A green and efficient synthesis of 1-chloromethyl -2,3,4,5-tetramethoxy-6-methylbenzene

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The title compound, a key intermediate for preparing coenzyme Q analogues, was prepared in excellent yield by a reaction sequence starting from the commercially available 3,4,5-trimethoxybenzadehyde via Wolff–Kishner reduction, selective bromination, methoxylation and Blanc chloromethylation reaction.

Keywords: coenzyme Q, 2,3,4,5-tetramethoxytoluene, Wolff–Kishner reduction, methoxylation, Blanc chloromethylation reaction

Coenzyme Q (CoQ or CoQn), also known as the ubiquinones, occur naturally in all cells and possess several important functions in the most of organisms. CoQ_{10}, the main homologue of CoQ existing in humans, is one of the most effective antioxidants. CoQ_{10} is widely used in the treatment of cardiovascular disease, hepatitis and cancer, and in the improvement of immunotherapy. The metabolites of CoQ homologues, and a number of synthetic CoQ analogues have shown significant biological activities related to its therapeutic effects.[1–3]

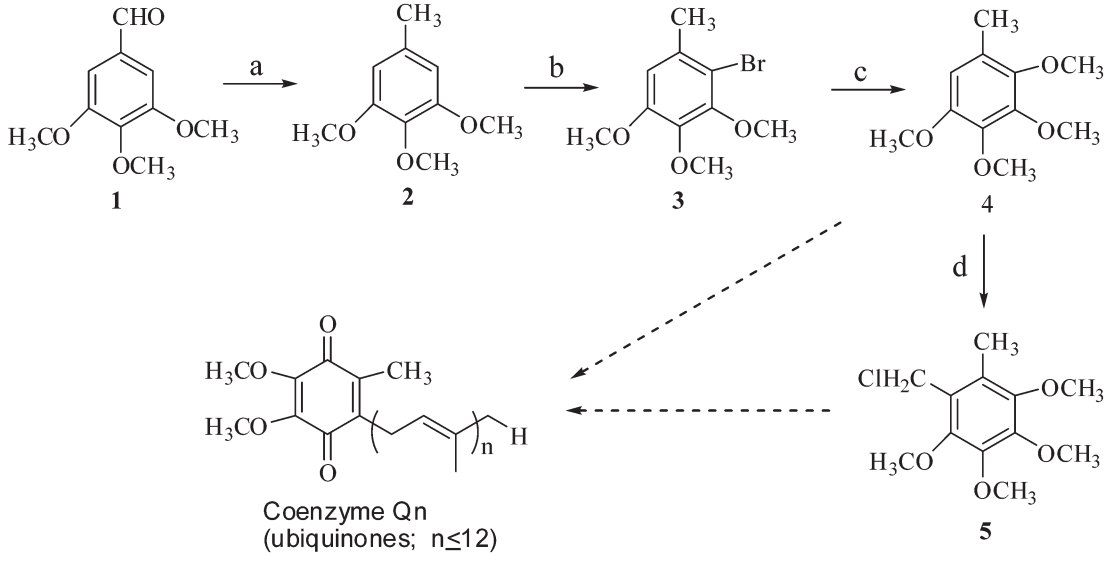
1-Chloromethyl-2,3,4,5-tetramethoxytoluene **5** is a key intermediate for the synthesis of coenzyme Q homologs[4–8]. There are several methods[4–8] for the preparation of the title compound **5**. All these methods require the synthesis of a key intermediate 2,3,4,5-tetramethoxytoluene **4**. However, none of them is attractive enough for the large-scale synthesis of **4** due to the drawbacks such as the use of some expensive, toxic mat erials(MeI,Me_2SO_4,CuI,CuCN), and complicated multistep procedures.[9–15] Therefore, a convenient and practical method for the synthesis of **4** is still in demand. We have developed a simple and efficient route for the synthesis of 2,3,4,5-tetramethoxytoluene **4**. The synthetic route is described in Scheme 1.

Treatment of **1** under Wolff–Kishner conditions (80%$NH_2NH_2{\cdot}H_2O$,ethylene glycol, KOH) provided **2** in nearly quantitative yield (97.8%) when we removed the water produced in the process by distillation. In addition, the reaction could be performed at the temperature of 150 °C rather than the usual 200 °C. Bromination with NaBr–H_2O_2 system as the brominating agent in acetic acid at 40 °C produced **3** in high yield (98.1%) in an environmentally friendly method. The bromide **3** was treated with CH_3ONa–CH_3OH in the presence of cuprous salts(CuCl) and dimethylformamide (DMF) at 120 °C for 4 h to afford **4** in 92.5% yield[15]. The chloromethylation of the ether **4** used paraformaldehyde and 37% HCl in the absence of solvent at 40 °C for 0.5h to give **5** in 96.4% yield.

