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An efficient chlorination of aromatic compounds using a catalytic amount of iodobenzene

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ABSTRACT

An efficient method was developed for chlorination of aromatic compounds with electron-donating groups using iodobenzene as the catalyst and *m*-chloroperbenzoic acid as the terminal oxidant in the presence of 4-methylbenzenesulfonic acid in THF at room temperature for 24 h, and a series of the monochlorinated compounds was obtained in good yields. In this protocol, the catalyst iodobenzene was first oxidized into the hypervalent iodine intermediate, which then treated with lithium chloride and finally reacted with aromatic compounds to form the chlorinated compounds.

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1. Introduction

The chemistry of hypervalent iodine organic compounds has experienced impressive developments since the early 1990s. Due to their low toxicity, ready availability, easy handling and reactivity similar to that of heavy metal reagents or anodic oxidation, hypervalent iodine compounds have received a great deal of attention [1–5]. They have been extensively used as mild, highly selective and environmentally friendly reagents in organic reactions, such as oxidations [6–9], substitutions [10–12], additions [13–16] and rearrangement reactions [17–19].

Aryl chlorides constitute an important segment of fine and specialty chemicals, dyes, flame-retardants, pharmaceuticals and agrochemicals. They also have been extensively used as precursors in the preparation of various bioactive molecules and pharma-ceuticals [20–23]. In carbon–carbon bond-forming reactions, such as Suzuki Miyaura cross-couplings, they play a vital role as important synthetic intermediates [24–26]. A number of methods have been used to synthesize aryl chlorides; however, various toxic catalysts or harmful solvents have been used so far [20,27]. Therefore, less toxic and more environmentally friendly reagents and solvents in chlorination of aromatic compounds are necessary.

Recently, Zhou and co-worker reported a novel method for monobromination of electron-rich aromatic compounds using catalytic hypervalent iodine (III) [28]. However, similar reactions

* Corresponding author. E-mail address: jieyan87@zjut.edu.cn (J. Yan). for catalytic chlorination of aromatic compounds have not been reported until now. In order to develop a new protocol for chlorination of aromatic compounds and extend the scope of catalytic use of hypervalent iodine reagents in organic synthesis, we have investigated the chlorination of anisole with *m*chloroperbenzoic acid (*m*CPBA) as the oxidant and lithium chloride (LiCl, 1.2 equiv.) as the chlorine source, using a catalytic amount of iodobenzene (PhI, 0.3 equiv.) as the catalyst in the presence of 4methylbenzenesulfonic acid (TsOH·H₂O) in THF at room temperature for 4 h. The reaction provided the desired product of 4chloroanisole with a good yield. Based on successful formation of the monochlorinated compound, the reaction conditions were optimized and the results are summarized in Table 1.

2. Experimental

A typical procedure for the catalytic chlorination of electron-rich aromatic compounds: To THF (4 mL), anisole (0.3 mmol, 32 mg), TsOH·H₂O (0.3 mmol, 57.1 mg), mCPBA (75%, 0.3 mmol, 69 mg), PhI (0.12 mmol, 25 mg) and LiCl (0.36 mmol, 16 mg) were added. The mixture was stirred at r.t. for 24 h. Then H₂O (10 mL), sat.aq. Na₂S₂O₃ (4 mL), and sat. aq. Na₂CO₃ (4 mL) were added. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layer was dried over anhydried Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified on silica gel plate (hexane/EtOAc = 20/1) to give the yellow oil product of 4-chloroanisole 35 mg (90%). IR (neat, cm⁻¹): 2941, 2868, 1695, 1598, 1503, 1482, 1432, 1297, 1227, 1170, 1097, 1030, 935, 871,

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Table 1

Optimization of the catalyzed chlorination of anisole.

