Two-Step Synthesis of 2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone

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Abstract: 2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone was readily synthesized from commercially available 3,4,5-trimethoxytoluene in two steps. First, 2,3-dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q_0) was obtained in one step by treatment of 3,4,5-trimethoxytoluene with hydrogen peroxide under metal-free conditions, followed by free-radical alkylation with 10-hydroxydecanoic acid in the presence of potassium peroxodisulfate and silver nitrate in a mixed solvent (MeCN–H_2O, 1:1) to afford the title compound in good yields (60%, based on coenzyme Q_0).

Key words: coenzyme Q_0, decarboxylative cross-coupling, idebenone analogue, free-radical alkylation

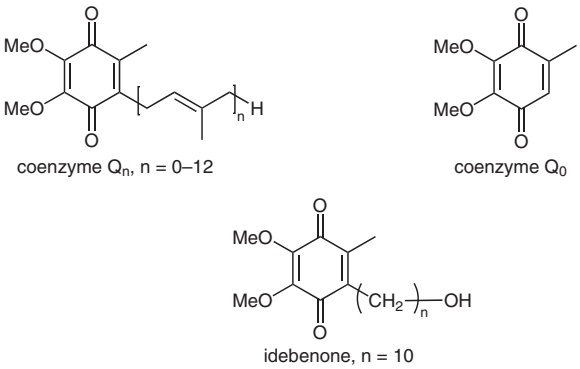

Figure 1

Coenzymes Q (CoQ or CoQn, Figure 1), also known as the ubiquinones, occur naturally in all cells, acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron-transport chain of mitochondria respiratory systems.[2] Coenzyme Q (CoQ) is also known to act as an antioxidant by reducing free radicals that can cause damage to structural lipids or proteins in membranes. Among the synthetic coenzyme Q analogues, idebenone (Figure 1) is an experimental drug intended for the treatment of various cognitive defects such as Alzheimer's and Parkinson's diseases. Idebenone was also shown to be a free radical scavenger for a variety of reactive species such as the oxidant peroxynitrite. In comparison with coenzyme Q_{10} (C40 side chain), idebenone (C10 side chain) has a shorter carbon side chain that facilitates interception of free radicals both in hydrophobic and hydrophilic environments.[3] In recent work,[4,5] some analogues of idebenone have shown ability to support oxygen consumption in the mitochondrial respiratory chain.

Currently, there are a number of synthetic methodologies available for the synthesis of idebenone and its analogues, these are shown in Scheme 1 and classified into two main routes starting from: (1) 3,4,5-trimethoxytoluene;[6] and (2) 2,3,4,5-tetramethoxytoluene.[4,7] However, these processes have the following drawbacks: (i) multistep synthesis, which leads to low overall yields; (ii) tedious reactions conditions (Friedel–Crafts, hydrogenation, Heck reaction, etc.); (iii) use of metallic catalysts [Fremy's salt, 10% Pd/C, $Pd(OAc)_2$, etc.].[7] Therefore, a convenient and practical method for the synthesis of idebenone analogues under mild reaction conditions is still in demand.

In recent years, transition-metal-catalyzed decarboxylative cross-coupling reactions using carboxylic acids as coupling partners have been widely studied in organic synthesis as novel methods for the formation of carbon–carbon bonds. Since carboxylic acids and their derivatives as cross-coupling components are nontoxic, stable, and structurally diverse, extensive studies have been accomplished in this area, particularly since Minisci reported the silver-catalyzed decarboxylative alkylation of pyridines and quinolines in the 1970s.[8,9] In this paper we report an easy method [Scheme 1 (3)] for a two-step synthesis of 2-(9-hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone (**3**) from 3,4,5-trimethoxytoluene (**1**). Firstly, 2,3-dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q_0) was obtained in single step by treatment of 3,4,5-trimethoxytoluene (**1**) with hydrogen peroxide in formic acid–acetic acid (2:1) without a metal catalyst, and this was followed by decarboxylative cross-coupling reaction of coenzyme Q_0 with 10-hydroxydecanoic acid (**2**) catalyzed by silver nitrate in acetonitrile–water (1:1) to achieved the desired compound **3** in good yields.

