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Simple and convenient two step synthesis of 5-bromo-2,3-dimethoxy-6-methyl-1,4-benzoquinone

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Abstract: 5-bromo-2,3-dimethoxy-6-methyl-1,4-benzoquinone **3**, a key intermediate for preparing coenzyme Q compounds, was readily synthesized in two steps by a reaction sequence starting from the commercially available 3,4,5-trimethoxytoluene **1** via bromination and oxidation reactions. Persulfate salts were first employed as oxidants to synthesize 1,4-benzoquinone, the overall yield of title compound **3** was 65%.

Keywords: coenzyme Q; 1,4-benzoquinone; bromination; persulfate

1 Introduction

In synthetic chemistry, researchers are always seeking new methods for synthesising a specific compound that are important in many areas such as pharmaceutical industry. 5-bromo-2,3-dimethoxy-6-methyl-1,4-benzoquinone **(3)** [1], is an important coenzyme Q compound [2], which facilitates electron-transfer activity [3] and radical properties in mitochondria [4]. In addition, compound **3** is also a key intermediate [5] in the preparation of other biologically active coenzyme Q analogues [6]. In 2000, Jung and co-workers [7] reported that coupling of compound **3** with isoprenylstannanes could efficiently produce coenzyme Q_{10} and its analogues, as shown in Scheme 1. CoQ_{10} is a lipid-soluble benzoquinone with a side-chain of 10 isoprenoid units (Scheme 1), acts as a free radical scavenging antioxidant [3]. CoQ_{10} has been widely used in the treatment of mitochondria disorders [8].

To date, methods for the synthesis of compound **3** are limited [9]. Most of the methods used CoQ_0 as starting material, compound **3** was obtained by reaction with toxic bromine [10], and few syntheses leading to compound **3** have been disclosed [11]. Hence, based on our previous work on the synthesis of CoQ analogues [12-16], we now report an efficient synthetic path for compound **3** as shown in Scheme 2. The reaction is operationally simple and could be used in the preparation of other coenzyme Q analogues.

2 Experimental

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 Avance III-HD 400 NMR and TripleTOF mass spectrometers, respectively. GC-Mass spectra were recorded on Triple Quadrupole GC/MS of Agilent 7890B-7000C. All reagents: e.g. NaBr, $Na_2S_2O_8$, $K_2S_2O_8$, $(NH_4)_2S_2O_8$ were purchased from Adamas, P. R. China, and used without further purification.

2.1 Synthetic procedure for 2-bromo-3,4,5-trimethoxytoluene (2)

A mixture of 3,4,5-trimethoxytoluene **1** (0.72 g, 4 mmol) and NaBr (0.42 g, 4 mmol) were dissolved in acetic acid (4 mL). A solution of 30% H_2O_2 (2 mL, 18 mmol) was added dropwise at 40°C over a period of 1 h. The resulting mixture

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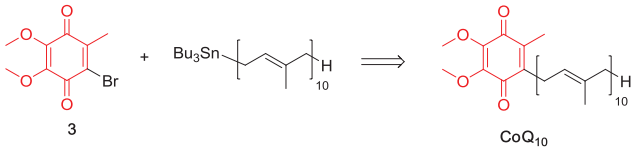
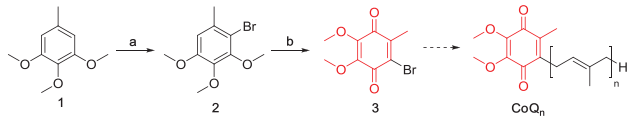


Scheme 1: Compound **3** and coenzyme Q_{10}.



Scheme 2: Reagents and conditions: (a) NaBr, 30% H_2O_2, HOAc, 40°C, 1 h, 100%; (b) Sodium persulfate, HOAc/H_2SO_4, 80°C, 2 h, 65%.

was quenched with water and extracted with petroleum ether. Combined the organic layers and evaporated in vacuo to afford a yellow oil **2** (1.04 g) in 100% yield.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.61 (s, 1H, ArH), 3.89 (s, 3H, OC**H**$_3$), 3.86 (s, 3H, OC**H**$_3$), 3.84 (s, 3H, OC**H**$_3$), 2.37 (s, 3H, C**H**$_3$).

^{13}C NMR (101MHz, $CDCl_3$): δ 152.2, 150.8, 141.1, 133.4, 110.8, 109.5, 61.1 (O**C**H$_3$), 60.9 (O**C**H$_3$), 56.1 (O**C**H$_3$), 23.2 (**C**H$_3$).

The data is consistent with the literature [13].

