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Submitted date: 12/05/2019 • Posted date: 15/05/2019

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Citation information: Luo, Wan-Yue; Zhao, Yan; Zhang, Tian-Li; Wang, Jin; Hu, Xiao (2019): Silver-Catalyzed Decarboxylative Cross-coupling Radical Reaction: Direct Synthesis of Coenzyme Q Compounds. ChemRxiv. Preprint.

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Silver-Catalyzed Decarboxylative Cross-coupling Radical Reaction: Direct Synthesis of Coenzyme Q Compounds

Yi-Yu Yan^{a#}, Wan-Yue Luo^{a#}, Yan Zhao^a, Tian-Li Zhang^a, Jin Wang^{a*}, Xiao Hu^{b*}

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Abstract

An efficient and general method for the synthesis of Coenzyme Q compounds through the activation of 1,4-benzoquinone C_{sp2}-H bond has been developed. This C-C bond formation reaction proceeds readily in an open flask by direct cross-coupling reaction of Coenzyme Q₀ with commercially available aliphatic carboxylic acids utilizing AgNO₃ as catalyst and K₂S₂O₈ as oxidant in aqueous solution. This radical reaction is operationally simple and amenable to gram-scale synthesis.

Keywords: Coenzyme Q, C-C bond formation, Cross-Coupling, carboxylic acids

1. Introduction

Coenzyme Q (CoQ_n), also known as the ubiquinones, is a vitamin-like 1,4-benzoquinone compound and functions as a potent antioxidant that scavenges free radicals. CoQ molecules are acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron transport chain of mitochondria. The metabolites of CoQ homologues and a number of synthetic CoQ compounds have been reported possess antineoplastic, anti-inflammatory and antimicrobial activities. CoQ₁₀ and idebenone are the most known Coenzyme Q drugs

which is widely used in the treatment of Friedreich's ataxia, Alzheimer's disease, Parkinson's disease and mitochondrial disorders. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone, known as Coenzyme Q₀ (CoQ₀), can serve as a key intermediate in the synthesis of coenzyme Q₁₀, idebenone and other CoQ Compounds (**Figure 1**).

Figure 1. Structures of CoQ₁₀, Idebenone, CoQ₀ and CoQ compound

To date, the most general methods for the preparation of CoQ compounds are starting from 3,4,5-trimethoxytoluene **1** or 2,3,4,5-tetramethoxytoluene **2** through multistep reactions (**Scheme 1a**). These methods involved tedious reaction conditions (Friedel-Crafts, hydrogenation, Heck reaction, etc.), use of toxic reagents or low total yields. Therefore, the development of novel and practical methods for the straightforward synthesis of CoQ compounds are highly desired.

Scheme 1. Various methods for CoQ compound

Arylboronic acids are widely used as cross-coupling reaction partners in the formation of C–C bonds. Baran *et al* and Yu *et al* reported a direct arylation of quinones with boronic acids to afford aryl substituted CoQ compounds (**Scheme 1b**). However, these reactions are time consuming, and the reagent arylboronic acids are expensive and not easily available. Compared with the boronic acids, the ready availability, high stability, and low cost of aliphatic carboxylic acids are good reagents for the decarboxylative reactions involving the cleavage of C(sp³)–COOH bonds to form a new C–C bond. Following our previous work on synthesis of Coenzyme Q analogues, herein, we report the first direct decarboxylative cross-coupling reaction of CoQ₀ with aliphatic carboxylic acids (**Scheme 1c**).

2. Results and discussion

Our initial trial commenced with the reaction of CoQ₀ and butanoic acid (1.2 equiv) by catalytic AgNO₃ (20%) in the presence of K₂S₂O₈ (2 equiv). Within 2 h, the reaction was complete and delivered the alkylated CoQ **3** in 43% yield after isolation.

