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

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A catalytic hypervalent iodine oxidation of *p*-dialkoxybenzenes using 4-iodophenoxyacetic acid (1) and $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) was developed. Reaction of *p*-dialkoxybenzenes (2) with a catalytic amount of 1 in the presence of Oxone® as a co-oxidant in 2,2,2-trifluoroethanol–water (1 : 2) gave the corresponding *p*-quinones (3) in excellent yields without purification. This procedure was applied to synthesis of blattellaquinone (9), the sex pheromone of the German cockroach, *Blattella germanica*.

Key words *p*-dialkoxybenzene; 4-iodophenoxyacetic acid; Oxone®; catalytic hypervalent iodine oxidation; *p*-quinone; blattellaquinone

Development of efficient methods for quinone synthesis is quite important in synthetic organic chemistry because they are structural components of numerous pharmacologically active compounds and useful synthetic intermediates.[1,2] Oxidation of phenols and phenol derivatives is a common method.[3—6] Among them, oxidative dearomatization of phenol ethers using metal oxidants, such as cerium(IV) ammonium nitrate (CAN)[7,8] and silver(II) oxide–nitric acid[9] *etc.*, is one of the most efficient procedures for synthesis of complex natural products because phenol ethers are stable under various conditions and are easily prepared. From the perspective of the synthesis of pharmacological and agricultural active compounds, however, environmentally benign methods that are free of heavy metal waste are strongly desired. A convenient metal-free procedure to produce quinones from phenol ethers, hypervalent iodine oxidation using phenyliodine(III) trifluoroacetate (PIFA), has been reported.[10] Hypervalent iodine reagents have been used extensively in recent organic synthesis because of their low toxicity, ready availability, and ease of handling.[11—15] However, the reagents are expensive, moreover, stoichiometric amounts of iodine reagents are necessary during oxidation to produce equimolar amounts of iodine waste. In addition, some of them are potentially explosive. To overcome these disadvantages of these reagents, catalytic hypervalent iodine oxidations were developed recently.[16—28] We also reported a catalytic hypervalent iodine oxidation of *p*-alkoxyphenols to *p*-quinones using a catalytic amount of 4-iodophenoxyacetic acid (**1**) with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a novel system.[29] This system presents the following advantages. The first is that reaction proceeds under mild conditions. The second is that Oxone® is inorganic, water-soluble, commercially available, and inexpensive with low toxicity.[30] The third is that solubility of **1** in alkaline solution facilitates its recovery without special operation. As a part of our study for development of practical and environmentally benign oxidations, we report herein an efficient synthesis of *p*-quinones from *p*-dialkoxybenzenes using a catalytic amount of **1** and Oxone® in 2,2,2-trifluoroethanol–water as a solvent system.

We examined reactions of 1,4-dimethoxy-2-(pivaloyloxymethyl)benzene (**2a**) with **1** in the presence of Oxone® under various conditions (Chart 1). The results are presented in Table 1. The dimethyl phenol ethers are usually less reactive under many oxidation conditions. Therefore an excess PIFA was required in the case of reported PIFA oxidation.[10] For that reason, we first investigated oxidation using an excess amount of **1** and Oxone®. The reaction was completed within 1 h to give the corresponding *p*-benzoquinone (**3a**) in quantitative yield when **2a** was treated with four equimolar amounts of **1** and Oxone® in acetonitrile–water (2 : 1) at room temperature[29] (entry 1). This result encouraged us to explore the catalytic use of **1** in the oxidation of **2a** to **3a**. Although use of 0.2 eq of **1** with 4 eq of Oxone® slowed the reaction, quantitative yield of **3a** was obtained after 10 h (entry 2). Because Kita and co-workers reported that water was quite effective as a solvent to PIFA oxidation of *p*-dimethoxybenzenes,[10] we examined the addition of water to the reaction mixture (entries 3—5). In a 1 : 2 mixture of acetonitrile–water, the reaction was completed within 2 h to give **3a** in quantitative yield (entry 4). However, further addition of water necessitated a longer reaction time to give a 1 : 2 mixture of **3a** and unreacted **2a**, which was observed using the ^{1}H-NMR spectrum of the crude mixture after 3 h (entry 5). A much slower reaction (24 h) was observed using 1 eq of Oxone® (entry 6). However, a similar reaction with 0.1 eq of **1** increased slightly the reaction time (4 h) (entry 7). No reaction was observed without **1** (entry 8). Next, we investigated to change the organic solvent. A similar reaction in a 1 : 2

Table 1. Oxidative Dearomatization of **2a** with **1** and Oxone®[a)]

