

Bromination of Activated Arenes by Oxone[®] and Sodium Bromide

Kee-Jung Lee,[†] Hye Kyung Cho, and Choong-Eui Song^{†,‡}

[†]Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea

[‡]Life Science Division, Korea Institute of Science and Technology, Seoul 130-650, Korea

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
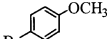

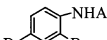
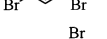

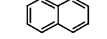
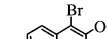

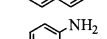

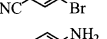

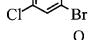

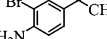

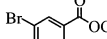

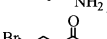
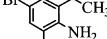

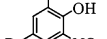


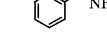


Brominated arenes are versatile intermediates in the synthesis of a wide variety of biologically active compounds and other speciality chemical products.¹ Many of the available methods of direct bromination of aromatic systems² involve the use of Br₂-Lewis acids,³ NBS-H₂SO₄-CF₃CO₂H,⁴ NBS-PTSA,⁵ NBS-NaOH,⁶ NBS-SiO₂,⁷ Br₂-Al₂O₃,⁸ Br₂-Zeolite,⁹ NBS-Amberlyst,¹⁰ NBS-HZSM-5,¹¹ Clayzib,¹² *tert*-BuOOH- or H₂O₂-HBr,¹³ and HBr-DMSO.¹⁴ Especially, bromination of some arenes with potassium bromide as alternative brominating reagent in the presence of sodium tungstate or ammonium molybdate as catalyst using hydrogen peroxide or sodium perborate as an oxidant has been developed.¹⁵ Also, regioselective monobromination of aromatic ethers can be accomplished with a combination of NaClO₂, NaBr, and Mn(acac)₃ catalyst with the aid of montmorillonite K10 or silica gel.¹⁶

Recent reports have dealt with the use of a triple salt (2KHSO₅·KHSO₄·K₂SO₄), which is commercially available as Oxone[®], and aqueous halides was conducted as a convenient halogenating reagent to achieve oxidation of α,β -enones,¹⁷ bromination of pyrimidines,¹⁸ oxidation of alcohols,¹⁹ side chain halogenation of toluene,²⁰ and *N*-chlorination of amides and carbamate.²¹ In addition, we have shown that sodium bromide combined with Oxone[®] serves as effective reagent of bromodecarboxylation of various cinnamic acids²² and arylpropionic acids,²³ bromodecarbonylation and bromodecarboxylation of electron-rich aromatic aldehydes and acids,²⁴ halogenation of aromatic methyl ketones,²⁵ and oxidation of benzyl alcohols.²⁶

In the course of our study to extend the scope of the Oxone[®]/NaBr reagent in organic synthesis, we have found that this reagent facilitates bromination of moderately activated aromatic compounds successfully.²⁷ The substrates examined in our studies and the results of the bromination are summarized in Table 1. The bromo compounds were identified by their ¹H NMR and mass spectral data and by comparison with literature data. Optimization of the reaction conditions revealed that simple stirring a solution of arene (1 equivalent), Oxone[®] (1 equivalent) and sodium bromide (1 equivalent) in a 1:1 mixture of CH₃CN/H₂O at room temperature effected the formation of bromoarene. It is noteworthy that bromination of anisole takes place regioselectively at the 4-position, whereas in the case of acetanilide dibromination occurs at the 2,4-position independent of the stoichiometry

of the bromide employed (entries 1-2), and in the case of naphthalene or 2-methoxynaphthalene, bromination occurs at the 1-position (entries 3-4). Disubstituted substrates furnished preferentially the monobrominated products (entries 5-8), however, 2-aminoacetophenone and 2-nitrophenol produced the corresponding dibromo compounds as sole products (entries 9-10) independent of the stoichiometry of the bromide employed. In the case of benzamide the expected *N*-bromobenzamide was obtained exclusively.²¹ Other unactivated aromatic compounds such as benzonitrile and methyl benzoate did not react. The reaction is carried out by the species produced as a result of the peroxy monosulfate-oxidation of the bromide anion.²⁸

Table 1. Bromination of Arenes by Oxone[®] and NaBr

| Entry | Substrate | Product | No. | oxone: NaBr | Time (h) | Yield (%) ^a |
|-------|---|---|-----|----------------|-------------|---------------------------|
| 1 |  |  | 1 | 1:1 | 0.5 | 94 |
| 2 |  |  | 2 | 3:3 | 0.5 | 86 |
| | |  | | 1:2 | 2 | 40 |
| 3 |  |  | 3 | 1:1 | 24 | 66 |
| | |  | | 1:1 | 24 | 66 |
| 4 |  |  | 4 | 1:1 | 0.5 | 75 |
| 5 |  |  | 5 | 1:1 | 0.5 | 90 |
| 6 |  |  | 6 | 1:1 | 0.5 | 73 |
| 7 |  |  | 7 | 1:1 | 0.5 | 93 |
| 8 |  |  | 8 | 1:1 | 1.5 | 76 |
| 9 |  |  | 9 | 1:2 | 0.5 | 83 |
| | |  | | 1:1 | 1 | 24 |
| 10 |  |  | 10 | 2:2 | 2 | 86 |
| | |  | | 1:1 | 2 | 36 |
| 11 |  |  | 11 | 1:1 | 1.5 | 85 |
| 12 |  | b | 12 | 1:1 | 24 | — |
| 13 |  | b | 13 | 1:1 | 24 | — |

[†]Corresponding author. E-mail: leekj@hanyang.ac.kr

^aYields in isolated products. ^bNo reaction.