(entry 2, **Table 1**). This reaction is operationally simple, is run under air, is clean and scalable. Without the catalyst silver salt, the reaction can not proceed (entry 1, **Table 1**). Examination of various solvents at 80 °C under open air for 2 h revealed that the best reaction solvent is acetonitrile (entry 2, **Table 1**). Several other silver catalysts were screened in the reaction, Ag_2CO_3 and AgOAc catalyzed the reaction with moderate efficiency (entries 9-10, **Table 1**), and AgNO_3 was ultimately chosen as the catalyst because it formed CoQ in the best yield. Oxidants $\text{K}_2\text{S}_2\text{O}_8$, $\text{Na}_2\text{S}_2\text{O}_8$ and $(\text{NH}_4)_2\text{S}_2\text{O}_8$, were also examined in the reaction (entries 11-13, **Table 1**), $\text{K}_2\text{S}_2\text{O}_8$ can catalyze this reaction with a best yield (57%, entry 11, **Table 1**). The effect of the amount of AgNO_3 and $\text{K}_2\text{S}_2\text{O}_8$ was examined, and the results showed that an increase in the amount of AgNO_3 and $\text{K}_2\text{S}_2\text{O}_8$ lead to higher conversion of Coenzyme Q_0 . (entries 14-17, **Table 1**). The optimal condition was using AgNO_3 (40%), and $\text{K}_2\text{S}_2\text{O}_8$ (2 equiv) in acetonitrile at 80 °C for 2 h (entry 15, **Table 1**).

Table 1. Silver-catalyzed decarboxylative reaction under different conditions

Entry	Catalyst (%)	Oxidant (equiv.)	solvent	Yield (%)
1	none	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	0
2	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	43
3	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	THF	20
4	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	Acetone	10
5	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	MeOH	0
6	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	EtOH	0
7	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	DMSO	Trace
8	$\text{AgNO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	DMF	0
9	$\text{Ag}_2\text{CO}_3(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	20
10	$\text{AgOAc}(10)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	32
11	$\text{AgNO}_3(20)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	57
12	$\text{AgNO}_3(20)$	$(\text{NH}_4)_2\text{S}_2\text{O}_8(2)$	CH_3CN	Trace
13	$\text{AgNO}_3(20)$	$\text{Na}_2\text{S}_2\text{O}_8(2)$	CH_3CN	50
14	$\text{AgNO}_3(30)$	$\text{K}_2\text{S}_2\text{O}_8(2)$	CH_3CN	64

15	AgNO ₃ (40)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	75
16	AgNO ₃ (50)	K ₂ S ₂ O ₈ (3)	CH ₃ CN	70
17	AgNO ₃ (60)	K ₂ S ₂ O ₈ (4)	CH ₃ CN	60

Reaction Conditions: **CoQ₀** (0.02mol), butanoic acid (1.2 equiv), 80 °C, 2 hour under open air

With the optimum reaction conditions in hand, we explored the substrate scope with regard to different carboxylic acid (**Table 2**). Delightfully, the substrate scope is quite general, commercial available long-chain carboxylic acids can be applied to this protocol, thus affording the corresponding CoQ compounds in good to excellent yields (entry 1-3, **Table 2**). It was interesting to note that a CoQ drug idebenone (**6**) was obtained in gram-scale by the reaction of 11-Hydroxyundecanoic acid with CoQ₀ in 75% yield with no by-product (entry 3, **Table 2**). However, when use the short carbon chains acetic acid or benzoic acid as coupling reaction partners to react with CoQ₀ under the same conditions, no CoQ products were observed (entry 4-5, **Table 2**).

Table 2. Cross-coupling of Coenzyme Q₀ with carboxylic acids

Entry	Carboxylic acids	R	CoQ	Yield (%)
1	HOOC-(CH ₂) ₈ -CH ₃	(CH ₂) ₈ -CH ₃	4	80
2	HOOC-(CH ₂) ₉ -OH	(CH ₂) ₉ -OH	5	70
3	HOOC-(CH ₂) ₁₀ -OH	(CH ₂) ₁₀ -OH	6	75
4	HOOC-CH ₃	CH ₃	7	trace
5	HOOC-Ph	Ph	8	0

Reaction Conditions: **CoQ₀** (0.02mol), carboxylic acid (1.5 equiv), AgNO₃ (40%), K₂S₂O₈ (2 equiv)

Based on the experiment results, a silver-catalyzed decarboxylative decarboxylative C_{sp2}-H cross-coupling reaction is tentatively illustrated in **Scheme 2**. Initially, Ag(I) was oxidized into Ag(II) intermediate by S₂O₈²⁻ and the carboxylic acids

(A) underwent an SET process to generate the corresponding carbon radical (B) and release CO₂. The carbon radical (B) then attack the C_{sp2}-H of CoQ₀ to afford intermediate (C), which can transfer to the product idebenone (D) by S₂O₈²⁻.