Entry	**1** (eq)	Oxone® (eq)	Solvent	Time (h)	Yield (%) of **3a**
1	4	4	CH_3CN–H_2O (2 : 1)	1	Quant
2	0.2	4	CH_3CN–H_2O (2 : 1)	10	Quant
3	0.2	4	CH_3CN–H_2O (1 : 1)	5	Quant
4	0.2	4	CH_3CN–H_2O (1 : 2)	2	Quant
5	0.2	4	CH_3CN–H_2O (1 : 5)	3	33[b)]
6	0.2	1	CH_3CN–H_2O (1 : 2)	24	Quant
7	0.1	4	CH_3CN–H_2O (1 : 2)	4	Quant
8	None	4	CH_3CN–H_2O (1 : 2)	No reaction	
9	0.1	4	THF–H_2O (1 : 2)	4	5[c)]
10	0.1	4	Acetone–H_2O (1 : 2)	5	[d)]
11	0.1	4	CF_3CH_2OH–H_2O (1 : 2)	1	Quant
12	0.05	4	CF_3CH_2OH–H_2O (1 : 2)	1	Quant
13	0.025	4	CF_3CH_2OH–H_2O (1 : 2)	4	Quant
14	0.01	4	CF_3CH_2OH–H_2O (1 : 2)	48	94

a) Reactions were carried out at room temperature. *b*) Unreacted **2a** was recovered (67%). *c*) Unreacted **2a** was recovered (95%). *d*) Reaction was not completed and gave **3a** with unknown by-product.

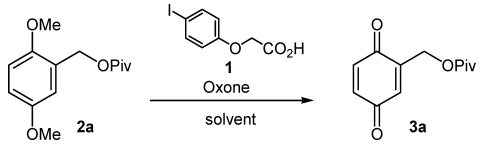

Chart 1

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mixture of tetrahydrofuran and water proceeded slowly to give **3a** and unreacted **2a** (1 : 20) after 4 h (entry 9). Acetone was not a suitable solvent (entry 10). In contrast, 2,2,2-trifluoroethanol[21] was proven effective in this oxidation reaction (entries 11—14). Both reactions of **2a** with 0.1 eq and 0.05 eq of **1** were finished within 1 h to give **3a** (entries 11, 12). The reaction was completed within 4 h to give **3a** in quantitative yield when **2a** was treated with 0.025 eq of **1** and 4 eq of Oxone® in CF_3CH_2OH–H_2O (1 : 2) at room temperature (entry 13). The reaction using 0.01 eq of **1** was finished after 48 h to afford **3a** in 94% yield (entry 14). The turnover number (TON) of this reaction was calculated as 94.

We next investigated the oxidation of various *p*-dialkoxyarenes (**2b**—**h**, **4**, **6**) with 0.05 eq of **1** and 4 eq of Oxone® in CF_3CH_2OH–H_2O (1 : 2) at room temperature as standard conditions[31] (Chart 2). The results are presented in Table 2. Reaction of *p*-dimethoxybenzene (**2b**) gave *p*-benzoquinone (**3b**) in good yield (entry 2). *p*-Diethoxybenzene (**2c**) was also oxidized to **3b** (entry 3). Although *p*-(*tert*-butyldimethylsilyloxy)methoxybenzene (**2d**) reacted smoothly to give **3b** (entry 4), the electron-withdrawing acetyl group decreased the reactivity to give **3b** in as low as 4% yield with the recovery of 96% of **2e** after 24 h (entry 5). Reactions of 1,4-dimethoxybenzenes (**2f**, **g**) having an alkyl group, such as methyl and bulky *tert*-butyl groups at the 2-position, were oxidized to the corresponding *p*-quinones (**3f**, **g**) with excellent yields (entries 6, 7). The propanoate (**2h**) was converted to the corresponding quinone (**3h**) in quantitative yield (entry 8). Low solubility of the starting materials in CF_3CH_2OH–H_2O (1 : 2) required a change of the ratio of CF_3CH_2OH to H_2O (entries 9, 10). Anthraquinone (**5**) was obtained in high yield (entry 9), but the yield of 1,4-naphthoquinone (**7**) was low because of its low stability under the reaction conditions used for this study (entry 10). In all cases, **1** was recovered in good yield (75—85%), and can be used for oxidation again after recrystallization.

A possible catalytic cycle for this oxidation is as follows: The iodoarene (**1**) is oxidized by Oxone® to hypervalent species,[27,28,32,33] which oxidize *p*-dimethoxybenzene to give the *p*-quinone and an iodoarene at a lower oxidation stage. The latter would be re-oxidized by Oxone® to a hypervalent species.

Finally, we applied this reaction to synthesis of blattellaquinone (**9**),[7] the sex pheromone of the German cockroach, *Blattella germanica*, isolated in 2005 (Chart 3). Reaction of commercially available 2,5-dimethoxybenzyl alcohol with isovaleryl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and pyridine gave acylated product **8** in 95% yield. Oxidation of **8** with 0.05 eq of **1** and 4 eq of Oxone® in CF_3CH_2OH–H_2O (1 : 2) at room temperature for 1 h afforded pure **9**[34] in 98% yield without purification. The CAN oxidation of **8** under standard conditions gave **9** in 69% yield after silica gel column chromatography.[35]

In summary, a practical catalytic hypervalent iodine oxidation of *p*-dimethoxybenzene derivatives using **1** was developed. Reaction of *p*-dialkoxybenzenes (**2**) with a catalytic amount of **1** in the presence of Oxone® as a co-oxidant in CF_3CH_2OH–H_2O (1 : 2) gave the corresponding *p*-quinones (**3**) in excellent yields without purification. This procedure was applied to synthesis of blattellaquinone (**9**), the sex pheromone of the German cockroach, *Blattella germanica*.

