A Novel Catalytic Hypervalent Iodine Oxidation of *p*-Alkoxyphenols to *p*-Quinones Using 4-Iodophenoxyacetic Acid and Oxone®

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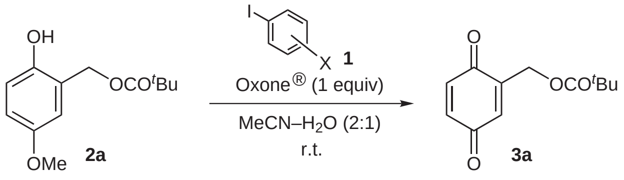
Abstract: A novel catalytic hypervalent iodine oxidation of phenol derivatives using 4-iodophenoxyacetic acid and Oxone® was developed. Reaction of *p*-alkoxyphenols with a catalytic amount of 4-iodophenoxyacetic acid in the presence of Oxone® as a co-oxidant in acetonitrile–water (2:1) gave the corresponding *p*-quinones in excellent yields without purification.

Key words: *p*-alkoxyphenol, *p*-quinone, catalysis, hypervalent iodine oxidation, 4-iodophenoxyacetic acid, Oxone®

Development of efficient methods for synthesis of *p*-quinone and *p*-quinone derivatives is one of the most important subjects in synthetic organic chemistry, since they are structural components of a large number of natural products and useful synthetic intermediates.[1] As one of the most convenient procedures to *p*-quinones, hypervalent iodine oxidation of *p*-alkoxyphenols using phenyliodine(III) trifluoroacetate (PIFA) was reported in 1989.[2] After this report, several groups investigated similar oxidations of phenol derivatives by phenyliodine(III) diacetate (PIDA) and other hypervalent iodine reagents.[3] Moreover, an efficient *p*-quinone synthesis via oxidative demethylation of phenyl ethers was reported using PIFA.[4]

Both PIFA and PIDA have been extensively used in recent organic syntheses owing to their low toxicity, ready availability and ease of handling.[5] Pentavalent iodine reagents such as Dess–Martin periodinane (DMP) and *o*-iodoxybenzoic acid (IBX) have also attracted considerable attention as mild and selective oxidizing agents.[6] However, these reagents are highly expensive and stoichiometric amounts of iodine reagents are required in the oxidation to produce equimolar amount of iodine waste. Moreover, pentavalent iodine reagents are potentially explosive. To overcome these disadvantages of these reagents, recyclable polymer-supported hypervalent iodine reagents have been developed.[7] Very recently, catalytic trivalent iodine oxidations[8] using *m*-chloroperbenzoic acid (MCPBA) as a co-oxidant were reported by Kita,[9] Ochiai,[10] and Togo[11] groups, respectively. Vinod[12] and Giannis[13] groups independently found a catalytic use of IBX generated from 2-iodobenzoic acid and Oxone® ($2KHSO_5\cdot KHSO_4\cdot K_2SO_4$). We report herein an efficient and practical oxidation of *p*-alkoxyphenols to *p*-quinones using a catalytic amount of 4-iodophenoxyacetic acid (**1a**)[14] and an equimolar amount of Oxone® as a co-oxidant.



Scheme 1

We chose Oxone® as an environmentally safe co-oxidant for the preparation of *p*-quinones, since Oxone® is an inorganic and water-soluble oxidant with a low order of toxicity, and moreover it is commercially available and inexpensive.[15] As alkoxyphenols have relatively high reactivity under oxidation conditions, we first investigated the oxidative ability of Oxone® alone.[16] Thus, a mixture of 2-pivaloyloxymethyl-4-methoxyphenol (**2a**) and an equimolar amount of Oxone® in acetonitrile–water (2:1) at room temperature gave the corresponding *p*-benzoquinone (**3a**), but the reaction was quite sluggish, and the yield of **3a** was only 13% along with 78% of recovered starting **2a** after 24 hours. Next, we examined reactions of **2a** with a catalytic amount of several iodoarenes in the presence of Oxone® (Scheme 1). The results are summarized in Table 1. According to the procedure reported by Vinod,[12] a mixture of **2a**, 0.2 equivalent of 2-iodobenzoic acid, and 1 equivalent of Oxone® in acetonitrile–water was heated at 70 °C for 19 hours to give a complicated mixture (entry 2). The oxidation at room temperature gave better results (entry 3). Iodobenzene showed moderate catalytic activity (entry 4). Methyl and methoxy groups on the benzene ring showed to enhance the reactivity of iodoarene (entries 5–8). Especially, when 0.2 equivalent of 4-iodoanisole were used as catalyst, the reaction was completed within 17 hours to give **2a** in 90% yield (entry 8). Acetoxy group, however, decreased reactivity of iodoarene (entry 9). Other iodobenzenes with a *p*-alkoxy group, such as *p*-OMOM, *p*-OCH_2CO_2Me, *p*-$O(CH_2)_3CO_2Me$, are also effective to catalyze the oxidation of **2a** to **3a** (entries 10–12). These results indicated that electron-donating alkoxy group at the *para* position on the benzene ring would increase catalytic efficiency of iodoarene, in contrast to the reported results using MCPBA as a co-oxidant.[9–11] Slower reaction was observed using 0.1 equivalent of 4-iodoanisole (entry 13),

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however, larger amounts (0.5–1 equiv) led to decreased reaction times with similar yields of **3a** (entries 14 and 15).

