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Synthesis of Alkyl Substituted *p*-Benzoquinones from the Corresponding Phenols Using Molecular Oxygen Catalyzed by Copper(II) Chloride-Amine Hydrochloride Systems[1)]

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2,4,6-Trimethylphenol was effectively oxidized to trimethyl-*p*-benzoquinone with molecular oxygen in the presence of a catalytic amount of copper(II) chloride–amines in alcohol at ambient temperature. Various amines could be used as a co-catalyst in the presence of acids, and especially hydroxylamine hydrochloride and acetone oxime coupled with hydrochloric acid showed high activity. 2,6-Dimethyl-*p*-benzoquinone was also obtained from 2,6-dimethylphenol in good yield in this catalytic oxidation system.

Many kinds of quinones play important roles in bioorganisms. Some show bioactivities or some are useful as intermediates for synthesizing medicines. Trimethyl-*p*-benzoquinone (TMQ) is an important intermediate in the industrial production of vitamin E. A current method of TMQ production on an industrial scale is *para*-sulfonation of 2,3,6-trimethylphenol (TMP), followed by oxidation with manganese dioxide. While several attempts for the one-step oxidation of TMP to TMQ have been investigated using oxidizing agents, such as hydrogen peroxide[2)] and peroxy acids,[3)] use of molecular oxygen as oxidant with catalysts would be the most attractive method. Although complexes of cobalt(II) *N,N'*-disalicylideneethylenediamine derivatives as catalysts show high activities in the oxidation of TMP, the catalyst life is very short.[4)] A copper(II) chloride-lithium chloride catalyst is more durable than the cobalt complexes, but its catalytic activity is so low that an almost stoichiometric amount of the copper(II) salt is required to complete the oxidation.[5,6)] We herein describe a greatly improved synthesis of TMQ attained by TMP oxidation with copper(II) chloride–amine hydrochloride system catalysts.

Results and Discussion

Experimental results obtained on the oxidation of TMP with copper(II) chloride–amine hydrochloride system catalysts are shown in Table 1. The maximum rates of oxygen consumption are also listed in the table. When TMP was stirred with $CuCl_2 \cdot 2H_2O$ in 1-hexanol under oxygen atmosphere at 60 °C (Run 1), a small amount of oxygen was consumed and TMQ was obtained only in 8.9% yield. 4-Chloro-2,3,6-trimethylphenol (CTP) and 2,2',3,3',5,5'-hexamethyl-4,4'-biphenyldiol (HBD) were also obtained in 8.9% and

Table 1. Oxidation of TMP with a $CuCl_2 \cdot 2H_2O$–Additive Catalyst$^{a)}$

Run No.	Additive	Rate$^{b)}$	Time	Conv.	Yield/%		
		mmol h^{-1}	h	%	TMQ	CTP	HBD
1	—	0.062	5	24.9	8.9	8.9	7.5
2	—$^{c)}$	0.225	5	79.4	0	0	36.6
3	LiCl	0.353	5	90.7	68.8	6.7	16.5
4	NH_4Cl	0.162	5	54.3	28.4	7.0	12.0
5	Me_4NCl	0.038	5	12.6	1.5	5.1	2.9
6	Et_4NCl	0.527	5	100	81.8	1.6	14.7
7	$Me_3N \cdot HCl$	1.13	5	100	82.6	0	20.4
8	$Et_3N \cdot HCl$	1.45	4	100	80.5	0	13.5
9	$Me_2NH \cdot HCl$	1.60	5	100	84.2	0	9.5
10	$Et_2NH \cdot HCl$	1.55	4	100	84.2	0	13.3
11	Et_2NH	1.19	4	100	76.7	0	0.9
12	$MeNH_2 \cdot HCl$	0.715	5	100	79.5	0	21.6
13	$EtNH_2 \cdot HCl$	1.27	4	100	79.2	0	13.3
14	$Pr^n{}_2NH \cdot HCl$	1.46	4	100	79.8	0	17.3
15	$Pr^n{}_3N+HCl^{d)}$	0.990	4	100	77.5	0	19.1
16	$Pr^n{}_3N$	1.13	4	100	26.0	0	0.7

a) TMP, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; additive, 0.2 mmol; 1-hexanol, 2 ml; reaction temperature, 60 °C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption. c) $Cu(OAc)_2 \cdot H_2O$ was used. d) Hydrochloric acid (0.2 mmol, 36% aqueous solution) was added.

