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# Oxidation of methoxybenzenes to *p*-benzoquinones catalyzed by methyltrioxorhenium(VII)

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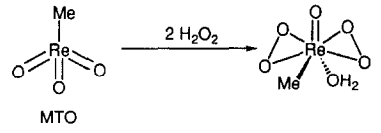
**Abstract**

Methoxy-substituted benzenes **1** are oxidized with aqueous hydrogen peroxide catalyzed by methyltrioxorhenium(VII) in acetic acid to yield the *p*-benzoquinones **3** in moderate yields. An intermediary diperoxo rhenium(VII) complex rather than peracetic acid is the dominating oxidizing species, since oxidation also proceeds in ethanol under peracid-free conditions. Acid played an important role, especially in the oxidation of *p*-methoxyphenols **2** to *p*-benzoquinones **3**. An arene oxide mechanism is postulated for the formation of *p*-benzoquinones, which would account for the participation of the acid and also overoxidation by cleavage of the arene oxide ring with hydrogen peroxide.

*Keywords*: Arene oxide ; *p*-Benzoquinone; Hydrogen peroxide; Methyltrioxorhenium; Oxidation; Peroxo complex

## 1. Introduction

Rhenium complexes were considered to be inactive in the oxidation of olefins [1] until the catalytic activity of methyltrioxorhenium ($CH_3ReO_3$, MTO) for the epoxidation of olefins by hydrogen peroxide was discovered [2]. $CH_3ReO_3$ forms with two equivalents of hydrogen peroxide a diperoxo complex (Scheme 1) whose structure was rigorously established by X-ray analysis [3]. It was confirmed that the isolated diperoxo rhenium complex $CH_3Re(O_2)_2O \cdot H_2O$ is the active species in olefin epoxidation.




Scheme 1.

$CH_3ReO_3$ also effectively catalyzes olefin metathesis [4], and aldehyde olefination [5]. However, its application for the catalytic oxidation of electron-rich arenes remained unexplored. Such *p*-benzoquinones, especially the alkoxy-substituted ones, are important for pharmaceutical purposes. For example, 2,3-dimethoxy-5-methyl-*p*-benzoquinone is a key intermediate in the synthesis of Coenzyme Q [6,7].

In view of our interest in the synthesis of *p*-benzoquinones by oxidation of arenes or phenols with peroxo compounds [7], we have now oxi-

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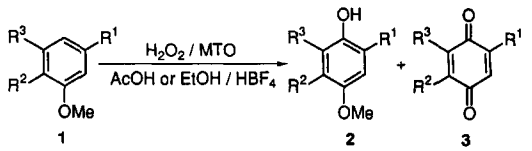
dized arenes with aqueous hydrogen peroxide catalyzed by $CH_3ReO_3$. Analogous to polycyclic arenes, [8] we show that the $CH_3ReO_3/H_2O_2$ system is also an effective oxidant for the electron-rich methoxybenzenes.

## 2. Results and discussion

The $CH_3ReO_3/H_2O_2$ oxidations of the methoxybenzenes **1a–d** (Scheme 2) were carried out in acetic acid in analogy to reported arene to quinone transformations [6]. The results in Table 1 (entries 1–4) show that the corresponding benzoquinones **3a–d** can be obtained in fair yields (30–60% based on converted starting material). The problem is overoxidation, presumably due to water-soluble, ring-opened products, as revealed by the poor mass balances (30–75%) even at partial consumption of the starting arene, e.g., arene **1d** (entry 4, Table 1). This substrate was investigated in greater detail.




| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | Me | MeO | H |
| b | Me | H | MeO |
| c | MeO | Me | MeO |
| d | Me | MeO | MeO |

Scheme 2.

In the presence of catalytic amounts of $CH_3ReO_3$ (MTO), 1,2,3-trimethoxy-5-methylbenzene (**1d**) affords 2,3-dimethoxy-5-methyl-*p*-benzoquinone (**3d**) in fair yield (entries 4 and 5, Table 1), along with a small amount of 2,3,4-trimethoxy-6-methylphenol (**2d**). The oxidation did not proceed without $CH_3ReO_3$ (control experiment). When a large amount of aqueous hydrogen peroxide was used, the yield of the *p*-benzoquinone **3d** decreased (compare entries 4 and 5). Water seems to retard the oxidation.

