Efficient Synthesis of *p*-Quinols Using Catalytic Hypervalent Iodine Oxidation of 4-Arylphenols with 4-Iodophenoxyacetic Acid and Oxone®

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Efficient synthesis of *p*-quinols (2) using catalytic hypervalent iodine oxidation of 4-arylphenols (1) with 4-iodophenoxyacetic acid (3) and Oxone® was developed. Reaction of 1 with a catalytic amount of 3 in the presence of Oxone® as a co-oxidant in tetrahydrofuran or 1,4-dioxane–water gave the corresponding 2 in excellent yields.

Key words *p*-quinol; 4-iodophenoxyacetic acid; Oxone®; catalytic hypervalent iodine oxidation; 4-arylphenol

Development of efficient methods for synthesis of *p*-quinols is quite important in synthetic organic chemistry because they are structural components of numerous natural products[1—4] as well as pharmacologically active compounds[5—7] and useful synthetic intermediates.[8,9] A commonly used methods for preparation of *p*-quinols is 4-substituted phenol oxidation. Among many reported oxidants for the oxidation of phenols,[10—17] hypervalent iodine(III) oxidants such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) trifluoroacetate (PIFA) are typically used[18—21] because of the non-toxic nature of hypervalent iodine(III) reagents and the method's simplicity.[22—26] However, this approach often gives low yields of the desired product because of competitive oligomerization, especially in the case of oxidation of 4-arylphenols. For example, Felpin reported in 2007 that the oxidation of 4-phenylphenol (**1a**) with PIDA gave the corresponding *p*-quinol (**2a**) in 43% yield. In fact, PIFA caused much more complication than PIDA to reduce the yield to 17% (Chart 1).[27] We recently reported a catalytic hypervalent iodine oxidation of 4-alkoxyphenols to *p*-quinones using a catalytic amount of 4-iodophenoxyacetic acid (**3**) with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a co-oxidant.[28,29] This oxidation system has the following advantages. The reaction proceeds under mild conditions. Oxone® is an inorganic, water-soluble, commercially available, and inexpensive co-oxidant that has low toxicity.[30] Moreover, the solubility of **3** in alkaline solution makes its separation and recovery steps easier to carry out without a purification step. As part of our study for development of catalytic hypervalent iodine oxidations,[31—45] we report herein an efficient synthesis of *p*-quinols directly from 4-arylphenols using catalytic amount of **3** and Oxone® in tetrahydrofuran (or 1,4-dioxane)–water (Chart 2).

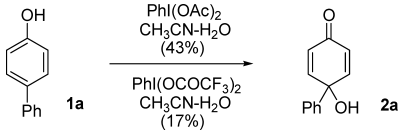
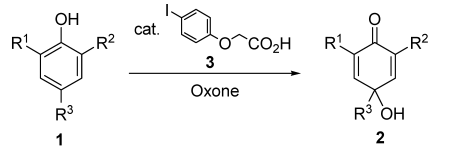


Chart 1

We first examined 4-phenylphenol (**1a**) as a model substrate (Table 1). Treatment of **1a** and 0.1 eq of **3** and 4 eq of Oxone® in acetonitrile–water (2 : 1) at room temperature for 24 h gave **2a** in only 38% yield. Addition of water shortened the reaction time, although yields were not improved (entries 2, 3). Next we investigated the solvent effect of other water-soluble organic solvent on the catalytic reactions. A similar reaction of **1a** in acetone–water (1 : 2) gave an almost identical result to that in acetonitrile–water (entry 4). Use of 2,2,2-trifluoroethanol (TFE), which is known to be an efficient solvent in catalytic hypervalent iodine reactions,[29,31,38] gave high yield (76%) of **2a**, but needed a longer reaction time (entry 5). However, it is interesting that an unfamiliar solvent in hypervalent iodine chemistry, tetrahydrofuran (THF) gave a better result than TFE did (entry 6). Use of 1,4-dioxane shortened the reaction time with a lower reaction yield (entry 7). When the reaction was conducted in a 1 : 5 mixture of THF–H_2O, the reaction was completed within 5 h. The best yield was obtained (entry 8). Further addition of water to the THF–H_2O solvent system was ineffective (entry 9). The catalytic oxidation proceeded even in water alone, but a longer reaction time, unfortunately, was required (entry 10). We then changed the amounts of **3** and Oxone® (entries 11—15). When the amount of Oxone® was reduced to 1 eq in a 1 : 5 mixture of THF–H_2O, the reaction was completed after 13 h to give 86% yield of **2a**. A similar reaction with 0.05 eq of **3** and 4 eq of Oxone® required 8 h to finish the reaction affording **2a** in 85% yield. When **1a** was treated with 0.025 eq of **3**