Inspired by reports[8,9] that radicals generated by decarboxylation of carboxylic acids with potassium peroxodisulfate and silver nitrate could be used for the alkylation of quinones, we envision that idebenone analogues might be synthesized from coenzyme Q_0 and a monocarboxylic acid via free-radical alkylation in the presence of potassium peroxodisulfate and silver nitrate. To test our hypothesis, commercially available 10-hydroxydecanoic acid (**2**) was selected as the monocarboxylic acid to react with co-

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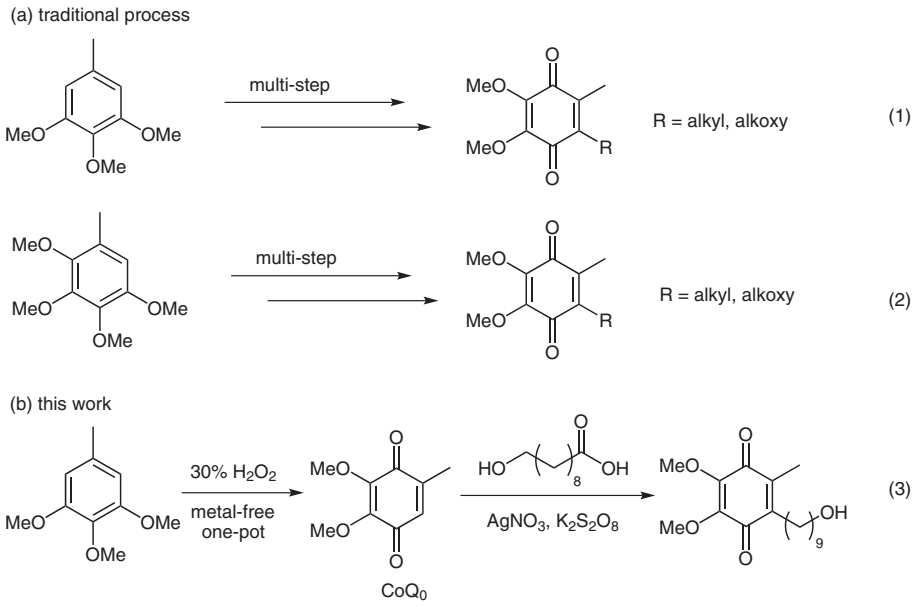
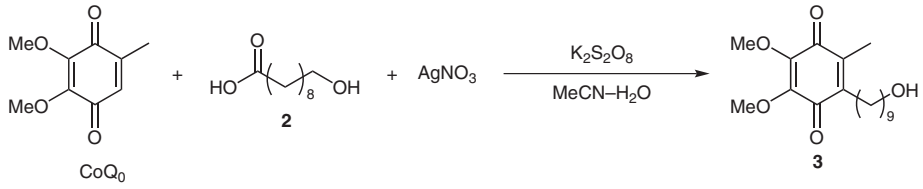


Scheme 1 Various approaches for idebenone and its analogues

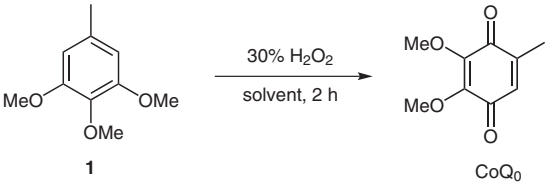


Scheme 2 Synthesis of 2-(9-hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone (**3**) from coenzyme Q_0 via free-radical alkylation

enzyme Q_0. As shown in Scheme 2, the use of acetonitrile–water (1:1) as the solvent at 75 °C yield the desired 2-(9-hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone in 60% yield.

To initiate our study, coenzyme Q_0 was obtained in one step by treatment of commercially available 3,4,5-trimethoxytoluene (**1**) with hydrogen peroxide in acetic acid without the use of a metal catalyst. This environmentally friendly procedure is based on the use of hydrogen peroxide as an oxygen atom donor, and the solvent was shown to play an important role in this transformation. The reaction of 3,4,5-trimethoxytoluene (**1**) and hydrogen peroxide (30% water solution) was thus investigated under different conditions, the results are summarized in Table 1. The use of a catalytic amount of concentrated sulfuric acid in acetic acid improved the reaction yield (entry 2). However, increasing the amount of sulfuric acid by using acetic acid–sulfuric acid (100:10) as the solvent system gave a low yield (entry 3). The reaction yield could be further improved by using the mixture of formic acid and acetic acid (entries 6–9) or acetic acid and polyphosphoric acid (entry 5) as the solvent system. The best yield was obtained using the solvent system formic acid–acetic acid (2:1), which gave the desired product coenzyme Q_0 in 86% yield.