The method described in this note is a simple nuclear bromination of activated arenes by Oxone[®]/NaBr in aqueous acetonitrile under the mild conditions. In many cases simple extraction (Et₂O) of reaction mixture and evaporation of the solvent provide the products in high yields. Since Oxone[®] and sodium bromide are cheap, nontoxic, stable, and easy to handle, the present method should be useful in synthetic organic chemistry.

Experimental Section

All chemicals used were purchased from commercial sources and were used as received unless otherwise stated. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Gemini 300 spectrometer. Mass spectra were obtained using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV.

General Procedure for the Preparation of Bromoarenes. Sodium bromide (5 mmol, 0.51 g) was added to a stirred solution of arenes (5 mmol) in 30 mL of CH₃CN-H₂O (2 : 1 v/v), and then followed by the dropwise addition of Oxone[®] (5 mmol, 3.07 g) in 10 mL of H₂O. Reactions were continuously monitored by thin-layer chromatography and stirred at r.t. for generally 0.5 h to 24 h. The reaction mixture was quenched with aqueous sodium thiosulfate, and extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The residue was crystallized with petroleum ether or chromatographed on a silica gel column and eluted with hexane-ethyl acetate 15 : 1 to give the products.

The spectral and analytical data of products are as follows:

1: Liquid (Lit.²⁹ 215°); ¹H NMR (CDCl₃) δ 3.78 (s, 3H), 6.78 (d, 2H, *J* = 9.16 Hz), 7.34 (d, 2H, *J* = 9.16 Hz); MS *m/z* (%) 188 (M+2, 76), 186 (M⁺, 100).

2: mp 144-145° (Lit.³⁰ 144.7°); ¹H NMR (CDCl₃) δ 2.24 (s, 3H), 7.43 (dd, 1H, *J* = 8.85 and 2.14 Hz), 7.56 (bs, 1H), 7.68 (d, 1H, *J* = 2.14 Hz), 8.26 (d, 1H, *J* = 8.85 Hz); MS *m/z* (%) 295 (M+4, 25), 293 (M+2, 48), 291 (M⁺, 22), 253 (52), 251 (100), 249 (50), 214 (69), 212 (69).

3: Liquid (Lit.²⁹ 139°/16 Torr); ¹H NMR (CDCl₃) δ 7.23-7.83 (m, 6H), 8.20-8.23 (m, 1H); MS *m/z* (%) 208 (M+2, 100), 206 (M⁺, 95), 127 (25).

4: mp 83-84° (Lit.²⁹ 85°); ¹H NMR (CDCl₃) δ 4.04 (s, 3H), 7.27-7.84 (m, 5H), 8.22 (d, 1H, *J* = 8.55 Hz); MS *m/z* (%) 238 (M+2, 100), 236 (M⁺, 98), 195 (53), 193 (56), 114 (17).

5: mp 108-110° (Lit.³¹ 109-111°); ¹H NMR (CDCl₃) δ 4.63 (s, 2H), 6.74 (d, 1H, *J* = 8.55 Hz), 7.38 (dd, 1H, *J* = 8.55 and 1.83 Hz), 7.70 (d, 1H, *J* = 1.83 Hz); MS *m/z* (%) 198 (M+2, 97), 196 (M⁺, 100), 117 (52), 90 (28).

6: mp 64-66° (Lit.³² 65-67°); ¹H NMR (CDCl₃) δ 4.07 (s, 2H), 6.69 (d, 1H, *J* = 8.55 Hz), 7.07 (dd, 1H, *J* = 8.55 and 2.44 Hz), 7.40 (d, 1H, *J* = 2.44 Hz); MS *m/z* (%) 207 (M+2, 100), 205 (M⁺, 71), 126 (8).

7: mp 154-155° (Lit.³³ 155-156°); ¹H NMR (CDCl₃) δ 2.50 (s, 3H), 4.61 (bs, 2H), 6.75 (d, 1H, *J* = 7.24 Hz), 7.74

(dd, 1H, *J* = 7.24 and 1.83 Hz), 8.06 (d, 1H, *J* = 1.83 Hz); MS *m/z* (%) 215 (M+2, 92), 213 (M⁺, 90), 200 (100), 198 (90).

8: mp 70-71° (Lit.³² 74°); ¹H NMR (CDCl₃) δ 3.87 (s, 3H), 5.75 (s, 2H), 6.56 (d, 1H, *J* = 8.85 Hz), 7.33 (dd, 1H, *J* = 8.85 and 2.44 Hz), 7.97 (d, 1H, *J* = 2.44 Hz); MS *m/z* (%) 231 (M+2, 96), 229 (M⁺, 100), 199 (59), 197 (62).

9: mp 119-121° (Lit.³⁴ 123-124°); ¹H NMR (CDCl₃) δ 2.59 (s, 3H), 6.82 (bs, 2H), 7.69 (d, 1H, *J* = 2.44 Hz), 7.81 (d, 1H, *J* = 2.44 Hz); MS *m/z* (%) 295 (M+4, 51), 293 (M+2, 100), 291 (M⁺, 52), 280 (36), 278 (76), 276 (36), 250 (12).

10: mp 116-117° (Lit.²⁹ 118°); ¹H NMR (CDCl₃) δ 7.99 (d, 1H, *J* = 2.44 Hz), 8.25 (d, 1H, *J* = 2.44 Hz), 11.06 (s, 1H); MS *m/z* (%) 299 (M+4, 51), 297 (M+2, 100), 295 (M⁺, 53), 241 (24), 239 (50), 237 (22).

11: mp 127-129° (Lit.³² 129-131°); ¹H NMR (CDCl₃) δ 6.79 (s, 1H), 7.39-7.56 (m, 3H), 7.77-7.81 (m, 2H); MS *m/z* (%) 121 (56), 105 (100), 77 (53), no M⁺.

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