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EXPERIMENTAL PAPER

A Simple and Convenient Two-step Synthesis of Idebenone

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Idebenone (Figure 1) is a synthetic analogue of Coenzyme Q_{10} (CoQ_{10}),[1] which functions as an antioxidant and free radical scavenging molecule. Structurally, idebenone and CoQ_{10} share the same 1,4-benzoquinone moiety but have a different side chain at the C-5 position. Idebenone has a hydroxydecyl side chain (10 carbon atoms) while CoQ_{10} has a long side chain of 10 isoprene moieties.[2] Both idebenone and CoQ_{10} are involved in the electron transport chain by neutralizing free radicals. Unlike natural CoQ_{10}, however, idebenone is more efficacious because it can bypass mitochondrial complex I and maintain normal ATP production.[3] Idebenone is a synthetic drug initially developed by Takeda Pharmaceutical company in 1980, and it has been widely used in the treatment of Friedreich's ataxia,[4] Alzheimer's disease, and other mitochondrial disorders.[5]

To date, methods for the synthesis of idebenone and its analogues are limited. Two main routes for the preparation of idebenone are shown in Scheme 1. The major differences between these protocols are the starting materials. Park and colleagues[6] started from 2,3,4,5-tetramethoxytoluene **1** to obtain idebenone in seven steps with a total yield of 16% (Scheme 1, eq. 1), while Bjørsvik and co-workers[7] reported a six-step synthesis of idebenone by starting from 3,4,5-trimethoxytoluene **2** in a total yield of 20% (Scheme 1, eq. 2). These approaches involved multistep procedures under harsh reaction conditions (including Friedel-Crafts or Heck reactions and hydrogenation) and the use of toxic reagents. Therefore, a general and practical method for an efficient idebenone synthesis would be in high 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 C-C bonds.[8] Practical C-H functionalization of 1,4-benzoquinone with boronic acids in the presence of $K_2S_2O_8$ and $AgNO_3$ was reported by Baran *et al.*[9] Following our recent work on the synthesis of Coenzyme Q analogues,[10] in this paper we now describe a two-step synthesis of idebenone starting from 3,4,5-trimethoxytoluene **2** with a total yield of 70% (Scheme 1, eq. 3).

As shown in Scheme 2, we here describe a two-step synthesis of idebenone by oxidation of 3,4,5-trimethoxytoluene **2** to obtain Coenzyme Q_0 (CoQ_0),[11–12] followed by a decarboxylative cross-coupling reaction of CoQ_0 with 11-hydroxyundecanoic acid under silver catalysis to afford the target compound. We began our study with the preparation

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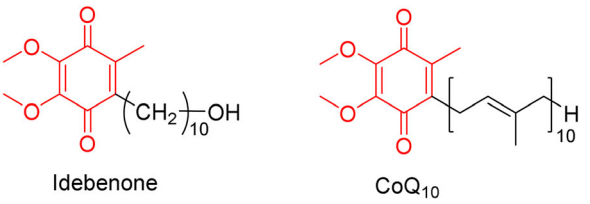
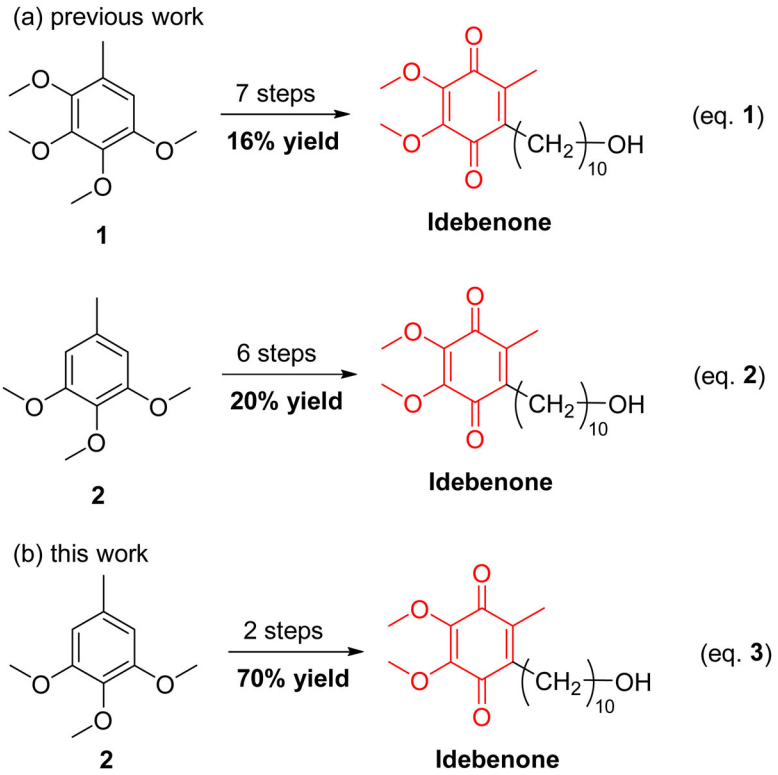
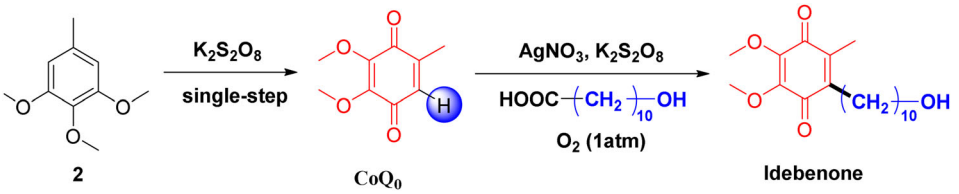