Table 1 Synthesis of Coenzyme Q_0 under Metal-Free Conditions[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	AcOH	35	20
2	AcOH–H_2SO_4 (100:1)	35	62
3	AcOH–H_2SO_4 (100:10)	35	32
4	HCO_2H	35	45
5	HCO_2H–PPA (1:1)	35	53
6	HCO_2H–AcOH (1:1)	35	54
7	HCO_2H–AcOH (1:2)	35	34
8	HCO_2H–AcOH (2:1)	35	86
9	HCO_2H–AcOH (3:1)	35	65

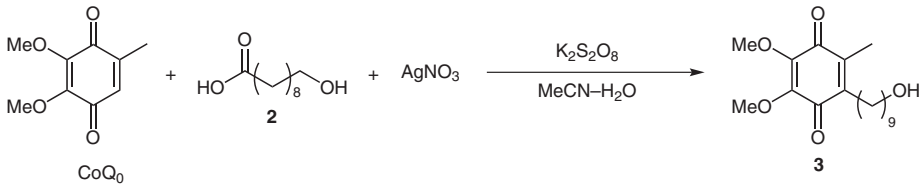
[a] Conditions: 3,4,5-trimethoxytoluene (**1**, 0.02 mol), 30% H_2O_2 (0.08 mol).
[b] Yield of pure isolated products.

According to the literature method,[8] acetonitrile–water (1:1) was chosen as reaction medium for the free-radical alkylation of coenzyme Q_0. Hence, reaction of coenzyme Q_0 with 10-hydroxydecanoic acid (**2**) in the presence of potassium peroxodisulfate and silver nitrate was studied at various temperatures (Table 2). The addition time of potassium peroxodisulfate solution and the reaction temperature played an important role in this transformation. It is important to note that better yields were obtained when potassium peroxodisulfate solution was added slowly over a longer period (entries 5–8); two hours was the best choice for the addition period. Lower yields were obtained when the reaction was carried out below 75 °C (entries 1 and 2). Then, the effects of the amount of potassium peroxodisulfate and silver nitrate were examined, the results showed that an increase in the amount of silver nitrate led to higher conversion of coenzyme Q_0 (entries 9–11). Disappointingly, when we reduced the amount of silver nitrate to 0.1 equivalents, a lower conversion of coenzyme Q_0 was obtained (entry 12). Therefore, optimal reaction conditions involved 1.2 equivalents of carboxylic acid **2**, silver nitrate (0.6 equiv) and potassium peroxodisulfate (1.5 equiv) in the mixed solvent of acetonitrile–water (1:1) at 75 °C with an addition time of two hours.

A plausible mechanism for this novel decarboxylative coupling reaction may be as follows (Scheme 3). Initially, an Ag(I) cation is oxidized to an Ag(II) cation by peroxodisulfate. Then, 10-hydroxydecanoic acid (**2**) reacts with the Ag(II) cation to form an alkyl radical by losing a proton, one molecule of carbon dioxide, and the Ag(I) cation. The obtained radical subsequently underwent hydrogen atom abstraction from the C5 position of coenzyme Q_0 forming the coupling hydroquinol radical. Subsequently the hydroquinol radical is oxidized by peroxodisulfate to give **3**.

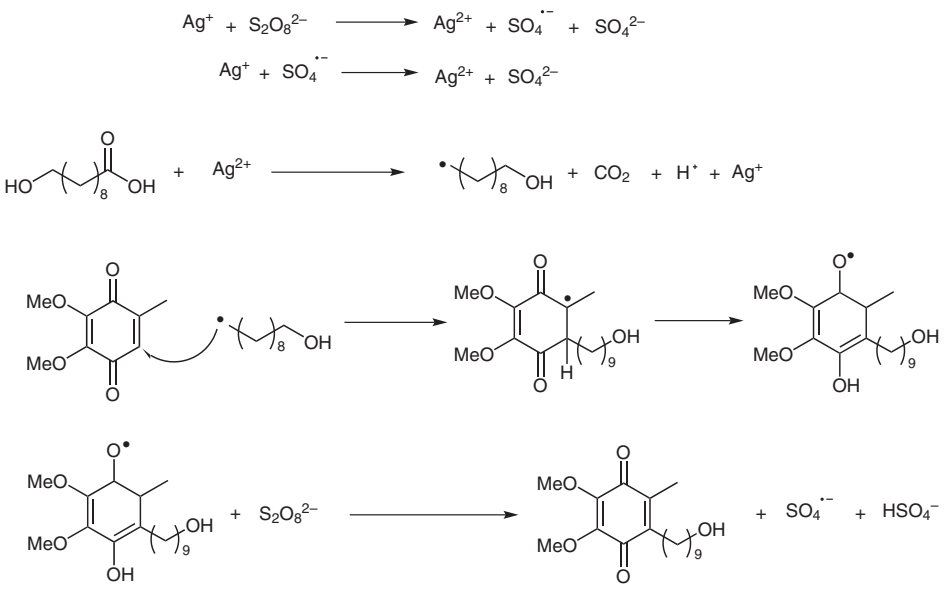
In summary, we have developed a metal-free and environmentally friendly procedure for the preparation of coenzyme Q_0 and a efficient silver-catalyzed decarboxylative direct C5-alkylation of coenzyme Q_0. Coenzyme Q_0 was obtained in 86% yield from one-pot reaction of 3,4,5-trimethoxytoluene (**1**) and 30% hydrogen peroxide in formic acid–acetic acid (2:1) under metal-free conditions. 2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone (**3**) was obtained in 60% yield by the free-radical alkylation of coenzyme Q_0 with 10-hydroxydecanoic acid (**2**) in the presence of potassium peroxodisulfate and silver nitrate in acetonitrile–water (1:1). To the best of our knowledge, this free-radical alkylation is the first example that uses a hydroxy acid as coupling partner to perform the direct C5-alkylation of coenzyme Q_0 to form coenzyme Q analogues. In comparison with the Minisci reaction, our decarboxylative alkylation of coenzyme Q_0 was carried

