Article

JOURNAL OF THE CHINESE
CHEMICAL SOCIETY

Cobalt-catalyzed Aerobic Oxidation of Eugenol to Vanillin and Vanillic Acid

Haifang Mao, Lizhi Wang, Feifei Zhao, Jianxin Wu, Haohua Huo and Jun Yu*
School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, P.R. China

(Received: Sept. 1, 2015; Accepted: Dec. 10, 2015; Published Online: Jan. 26, 2016; DOI: 10.1002/jccs.201500357)

A novel, simple, one-step method of synthesizing vanillin and vanillic acid from eugenol has been developed. The method uses ligand- and additive-free $Co(OAc)_2 \cdot 4H_2O$ as catalyst and molecular oxygen as oxidant to achieve catalytic process without isomerizing eugenol. Extensive screening efforts were used to optimize eugenol to obtain vanillin and vanillic acid. Under optimal conditions, the reaction provided vanillin and vanillic acid with 68.5% and 15.2% yields, respectively. Apart from the desired products, coniferyl alcohol 9-methyl ether and 4-hydroxy-3-methoxycinnamaldehyde as two intermediates were also detected in the reaction process. Level changes of all compounds over time were presented in the reaction. The reaction pathway from eugenol to vanillic acid was validated by conducting several control experiments. Furthermore, a possible reaction mechanism dominated by a circular redox reaction from Co(III) and Co(II) species was proposed. This method offers a potentially practical alternative for manufacturing vanillin and vanillic acid efficiently.

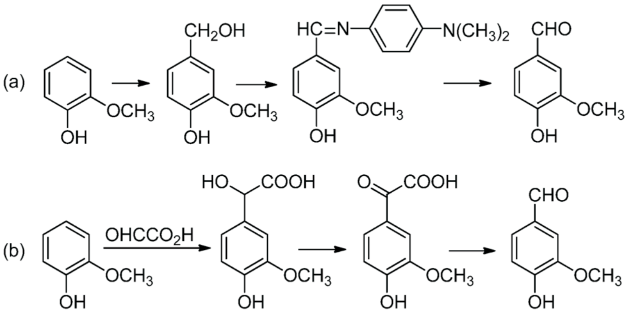
Keywords: Eugenol; Vanillin; Molecular oxygen; Oxidation; Catalysis.

INTRODUCTION

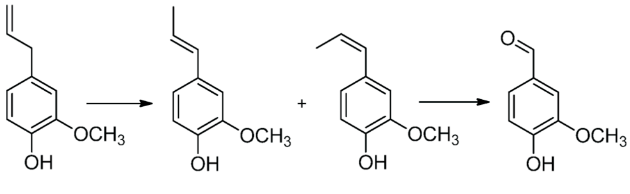
Vanillin (4-hydroxy-3-methoxybenzaldehyde) and vanillic acid (4-hydroxy-3-methoxybenzoic acid) are two types of popular flavoring materials used worldwide.[1-2] Both are widely employed in the pharmaceutical industry.[3] Moreover, vanillin has a wide range of applications in the manufacture of food, beverages, flavors, and fragrances.[4] The market demand for vanillin in 2010 was over 15000 tons, and this demand increases year by year. However, the market supply of vanillin is only 10000 tons per year.[5]

Nowadays, most vanillin is synthesized *via* nitrose method (Scheme 1a) and glyoxylic acid method (Scheme 1b).[6-8] With dwindling petroleum resources, renewable methods for producing vanillin should be investigated.[9-10] Recently, eugenol has been used as a substrate for manufacturing vanillin because of its economic and commercial availability.[11] The normal chemical synthesis of vanillin from eugenol requires two steps (Scheme 2). First, the eugenol is isomerizated to isoeugenol under basic conditions.[12] Then, the isoeugenol is oxidized into vanillin by using oxidants, such as potassium permanganate,[13] iodobenzene diacetate,[14] or hydrogen peroxide.[15] However, the above process usually requires high temperatures and generates excessive waste materials.[8,13] Thus, new alternative and environmentally friendly chemical processes are necessary.

