Alternative synthesis of 5-chloromethyl-2,3-dimethoxy-6-methyl-1, 4-benzoquinone: a key intermediate for preparing coenzyme Q analogues

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The title compound, a key intermediate for preparing Coenzyme Qn family, was prepared in high yield by a reaction sequence starting from the commercially available 3, 4, 5-trimethoxy-benzadehyde via Wolff–Kishner reduction, Vilsmeier–Haack reaction, Blanc chloromethylation reaction, Dakin reaction and oxidation.

Keywords: Coenzyme Q, Wolff–Kishner reduction, Blanc chloromethylation reaction, Dakin reaction

The Coenzyme Qn (CoQn) family, also known as the ubiquinones (Fig. 1), have a number of important biofunctions that include acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron transport chain of mitochondria and bacterial respiratory systems.[1–3] Coenzyme Q (CoQ) is also known to act as an antioxidant by reducing free radicals that can cause damage to structural lipids or proteins in the membrane, not only in mitochondria but in any cellular CoQ containing membranes.[3] In addition, CoQ is a valuable medicine, especially CoQ_{10}, which have a beneficial effect on various heart-related diseases. It is sold as a drug or dietary supplement in many countries, and there is an increasing market demand.[4] For these reasons it is important to find an efficient synthetic route for the preparation of CoQ and its analogues.

Among the published syntheses of CoQ, Lipshutz and his coworkers's approach gives a high yield and has excellent stereoselectivity. $CoQ_{3–10}$ were prepared in good yield (82–89%) and >98% isomerically pure in the final coupling step utilising a Ni(0) catalysis (Scheme 1).[5–11]

The chloromethylated CoQ_0 (**7**) starting material 5-chloromethyl-2,3-dimethoxy-6-methyl-1,4-benzoquinone, a key coupling partner for the synthesis of coenzyme Qn, is conveniently derived from 2, 3, 4, 5-tetramethoxytoluene (**10**),[6,8] However, previous syntheses of **10** are time consuming, complex and low yielding. A review of the literature shows that a number of groups have synthesised **10** via complicated multistep procedures starting from highly functionalised starting materials such as glucose, and pyrogallol.[12,13]

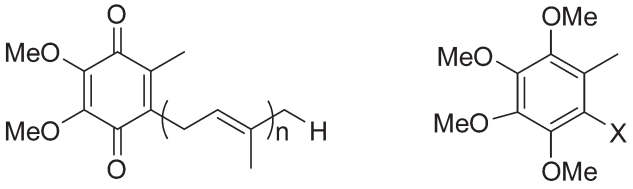


Fig. 1 Coenzyme Q and 2, 3, 4, 5-tetramethoxytoluene.

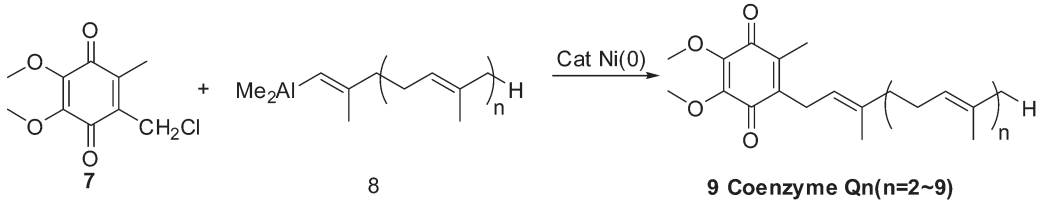
We now present an efficient and reproducible synthesis of **7** starting from commercially available 3, 4, 5-grimethoxybenzadehyde **1** via Wolff–Kishner reduction, Vilsmeier–Haack reaction, Blanc chloromethylation reaction, Dakin reaction and oxidation resulting in an overall overall yield of 51.2% (Scheme 2) based on **1**. The electron-donating effect of methoxy and methyl groups have a beneficial influence on the Wolff–Kishner reduction and Vilsmeier–Haack reaction leading to an excellent yield of **3** (90.4%) based on **1**. Dakin reaction of the aldehyde **3** in methanol with $NaHSO_4$ and hydrogen peroxide (30%) furnished 2, 3, 4-trimethoxy-6-methylphenol **4** in 51.0% yield. However, we could not obtain the desired compound **6** from **4** via Blanc chloromethylation reaction due to the effect of hydroxyl group in aromatic ring. Fortunately, we found a new route for synthesis of **6** from **3** via a Blanc chloromethylation reaction and Dakin reaction to give an overall yield of 74.5% (based on **3**). Moreover, we used the cheaper oxidant ferric chloride ($FeCl_3{\cdot}6H_2O$) instead of the large amounts of cericammoniumnitrate (CAN) to afford **7** in yield of 76.1% (based on **6**).

