An Efficient Catalytic Oxidation of *p*-Alkoxypenols to *p*-Quinones Using Tetrabutylammonium Bromide and Oxone®

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A catalytic oxidation of *p*-alkoxyphenols was developed using tetrabutylammonium bromide (TBAB) and Oxone®. The reaction of *p*-alkoxyphenol (1) with a catalytic amount of TBAB in the presence of Oxone® as a co-oxidant in acetonitrile–water (2 : 1) gave the corresponding *p*-quinone (2) in excellent yield without special treatment.

Key words *p*-alkoxyphenol; *p*-quinone; catalytic oxidation; tetrabutylammonium bromide; Oxone®

Development of efficient methods for the synthesis of *p*-quinones 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—6] Recently, we reported the catalytic hypervalent iodine oxidation of 4-alkoxyphenols to *p*-quinones by using a catalytic amount of 4-iodophenoxyacetic acid with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an environmentally benign, practical, and useful procedure for *p*-quinone synthesis[7,8] (Chart 1). The reaction proceeds readily under mild conditions. Oxone® is an inorganic, water-soluble, commercially available, and inexpensive oxidant that has low toxicity.[9] However, this procedure requires excess amount of Oxone® and the expensive 2,2,2-trifluoroethanol (TFE) as a co-solvent. When acetonitrile is used instead of TFE, the reaction requires much more catalyst and a longer reaction time. These drawbacks stimulated us to develop a more efficient catalytic oxidation of *p*-alkoxyphenols to *p*-quinones. Here, we wish to report that tetrabutylammonium bromide (TBAB) acts as an efficient alternative catalyst.

We first investigated the reaction of 4-methoxyphenol (**1a**) with a catalytic amount of 4-iodophenoxyacetic acid and Oxone® in a two-phase solvent system, according to Giannis' procedure.[10] Thus, the reaction was carried out in ethyl acetate and water in the presence of tetrabutylammonium hydrogensulfate. However, the reaction was not complete after 26 h, yielding only a trace amount of quinone. Next, TBAB was examined as an alternative phase-transfer catalyst. Interestingly, this reaction proceeded quickly, giving *p*-benzoquinone (**2a**) in moderate yield within only 15 min. This result indicated that the true oxidant would be formed by the reaction of TBAB with Oxone®, not the iodine compound. It is known that bromide is oxidized to form a bromonium ion, which can work as an oxidizing agent. For example, the reaction of benzylic alcohols with NaBr and Oxone® afforded the corresponding benzaldehydes,[11] the reaction of primary aliphatic alcohols with KBr (or TBAB) and Oxone® gave the corresponding symmetric esters,[12] the oxidation of benzylic alcohols with KBr and Oxone® under solar light provided the corresponding acids,[13] and the photo-catalytic oxidation of benzyl alcohols with TBAB and Oxone® in water produced aldehydes.[14] The oxidative halogenations of aromatic compounds using a halide and a suitable oxidant have studied extensively, and an excellent review was recently published.[15] However there has been no reports of the application to quinone synthesis. Therefore, we decided to investigate the reaction without 4-iodophenoxyacetic acid. Treatment of **1a** with 0.1 eq of TBAB in the presence of Oxone® in EtOAc and H_2O gave **2a** in good yield. The similar reaction in acetonitrile and water was complete within only 5 min to give **2a** in quantitative yield. Using either a combination of tetrabutylammonium hydrogensulfate and Oxone® or Oxone® alone[7,8] did not induce complete conversion of **1a** to **2a**. These observations suggest that the bromide ion must be essential for this oxidation.