7.5% yield, respectively. In the case of the reaction with copper(II) acetate monohydrate (Run 2), no TMQ formed but a substantial amount of HBD was obtained instead. As claimed in the patents,[6] addition of lithium chloride to $CuCl_2 \cdot 2H_2O$ (Run 3) increased the catalytic activity. Both ammonium chloride and tetramethylammonium chloride caused a lowering in the activity (Runs 4 and 5), even though tetraethylammonium chloride showed substantial activity (Run 6). Surprising increases in both the TMQ yields and the reaction rates were observed when amine hydrochlorides were employed as the additive instead of lithium chloride (Runs 7—10 and 12—14). Although addition of free amines except for diethylamine did not increase yields of TMQ, the yield of TMQ became high when the amines were used as the hydrochlorides or mixtures of equimolecular amount of the amines and hydrochloric acid. Secondary amines, in general, were preferable than primary or tertiary amines as the additives.

Table 2 shows the results obtained with the copper(II) chloride–bidentate amine compound system catalysts. 2-Aminoethanol hydrochloride was effective as the additive to produce TMQ in 77.7% yield. Glycine hydrochloride was not effective as the additive. However, *N*,*N*-dimethylglycine hydrochloride and glycine ethyl ester hydrochloride, both of which do not act as bidentate ligands, showed high activities. Neither 1,2-ethanediamine nor 2,2′-bipyridyl was effective at all as the additive. It seems thus that the strong bidentate ligands occupy the active site of the copper resulting in low activity.

Use of hydroxylamine hydrochloride as well as sulfate as the additive greatly enhanced the activity of the copper catalysts (Table 3); the oxidation was greatly accelerated when compare with the case of using lithium chloride or other amine hydrochlorides as the additives. Furthermore, the yield of TMQ was very high and no formation of by-products, CTP and HBD, was observed.

Oximes were also effective as the additive (Runs 25 and 26) except for dimethylglyoxime which formed an insoluble greenish complex with copper(II) chloride. Oxidation of TMP with a copper–acetone oxime/O_2 system afforded TMQ in 80.4% yield. When hydrochloric acid was added to the oxidation system, both the reaction rate and the yield of TMQ increased. The yield of TMQ reached 85.0% by the use of *t*-butyl alcohol as solvent. It was experimentally confirmed that an oxime was hydrolyzed to form the corresponding carbonyl compound, e.g., acetophenone oxime was treated under the oxidation conditions to yield acetophenone in about 50%. It is likely that oximes are hydrolyzed to form hydroxylamine and carbonyl compounds and the former can work as a co-catalyst.

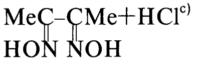
The oxidations in the $CuCl_2 \cdot 2H_2O$–hydroxylamine hydrochloride system were carried out using several alcoholic solvents (Table 4). In methanol, both the reaction rate and the yield of TMQ were low and a substantial amount of HBD was obtained as the by-product (Run 28). Addition of aromatic solvent, such

Table 2. Oxidation of TMP with a $CuCl_2 \cdot 2H_2O$–Bidentate Amine Catalyst[a)]

Run No.	Amine	Rate[b)] mmol h^{-1}	Time h	Conv. %	Yield/% TMQ	CTP	HBD
17	$NH_2CH_2CH_2OH+HCl$[c)]	0.516	5	100	77.7	—	17.9
18	$NH_2CH_2CO_2H \cdot HCl$	0.130	4	25.2	3.2	12.4	3.6
19	$MeNHCH_2CO_2H+HCl$[c)]	0.336	5	77.4	55.0	1.9	17.0
20	$Me_2NCH_2CO_2H \cdot HCl$	0.670	5	100	79.1	3.8	17.7
21	$Me_2NCH_2CO_2Me+HCl$[c)]	1.86	4	100	81.1	—	1.8
22	$NH_2CH_2CO_2Et \cdot HCl$	1.48	5	100	78.5	—	15.0

a) TMP, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; additive, 0.2 mmol; 1-hexanol, 2 ml; reaction temperature, 60 °C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption. c) Hydrochloric acid (0.2 mmol, 36% aqueous solution) was added.