Table 1
Oxidation of methoxy-substituted benzenes to *p*-benzoquinones by $H_2O_2$ in the presence of MTO as catalyst [a]

| Entry | Substrate | $H_2O_2$ | | Solvent | Time | Conv. | m.b. [b] | Yield [c] (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % | equiv. | | (h) | (%) | (%) | **2** | | **3** | |
| 1 | **1a** | 35 | 5.0 | AcOH | 4 | 43 | 75 | – | | 19 | (43) |
| 2 [d] | **1b** | 85 | 2.5 | AcOH | 1 | 100 | 60 | – | | 46 | (46) |
| 3 | **1c** | 85 | 5.0 | AcOH | 1 | 99 | 35 | – | | 34 | (34) |
| 4 | **1d** | 35 | 5.0 | AcOH | 1 | 65 | 66 | 3 | (5) | 28 | (43) |
| 5 | **1d** | 35 | 2.5 | AcOH | 1 | 69 | 73 | 1 | (1) | 41 | (59) |
| 6 | **1d** | 85 | 5.0 | AcOH | 1 | 98 | 60 | 1 | (1) | 57 | (59) |
| 7 [e] | **1d** | 35 | 2.5 | EtOH–$HBF_4$ | 4 | 50 | 85 | 1 | (2) | 33 | (67) |
| 8 [e,f] | **1d** | 35 | 2.5 | EtOH | 4 | 27 | 90 | 15 | (55) | 2 | (9) |
| 9 [e,g] | **1d** | 35 | 2.5 | EtOH–$HBF_4$ | 4 | 15 | 94 | 6 | (39) | 3 | (19) |
| 10 [e] | **1d** | 3.5 | 2.5 | EtOH–$HBF_4$ | 4 | 58 | 77 | 9 | (16) | 29 | (50) |
| 11 [e] | **1d** | 35 | 2.5 | EtOH–$HBF_4$ | [h] | 90 | 60 | – | | 51 | (56) |
| 12 [f,g,i] | **2d** | 35 | 2.5 | EtOH | 4 | 10 | 96 | – | | 6 | (58) |
| 13 [f,i] | **2d** | 35 | 2.5 | EtOH | 4 | 51 | 71 | – | | 22 | (43) |
| 14 [i] | **2d** | 35 | 2.5 | EtOH–$HBF_4$ | 4 | 95 | 84 | – | | 79 | (83) |

[a] Reaction conditions: 1 mmol substrate; 0.02 mmol MTO; 5 ml AcOH; room temperature; $N_2$.
[b] Mass balance of recovered substrate and products **2** and **3**.
[c] The yields in parentheses are corrected for converted starting material.
[d] 2-Hydroxy-5-methoxy-3-methyl-*p*-benzoquinone was obtained in 14% yield.
[e] Reaction conditions: 0.8 mmol substrate; 0.016 mmol MTO; 3 ml EtOH; 1 ml $HBF_4$ (54% in diethyl ether); room temperature; $N_2$.
[f] In the absence of acid.
[g] In the absence of MTO.
[h] After 4 h, a new batch of MTO (0.016 mmol) was added and the reaction was carried out for an additional 4 h.
[i] Reaction conditions: 0.5 mmol substrate; 0.01 mmol MTO, 2 ml EtOH; 0.65 ml $HBF_4$ (54% in dicthyl ether); room temperature; $N_2$.

Therefore, the use of 85% hydrogen peroxide is advantageous, which gave both a higher conversion of arene **1d** and a better yield of benzoquinone **3d** (entry 6). Larger amounts of $CH_3ReO_3$ improved the yields, especially if administered in several batches, which implies that the catalyst decomposes during oxidation.

Since the $CH_3ReO_3/H_2O_2$ oxidations were carried out in acetic acid and the peroxo rhenium complex $CH_3Re(O_2)_2O\cdot H_2O$ constitutes a relatively strong Lewis acid, the possibility needed to be tested whether in situ-formed peracetic acid also serves as an oxidizing agent. When arene **1d** was treated with 2.5 equiv. of 40% peracetic acid in acetic acid at room temperature for 1 h, the *p*-benzoquinone **3d** was obtained (22% yield at 41% conversion) but at a significantly lower reaction rate than with the $CH_3ReO_3/H_2O_2$ oxidation system.

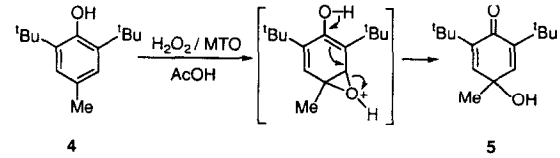
To avoid the formation of peracetic acid, $CH_3ReO_3/H_2O_2$ oxidations were performed in ethanol instead of acetic acid as the solvent. A control experiment (permanganate titration [9]) confirmed that no peracetic acid was formed when a hydrogen peroxide solution in ethanol in the presence of MTO was stirred at room temperature for 4 h. Under these peracid-free conditions, the $CH_3ReO_3/H_2O_2$ oxidation of arene **1d** in ethanol in the presence of tetrafluoroboric acid (54% in diethyl ether) gave the *p*-benzoquinone **3d** in moderate yield (entry 7). The oxidation was very slow in the absence of $HBF_4$ (entry 8) or MTO (entry 9) and the phenol **2d** became a major product in both cases. Control experiments revealed that oxidation did not occur in the absence of both $HBF_4$ and $CH_3ReO_3$. Since under peracid-free reaction conditions the oxidation took place, the known diperoxo rhenium complex $CH_3Re(O_2)_2O\cdot H_2O$ must be the major active species. That the diperoxo rhenium complex oxidizes arenes to quinones has been confirmed by a control experiment with the arene **1d**, for which stoichiometric amounts (**1d**: complex 1:2) of the authentic complex in ethanol afforded the quinone **3d** in 38% yield at 93% conversion after 4 h at room temperature.

