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Catalytic Oxidation of Phenols to *p*-Quinones with the Hydrogen Peroxide and Methyltrioxorhenium(VII) System

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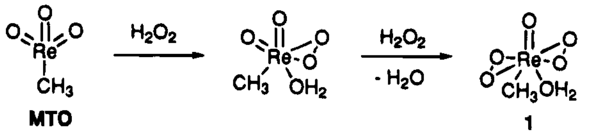
Introduction

It is well-known that quinones possess pronounced bioactivity[1] and, consequently, are important for medicine.[2] For example, 2-methyl-1,4-naphthoquinone, vitamin K_3, constitutes an important additive in animal feed, which is used commercially in large quantities. Furthermore, alkyl-substituted *p*-benzoquinones serve as useful dienophiles in Diels–Alder reactions and are versatile starting materials in the synthesis of many natural products. Thus, trimethyl-*p*-benzoquinone and 2,3-dimethoxy-5-methyl-*p*-benzoquinone are especially valuable starting materials for the synthesis of vitamin E and coenzyme Q.[3]

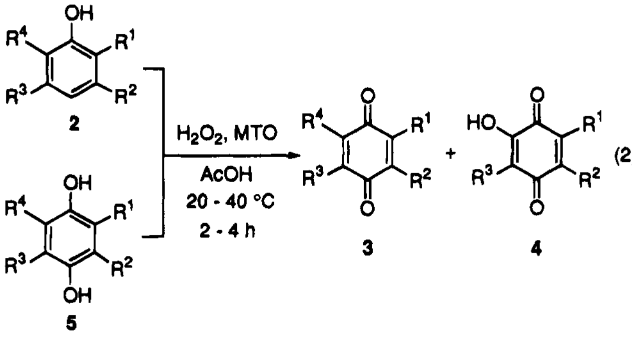
Since many substituted phenols are readily available and usually quite inexpensive, they serve as desirable starting materials for the synthesis of *p*-benzoquinones, which constitute important oxidations in organic synthesis. When hydrogen peroxide is employed as oxidant, activation is normally required, which is generally accomplished by transition metal catalysts. A novel catalyst,[4] potentially useful for this purpose, is methyltrioxorhenium(VII) (CH_3ReO_3, MTO), which is stepwise converted by hydrogen peroxide (eq 1) into the mono- and bis(peroxo)rhenium complex $CH_3Re(O_2)_2O{\bullet}H_2O$ (**1**). The latter one has been isolated and fully characterized by X-ray crystallography,[4a] and it exhibits high activity and selectivity in the epoxidation of olefins[4,5] and more recently for the oxidation of arenes to quinones.[6] In the latter case, for other oxidation systems,[7] mono- and dihydroxy arenes were proposed as intermediates. Consequently, we applied the novel H_2O_2/MTO oxidant to hydroxy arenes and provide herein a convenient catalytic oxidation procedure for the preparation of *p*-quinones.



(1)

Results and Discussion

The results of the MTO-catalyzed oxidation of phenols and naphthols **2** to quinones **3** and **4** with H_2O_2 in acetic acid (eq 2) are summarized in Table 1. Thus, in the presence of catalytic amounts of MTO (2 mol %), the corresponding *p*-quinones **3a-l** were obtained in fair to high yields. In a control experiment without MTO the oxidation was very slow. For example, less than 10% of the quinone was obtained after 4 h at 40 °C in the oxidation of 2,3,6-trimethyl- or 2,6-dimethylphenol. Consequently, MTO is necessary for the oxidation. Furthermore, under the conditions of the H_2O_2/MTO/AcOH oxidation, the quinones **3** were quite stable, as confirmed for 2-methyl-1,4-naphthoquinone or trimethyl- and 2,6-dimethyl-*p*-benzoquinones, which were recovered in over 93% after 4 h at 40 °C. Therefore, hydroxy-substituted *p*-quinones **4** (overoxidation products) are not derived from further oxidation of the *p*-quinones **3**.