Table 3. Oxidation of TMP with $CuCl_2 \cdot 2H_2O$–Hydroxylamine and $CuCl_2 \cdot 2H_2O$–Oxime Catalysts[a)]

Run No.	Additive	Rate[b)] mmol h^{-1}	Time h	Conv. %	Yield/% TMQ	CTP	HBD
23	$NH_2OH \cdot HCl$	4.90	1	100	80.1	0	0
24	$NH_2OH \cdot 0.5H_2SO_4$	2.80	2	100	83.8	0	0
25	$Me_2C{=}NOH+HCl$[c)]	2.59	2	100	84.6	0	2.0
26	$Me_2C{=}NOH$	1.65	2.5	100	80.4	0	0
27	 $MeC(=NOH)-C(=NOH)Me+HCl$[c)]	0.022	5	0	0	0	0

a) TMP, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; additive, 0.2 mmol; 1-hexanol, 2 ml; reaction temperature, 60 °C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption. c) Hydrochloric acid (0.2 mmol, 36% aqueous solution) was added.

Table 4. Solvent Effect of TMP Oxidation with a $CuCl_2 \cdot 2H_2O$–Hydroxylamine Catalyst[a)]

Run	Solvent	Rate[b)]	Time	Conv.	Yield/%		
No.	(ml)	$mmol\,h^{-1}$	h	%	TMQ	CTP	HBD
28	MeOH(2)	1.91	5	95.8	55.9	2.4	18.1
29	Benzene(1)+MeOH(1)	1.89	4	100	73.4	0	6.2
30	EtOH(2)	4.10	4	100	84.5	0	0
31	Toluene(1)+EtOH(1)	4.88	4	100	86.7	0	0.6
32	$Pr^nOH(2)$	4.72	3	100	86.0	0	0
33	$Toluene(1)+Pr^nOH(1)$	4.46	3	100	88.4	0	0
34	$Pr^iOH(2)$	9.72	3	100	90.6	0	0
35	$Toluene(1.5)+Pr^iOH(0.5)$	5.50	3	100	93.1	0	0
36	$Bu^sOH(2)$	7.14	3	100	88.8	0	0
37	$Bu^tOH(2)$	11.0	3	100	91.1	0	0
38	$Pr^n(Me)CHOH(2)$	4.00	3	100	88.8	0	0
39	$Et_2CHOH(2)$	5.64	3	100	92.4	0	0
40	$Me_2(Et)COH(2)$	7.12	3	100	92.6	0	0

a) TMP, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; $NH_2OH \cdot HCl$, 0.2 mmol; reaction temperature, 60 °C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption.

Table 5. Repetitive Reaction of TMP Oxidation with a $CuCl_2 \cdot 2H_2O$–$NH_2OH \cdot HCl$ Catalyst[a)]

Repetition No.	$NH_2OH \cdot HCl$	Rate[b)]	Conv.	Yield/%		
	mmol	$mmol\,h^{-1}$	%	TMQ	CTP	HBD
1	2.5	18.3	100	55.7	0	0
2	0	0	3.8	0	0	2.2
3	0.5	8.2	80.4	35.0	0	18.2
4	1.0	22.4	100	75.6	0	0
5	1.5	31.8	100	82.2	0	0
6	2.0	36.6	100	89.2	0	0
7	2.5	29.0	100	89.8	0	0
8	2.5	25.0	100	93.0	0	0
9	2.5	34.0	100	92.4	0	0
10	2.5	36.0	100	92.0	0	0

a) TMP, 5 mmol; $CuCl_2 \cdot 2H_2O$, 1 mmol; water, 5 ml; *t*-butyl alcohol, 5 ml; toluene, 5 ml; reaction time, 1 h; reaction temperature, 60 °C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption.

as benzene or toluene, increased the yield of TMQ and decreased formation of HBD (Run 29). In ethanol, the oxidation proceeded rather effectively than in methanol and addition of aromatic solvents also caused increase in the yield and reaction rate (Run 31). When secondary or tertiary alcohols were employed as solvent, TMQ was obtained in high yields and with high reaction rates (Runs 34—40). A similar tendency of the effects of solvent was observed in the case of using the $CuCl_2 \cdot 2H_2O$–acetone oxime/O_2 system.

