Aerobic oxidation of p-cresols to 4-hydroxy benzaldehydes catalyzed by cobaltous chloride/NHPI/ salen-Cu(II) catalytic system

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Received: 22 June 2013/Accepted: 15 November 2013 © Springer Science+Business Media Dordrecht 2013

Abstract Oxidation of 2-methoxy-p-cresol, p-cresol, 2-bromo-p-cresol to their corresponding 4-hydroxybenzaldehydes with atmospheric molecular oxygen as oxidant and a combination of cobaltous chloride and N-hydroxyphthalimide (NHPI) as catalyst in methanol has been investigated for the first time. The results indicated that the reaction progress was related to the substituents in the structures of the substrates: the electron-donating group methoxy favors the aerobic reaction but the electron-withdrawing group Br is detrimental to the reaction. The introduction of salen-Cu(II) complexes as the third component into the cobaltous chloride/NHPI catalytic system can considerably improve the aerobic oxidation of p-cresol and 2-brom-p-cresol to the corresponding 4-hydroxybenzaldes.

 $\label{eq:keywords} \begin{array}{ll} \mbox{p-cresol} \cdot \mbox{2-bromo-p-cresol} \cdot \mbox{Aerobic oxidation} \cdot \mbox{Cobaltous chloride} \cdot \mbox{N-hydroxyphthalimide} \cdot \mbox{Cu(II)-salen complexes} \end{array}$

Introduction

4-Hydroxybenzaldehydes are important chemical intermediates for preparing pharmaceuticals, pesticides, fragrances, petrochemicals, and electroplating chemicals [1– 3]. For example, vanillin (4-hydroxy-3-methoxybenzaldehyde) is the major component of vanilla, which is one of the most widely used and important flavoring materials worldwide [4, 5]; 3,5-dimethyl-4-hydroxy benzaldehyde is used for the synthesis of potential antioxidant cancer chemopreventive agents [6]. Methods that have been employed to synthesize 4-hydroxybenzaldehydes include reacting phenols with formaldehyde [7], glyoxylic acid [8], or chloroform [9, 10], and the use of stoichiometric amounts of inorganic oxidants [11–14]. All these methods suffer from

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one or more disadvantages such as consuming high energy, using heavy metal catalysts, and generating large amounts of inorganic salts as by-products, which may cause serious environmental problems [15]. Increasing the awareness towards a clean environment, the catalytic partial oxidation of 4-cresols or 4-hydroxybenzyl alcohols with molecular oxygen to 4-hydroxybenzaldehydes is an attractive new alternative for the synthesis of 4-hydroxybenzaldehydes. Many catalysts or catalytic systems have been developed to achieve these transformations [15–19]. Among all the methodologies, the aerobic oxidation of 4-cresols catalyzed by cobalt-based catalysts in strong basic medium is the most attractive and has been studied in detail.

Recently, we successfully used a combination of cobaltous chloride and N-hydroxyphthalimide (NHPI) as catalyst and atmospheric molecular oxygen as oxidant to oxidize 2-methoxy-p-cresol to vanillin (4-hydroxy-3-methoxybenzaldehyde) in methanol [20]. Under the optimized conditions, the yield of vanillin was 90.1 %. However, when the combination catalyst was applied to the oxidation of p-cresol and 2-brom-p-cresol under the same conditions, low reaction conversions and yields were received. It was learned from the literature that 4-hydroxybenzyl alcohols as intermediates are involved in the transformation of 4-cresols to 4-hydroxybenzaldehydes; meanwhile, p-hydroxybenzoic acids and 4-hydroxybenzyl methyl ether as by-products could be formed in the process (Scheme 1) [15, 21, 22]. GC analysis confirmed that the low selectivity of 4-hydroxybenzaldes is mainly due to a considerable amount of 4-hydroxybenzyl alcohols present in the reaction mixtures. If the 4-hydroxybenzyl alcohols are oxidized further to 4-hydroxybenzaldehydes, the yields can be greatly improved.

It has been found in the literature that salen-Cu(II) complex/TEMPO [23] and bis (3,5-di-tert-butyl salicylaldimine) copper(II) complexes/TEMPO [24] systems are highly efficient for the aerobic oxidation of primary benzylic and allylic alcohols to their corresponding aldehydes under mild reaction conditions. However, the catalytic systems are generally of high cost due to the use of the expensive TEMPO. NHPI is similar to TEMPO in function but much cheaper, which may become an alternative to TEMPO in the aerobic oxidation of alcohols. This idea in combination with our experience in the synthesis and application of salen-metal complexes [25–27] inspired us to introduce salen-Cu(II) complexes into the cobaltous chloride/ NHPI system, which constructs three-component catalytic systems, to improve the aerobic oxidation of p-cresol and 2-brom-p-cresol to their corresponding hydrox-yaldehydes. It has been found that the three-component catalytic systems are very effective in improving the oxidation reaction. Here, we report the results.