b: R^1=H, R^2=H, R^3=*p*-Me-C_6H_4
c: R^1=H, R^2=H, R^3=*p*-PivOCH_2-C_6H_4
d: R^1=H, R^2=H, R^3=*p*-Br-C_6H_4
e: R^1=H, R^2=H, R^3=*p*-CN-C_6H_4
f: R^1=Me, R^2=H, R^3=Ph
g: R^1=^{n}Pr, R^2=H, R^3=Ph
h: R^1=Ph, R^2=H, R^3=Ph
i: R^1=Br, R^2=H, R^3=Ph
j: R^1=R^2=R^3=Me

Chart 2

Table 1. Oxidation of **1a** with **3** and Oxone® *a)*

Entry	**3** (eq)	Oxone (eq)	Solvent	Time (h)	Yield of **2a** (%)
1	0.1	4	CH_3CN–H_2O (2 : 1)	24	38
2	0.1	4	CH_3CN–H_2O (1 : 1)	2.5	35
3	0.1	4	CH_3CN–H_2O (1 : 2)	1	43
4	0.1	4	Acetone–H_2O (1 : 2)	2	46
5	0.1	4	CF_3CH_2OH–H_2O (1 : 2)	12	76
6	0.1	4	THF–H_2O (1 : 2)	10	80
7	0.1	4	1,4-Dioxane–H_2O (1 : 2)	3	60
8	0.1	4	THF–H_2O (1 : 5)	5	89
9	0.1	4	THF–H_2O (1 : 10)	8	81
10	0.1	4	H_2O	16	54 (30) *b)*
11	0.1	1	THF–H_2O (1 : 5)	13	86
12	0.05	4	THF–H_2O (1 : 5)	8	85
13	0.025	4	THF–H_2O (1 : 5)	13	88
14	0.01	4	THF–H_2O (1 : 5)	24	53 (26) *b)*
15	None	4	THF–H_2O (1 : 5)	No reaction	

a) Reactions were carried out at room temperature. *b*) Parentheses are recovery of **1a**.

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Table 2. Catalytic Hypervalent Iodine Oxidation of *p*-Aryl Phenols (**1**)[a]

Entry	1	Solvent[b]	Time (h)	Yield (%)
1	**b**	A	16	67
2[c]	**c**	A	24	58
3	**c**	B	3	87
4	**d**	B	4	66
5[d]	**e**	B	8	48
6	**f**	B	5	43
7	**g**	B	4	77
8[d]	**h**	B	4	85
9[d]	**i**	A	7	79
10	**j**	B	2	75

a) Reactions were carried out using 0.05 eq of **3** and 4 eq of Oxone® at room temperature. *b*) A: THF–H_2O=1 : 5, B: 1,4-dioxane–H_2O=1 : 2. *c*) Reaction was carried out using 0.2 eq of **3**. *d*) Reaction was carried out using 0.1 eq of **3**.

and 4 eq of Oxone®, the reaction time was increased to 13 h (entry 13). Reaction using 0.01 eq of **3** was not finished after 24 h to afford **3a** in 53% yield along with 26% of recovered **1a** (entry 14). Reaction of **1a** with Oxone® in the absence of **3** did not occur (entry 15).[16]

