A Convenient Two-Step Synthesis of Coenzyme Q_1

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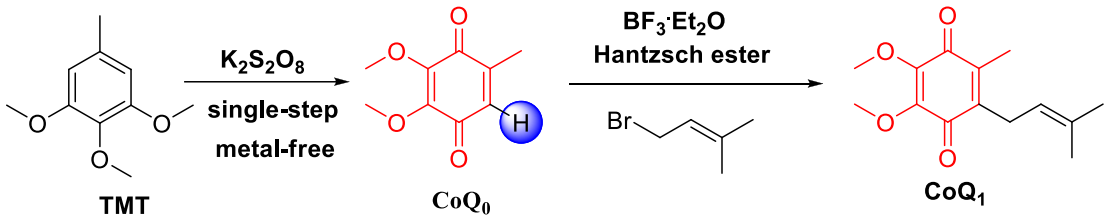


total yield 60%; Redox Chain Reaction; gram-scale synthesis

Abstract

A convenient method for the preparation of Coenzyme Q_1 from the cheap and readily available 3,4,5-Trimethoxytoluene was developed. CoQ_1 was synthesized in moderate yield by a two-step procedure involving the key reaction of allyl bromide with CoQ_0 through a redox chain reaction. The reaction is efficient and could be used for the synthesis of other CoQ compounds.

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

Introductions

Coenzyme Q_{10} (CoQ_{10}, **Fig.1**) is a isoprenoid quinones compound[1] and play 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, **Fig.1**) is an important fragment of Coenzyme Q series which function 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]

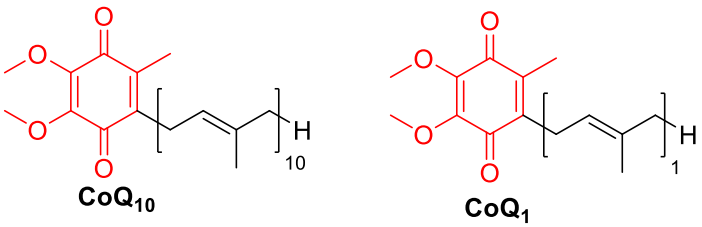
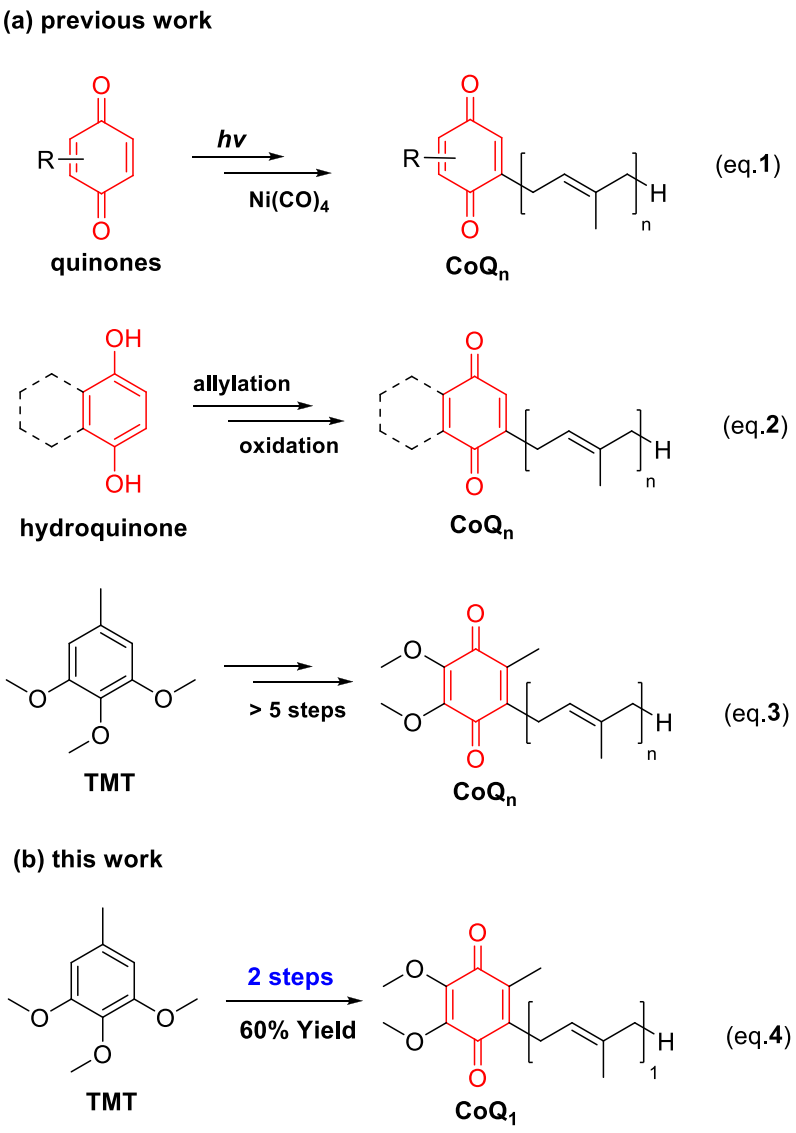


Fig. 1 Structures of CoQ_{10} and CoQ_1

There have been several methods published for the preparation of Coenzyme Q_1, most of methods involved a Lewis acid-catalyzed reaction between the allylic alcohol and hydroquinone, followed by oxidation to the quinones. Hegedus *et al*[2] and Sato *et al*[6] synthesized the CoQ_1 by reaction of π-allylic nickel complexe 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 reaction conditions, the key reagents π-allylnickel bromide complex and organotellurium 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 *et al* [5] and Bovicelli *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 demanded. Here, we reported a two-step synthesis of CoQ_1 by starting from 3,4,5-trimethoxytoluene (**TMT**) with a total yield of 60% (**Scheme 1,** eq.4).