Scheme 1 Synthesis of vanillin from guaiacol



Scheme 2 Normal synthesis of vanillin from eugenol



Transition-metal catalyzed oxidation reactions utilizing molecular oxygen as oxidant offer attractive industrial prospects.[16-17] A variety of transition-metal catalysts, such as copper, cobalt, nickel, iron, and manganese, has been employed for benzylic oxidation of aromatic compounds.[16] Commercially available cobalt salts, which are inexpensive and have low toxicity, are widely used in straightforward benzylic $C(sp^3)$-H oxyfunctionalization.[7] Li *et al.* synthesized a Co-[Salen-Py][PF_6]$_2$ catalyst for the oxidation of

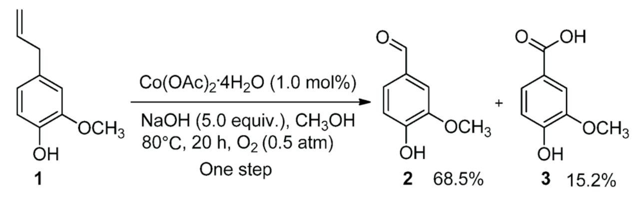
---

* Corresponding author. Tel: +86-021-6087223; Fax: +86-021-60877231; Email: yujun@sit.edu.cn

4-methyl guaiacol to vanillin by using ethylene glycol as the solvent. A circular redox reaction from Co(III) and Co(II) species is the key for oxidation.[6] However, this catalyst is rather complex and hard to synthesize. In addition, despite ethylene glycol being an ideal solvent, its high boiling point makes it difficult to recycle. Hence, industrial production of these products is constrained by the use of impractical metal-ligand-coordinated catalysts and high-boiling ethylene glycol.

In this study, $Co(OAc)_2$ without ligand and additive was used as the reaction catalyst, and its catalytic performance for aerobic oxidation of eugenol to vanillin and vanillic acid was investigated for the first time (Scheme 3). The reaction was performed under the mediation of NaOH and methanol without isomerizing eugenol. The effects of main reaction parameters, NaOH amount, temperature, and catalyst loading were also analyzed. The desired products and two intermediates were separated in the reaction process. Level changes of all compounds as a function of time were clearly presented. Then, the reaction pathway from eugenol to vanillic acid was determined by several control experiments. In addition, a possible reaction mechanism was proposed through further studies.

