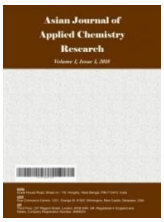


Asian Journal of Applied Chemistry Research

2(3-4): 1-4, 2018; Article no.AJACR.47908

Single-step Syznthesis of Coenzyme Q_0

Yi-Yu Yan[1#], Yong-Fu Qiu[1#], Tian-Li Zhang[1#], Yu-Bei He[1#], Shi Qi[1], Jian-Hua Tian[1], Wan-Yue Luo[1], Yan Zhao[1] and Jin Wang[1*]

[1]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.

Authors' contributions

This work was carried out in collaboration among all authors. Author JW designed the study. Author YYY performed the statistical analysis. Author YFQ wrote the protocol. Author TLZ wrote the first draft of the manuscript. Authors YBH and SQ managed the analyses of the study. Authors WYL and YZ managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJACR/2018/v2i3-430080
Editor(s):
(1) Dr. Musri Musman, Professor, Department of Chemistry, Syiah Kuala University, Indonesia.
Reviewers:
(1) Godson O. Osuji, Prairie View A & M University, USA.
(2) A. Veerareddy, India.
(3) A. Ayeshamariam, Khadir Mohideen College, India.
Complete Peer review History: http://www.sdiarticle3.com/review-history/47908

Original Research Article

Received 25 December 2018
Accepted 13 March 2019
Published 19 March 2019

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.

1. 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,

**Corresponding author: Email: jaxdon@126.com, wangj01@yctu.edu.cn;*
[#] These authors contributed equally to this work

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].

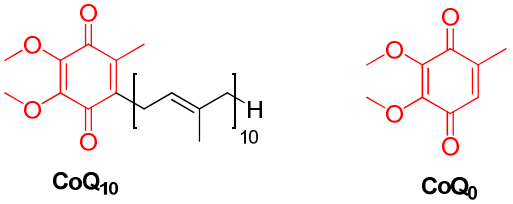


Fig. 1. Structures of CoQ_{10} and CoQ_0

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) [10] to produce CoQ_0, which imposed practical problems related to reactor corrosion and safety risks. Based on our previous study [11], 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).

2. 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).

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

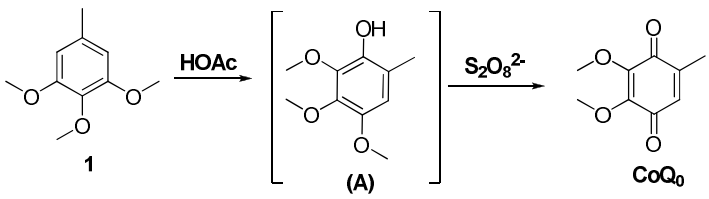
^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (q, J = 1.7 Hz, 1H), 4.02 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 2.04 (d, J = 1.6 Hz, 3H, CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 184.4 (C=O), 184.2(C=O), 145.0, 144.8, 144.0, 131.2, 61.2 (OCH_3), 61.1 (OCH_3), 15.4 (CH_3).

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

3. RESULTS AND DISCUSSION

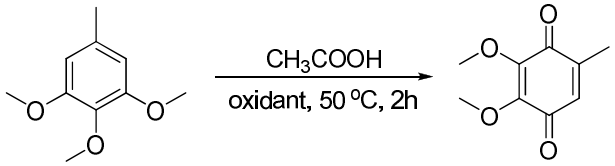
As shown in Table 1, the reaction is conducted in acetic acid at 50°C in less than 2 h and without using any metal catalyst. The traditional method employing 30% H_2O_2 as oxidant give a yield of 50% (entry 1, Table 1). The use of $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ can improve the reaction yield (entry 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 (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.

Based on the experiment results, a proposed reaction mechanism was illustrated in Scheme 1. Initially, compound 1 was transformed to intermediate (A) in the presence of HOAc solvent, then A was oxidated by $S_2O_8^{2-}$ to give product CoQ_0 in situ.



Scheme 1. Proposed reaction mechanism

Table 1. Single-step synthesis of CoQ_0



1 **CoQ_0**

Entry	oxidant	Solvent	Temp (^oC)	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

4. 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.

ACKNOWLEDGEMENTS

This study was supported by the National Natural Science Foundation of China (Nos. 31600740 and 81803353), the Natural Science Foundation of Jiangsu Province (BK20160443), the Six Talent Peaks Project in Jiangsu Province (SWYY-094), The Jiangsu Provincial Key Laboratory for Bioresources of Saline Soils (Nos. JKLBS2016013 and JKLBS2017010).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wang J, Yang J, Yang B, Hu X, Sun JQ, Yang T. A green and efficient synthesis of 1-chloromethyl -2,3,4,5-tetramethoxy6-methylbenzene. J. Chem. Res. 2010;34: 717.
2. Khattab A, Hassanin L, Zaki N. Self-nanoemulsifying drug delivery system of coenzyme (Q10) with improved dissolution, bioavailability, and protective efficiency on liver fibrosis. AAPS PharmSciTech. 2017;18:1657.
3. Hirano M, Garone C, Quinzii CM. CoQ_{10} deficiencies and MNGIE: Two treatable mitochondrial disorders. BBA-Gen. Subjects. 2012;1820:625.
4. Davis BM, Tian K, Pahlitzsch M, Brenton J, Ravindran N, Butt G, Malaguarnera G, Normando EM, Guo L, Cordeiro MF. Topical coenzyme Q10 demonstrates mitochondrial-mediated neuroprotection in a rodent model of ocular hypertension. Mitochondrion. 2017;36:114.
5. Fan Q, Zhang Y, Yang H, Wu Q, Shi C, Zhang C, Xia X, Wang X. Effect of coenzyme Q0 on biofilm formation and attachment-invasion efficiency of *Listeria monocytogenes*. Food Control. 2018;90: 274.
6. Matsumoto M, Kobayashi H. Hexacyanoferrate-catalyzed oxidation of trimethoxybenzenes to dimethoxy-p-benzoquinones with hydrogen peroxide. J. Org. Chem. 1985;50:1766.
7. Bernini R, Mincione E, Barontini M, Fabrizi G, Pasqualetti M, Tempesta S. Convenient oxidation of alkylated phenols and methoxytoluenes to antifungal 1,4-benzoquinones with hydrogen peroxide (H_2O_2)/methyltrioxorhenium (CH_3ReO_3) catalytic system in neutral ionic liquid. Tetrahedron. 2006;62:7733.
8. Yoshida R, Isozaki K, Yokoi T, Yasuda N, Sadakane K, Iwamoto T, Takaya H, Nakamura M. Org. Biomol. Chem. 2016;14: 7468.
9. Zalomaeva OV, Evtushok VY, Maksimov GM, Maksimovskaya RI, Kholdeeva OA. Dalton. 2017;46:5202.

10. Occhipinti G, Liguori L, Tsoukala A, Bjørsvik HR. A switchable oxidation process leading to two various versatile pharmaceutical intermediates. Org. Process. Res. Dev. 2010;14:1379.
11. Wang J, Hu X, Yang J. Two-step synthesis of 2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone. Synthesis. 2014;46:2371.
12. Wang J, Li S, Yang T, Yang J. Synthesis and antioxidant activities of coenzyme Q analogues. Eur. J. Med. Chem. 2014;86:710.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle3.com/review-history/47908