Although *p*-alkoxyiodobenzenes gave satisfactory results, unfortunately, the reactions required careful purification by column chromatography in order to separate the product and the recovered catalyst. Thus, we selected 4-iodophenoxyacetic acid (**1a**),[14] which was easily prepared from 4-iodophenol, in the hope of becoming a more practical catalyst because **1a** has an electron-donating group at the *para* position and is soluble in alkaline solution. A similar reaction of **2a** with 0.2 equivalent of **1a** in the presence of 1 equivalent of Oxone® proceeded smoothly to afford pure **3a** in 99% yield and 75% of recovered **1a** without column chromatography (entry 16).

Table 1 Oxidation of **2a** with **1** and Oxone®[a]

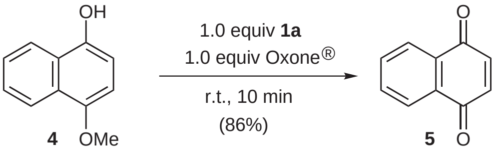
Entry	**1** X	(equiv)	Time (h)	Yield of **3a** (%)
1	None		24	13 (78)[b]
2[c]	*o*-CO_2H	0.2	19	6 (4)[b]
3	*o*-CO_2H	0.2	24	39 (6)[b]
4	H	0.2	24	64 (24)[b]
5	*p*-Me	0.2	24	77 (14)[b]
6	*o*-OMe	0.2	24	71 (14)[b]
7	*m*-OMe	0.2	24	77 (4)[b]
8	*p*-OMe	0.2	17	90
9	*p*-OCOMe	0.2	24	54 (40)[b]
10	*p*-OMOM	0.2	22	92
11	*p*-OCH_2CO_2Me	0.2	21	94
12	*p*-$O(CH_2)_3CO_2Me$	0.2	40	86
13	*p*-OMe	0.1	24	73 (18)[b]
14	*p*-OMe	0.5	9	92
15	*p*-OMe	1.0	5	94
16	*p*-OCH_2CO_2H **1a**	0.2	19	99

[a] Reactions were carried out in the presence of 1 equiv of Oxone® in MeCN–H_2O (2:1) at r.t.

[b] Parentheses are recovery of **2a**.

[c] Reaction was carried out at 70 °C.

A variety of *p*-alkoxyphenols (**2a**–**i**) were oxidized with a catalytic amount of **1a** and Oxone® to the corresponding *p*-quinones (Table 2). When 0.7 equivalent of Oxone® were used in the reaction of **2a** in the presence of 0.2 equivalent of **1a**, the reaction was completed within longer 48 hours to give 92% yield of **3a** (entry 2). On the other hand, a similar reaction using 0.5 equivalent of Oxone® was not finished after several days (entry 3). These results suggested that the most efficient amount of Oxone® for this oxidation would be an equimolar amount. So, the use of 0.2 equivalent of **1a** and 1 equivalent of Oxone® was selected as standard condition. Reaction of simple *p*-methoxy-, *p*-ethoxy-, and *p*-butoxyphenols (**2b**–**d**) gave *p*-benzoquinone (**3b**) in good yields, respectively (entries 4–6). This oxidation system was also effective to phenols bearing a bulky substituent at the *ortho* position (entries 7 and 8). *tert*-Butyldiphenylsilyloxy (TBDPS) and azide groups were tolerable under the reaction conditions (entries 9 and 10). Oxidation of phenol having succinimide group (**2i**) proceeded in high yield using 0.4 equivalent of **1a** (entry 11). Reaction of 4-methoxy-1-naphthol (**4**) with catalytic amount of **1a** in the presence of Oxone® gave rise to low yield of 1,4-naphthoquinone (**5**) with a complex mixture. This result should be caused by decomposition of **4** by Oxone®, because **4** would be sensitive under oxidation conditions. However, stoichiometric use of **1a** produced **5** within 10 minutes in 86% yield (Scheme 2). In all cases, **1a** was recovered in good yield (75–85%) and it can be used for the oxidation again after recrystallization.