There was little difference in the yields of quinone when concentrated or diluted hydrogen peroxide (entries 7 and 10) were used. Thus, water does not interfere when the oxidations are conducted in ethanol. Since longer reaction times or the use of larger amounts of hydrogen peroxide did not improve the conversion of starting arene **1d** or the yield of the *p*-benzoquinone **3d**, this suggested that the $CH_3ReO_3$ catalyst was deactivated within the reaction time (4 h). Therefore, the use of more $CH_3ReO_3$ or the addition of several batches during the reaction was advantageous (entry 11).

The $CH_3ReO_3/H_2O_2$ oxidation of the *p*-methoxyphenol **2d** was carried out in ethanol (entries 12–14, Table 1). In the absence of both $CH_3ReO_3$ and $HBF_4$ (entry 12), there was little conversion to **3d**. However, in the presence of $CH_3ReO_3$ the *p*-benzoquinone **3d** was formed in moderate yield (entry 13), and in the presence of both $CH_3ReO_3$ and acid the yields of **3d** were best (entry 14).

When 2,6-di-*t*-butyl-4-methylphenol (**4**) was treated with the $CH_3ReO_3/H_2O_2$ oxidant in acetic acid, 2,6-di-*t*-butyl-4-methyl-2,5-cyclohexadien-1-one-4-ol [10] (**5**) was formed and isolated in 30% yield. The dienone **5** was also reported in the oxidation of phenol **4** with dimethyldioxirane [11]. However, with peracetic acid the starting phenol was recovered completely; not even traces of dienone **5** were detected. The peroxo rhenium complex is thus a significantly stronger oxidant as compared to peracetic acid and is at least as effective as dimethyldioxirane.

Since an arene oxide intermediate was postulated [7e] for the dioxirane oxidation, (rearranging to the dienone **5**), we propose a similar mechanism for the MTO-catalyzed transformation of phenol **4** to the dienone **5** by $H_2O_2$ in the presence of acids (Scheme 3). Such an arene oxide mechanism could also operate in the




4 5

Scheme 3.

Table 2
Oxidation of 1,2,3-trimethoxy-5-methylbenzenes **1d** to 2,3-dimethoxy-5-methyl-*p*-benzoquinone **3d** by peroxidic oxidants

| Reagent | Catalyst | Solvent | Time | Temp. | Conv. (%) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
| $H_2O_2$ | $H_2SO_4$ | AcOH | 40 h | r.t. | – | 70 | [a] |
| | | | 12 h | r.t. | – | 25 | [b] |
| | | | 43.5 h | r.t. | – | 33 | [c] |
| $H_2O_2$ | – | AcOH | 8 days | r.t. | – | 75 | [a] |
| | | | 8 days | r.t. | – | 47 | [c] |
| $H_2O_2$ | $CF_3CO_2H$ | $CH_2Cl_2$ | 5 h | −5°C | – | 68 | [d] |
| $H_2O_2$ | – | $HCO_2H$ | 1 h | 30°C | 97 | 49 [e] | [f] |
| $H_2O_2$ | $H_3[PMo_{12}O_{40}]$ | AcOH | 5 h | 30°C | 75 | 73 [e] | [g] |
| $H_2O_2$ | $K_3[Fe(CN)_6]$ | MeCN | 42 h | r.t. | 55 | 43 [e] | [h] |
| AcOOH | – | | | r.t. | – | 19 | [i] |
| $(NH_4)_2S_2O_8$ | $H_2SO_4$ | $AcOH/H_2O$ | | 35–65°C | – | 85 | [j] |
| $(NH_4)_2S_2O_8$ | $H_2SO_4$ | MeOH | 25 min | 70°C | – | 54 | [k] |
| $H_2O_2$ | MTO | AcOH | 1 h | r.t. | 98 | 59 [e] | [l] |
| $H_2O_2$ | MTO | EtOH–$HBF_4$ | 4 h | r.t. | 50 | 67 [e] | [l] |

