Original Research Article

Single-step synthesis of Coenzyme Q_0

Yi-Yu Yan[#], Yong-Fu Qiu [#], Tian-Li Zhang [#], Yu-Bei He, Shi Qi, Jian-Hua Tian, Wan-Yue Luo, Yan Zhao, Jin Wang*

School of Pharmacy, Jiangsu Key Laboratory for Bioresources of Saline Soils, Yancheng Teachers University, Hope Avenue South Road No.2, Yancheng, 224007, Jiangsu Province, P. R. China

[#] *These authors contributed equally to this work*
Corresponding authors e-mail: jaxdon@126.com or wangj01@yctu.edu.cn(Jin WANG)

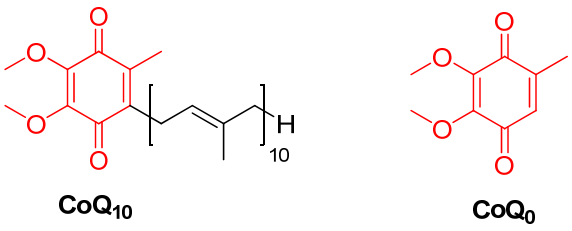
Abstract

A new method for the preparation of 2-methyl-5,6-dimethoxy-1,4-benzoquinone (Coenzyme Q_0) was developed. This improved process in one step by the oxidation of 3,4,5-trimethoxytoluene to coenzyme Q_0 by simple oxidation using potassium or ammonium persulfate under transition -metal free conditions.

Keywords: Coenzyme Q_0, 3,4,5-trimethoxytoluene, potassium persulfate

Introduction

Coenzyme Q_{10} (CoQ_{10}, **Fig.1**), also known as ubiquinone, is a vitamin-like 1,4-benzoquinone compound[1] and functions as a potent antioxidant that scavenges free radicals.[2] CoQ_{10} is widely used in the treatment of cardiovascular disease, mitochondrial disorders,[3] and in the improvement of immunotherapy.[4] 2,3-Dimethoxy-5-methyl-1,4-benzoquinone, known as Coenzyme Q_0 (CoQ_0, **Fig.1**), is a key constituent part of coenzyme Q_{10}. Coenzyme Q_0 has been reported possess antineoplastic, anti-inflammatory and antimicrobial activities.[5]



CoQ_{10} **CoQ_0**

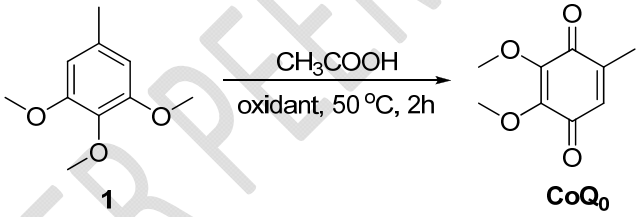
UNDER PEER REVIEW

Fig. 1 Structures of CoQ_{10} and CoQ_0

There have been several methods published for the preparation of Coenzyme Q_0 through oxidation of commercially available 3,4,5-trimethoxytoluene (**1**) with the oxidant-hydrogen peroxide (H_2O_2) system. Among metal catalysts applied were potassiumhexacyanoferrate(III) $K_3Fe(CN)_6$,[6] methyltrioxorhenium (CH_3ReO_3),[7] ruthenium complex-bound norvaline,[8] and γ-Keggin divanadium-substituted phosphotungstate.[9] Recently, Bjørsvik *et al* utilized hydrogen peroxide in combination with mineral acids (HNO_3)[11] to produce CoQ_0, which imposed practical problems related to reactor corrosion and safety risks. Based on our previous study,[10] here we described a single step synthesis of CoQ_0 by treatment of 3,4,5-Trimethoxytoluene **1** with persulfate ($K_2S_2O_8$, $Na_2S_2O_8$, $(NH_4)_2S_2O_8$) under transition metal-free conditions (**Table 1**).

Results and discussion

Table 1 Single-step synthesis of CoQ_0



Entry	oxidant	Solvent	Temp (°C)	Yield (%)
1	30% H_2O_2	CH_3COOH	50	50
2	**$K_2S_2O_8$**	**CH_3COOH**	**50**	**80**
3	$(NH_4)_2S_2O_8$	CH_3COOH	50	70
4	$Na_2S_2O_8$	CH_3COOH	50	60

Reaction Conditions: compound **1** (0.01mol), oxidant (1.5 equiv), 2 hour under open air

As shown in **Table 1,** the reaction is conducted in acetic acid at 50 °C in less than 2 h and without using any metal catalyst. The traditional method employing 30% H_2O_2 as oxidant give a yield of 50% (entry 1, **Table 1**). The use of $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ can improve the reaction yield (entry 3-4, **Table 1**). The best yield was obtained using $K_2S_2O_8$ as oxidant to afford the desired product CoQ_0 in 80% yield

UNDER PEER REVIEW

(entry 2, **Table 1**). Persulfate salts were first employed as oxidants instead of transition metal complexes as the catalyst to synthesize 1,4-benzoquinone under mild condisitons, this chemistry is clean and easy to work up.

