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A convenient two-step synthesis of Coenzyme Q_1

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Abstract

A convenient method for the preparation of Coenzyme Q_1 from cheap and readily available 3,4,5-trimethoxytoluene is developed. Coenzyme Q_1 is synthesized in a moderate yield by a two-step procedure involving the key reaction of an allyl bromide with Coenzyme Q_0 through a redox chain reaction. The reaction is efficient and can be used for the synthesis of other Coenzyme Q compounds.

Keywords

3,4,5-trimethoxytoluene, chain reaction, Coenzyme Q

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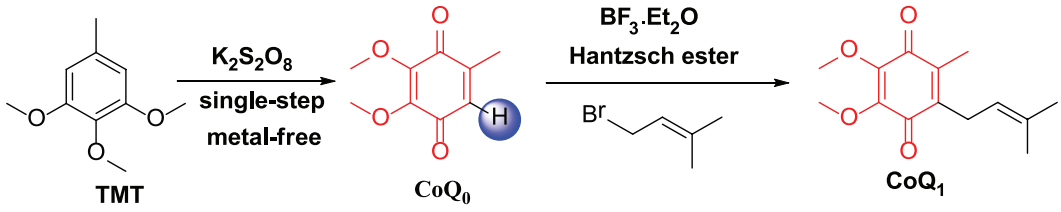

total yield 60%; redox chain reaction; gram-scale synthesis

Introduction

Coenzyme Q_{10} (CoQ_{10}; Figure 1) is an isoprenoid quinone compound[1] and plays a pivotal role in the electron transport chain in respiratory processes.[2] CoQ_{10} is a natural antioxidant that scavenges free radicals.[3] It is widely used in the treatment of cardiovascular disease and mitochondrial disorders.[4] Coenzyme Q_1 (CoQ_1; Figure 1) is an important fragment of the Coenzyme Q (CoQ) series which are active in the electron transport and oxidative phosphorylation processes in mitochondria. CoQ_1 also acts as a key intermediate in the synthesis of higher CoQ analogues.[5]

There have been several methods published for the preparation of CoQ_1, most of which involve a Lewis acid-catalyzed reaction between an allylic alcohol and hydroquinone, followed by oxidation to the quinones. Hegedus and Waterman[2] and Sato et al.[6] synthesized CoQ_1 by reaction of π-allylic nickel complexes with quinones in 26% yield (Scheme 1, eq 1). Yamago et al.[7] reported a radical-mediated synthesis of substituted quinones with organotellurium compounds.[8] However, these reactions were quite sensitive to the reaction conditions, the key reagents π-allylnickel bromide complex and the requisite organotellurium reagent were difficult to prepare. Tabushi et al.[9] reported a β-cyclodextrin-catalyzed allylation–oxidation of hydroquinone to form CoQ_1 in 11% yield (Scheme 1, eq 2). Recently, Chen[5] and Borioni et al.[10] started from 3,4,5-tetramethoxytoluene (TMT) to obtain CoQ_1 in multiple steps (Scheme 1, eq 3). Unfortunately, all these methods generally gave low yields and complex by-products. Therefore, a general and practical method for efficient CoQ_1 synthesis is highly desirable. Here, we report a two-step synthesis of CoQ_1 by starting from 3,4,5-trimethoxytoluene with a total yield of 60% (Scheme 1, eq 4).

