Available online at www.sciencedirect.com

ScienceDirect

Catalysis Today 131 (2008) 423–426

CATALYSIS TODAY

www.elsevier.com/locate/cattod

A facile synthesis of 3,5-dimethyl-4-hydroxybenzaldehyde via copper-mediated selective oxidation of 2,4,6-trimethylphenol

Xiaojiao Sun [a], Zaher M.A. Judeh [a,*], Basem F. Ali [b], Solhe F. Alshahateet [c]

[a] *School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, N1.2 B1-14, Singapore 637459*
[b] *Department of Chemistry, Al al-Bayt University, Mafraq, Jordan*
[c] *Department of Chemistry, Taibah University, P.O. Box 30002, Madina, Saudi Arabia*

Abstract

2,4,6-Trimethylphenol was selectively oxidized to 3,5-dimethyl-4-hydroxybenzaldehyde in very good yields using catalytic or equivalent amounts of $CuCl_2$ in the presence of K_2CO_3 and H_2O_2 in *i*-PrOH at 65 °C. The effect of the molar ratios of $CuCl_2$, K_2CO_3 and H_2O_2 on the yields and product distribution was examined. The oxidation reaction was found to proceed smoothly without the use of additives or ligands which were reported to be necessary.

Keywords: Oxidation; Copper(II) chloride; Mesitol; 2,6-Dimethyl-4-(isopropoxymethyl)phenol; 3,5-Dimethyl-4-hydroxybenzaldehyde

1. Introduction

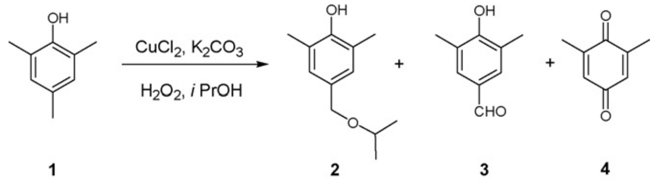
The use of substituted 4-hydroxybenzaldehydes as intermediates in the pharmaceutical, perfume, dye and agrochemical industries continues to drive interest in finding more effective and practical routes for their synthesis [1,2]. For example, 3,5-dimethyl-4-hydroxybenzaldehyde **3** (Scheme 1), used for the synthesis of potential antioxidant cancer chemopreventive agents [3], is mainly synthesized by the oxidation of the far less useful 2,4,6-trimethylphenol **1** (Scheme 1). Methods that have been employed to synthesize 4-hydroxybenzaldehydes include reacting phenols with formaldehyde [4], glyoxylic acid [5] or chloroform [6] and the use of stoichiometric amounts of inorganic oxidants such as iodine, bromine and potassium dichromate [7–11] as well as electric or electrocatalytic oxidation techniques [12]. However, the most appealing synthetic approaches surveyed in the literature remains to be direct catalytic oxidations. Interestingly, there have been only a few catalyst selective oxidation routes for the synthesis of **3** from **1.** These systems include cobalt(II)-Schiff base complex [1,13], iron-based catalysts [14,15], copper(II)-amine complex [16,7], and copper(II)-neocuproine sodium methoxide complex [17]. We noted that the above catalytic systems required the use of additives/ligands and/or higher pressure to achieve good yields [16,17]. For example, it was reported [16,17] that the catalytic oxidation reaction of **1** hardly afforded **2** or **3** in the absence of amine additives/ligands. Moreover, it was found that while copper(II)-neocuproine catalyst system gave excellent yields of **3**, copper(II)-2,2′-bipyridine complex was found to be inactive [17]. The inactivity was attributed to the less crowdedness of the 2,2′-bipyridine complex compared to the neocuproine complex where the *ortho*-methyl groups are said to provide the required stability of the tetrahedral geometry of the Cu(I) ions [17]. In view of the above findings and during the course of study on the synthesis and catalytic application of 1,1′-bisisoquinolines [18–20], we became interested in the synthesis of **3** via the catalytic oxidation of **1** with and without the use of additives/ligands.

