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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 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_{2}S_{2}O_{3}, K_{2}S_{2}O_{8}, (NH_{4})_{2}S_{2}O_{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 (0.62 g, 4 mmol) were dissolved in acetic acid (4 mL). A solution of 30% H_{2}O_{2} (2 mL, 18 mmol) was added dropwise at 40°C over a period of 1 h. The resulting mixture
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.

\[ \text{\textsuperscript{1}H NMR (400MHz, CDCl}_3): \delta 6.61 (s, 1H, ArH), 3.89 (s, 3H, OCH\textsubscript{3}), 3.84 (s, 3H, OCH\textsubscript{3}), 2.37 (s, 3H, CH\textsubscript{3}) \]

\[ \text{\textsuperscript{13}C NMR (101MHz, CDCl}_3): \delta 152.2, 150.8, 141.1, 133.4, 110.8, 109.5, 61.1 (OCH\textsubscript{3}), 60.9 (OCH\textsubscript{3}), 56.1 (OCH\textsubscript{3}), 23.2 (CH\textsubscript{3}). \]

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\textsubscript{2}SO\textsubscript{4} (0.25 mL), then a solution of Na\textsubscript{2}SO\textsubscript{4} (0.80 g, 3.4 mmol) in H\textsubscript{2}O (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\textsubscript{2}O and NaHCO\textsubscript{3}, dried over Na\textsubscript{2}SO\textsubscript{4}, and evaporated in vacuo. The residue oil was purified by a flash column to give red solid 3 (0.17 g, 40% yield).

Method (2): A solution of K\textsubscript{2}SO\textsubscript{4} (3.4 mmol) in H\textsubscript{2}O (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\textsubscript{2}SO\textsubscript{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\textsubscript{2}O and Brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, and evaporated in vacuo. The residue oil was purified by a flash column to give red solid 3 (0.26 g, 65% yield).

Method (3): To a mixture of Compound 2 (0.44 g, 1.7 mmol) in HOAc (2.5 mL) and H\textsubscript{2}SO\textsubscript{4} (0.25 mL) was added dropwise by a solution of (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4} (3.4 mmol) in H\textsubscript{2}O (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\textsubscript{2}O and NaHCO\textsubscript{3}, dried over Na\textsubscript{2}SO\textsubscript{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.

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3): \delta 4.04 (s, 3H, OCH=O), 181.0 (C=O), 176.7, 145.2, 144.1, 143.8, 133.6, 61.58 (OCH\textsubscript{3}), 61.33 (OCH\textsubscript{3}), 16.75 (CH\textsubscript{3}). \]

\[ \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3): \delta 144.1, 143.8, 133.6, 61.58 (OCH\textsubscript{3}). \]

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

The data is consistent with the literature [4].

### 3 Results and discussion

As shown in Scheme 2, treatment of 3,4,5-trimethoxytoluene (I) 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\textsubscript{2}SO\textsubscript{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\textsubscript{2}SO\textsubscript{4} solvent as proton atom in this transformation [2]. The use of (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4} as oxidant in HOAc-H\textsubscript{2}SO\textsubscript{4} (10:1) mixed solvent gave 3 in a yield of 40% (entry 3, Table 1). When utilized K\textsubscript{2}SO\textsubscript{4} as oxidant in the same mixed solvent HOAc-H\textsubscript{2}SO\textsubscript{4} (10:1) can improve the reaction yield to 60% (entry 2, Table 1). The best yield was obtained using Na\textsubscript{2}SO\textsubscript{4} as oxidant in HOAc-H\textsubscript{2}SO\textsubscript{4} (10:1) solvent system, which gave the desired compound 3 in 65% yield (entry 1, Table 1).

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

| Entry | Oxidant    | Time (h) | Temp (°C) | Yield (%) |
|-------|------------|----------|-----------|-----------|
| 1     | Na\textsubscript{2}SO\textsubscript{4} | 2        | 80        | 65        |
| 2     | K\textsubscript{2}SO\textsubscript{4} | 2        | 80        | 60        |
| 3     | (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4} | 2        | 80        | 40        |

Conditions: 2 (1.7 mmol), persulfate (3.4 mmol), HOAc-H\textsubscript{2}SO\textsubscript{4} (v/v = 10:1).
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 utilized NaBr–H₂O₂ 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 conditions, the chemistry was clean and easy work up. This method is potentially applicable for the synthesis of a wide variety of coenzyme Q compounds.

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