Simple Bromination of Activated Arenes by IBX Amide Resin and Tetraethylammonium Bromide

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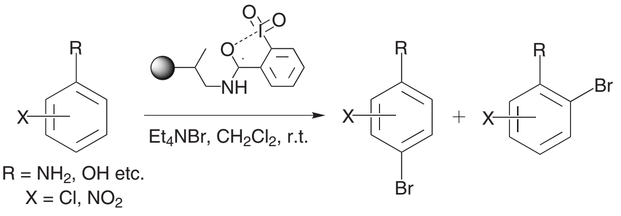
Abstract: A mild and operationally simple method of brominating activated aromatic compounds using a polymer supported IBX reagent (IBX amide resin) and tetraethylammonium bromide (TEAB) was developed. The activated aromatics, when reacted with IBX amide resin in the presence of TEAB, were easily converted into the brominated aromatics in high yields (>80%) at room temperature.

Key words: bromination, IBX amide, tetraethylammonium bromide

Brominated aromatic compounds are versatile synthetic intermediates for many organic reactions, ranging from the formation of functional aromatic compounds to that of aryl organometallic reagents.[1] Consequently, a variety of methods have been reported for the bromination of aromatics.[2] Among the various bromination reagents that can be used, elemental bromine and *N*-halo compounds are well known for their high efficiency. However, methods involving detrimental chemicals such as bromine and hydrogen bromide cannot be used in the open laboratory.[3] Thus, a more eco-friendly, stable, regioselective, operationally simple and cost-effective bromination method is very much needed. In recent years, several research groups have reported environmentally acceptable bromination methods.[4]

2-Iodoxybenzoic acid (IBX) is a versatile mild oxidizing agent, which is widely used because of its high efficiency, easy availability and its stability against moisture and air.[5] The use of polymer supported IBX reagents[6] provides an additional advantage, in that they require only a simple work up to remove the reagents from the reaction mixture by filtration. Recent reports have shown that the use of IBX could be extended to other elegant oxidative transformations if used with additives.[7] In this regard, the oxidation of sulfides to sulfoxides with IBX and tetraethylammonium bromide (TEAB) is particularly noteworthy.[8] KBr has previously been used as a catalyst in the oxidation of alcohols with IBX ester.[9] The bromide ion has previously been used as an effective catalyst in the oxidation of alcohols with PhIO.[10]

We recently initiated alcohol oxidation studies with polymer supported IBX amide reagents (IBX amide resins).[11] During the course of our attempts to extend the scope of IBX amide resin to other organic reactions, we unexpectedly found that the IBX amide resin facilitated the bromination of aromatic compounds in the presence of TEAB. To the best of our knowledge, there have been no previous examples of the IBX amide mediated bromination of aromatics. Herein, we report a new, simple and clean bromination method using IBX amide resin and TEAB (Scheme 1).



Scheme 1

Our method is based on the oxidation of the bromide ion by IBX amide resin, ultimately leading to the formation of the tribromide ion as an active brominating agent (Scheme 2). Several organic ammonium tribromides (OATB) have previously been reported.[12] We confirmed the presence of OATB in the reaction mixture by UV spectroscopy (λ_{max} = 266 nm).[13]

$$\mathrm{Et_4NBr} \xrightarrow{\text{IBX amide resin}} \mathrm{Et_4NBr_3}$$

Scheme 2

The aromatic compounds examined in our studies and the results of the bromination reactions are summarized in Table 1. The structures of the bromo compounds were identified by means of their GC-MS data.

In a typical experiment, a mixture of the activated arene, IBX amide resin (1–4 equiv) and TEAB (1–4 equiv) were stirred in CH$_2$Cl$_2$ for 0.5–2.5 hours at room temperature yielding the brominated arene.

