

An Efficient and Regioselective Monobromination of Electron-Rich Aromatic Compounds Using Catalytic Hypervalent Iodine(III) Reagent

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Abstract: An efficient and regioselective monobromination of electron-rich aromatic compounds is reported in which iodobenzene is used as the recyclable catalyst in combination with *m*-chloroperbenzoic acid as the terminal oxidant. The bromination of electron-rich aromatic compounds with lithium bromide was fast in tetrahydrofuran at room temperature, providing regioselective monobrominated products in good yields.

Key words: monobromination, hypervalent iodine reagent, catalytic oxidation

Brominated aromatic compounds have considerable importance in the bulk and fine chemical industries, and they also find widespread use as intermediates in organic chemistry, for example, in cross-coupling reactions.¹ The preparation of brominated aromatic compounds with molecular bromine is a well-known reaction in organic chemistry.^{1c,d} This method requires transition-metal-based catalysts and the side product generated in the course is the corrosive and toxic hydrogen bromide. To improve the bromination process, considerable efforts, especially recently, have been devoted and several bromination reagents have been successfully used in place of molecular bromine, such as a bromide reagent with a stoichiometric oxidant² or with a combination of a metal catalyst and a stoichiometric oxidant.³ *N*-Bromosuccinimide (NBS) and those that feature the N–Br bond reagents were also preferred in the bromination process.⁴

Organic hypervalent iodine reagents have received much attention due to their low toxicity, mild reactivity, ready availability, high stability, and easy handling. They have found broad application in organic chemistry as alternatives replacing the highly toxic Hg(II), Tl(III), and Pb(IV) heavy-metal oxidants⁵ and some reports on the bromination of electron-rich aromatic compounds using hypervalent iodine reagents have been published.⁶ Recently, the catalytic utilization of hypervalent iodine reagents is increasing in importance, with the growing interest in the development of environmentally benign synthetic transformations.⁷ In these reactions, a catalytic amount of an iodine-containing molecule together with a stoichiometric oxidant is used. The oxidant generates the hypervalent io-

dine reagent in situ, and after the oxidative transformation, the reduced iodine-containing molecule is reoxidized. In order to extend the scope of catalytic hypervalent iodine reagents in organic synthesis, we have explored some reactions and reported the phosphoryloxylactonization of pentenoic acids with catalytic hypervalent iodine reagent this year.⁸ We now report a novel and efficient bromination of electron-rich aromatic compounds catalyzed by hypervalent iodine reagent, to prepare a series of monobrominated compounds.

Initially, the bromination of anisole was examined with one equivalent of lithium bromide as the bromine source, *m*-chloroperoxybenzoic acid as the oxidant, and 0.1 equivalent of iodobenzene as the catalyst. It was found that the reaction was complete in one hour, giving the monobrominated 4-bromoanisole in good yield. Then, the reaction conditions were optimized (Scheme 1) and the results are summarized in Table 1.

Table 1 Optimization of the Hypervalent Iodine(III)-Catalyzed Bromination of Anisole

Entry	PhI (equiv)	<i>m</i> CPBA (equiv)	LiBr (equiv)	TsOH·H ₂ O (equiv)	Solvent	Yield (%) ^{a,b}
1	0.1	1	1	1	MeOH	95
2	0.1	1	1	1	CH ₂ Cl ₂	96
3	0.1	1	1	1	MeCN	87
4	0.1	1	1	1	THF	98
5	0.1	1	KBr (1)	1	THF	47
6	0.1	1	NaBr (1)	1	THF	52
7	0.1	1	NH ₄ Br (1)	1	THF	63
8	0.05	1	1	1	THF	96
9	0.02	1	1	1	THF	95
10	0	1	1	1	THF	75
11	0.1	1	1	0	THF	76
12	0.1	2	2	1	THF	99
13	0.1	0	1	1	THF	0

^a All reactions were completed in 1 h.

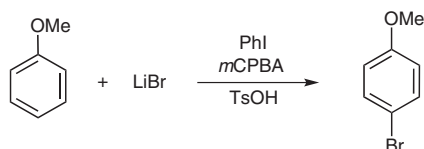
^b Isolated yields.

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Scheme 1

All the reactions shown in Table 1 were complete in one hour. As the solvent, methanol, dichloromethane, and tetrahydrofuran were preferred, but tetrahydrofuran was found to be the best choice (Table 1, entries 1–4). Potassium bromide, sodium bromide, and ammonium bromide were not good bromine sources for the reaction (entries 5–7). When the amount of iodobenzene was decreased to 0.02 equivalent, the presence of catalyst was still preferred (entries 4, 8, and 9), but in the absence of it, the yield was only of 75% (entry 10), and the mechanism of the reaction was not the same as with the catalyzed bromination.⁹ The inclusion of *p*-toluenesulfonic acid gave better results (entries 4, 11), since it participated in the formation of the hypervalent iodine reagent, hydroxy(tosyloxy)iodobenzene (HTIB, Koser's reagent).^{6b}

Table 2 Bromination of Electron-Rich Aromatic Compounds

Entry	Substrate	Product	Yield (%) ^a	Entry	Substrate	Product	Yield (%) ^a
1			98	7			85
2			97	8			60 ^b
3			95	9			97
4			98	10			86
5			81	11			51
6			2	12			2 ^c

^a Isolated yields.