Next, oxidation reactions of **1a** with several catalysts in the presence of Oxone® were investigated (Chart 2). In addition, the influences of the solvent systems and the amounts of catalyst and Oxone® were examined. The results are summarized in Table 1. When **1a** was reacted with 10 mol% of TBAB and 1 eq of Oxone® in CH_3CN–H_2O (2 : 1), the oxidation proceeded smoothly and was complete within 5 min to give pure **2a** in 91% yield without further purification (entry 1). The oxidation with NaBr as the supplier of the bromide ion was complete within 10 min (entry 3), whereas the reaction using KBr was not complete even after 24 h (entry 4). *N*-Bromosuccinimide (NBS), which serves as a bromonium ion, was also effective for the oxidation of **1a** (entry 5). Iodide compounds also catalyzed the oxidation, although they needed longer reaction times (entries 6, 7). Tetrabutylammonium chloride did not work as a catalyst (entry 8). TBAB was also effective in a 1 : 2 mixture of CH_3CN and H_2O (entry 9). The similar reaction with TBAB in tetrahydrofuran

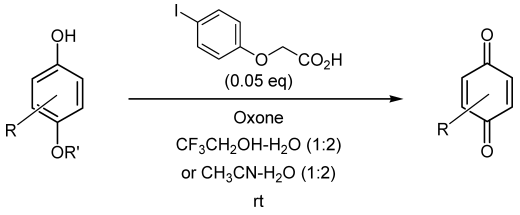

Chart 1

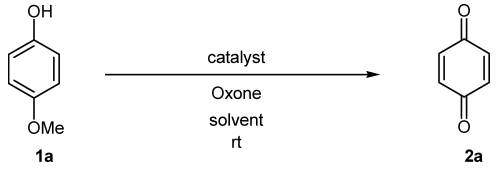

Chart 2

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Table 1. Oxidation of **1a** with Oxone in the Presence of Catalyst[a)]

Entry	Catalyst (mol%)	eq of Oxone	Solvent	Time (min)[b)]
1	*n*-Bu_4NBr (10)	1	CH_3CN–H_2O (2 : 1)	5
2	*n*-Bu_4NHSO_4 (10)	1	CH_3CN–H_2O (2 : 1)	>24 h
3	NaBr (10)	1	CH_3CN–H_2O (2 : 1)	10
4	KBr (10)	1	CH_3CN–H_2O (2 : 1)	>24 h[c)]
5	NBS (10)	1	CH_3CN–H_2O (2 : 1)	15
6	*n*-Bu_4NI (10)	1	CH_3CN–H_2O (2 : 1)	30
7	NaI (10)	1	CH_3CN–H_2O (2 : 1)	75
8	*n*-Bu_4NCl (10)	1	CH_3CN–H_2O (2 : 1)	>24 h[c)]
9	*n*-Bu_4NBr (10)	1	CH_3CN–H_2O (1 : 2)	5
10	*n*-Bu_4NBr (10)	1	THF–H_2O (2 : 1)	10
11	*n*-Bu_4NBr (10)	1	acetone–H_2O (2 : 1)	>24 h[c)]
12	*n*-Bu_4NBr (10)	1	TFE–H_2O (2 : 1)	>24 h[c)]
13	*n*-Bu_4NBr (1)	1	CH_3CN–H_2O (2 : 1)	5
14	*n*-Bu_4NBr (0.5)	1	CH_3CN–H_2O (2 : 1)	15
15	*n*-Bu_4NBr (0.4)	1	CH_3CN–H_2O (2 : 1)	130
16	*n*-Bu_4NBr (0.1)	1	CH_3CN–H_2O (2 : 1)	>24 h[c)]
17	*n*-Bu_4NBr (0.5)	0.7	CH_3CN–H_2O (2 : 1)	15
18	*n*-Bu_4NBr (0.5)	0.6	CH_3CN–H_2O (2 : 1)	50
19	*n*-Bu_4NBr (0.5)	0.5	CH_3CN–H_2O (2 : 1)	>24 h[c)]