Scheme 3 One-step synthesis of vanillin and vanillic acid from eugenol



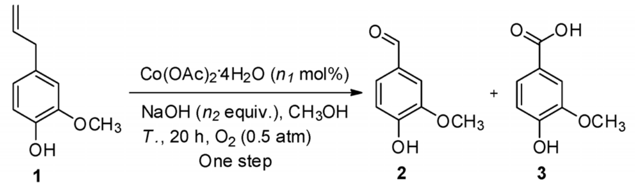
RESULTS AND DISCUSSION

Selected optimizations for oxidation

Table 1 shows the effects of NaOH content, reaction temperature, and catalyst loading on the catalytic performance of eugenol during aerobic oxidation. It can be seen that $Co(OAc)_2{\cdot}4H_2O$ proved to be an effective catalyst for producing vanillin (2) and vanillic acid (3) with the yields of 51.5% and 9.6% at 70 °C, respectively (entry 1). Furthermore, an enhanced reaction temperature of 80 °C remarkably increased the yields of 2 and 3 to 64.3% and 12.8%, respectively (entry 2). However, an increased temperature of 90 °C resulted in minimal change, indicating that high temperatures are not necessary for screening (entry 3). The reason may be that properly elevating the temperature improves oxidation efficiency. Obviously, the oxidation reaction could not proceed with the absence of NaOH (entry 4). However, a 5.0 equiv. of NaOH turned out to be sufficient to produce the highest yields for 2 and 3 at 66.7% and 16.2%, respectively (entry 5). However, minimal change was observed in these yields when NaOH content was increased to 6.0 equiv. (entry 6). It is indicated that NaOH is important in triggering the oxidation. The large excess of NaOH, offering strong alkaline conditions, was necessary to maintain high selectivity for the desired products.[21] The same yields were achieved using 1.5 or 1.0 mol% $Co(OAc)_2{\cdot}4H_2O$ (entries 5 and 7; entry 7 with optimal reaction condition). When using a lower catalyst loading of 0.5 mol%, the yields of 2 and 3 dropped sharply to 61.4% and 11.9%, respectively, and most impurities were formed (entry 8). One possible reason for this observation was that a small amount of catalyst limited the generation of products. In addition, only trace amounts of 2 and 3 were observed under nitrogen atmosphere without oxygen (entry 9).

Level changes of all compounds over time are labeled in Figure 1. It shows that, apart from the desired products 2 and 3, coniferyl alcohol 9-methyl ether (4) and 4-hydroxy-3-methoxycinnamaldehyde (5) were also isolated in the reaction process (the structures of all compounds are shown

Table 1. Selected optimizations for the reaction conditions[a]



Entry	$Co(OAc)_2{\cdot}4H_2O$ [n_1]	NaOH [n_2]	*T.* [°C]	Yield [%][b] 2	3
1	1.5	4.0	70	51.5	9.6
2	1.5	4.0	80	64.3	12.8
3	1.5	4.0	90	63.0	13.4
4	1.5	0	80	0	0
5	1.5	5.0	80	66.7	16.2
6	1.5	6.0	80	65.4	16.6
7	1.0	5.0	80	68.5	15.2
8	0.5	5.0	80	61.4	11.9
9[c]	1.0	5.0	80	trace	trace

[a] *Reaction conditions*: **1** (0.2 mol), $Co(OAc)_2{\cdot}4H_2O$ (n_1 mol%), NaOH (n_2 equiv.), CH_3OH (150 mL), *T.*, O_2 (0.5 atm), reaction time (20 h).
[b] Isolated yield.
[c] Performed under nitrogen atmosphere without oxygen.

Level Changes of All Compounds over Time

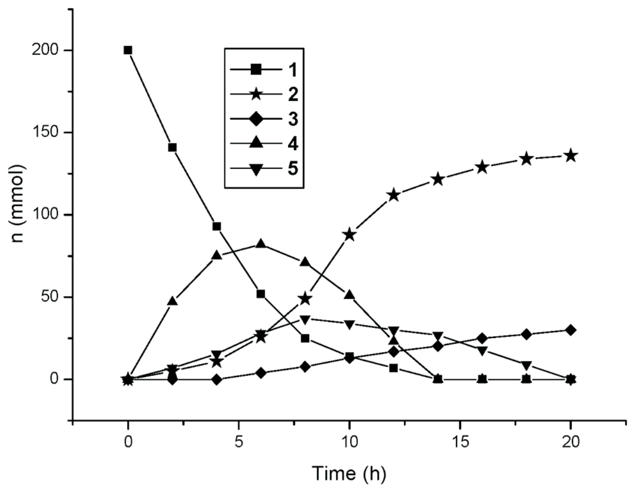
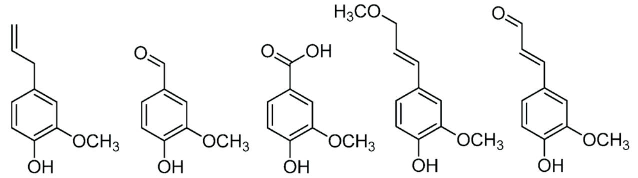


Fig. 1. Time-dependent changes for the levels of all compounds. Reaction conditions: 1 (0.2 mol), $Co(OAc)_2{\cdot}4H_2O$ (1.0 mol%), NaOH (5.0 equiv.), CH_3OH (150 mL), 80 °C, O_2 (0.5 atm).