Because aniline and phenol (entries 1 and 2) were so reactive, they were converted to the corresponding di- or tribrominated products. When 3 equivalents of IBX amide resin and TEAB were used, the bromination of aniline provided mono-brominated aniline as the major product, whereas in the case of phenol, dibromination occurred. These results demonstrate that phenol was more reactive than aniline under the reaction conditions employed in our

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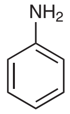
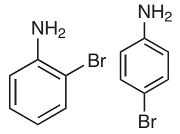
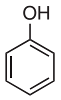
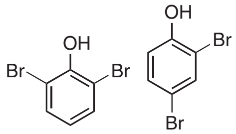
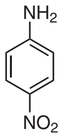
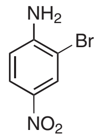
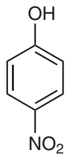
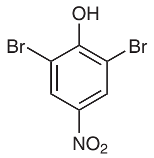
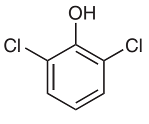
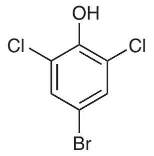
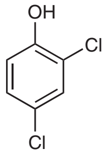
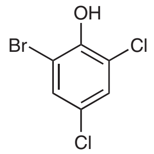
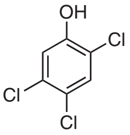
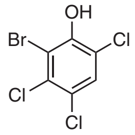
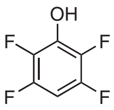
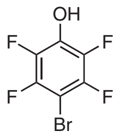
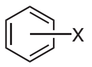
Table 1 Bromination[a] of Aromatic Compounds by IBX Amide Resin and TEAB

Entry	Substrate	Product	IBX[b]:TEAB (equiv)	Time (h)	Yield (%)[c]
1		 (1:6.4)[d]	3:3	0.5	82.8
2		 (1:25)[d]	3:3	0.5	41.5
3			4:4	1	51.6
4			1:1 3:3	2.5 0.5	38.5 95.0
5			1:1 2:2	2.5 0.5	94.5 94.4
6			2:2	0.5	91.7
7			2:2	0.5	91.8
8			1.4:1.4	0.5	95.2
9[e]	 X = NO_2, CHO	–	–	–	–

[a] Reactions were monitored by TLC and GC-MS.

[b] IBX amide resin.

[c] GC-MS yields.

[d] Confirmed by GC-MS, external method.

[e] Unreacted aromatics (benzene, nitrobenzene, benzaldehyde, toluene, naphthalene)

experiment. Also, the bromination of 4-nitroaniline (entry 3) gave rise to the mono-brominated compound as the major product, whereas in the case of 4-nitrophenol (entry 4), dibromination occurred at both the 2- and 6-position, independent of the stoichiometry of the bromide employed. In the case of the phenol derivatives (entries 4–8), bromination produced excellent yields, in spite of the presence of electron withdrawing substituents such as the chloro, fluoro and nitro groups. In particular, 2,3,5,6-tetrafluorophenol (entry 8) was converted to the corresponding bromo compound when 1.4 equivalents of IBX amide resin and TEAB were used. It means that our method was very efficient and opened an opportunity to gain easy access to a variety of bromoorganics. Furthermore, reaction of soluble IBX amide[14] with 2,6-dichlorophenol in DMSO solution gave 4-bromo-2,6-dichlorophenol within 0.5 hours, which was confirmed by GC-MS.[15] Although the soluble IBX amide and the IBX amide resin showed similar reactivity, recovery of iodoso compound, reduced product of IBX amide, was troublesome in solution-phase chemistry. Moreover, our method avoids the use of highly polar organic solvents such as DMSO. Bromination studies with various arenes revealed that only activated arenes underwent bromination, and this to yield preferably the *para* brominated products, unless the *para* position were blocked, in which case *ortho* bromination occurred. However, in the case of the deactivated arenes, such as benzene, nitrobenzene, benzaldehyde, toluene and naphthalene, no bromination occurred at all under the same reaction conditions.

After the reactions, polymer supported iodoso compound, reduced product of IBX amide resin, can be reoxidized to an activated IBX amide resin by using the previous procedures.[11] The regenerated IBX amide resin was indistinguishable from the IBX amide resin freshly prepared from iodobenzamide resin (Figure 1).