In this paper, we report a facile synthesis of 3,5-dimethyl-4-hydroxybenzaldehyde **3** via the oxidation of 2,4,6-trimethylphenol **1** (mesitol) using $CuCl_2$–K_2CO_3–H_2O_2 (30%) catalytic system at atmospheric pressure without the use of additives/ligands (Scheme 1). The use of 1,1′-bisisoquinoline as ligands for this oxidation will be reported in a separate paper.

---

* Corresponding author. Tel.: +65 67906738; fax: +65 67947553.
E-mail address: zaher@ntu.edu.sg (Z.M.A. Judeh).

0920-5861/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2007.10.062



Scheme 1. Oxidation of 2,3,4-trimethylphenol 1.

2. Experimental

In a typical experiment, a mixture of 2,4,6-trimethylphenol **1** (1.5 mmol), K_2CO_3 (0.3–2 molar eq.) and 1,2,4,5-tetrabromobenzene (0.05 molar eq., as an internal standard) was vigorously stirred together in *i*-PrOH (6 ml) under nitrogen atmosphere in a 25 ml reaction tube and heated at 65 °C. Immediately, solid anhydrous $CuCl_2$ (0.3–1 molar eq.) was added to the above mixture and the reaction was stirred for 5 min. The reaction tube was then removed from the heating station whereby H_2O_2 (30%, 1–5 molar eq.) was carefully added under vigorous stirring. After H_2O_2 addition, the mixture was stirred at 65 °C for 6 h. The reaction mixture was evaporated under reduced pressure, the residue obtained was diluted with $CHCl_3$ (10 ml) and the organic layer was separated. The organic phase was washed with 4% HCl (25 ml) and the aqueous phase was further extracted with $CHCl_3$ (2 × 10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a brown gum.

3. Results and discussion

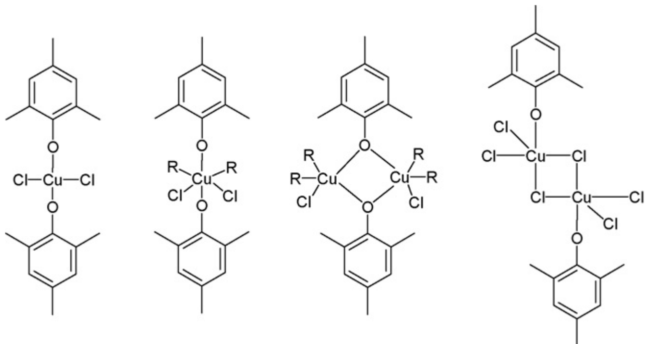
The experimental results are shown in Table 1. Initially, the oxidation reaction (Scheme 1) was performed using an equivalent molar ratio (based upon **1**) of 1:1:3 of $CuCl_2$, K_2CO_3 and H_2O_2, respectively, (entry 1). Interestingly, aldehyde **3** was obtained in 32% yield accompanied with product **2** which was obtained in 57% yield (entry 1). In fact, product **2** is an intermediate necessary to form aldehyde **3** [21]. This result was significant; it proved that the above catalytic system successfully oxidized **1** to **3** albeit with the formation of intermediate **2** and byproduct **4**[1] (1% yield). Therefore, the effect of the molar ratios of CuCl, K_2CO_3 and H_2O_2 on the yields and products distributions was investigated. An increase in the amount of base to 2 molar eq. (entry 2) resulted in the decrease in the yields of both aldehyde **3** (23% yield) and intermediate **2** (35% yield). The decrease in the yield of **2** and **3** was accompanied by an increase in the yield of byproduct **4** from 1% (entry 1) to 17%. It was concluded that an increase in the amount of base is not desirable. However, when the amount of base was decreased to 0.3 molar eq. (entry 3), an obvious increase in the yield of the desired aldehyde **3** (74%) was observed and no traces of any other products could be observed in the ^1H NMR spectrum. Therefore, the favorable ratio of the base was concluded to be 0.3 molar eq. based upon **1**. When comparing entries 1 and 2, the yields of products **2** and **3** using 1 molar eq. of the base were higher (57 and 32%, respectively) than those (35 and 23%, respectively) employing 2 molar eq. Considering that 1 eq. of the base is needed to react with **1** to form the phenolate anion **5** (Fig. 1), the other 1 molar eq. may react with $CuCl_2$ to form $CuCO_3$ or Cu_2CO_3. As a result, the active amount of [Cu] may have been decreased leading to low yields of **2** and **3**. In fact, during the experiment, greenish precipitates were observed when $CuCl_2$ was added to the reaction mixture indicating the apparent formation of $CuCO_3$.The use of 1 molar eq. of H_2O_2 (entry 4) resulted in 36% yield of the aldehyde **3** accompanied by 19% yield of byproduct **4**. When the number of molar eq. of H_2O_2 was increased from 1 to 2, 3 or 4 molar eq. (entries 5, 3 and 6, respectively), the yield of the desired aldehyde **3** increased from 36 to 70, 74 and 77%, respectively. A further increase in the number of molar eq. of H_2O_2 to 5 molar eq. (entry 7) resulted in a slight decrease in the yield of aldehyde **3** to 73%. Therefore, the favorable number of molar eq. of H_2O_2 was inferred to be 3–4 eq. The use of H_2O_2 in this oxidation reaction was essential to reoxidize Cu(I) to Cu(II) since molecular oxygen was found to be inefficient for this reoxidation [17].

