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Efficient synthesis of 2,3-dimethoxy-5-methyl-6-morpholinomethyl-1,4-benzoquinone hydrochloride

Abstract: The title compound (**5**) was prepared by a reaction sequence starting from 2,3,4,5-tetramethoxytoluene (**1**) via the Blanc reaction, oxidation and alkylation. The described method provides a good yield of the C-6 heterocyclic-substituted benzoquinone derivative and is suitable for the synthesis of other benzoquinone derivatives.

Keywords: benzoquinone derivative; blanc reaction; coenzyme Q analogs.

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1 Introduction

The ubiquinone coenzyme Q (CoQ, or CoQn) is biosynthesized in mitochondria and occurs naturally in our dietary foods (beef, pork, fish, oils, etc.), which is a benzoquinone with a side-chain of different hydrophobic isoprenoid units (Fig. 1), acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron transport chain of mitochondria [1, 2]. CoQ_{10}, the main homolog of CoQ existing in humans, is our only lipid-soluble antioxidant synthesized endogenously and efficiently prevents the oxidation of proteins, lipids and DNA. CoQ_{10} is widely used in the treatment of cardiovascular disease, neurodegenerative disorders and in the improvement of immunotherapy [3, 4]. CoQ_{10} is also used as a food supplement in many countries, and there is an increasing market demand [5].

Previous studies [2, 6] have shown that some metabolites of CoQ_{10}, and a number of short-chain CoQ analogs exhibit significant biological activities, such as inhibition of mitochondrial complex I (NADH-ubiquinone reductase), cardiotonic activity, 5-lipoxygenase suppressant activity, blood platelet aggregation inhibition, etc. [7, 8]. Among the previously synthesized CoQ analogs, some C-6 heterocyclic-substituted benzoquinone derivatives can be used as drugs [9, 10]. However, the methods described in the literature [8–10] for the preparation of these heterocyclic-substituted CoQ analogs have significant drawbacks such as tedious reaction conditions, low yields of the products and difficult work-up. In view of the difficulties associated with the preparation of previous CoQ analogs [5–10], the availability of compound **1** [11–18] prompted us to devise a practical route to 2,3-dimethoxy-5-methyl-6-morpholinomethyl-1,4-benzoquinone hydrochloride (**5**), a heterocyclic-substituted CoQ analog which showed good activity to restore succinate oxidation [9]. In order to better understand the relationship between the different heterocyclic-substituted side chains and the biological activities, the development of simple and efficient methods for the synthesis of C-6 heterocyclic-substituted CoQ analogs are therefore desirable.

We now report a convenient and efficient synthesis of 2,3-dimethoxy-5-methyl-6-morpholinomethyl-1,4-benzoquinone hydrochloride (**5**) from the easily available 2,3,4,5-tetramethoxytoluene (**1**). The synthetic route is shown in Scheme 1.

2 Results and discussion

As shown in Scheme 1, first, bromomethylation of **1** using paraformaldehyde and 47% HBr (Blanc reaction) under solvent-free conditions provided **2** at 40 °C in an excellent yield (97 %) [12]. Then, direct transfer of **2** to benzoquinone **3** by employing ceric ammonium nitrate (CAN) as

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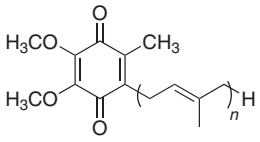


Coenzyme Qn
(ubiquinones; $n < 12$)

Fig. 1: Coenzyme Q (CoQ, or CoQn).

a selective oxidant, gave a good yield (84 %) of **3** which is the key intermediate for the preparation of CoQ_{10} and its analogs. In this transformation, benzoquinone **3** is the major product, but we also detected a small amount of other benzoqunione by-product on the TLC. Finally, direct alkylation of **2** with morpholine in the presence of K_2CO_3 under mild conditions provided **4** (81 % yield, based on **3**), which was subsequently converted into its hydrochloride salt **5** in a good yield by addition of concentrated hydrochloric acid in ethanol.

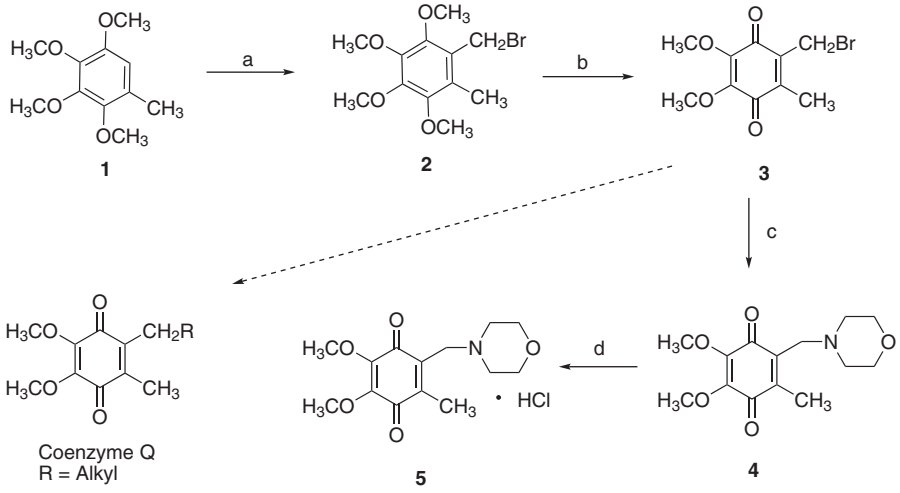
In conclusion, a short route for the synthesis of compound **5** has been found in an overall yield (63 %, based on **1**). From the synthetic point of view, an approach based on the reactions with **3** looked promising for the synthesis of C-6 substituted CoQ analogs bearing a heterocyclic ring, which also avoids the heterocyclic ring being oxidized by the oxidant CAN during the reaction. Moreover, this method not only has the advantages of mild conditions, easily accessible starting materials and facile separation, but it is also less expensive, more practical, and environmentally friendly. Hence, we believe that this experimentally simple approach could be a useful addition to the reported methods for the preparation of CoQ analogs.