Materials and methods

Materials and apparatus

Salen-Cu(II) complexes were synthesized using the method in the literature [28]. NHPI was purchased from Acros Organics. 2-Methoxy-p-cresol, p-cresol, 2-bromo-p-cresol cobaltous chloride (CoCl₂·6H₂O), sodium hydroxide (NaOH), and HPLC-grade methanol, acetonitrile, and phosphoric acid were obtained from Tianjin Fuchen Chemical Reagent Factory, China. All the chemicals were used as received.



Scheme 1 Pathways for the formation of hydroxybenzaldehydes and by-products

HPLC experiments were performed with a Shimadzu (Kyoto Japan) SPD-10ATvp plus chromatograph equipped with an SPD-10Avp detector and C18 reversed-phase column (4.6 mm i.d. $\times 250$ mm). The mobile phase was 25 % acetonitrile–water containing 0.1 % phosphoric acid.

Catalytic Procedure

Oxidation reactions were conducted in a 10-ml two-necked flask equipped with a condenser and a thermometer. A balloon filled with oxygen was connected to the top of the condenser. All reactions were conducted at atmospheric pressure and stirred with an electromagnetic stirrer at a constant rate.

In a typical process, a mixture of NaOH (10.9 mmol) and methanol (2.0 ml) was introduced into the flask. The mixture was vigorously stirred at room temperature. When the NaOH had completely dissolved, 2-bromo-p-cresol (3.62 mmol) was added and the mixture was stirred for half an hour to ensure the substrate had been converted into its sodium salt. Cobaltous chloride, NHPI, and salen-Cu(II) complex were then quickly added. Chilled water was circulated through the condenser to minimize loss of the solvent. The mixture was heated to the desired temperature (65 °C), then the oxygen from the balloon was introduced, and controlled by use of a triple valve. After a specific time, the introduction of oxygen was stopped and the reaction mixture was left to cool to room temperature. The cooled reaction mixture was analyzed as described below.

Analysis of the reaction mixture

After the reaction, the whole reaction mixture was accurately weighed to obtain the total weight (w_t) . An accurately weighed amount (approx. 0.1 g) of the reaction mixture (w_0) was placed in a 10-ml volumetric flask, then an appropriate amount of

concentrated hydrochloric acid was added to neutralize the NaOH. The neutralized mixture was dissolved in mobile phase to a constant volume. The amounts of p-cresols and 4- hydroxyaldehydes (w_{s0} and w_{v0}) were determined by HPLC with use of an external standard.

The weight of 4-hydroxybenzaldehydes in the reaction mixture can be obtained by use of Eq. 1:

$$\mathbf{w}_{\mathbf{p}} = \left(\mathbf{w}_{\mathbf{t}} \times \mathbf{w}_{\mathbf{p}0}\right) / \mathbf{w}_{\mathbf{0}}(\mathbf{g}) \tag{1}$$

The weight of p-cresols left in the reaction mixture can be obtained by use of Eq. 2:

$$\mathbf{w}_{s} = \left(\mathbf{w}_{t} \times \mathbf{w}_{s0}\right) / \left(\mathbf{w}_{0}(\mathbf{g})\right) \tag{2}$$

Conversion (%) =
$$\frac{\text{moles of p-cresol reduced}}{\text{moles of p-cresol charged}} \times A'100\%$$
 (3)

Selectivity (%) =
$$\frac{\text{moles of p-hydroxybenzaldehydes obtained}}{\text{moles of p-cresol reduced}} \times A'100\%$$
 (4)

Yield
$$(\%)$$
 = Conversion × Selectivity (5)

Results and discussion

First, liquid-phase oxidation of 2-methoxy-p-cresol (A), p-cresol (B), 2-brom-pcresol (C) to their corresponding 4-hydroxybenzaldehydes was carried out by using the combination of cobaltous chloride and N-hydroxyphthalimide (NHPI) as catalyst in the presence of NaOH in methanol under atmospheric oxygen pressure. The reaction results under optimized conditions are listed in Table 1.