Table 1
Synthesis of 3,5-dimethyl-4-hydroxybenzaldehyde **3** via selective oxidation of 2,4,6-trimethylphenol **1**[a]

Entry	$CuCl_2$ (molar eq.)	K_2CO_3 (molar eq.)	H_2O_2 (molar eq.)	Yield (%)[a]		
				2	**3**	**4**
1	1	1	3	57	32	1
2	1	2	3	35	23	17
3	1	0.3	3	–	74	–
4	1	0.3	1	–	36	19
5	1	0.3	2	9	70	5
6	1	0.3	4	–	77	–
7	1	0.3	5	–	74	–
8	0.5	0.3	3	6	60	–
9	0.3	0.3	3	6	65	8

[a] The yields (±5%) were determined by ^1H NMR spectroscopy using 1,2,4,5-tetrabromobenzene as an internal standard after work-up and based on complete conversion of **1**.

In entries 1–7, the amount of $CuCl_2$ was kept at 1 molar eq. (stoichiometric) to explore the effect of the change in ratios of

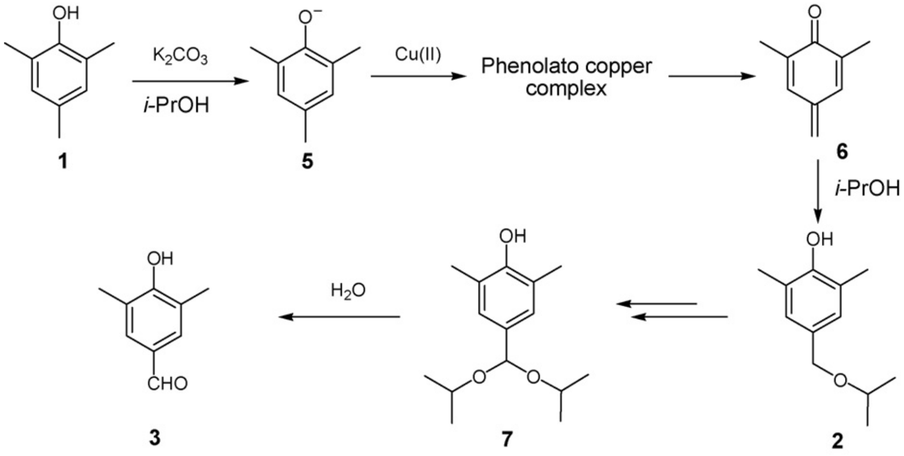


R = Base, water and/or *i*-PrOH

Fig. 1. Phenolato copper complexes.

