A Novel Synthesis of Trimethyl-*p*-benzoquinone: Copper(II)–hydroxylamine catalysed Oxygenation of 2,3,6-Trimethylphenol with Dioxygen

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2,3,6-Trimethylphenol was efficiently oxygenated to trimethyl-*p*-benzoquinone with molecular oxygen in the presence of a catalytic amount of copper(II) chloride–hydroxylamine in an alcoholic solvent at ambient temperature.

Recently we have reported that copper(II) chloride–amine complex catalyst revealed a high activity in the oxidation of 2,3,6-trimethylphenol (TMP) to trimethyl-*p*-benzoquinone (TMQ) with dioxygen in alcoholic solvents.[1] TMQ is a key compound for vitamin E synthesis, and the current method of its production on an industrial scale is *p*-sulphonation of TMP followed by oxidation with MnO_2. Several attempts for its one step synthesis by TMP oxidation with dioxygen have been made using cobalt(II)–Shiff base complex[2] and copper(II) chloride–lithium chloride[3] as catalysts. The former is not stable enough to sustain the oxidation for a long period despite its high activity, while the catalytic activity of the latter, which seems rather more durable than the former, is so low that an almost stoicheiometric amount of copper(II) salt is required to complete the oxidation.[4] Improvement of the copper(II) system catalyst has therefore been long-expected, and partly achieved by complexation with amine as reported previously by us.[1] We herein describe a novel and greatly improved synthesis of TMQ attained by TMP oxidation with copper(II) chloride–hydroxylamine system catalysts.

The oxidation of TMP was carried out with a catalytic amount of copper(II) salt and hydroxylamine under atmospheric pressure of oxygen in an alcoholic solvent at ambient temperature. A time course of the reaction was monitored by measuring the amount of consumed oxygen with a gas burette. The reaction 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 Thermon 3000 and Inertsil ODS as columns, respectively.

Typical results obtained on the oxidation of TMP with the copper(II) system catalyst at 40 °C in propan-2-ol are shown in Table 1. The maximum rate of oxygen consumption ($dO_{2(max)}/dt$) is also listed in Table 1. While the $CuCl_2$–LiCl system showed a very low activity in the present conditions (entry 1), a replacement of LiCl by amine hydrochloride resulted in a substantial increase in the activity (entry 2), which is consistent with our recent results.[1] Use of hydroxylamine hydrochloride as well as sulphate as the additive greatly enhanced activity, *i.e.*, one hundred fold higher in the reaction rate compared to that of $CuCl_2$–LiCl system catalyst together with

Table 1. Copper(II)-catalysed TMP oxidation in propan-2-ol.[a]

Entry	Additive/mmol	$dO_{2(max)}/dt$ (mmol/h)	Conversion of TMP/%	Yield/% of TMQ	Yield/% of (1)	Yield/% of (2)	Reaction time/h
1	LiCl (0.2)	0.063	14.8	2.9	3.7	1.3	5
2	$Et_2NH{\cdot}HCl$ (0.2)	0.188	46.5	15.8	3.8	7.5	5
3	$NH_2OH{\cdot}HCl$ (0.2)	6.80	100	90.9	0	0	2
4	$(NH_2OH)_2{\cdot}H_2SO_4$ (0.1)	5.02	100	88.8	0	0	2
5[b]	$NH_2OH{\cdot}HCl$ (0.4)	2.43	100	75.7	0	0	4

[a] TMP, 2 mmol; $CuCl_2{\cdot}H_2O$, 0.1 mmol. [b] $Cu(OAc)_2{\cdot}H_2O$, 0.2 mmol; propan-2-ol, 2 ml; reaction temperature, 40 °C; oxygen pressure, 114.7 kPa.