Scheme 2. Proposed reaction mechanism

Conclusion

In summary, we have developed a practical and convenient synthesis of Coenzyme Q compounds by the use of catalytic silver-(I) nitrate in the presence of K₂S₂O₈ as co-oxidants. This decarboxylative C-C cross-coupling reaction between CoQ₀ and aliphatic carboxylic acids proceed well under open air conditions. This method is easily operational, mild and efficient. It has been applied to the gram-scale synthesis of CoQ drug idebenone (6) with a yield of 75%, which makes the method highly applicable. This chemistry provided a novel C_{sp2}-H alkylation approach leading to other alkylated CoQ compounds which are of high synthetic value. Studies on the applications in natural CoQ syntheses are ongoing in our laboratory.

Experimental Section

All reactions were monitored by TLC (SiO₂, 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 (K₂S₂O₈), Ammonium persulphate ((NH₄)₂S₂O₈), acetic acid (HOAc) were purchased from Adamas, P. R. China, and used

without further purification.

Synthesis of CoQ compounds

To a solution of Coenzyme Q₀ (3.64 g, 0.02 mol) and carboxylic acids (0.024mol) in acetonitrile 80 mL was added AgNO₃ (1.35 g, 8 mmol). The mixture was heated to 80 °C and a solution of K₂S₂O₈ (10.81 g, 0.04 mol) in distilled water 80 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 CH₂Cl₂. The organic layer was washed with water, then dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel (PE/EtOAc= 5:1) to give CoQ compounds.

Acknowledgments

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) and the College students practice innovation training program of Yancheng Teachers University (Provincial key projects).

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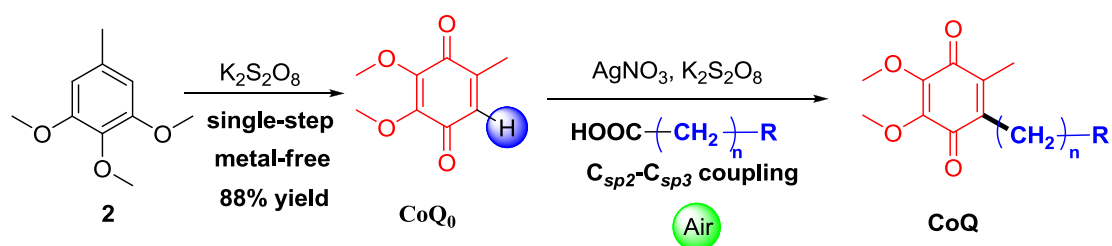
Yi-Yu Yan^{a#}, Wan-Yue Luo^{a#}, Yan Zhao^a, Tian-Li Zhang^a, Jin Wang^{a*}, Xiao Hu^{b*}

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Abstract

An efficient and general method for the synthesis of Coenzyme Q compounds through the activation of 1,4-benzoquinone C_{sp^2} -H bond has been developed. This C-C bond formation reaction proceeds readily in an open flask by direct cross-coupling reaction of Coenzyme Q₀ with commercially available aliphatic carboxylic acids utilizing $AgNO_3$ as catalyst and $K_2S_2O_8$ as oxidant in aqueous solution. This radical reaction is operationally simple and amenable to gram-scale synthesis.