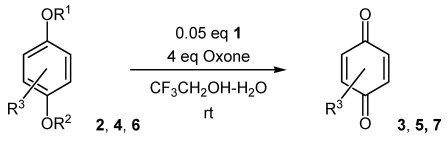
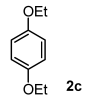
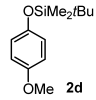
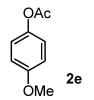
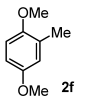
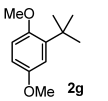
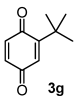
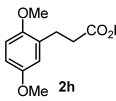
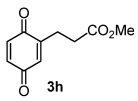
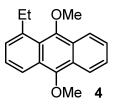
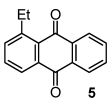
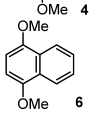
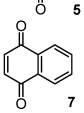


Chart 2

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

Entry	Dialkoxyarene	Quinone	Time (h)	Yield (%)
1[b]	**2a**	**3a**	1	Quant
2	 **2b**	 **3b**	1	86
3	 **2c**	**3b**	1	94
4	 **2d**	**3b**	1.5	79
5	 **2e**	**3b**	24	4[c]
6	 **2f**	 **3f**	0.5	89
7	 **2g**	 **3g**	1	Quant
8	 **2h**	 **3h**	1	Quant
9[d]	 **4**	 **5**	2	79
10[d]	 **6**	 **7**	1	34

a) Reactions were carried out using 0.05 eq of **1** and 4 eq of Oxone® in CF_3CH_2OH–H_2O (1 : 2) at room temperature. *b*) Same as entry 12, Table 1. *c*) Unreacted **2e** was recovered (96%). *d*) Reaction was carried out in CF_3CH_2OH–H_2O (2 : 1).

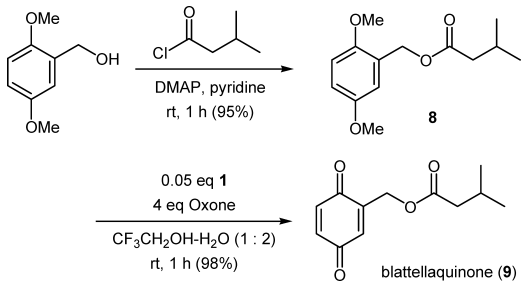


Chart 3

For synthesis of **9**, this catalytic oxidation was more efficient than the usual CAN oxidation.

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31) Typical reaction procedure: Compound **1** (0.050 mmol) was added to a solution of **2** (1.0 mmol) in CF_3CH_2OH–H_2O (1 : 2, 10 ml), followed by Oxone® (4 mmol) at room temperature, the resulting mixture was stirred at the same temperature. After **2** was consumed completely, as indicated by TLC, the mixture was diluted with ethyl acetate and washed with water. The organic layer was then washed with aqueous saturated sodium bicarbonate solution and dried, then concentrated to give pure **3**. If necessary, the product was purified using column chromatography on silica gel to give pure quinone. The alkaline solution was acidified by 10% hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium thiosulfate solution and dried, then concentrated to recover **1** (75—85%) which was purified by recrystallization from diethyl ether–hexane. All new compounds gave satisfactory spectrospecific data.
32) It remains unclear whether iodine(V) or iodine(III) species was formed during the reaction. The experiment of ^{1}H-NMR of a mixture of **1** and an excess Oxone® in CD_3CN–D_2O showed no presence of hypervalent iodine species.
33) Many reports for the formation of hypervalent iodine species by the oxidation of iodoarene with Oxone® have appeared.[36—41]
34) Compound **9**: yellow crystals, mp 46—47 °C (hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (6H, d, J=6.6 Hz), 2.07—2.22 (1H, m), 2.30 (2H, d, J=6.9 Hz), 5.00 (2H, d, J=1.9 Hz), 6.69 (1H, br q, J=2.0 Hz), 6.77 (1H, d, J=10.0 Hz), 6.80 (1H, dd, J=10.0, 1.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5 (2), 25.7, 43.1, 59.2, 131.3, 136.3, 136.4, 143.1, 171.9, 185.9, 186.7. IR (KBr) cm^{-1}: 1744, 1648. MS (EI) m/z: 222 (M^+). HR-MS (EI) m/z: 222.08822 (Calcd for $C_{12}H_{14}O_4$: 222.08921).
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