. 64°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:9).

4-bromo-3-methylphenol:[20] m.p. 62–63°C (lit[25]. 62°C). The compound was purified over silica (finer than 200mesh) column (EtOAc : hexane, 1:9).

2-bromo-4-methylphenol:[21] m.p. 55–57°C (lit[24]. 56–57°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:9).

4-bromo-2-nitrophenol:[22] m.p. 90–93°C (lit[26]. 92°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:4).

4-bromo-2-chlorophenol:[7] The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:9).

4-bromo acetanilide:[23] m.p. 167–169°C (lit[24]. 168°C). The compound was purified over silica (finer than 200 mesh) column (EtOAc : hexane, 1:1).

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