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A CONVENIENT SYNTHESIS OF ALKYL-SUBSTITUTED p-BENZOQUINONES FROM PHENOLS BY A H_2O_2/HETEROPOLYACID SYSTEM

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Summary: Alkyl-substituted *p*-benzoquinones were easily synthesized in good yields by the oxidation of the corresponding phenols with a hydrogen peroxide/heteropolyacid couple in acetic acid.

It is well-known that many kinds of quinone derivatives play important roles in biosystems. Furthermore, some of quinones show bioactivities and some are useful as intermediates of medicines. For example, trimethyl-p-benzoquinone is a key compound for the synthesis of vitamin E, and 2,3-dimethoxy-5-methyl-p-benzoquinone is used for producing coenzyme Q.[1] The methods for one-step synthesis of p-benzoquinones by the oxidation of phenols have been investigated using many oxidizing reagents.[2] However, there are few papers concerning the oxidation of alkyl-substituted phenols by hydrogen peroxide; $RuCl_3$[3] or polyvanadates[4] catalyze the oxidation of 2,3,6-trimethylphenol to trimethyl-p-benzoquinone. However, the former catalyst contains an expensive metal and the latter requires a special technique for their preparations. We herein communicate a novel and convenient synthesis of alkyl-substituted p-benzoquinones from the corresponding phenols by using hydrogen peroxide as an oxidizing reagent in the presence of commercially available 12-heteropolyacid.

Hydrogen peroxide (60 %, 2.0 ml, ca. 44 mmol) was added dropwise to a solution of a phenol (2 mmol) and heteropolyacid (100 mg) in acetic acid (10 ml), and then the mixture was stirred for 5 h at 30 °C under nitrogen atmosphere. The yield of p-benzoquinone was determined by GLC method using a Thermon 3000 column.

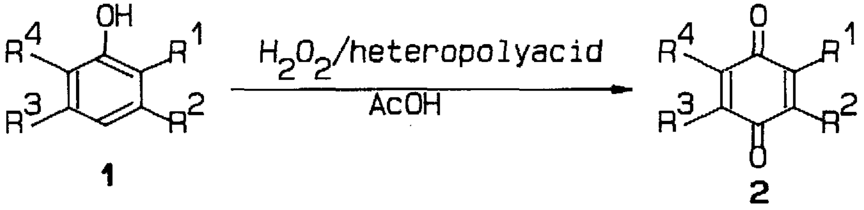


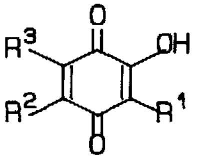
Table 1. Oxidation of trimethylphenols by the H_2O_2/heteropolyacid couple

Phenol	Heteropolyacid	Product	Conv. (%)	Yield (%)	Select. (%)	Yield of **3a** (%)
1a	$H_3PW_{12}O_{40}\cdot nH_2O$	**2a**	93.7	63.2	67.5	-
1a	$H_3PMo_{12}O_{40}\cdot nH_2O$	**2a**	99.9	78.3	78.3	-
1a	$H_3PMo_{12}O_{40}\cdot nH_2O$[a]	**2a**	79.4	61.5	77.5	-
1a	$H_4SiW_{12}O_{40}\cdot nH_2O$	**2a**	99.9	64.0	64.0	-
1a	$H_4SiMo_{12}O_{40}\cdot nH_2O$	**2a**	96.2	66.6	69.2	-
1a	none	**2a**	30.3	24.5	80.9	-
1b	$H_3PW_{12}O_{40}\cdot nH_2O$	**2a**	100.0	57.8	57.8	5.0
1b	$H_3PMo_{12}O_{40}\cdot nH_2O$	**2a**	100.0	72.0	72.0	tr
1b	$H_3SiW_{12}O_{40}\cdot nH_2O$	**2a**	100.0	58.7	58.7	13.2
1b	$H_3SiMo_{12}O_{40}\cdot nH_2O$	**2a**	100.0	70.9	70.9	tr

[a] 30 % H_2O_2 was used.

The results of the synthesis of trimethyl-p-benzoquinone are shown in Table 1. Both two trimethylphenol isomers, 2,3,6-trimethylphenol (**1a**) and 2,3,5-trimethylphenol (**1b**), afforded trimethyl-p-benzoquinone (**2a**) in good yields. Among four kinds of heteropolyacids, phosphomolybdic acid showed the highest activity. Use of aliphatic acid, e.g., formic, acetic, or propionic acid as the solvent resulted in a good yield of the quinone, while no quinone was afforded in methanol or acetonitrile. Although oxidation of the phenols proceeded even in the absence of heteropolyacid in acetic acid, the yield was very low. All the reactions were carried out on a small scale sufficient to be analyzed by GLC. It was possible to synthesize a large quantity of p-benzoquinone; when **1a** (1.36 g, 10 mmol) was treated with 60 % H_2O_2 (5.0 ml) in acetic acid (20 ml) in the presence of phosphomolybdic acid (200 mg) for 5 h, p-benzoquinone (**2a**, 0.854 g) was isolated from the reaction mixture in 57 % yield.[5]