3 Experimental section

All reactions were monitored by TLC, the melting points were measured with an YRT-3 temperature apparatus (Tianda Tianfa Technology Co., Ltd. Tianjin, China) and are uncorrected. IR spectra were recorded on an Impact 400 FT-IR instrument (PerkinElmer, USA). ^{1}H NMR spectra were recorded on a Bruker DRX NMR spectrometer (Bruker, Germany) and mass spectra were obtained on a LC mass spectrometer (Shimadzu 30& Triple QUAD 5500, Japan), respectively. All reagents were purchased from Adamas-beta, P. R. China, and used without further purification. 2,3,4,5-tetramethoxytoluene (**1**) was prepared by methods mentioned in the literature [11–15, 19, 20].

3.1 1-(Bromomethyl)-2,3,4,5-tetramethoxy-6-methylbenzene (2)

To a stirred mixture of compound **1** (0.212 g, 0.001 mol) and paraformaldehyde (0.060 g, 0.002 mol) was added 47 % HBr (8 mL) dropwise at room temperature. Then the mixture was stirred at 40 °C for 1 h, quenched with water, and the mixture was extracted with petroleum ether, the combined organic layers were washed with brine. The solution was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to afford **2** (0.295 g, 97 % yield) as a yellow oil. – IR (KBr): ν = 2979, 2940, 1473, 1415, 1278, 1213, 1116 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (s, 2H, CH_2Br), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3). ^{1}H NMR data were in agreement with values found in the literature [21].



Scheme 1: Reagents and conditions: (a) $(HCHO)_n$, 47 % HBr, 40 °C, 97 %; (b) CAN, THF/H_2O, 0 °C, 84 %; (c) K_2CO_3, ethanol, 60 °C, 81 %; (d) 37 % HCl, ethanol, 0 °C, 95 %.

3.2 2-Bromomethyl-5, 6-dimethoxy-3-methyl-[1, 4]benzoquinone (3)

Excess CAN (62.5 g, 0.114 mol) in water (120 mL) was added dropwise at 0 °C to a solution of compound **2** (11.6 g, 0.038 mol) in THF (20 mL). The mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude was extracted with three portions of CH_2Cl_2 (15 mL). The orange extracts were washed with brine until the water phase was neutral (PH~7), then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified using silica-gel column chromatography with petroleum ether and EtOAc (3:1) as an eluent to give the desired benzoquinone **5** (8.7 g, 84 % yield) as an orange oil. – IR (KBr): ν = 2949, 1665, 1619, 1457, 1282, 1211, 1159, 1113, 1023 cm^{-1}. – ^1H NMR (500 MHz, C_5D_5N): δ = 4.29 (s, 2H, CH_2Br), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.99 (s, 3H, CH_3). – ^{13}C NMR (125 MHz, MeOD): δ = 183.7 (C = O), 181.6 (C = O), 144.7, 144.2, 142.3, 136.7, 61.2 (OCH_3), 61.1 (OCH_3), 35.0 (CH_2Br), 11.8 (CH_3). ^1H NMR and ^{13}C NMR data were in agreement with the values in the literature [22].

3.3 2,3-Dimethoxy-5-methyl-6-morpholino-methyl-1,4-benzoquinone (4)

Benzoquinone **(3)** (0.41 g, 1.5 mmol), morpholine (0.14 mL, 1.6 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) in ethanol (2 mL) were heated at 60 °C for 2 h, the progress of the reaction was monitored by TLC. After completion of the reaction, the crude product was extracted with three portions of CH_2Cl_2 (10 mL). The orange extracts were washed with brine until the water phase was neutral (PH~7), then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified using a silica-gel column chromatography with petroleum ether and EtOAc (5:1) as an eluent to give the desired compound **4** (0.34 g, 81 % yield). – IR (KBr): ν = 3437, 2955, 2852, 1645, 1454, 1264, 1202, 1039 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.65 (t, J = 4 Hz, 4H, H-morpholino), 3.38 (s, 2H, CH_2), 2.44 (t, J = 4 Hz, 4H, H-morpholino), 2.16 (s, 3H, CH_3). ^1H NMR data were in agreement with the values in the literature [9].

3.4 2,3-Dimethoxy-5-methyl-6-morpholinomethyl-1,4-benzoquinone hydrochloride (5)

Compound **4** (0.30 g, 1.06 mmol) was dissolved in ethanol (1 mL) and concentrated HCl was added dropwise until the pH of the solution was 1–2. An orange precipitate was formed immediately, the solids were filtered and recrystallized from ethanol to afford the required hydrochloride salts **5** (0.32 g, 95 % yield). M. p. 164–166 °C (lit. 163–165 °C) [9]. – IR (KBr): ν = 3443, 2538, 2435, 1671, 1649, 1605, 1463, 1266, 1206, 1020 cm^{-1}. – ^1H NMR (500 MHz, D_2O): δ = 4.15 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.4 (brs, 8H, H-morpholino), 2.04 (s, 3H, CH_3). – MS (API): m/z = 282 $[M+H]^+$. ^1H NMR and ^{13}C NMR data were in agreement with the values in the literature [9].

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