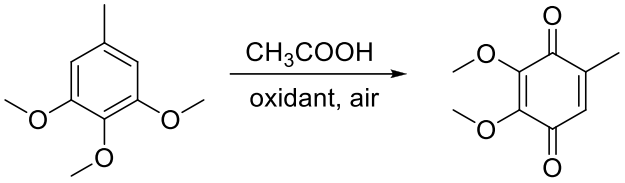
Scheme 1. Various methods for CoQn

Results and Discussion

Firstly, a single-step synthesis of CoQ_0 was 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 enviromentally friendly procedure is based on the oxidant as an oxygen atom donor, and the acidic solvent acetic acid played an important role in this transformation. 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 85% yield (entry 2, **Table 1**). However,

when utilize Ammonium Cerium Nitrate (CAN) as oxidant we did not observe any product CoQ_0. (entry 5, **Table 1**).

Table 1 Single-step synthesis of CoQ_0



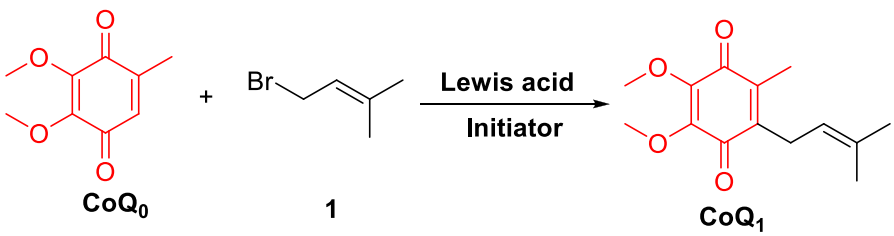
TMT **CoQ_0**

Entry	oxidant	Solvent	Temp (°C)	Yield (%)
1	30% H_2O_2	CH_3COOH	50	50
2	**$K_2S_2O_8$**	**CH_3COOH**	**50**	**85**
3	$(NH_4)_2S_2O_8$	CH_3COOH	50	70
4	$Na_2S_2O_8$	CH_3COOH	50	60
5	CAN	CH_3COOH	50	0

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

Inspired by Li'work on the alkylation of p-Quinones by a redox chain reaction,[11] herein we tried to synthesize CoQ_1 by allylation of CoQ_0 with 1-bromo-3-methyl-2-butene **(1)**, the results were shown in **Table 2.** Diethyl 1,4-dihydro-2,6-dimethy-3,5-pyridinedicarboxylate (Hantzsch ester) was selected as initiator according to literature,[12] and the reaction works with many Lewis as catalysts in dichloromethane solvent at room temperature. Normal Lewis acids catalysts were screened in the reaction, $AlCl_3$, $ZnCl_2$ and $FeCl_3$ could not catalyze the reaction (**Table 2**, entries1-3). Solvents were crucial for this reaction, using Acetone, THF, CH_3CN or Toluene as solvent led to a low yield of CoQ_1 (**Table 2**, entries 5-8). On the basis of these screening studies, the optimal condition was using $BF_3{\cdot}Et_2O$ as catalyst and dichloremethane as solvent.

Table 2 Redox Chain Reaction for CoQ_1



CoQ_0 **1** **CoQ_1**

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

Reaction Conditions: CoQ_0 (0.01 mol), Compound **1** (0.01 mol), Hantzsch ester(1 mmol), Lewis acid (0.01 mol), r.t., under N_2 atmosphere; N.R.= no reaction.

Conclusion

In summary we have developed a convenient synthetic protocol for the preparation of Coenzyme Q_1 from the cheap and readily available 3,4,5-Trimethoxytoluene **TMT** within two steps. The overall yield of CoQ_1 is 60%. The intermediate CoQ_0 was also obatained 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 into quinones in good yield. 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, Ammonium persulphate, Hantzsch ester, $BF_3{\cdot}Et_2O$ 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 (10 mL) and catalytic H_2SO_4, then a solution of oxidant (15 mmol) was added dropwise over 10 minutes. The mixture was stirred and heated at 50 ^oC for 1 hour and extracted with CH_2Cl_2 (3 x 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 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.[13] 57-59 °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 is in accord with literature [13].

General method for preparation of **CoQ$_1$**

1-bromo-3-methyl-2-butene **(1)** (1.49g, 0.01mol), Hantzsch ester (0.25g, 1 mmol) and CoQ_0 (1.82g, 0.01mol) were dissolved in dichloromethane (10 mL) under a nitrogen atmosphere. After stirring for 30 minutes, a solution of Lewis acids (0.01mol) was added and the mixture solution was stirred at r.t. for 2 hour and extracted with CH_2Cl_2 (3 x 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 a silica-gel column chromatography (PE/EtOAc 8:1) to give **CoQ$_1$**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3 H, C**H**$_3$), 1.75 (s, 3 H, C**H**$_3$), 2.14 (s, 3 H, C**H**$_3$), 3.12 (d, 2 H, *J* = 7.0 Hz, C**H**$_2$), 3.96 (s, 3 H, C**H**$_3$O), 3.94 (s, 3 H, C**H**$_3$O), 4.32 (t, 1 H, *J* = 7.0 Hz, C=C**H**).

^{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 is in accord with literature [5].

Acknowledgments

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