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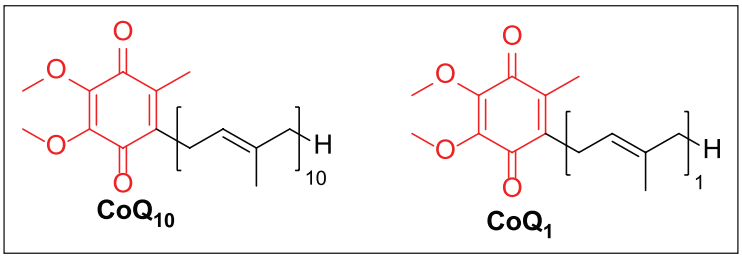
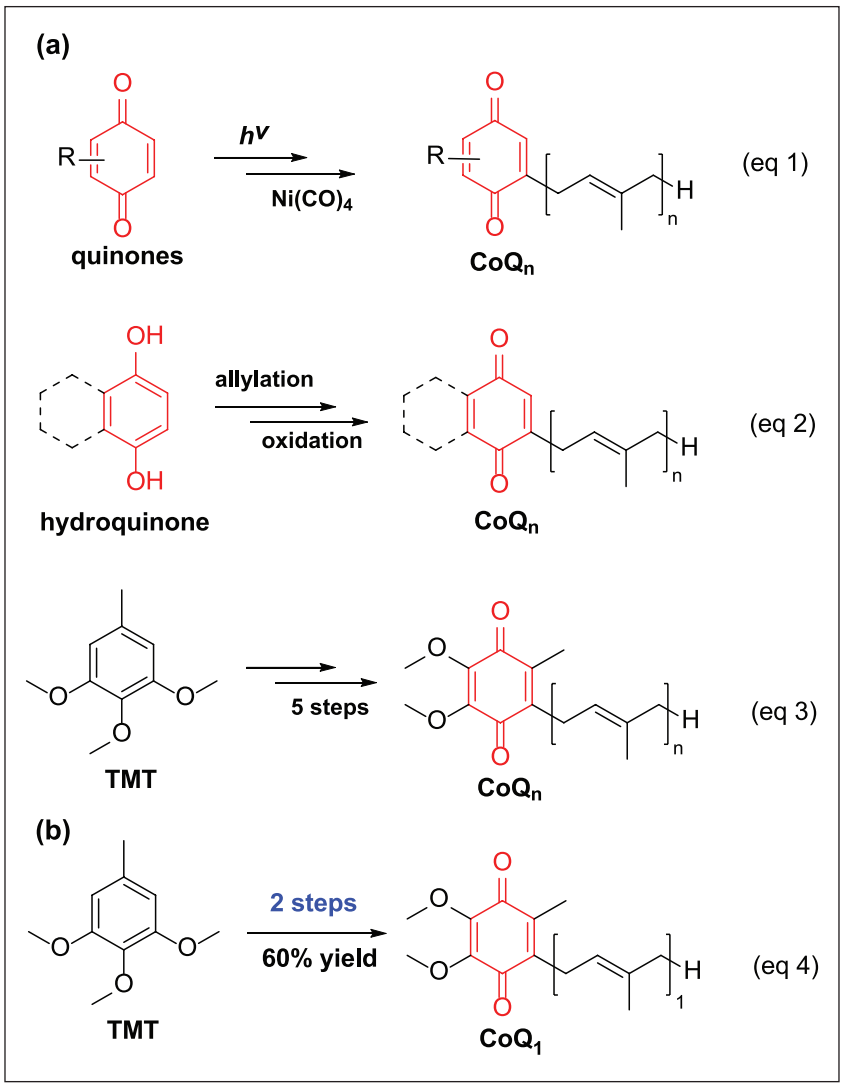


Figure 1. Structures of CoQ_{10} and CoQ_1.



Scheme 1. Various methods for the syntheses of CoQ_n: (a) previous work and (b) this work.

Results and discussion

First, a single-step synthesis of CoQ_0 is shown in Table 1; this oxidation reaction of TMT is conducted in acetic acid at 50°C in less than 2 h and without using any metal catalyst. This environmentally friendly procedure is based on the oxidant as an oxygen atom donor, and the acidic solvent acetic acid plays an important role in the transformation. The traditional method employing 30% H_2O_2 as an oxidant gave a yield of 50% (Table 1, entry 1). The use of $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ improved the reaction yield (Table 1, entries 3 and 4). The best yield was obtained using $K_2S_2O_8$ as an oxidant to afford the desired product CoQ_0 in 85% yield (Table 1, entry 2). However, when cerium ammonium nitrate (CAN) was used as the oxidant, we did not observe any product CoQ_0 (Table 1, entry 5).

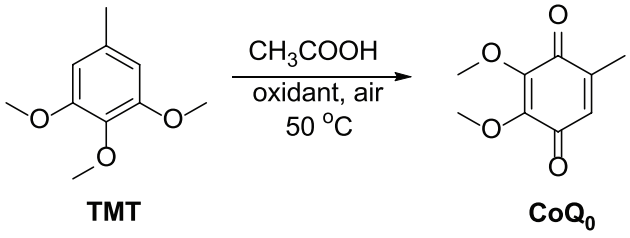
Inspired by Xu and Li's[11] work on the alkylation of *p*-quinones by a redox chain reaction, we tried to synthesize CoQ_1 by the allylation of CoQ_0 with 1-bromo-3-methyl-2-butene 1; the results are shown in Table 2. Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester) was selected as an initiator which can accelerate the alkylation according to the literature,[12] and

the reaction works with many Lewis acids as catalysts in dichloromethane as the solvent at room temperature (r.t.). Typical Lewis acid catalysts were screened in the reaction; however, $AlCl_3$, $ZnCl_2$, and $FeCl_3$ did not catalyze the reaction (Table 2, entries 1–3). The solvents used for this reaction was crucial, acetone, tetrahydrofuran (THF), CH_3CN, or toluene as the solvent led to low yields of CoQ_1 (Table 2, entries 5–8). On the basis of these screening studies, the optimum conditions employed $BF_3{\cdot}Et_2O$ as the catalyst and dichloromethane as the solvent.

Conclusion

In summary, we have developed a convenient synthetic protocol for the preparation of CoQ_1 from cheap and readily available 3,4,5-trimethoxytoluene (TMT) in two steps. The overall yield of CoQ_1 is 60%. The intermediate CoQ_0 was also obtained in 85% yield in the first step. The second redox chain reaction between allyl bromide and CoQ_0 provided a one-step procedure for the direct introduction of allyl groups on quinones in good yield. The reaction is efficient, clean, and the workup is easy. This method may find use for the synthesis of other CoQ compounds.

Table 1. Single-step synthesis of CoQ_0.