Figure 1. Structures of Idebenone and CoQ_{10}.



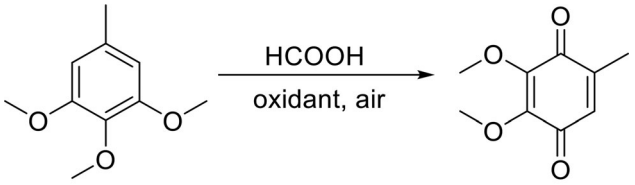
Scheme 1. Various approaches for Idebenone.



Scheme 2. Two-step synthesis of Idebenone.

of CoQ_0, by the oxidation of commercially available 3,4,5-trimethoxytoluene **2** with different oxidants in acetic acid (Table 1).

Table 1. Single-step synthesis of CoQ_0.



2 **CoQ_0**

Entry	oxidant	Temp (°C)	Yield (%)
1	30% H_2O_2	25	30
2	**$K_2S_2O_8$**	**25**	**88**
3	$(NH_4)_2S_2O_8$	25	62
4	CAN	25	0

Reaction Conditions: **2** (0.02 mol), oxidant (1.5 equiv), 4 hr.

As shown in Table 1, the oxidation was conducted in formic acid at 25 °C in air without using any metal catalyst. The traditional method employing 30% H_2O_2 as oxidant gave a yield of 30% (entry 1, Table 1). The use of $(NH_4)_2S_2O_8$ as oxidant improved the reaction yield to 62% (entry 3, Table 1). The best yield was obtained when using $K_2S_2O_8$ as oxidant, which gave the desired product CoQ_0 in 88% yield (entry 2, Table 1). When ceric ammonium nitrate (CAN) was used as oxidant we did not observe any product CoQ_0 (entry 4, Table 1).

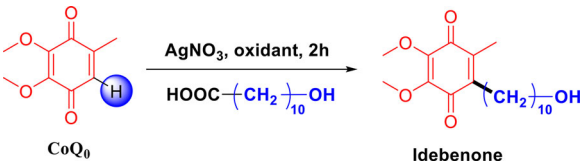
Our initial optimization studies of the $AgNO_3$-catalyzed decarboxylative coupling reaction between CoQ_0 and 11-hydroxyundecanoic acid focused on different reaction atmospheres (Table 2). The reaction was performed in N_2 (1 atm), O_2 (1 atm) and ambient air. Interestingly we found that the yield increased to 80% yield when the reaction was performed under an O_2 atmosphere (entry 3, Table 2). Examination of different solvents at 80 °C under O_2 (1 atm) for 2 h revealed that the best reaction solvent was acetonitrile (entry 3-8, Table 2). Several other oxidants were screened in the reaction. We found that $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ catalyzed the reaction with moderate efficiency (entry 9-10, Table 2). Without the silver salt oxidant, the reaction cannot proceed (entry 11, Table 2). The optimal conditions employed $AgNO_3$ (20%), and $K_2S_2O_8$ (1.5 equiv) in acetonitrile at 80 °C for 2 h (entry 3, Table 2).