---

[1] Although no attempts were made to separate byproduct **4**, ^1H NMR analysis suggest it to be 2,6-dimethy-*p*-benzoquinone, a byproduct that has been previously observed in this oxidation reaction [7].



Scheme 2. Proposed mechanism of the formation of 3,5-dimethyl-4-hydroxybenzaldehyde 3.

K_2CO_3 and H_2O_2. When the number of molar eq. of $CuCl_2$ was reduced to 0.5 (entry 8), the yield of aldehyde **3** was reduced to 60%. A further decrease in the amount of $CuCl_2$ to 0.3 molar eq. (entry 9) resulted in an increase in the yield of aldehyde **3** to 65%. In both cases it is noted that the yield of product **2** remained constant at 6% (entries 8 and 9) while the yield of the byproduct increased to 8% (entry 9). The higher yields observed in entries 3, 6 and 7 may be attributed to the fact that an equivalent amount of Cu (II) was available to complex with the phenoxide anion formed in the presence of K_2CO_3 (Fig. 1). In contrast, the lower yields obtained when the amount of $CuCl_2$ was reduced to 0.5 (60%, entry 8) or 0.3 (65%, entry 9) may be attributed to the less Cu(II) that was available to form the phenolato copper complex.[2] The formation of the phenolato complex is important for the activation of the *para*-benzylic protons (Fig. 1) to undergo oxidation.

These results showed that the $CuCl_2$–K_2CO_3–H_2O_2 (30%) system was effective in oxidizing **1** to give **2** and/or **3** in very good yields reaching up to 77% without the need of any special additives/ligands. Attempts to optimize the catalytic amount of $CuCl_2$ are ongoing.

It is established that phenols can coordinate to copper to form various phenolato copper complexes [22–25]. With the present system, a mono and/or dinuclear complexes (Fig. 1) can be suggested to operate. A plausible reaction pathway can be proposed as shown in Scheme 2 [7,17,26,27]. Phenol **1** is converted to the phenolate anion **5** under alkaline conditions (K_2CO_3). A phenolato copper complex is formed by the reaction between the phenolate anion **5** and $CuCl_2$ (Fig. 1). As a result to this complexation, the *para*-benzylic protons are activated and a very reactive transitorily *para*-benzoquinone methide **6** is formed. The nucleophilic addition of *i*-PrOH to the *para*-benzoquinone methide **6** leads to the formation of intermediate **2**. Addition of another molecule of *i*-PrOH in the same fashion leads to the formation of an intermediate ketal **7** which upon hydrolysis gives product **3**. The identity of the phenolato copper complex is under investigation.

4. Conclusion

3,5-Dimethyl-4-hydroxybenzaldehyde **3** was obtained in yields up to 77% via selective oxidation of the less useful 2,4,6-trimethylphenol **1** using catalytic or stoichiometric amounts of $CuCl_2$. The reaction proceeded smoothly without the need of additive/ligands. Excess K_2CO_3 was found to inhibit the formation of 3,5-dimethyl-4-hydroxybenzaldehyde **3** while excess H_2O_2 was found to be beneficial. The favorable ratio of the catalyst system was found to be 1:0.3:3 of $CuCl_2$, K_2CO_3 and H_2O_2, respectively.

Acknowledgement

We would like to thank the Nanyang Technological University (NTU) for financial support.