2.2 Synthesis of compound 3

Method (**1**): Compound **2** (0.44 g, 1.7 mmol) was dissolved in a mixture solvent of acetic acid (2.5 mL) and H_2SO_4 (0.25 mL), then a solution of $Na_2S_2O_8$ (0.80 g, 3.4 mmol) in H_2O (5 mL) was added dropwise over 5 min. The mixture was stirred and heated at 80°C for another 2 h and extracted with dichloromethane. Combined organic layers, and washed with H_2O and $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by a flash column (PE/EtOAc 6:1) to give red solid **3** (0.28 g, 65% yield).

Method (**2**): A solution of $K_2S_2O_8$ (3.4 mmol) in H_2O (8 mL) was added dropwise to a mixture of compound **2** (0.44 g, 1.7 mmol) in acetic acid (2.5 mL) and H_2SO_4 (0.25 mL). The reaction mixture was heated at 80°C for 2 h, quenched with water and extracted with dichloromethane. The organic phases were washed with H_2O and Brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue oil was purified by a flash column to give red solid **3** (0.26 g, 60% yield).

Method (**3**): To a mixture of Compound **2** (0.44 g, 1.7 mmol) in HOAc (2.5 mL) and H_2SO_4 (0.25 mL) was added dropwise by a solution of $(NH_4)_2S_2O_8$ (3.4 mmol) in H_2O (6 mL) over 5 min. The reaction mixture was heated at 80°C for 2 h and extracted with dichloromethane. The combined organic phases were washed with H_2O and $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. The residue oil was purified by a flash column to give red solid **3** (0.17 g, 40% yield).

m.p. 68 - 69°C (lit. 67-69°C [10]). 96% purity by HPLC.

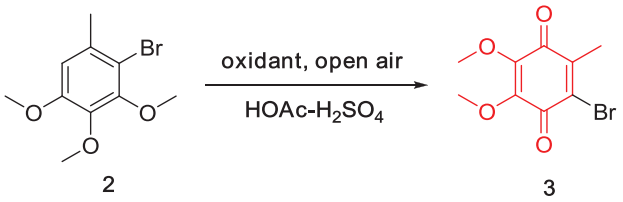
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 3H, OC**H**$_3$), 4.01 (s, 3H, OC**H**$_3$), 2.21 (s, 3H, C**H**$_3$).

^{13}C NMR (101MHz, $CDCl_3$): δ 181.0 (**C**=O), 176.7 (**C**=O), 145.2, 144.1, 143.8, 133.6, 61.58 (O**C**H$_3$), 61.33 (O**C**H$_3$), 16.75 (**C**H$_3$).

GC-MS (EI): m/z = 260.

The data is consistent with the literature [4].

Table 1: Synthesis of compound **3** under different persulfate.



Entry	Oxidant	Time (h)	Temp (°C)	Yield (%)
1	$Na_2S_2O_8$	2	80	65
2	$K_2S_2O_8$	2	80	60
3	$(NH_4)_2S_2O_8$	2	80	40

Conditions: **2** (1.7 mmol), persulfate (3.4 mmol), HOAc-H_2SO_4 (v/v = 10:1).

3 Results and discussion

As shown in Scheme 2, treatment of 3,4,5-trimethoxy-toluene (**1**) with NaBr and 30% in acetic acid at 40°C gave compound **2** in 100% yield. Finally, compound **2** was oxidized with a persulfate compound in HOAc-H_2SO_4 mixed solvent (v/v = 10:1) to afford compound **3** (Table 1). The reaction is conducted without using any metal catalyst. This environmentally friendly procedure is based on the persulfate oxidant as an oxygen atom donor, and the HOAc-H_2SO_4 solvent as proton atom in this transformation [2]. The use of $(NH_4)_2S_2O_8$ as oxidant in HOAc-H_2SO_4 (10:1) mixed solvent gave **3** in a yield of 40% (entry 3, Table 1). When utilized $K_2S_2O_8$ as oxidant in the same mixed solvent HOAc-H_2SO_4 (10:1) can improve the reaction yield to 60% (entry 2, Table 1). The best yield was obtained using $Na_2S_2O_8$ as oxidant in HOAc-H_2SO_4 (10:1) solvent system, which gave the desired compound **3** in 65% yield (entry 1, Table 1).

4 Conclusion

In summary, we developed a two-step synthetic protocol for the preparation of 5-bromo-2,3-dimethoxy-6-methyl-1,4-benzoquinone (**3**) from the cheap and readily available 3,4,5-trimethoxytoluene (**1**). The bromination reaction utilize NaBr–H_2O_2 system as a green brominating agent instead of bromine and NBS, the reaction is clean and easy work up without purification. Persulfate salts were first employed as oxidants to synthesize 1,4-benzoquinone under mild condisitons, the chemistry was clean and easy work up. This method is potentially applicable for the the synthesis of a wide variety of coenzyme Q compounds [14,15].

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