Table 2. TMP oxidation with copper(II) chloride–hydroxylamine hydrochloride.[a]

Entry	Solvent/ml	$dO_{2(max)}/dt$ (mmol/h)	Conversion of TMP/%	Yield/% of TMQ	Yield/% of (1)	Yield/% of (2)	Reaction time/h
6	MeOH (2)	1.91	95.8	55.9	2.4	18.1	5
7	Bz (1) + MeOH (1)	1.89	100	73.4	0	6.2	4
8	EtOH (2)	4.10	100	84.5	0	0	4
9	PhMe (1) + EtOH (1)	4.88	100	86.7	0	0.6	4
10	PrOH (2)	4.72	100	86.0	0	0	3
11	PhMe (1) + PrOH (1)	4.46	100	88.4	0	0	3
12	Pr^iOH (2)	9.72	100	90.6	0	0	3
13	PhMe (1.5) + Pr^iOH (0.5)	5.50	100	93.1	0	0	3
14	Bu^sOH (2)	7.14	100	88.8	0	0	3
15	Bu^tOH (2)	11.0	100	91.1	0	0	3
16[b]	Bu^tOH (2)	6.92	100	96.0	0	0	2
17	2-PeOH (2)	4.00	100	88.8	0	0	3
18	Am^sOH (2)	5.64	100	92.4	0	0	3
19	Am^tOH (2)	7.12	100	92.6	0	0	3

[a] TMP, 2 mmol; $CuCl_2{\cdot}H_2O$, 0.2 mmol. [b] 0.1 mmol; $NH_2OH{\cdot}HCl$, 0.2 mmol; reaction temperature, 40 °C; oxygen pressure, 114.7 kPa. [Bz = benzene, 2-Pe = Pr^nCHMe–, Am^s = Et_2CH–, Am^t = $Me_2(Et)C$–].

the high selectivity (90%) of TMQ production (entries 3 and 4). Copper(II) chloride could be replaced by copper(II) acetate, the activity of which was however lowered (entry 5).

$$\text{TMP} \xrightarrow[\text{CuCl}_2]{\text{O}_2} \text{TMQ} + (\mathbf{1}) + (\mathbf{2}) \qquad (1)$$

As reported previously,[1] the oxidation seems to proceed as follows: TMP is mainly oxidized to TMQ accompanied by the formation of a small amount of (**2**), and a part of TMQ can be formed *via* (**1**) (equation 1). A characteristic feature of the oxidation with the copper(II)–hydroxylamine system is a distinct decrease in the production of (**2**) compared to the copper(II)–amine system. In the oxidation with the former system, oxygen was rapidly consumed; its amount reached a value of 2 mmol within about 1/2 h and then remained constant. This suggests incorporation of one atom of oxygen molecule into TMP with the copper(II)–hydroxylamine catalyst.

The oxidations were carried out using several alcoholic solvents (Table 2). In methanol alone, both the reaction rate and the yield of TMQ were low and a substantial amount of (**2**) was detected as the by-product (entry 6). Use of a mixed solvent of methanol and benzene caused an increase in the yield to TMQ and, oppositely, a decrease in that of (**2**) (entry 7). Ethanol or propan-1-ol alone as the solvent afforded a good yield of TMQ (entries 8 and 10), its mixing with aromatic solvent caused a further increase in the yield of TMQ (entries 9 and 11). When propan-2-ol was used, the influence of the volume ratio of propan-2-ol to toluene on the oxidation was tested; toluene alone was not effective at all as the solvent and a small ratio of propan-2-ol to toluene, *e.g.*, 0.5, was preferable for attaining good production of TMQ (entry 13). A branched alcohol, *i.e.*, s- or t-alcohol was highly effective by itself as the solvent without the aromatic compound. The greater the degree of branching, the higher both the rate of oxidation and the yield of TMQ production became (entries 14, 15, 17—19). The highest reaction rate was obtained with t-butylalcohol as the solvent (entry 15), in which a lowering of the copper(II) catalyst concentration resulted in an increase in the yield of TMQ, although the reaction rate was fairly decreased (entry 16). The oxidations apparently took place in homogeneous solution. Hydroxylamine was not stable and was slowly consumed during the oxidation. It seems however that hydroxylamine worked catalytically because the amount of TMQ reached a value of 20-fold higher than the amount of hydroxylamine used.

The activity of the $CuCl_2{\cdot}2H_2O$–hydroxylamine hydrochloride system catalyst thus obtained was one hundred-fold higher than that of the well known $CuCl_2{\cdot}2H_2O$–LiCl system catalyst and the yield of TMQ reached a value of 96.0%. Attempts to improve the catalytic behaviour of the copper(II)–hydroxylamine system and to establish a more complete view of the catalytic mechanism of the TMP oxidation are under way.

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