Conclusion

In summary we have developed a high-yielding and selective synthetic protocols for the preparation of 2,3- dimethoxy-5-methyl-[1,4]benzoquinone (Coenzyme Q_0) from the cheap and readily available 3,4,5-Trimethoxytoluene **1** by oxidation using potassium persulfate in the presecnce of catalytic sulphuric acid. The reaction is efficient, clean and easy work-up. This method could be used for the synthesis of other coenzyme Q compounds.

Experimental Section

All reactions were monitored by TLC (SiO_2, petrol ether/EtOAc 5:1), Melting points were measured on Melting Point M-565 (BUCHI). NMR and mass spectra were recorded on a Bruker Avanc III-HD 400 NMR and a TripleTOF Mass spectrometers, respectively. All reagents: e.g. Potassium Persulfate ($K_2S_2O_8$), Ammonium persulphate ($(NH_4)_2S_2O_8$), acetic acid were purchased from Adamas, P. R. China, and used without further purification.

General method for preparation of CoQ_0

3,4,5-Trimethoxytoluene (1.82 g, 10 mmol) was dissolved in a mixture of acetic acid (99%, 10 mL) and catalytic H_2SO_4 (0.1 mL), then a solution of oxidant (15 mmol) was added dropwise over 10 minutes. The mixture was stirred and heated at 50 °C for 1 hour and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with H_2O and saturated $NaHCO_3$, then dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by a silica-gel column chromatography (PE/EtOAc 5:1) to give coenzyme Q_0.

Coenzyme Q_0, red-colored needles, m.p. 55-58 °C (Lit.[12] 57-59 °C).

UNDER PEER REVIEW

IR (KBr/cm^{-1}): 3590, 3415, 1661, 1603, 1291, 1226, 999.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (q, *J* = 1.7 Hz, 1H), 4.02 (s, 3H, OC**H**$_3$), 4.00 (s, 3H, OC**H**$_3$), 2.04 (d, *J* = 1.6 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 184.4 (**C**=O), 184.2(**C**=O), 145.0, 144.8, 144.0, 131.2, 61.2 (O**C**H$_3$), 61.1 (O**C**H$_3$), 15.4 (**C**H$_3$).

MS (ESI): m/z = 205 $[M+Na]^+$.

References

[1] J. Wang, J. Yang, B. Yang, X. Hu, J. Q. Sun, T. Yang, *J. Chem. Res.,* **2010**, *34*, 717.

[2] A. Khattab, L. Hassanin, N. Zaki, *AAPS PharmSciTech* **2017**, *18*, 1657.

[3] M. Hirano, C. Garone, C. M. Quinzii, *BBA-Gen.Subjects.,* **2012**, *1820*, 625.

[4] B. M. Davis, K. Tian, M. Pahlitzsch, J. Brenton, N. Ravindran, G. Butt, G. Malaguarnera, E. M. Normando, L. Guo, M. F. Cordeiro, *Mitochondrion* **2017**, *36*, 114.

[5] Q. Fan, Y. Zhang, H. Yang, Q. Wu, C. Shi, C. Zhang, X. Xia, X. Wang, *Food Control* **2018**, *90*, 274.

[6] M. Matsumoto, H. Kobayashi, *J.Org. Chem.,* **1985**, *50*, 1766.

[7] R. Bernini, E. Mincione, M. Barontini, G. Fabrizi, M. Pasqualetti, S. Tempesta, *Tetrahedron* **2006**, *62*, 7733.

[8] R. Yoshida, K. Isozaki, T. Yokoi, N. Yasuda, K. Sadakane, T. Iwamoto, H. Takaya, M. Nakamura, *Org.Biomol. Chem.,* **2016**, *14*, 7468.

[9] O. V. Zalomaeva, V. Y. Evtushok, G. M. Maksimov, R. I. Maksimovskaya, O. A. Kholdeeva, *Dalton.,***2017**, *46*, 5202.

[10] J. Wang, X. Hu, J. Yang, *Synthesis* **2014**, *46*, 2371.

[11] G. Occhipinti, L. Liguori, A. Tsoukala, H.-R. Bjørsvik, *Org. Process. Res. Dev.,* **2010**, *14*, 1379.

[12] J. Wang, S. Li, T. Yang, J. Yang, *Eur. J. Med. Chem.,* **2014**, *86*, 710.

UNDER PEER REVIEW