Various 4-substituted phenols (**1b**—**j**) were oxidized with 0.05 eq of **3** and 4 eq of Oxone® to the corresponding *p*-quinols (Chart 2, Table 2).[46] When 4-(4-tolyl)phenol (**1b**) was treated with 0.05 eq of **3** and Oxone® in THF–H_2O (1 : 5) at room temperature, the reaction was finished within 16 h to give 67% of *p*-quinol (**2b**) (entry 1). A similar reaction of 4-(4-pivaloyloxymethylphenyl)phenol (**1c**) in THF–H_2O proceeded slowly to give 58% yield of the corresponding **2c** after 24 h stirring with 0.2 eq of **3**. In contrust, **1c** reacted more smoothly in 1,4-dioxane–H_2O (1 : 2) than in THF–H_2O to afford **2c** in 87% yield (entries 2, 3). Oxidation of 4-bromo derivative (**1d**) in 1,4-dioxane–H_2O gave the corresponding *p*-quinol (**2d**) in 66% yield (entry 4). 4-Arylphenol (**2e**) bearing the electron-withdrawing cyano group at the *para* position of 4-phenyl group showed lower reactivity to require 0.1 eq of **3** and longer reaction time, and to give **2e** in lower yield (entry 5). Similar reactions of **1f** and **1g** having alkyl groups at the *ortho* position in 1,4-dioxane–H_2O (1 : 2) afforded the corresponding **2f** and **2g** in 43 and 77% yields, respectively (entries 6, 7). Oxidation of 2,4-diphenylphenol (**1h**) with 0.1 eq of **3** and 4 eq of Oxone® was occurred only at the *para* position to produce *p*-quinol (**2h**) (entry 8). Also, 2-bromo-4-phenylphenol (**1i**) was oxidized at the *para* position to yield **2i** in 79% yield (entry 9). Reaction of 4-alkylphenol such as 2,4,6-trimethyl derivative (**1j**) was clean reaction, affording **2j** in 75% yield (entry 10).

In contrast to the oxidation of 4-alkylphenols with stoichiometric trivalent iodine compound to yield *p*-quinols,[18—21] oxidation by pentavalent iodines usually takes place at the *ortho* position of the phenols. Ranganathan and co-workers described that *N*-benzoyltyrosine methyl ester was reacted with 4-*tert*-butyliodylbenzene in refluxing toluene to give the corresponding *o*-quinone in 30% yield.[47] Oxidation with *o*-iodylbenzoic acid (IBX) also occurred at the *ortho* position, reported respectively by Pettus' group[48] and Quideau's group.[49,50] These results strongly suggested that a trivalent iodine species is generated *in situ* by **3** and Oxone®, it then oxidizes the phenols to produce *p*-quinols. Many reports in the literature have described oxidation of iodoarene with Oxone® to give iodine(V) compound.[44,45,51—57] However,

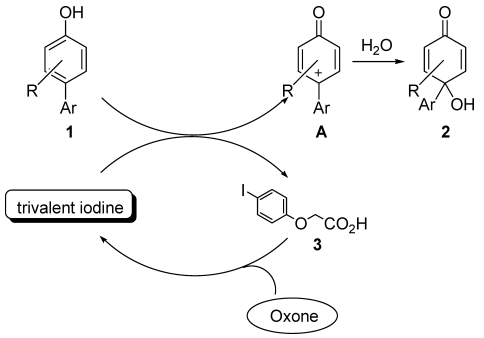

Chart 3

iodine(III) species might exist as an intermediate. A possible catalytic cycle for this oxidation is shown in Chart 3. Iodoarene would be oxidized by Oxone® to iodine(III) species.[58] The resultant trivalent iodine species reacts with 4-arylphenol to give cationic intermediate (**A**) stabilized by 4-aryl group and iodine(I) derivative, before its further oxidation to iodine(V) species. The intermediate (**A**) is then hydrolyzed to *p*-quinol. In the case of the reaction of **1e** having electron-withdrawing cyano group, the weaker stabilization of **A** is expected to decrease its reactivity to give low yield.

In summary, an efficient and practical method for the preparation of *p*-quinols using a novel catalytic hypervalent iodine oxidation of phenols with **3** and Oxone® was developed. Reaction of 4-arylphenols (**1**) with a catalytic amount of **3** in the presence of Oxone® as a co-oxidant in THF or 1,4-dioxane–water gave the corresponding *p*-quinols (**2**) in excellent yields.

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46) Typical reaction procedure for oxidation of 4-arylphenols **1**: Compound **3** (0.050 mmol) was added to a solution of **1** (1.0 mmol) in THF–water (1 : 5, 6 ml), followed by Oxone® (4 mmol) at room temperature. After **1** was completely consumed, 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, concentrated. The residue was purified by column chromatography on silica gel to give pure **2**. The alkaline solution was acidified by 10% hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried and concentrated to give recovered **3**, which can be used after recrystallization from diethyl ether-hexane. All new compounds gave satisfactory spectrospecific data.
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58) It remains unclear whether iodine(III) or iodine(V) species was formed during the reaction. The experiment of ^{1}H- and ^{13}C-NMR of a mixture of **3** and an excess Oxone® in CD_3CN–D_2O showed no presence of hypervalent iodine species.