(2)

	R^1	R^2	R^3	R^4
2 - 5a	Me	Me	Me	H
2b	Me	Me	H	Me
2, 3c	Me	Me	H	H
2 - 4d	Me	H	Me	H
2 - 4e	*i*Pr	H	Me	H
2f	Me	H	H	Me
2g	*t*Bu	H	H	*t*Bu
2 - 5h	H	Me	Me	H
2 - 4i	H	*t*Bu	*t*Bu	H
2, 3j	Me	H	H	H
2, 3k	H	Me	H	H
2, 3l	H	H	H	H
2 - 5m	-CH:CHCH:CH-		H	H
2, 3, 5n	-CH:CHCH:CH-		H	Me
2, 3o	-CH:CHCH:C(OH)-		H	H
3, 5p	Me	Me	Me	Me

The reaction temperature has a pronounced effect on the oxidation since at higher temperature higher conversion at little lower selectivity were obtained (Table 1, entries 8 and 10). When a larger number of equivalents (Table 1, entries 8 and 9) and higher concentrations of hydrogen peroxide (Table 1, entries 8 and 11) were employed, better conversions of the phenol **2g** and higher yields of the quinone **3g** were achieved. Apparently,

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Table 1. MTO-Catalyzed Oxidation of Alkyl-Substituted Phenols to *p*-Quinones and Hydroxyquinones by H_2O_2[a]

entry	phenol	H_2O_2 (%) (equiv)	temp (°C)	time (h)	convn (%)	yield[b] (%)	
						3[c]	**4**[d]
1	**2a**	83 (5)	40	2	100	70	3
2	**2b**	83 (5)	20	2	100	50	2
3	**2c**	83 (5)	40	2	100	36	
4	**2d**	83 (5)	40	2	100	45	3
5	**2e**	83 (5)	40	2	100	4	8
6[e]	**2f**	83 (10)	40	4	95	50 (53)	5 (5)
7[f]	**2f**	35 (5)	40	4	54	25 (46)	11 (21)
8	**2g**	83 (5)	40	4	86	63 (74)	7 (8)
9	**2g**	83 (10)	40	4	92	68 (74)	2 (2)
10	**2g**	83 (5)	20	4	58	45 (77)	11 (19)
11	**2g**	35 (5)	40	4	58	41 (71)	9 (15)
12	**2h**	83 (5)	40	2	100	43	7
13	**2h**	83 (5)	20	2	87	39 (45)	10 (11)
14[g]	**2i**	83 (5)	40	4	81	9 (11)	2 (2)
15	**2j**	83 (10)	40	4	93	42 (45)	
16	**2k**	83 (5)	40	2	100	24	
17	**2l**	83 (10)	40	4	85	31 (37)	
18	**2m**	83 (5)	20	2	100	57	
19	**2n**	83 (5)	20	2	100	74	6
20	**2o**	83(5)	20	2	100	41	

[a] Reaction conditions: mol ratio **2**:MTO = 1:0.02, acetic acid as solvent, N_2 atmosphere. [b] Yield of isolated product; in parentheses are given the yields corrected for converted starting material. [c] **3b** ≡ **3a**, **3f** ≡ **3h**, **3g** ≡ **3i**. [d] **4b** ≡ **4a**, **4f** ≡ **4h**, **4g** ≡ **4i**, **4n** is 2-methyl-3-hydroxynaphthoquinone. [e] Also 23% Diels–Alder dimer **6f** was obtained. [f] Also 17% Diels–Alder dimer **6f** was obtained. [g] Also 5% anhydride **7i** was obtained.

water retards the H_2O_2/MTO/AcOH oxidation system, and therefore, the use of concentrated hydrogen peroxide is advantageous.

As previously reported,[6] MTO is a strong Lewis acid and catalyzes the formation of peroxyacetic acid between AcOH and H_2O_2. Therefore, a control experiment was conducted to assess how effectively authentic peroxyacetic acid oxidizes phenol **2a** to the quinone **3a** and the hydroxyquinone **4a** under the H_2O_2/MTO/AcOH oxidation conditions. Since only <10% quinone **3a** was produced from 2,3,6-trimethylphenol (**2a**) and at a significantly lower reaction rate than with H_2O_2/MTO/AcOH oxidation system, it is concluded that the bis(peroxo)rhenium complex **1** constitutes the dominant active species in the present phenol oxidation. That bis(peroxo)complex **1** oxidizes phenols to quinones has been confirmed by a control experiment for derivative **2a**, for which stoichiometric amounts (**2a**:**1** = 1:3.6) of the isolated complex **1** afforded the quinone **3a** in high yield (> 90%).