Keywords: Coenzyme Q, C-C bond formation, Cross-Coupling, carboxylic acids

1. Introduction

Coenzyme Q (CoQ_n), also known as the ubiquinones, is a vitamin-like 1,4-benzoquinone compound and functions as a potent antioxidant that scavenges free radicals.^[1] CoQ molecules are acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron transport chain of mitochondria.^[2] The metabolites of CoQ homologues and a number of synthetic CoQ compounds have been reported possess antineoplastic, anti-inflammatory and antimicrobial activities.^[3] CoQ₁₀ and idebenone are the most known Coenzyme Q drugs which is widely used in the treatment of Friedreich's ataxia,^[4] Alzheimer's disease, Parkinson's disease and mitochondrial disorders.^[5] 2,3-Dimethoxy-5-methyl-1,4-benzoquinone, known as Coenzyme Q₀ (CoQ₀), can serve as a key intermediate in the synthesis of coenzyme Q₁₀, idebenone and other CoQ Compounds (**Figure 1**).^[6]

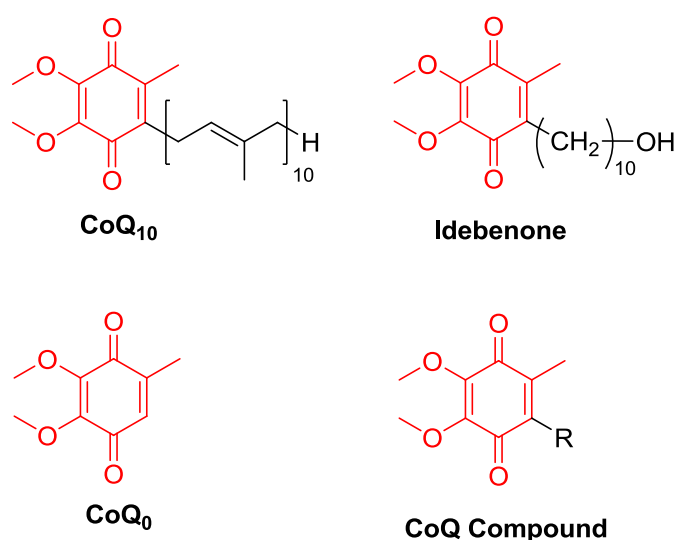
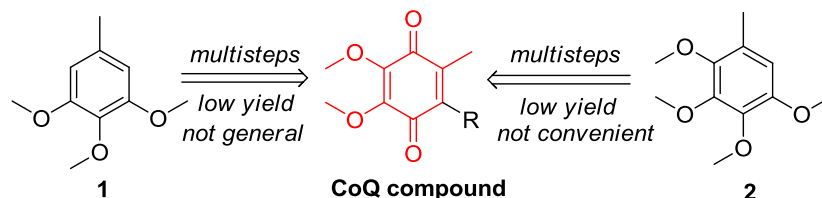


Figure 1. Structures of CoQ₁₀, Idebenone, CoQ₀ and CoQ compound

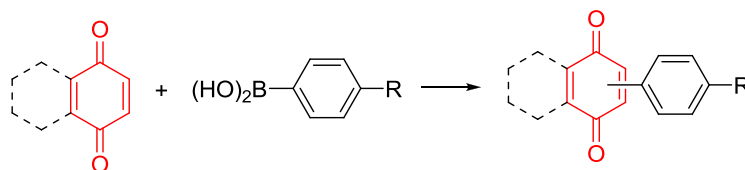
To date, the most general methods for the preparation of CoQ compounds are starting from 3,4,5-trimethoxytoluene **1** ^[7] or 2,3,4,5-tetramethoxytoluene **2** ^[8] through multistep reactions (**Scheme 1a**). These methods involved tedious reaction conditions (Friedel-Crafts, hydrogenation, Heck reaction, etc.), use of toxic reagents or low total yields. Therefore, the development of novel and practical methods for

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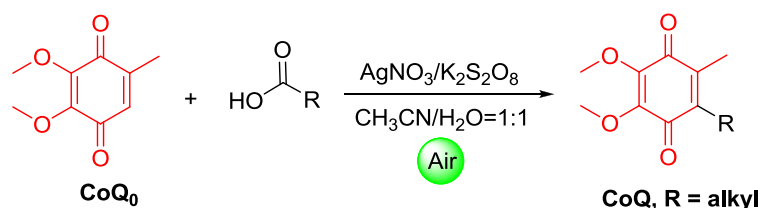
a) classical method for CoQ compound (previous work)



b) C-H Functionalization of Quinones with Boronic Acids (*Phil S. Baran et al* and *Xiao-Qi Yu et al*)



c) Silver-Catalyzed Decarboxylative Cross-coupling of CoQ₀ with Carboxylic Acids (this work)