Trimethylhydroquinone (**4**, 2mmol), which is considered as the reaction intermediate, was quantitatively oxidized to trimethyl-p-benzoquinone **2a** using



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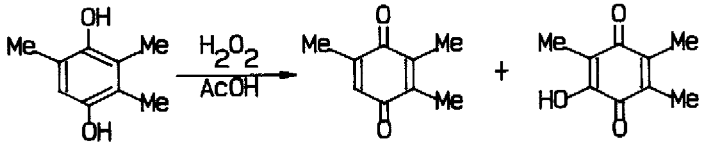
a: $R^1=R^2=R^3=Me$

b: $R^1=Me$, $R^2=H$, $R^3=i\text{-}Pr$

c: $R^1=R^2=Me$, $R^3=H$



4 **2a** **3a**

H_2O_2 (60 %, 1.0 ml) in acetic acid (10 ml) even in the absence of heteropolyacids. This oxidation was accelerated in the presence of heteropolyacids. When trimethylhydroquinone was treated with H_2O_2 in the presence of phosphomolybdic acid (100 mg), hydroxytrimethyl-p-benzoquinone[6] (**3a**) was obtained as a by-product in 14% yield. However, trimethyl-p-benzoquinone (**2a**) afforded no **3a** under the same treatment, and **2a** was recovered completely. These results suggest that heteropolyacid catalyzed hydroxylation of the benzene rings of phenols, and that hydroquinones thus formed were easily oxidized to p-benzoquinones by H_2O_2.

Di- and monoalkyl-substituted phenols were also oxidized under the same conditions (Table 2). Various alkyl-substituted p-benzoquinones were obtained from the corresponding phenols. Better yields of quinones were obtained in the reaction of disubstituted phenols than monosubstituted ones. Phenol itself gave only a trace amount of p-benzoquinone. When the reactivity is compared between **1g** and **1h**, the phenol **1h** the para position of which is crowded sterically showed higher reactivity and gave better yield of the benzoquinone **2e** than the phenol **1g**, in which the para position corresponds to the meta position for the two methyl groups. It seems thus that the oxidation of phenols proceeds under the ortho and para inductive effect of substituents.

Table 2. Oxidation of phenols by the H_2O_2/phosphomolybdic acid couple

Phenol	R^1	R^2	R^3	R^4	Product	Conv. (%)	Yield (%)	Select. (%)	Yield of 3 (%)
1c	i-Pr	H	Me	H	**2b**	96.0	64.0	66.6	13.2(**3b**)
1d	Me	H	i-Pr	H	**2b**	89.2	48.4	54.3	tr (**3b**)
1e	Me	Me	H	H	**2c**	99.9	55.5	55.5	-
1f	Me	H	Me	H	**2d**	92.6	66.9	72.2	-
1g	Me	H	H	Me	**2e**	51.4	25.3	49.3	-
1h	H	Me	Me	H	**2e**	100.0	62.7	62.7	tr (**3c**)
1i	Me	H	H	H	**2f**	50.2	12.8	25.4	-
1j	H	Me	H	H	**2f**	71.1	39.1	55.0	-

Some phenols gave hydroxy-p-benzoquinones[6] (**3**) as by-products. In the case of the oxidation of phenols which have no substituent on the ortho position, the hydroxylation can also occur in the ortho position of the phenols. According to the fact that hydroxy-p-benzoquinone **3a** was not formed by the oxidation of benzoquinone **2a**, it is considered that **3b** was not produced via **2b** as the intermediate but formed directly by the oxidation of **1c** and **1d**. The former phenol **1c** afforded a higher yield of **3b** than the latter (**1d**). The hydroxy-p-benzoquinone **3** can be obtained by the hydroxylation in both ortho and para positions of phenol **1c**; this is the case. However, in the case of the oxidation of **1d** to **3b**, only para-hydroxylation of the phenol **1d** must occur as the first step followed by the second oxidation to form **3d**, because of the difficulty in direct meta-hydroxylation of phenol. This can reflect the low yield of **3b** from **1d**.

It is concluded that alkyl-substituted phenols were oxidized to the corresponding p-benzoquinones by a hydrogen peroxide/heteropolyacid system. It seemed that heteropolyacid catalyzed hydroxylation of the benzene rings. Attempt to establish a more complete view of the mechanism of the oxidation is in progress.

REFERENCES AND NOTES

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5. Procedure for isolation: The reaction mixture was diluted with 30 ml of water, and extracted twice with 10 ml of dichloromethane. The extract was washed with 20 ml of water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was distilled under reduced pressure [**2a**: bp 150°C/10 mmHg (Kugelrohr)].
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