Entry	Oxidant	Yield (%)
1	30% H_2O_2	50
2	**$K_2S_2O_8$**	**85**
3	$(NH_4)_2S_2O_8$	70
4	$Na_2S_2O_8$	60
5	CAN	0

CAN: cerium ammonium nitrate.
Reaction conditions: TMT (0.01 mol), oxidant (1.5 equiv.), 2 h, open air.
Bold values represents the best condition.

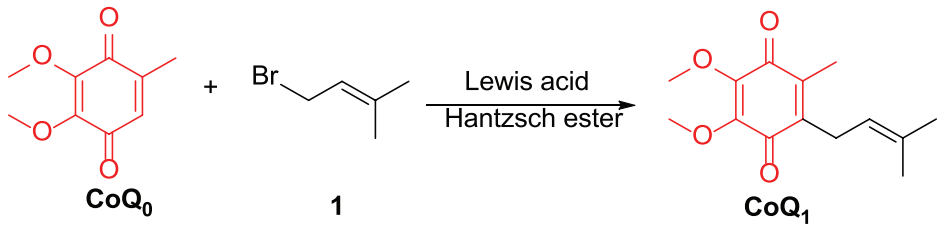
Experimental section

All reactions were monitored by thin-layer chromatography (TLC; SiO_2, petroleum ether (PE; b.p. 50°C–70°C)/ethyl acetate (EtOAc), 5:1). Melting points were measured on BUCHI Melting Point M-565. Nuclear magnetic resonance (NMR) and mass spectra were recorded on a Bruker Avance III-HD 400 NMR and a TripleTOF mass spectrometer, respectively. Potassium persulfate, ammonium persulfate, Hantzsch ester, and $BF_3{\cdot}Et_2O$ were purchased from Adamas, P. R. of China, and used without further purification.

General method for the preparation of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (CoQ_0)

3,4,5-Trimethoxytoluene (1.82 g, 10 mmol) was dissolved in a mixture of acetic acid (10 mL) and catalytic H_2SO_4 (0.01 mL), then a solution of the oxidant (15 mmol) was added dropwise over 10 min. The mixture was stirred and heated at 50°C for 1 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with H_2O and $NaHCO_3$, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was

Table 2. Redox chain reaction for the synthesis of CoQ_1.



Entry	Lewis acid	Solvents	Yield (%)
1	$AlCl_3$	CH_2Cl_2	N.R.
2	$ZnCl_2$	CH_2Cl_2	N.R.
3	$FeCl_3$	CH_2Cl_2	N.R.
4	**$BF_3{\cdot}Et_2O$**	CH_2Cl_2	**70**
5	$BF_3{\cdot}Et_2O$	Acetone	8
6	$BF_3{\cdot}Et_2O$	THF	32
7	$BF_3{\cdot}Et_2O$	CH_3CN	20
8	$BF_3{\cdot}Et_2O$	Toluene	10

CoQ_1: coenzyme Q_1; N.R.: no reaction; THF: tetrahydrofuran; r.t.: room temperature.
Reaction conditions: CoQ_0 (0.01 mol), compound **1** (0.01 mol), Hantzsch ester (1 mmol), Lewis acid (0.01 mol), r.t., N_2 atmosphere.
Bold values represents the best condition.

purified by silica gel column chromatography (PE/EtOAc, 5:1) to give CoQ_0.

CoQ_0, red-colored needles, m.p. 55°C–58°C (Lit.[13] 57°C–59°C).

^{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 $[M + Na]^+$.

The spectroscopic data are in accord with the literature.[13]

General method for the preparation of 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone (CoQ_1)

1-Bromo-3-methyl-2-butene (**1**; 1.49 g, 0.01 mol), Hantzsch ester (0.25 g, 1 mmol), and CoQ_0 (1.82 g, 0.01 mol) were dissolved in dichloromethane (10 mL) under a nitrogen atmosphere. After stirring for 30 min, a solution of $BF_3{\cdot}Et_2O$ (1.2 mL, 0.01 mol) in dichloromethane (1 mL) was added, and the solution was stirred at r.t. for 2 h. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with H_2O and brine, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc, 8:1) to give **CoQ_1**.

^{1}H NMR (400 MHz, CDCl3): δ = 4.32 (t, 1H, *J* = 7.0 Hz, C=C*H*), 3.96 (s, 3H, C*H*3O), 3.94 (s, 3H, C*H*3O), 3.12 (d, 2H, *J* = 7.0 Hz, C*H*2), 2.14 (s, 3H, C*H*3), 1.75 (s, 3H, C*H*3), 1.65 (s, 3H, C*H*3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.0 (*C*=O), 175.6(*C*=O), 144.1, 143.0, 142.7, 132.6, 126.5, 123.4, 60.5 (O*C*H$_3$), 60.3 (O*C*H$_3$), 30.4, 29.1, 25.4, 15.7(*C*H$_3$).

MS (ESI): m/z = 251 $[M + H]^+$.

The spectroscopic data are in accord with the literature.[5]

Declaration of conflicting interests

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