Scheme 1. Various methods for CoQ compound

Arylboronic acids are widely used as cross-coupling reaction partners in the formation of C–C bonds. Baran *et al*^[9] and Yu *et al*^[10] reported a direct arylation of quinones with boronic acids to afford aryl substituted CoQ compounds (**Scheme 1b**). However, these reactions are time consuming, and the reagent arylboronic acids are expensive and not easily available. Compared with the boronic acids, the ready availability, high stability, and low cost of aliphatic carboxylic acids are good reagents for the decarboxylative reactions involving the cleavage of C(sp³)–COOH bonds to form a new C–C bond.^[11] Following our previous work on synthesis of Coenzyme Q analogues,^[12] herein, we report the first direct decarboxylative cross-coupling reaction of CoQ₀ with aliphatic carboxylic acids (**Scheme 1c**).

2. Results and discussion

Our initial trial commenced with the reaction of CoQ₀ and butanoic acid (1.2 equiv) by catalytic AgNO₃ (20%) in the presence of K₂S₂O₈ (2 equiv). Within 2 h, the

reaction was complete and delivered the alkylated CoQ **3** in 43% yield after isolation. (entry 2, **Table 1**). This reaction is operationally simple, is run under air, is clean and scalable. Without the catalyst silver salt, the reaction can not proceed (entry 1, **Table 1**). Examination of various solvents at 80 °C under open air for 2 h revealed that the best reaction solvent is acetonitrile (entry 2, **Table 1**). Several other silver catalysts were screened in the reaction, Ag₂CO₃ and AgOAc catalyzed the reaction with moderate efficiency (entries 9-10, **Table 1**), and AgNO₃ was ultimately chosen as the catalyst because it formed CoQ in the best yield. Oxidants K₂S₂O₈, Na₂S₂O₈ and (NH₄)₂S₂O₈, were also examined in the reaction (entries 11-13, **Table 1**), K₂S₂O₈ can catalyze this reaction with a best yield (57%, entry 11, **Table 1**). The effect of the amount of AgNO₃ and K₂S₂O₈ was examined, and the results showed that an increase in the amount of AgNO₃ and K₂S₂O₈ lead to higher conversion of Coenzyme Q₀. (entries 14-17, **Table 1**). The optimal condition was using AgNO₃ (40%), and K₂S₂O₈ (2 equiv) in acetonitrile at 80 °C for 2 h (entry 15, **Table 1**).

Table 1. Silver-catalyzed decarboxylative reaction under different conditions

CoQ₀ $\xrightarrow[\text{HOOC}-(\text{CH}_2)_2-\text{CH}_3]{\text{catalyst, oxidant, air}}$ **3**

Entry	Catalyst (%)	Oxidant (equiv.)	solvent	Yield (%)
1	none	K ₂ S ₂ O ₈ (2)	CH ₃ CN	0
2	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	43
3	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	THF	20
4	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	Acetone	10
5	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	MeOH	0
6	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	EtOH	0
7	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	DMSO	Trace
8	AgNO ₃ (10)	K ₂ S ₂ O ₈ (2)	DMF	0
9	Ag ₂ CO ₃ (10)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	20
10	AgOAc(10)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	32
11	AgNO ₃ (20)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	57
12	AgNO ₃ (20)	(NH ₄) ₂ S ₂ O ₈ (2)	CH ₃ CN	Trace
13	AgNO ₃ (20)	Na ₂ S ₂ O ₈ (2)	CH ₃ CN	50

14	AgNO ₃ (30)	K ₂ S ₂ O ₈ (2)	CH ₃ CN	64
15	AgNO₃(40)	K₂S₂O₈(2)	CH₃CN	75
16	AgNO ₃ (50)	K ₂ S ₂ O ₈ (3)	CH ₃ CN	70
17	AgNO ₃ (60)	K ₂ S ₂ O ₈ (4)	CH ₃ CN	60