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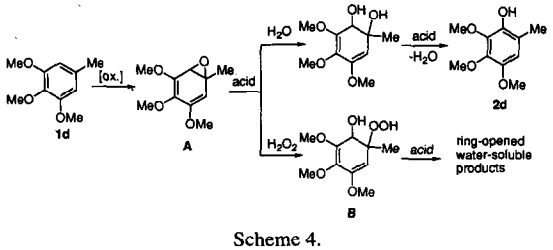
$CH_3ReO_3/H_2O_2$ oxidation of the methoxy-substituted arenes **1** to the benzoquinones **3** through the phenols **2**; however, it would be too speculative at this stage to elaborate details. Nonetheless, the arene oxide mechanism provides a rationale for the observed overoxidation (Scheme 4). Control experiments with the benzoquinone derivative **3c** revealed that this substrate is quite stable under the oxidation system $H_2O_2/MTO/AcOH$ and ca. 90% of the quinone was recovered after 2 h at room temperature. Therefore, the overoxidation products were not formed by the direct oxidation of the benzoquinones **3**. As illustrated for arene **1d**, in view of the observed regiochemistry of the intermediary phenol **2d** and final *p*-benzoquinone **3d**, the initial arene oxide should be **A**. Acid-catalyzed addition of $H_2O$ would afford the phenol




Scheme 4.

**2d** and addition of $H_2O_2$ the hydroperoxide **B**. While the former is further oxidized to the benzoquinone **3d**, again by way of arene oxides, the hydroperoxide **B** suffers acid-catalyzed Hock-type cleavage to afford water-soluble, ring-opened products that are lost in the work-up. Since $CH_3ReO_3$ is itself a relatively strong acid [12], it is difficult under these oxidation conditions to avoid the ring cleavage reaction.

As already mentioned, acid is required for the efficient oxidation of arenes **1** to *p*-benzoquinones **3** by the oxidation system $H_2O_2/MTO$ (cf. entries 8 and 10, Table 1). Acid catalysis facilitates on the one hand the formation of the phenols **2** from the intermediary arene oxide **1** in Scheme 4 and on the other hand it promotes ring opening of the arene oxides of phenols (cf. Scheme 3) to form the *p*-benzoquinones. Whether acid catalysis also activates the peroxo complex for oxidation remains to be assessed.

The present results compare well with those reported in the literature (Table 2). The principal oxidizing species is the rhenium complex $CH_3Re(O_2)_2O\cdot H_2O$ accompanied by peracetic acid, if the oxidation is conducted in acetic acid.

In case of solvents such as ethanol, an acid source is necessary to obtain *p*-benzoquinones. In analogy to dioxirane oxidations [7e], arene oxides constitute plausible intermediates.

## 3. Experimental

*Materials*: The starting materials **1c**, **1d**, and **5** were commercially available and of analytical quality. 1,2-Dimethoxy-4-methylbenzene [13] (**1a**) and 1,3-dimethoxy-5-methylbenzene [14] (**1b**) were prepared analogously to known methods. The catalyst $CH_3ReO_3$ was prepared as reported [15].

*General procedure for oxidations of methoxy-substituted benzenes **1a–d** in acetic acid*: To a solution of the particular methoxybenzene (1 mmol) and $CH_3ReO_3$ (0.02 mmol) in acetic acid (5 ml) was added 2.5–5.0 mmol of aqueous hydrogen peroxide (35 or 85%). The reaction mixture was stirred at room temperature under a nitrogen gas atmosphere for 1–4 h and subsequently diluted with water, extracted with $CH_2Cl_2$ ($3\times10$ ml), and the combined organic layers were washed with 100 ml water and dried over $MgSO_4$. The solvent was evaporated and the crude product mixture was chromatographed on silica gel by using $CH_2Cl_2$ or a mixture of $CH_2Cl_2$/ethyl acetate (20:1) as eluents. The ratio of the products was determined by $^1H$ NMR spectroscopy.

*General procedure for oxidations of methoxy-substituted benzenes **1a–d** in alcohol*: To a solution of the particular methoxybenzene (0.8 mmol), $CH_3ReO_3$ (0.016 mmol), and $HBF_4$ (54% in diethyl ether, 1 ml) in ethanol (3 ml) was added 2.5 mmol of aqueous hydrogen peroxide. The reaction mixture was stirred at room temperature under a nitrogen gas atmosphere for 4 h and subsequently diluted with water, extracted with $CH_2Cl_2$ ($3\times10$ ml), and the combined organic layers were washed with 100 ml water and dried over $MgSO_4$. The solvent was evaporated and the crude product mixture was chromatographed on silica gel by using $CH_2Cl_2$ or a mixture of $CH_2Cl_2$/ethyl acetate (20:1) as eluents. The ratio of the products was determined by $^1H$ NMR spectroscopy.

The products **2–4** [8] and **6** [10] were identified by comparison with their reported physical and spectral data.

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