in Scheme 4). The quantity of 1 decreased sharply during the initial 8 h and disappeared at 14 h. The yield of product 2 increased slowly during the first 4 h and rapidly in the next 8 h, after which it increased slowly and achieved the best yield of 68.5% at 20 h. Product 3 was produced at 4 h, after which its yield increased slowly to 15.2% at 20 h. The level of compound 4 rapidly increased in the beginning and peaked with a 41% yield at 6 h before dropping gradually and disappearing by 14 h. Similarly, compound 5 initially increased and peaked (18.5% yield) at 8 h and gradually decreased before disappearing by 20 h. The disappearance of compounds 4 and 5 at the end of the reaction indicated that they are intermediates in the reaction. Figure 1 shows the changes of all compound levels as a function of time in the reaction process. However, these changes cannot explain the specific pathway of the reaction.

Scheme 4 The structures of all compounds of the reaction

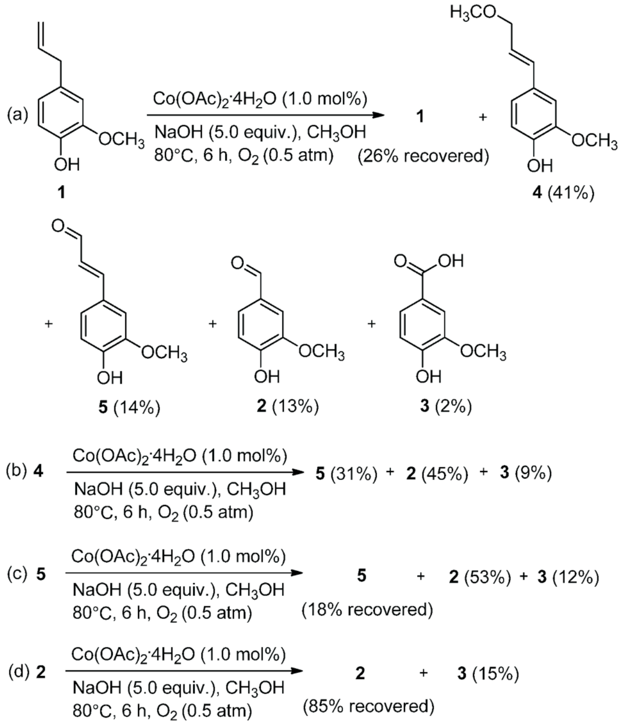


1 2 3 4 5

Reaction pathway

All pure products and intermediates were isolated through column chromatography on silica gel (200–300 mesh). Several control experiments were then conducted to investigate the reaction pathway (Scheme 5). Under optimal conditions, using 1 as reaction substrate produced intermediates 4 (41% yield) and 5 (14% yield), as well as the desired oxidation products 2 and 3 (13% and 2% yields, respectively) at 80 °C for 6 h (Scheme 5a). Using 4 instead of 1, the reaction provided compounds 5, 2, and 3 with 31%, 45%, and 9% yields, respectively (Scheme 5b). 5 produced the desired products 2 and 3 with yields of 53% and 12% (Scheme 5c). Furthermore, a small amount of 3 (15% yield) also could be obtained using 2 as the reaction substrate (Scheme 5d). The results show that substrate 1 gradually generated two intermediates and two desired products. When 4 was employed as the substrate, compounds 5, 2, and 3 were produced in the reaction. By contrast, 5 was converted to 2 and 3 without any 4 being detected in the process. In addition, no 5 was observed in the oxidation of 2 to 3. In conclusion, substrate 1 initially generated 4, which was transformed into 5 followed by the subsequent transformations of 5 to 2 and 2 to 3 in the process, forming the reaction pathway (Scheme 6).