^b Reaction time was 2 h.

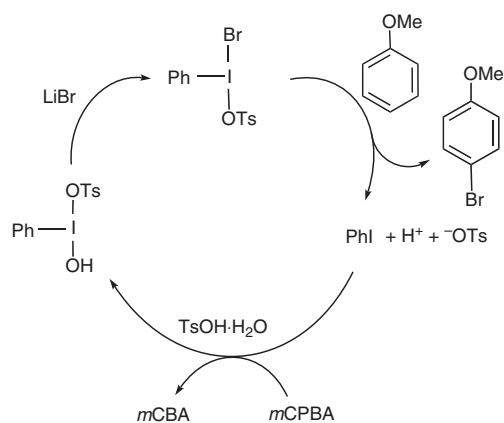
^c Reaction time was 12 h.

Under the optimum reaction conditions, the catalytic bromination of aromatic compounds with one equivalent of lithium bromide, *m*-chloroperoxybenzoic acid, and tosic acid monohydrate, and 0.1 equivalent of iodobenzene in tetrahydrofuran at room temperature in one hour was investigated and the results are summarized in Table 2.

Good yields of monobrominated products were obtained for a series of electron-rich aromatic ethers (Table 2, entries 1–5), in which regioselective formation of 4-bromination products was observed, the isomeric 2-bromination products were not found (entries 1–3). The *para*-substituted aromatic ethers only provided 2-bromination products (entries 4, 5). 1,3,5-Trimethylbenzene gave the product in good yield and 1,2,4,5-tetramethylbenzene also provided the desired product in 60% of yield after two hours, but the bromination was difficult for toluene (entries 6–8). *N,N*-Dimethylaniline and 2-methylthiophene, both participated in the reaction and the monobrominated products were obtained in good yields (entries 9, 10). The bromination of 4-chloroanisole was poor due to the electron-withdrawing chlorine, which agreed with the observation that dibrominated product was not found for anisole when ex-

cess of lithium bromide was present in the reaction (entry 12).

A proposed mechanism and catalytic cycle is shown in Scheme 2, which included the transformation of the hypervalent iodine reagent (Koser's reagent) to $\text{PhI}(\text{OTs})\text{Br}$, and then an electrophilic substitution with anisole to form the monobrominated product. The reduced by-product iodobenzene was again transformed into hypervalent iodine reagent by the oxidation of *m*-chloroperoxybenzoic acid.



Scheme 2

In summary, we have developed an efficient and regioselective bromination of electron-rich aromatic compounds to give monobrominated compounds in good yields. This method provides some advantages such as mild reaction conditions, simple procedure, and good yields.

IR spectra were recorded on a Thermo-Nicolet 6700 instrument, ^1H NMR spectra were measured on a Bruker Avance III (500 M) spectrometer, and mass spectra were determined on Thermo-ITQ 1100 mass spectrometer. Iodobenzene, *m*CPBA, TsOH, LiBr, and all aromatic compounds are commercially available.

Catalytic Bromination of Electron-Rich Aromatic Compounds; Typical Procedure

Anisole (32 mg, 0.3 mmol), LiBr (26 mg, 0.3 mmol), *m*CPBA (75%, 69 mg, 0.3 mmol), TsOH·H₂O (57 mg, 0.3 mmol), and iodobenzene (18 mg, 0.03 mmol) were mixed in THF (2 mL). The mixture was stirred at r.t. for 1 h and then H₂O (5 mL), sat. aq Na₂S₂O₃ (1 mL), and sat. aq Na₂CO₃ (1 mL) were added. The mixture was extracted with CH₂Cl₂ (2 × 5 mL), the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using (3:1 hexane–EtOAc) as eluent to give 4-bromoanisole; yield: 55 mg (98%); oil (Table 2).

^1H NMR (500 MHz, CDCl₃): δ = 7.37 (ddd, *J* = 10.0, 5.5, 3.0 Hz, 2 H), 6.78 (ddd, *J* = 10.0, 5.5, 3.0 Hz, 2 H), 3.78 (s, 3 H).

^{13}C NMR (125 MHz, CDCl₃): δ = 158.8, 137.5, 115.8, 112.9, 55.5.

MS (EI): *m/z* = 186, 188 [M⁺].

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