It can be seen that 2-methoxy-p-cresol and p-cresol were oxidized to vanillin and 4-hydroxybenzaldehyde in excellent and moderate yields, respectively. However, 2-bromo-p-cresol was converted to 3-bromo-4-hydroxybenzaldehyde only in low conversion and yield. These results indicated that the catalytic aerobic oxidation of p-cresols to hydroxybenzaldes is related to the substituents in the structures of the substrates. The electron-donating group facilitates the oxidation reaction; in contrast, the electron-withdrawing group is unfavorable to the reaction. As described in the "Introduction", the low yield of the reaction is mainly due to a considerable amount of the 4-hydroxybenzyl alcohols not being converted to their corresponding 4-hydroxybenzaldes. Therefore, two salen-Cu(II) complexes (1 and 2) were respectively introduced to the system to construct three-component catalysts to improve the oxidation reaction. The results are present in Table 2. It can be seen that both complexes can improve the selectivity towards 4-hydroxybenzalde in the oxidation of p-cresol; c1 performed better than c2 in view of the selectivity and yield of 4-hydroxybenzalde. When the molar ratio of c2 to p-cresol was 0.46 %, the selectivity of hydroxybenzalde increased from 74.4 to 83.9 %. The poor performance of c2 compared to c1 on the improvement of the selectivity of the target product is due to the fact that c2 is more active than c1 in promoting the transformation of the intermediate 4-hydroxybenzy alcohol to

| Entry | Sub | NaOH/Sub (mol/mol) | Methanol (ml) | Conversion (%) | Selectivity (%) | Yield (%) |
|-------|-----|-----------------------|---------------|-------------------|--------------------|--------------|
| 1 | А | 6.0:1 | 3 | 100.0 | 90.1 | 90.1 |
| 2 | В | 3.5:1 | 3 | 93.6 | 74.4 | 69.3 |
| 3 | С | 3.0:1 | 2 | 33.6 | 72.0 | 24.2 |

Table 1 Aerobic oxidation of p-cresols catalyzed by CoCl₂/NHPI

Reaction conditions: substrate 3.62 mmol; cobaltous chloride 0.0173 mmol; NHPI 0.0725 mmol; reaction temperature 65 °C; reaction time 7 h; atmospheric oxygen pressure

| Entry | Sub | Salen-Cu(II) | Time (h) | Conversion (%) | Selectivity (%) | Yield (%) |
|-------|---------------------------|--------------|----------|----------------|-----------------|-----------|
| 1 | \mathbf{B}^{a} | c1 | 7 | 94.8 | 83.9 | 79.5 |
| 2 | \mathbf{B}^{a} | c2 | 7 | 97.3 | 76.3 | 74.2 |
| 3 | C^b | c1 | 5 | 35.6 | 77.0 | 27.4 |
| 4 | C^{b} | c2 | 5 | 52.3 | 82.4 | 43.1 |
| 5 | C^b | c2 | 7 | 56.8 | 89.3 | 50.7 |
| 6 | C^b | c2 | 9 | 57.2 | 86.5 | 49.5 |

Table 2 Aerobic oxidation of p-cresols catalyzed by CoCl₂/NHPI/salen-Cu(II)

Reaction conditions: substrate 3.62 mmol; cobaltous chloride 0.0173 mmol; NHPI 0.0725 mmol; salen-Cu(II) 0.0166 mmol (salen-Cu(II) : substrate = 0.46 %); reaction temperature 65 °C; reaction time 7 h; atmospheric oxygen pressure

^a NaOH:substrate = 3.5:1, methanol 3 ml

^b NaOH:substrate = 3.0:1, methanol 2 ml

4-hydroxybenzaldehyde, and then leading to more 4-hydroxybenzoic acid formation from the further oxidation of 4-hydroxybenzaldehyde in the reaction system.

In the case of 2-bromo-p-cresol as substrate, both the complexes can obviously also increase the conversion of 2-bromo-p-cresol and the selectivity of the target product, but the conversion and selectivity are still low. Prolonging the reaction time can increase the conversion of 2-bromo-p-cresol gradually, while the selectivity of the target product also increased with reaction time at the beginning, but began to decrease when the conversion was higher than 56.8 %. No further improvement on the oxidation of 2-bromo-p-cresol was received by changing the reaction parameters.