In conclusion, a new sequence has been developed leading to the substituted *para*-quinone headgroup **7**, thereby reducing the extent of manipulation of the (relatively costly) side-chain and eliminating two synthetic steps late in the synthesis of CoQ_{10}.[14] Furthermore, it eliminates the use of large amounts of cericammoniumnitrate (CAN) and overcomes the drawbacks of the known oxidation methods. This economical and environmentally-friendly method provides a potential new synthesis of an intermediate for the industrial synthesis of CoQ_{10} and it should provide a general method for synthesising higher homologues.

Experimental

All reactions were monitored by TLC, Melting points were measured on a YRT-3 temp apparatus and are uncorrected. IR spectra were recorded on impact 400 FT-IR instrument. NMR spectra and MS data were recorded on a Bruker DRX 500 NMR spectrometer and a ZAB-2F mass spectrometer, respectively.

3,4,5-Trimethoxytoluene **(2):** 3, 4, 5-Trimethoxybenzadehyde **1** (19.6 g, 0.10 mol), 80% hydrazine hydrate (10 mL, 0.20 mol), and KOH (2.0 g, 0.036 mol) in glycol (80 mL) were heated at 70 °C for 2 h, and then the mixture was further heated at 120 °C for 1 h and 150 °C for another 2 h. Water (120 mL) were added and the resulting



Scheme 1

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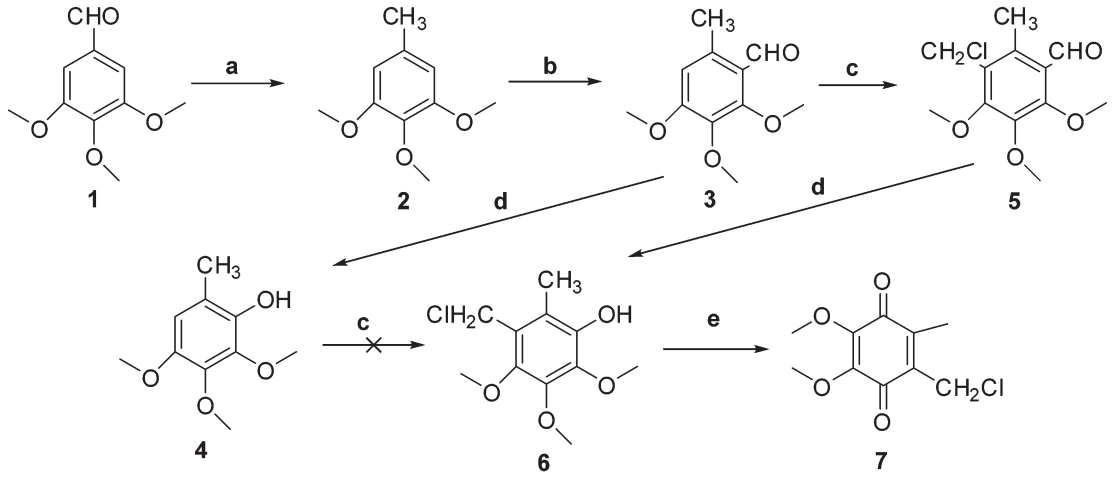

Scheme 2 Reagents and conditions: (a) 80%$N_2H_4{\cdot}H_2O$, glycol, KOH, 70 °C /2h, 150 °C /2h, 97.8%; (b) $POCl_3$ DMF, 80 °C, 6 h, 92.4%; (c) (HCHO)n, 37%HCl, 50 °C /2h, 96.4%; (d) 30%H_2O_2, PTSA, 0 °C, 1 h, 77.3%; (e) $FeCl_3$, EtOH, 25 °C /2h, 76.1%.

mixture was extracted with petroleum ether (4×30 mL), and the combined extracts were washed with brine (4×30 mL). The solution are dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to afford a yellow solid **2** (17.8 g) in 97.8% yield; m.p. 31.4–33.9 °C (lit.[15] 32.7–35.4 °C). IR (KBr)/cm^{-1}:3009, 2949, 2838, 1600, 1509, 1463, 1340, 1236, 1133, 1016, 828, 782. ^{1}H NMR(500 MHz, $CDCl_3$): 6.35 (s, 2H, ArH), 3.77–3.79 (d, 9H, –OCH_3), 2.26 (s, 3H, –CH_3). MS (*m/z*): 182(M^+).