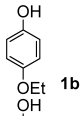
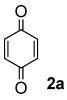
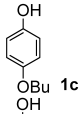
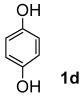
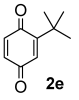
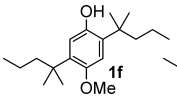
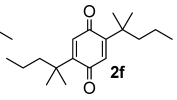
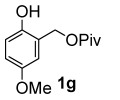
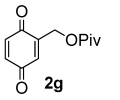
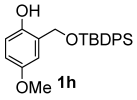
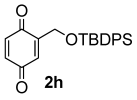
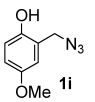
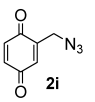
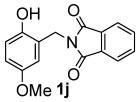
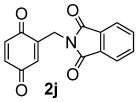
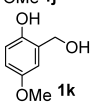
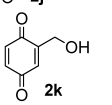
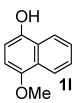
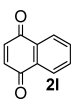
a) Reactions were carried out at room temperature. *b*) Starting **1a** was completely consumed within the indicated time. *c*) Reaction was not completed.

(THF) and water required a slightly longer reaction time than that in CH_3CN–H_2O (entry 10). Interestingly, it was found that neither TFE, the best co-solvent in catalytic hypervalent iodine oxidation,[8)] nor acetone was suitable for this oxidation (entries 11, 12). The minimum amounts of catalyst and oxidant necessary to achieve a satisfactory result can be identified as 0.5 mol% TBAB and 0.6 eq of Oxone® (entry 18).

A variety of *p*-alkoxyphenols (**1b**—**1l**) were oxidized with a catalytic amount of TBAB and 0.6 eq of Oxone® in CH_3CN–H_2O (2 : 1) to give the corresponding *p*-quinones. The results are presented in Table 2. The reactions of simple *p*-ethoxy- and *p*-butoxyphenols (**1b**, **c**) and hydroquinone (**1d**), respectively, gave **2a** in high yield (entries 1—3). This oxidation system was also effective for phenols bearing a bulky substituent at the *ortho* position (entries 4, 5). Ester, *tert*-butyldiphenylsilyloxy (TBDPSO), azide and succinimide groups were tolerable under the reaction conditions (entries 6—9). Because the TBAB–Oxone® system can oxidize benzylic alcohols to the corresponding carbonyl groups,[11—14,16)] it is interesting to clarify the chemoselectivity between phenol and alcohol. When 2-hydroxymethyl-4-methoxyphenol (**1k**) was treated with TBAB–Oxone® under the same conditions, the oxidation selectively occurred at the phenolic hydroxy group to give 2-hydroxymethyl-1,4-benzoquinone[17,18)] (**2k**) in high yield (entry 10). The naphthol derivative (**1l**) reacted to give naphthoquinone (**2l**) in excellent yield (entry 11). However, oxidation of electron-poor phenols such as **3** did not work. The reactions of *p*-methylphenol (**4**), and *p*-dimethoxybenzene (**5**) gave complex mixtures due to bromination of the aromatic ring, in contrast to the catalytic hypervalent iodine oxidations[19—21)] (Fig. 1).

A possible catalytic cycle for this oxidation is as follows: The bromide ion from TBAB is oxidized by $KHSO_5$ included in Oxone® to form a bromonium ion[11—14)] which oxidizes **1** to give **2** with removal of the bromide ion. This would be re-oxidized by $KHSO_5$ to further form a bromonium ion, which is used in the next oxidation (Chart 3).

Table 2. Catalytic Oxidation of **1** with *n*-Bu_4NBr and Oxone[a)]

Entry	Phenol	Quinone	*n*-Bu_4 NBr (mol%)	Time (min)	Yield (%)
1	 **1b**	 **2a**	0.5	60	92
2	 **1c**	**2a**	0.5	60	92
3	 **1d**	**2a**	0.5	40	91
4	 **1e**	 **2e**	2	35	99
5	 **1f**	 **2f**	2	5	quant.
6	 **1g**	 **2g**	1	20	98
7	 **1h**	 **2h**	3	45	95
8	 **1i**	 **2i**	1	55	95
9	 **1j**	 **2j**	1	30	95
10	 **1k**	 **2k**	2	5	96
11	 **1l**	 **2l**	5	60	quant.

a) Reactions were carried out using 0.6 eq of Oxone at room temperature.