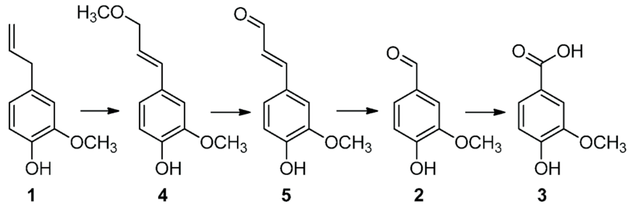
Scheme 5 Studies for oxidation process of eugenol



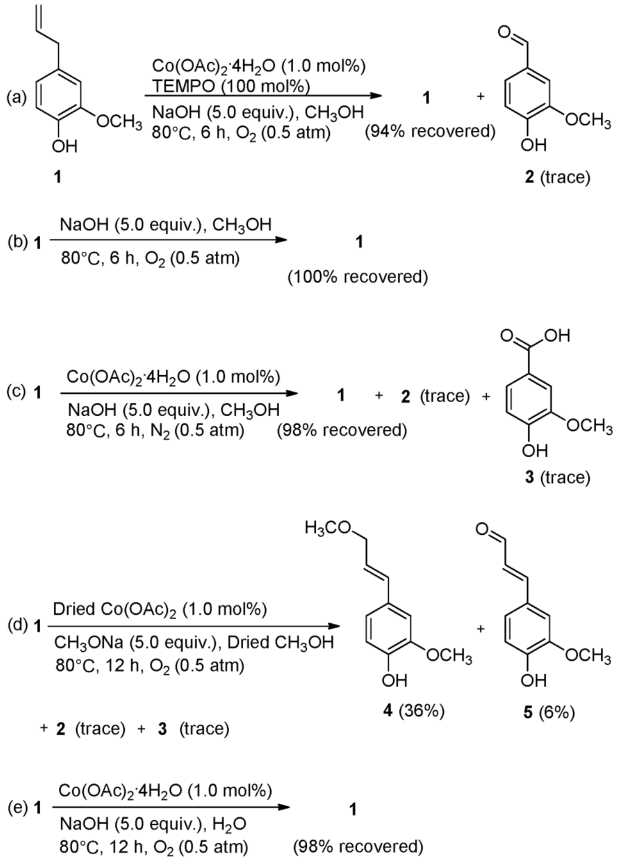
Reaction mechanism and role of Co

Several control experiments were conducted to further explore the mechanism of the oxidation reaction

Scheme 6 Oxidation process of eugenol



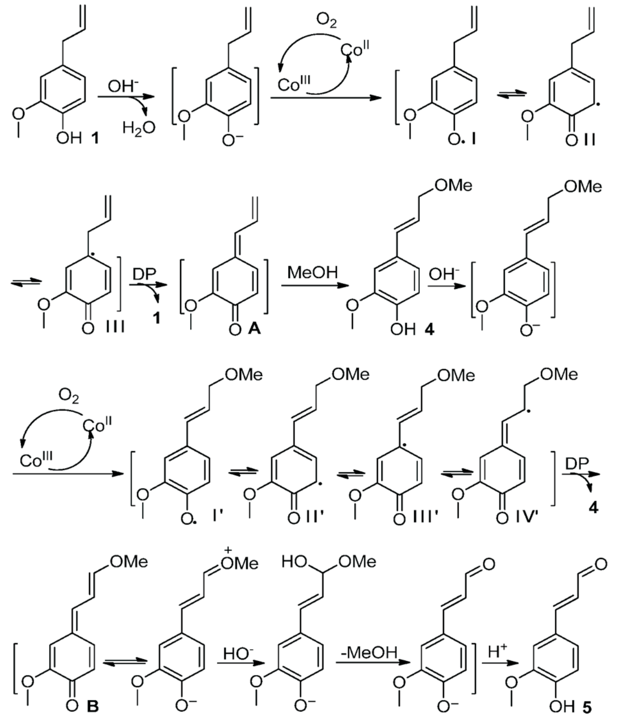
Scheme 7 Mechanistic studies for intermediates