As expected from the electrophilic H_2O_2/MTO/AcOH oxidant, the more electron-rich phenol, the higher the oxidation rate as expressed by the extent of conversion of the aromatic substrate (Table 1). This is evident in the oxidation of 2,3,6-trimethylphenol (**2a**) *versus* the parent phenol **2l** (Table 1, entries 1 and 17) for which under otherwise identical conditions double reaction time was necessary for 85% conversion compared to 100% for the trimethylphenol **2a**. A more direct comparison offers 2,3,5-trimethylphenol (**2b**) *versus* 3,5-dimethylphenol (**2h**), *cf.* entries 2 and 13 in Table 1, which under the same conditions proceed in 100% and 87% conversion. Furthermore, comparison of the phenols **2a,f,j,l** (Table 1, entries 1, 6, 15, and 17) reveals that better yields of quinone are obtained with a higher degree of methyl substitution, *i.e.*, **2a** > **2f** > **2j** > **2l**.

It is worthy of note that under the same reaction conditions, almost the same extent of conversion was obtained for 2,6-dimethyl- (**2f**) and 2,6-di-*tert*-butylphenol (**2g**) by the H_2O_2/MTO/AcOH oxidant (Table 1, entries 6 and 9, 7 and 11). These results indicate that the oxidation of 2,6-dialkyl-substituted phenols is not sensitive to steric effects of the alkyl substituents. Thus, it seems that the hydroxy group of the phenol is not attacked first by the bis(peroxo)rhenium complex **1** since steric effects would be expected.

Some phenols gave the hydroxylated *p*-benzoquinone **4** as byproducts (Table 1). Since the latter were not formed by overoxidation of the corresponding quinone **3** (control experiment), the hydroquinones **5** may serve as likely intermediates. As anticipated, the oxidation of the hydroquinones **5a,h,m,n,l** (for structures cf. eq 2) by H_2O_2 in the presence of MTO (2 mol %) in AcOH led to high yields (90–100%) of quinones **3**, but also some hydroxylated quinones **4** (8–9%) were obtained, except in the case of 2,3,5,6-tetramethylhydroquinone (**5p**). For the latter, all remaining positions are blocked by methyl groups and the quinone **3p** is produced quantitatively.

H_2O_2/MTO is a powerful epoxidizing agent for olefins,[4,5] and therefore, a plausible mechanism, which involves as the initial step arene oxide formation, is proposed in Scheme 1. We suggest that the first oxidation step may afford the two arene oxides **A** and **B**. Since the major products in the oxidation of the phenols **2** are the quinones **3** (Table 1), formation of the intermediary epoxide **A** dominates presumably for steric reasons. Acid-catalyzed isomerization to the hydroquinone **5** and subsequent oxidation affords the quinones **3** and **4**, again through arene oxides.

Evidence for the formation of arene oxide **B** is provided by the minor products observed in the oxidation of 2,6-dimethylphenol (**2f**) and 3,5-di-*tert*-butylphenol (**2i**), namely the quinol dimer **6f** and the muconic anhydride **7i** (Table 1, entries 6, 7 and 14). As shown in Scheme 1, the hydroxy epoxide **B** derived from phenol **2f** should open up spontaneously to its *o*-quinol, which is known to dimerize.[8] In the case of phenol **2i**, the catechol derivative is formed accordingly, and its further oxidation[9] through the *o*-quinone affords the anhydride **7i**. A control experiment with the authentic *o*-quinone gave quantitatively **7i** under the conditions of the H_2O_2/MTO/AcOH oxidation.

In summary, MTO-catalyzed oxidation of hydroxy-substituted arenes **2** by 83% aqueous hydrogen peroxide in acetic acid affords the corresponding *p*-quinones **3** in rather high yield, in which the bis(peroxo)rhenium complex **1** plays the dominant role as the active oxidant. The present catalytic method compares well with those reported in the literature for the oxidation of 2,6-dimethyl- and 2,3,6-trimethylphenols to their *p*-quinones (Table 2) and constitutes a convenient and novel direct synthesis of *p*-quinones from phenols under environmentally acceptable conditions.