References

[1] S. Raic-Malic, L. Tomaskovic, D. Mrvos-Sermek, P. Biserka, C. Mario, G. Mira, P. Kresimir, M. Albrecht, B. Jan, D. Erik, M. Mladen, Bioorg. Med. Chem. 12 (2004) 1037–1045.
[2] C. Lottner, K.-C. Bart, G. Bernhardt, H. Brunner, J. Med. Chem. 45 (2002) 2079–2089.
[3] K.M. Youssef, M.A. El-Sherbeny, F.S. El-Shafie, H.A. Farag, O.A. Adeeb, S.-A.A. Awaddalla, Arch. Pharm. 337 (2004) 42–54.
[4] M. Komiyama, H. Hirai, J. Am. Chem. Soc. 105 (1983) 2018–2021.
[5] K. Nishizawa, K. Hamada, T. Aratani, Eur. Patent Appl. 0012939 (1979). K. Nishizawa, K. Hamada, T. Aratani, Chem. Abstr. 94 (1981) 46967q.
[6] A. Schouteen, Y. Christidis, Eur. Patent Appl. 0019531 (1980).
[7] M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, K. Takehira, Bull. Chem. Soc. Jpn. 66 (1993) 251–257.
[8] K. Omura, J. Org. Chem. 49 (1984) 3046–3050.
[9] S.L. Goldstein, E. Mcnelis, J. Org. Chem. 49 (1984) 1613–1620.
[10] G.M. Coppinger, T.W. Campbell, J. Am. Chem. Soc. 75 (1953) 734–736.
[11] S.G. Grundy, K.M. Reeve, M.C. Rocca, Eur. Patent Appl. P 569892 A2 (1993).
[12] H. Ohmori, C. Ueda, Y. Tokuno, H. Maeda, M. Masui, Chem. Pharm. Bull. 33 (1985) 4007–4011.
[13] P.A. Ganeshpure, S. Satish, Tetrahedron Lett. 29 (1988) 6629–6632.

---

[2] These results have to be taken in a context of the accuracy of the measurements of the yields from the ^{1}H NMR spectra (±5%).

[14] K.-T. Li, P.-Y. Liu, Appl. Catal. A: Gen. 272 (2004) 167–174.

[15] K.-T. Li, P.-Y. Liu, J. Mol. Catal. A: Chem. 241 (2005) 72–78.

[16] K. Takehira, M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, Tetrahedron Lett. 31 (1990) 2607–2608.

[17] C. Boldron, P. Gamez, D.M. Tooke, A.L. Spek, J. Reedijk, Angew. Chem. Int. Ed. 44 (2005) 3585–3587.

[18] D.C. Craig, Z.M.A. Judeh, R. Read, Tetrahedron 59 (2003) 461–472.

[19] Z.M.A. Judeh, C.B. Ching, J. Bu, A. McCluskey, Tetrahedron Lett. 43 (2002) 5089–5091.

[20] S. Busato, D.C. Craig, Z.M.A. Judeh, R. Read, Aust. J. Chem. 55 (2002) 733–736.

[21] M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, K. Takehira, Bull. Chem. Soc. Jpn. 65 (6) (1991) 1522–1526.

[22] H.-S. He, Acta Cryst. E62 (2006) m1782–m1783.

[23] Y.-M. Yang, Acta Cryst. E61 (2005) m1616–m1617.

[24] N.E. Kuz'mina, K.K. Plkina, N.V. Polyakova, I.N. Golubev, A.N. Medvedev, O.V. Koval'chukova, S.B. Strashnova, B.E. Zaitsev, A.N. Levov, F. Toze, Zhurnal Neorganicheskoi Khimii 47 (2002) 1843–1847.

[25] I.I. Seifullina, L.S. Skorokhod, O.D. Chursina, Zhurnal Neorganicheskoi Khimii 36 (1991) 969–973.

[26] R.A. Sheldon, N. de Heij, in: W. Ando, Y. Moro-Oka (Eds.), Studies in Organic Chemistry: The Role of Oxygen in Chemistry and Biochemistry, Elsevier, Amsterdam, 1988, pp. 243–256.

[27] C. Boldron, S. Ozalp-Yaman, P. Gamez, D.M. Tooke, A.L. Spek, J. Reedijk, Dalton Trans. (2005) 3535–3541.