Entry	Oxidant (equiv.)	Cl- (equiv.)	TsOH·H ₂ O (equiv.)	PhI (equiv.)	Solvent	Yield (%) ^a
1	<i>m</i> CPBA	LiCl	1.0	0.3	CH₃OH	31
2	mCPBA	LiCl	1.0	0.3	EtOAc	80
3	mCPBA	LiCl	1.0	0.3	THF	83
4	mCPBA	LiCl	1.0	0.3	EtOH	69
5	mCPBA	LiCl	1.0	0.3	MeCN	78
6	mCPBA	LiCl	1.0	0.3	CH_2Cl_2	38
7	Oxone	LiCl	1.0	0.3	THF	71
8	NaBO ₃ ·4H ₂ O	LiCl	1.0	0.3	THF	39
9	mCPBA	NaCl	1.0	0.3	THF	80
10	<i>m</i> CPBA	KCl	1.0	0.3	THF	64
11	mCPBA	NH ₄ Cl	1.0	0.3	THF	29
12	mCPBA	LiCl	1.0	0	THF	17
13	mCPBA	LiCl	1.0	0.1	THF	45
14	mCPBA	LiCl	1.0	0.2	THF	53
15	<i>m</i> CPBA	LiCl	1.0	0.4	THF	87
16	mCPBA	LiCl	1.0	0.5	THF	82
17	mCPBA	LiCl	0	0.4	THF	16
18	mCPBA	LiCl	1.5	0.4	THF	83
19	mCPBA	LiCl	2.0	0.4	THF	73
20	mCPBA	LiCl	1.0	0.4	THF	90 ^b

^a Isolated yield.

^b Reaction time was 24 h.

799, 695. ¹H NMR (500 Hz, CDCl₃): δ 7.25 (d, 2H, *J* = 9.0 Hz), 6.84 (d, 2H, *J* = 9.0 Hz), 3.80 (s, 3H).

3. Results and discussion

0As shown in Table 1, solvent influenced the reaction greatly and THF was superior to other solvents with a good yield of 83%

Table 2

The results of the catalytic chlorination of aromatic compounds.

$$\begin{array}{rcl} \text{Ar-H} &+ \text{LiCl} &+ \text{PhI} & & & \\ \hline 1 & & & & \\ \hline 1 & & & \\ 1 & &$$

CDD A

Scheme 1. The chlorination of aromatic compounds using iodobenzene as catalyst.

(Table 1, entries 1–6). Oxidants mCPBA, NaBO₃·4H₂O, and Oxone were tested under the same reaction conditions; however, oxone gave the relatively low yield of 71%, and NaBO₃·4H₂O produced even lower yields (entries 7 and 8). Therefore, mCPBA was chosen for use in this experiment. Besides LiCl, various kinds of chlorides such as sodium chloride, potassium chloride and ammonium chloride were tried as the chlorine source, and LiCl offered the highest yield among them (entries 3, 9-11). The amount of PhI was also investigated, and 0.4 equiv. of it was the best choice (entries 3, 13–16). Without PhI, the product was obtained only in 17% yield (entry 12). 1.0 Equiv. of TsOH·H₂O allowed the conversion of anisole into the desired product in good yield of 87%; whereas in the absence of it, the yield decreased to less than 16% (entries 15, 17-19). As reported by Zhou, bromination of aromatic compounds only needed 1 h to complete with bromides. Considering the differences between chlorine and bromine, the reaction time was extended to 24 h to complete the reaction (entry 20).

Having established the optimal reaction conditions for chlorination of anisole, the scope of chlorination of aromatic compounds was evaluated for a range of substrates (Scheme 1, Table 2). It is shown from Table 2 that a variety of electron-rich aromatic compounds such as aromatic ethers were easily transformed into the chlorinated products with good yields (Table 2, entries 1–6), with regioselectivity towards 4-chlorinated compounds (entries 1–3). As to other three aromatic ethers with groups in 4-position, only 2-chlorinated products were found in moderate yields (entries 8–10). 1,3,5-Trimethylbenzene and 1,2,4,5-tetramethylbenzene also gave the corresponding products; however, the yields were relatively low compared with aromatic ethers (entries 11 and 12). As the representative with an electron-withdrawing group on an aromatic ring, chlorobenzene was also tried under the same





^a Isolated yield.

^b Determined by GC technique.

^c Isolate yield when 2 equiv. of LiCl was used.