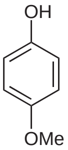
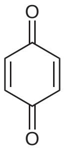
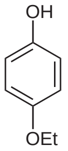
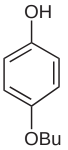
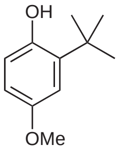
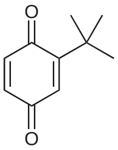
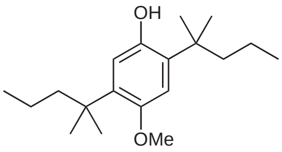
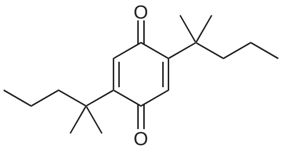
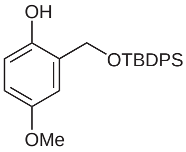
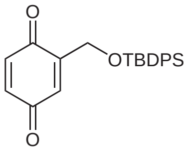
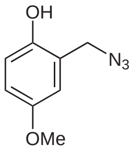
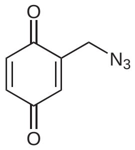
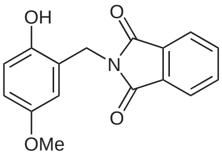
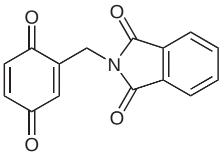


Scheme 2

A possible catalytic cycle for this oxidation is shown in Scheme 3. Iodoarene would be oxidized by Oxone® to iodine(V) species[12,13,17] which reacts with *p*-alkoxyphenol[18] to give *p*-quinone and iodine(III) species. The trivalent iodine species should be reduced further to monovalent derivative to result in the oxidation of another phenol[2] to quinone.[19] Iodoarenes with electron-donating substituents such as methoxy and methyl groups may be more easily oxidized by Oxone® to cause rapid reactions, whereas an electron-withdrawing substituent such as a carboxyl group may decrease the reactivity of iodoarene against the oxidant.

In summary, a novel and practical catalytic hypervalent iodine oxidation of phenol derivatives using **1a** was developed. Reaction of *p*-alkoxyphenols **2** with a catalytic amount of **1a** in the presence of Oxone® as a co-oxidant in acetonitrile–water (2:1) gave the corresponding *p*-quinones **3** in excellent yields without purification. The substituent effect on iodobenzene ring in the oxidation was observed; *p*-alkoxy is the most effective, with the series following the approximate order *p*-RO > *p*-Me, *o*-MeO, *m*-MeO > H > *o*-CO_2H.

Table 2 Catalytic Hypervalent Iodine Oxidation of **2** with **1a** and Oxone®[a,20]

Entry	Phenol	Quinone	Time (h)	Yield (%)
1[b]	**2a**	**3a**	19	99
2[c]	**2a**	**3a**	48	92
3[d]	**2a**	**3a**	8 d	incomplete
4	 **2b**	 **3b**	16	80
5	 **2c**	**3b**	17	79
6	 **2d**	**3b**	17	77
7	 **2e**	 **3e**	24	53
8	 **2f**	 **3f**	23	80
9	 **2g**	 **3g**	24	96
10	 **2h**	 **3h**	22	92
11[e]	 **2i**	 **3i**	40	89

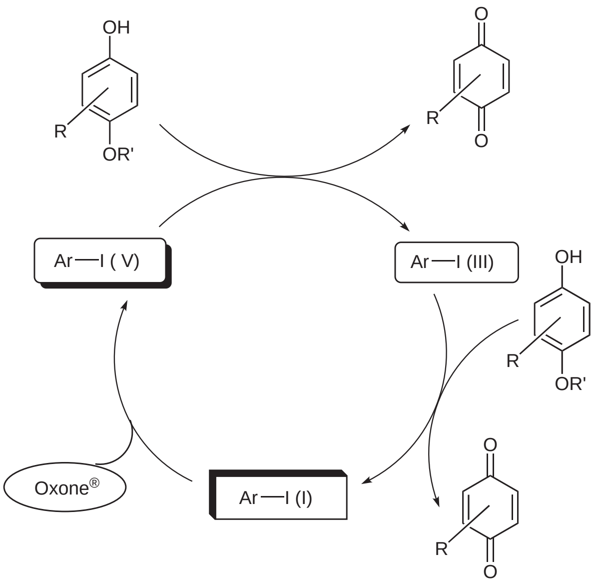
[a] Reactions were carried out using 0.2 equiv of **1a** and 1 equiv of Oxone® in MeCN–H_2O (2:1) at r.t.

[b] Same as entry 16, Table 1.

[c] 0.7 Equiv of Oxone® were used.

[d] 0.5 Equiv of Oxone® were used.

[e] 0.4 Equiv of **1a** were used.



Scheme 3

Acknowledgment

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(19) It is possible that iodine(III) species may be oxidized by Oxone® to regenerate iodine(V) species before the reaction of iodine(III) with phenol.

(20) **Typical Reaction Procedure**: To a solution of **2** (1 mmol) in MeCN–H_2O (2:1, 6 mL) was added **1a** (0.2 mmol) followed by Oxone® (1 mmol) at r.t. and the resulting mixture was stirred at the same temperature. After **2** was completely consumed indicated by TLC, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was then washed with aq sat. $NaHCO_3$ solution and dried, concentrated to give pure **3**. If necessary, the product was purified by column chromatography on silica gel to give pure quinone.
The alkaline solution was acidified by 10% HCl solution and extracted with EtOAc. The organic layer was washed with aq $Na_2S_2O_3$ solution and dried, then concentrated to give recovered **1a** which was purified by recrystallization from Et_2O–hexane.
All new compounds gave satisfactory spectroscopic data.

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