(Scheme 7). When the radical inhibitor 2, 2, 6, 6-tetramethylpiperidine-N-oxyl (TEMPO) [22] (100 mol%) was added into the reaction, only a trace amount of 2 was isolated (Scheme 7a). No product was observed at the absence of the catalyst (Scheme 7b). Only trace amounts of 2 and 3 were detected under nitrogen atmosphere (Scheme 7c). Using dried $Co(OAc)_2$ (1.0 mol%), dried methanol, and CH_3ONa (5.0 equiv.) instead of NaOH at 80 °C for 12 h, the reaction produced 4 and 5 with 36% and 6% yields, respectively (Scheme 7d). Additionally, no product resulted from the reaction using pure H_2O as solvent (Scheme 7e). The results indicate that a free radical oxidation process exists, in which TEMPO could efficiently suppress oxidation reaction. No product could be produced without using a catalyst or oxygen in the reaction. This finding indicates that a radical oxidation process occurred, in which the catalyst and oxygen acted as the initiator. A large amount of 4 wasn't translated into 5 when all the dried reagents and neat methanol were employed, indicating the direct involvement of H_2O in the transformation process. However, a small amount of 5 was still produced in the control experiment (Scheme 7d). The reason for this finding could be that the reaction system containing Co(II) species can generate a small amount of H_2O in the presence of oxygen. That is to say, in the Co(II)/O_2 system, Co(II) species reacted with $1/4O_2$ to form Co(III) species and $1/2H_2O$. The transformation of 1 to 4 suggests the involvement of methanol in the formation of intermediate 4 (Scheme 6). On the other hand, the results also indicated that the reaction could not proceed with the use of H_2O as solvent (Scheme 7e). These findings proved that mediation of methanol is indispensable for this oxidation reaction.

Based on the above findings and Baik-Ji-type mechanism beginning with a phenoxy radical,[17,23] a similar radical reaction mechanism was proposed to rationalize the alkaline $Co(OAc)_2{\cdot}4H_2O$-catalyzed oxidation of 1 (Scheme 8). A hydrogen ion is abstracted from the phenolic hydroxyl of 1 by NaOH to form a phenolate anion in the basic system.[21] During the first phase, the oxidation of phenolate anion is activated to generate phenoxy radical I by single-electron transfer from the phenoxide to the oxidant Co(III) species, which can be produced from the oxygenation of $Co(OAc)_2{\cdot}4H_2O$. The phenoxy radical I is subsequently translated into radical III through resonance and rearranging.[24-26] The radical III is then disproportionated to the primary substrate 1 and the transient, highly active para-benzoquinone derivative A.[17,23] This derivative further reacts with methanol to produce the intermediate 4 by nucleophilic addition reaction. In the second phase, 4 is oxidized to the transitory B, which produces intermediate 5 upon a rapidly spontaneous aromatization followed by the fast release of methanol.[27-29] Finally, the para-phenoxy radical triggers the mild reaction through conveying reactivity to the remote benzyl group. NaOH is essential to the formation of phenoxy radical. The proposed mechanism is characterized by (1) a powerful generation of the high redox active Co(III) species derived from Co(II) species *via* oxygenation and two phenoxy radical processes;[30-31] and (2) the mediation of methanol and two functional formations of para-benzoquinone derivatives.

Scheme 8 A possible mechanism for the formation of intermediates



DP= disproportionation

EXPERIMENTAL

Materials and Instruments: All reagents and solvents were purchased from Sinopharm Chemical Reagent Co., Ltd and used without additional purification. 1H NMR spectra were recorded on a Bruker DPX 500 MHz spectrometer in $CDCl_3$ and DMSO-d6 with Me_4Si (TMS) as internal standard at room temperature. Chemical shifts are given in ppm. Mass spectra were recorded on a Waters Micromass GCT Premier mass spectrometer. Melting points (m.p.) were determined by employing a Hanon MP470 automated melting point instrument without further correction.