The oxidation was repeated several times by recycling the catalyst and the results are shown in Table 5. The oxidation was carried out with the catalyst system of $CuCl_2 \cdot 2H_2O/NH_2OH \cdot HCl$ in mixture of water, *t*-butyl alcohol, and toluene as solvent. After the oxidation was completed, the organic layer containing TMQ was separated from the reaction mixture. Then the residual aqueous layer containing the copper catalyst was used repeatedly for the next reaction of TMP oxidation in mixture of *t*-butyl alcohol and toluene, resulting in, however, neither oxygen consumption nor TMQ production (repetition No. 2). When a small amount of hydroxylamine hydrochloride was added to this system, the oxidation began to proceed (repetition No. 3); increase in the amount of $NH_2OH \cdot HCl$ resulted in good yield of TMQ. These results suggest that copper(II) chloride is active for the oxidation of TMP to TMQ only under the presence of hydroxylamine hydrochloride, which was consumed during the oxidation. However, hydroxylamine hydrochloride was not consumed stoichiometrically but worked catalytically: one mole of hydroxylamine hydrochloride produced about 20 mole of TMQ at least. It is thus suggested that copper can be used repeatedly without deactivation in the present oxidation systems. Therefore, oximes became good additive because they hydrolyzed and supplied hydroxylamine gradually in the reaction solution.

The present oxidation system was applied for other phenols. When 2,6-dimethylphenol was oxidized using the $CuCl_2 \cdot 2H_2O$–hydroxylamine sulfate/O_2 catalyst system, 2,6-dimethyl-*p*-benzoquinone was obtained in good yield (Table 6). However, oxidations of other

Table 6. Oxidation of 2,6-Dimethylphenol to 2,6-Dimethyl-*p*-benzoquinone with a $CuCl_2 \cdot 2H_2O$–Additive Catalyst[a)]

Run No.	Additive	Time	Conv.	Yield
		h	%	%
41	LiCl	5	10.1	0
42	$Et_2NH \cdot HCl$	5	42.6	3.6
43	$NH_2OH \cdot HCl$	3	100	73.2
44	$NH_2OH \cdot 0.5H_2SO_4$	2	100	82.5
45	$Me_2C{=}NOH{+}HCl$[b)]	5	78.7	32.3

a) 2,6-Dimethylphenol, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.1 mmol; additive, 0.2 mmol; *t*-butyl alcohol, 2 ml; reaction temperature, 40 °C; oxygen pressure, 114.7 kPa. b) Hydrochloric acid (0.2 mmol, 36% aqueous solution) was added.

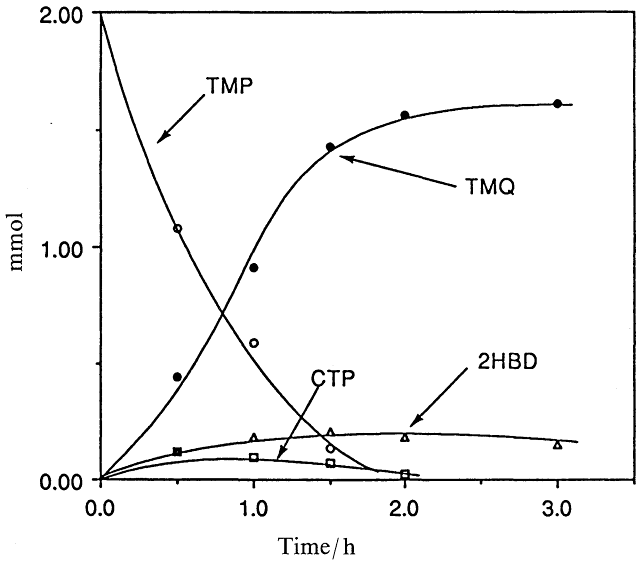
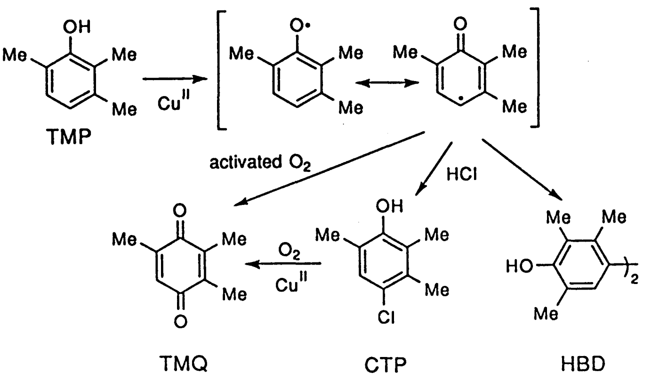


Fig. 1. Oxidation of TMP with a $CuCl_2 \cdot 2H_2O$–$Et_2NH \cdot HCl$ catalyst. TMP, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; $Et_2NH \cdot HCl$, 0.2 mmol; 1-hexanol, 2 ml; temperature, 60 °C; p_{O_2} 114.7 kPa.

phenols, e.g., 2-methyl-, 3-methyl-, 2,3-dimethyl-, 2,4-dimethyl-, and 3,5-dimethylphenols, did not afforded the corresponding *p*-benzoquinones.

