

## A NOVEL OXYGENATION OF 2,4,6-TRIMETHYLPHENOL TO 3,5-DIMETHYL-4-HYDROXYBENZALDEHYDE BY DIOXYGEN WITH COPPER(II)-AMINE COMPLEX CATALYST

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**Summary:** 2,4,6-Trimethylphenol was efficiently oxygenated to 3,5-dimethyl-4-hydroxybenzaldehyde by molecular oxygen in the presence of catalytic amount of copper(II) chloride/amine (1/1) complex in alcoholic solvent at ambient temperature.

Aromatic aldehydes are important intermediate in the industrial synthesis of a wide variety of speciality chemicals, such as pharmaceuticals, flavour chemicals, dyes, and agrochemicals. Several methods for the aromatic aldehydes synthesis from toluenes have been developed:<sup>1)</sup> chlorination followed by hydrolysis, stoichiometric oxidation with inorganic oxydants, electric/electrocatalytic oxidation, and catalytic oxygen transfer with some oxygen donnors. The most promising methods seems a catalytic oxygenation with molecular oxygen. *p*-Cresols are oxidized with molecular oxygen to the corresponding *p*-hydroxybenzaldehydes in the presence of catalytic amount of cobalt shiff base (yield $\leq$  45%)<sup>2)</sup> or cobaltous chloride (yield $\leq$  78%)<sup>1,3,4)</sup> in methanol. The latter process seems promising but requires long reaction time and strongly basic conditions in the presence of a large amount of sodium hydroxide. Moreover, the consumption of both methanol and base is accompanied by the formation of carbon dioxide, because it is likely that the former functions as a reducing agent and continuously provides for a generations of cobalt(II) where necessary.<sup>1)</sup> We herein describe a novel oxygenation of 2,4,6-trimethylphenol (2,4,6-TMP) to the corresponding *p*-hydroxybenzaldehyde with copper(II) chloride-amine catalyst.

The oxidation of 2,4,6-TMP was carried out with a catalytic amount of copper(II) chloride and amine 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 oxygen consumed with a gas burette. The reaction products, 3,5-dimethyl-4-hydroxybenzaldehyde (1) and 2,6-dimethyl-*p*-benzoquinone (2) were determined by GLC using Thermon 3000 as column.

Typical results obtained on the oxidation of 2,4,6-TMP with the copper(II)-amine system catalyst at 60°C in hexan-1-ol are shown in Table 1. The maximum rate of oxygen consumption ( $dO_2(\max)/dt$ ) is also listed in Table 1. While  $CuCl_2 \cdot 2H_2O$  alone showed very low activity(entry 1), addition of diethylamine greatly enhanced the activity (entries 2, 3 and 4). The reaction rate increased with increasing amount of diethylamine added, but the highest yield was obtained with the equimolar amount of diethylamine to the catalyst and a further increase of diethylamine resulted in dramatically no production of 1 even though the rate of  $O_2$  consumption increased (entry

Table 1. 2,4,6-Trimethylphenol oxidation with copper-amine catalyst<sup>a)</sup>

Entry	Copper (mmol)	Amine (mmol)	dO <sub>2</sub> (max)/dt (mmol/h)	Conv. (%)	Yield (%) of (1)	Yield (%) of (2)	Reaction time (min)
1	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	-	0.144	40.0	2.7	2.7	300
2	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>2</sub> NH(0.1)	0.498	98.2	71.0	2.1	300
3	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>2</sub> NH(0.2)	0.815	97.6	77.7	3.7	240
4	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>2</sub> NH(0.3)	1.92	98.2	-	1.4	120
5	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Pr <sub>2</sub> NH(0.2)	1.03	96.4	75.0	5.4	180
6	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Pr <sub>2</sub> NH(0.4)	3.14	100	2.7	-	120
7	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Bu <sub>2</sub> NH(0.2)	0.79	95.7	46.9	5.9	180
8	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Bu <sub>2</sub> NH(0.4)	2.35	100	-	-	120
9	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>3</sub> N(0.2)	1.73	95.1	42.1	3.7	212
10	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>3</sub> N(0.4)	1.94	100	15.7	-	180
11	CuCl <sub>2</sub> ·2H <sub>2</sub> O(0.2)	Et <sub>2</sub> NH·HCl(0.2)	0.497	95.0	44.5	4.2	300
12	CuCl(0.2)	Et <sub>2</sub> NH(0.2)	2.15	99.1	1.4	-	120

<sup>a)</sup>2,4,6-TMP, 2 mmol; hexan-1-ol, 2 ml; reaction temperature, 60°C; oxygen pressure, 114.7 kPa.

4). When diethylamine was replaced by the other amines, a similar tendency was observed: use of a equimolar amount of amine to CuCl<sub>2</sub>·2H<sub>2</sub>O afforded a good yield of 1, while the excess amount caused formation of reddish brown precipitates which is likely to be polymer(entries 5-10). These suggest that copper-amine (1/1) complex is the reactive species for production of 1, but the presence of free amine induces the oxidative polymerization. The fact that dialkylamines are more effective than that of trialkylamines suggests that bulky amines is sterically hindered to coordinate to copper. Use of diethylamine hydrochloride caused a decrease in both the rate of reaction and the yield of 1 (entry 11), in contrast to the favorable effect observed previously by us in 2,3,6-trimethylphenol oxidation to trimethyl-*p*-benzoquinone with copper(II)-amine catalyst<sup>5)</sup>. It is well known that amines easily coordinate to copper to form various complexes, some of which, *e.g.*, dicopper(I) complexes, interestingly activate dioxygen as models of Type 3 copper protein.<sup>6)</sup> However, use of CuCl instead of CuCl<sub>2</sub>·2H<sub>2</sub>O resulted in almost no production of 1(entry 12). Further characterization of this oxidation is undergoing in this laboratory.

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