2,3,4-Trimethoxy-6-methylbenzadehyde **(3):** To a solution of **2** (9.1 g, 0.05 mol) in dry DMF (10 mL), $POCl_3$ (10.0 g, 0.07 mol) was added dropwise below 5 °C over a period of 1 h under an N_2 atmosphere. Then the reaction mixture was intensely stirred at 80 °C for another 6 h. The resulting solution was poured into water (200 mL) and then neutralised to pH 7 with 30% aqueous NaOH. The mixture was cooled to 0 °C, and the precipitate was filtrated and dried *in vacuo* to obtain **3** (9.7 g) as a light yellow solid in 92.4% yield; m.p. 58.9–60.2 °C (lit.[15] 59.5–61.0 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 10.28 (s, 1H, –CHO), 3.86–3.73 (t, 9H, –OCH_3), 2.44(s, 3H, –CH_3). MS (*m/z*): 210(M^+).

5-Chloromethyl-2,3,4-Trimethoxy-6-methylbenzadehyde **(5):** To a stirred mixture of **3** (3.2 g, 0.015 mol) and paraformaldehyde (1.2 g, 0.04 mol) was added 37% HCl (10 mL) at room temperature. Then the mixture was stirred at 50 °C for 2 h, Water (20 mL) were added and the mixture was extracted with petroleum ether (4×10 mL), and the combined extracts were washed with brine until neutrality. The solution are dried over $NaSO_4$ and solvent was removed *in vacuo* to afford a white solid **5** (3.8 g) in 98.0% yield; m.p. 67.8–69.2 °C (lit.[16] 67–69 °C). IR (KBr)/cm^{-1}: 2960, 1695, 1565, 1480, 1330, 1105, 1040, 965, 750, 680, 615. ^{1}H NMR (500 MHz, $CDCl_3$): 10.43 (s, 1H, –CHO), 4.78 (s, 2H), 3.87–4.06 (t, 9H, –OCH_3), 2.59(s, 3H, –CH_3). MS (*m/z*): 258(M^+).

***2**-Chloromethyl-6-hydroxyl-3,4,5-trimethoxytoluene* **(6):** Compound **5** (3.8 g, 14.7 mmol) and 1.6 g (9.3 mmol) of p-toluenesulfonic acid (PTSA) were mixed with 40 mL of MeOH. To the mixture, 7 mL (67.9 mmol) of a 30% solution of hydrogen peroxide was added at 0 °C for 30 min, then the mixture was stirred at room temperature for another 1 h. MeOH was removed under a vacuum at room temperature, and the crude was extracted with CH_2Cl_2. The organic solution was washed with brine until neutrality, then dried over Na_2SO_4 and evaporated under reduced pressure to give a brown oil phenol **6** (2.8g) in 77.3% yield. ^{1}H NMR (500MHz, $CDCl_3$): 5.75 (s, 1H, –OH), 4.45 (s, 2H), 3.81–3.97 (t, 9H, –OCH_3), 2.22 (s, 3H, –CH_3). MS (*m/z*): 246(M^+).

5-Chloromethyl-2,3-Dimethoxy-6-methyl-1,4-benzoquinone **(7):** A solution of 6 (2.8 g, 11.4 mmol) in EtOH (10 mL) was diluted with water (10 mL), and an excess solution of $FeCl_3{\cdot}6H_2O$ (7.2 g, 26.6 mmol) in 40 mL water was added at 0 °C. The mixture was stirred at room temperature for 2 h, EtOH was removed under a vacuum at room temperature, and the crude was extracted with three portions of CH_2Cl_2 (20 mL). The red extracts were washed with brine brine until neutrality, then dried over Na_2SO_4 and evaporated under reduced pressure to give a red oil **7** (2 g) in 76.1% yield. IR (KBr)/cm^{-1}: 3004, 2952, 2845, 1655, 1611, 1451, 1380, 1343, 1279, 1210, 1155, 1108, 1011, 934;^{1}H NMR (500MHz, $CDCl_3$): 4.42 (s, 2H, $ArCH_2Cl$–), 4.01 (s, 3H, –OCH_3), 3.99 (s, 3H, OCH_3), 2.16 (s, 3H, –CH_3). MS (*m/z*): 230(M^+).

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