In conclusion, a practical and convenient two-step total synthesis of idebenone by oxidation and silver-catalyzed decarboxylative cross-coupling has been developed. The 70% overall yield is suitable for large-scale industrial production. Firstly, CoQ_0 can be synthesized in a single step from the cheap and readily available 3,4,5-trimethoxytoluene **2** by oxidation without using a metal catalyst. It is of course worthy of note that CoQ_0 can serve as a key intermediate for the synthesis of a vast number of Coenzyme Q compounds, not just idebenone. Secondly, the silver-catalyzed decarboxylative cross-coupling reaction between CoQ_0 and carboxylic acids is operationally simple, mild, efficient, and amenable to the gram-scale synthesis of idebenone. It is our expectation that the methods described here will lead to further explorations of high value Coenzyme Q analogues.

Experimental section

All reactions were monitored by TLC (SiO_2, petroleum ether (PE)/EtOAc 5:1). Melting points were measured on Melting Point M-565 (BUCHI) apparatus and are uncorrected.

Table 2. $AgNO_3$-catalyzed decarboxylative reaction under different conditions.



No.	Oxidant	solvent	atmosphere	Yield (%)
1	$K_2S_2O_8$	CH_3CN	N_2	50
2	$K_2S_2O_8$	CH_3CN	air	60
3	**$K_2S_2O_8$**	**CH_3CN**	**O_2**	**80**
4	$K_2S_2O_8$	Acetone	O_2	20
5	$K_2S_2O_8$	THF	O_2	35
6	$K_2S_2O_8$	DMSO	O_2	trace
7	$K_2S_2O_8$	DMF	O_2	trace
8	$K_2S_2O_8$	Ethanol	O_2	trace
9	$(NH_4)_2S_2O_8$	CH_3CN	O_2	45
10	$Na_2S_2O_8$	CH_3CN	O_2	50
11	none	CH_3CN	O_2	trace

Reaction Conditions: CoQ_0 (0.02 mol), 11-hydroxyundecanoic acid (1.0 equiv), $AgNO_3$ (10 mol %), oxidant (0.6 equiv), 80 °C.

NMR and mass spectra were recorded on a Bruker Avance III-HD 400 NMR and a TripleTOF mass spectrometer, respectively. All reagents were purchased from Adamas-beta®, P. R. China, and used without further purification.

Preparation of CoQ_0

3,4,5-Trimethoxytoluene **2** (3.64 g, 0.02 mol) was dissolved in formic acid (10 mL), then a solution of $K_2S_2O_4$ (8.1 g, 0.03 mol) in H_2O (15 mL) was added dropwise over 10 minutes. The mixture was stirred and heated at 25 °C for 4 hours 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, filtered and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (PE/EtOAc 4:1) and recrystallization from hexane to give Coenzyme Q_0, 3.20 g, 88% yield, red-colored needles, m.p. 55-58 °C (lit.[13] 57-59 °C). Rf 0.50 (silica gel, PE/EtOAc 4:1). IR: (cm^{-1}) 2954, 1672, 1685, 1467. ^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). The spectroscopic data are in accord with the literature.[13]

Idebenone

To a solution of CoQ_0 (3.64 g, 0.02 mol) and 11-hydroxyundecanoic acid (4.34 g, 0.02 mol) in acetonitrile (40 mL) was added $AgNO_3$ (0.3 g, 2 mmol) under an O_2 atmosphere. The mixture was heated to 80 °C and a solution of oxidant ($K_2S_2O_8$, 12 mmol) in distilled water 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 water, then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel (PE/EtOAc= 5:1) to give idebenone 5.40 g, 80% yield, orange solid, m.p. 53-55 °C (lit.[10] 52-54 °C). Rf 0.25 (silica gel, PE/EtOAc 4:1). IR: (cm^{-1}) 2910,1680,1610, 1460. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 3H, OCH_3),3.99 (s,3H, OCH_3), 3.62-3.66 (m, 2H, CH_2), 2.45 (t, 2H, J = 8.0 Hz, CH_2), 2.01 (s, 3H, CH_3), 1.61 (s,1H,OH), 1.59-1.52 (m, 2H), 1.42-1.22 (m, 14H).^{13}C NMR (100 MHz, $CDCl_3$): 184.7 (C = O), 184.2 (C = O), 144.3, 144.2, 143.1, 138.7, 63.1, 61.2, 32.8, 29.8, 29.5, 29.4, 29.3,28.7, 26.4, 25.7, 11.9 (**C**H_3). The spectroscopic data were in accord with the literature.[10]

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