Time course of the oxidation of TMP to TMQ with the $CuCl_2 \cdot 2H_2O$–$Et_2NH \cdot HCl$ catalyst is shown in Fig. 1. CTP and HBD formed as the by-product; the former showed the maximum yield and then disappeared suggesting that CTP is an intermediate during the oxidation. A plausible oxidation mechanism from TMP to TMQ is as follows: A phenolic proton is abstracted by copper(II) ion to form 2,3,6-trimethylphenoxyl radical and the copper(II) ion is reduced to copper(I) which can activate oxygen molecule. The phenoxyl radical tautomerizes to a 4-oxo-2,5-cyclohexadienyl radical, which reacts with the activated oxygen, hydrogen chloride, and another radical to yield TMQ, CTP, and HBD, respectively. CTP can be also oxidized to TMQ in the oxidation system (Scheme 1). The molar amount of oxygen consumed corresponded well to that of TMQ formed during the oxidation. This suggests occurrence of monooxygenation of TMP to TMQ. It is likely that the oxidation of TMP with the $CuCl_2 \cdot 2H_2O$–$NH_2OH \cdot HCl$ catalyst proceeded in a similar mechanism with the $CuCl_2 \cdot 2H_2O$–$Et_2NH \cdot HCl$ catalyst. However, this oxidation proceeded too fast to observe the intermediates.



Scheme 1.

It is concluded that trimethyl-*p*-benzoquinone and 2,6-dimethyl-*p*-benzoquinone are obtained in good yields by the oxidations of 2,3,6-trimethylphenol and 2,6-dimethylphenol, respectively, by using the $CuCl_2 \cdot 2H_2O$–amine/O_2 system. When hydroxylamine hydrochloride was used as additive, the activity of the oxidation system became over one hundred times higher in the reaction rates than that of the reported $CuCl_2 \cdot 2H_2O$–LiCl system catalyst.

Experimental

Gas chromatographic analyses and liquid chromatographic analyses were performed on a Shimadzu GC-R1A gas chromatograph fitted with a Thermon 3000 column and a Shimadzu LC-3A liquid chromatograph fitted with an Inertsil ODS column, respectively.

General Procedure for the Oxidation of TMP. The oxidations were carried out using a gas-sealed system. TMP (2 mmol), copper(II) chloride dihydrate (0.2 mmol), and an amine hydrochloride (0.2 mmol) were put into a 10 ml of glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. A solvent (2 ml) was added to the mixture and the reaction was started under oxygen atmosphere (114.7 kPa) with vigorous stirring at 60 °C. The amount of consumed oxygen was measured by a gas burette. The yields of the products were determined by GLC except for HBD determined by liquid chromatography.

Repetitive Oxidation of TMP with a $CuCl_2 \cdot 2H_2O$–$NH_2OH \cdot HCl$ Catalyst. TMP (5 mmol), copper(II) chloride dihydrate (1 mmol), and hydroxylamine hydrochloride (2.5 mmol) were put into a 50 ml of glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. Water (5 ml), *t*-butyl alcohol (5 ml), and toluene (5 ml) were added to the mixture and the reaction was carried out under oxygen atmosphere (114.7 kPa) with vigorous stirring at 60 °C for 1 h. The amount of consumed oxygen was measured by a gas burette. After the reaction, organic layer was separated from the reaction mixture, and products were analyzed with GLC and liquid chromatography. To the residual aqueous layer, TMP (5 mmol), *t*-butyl alcohol (5 ml), and toluene (5 ml) were added, and the oxidation was repeated as described above by changing an amount of hydroxylamine hydrochloride added.

General Procedure for the Oxidation of 2,6-Dimethylphenol. The oxidations were carried out using a gas-sealed system. 2,6-Dimethylphenol (2 mmol), copper(II) chloride dihydrate (0.1 mmol), and an additive (0.2 mmol) were put into a 10 ml of glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. *t*-Butyl alcohol (2 ml) was added to the mixture and the reaction was started under oxygen atmosphere (114.7 kPa) with vigorous stirring at 40 °C. The amount of consumed oxygen was measured by a gas burette. The yields of the products were determined by GLC.

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