General reaction procedure: The oxidation reactions were carried out in a 500 mL autoclave equipped with a thermometer and a mechanical stirrer.

In a typical reaction, NaOH (40.0 g; 5.0 equiv.) and methanol (150 mL) were added into the reactor and vigorously stirred at room temperature. When the alkali had dissolved completely, eugenol (32.8 g; 0.2 mol) was added to the system and stirred for 10 min to ensure the conversion of eugenol to sodium salt. $Co(OAc)_2{\cdot}4H_2O$ (1.0 mol%) was then introduced quickly. Reactions were performed at 80 °C (Psystem, 1.0 atm without O_2) with the reaction system (1.5 atm) filled with pure O_2 (0.5 atm) and concluded at 20 h.

After neutralization of the reaction system, methanol was removed in vacuo. The resulting solution was extracted with toluene (3 × 200 mL), and the organic layers were combined and concentrated in vacuo to give a yellow solid. vanillin (2) was obtained by recrystallization from ethanol–water mixtures (150 mL). The mother liquor was concentrated in vacuo to give a yellow solid. After flash chromatography on silica gel (200–300 mesh), vanillic acid (3) and the remaining vanillin (2) were separated.

Procedure related to the mechanism: Another reaction was conducted under similar conditions as the above to determine the reaction mechanism. The reaction mixture was removed as a function of time.

After neutralization of the reaction mixture, methanol was removed in vacuo. The resulting solution was extracted with toluene (3 × 200 mL), and the organic layers were combined and concentrated in vacuo to give a yellow solid. After flash chromatography on silica gel (200–300 mesh), vanillin (2), vanillic acid (3), coniferyl alcohol 9-methyl ether (4), and 4-hydroxy-3-methoxycinnamaldehyde (5) were isolated.

CONCLUSIONS

A novel, simple, one-step method to synthesize vanillin and vanillic acid from eugenol has been developed. The process uses ligand- and additive-free $Co(OAc)_2{\cdot}4H_2O$ as catalyst and molecular oxygen as oxidant to achieve the catalytic process without isomerizing eugenol. The effects of the main reaction parameters, such as NaOH amount, temperature, and catalyst loading, were investigated to optimize the oxidation of eugenol to vanillin and vanillic acid. Under the optimal reaction condition of 80 °C, $Co(OAc)_2{\cdot}\ 4H_2O$ (1.0 mol%) and NaOH (5.0 equiv.), the reaction produced vanillin and vanillic acid with 68.5% and 15.2% yields, respectively. Apart from these products, coniferyl alcohol 9-methyl ether and 4-hydroxy-3-methoxycinnamaldehyde as two intermediates were also isolated in the reaction process. Level changes of all compounds as a function of time were then presented. Several control experiments were conducted to investigate the reaction pathway. This pathway involves generating coniferyl alcohol 9-methyl ether from eugenol. The ether then produces 4-hydroxy-3-methoxycinnamaldehyde, which subsequently transforms to vanillin and vanillic acid. More efforts were employed to further explore the mechanism of the oxidation reaction. Finally, a mechanism that involves a powerful generation of the high redox active Co(III) species derived from Co(II) species via oxygenation, two phenoxy radical processes, mediation of methanol, and two functional formation of para-benzoquinone derivatives was proposed.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the started project of scientific research for the introduction of talent of Shanghai Institute of Technology New Process for Synthesis of Vanillin (No.1010k13608-YJ 2013-50), "Research center of analysis and measurement of Shanghai Institute of Organic Chemistry (SIOC)" for high-resolution mass spectrometry measurements and Leading Academic Discipline Project of Shanghai Education Committee.