Scheme 2. A proposed mechanism for the chlorination.

reaction conditions and no desired chlorinated product was found, which agreed with the observation that dichlorinated products were not formed for the above substrates (entry 7). An exception was also found that when another electron-rich aromatic compound, *N*,*N*-dimethylaniline was used in the reaction, an unexpected product of 2,4-dichloro-*N*,*N*-dimethylaniline was obtained in good yield of 86% (entry 13).

A proposed mechanism for this reaction is shown in Scheme 2. First, PhI is oxidized to a hypervalent iodine (III) reagent (Koser's reagent) by *m*CPBA in the presence of $TsOH \cdot H_2O$, which is then transformed to another active hypervalent iodine (III) intermediate PhI(OTs)Cl, and finally an electrophilic substitution with anisole follows to form the chlorinated product. The reduced by-product PhI is reoxidized into the hypervalent iodine reagent by *m*CPBA to complete the recycling reaction.

4. Conclusion

A novel and efficient method of chlorination of electron-rich aromatic compounds has been developed with the use of PhI as a catalyst, which is oxidized to the hypervalent iodine reagent by mCPBA in the presence of TsOH·H₂O. This method has several advantages such as simple procedure, mild reaction conditions, and good yield. Further investigation of the catalytic chlorination of aromatic compounds will be reported in due course.

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References

- P.J. Stang, V.V. Zhdankin, Organic polyvalent iodine compounds, Chem. Rev. 96 (1996) 1123–1178.
- [2] V.V. Zhdankin, P.J. Stang, Recent developments in the chemistry of polyvalent iodine compounds, Chem. Rev. 102 (2002) 2523–2584.
- [3] T. Dohi, Y. Kita, Hypervalent iodine reagents as a new entrance to organocatalysts, Chem. Commun. (2009) 2073–2085.
- [4] M. Ochiai, Nucleophilic vinylic substitutions of λ^3 -vinyliodanes, J. Organomet. Chem. 611 (2000) 494–508.
- [5] T. Okuyama, Solvolysis of vinyl iodonium salts. New insights into vinyl cation intermediates, Acc. Chem. Res. 35 (2002) 12–18.
- [6] M. Frigerio, M. Santagostino, A mild oxidizing reagent for alcohols and 1,2diols: o-iodoxybenzoic acid (IBX) in DMSO, Tetrahedron Lett. 35 (1994) 8019–8022.
- [7] K.C. Nicolaou, Y.L. Zhong, P.S. Baran, New synthetic technology for the rapid construction of novel heterocycles—part 1: the reaction of Dess–Martin periodinane with anilides and related compounds, Angew. Chem. Int. Ed. 39 (2000) 622–625.
- [8] T. Dohi, M. Ito, N. Yamaoka, et al., Hypervalent iodine(III): selective and efficient single-electron-transfer (SET) oxidizing agent, Tetrahedron 65 (2009) 10797– 10815.
- [9] M. Traoré, S. Ahmed-Ali, M. Peuchmaur, et al., Hypervalent iodine(III)-mediated tandem oxidative reactions: application for the synthesis of bioactive polyspirocyclohexa-2,5-dienones, Tetrahedron 66 (2010) 5863–5872.
- [10] M. Arisawa, N.G. Ramesh, M. Nakaima, et al., Hypervalent iodine(III)-induced intramolecular cyclization of α -(aryl) alkyl- β -dicarbonyl compounds: a convenient synthesis of benzannulated and spirobenzannulated compounds, J. Org. Chem. 66 (2001) 59–65.
- [11] H. Tohma, H. Morioka, S. Takizawa, et al., Efficient oxidative biaryl coupling reaction of phenol ether derivatives using hypervalent iodine(III) reagents, Tetrahedron 57 (2001) 345–352.
- [12] H. Hamamoto, G. Anilkumar, H. Tohma, et al., A novel and useful oxidative intramolecular coupling reaction of phenol ether derivatives on treatment with a combination of hypervalent iodine(III) reagent and heteropoly acid, Chem. Eur. J. 8 (2002) 5377–5383.
- [13] L. Shi, Y.J. Kim, D.Y. Gin, C2-acyloxyglycosylation with glycal donors, J. Am. Chem. Soc. 123 (2001) 6939–6940.
- [14] J. Barluenga, M. Maro-Arias, F. González-Bobes, et al., Reaction of alkenes with hydrogen peroxide and sodium iodide: a nonenzymatic biogenic-like approach to iodohydrins, Chem. Eur. J. 10 (2004) 1677–1682.
- [15] K.C. Nicolaou, K. Sugita, P.S. Baran, et al., Iodine(V) reagents in organic synthesis. Part 1. Synthesis of polycyclic heterocycles via Dess–Martin periodinane-mediated cascade cyclization: generality, scope, and mechanism of the reaction, J. Am. Chem. Soc. 124 (2002) 2212–2220.
- [16] M.S. Yusubov, L.A. Drygunova, V.V. Zhdankin, 4,4-Bis(dichloroiodo)biphenyl and 3-(dichloroiodo)benzoic acid: new recyclable hypervalent iodine reagents for vicinal halomethoxylation of unsaturated compounds, Synthesis (2004) 2289–2292.
- [17] V.G. Shukla, P.D. Salgaonkar, K.G. Akamanchi, Molecular-iodine-catalyzed onepot synthesis of 1,5-benzodiazepine derivatives under solvent-free conditions, Synlett (2005) 1337-1339.
- [18] K.S. Feldman, D.B. Vidulova, Use of Stang's reagent, PhI(CN)OTf, to promote Pummerer-like oxidative cyclization of 2-(phenylthio)indoles, Tetrahedron Lett. 45 (2004) 5035–5037.
- [19] M.W. Justik, G.F. Koser, Oxidative rearrangements of arylalkenes with [hydroxy(tosyloxy)iodo]benzene in 95% methanol: a general, regiospecific synthesis of α-aryl ketones, Tetrahedron Lett. 45 (2004) 6159–6163.
- [20] L. Saikia, M. Rajesh, D. Srinivas, et al., Regiospecific oxyhalogenation of aromatics over SBA-15-supported nanoparticle group IV–VI metal oxides, Catal. Lett. 137 (2010) 190–201.
- [21] D.C. Crans, J.J. Smee, E. Gaidamauskas, et al., The chemistry and biochemistry of vanadium and the biological activities exerted by vanadium compounds, Chem. Rev. 104 (2004) 849–902.