Reaction Conditions: **CoQ₀** (0.02mol), butanoic acid (1.2 equiv), 80 °C, 2 hour under open air

With the optimum reaction conditions in hand, we explored the substrate scope with regard to different carboxylic acid (**Table 2**). Delightfully, the substrate scope is quite general, commercial available long-chain carboxylic acids can be applied to this protocol, thus affording the corresponding CoQ compounds in good to excellent yields (entry 1-3, **Table 2**). It was interesting to note that a CoQ drug idebenone (**6**) was obtained in gram-scale by the reaction of 11-Hydroxyundecanoic acid with CoQ₀ in 75% yield with no by-product (entry 3, **Table 2**). However, when use the short carbon chains acetic acid or benzoic acid as coupling reaction partners to react with CoQ₀ under the same conditions, no CoQ products were observed (entry 4-5, **Table 2**).

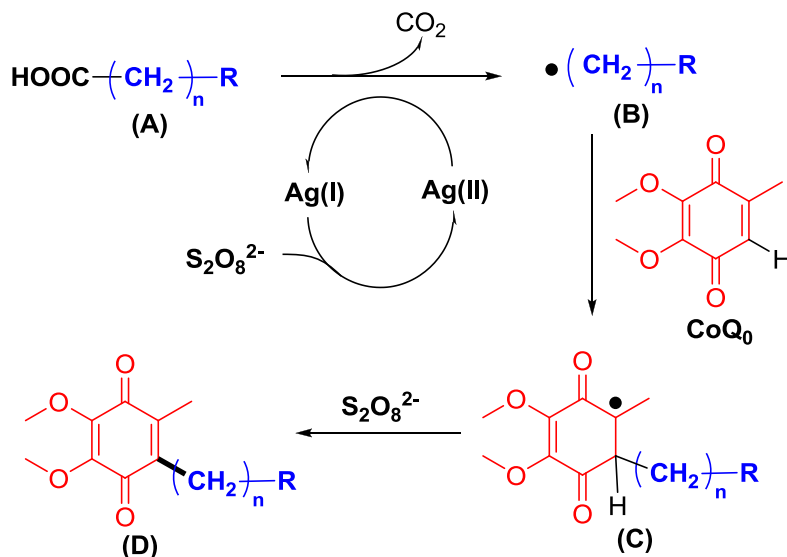
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Reaction Conditions: **CoQ₀** (0.02mol), carboxylic acid (1.5 equiv), AgNO₃ (40%), K₂S₂O₈ (2 equiv)

Based on the experiment results, a silver-catalyzed decarboxylative decarboxylative C_{sp2}-H cross-coupling reaction is tentatively illustrated in **Scheme 2**. Initially, Ag(I) was oxidized into Ag(II) intermediate by S₂O₈²⁻ and the carboxylic

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Scheme 2. Proposed reaction mechanism

Conclusion

In summary, we have developed a practical and convenient synthesis of Coenzyme Q compounds by the use of catalytic silver-(I) nitrate in the presence of K₂S₂O₈ as co-oxidants. This decarboxylative C-C cross-coupling reaction between CoQ₀ and aliphatic carboxylic acids proceed well under open air conditions. This method is easily operational, mild and efficient. It has been applied to the gram-scale synthesis of CoQ drug idebenone (**6**) with a yield of 75%, which makes the method highly applicable. This chemistry provided a novel C_{sp2}-H alkylation approach leading to other alkylated CoQ compounds which are of high synthetic value. Studies on the applications in natural CoQ syntheses are ongoing in our laboratory.

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Synthesis of CoQ compounds

To a solution of Coenzyme Q₀ (3.64 g, 0.02 mol) and carboxylic acids (0.024mol) in acetonitrile 80 mL was added AgNO₃ (1.35 g, 8 mmol). The mixture was heated to 80 °C and a solution of K₂S₂O₈ (10.81 g, 0.04 mol) in distilled water 80 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 CH₂Cl₂. The organic layer was washed with water, then dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel (PE/EtOAc= 5:1) to give CoQ compounds.

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