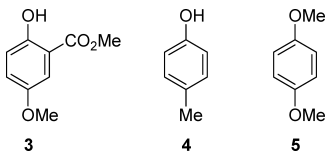


Fig. 1. Other Phenol Derivatives (**3**—**5**)

In summary, an efficient catalytic oxidation of *p*-alkoxyphenols was developed using TBAB and Oxone®. Reaction of *p*-alkoxyphenol (**1**) with a catalytic amount (0.5—5 mol%) of TBAB in the presence of 0.6 eq of Oxone® as a co-oxidant in acetonitrile–water (2 : 1) gave the corresponding *p*-quinone (**2**) in excellent yield without special treatment. This reaction proved to be one of the best and environmentally benign procedures for the synthesis of *p*-quinones from *p*-alkoxyphenols.

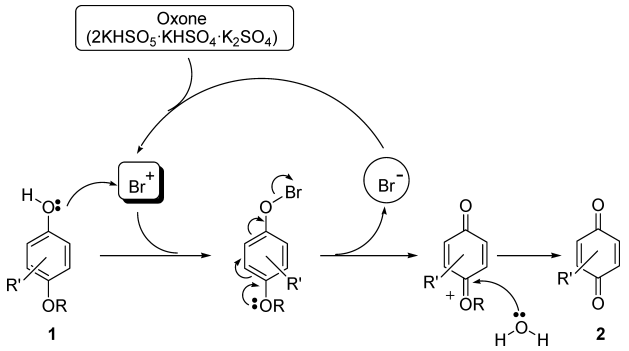


Chart 3

Experimental

Melting points are uncorrected. IR spectra were recorded using JASCO FT/IR-460 Plus spectrophotometer. ^{1}H-NMR spectra were determined with Varian Gemini 300 (300 MHz) spectrometers, tetramethylsilane as an internal standard. TBAB and Oxone® were purchased from Aldrich and Wako Pure Chemical Industries, Ltd., respectively. Both were used as received. Phenols (**1a**—**f**, **k**) and 4-methoxy-1-naphthol (**1l**) were commercially available. Other phenols (**1g**—**j**) were prepared by the usual methods.[8] The resulting *p*-quinones (**2a**—**j**) were directly identical to authentic samples prepared by our previous reported hypervalent iodine oxidation of the corresponding *p*-alkoxyphenols.[8]

TBAB Catalyzed Oxidation of 1a, General Procedure A suspension of **1a** (124 mg, 1 mmol), TBAB (1.5 mg, 0.005 mmol) and Oxone® (368 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) was stirred at room temperature for 50 min. The mixture was diluted with ethyl acetate and washed with water, dried, and concentrated to give pure 1,4-benzoquinone (**2a**) (98 mg, 91%) as yellow crystals.

TBAB Catalyzed Oxidation of 1b Following the general procedure, **1b** (138 mg, 1 mmol) was treated with TBAB (1.5 mg, 0.005 mmol) and Oxone® (368 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) to give **2a** (99 mg, 92%) as yellow crystals.

TBAB Catalyzed Oxidation of 1c Following the general procedure, **1c** (166 mg, 1 mmol) was treated with TBAB (1.5 mg, 0.005 mmol) and Oxone® (368 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) to give **2a** (99 mg, 92%) as yellow crystals.

TBAB Catalyzed Oxidation of 1d Following the general procedure, **1d** (110 mg, 1 mmol) was treated with TBAB (1.5 mg, 0.005 mmol) and Oxone® (368 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) to give **2a** (98 mg, 91%) as yellow crystals.

