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A NOVEL OXYGENATION OF 2,3,6-TRIMETHYLPHENOL TO TRIMETHYL-*p*-BENZOQUINONE BY DIOXYGEN WITH COPPER(II) CHLORIDE / AMINE HYDROCHLORIDE CATALYST

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Summary: 2,3,6-Trimethylphenol was efficiently oxygenated to trimethyl-*p*-benzoquinone by molecular oxygen in the presence of catalytic amount of copper (II) chloride/amine hydrochloride in alcoholic solvent at ambient temperature.

Trimethyl-*p*-benzoquinone (**TMQ**) is a key compound in the vitamin E synthesis and the current method for its production in the industrial scale is *para* -sulfonation of 2,3,6-trimethylphenol (**TMP**) followed by oxidation with MnO_2. The methods for the one step oxidation of **TMP** to **TMQ** have been investigated so far using oxidizing reagents, such as hydrogen peroxide1) and molecular oxygen. Use of the latter reagent coupled with cobalt(II) - Shiff base2) and copper(II) chloride - lithium chloride3, 4) catalysts seems the most promising method. However, the life time of the former is very short though its catalytic activity is high, while the activity of the latter is so low that an almost stoichiometric amount of copper(II) salt is required to complete the oxidation.4) We herein communicate a novel oxygenation of **TMP** to **TMQ** by copper(II) chloride / amine hydrochloride catalyst, which was found quite satisfactory.

The oxidation of **TMP** (2 mmol) was carried out using $CuCl_2 \cdot 2H_2O$ (0.2 mmol) and an additive (0.2 mmol) as the catalyst in *n*-hexanol (2 ml) at 60°C under 1 atm. of oxygen atmosphere, where the amount of oxygen consumed was measured by a gas burette. The products **TMQ**, 4-chloro-2,3,6-trimethylphenol (**1**) and 4,4'-dihydroxy-2,2',3,3',5,5'-hexamethylbiphenyl (**2**) were determined by GLC and HPLC using a Thermon 3000 and an Inertsil ODS columns, respectively.

The experimental results are shown in Table 1. The maximum rate of O_2 consumption is shown as "dO_2/dt." $CuCl_2 \cdot 2H_2O$ alone showed a very low activity for the production of **TMQ**. Addition of LiCl to this system increased the activity as claimed in the several patents.4) The highest activity was obtained, when the equimolar amount of LiCl was used, suggesting the formation of a 1/1 active complex between $CuCl_2$ and LiCl. A replacement of LiCl by amine hydrochloride activate the reaction while NH_4Cl or $(CH_3)_4NCl$ caused a deactivation. The use of CuCl caused generally a rapid consumption of both **TMP** and oxygen, but the amount of **TMQ** formed was substantially low. As **TMQ** is stable and not oxidized further under the reaction conditions, CuCl catalyzes the oxidation of phenolic aromatic ring other than *para*-position, resulting in the ring cleavage.5) Almost all amines tested were effective when used as the salt form with inorganic proton acid. Secondary amines, such as $(CH_3)_2NH \cdot HCl$ or $(C_2H_5)_2NH \cdot HCl$ was preferable than primary or tertiary amine. When the amount of amine $(C_2H_5)_2NH \cdot HCl$ was changed, the highest activity was obtained by its use of 0.2 mmol, suggesting the formation of a 1/1 active complex between $CuCl_2$ and $(C_2H_5)_2NH$. The activity of the $CuCl_2 \cdot 2H_2O$ - $(C_2H_5)_2NH \cdot HCl$ system catalyst thus obtained was 5 - 6 times higher than that

Table 1. Oxidation with $CuCl_2\cdot 2H_2O$-additive catalyst.

Additive (0.2 mmol)	dO_2/dt (mmol/h)	Conv. (%)	Yield (%) of TMQ	1	2	React. time (h)
-	0.062	24.9	8.9	8.9	8.9	5
LiCl	0.353	90.7	68.8	6.7	16.5	5
$CH_3NH_2\cdot HCl$	0.715	100	79.5	0	21.6	5
$(CH_3NH_2)_2\cdot H_2SO_4$[a]	1.28	95.8	71.3	3.4	21.4	5
$(CH_3)_2NH\cdot HCl$	1.60	100	84.2	0	13.3	5
$C_2H_5NH_2\cdot HCl$	1.27	100	79.2	0	13.3	4
$C_2H_5NH_2\cdot HBr$	1.21	100	83.3	0	15.4	4
$(C_2H_5)_2NH\cdot HCl$	1.55	100	84.2	0	13.3	4
$(n\text{-}C_3H_7)_2NH$	1.07	100	50.0	1.9	0	4
$(n\text{-}C_3H_7)_2NH\cdot HCl$	1.46	100	79.8	0	17.3	4
$(n\text{-}C_3H_7)_3N$	1.13	100	26.0	0	0.7	4
$(n\text{-}C_3H_7)_3N + HCl$[b]	0.990	100	77.5	0	19.1	4

[a] 0.1 mmol was used. [b] 0.2 mmol of HCl was used as the 36% aqueous solution.

of the well known $CuCl_2\cdot 2H_2O$ - LiCl system catalyst and the yield of **TMQ** reached a value of about 85%. Cyclic amine, such as morpholine, aromatic amine, such as aniline, and aminoalcohol, such as ethanolamine, were also effective as the co-catalyst in the presence of hydrochloric acid. Amino acids were also useful when the amino group was substituted by alkyl group or the carboxyl group was esterified: glycine was not effective even when coupled by hydrochloric acid, while N,N-dimethyglycine or glycine ethyl ester coupled by hydrochloric acid showed a high activity. Neither diamine, such as ethylenediamine, nor dipyridyl was effective as the co-catalyst. It seems thus that the bidentate ligand occupies the active site of the copper complex resulting in the low activity.

All the amine compounds tested did not reveal the activity in the form of free amine, *i.e.*, in the absence of an inorganic proton acid: the addition of the acid caused an increase in the activity of copper - amine system catalyst. Time course of the reaction with this catalyst suggests a plausible oxidation scheme as follows: a main pass may be a direct oxidation of **TMP** to **TMQ** *via* 2,3,6-trimethylphenoxy radical formation by hydrogen abstraction of **TMP** with Cu(II), accompanied reasonably by a production of small amount of **2** by the radical coupling reaction. A small part of **TMQ** can be also formed *via* **1**, *i.e.*, by *para*-chlorination of **TMP**. The molar amount of O_2 consumed well corresponded to that of **TMQ** formed during the oxidation, suggesting an occurrence of monooxygenation. When the amount of HCl added to the $CuCl_2\cdot 2H_2O$ (0.2 mmol) - $(C_2H_5)_3N.HCl$ (0.2 mmol) system was changed, **TMQ** yield increased with increase in the amount up to about 0.2 mmol and kept constant value above 80 % even with the further addition of HCl. It seems thus likely that the acids works as the proton source during the oxidation of **TMP** to **TMQ**. This may arouse interest in the oxidation mechanism because a hydroperoxo species can be formed by protonation of activated dioxygen and considered as the active species in the biomimetic oxidation by dicopper(I) complex as a model of Type 3 copper protein.[6]

Attempts to establish a more complete view of the mechanism of the **TMP** oxidation are under way.

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