To our knowledge, no catalytic oxidation of 2-bromo-p-cresol with molecular oxygen has been reported in the literature. However, many homogeneous and heterogeneous catalysts for the oxidation of 4-hydroxybenzy alcohol with molecular oxygen can be retrieved [16, 21, 22, 29]. For comparison, Table 3 presents the catalytic results of the current three-component catalyst and the other catalysts reported recently. It can be seen that the current three-component catalyst performed better than the other homogeneous catalysts reported in the literature in the conversion and selectivity towards 4-hydroxybenzalde. The heterogeneous catalysts

| Catalyst | Туре | Pressure (MPa) | Temperature (°C) | Conversion (%) | Selectivity (%) | Ref. |
|--------------------------------------|-------------------------|-------------------|---------------------|-------------------|--------------------|------------|
| CoCl ₂ /NHPI/c1 | Homogeneous | 0.1 | 65 | 94.8 | 83.9 | This study |
| TPPCo | Homogeneous | 0.1 | 70 | 69.6 | 66.0 | [15] |
| Co(salen)-Mont | Immobilized homogeneous | 0.1 | 65 | 37.0 | 88.0 | [28] |
| PVDF-CoP ₂ O ₇ | Heterogeneous | 1.0 | 75 | 94.2 | 94.4 | [29] |
| Co ₃ O ₄ | Heterogeneous | 0.8 | 100 | 98.0 | 95.0 | [21] |

Table 3 Comparison of the current three-component catalyst with the other catalysts in the literature

showed good performances compared to the current catalyst; however, harsh reaction conditions such as high oxygen pressure and reaction temperature were required.

It is well known that Co/NHPI can efficiently catalyze the oxidation of alkanes with molecular oxygen, and the mechanism has been described in detail by Ishii [30]. The initial step is the complexation of Co(II) with O_2 to generate a labile dioxygen complex such as superoxocobalt(III). The second step is the formation of the free radical PINO by the reaction of the NHPI with the cobalt(III)–oxygen complex. The third step in the oxidation involves the hydrogen abstraction from RH by the PINO to form R_{\cdot} , which is readily trapped by dioxygen to provide ROOfollowed by ROOH and eventually the formation of alcohols, ketones, and/or carboxylic acids (Fig. 1).

$$Co^{II} + O_2 \longrightarrow Co^{III} - O - O \bullet$$
 (6)

$$C_{0}^{III}-O-O^{\bullet} + \bigvee_{O}^{O} NOH \longrightarrow \bigvee_{O}^{O} NO^{\bullet} + C_{0}^{III}-O-OH$$
(7)
NHPI PINO

In the current three-component catalyst, the formed free radical PINO also combined with salen-Cu(II) to promote the oxidation of 4-hydroxybenzy alcohol, being an intermediate in the oxidation of p-cresol to 4-hydroxybenzaldehyde. A plausible pathway for the salen-Cu(II)-promoted oxidation of the 4-hydroxybenzy alcohol to 4-hydroxybenzaldehyde is shown in Fig. 2. The 4-hydroxybenzy alcohol firstly coordinates with the central Cu(II) of the salen-Cu(II) complex, where one of the phenoxide groups is converted to phenol [31–33]. Subsequently, an intramole-cular abstraction of β -hydrogen with PINO occurs and the corresponding aldehyde, NHPI, and Cu(I) species are formed. In the presence of oxygen superoxocobalt(III) generated from Co(II) and oxygen, the PINO is regenerated back to PINO; meanwhile, the oxygen reoxidizes the Cu(I) species back to the original salen-Cu(II) complex [24].





c1: R = H; **c2**: R = C(CH₃)₃



Fig. 2 A plausible pathway for the oxidation of the 4-hydroxybenzy alcohols to 4-hydroxybenzaldehydes catalyzed by salen-Cu(II)

It is worth mentioning that our purpose in investigating the aerobic oxidation of 2-methoxy-p-cresol, p-cresol, and 2-bromo-p-cresol to the corresponding 4-hydroxybenzaldes is to establish a route for synthesizing vanillin from p-cresol. In principle, there are three possible synthetic routes (a, b, and c) to vanillin from p-cresol as shown in Scheme 2. The respective oxidation of 2-methoxy-p-cresol, p-cresol, and 2-bromo-p-cresol is one elementary step in the corresponding synthetic routes. Due to the very low conversion and selectivity towards 3-bromo-4hydroxybenzaldehyde in the aerobic oxidation of 2-brom-p-cresol, route b can be excluded from the synthesis of vanillin from p-cresol.



Scheme 2 Possible routes for synthesis of vanillin from p-cresol

Conclusions

The cobaltous chloride/NHPI catalyzed aerobic oxidation of p-cresols to the corresponding 4-hydroxybenzaldes is related to the structures of the substrates. The electron-donating group facilitates the oxidation reaction; in contrast, the electron-withdrawing group is unfavorable to the reaction. The introduction of salen-Cu(II) complexes as the third component into the cobaltous chloride/NHPI catalytic system can obviously improve the aerobic oxidation of p-cresol and 2-brom-p-cresol to the corresponding 4-hydroxybenzaldes.

Acknowledgment The authors are grateful for financial support from the National Natural Science Foundation of China (No. 21276061).

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