Experimental Section

Methyltrioxorhenium(VII) and methyl bis(peroxo)rhenium (**1**) were prepared according to the previously reported methods.[4,10]

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Scheme 1

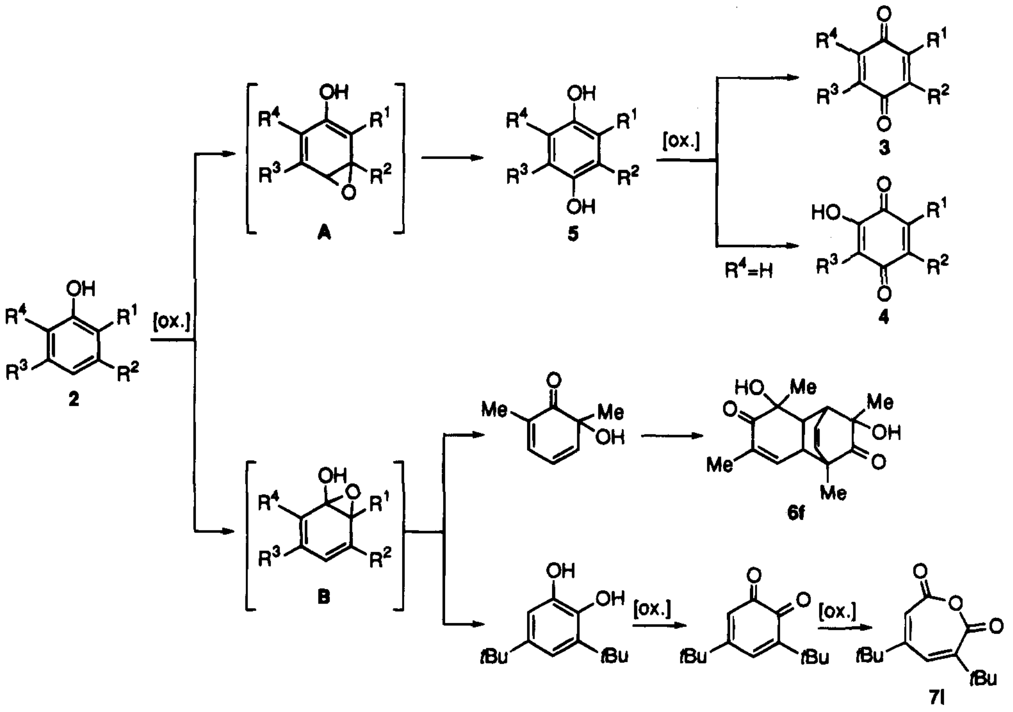

Table 2. Oxidation of Phenols 2a,f to Benzoquinones 3a,f with H_2O_2 Catalyzed by Transition Metal Compounds

entry[a]	phenol	catalyst	solvent	temp (°C)	time (h)	convn (%)	quinone	yield (%)	ref
1	**2a**	$RuCl_3$	H_2O	r.t.	<5	99	**3a**	90	11
2	**2a**	$H_3PMo_{12}O_{40}$	AcOH	30	5	100	**3a**	78	12
3	**2a**	CH_3ReO_3	AcOH	40	2	100	**3a**	70	b
4	**2f**	$TiCl_3$	AcOH	60	4–5		**3f**	51	13
5	**2f**	$H_3PMo_{12}O_{40}$	AcOH	30	5	51	**3f**	25	12
6	**2f**	CH_3ReO_3	AcOH	40	4	95	**3f**	53[c]	b

[a] Best runs were chosen except entries 3 and 5. [b] This work (Table 1, entry 1 and 6). [c] Corrected for converted starting phenol.

2,6-Dimethyl-1,4-benzenediol[14] and 2,3,5,6-tetramethyl-1,4-benzenediol[15] were obtained by the literature method. All other reagents were purchased from standard chemical suppliers and purified before use when not of analytical quality. H_2O_2 (83%) was purchased from Peroxid-Chemie GmbH, Pullach bei München, Germany.

Caution! *Concentrated H_2O_2 is potentially explosive. Appropriate safety precautions must be taken such as working in the hood behind a safety shield.*

IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. UV–vis spectra were taken on a Hitachi U-3200 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Bruker AC 250 spectrometer. The melting points were determined on a Büchi SMP melting point apparatus.

General Procedure for the Oxidation of Arenes. To a solution of the particular arene (1.0 mmol) and methyltrioxorhenium(VII) (0.02 mmol) in the appropriate solvent (2 mL) was added 35% or 83% aqueous hydrogen peroxide (3.0–5.0 mmol). The reaction mixture was stirred at the desired temperature (20–40 °C) under a nitrogen gas atmosphere for the specified time (2 or 4 h). It was then diluted with 5 mL of water and subsequently extracted with methylene chloride (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure (ca. 20–40 °C/20 Torr). The oxidation products were separated by flash column chromatography on silica gel (32–63 μm mesh), identified by comparison with their reported physical and spectral data. The quantitative product data (Table 1) were determined by ^1H NMR analysis.

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