- [22] A. Butler, J.N. Carter-Franklin, The role of vanadium bromoperoxidase in the biosynthesis of halogenated marine natural products, Nat. Prod. Rep. 21 (2004) 180–188.
- [23] P.D. Nightingale, G. Malin, P.S. Liss, Production of chloroform and other lowmolecular-weight halocarbons by some species of macroalgae, Limnol. Oceanogr. 40 (1995) 680–689.
- [24] G.A. Molander, O.A. Argintaru, I. Aron, et al., Nickel-catalyzed cross-coupling of potassium aryl and heteroaryltrifluoroborates with unactivated alkyl halides, Org. Lett. 12 (2010) 5783–5785.
- [25] G.A. Molander, I. Shin, L. Jean-Gerard, Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of enantiomerically enriched potassium

 $\beta\text{-trifluoroboratoamides}$ with various aryl- and hetaryl chlorides, Org. Lett. 12 (2010) 4384–4387.

- [26] S.D. Dreher, S.E. Lim, D.L. Sandrock, et al., Suzuki–Miyaura cross-coupling reactions of primary alkyltrifluoroborates with aryl chlorides, J. Org. Chem. 74 (2009) 3626–3631.
- [27] Y. Kuwahara, A. Zhang, H. Soma, et al., Photochemical molecular storage of Cl₂, HCl, and COCl₂: synthesis of organochlorine compounds, salts, ureas, and polycarbonate with photodecomposed chloroform, Org. Lett. 14 (2012) 3376–3379.
- [28] Z.S. Zhou, X.H. He, An efficient and regioselective monobromination of electronrich aromatic compounds using catalytic hypervalent iodine(III) reagent, Synthesis (2011) 207–209.