In conclusion, a shorter route for the synthesis of the compound **4** has been achieved in overall 88.7% yield and the title compound **5** in overall 85.6% yield. The present route eliminates the use of large amounts of bromine. Moreover, this method not only has the advantages of mild conditions, easily accessible starting materials and facile of separation, and it is also less expensive, more practical, and environmentally friendly. It could be a promising for the industrial synthesis of Coenzyme Q series and it should provide a general method for synthesising higher analogues.

Experimental

All reactions were monitored by TLC, Melting points were determined by the capillary method without correction. IR spectra were recorded on impact 400 FT-IR instrument. ^{1}H NMR spectra and MS data were recorded on a Bruker DRX 500 NMR spectrometer and a ZAB-2F mass spectrometer, respectively.



Scheme 1 Reagents and conditions: (a) 80%$NH_2NH_2{\cdot}H_2O$,ethylene glycol, KOH, 70 °C/2 h, 150 °C/2 h, 97.8%; (b) NaBr, 30%H_2O_2, HOAc, 40 °C, 98.1%; (c) CH_3ONa, CH_3OH, CuCl, DMF120 °C, 92.5%; (d) (HCHO)n, 37%HCl, 40 °C/0.5 h,96.4%.

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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 (60 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 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.[14] 32.7–35.4 °C). IR(KBr)/cm^{-1}: 3009, 2949, 2838, 1600, 1509, 1463, 1340, 1236, 1133, 1016, 828, 782. ^{1}H NMR(500MHz, $CDCl_3$): 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-Bromo-3,4,5-trimethoxytoluene **(3):** A stirred mixture of **2** (18.2 g, 0.1 mol) and NaBr (11 g, 0.11 mol) in acetic acid (100 mL) was treated dropwise with 30% H_2O_2 (50 mL, 0.45 mol) for 2 h at 40 °C. Water (150 mL) and petroleum ether (100 mL) were then added, and stirring was continued for 5 min. The two layers were separated, and the aqueous layer was extracted with petroleum ether (2 × 80 mL) again. The organic layer and the extracts were combined, washed with water, dried, and evaporated *in vacuo* to afford a yellowish oil **3** (25.5 g) in 98.1% yield. IR (KBr) /cm^{-1}: 3059, 2975, 2942, 1574, 1489, 1398, 1210, 1120, 821.^{1}H NMR (500MHz, $CDCl_3$): 2.4 (s, 3H, –CH_3), 3.8 (s, 3H, –OCH_3), 3.9 (s, 3H, –OCH_3), 4.0 (s, 3H, –OCH_3), 6.6 (s, 1H, ArH). MS (*m/z*): 260(M^+).

2,3,4,5-Tetramethoxytoluene **(4):** The mixture of **3** (26.0 g, 0.1 mol) and DMF (3 mL) were added in sequence under an N_2 atmosphere to a solution of CH_3ONa(11.2 g, 0.20 mol) in 10 mL methanol, CuCl (1 g, 0.01 mol) and. The mixture was stirred at 110 °C for 8 h . Then, 40 mL 5M HCl was added, and the mixture was refluxed for another 0.5 h , The mixture was cooled and extracted with petroleum ether (3 × 80 mL), and the combined extracts were washed with brine (4 × 80 mL). The solution are dried over anhydrous sodium sulfate and solvent was removed *in vacuo* to afford a slightly yellow oil **4**(19.6 g) in 92.5% yield. IR (KBr/cm^{-1}): 3001, 2942, 2845, 1593, 1496, 1411, 1347, 1236, 1133, 1094, 1042.^{1}H NMR (500 MHz, $CDCl_3$): 2.24 (s, 3H, –CH_3), 3.74 (s, 3H, -OCH_3), 3.78 (s, 3H, –OCH_3), 3.85 (s, 3H, –OCH_3), 3.92 (s, 3H, –OCH_3), 6.40 (s, 1H, ArH). MS (*m/z*): 212(M^+).

1-Chloromethyl-2,3,4,5-tetramethoxy-6-methylbenzene **(5):** 37% HCl (30 mL) was added to a stirred mixture of **4** (21.2 g, 0.10 mol) and paraformaldehyde (4.5 g, 0.15 mol) at room temperature. Then the mixture was stirred at 40 °C for 1 h, Water (100 mL) were added and the 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 oil **5** (25.1 g) in 96.4% yield. IR (KBr/cm^{-1}): 2971, 2937, 2863, 2831, 1466, 1408, 1357, 1280, 1109, 1074, 1040.^{1}H NMR (500MHz, $CDCl_3$): 2.29 (s, 3H, –CH_3), 3.79 (s, 3H, –OCH_3), 3.90 (s, 3H, –OCH_3), 3.92(s, 3H, –OCH_3), 3.93 (s, 3H, –OCH_3), 4.69 (s, 2H, $ArCH_2$). MS (*m/z*): 260(M^+).

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