REFERENCES

1. Walton, N. J.; Mayer, M. J.; Narbad, A. *Phytochemistry* **2003**, *63*, 505-515.
2. Pometto, A. L.; Crawford, D. L. *Appl. Environ. Microbiol.* **1983**, *45*, 1582-1585.
3. Bare, G.; Gerard, J.; Jacques, P.; Delaunois, V.; Thonart, P. *Appl. Biochem. Biotechnol.* **1992**, *34-35*, 499-510.
4. Pacek, A. W.; Ding, P.; Garrett, M.; Sheldrake, G.; Nienow, A. W. *Ind. Eng. Chem. Res.* **2013**, *52*, 8361-8372.
5. Zamzuri, N. A.; Abd-Aziz, S. *J. Sci. Food Agr.* **2013**, *93*, 429-438.
6. Hu, J.; Hu, Y.; Mao, J.; Yao, J.; Chen, Z.; Li, H. *Green Chem.* **2012**, *14*, 2894-2898.
7. Jiang, J. A.; Chen, C.; Guo, Y.; Liao, D. H.; Pan, X. D.; Ji, Y. F. *Green Chem.* **2014**, *16*, 2807-2814.
8. Bjørsvik, H.-R.; Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2000**, *4*, 534-543.
9. Liu, S. W.; Shi, Z. L.; Li, L.; Yu, S. T.; Xie, C. X.; Song, Z. Q. *RSC Adv.* **2013**, *3*, 5789-5793.
10. Ferrazza, R.; Rossi, B.; Guella, G. *J. Phys. Chem. B* **2014**, *118*, 7147-7155.
11. Mishra, S.; Sachan, A.; Sachan, S. G. *J. Ind. Microbiol. Biotechnol.* **2013**, *40*, 545-550.
12. Jinesh, C. M.; Rives, V.; Carriazo, D.; Antonyraj, C. A.; Kannan, S. *Catal. Lett.* **2010**, *134*, 337-342.
13. Luu, T. X.; Lam, T. T.; Le, T. N.; Duus, F. *Molcules* **2009**, *14*, 3411-3424.
14. Alvarez, H. M.; Barbosa, D. P.; Fricks, A. T.; Aranda, D. A. G.; Valdés, R. H.; Antunes, O. A. C. *Org. Process Res. Dev.* **2006**, *10*, 941-943.
15. Gusevskaya, E. V.; Menini, L.; Parreira, L. A.; Mesquita, R. A.; Kozlov, Y. N.; Shul'pin, G. B. *J. Mol. Catal. A: Chem.* **2012**, *363-364*, 140-147.
16. Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381-3430.
17. Jiang, J. A.; Chen, C.; Huang, J. G.; Liu, H. W.; Cao, S.; Ji, Y. F. *Green Chem.* **2014**, *16*, 1248-1254.
18. Bird, C. W.; Chauhan, Y. P. S. *Org. Prep. Proced. Int.* **1980**, *12*, 201-202.
19. Misani, F.; Bogert, M. T. *J. Org. Chem.* **1945**, *10*, 347-365.
20. Bogatskii, A. V.; Bogatskaya, Z. D.; Pipikova, T. E. *Ukr. Khim. Zh+ (Russian Edition)* **1966**, *32*, 1321-1328.
21. Jiang, Q.; Sheng, W.; Guo, X.; Tang, J.; Guo, C. *J. Mol. Catal. A: Chem.* **2013**, *373*, 121-126.
22. Bilis, G.; Stathi, P.; Mavrogiorgou, A.; Deligiannakis, Y.; Louloudi, M. *Appl. Catal. A: Gen.* **2014**, *470*, 376-389.
23. Baik, W.; Lee, H. J.; Jang, J. M.; Koo, S.; Kim, B. H. *J. Org. Chem.* **2000**, *65*, 108-115.
24. Onopchenko, A.; Schulz, J. G. D.; Seekircher, R. *J. Org. Chem.* **1972**, *37*, 1414-1417.
25. Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502-6507.
26. Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 1154-1159.
27. Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murrill, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413-423.
28. Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818-2822.
29. Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228-7233.
30. Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622-1625.
31. Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446-3449.