TBAB Catalyzed Oxidation of 1e Following the general procedure, **1e** (180 mg, 1 mmol) was treated with TBAB (6.5 mg, 0.02 mmol) and Oxone® (368 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) to give 2-*tert*-butyl-1,4-benzoquinone (**2e**) (162 mg, 99%) as orange crystals.

TBAB Catalyzed Oxidation of 1f Following the general procedure, **1f** (90 mg, 0.31 mmol) was treated with TBAB (2 mg, 0.0062 mmol) and Oxone® (114 mg, 0.19 mmol) in CH_3CN–H_2O (2 : 1, 0.75 ml) to give 2,5-bis-(1,1-dimethylbutyl)-1,4-benzoquinone (**2f**) (86 mg, quant.) as orange crystals.

TBAB Catalyzed Oxidation of 1g Following the general procedure, **1g** (120 mg, 0.5 mmol) was treated with TBAB (1.6 mg, 0.005 mmol) and Oxone® (185 mg, 0.3 mmol) in CH_3CN–H_2O (2 : 1, 1.25 ml) to give 3,6-dioxocyclohexa-1,4-dienylmethyl 2,2-dimethylpropanoate (**2g**) (110 mg, 98%) as yellow crystals.

TBAB Catalyzed Oxidation of 1h Following the general procedure, **1h** (80 mg, 0.2 mmol) was treated with TBAB (1.9 mg, 0.006 mmol) and Oxone® (73 mg, 0.12 mmol) in CH_3CN–H_2O (2 : 1, 0.5 ml) to give 2-(*tert*-butyldiphenylsilyloxymethyl)-1,4-benzoquinone (**2h**) (73 mg, 95%) as yellow solid.

TBAB Catalyzed Oxidation of 1i Following the general procedure, **1i** (100 mg, 0.56 mmol) was treated with TBAB (1.8 mg, 0.0056 mmol) and Oxone® (209 mg, 0.64 mmol) in CH_3CN–H_2O (2 : 1, 1.4 ml) to give 2-azidomethyl-1,4-benzoquinone (**2i**) (86 mg, 95%) as yellow needles.

TBAB Catalyzed Oxidation of 1j Following the general procedure, **1j** (28 mg, 0.1 mmol) was treated with TBAB (0.3 mg, 0.001 mmol) and Oxone® (37 mg, 0.06 mmol) in CH_3CN–H_2O (2 : 1, 0.25 ml) to give 2-(3,6-dioxocyclohexa-1,4-dienylmethyl)isoindole-1,3-dione (**2j**) (25 mg, 95%) as yellow needles.

TBAB Catalyzed Oxidation of 1k Following the general procedure, **1k** (105 mg, 0.68 mmol) was treated with TBAB (4.4 mg, 0.012 mmol) and Oxone® (252 mg, 0.41 mmol) in CH_3CN–H_2O (2 : 1, 2 ml) to give 2-hydroxymethyl-1,4-benzoquinone (**2k**) (90 mg, 96%) as yellow crystals, mp 76—77 °C (CH_2Cl_2–hexane) (lit.[17] 76—77 °C). IR (KCl) cm^{-1}: 1655, 1640, 1590. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (1H, br s), 4.56 (2H, d, J=2 Hz), 6.7—6.9 (3H, m).

TBAB Catalyzed Oxidation of 1l Following the general procedure, **1l** (174 mg, 1 mmol) was treated with TBAB (16 mg, 0.05 mmol) and Oxone® (369 mg, 0.6 mmol) in CH_3CN–H_2O (2 : 1, 2.5 ml) to give 1,4-naphthoquinone (**2l**) (168 mg, quant.) as yellow crystals, which was directly identical to the commercial sample supplied by Tokyo Chemical Industry (TCI) Co., Ltd.

References and Notes

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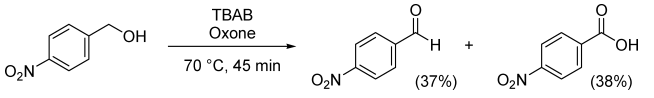

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