Table 2 Synthesis of 2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone (**3**) via Free-Radical Alkylation under Different Conditions[a]



Entry	$AgNO_3$ (equiv)	$K_2S_2O_8$ (equiv)	Addition time (h)	Temp (°C)	Yield[b] (%)
1	0.2	1.3	2	45	31
2	0.2	1.3	2	55	36
3	0.2	1.3	2	75	50
4	0.2	1.3	2	85	48
5	0.2	1.3	0.5	75	33
6	0.2	1.3	1	75	41
7	0.2	1.3	1.5	75	47
8	0.2	1.3	3	75	49
9	0.4	1.5	2	75	54
10	0.6	1.5	2	75	60
11	0.8	2	2	75	60
12	0.1	1.5	2	75	28

[a] Conditions: coenzyme Q_0 (2 mmol), **2** (1.2 equiv), $AgNO_3$, oxidant, MeCN–H_2O (1:1, 5 mL).
[b] Yield of pure isolated products.



Scheme 3 Plausible mechanism

out under acid-free conditions. The advantages of these reactions are that they are operationally simple, easy to workup, and take place under mild reaction conditions. The reactions are potentially applicable for the preparation of a wide variety of biologically active coenzyme Q analogues.

All reactions were monitored by TLC, Melting points were measured on a YRT-3 temp apparatus and are uncorrected. NMR spectra data were recorded on a Bruker DRX 500 NMR spectrometer and a ZAB-2F mass spectrometer, respectively.

2,3-Dimethoxy-5-methyl-1,4-benzoquinone (Coenzyme Q_0)
3,4,5-Trimethoxytoluene (**1**, 3.6 g, 0.02 mol) was dissolved in a mixture of HCO_2H (5 mL) and AcOH (2.5 mL); 30% H_2O_2 solution (9 mL, 0.08 mol) was added dropwise over 10 min. The mixture was stirred and heated at 35 °C for 2 h and diluted with H_2O and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with H_2O until pH 7, then dried (anhyd Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatograph (silica gel, petroleum ether–EtOAc, 5:1) to give coenzyme Q_0 (3.1 g, 86% isolated yield) as red-colored needles; mp 55–58 °C (Lit.[10] 57–59 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.42 (s, 1 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 2.02 (s, 3 H).

MS (ESI): *m*/*z* =183 (M^+ + H).

2-(9-Hydroxynonyl)-5,6-dimethoxy-3-methyl-1,4-benzoquinone (3)[6a]
To a solution of coenzyme Q_0 (1.20 g, 6.59 mmol) and 10-hydroxydecanoic acid (2, 1.50 g, 7.91 mmol) in MeCN (20 mL) and distilled H_2O (20 mL) was added $AgNO_3$ (0.67 g, 3.95 mmol). The mixture was heated to 75 °C and a solution of $K_2S_2O_8$ (2.50 g, 9.22 mmol) in distilled H_2O (30 mL) was added dropwise over 2 h; then the reaction mixture was stirred for another 2 h, with TLC monitoring until the starting material was consumed. The resulting mixture was cooled and extracted with CH_2Cl_2; the organic layer was washed with H_2O, then dried (anhyd Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatograph (silica gel, petroleum ether–EtOAc, 4:1) to give product 3 (1.34 g, 60% isolated yield) as yellow needles; mp 42–44 °C (Lit.[6a] 45 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6 H), 3.57–3.53 (t, *J* = 6.3 Hz, 2 H), 2.52 (br s, 1 H), 2.37–3.35 (m, 2 H), 2.00 (s, 3 H), 1.48–1.47 (m, 2 H), 1.22 (br s, 12 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 184.5, 183.9, 144.0, 142.8 (2 C), 138.5, 62.6, 60.9, 32.5, 29.6, 29.2, 29.1, 29.0, 28.5, 26.2, 25.5, 11.7.

MS (ESI): *m*/*z* = 325 (M^+ + H).

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