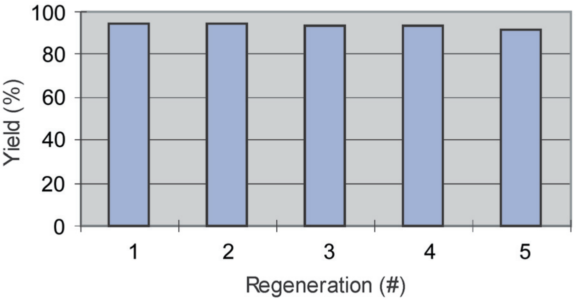


Figure 1 Bromination results after repetitive use of regenerated IBX amide resin; substrate: 2,6-dichlorophenol, IBX amide resin:TEAB (equiv) = 2:2, reaction time: 0.5 h.

In conclusion, we presented an environmentally acceptable and convenient method for the bromination of activated arenes, using IBX amide resin and TEAB in CH_2Cl_2 under mild reaction conditions. The simple filtration of the reaction mixture, followed by purification using a short silica column and the evaporation of the solvent, allows the products to be obtained in high yield. This method represents an efficient and stable alternative to the rather hazardous and cumbersome classical bromination methods.

Experimental Section

To a reaction vial (20 mL) containing IBX amide resin (1 g, 0.987 mmol, 100–200 mesh), TEAB (207.4 mg, 0.987 mmol) and an aromatic compound (1 equiv or 1/2 equiv or 1/3 equiv or 1/4 equiv) were added. After shaking for appropriate time (0.5 h or 2 h or 2.5 h, etc.) in CH_2Cl_2 (10 mL), the reaction was terminated by filtration and the filtered resin was washed (15 × 3 mL) with CH_2Cl_2, and then the filtrate and the washing solvent was combined and evaporated. The product was dissolved again in EtOAc and purified by short silica column (about 5 mL). The yield was measured by GC-MS.

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(14) Thionyl chloride (5.9 mL) was added to 2 g (8 mmol) of 2-iodobenzoic acid under stirring and was refluxed for 1 h. After cooling the reaction mixture, excess thionyl chloride was removed in vacuo to give the 2-iodobenzoyl chloride which was used without further purification. To a solution of the above 2-iodobenzoyl chloride in CH_2Cl_2, 2 equiv of benzyl amine (1.76 mL) were added and the mixture was stirred at r.t. for 2 h. The reaction mixture was washed with EtOAc and the solvent was removed in vacuo. The crude product was purified by dry column chromatography affording the desired *N*-benzyl-2-iodobenzamide (2.4 g, yield 88%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.85$ (d, 1 H, $J = 9$ Hz), 7.25–7.42 (m, 7 H), 7.05–7.11 (m, 1 H), 6.05 (s, 1 H), 4.64 (d, 2 H, $J = 6$ Hz). To a solution of *N*-benzyl-2-iodobenzamide (2.4 g, 7.1 mol) in CH_2Cl_2 (50 mL), oxone (5.7 g, 1.3 equiv) was added. The reaction mixture was warmed to 40–45 °C over 20 min and stirred at this temperature for 24 h (0.21 g, yield 20%). ^1H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 9.89$ (t, 1 H, $J = 6$ Hz), 8.30 (d, 1 H, $J = 6$ Hz), 8.22 (d, 1 H, $J = 6$ Hz), 7.95 (t, 1 H, $J = 15$ Hz), 7.75 (t, 1 H, $J = 15$ Hz), 7.27–7.36 (m, 5 H), 4.58 (d, 2 H, $J = 6$ Hz).

(15) 2,6-Dichlorophenol (22 mg, 0.135 mmol) was added to a solution of IBX amide (100 mg, 0.27 mmol) and TEAB (57 mg, 0.27 mmol) in DMSO (2 mL). After 0.5 h, the reaction mixture was diluted with H_2O (20 mL), extracted with Et_2O (6×20 mL), and the organic layers was dried ($MgSO_4$) and evaporated. The crude product was purified by dry column chromatography to give 4-bromo-2,6-dichlorophenol (30.6 mg, yield 94%).