An alternative route for the synthesis of 2,3,4,5-tetramethoxytoluene

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The transformation of the commercially available 2,3,4-trimethoxybenzaldehyde to 2,3,4,5-tetramethoxytoluene using a Dakin reaction to insert the extra oxygen, formylation, reduction and methylation of the phenolic hydroxyl group is described.

Keywords: 2,3,4-methoxybenzaldehyde, coenzyme Q_{10}, Dakin reaction, formylation, catalytic hydrogenation, methoxylation

Coenzyme Q_{10} **6** (also known as ubiquinone) has been used as a drug in the treatment of various heart-related diseases.[1] Its role as an anti-oxidant in preventing lipid and DNA oxidation and quenching free radicals[2,3] has encouraged several organic chemists to seek an efficient synthetic route[4] for the preparation of coenzyme Q_{10}. In connection with our studies on bioactive natural products, we needed to develop a simple and efficient route for the synthesis of 2,3,4,5-tetramethoxytoluene. The results of our efforts are described in the present report. The synthetic route is described in Scheme 1.

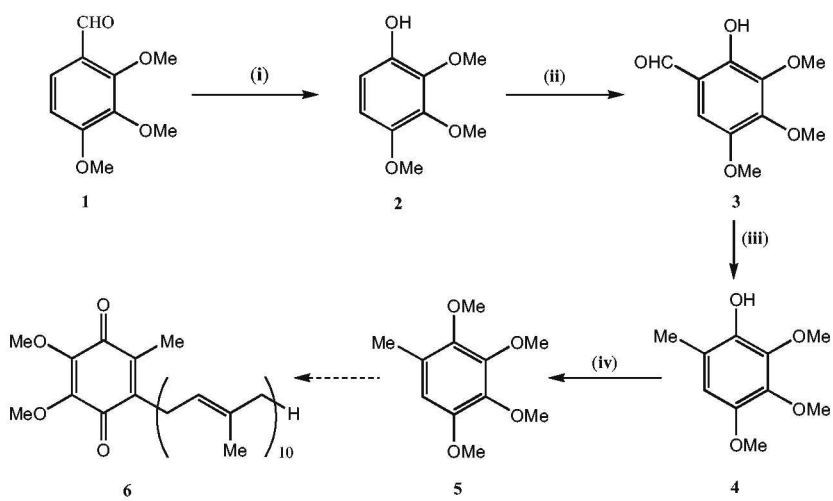
The commercially available 2,3,4-trimethoxybenzaldehyde **1** was considered a promising starting material for the synthetic entry into the title compound **4**. Dakin reaction[5] of the aldehyde **1** in methanol with sulfuric acid (conc.) and hydrogen peroxide (30%) furnished 2,3,4-trimethoxyphenol **2** in 95% yield. It was formylated[6] with paraformaldehyde, triethylamine and magnesium chloride to obtain the aldehyde **3**. The formation of the aldehyde **3** was confirmed by its ^{1}H NMR spectrum which exhibited aldehyde proton at δ 9.72 ppm and also by the signal at δ 194.81 ppm in the ^{13}C NMR spectrum. It showed a band at 1650 cm^{-1} in the IR spectrum and a molecular ion at 212 amu (M^+) in the mass spectrum. As the aldehyde **3** and phenol **2** had very similar R_f values on TLC plates their separation could not be achieved by any chromatographic technique. An analysis of the ^{1}H NMR spectrum of the mixture of phenol **2** and aldehyde **3** clearly indicated the formation of the aldehyde **3** in 33% yield. The mixture was hydrogenated over Pd–C (10%) in ethanol under hydrogen at 500 psi (35 atm) at room temperature. The methylphenol **4** was obtained almost in quantitative yield. The formylation was also attempted by Reimer–Tiemer reaction[7] and Vilsmeier–Haack reaction[8] but the yield of the aldehyde **3** could not be improved. The methylphenol **4** on methylation with dimethylsulfate and sodium hydroxide furnished the target compound 2,3,4,5-tetramethoxytoluene **5** in 73% yield whose identity was confirmed by spectroscopic data.

In conclusion a simple approach for the synthesis of the compound **5** has been achieved in moderate yield. We believe that the yield of the aldehyde **3** can be improved by changing the experimental conditions for formylation and such a project is under investigation along with the accumulation of sufficient material of compound **5** for its conversion to the coenzyme Q_{10}.

Experimental

Unless otherwise stated, IR spectra were taken on a Nicolet FT spectrophotometer, a Bruker AM 300 MHz spectrometer was employed for the determination of ^{1}H and ^{13}C NMR spectra with deuteriumchloroform as solvent. Mass spectra were run on Kratos MS25RFA and GCMs-ma-Hewlett Packard 5890 Quadrupole 5972 Series S. The expression "work up" indicates that the reaction mixture was diluted with water, extracted with ether, washed with brine, dried over $MgSO_4$ and solvent evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck grade 60, 70–230 mesh). Microanalyses were carried out at the Chemistry Department, IVIC, Caracas, Venezuela.

2,3,4-Trimethoxyphenol **2**: Conc. Sulfuric acid (0.5 mL, 6.4 mmol) was added to a stirred solution of the aldehyde **1** (2 g, 10.2 mmol) dissolved in methanol (20 mL), cooled to 10 °C, and then hydrogen peroxide (30%, 1 mL, 32.6 mmol) was added dropwise. The reaction mixture was stirred at 10 °C for 30 min and 24 h at room temperature, diluted with water and extracted with dichloromethane. The organic extract was washed with brine, then with an aqueous solution of sodium bicarbonate (5%). It was dried and the solvent evaporated to



Scheme 1 Reagents: (i) MeOH, H_2SO_4 conc., H_2O_2 (30%). (ii) $MgCl_2$, Et_3N, $(CH_2O)_n$, THF. (iii) H_2, Pd/C (10%). (iv) Me_2SO_4, EtOH, NaOH

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give the phenol **2** (1.78 g, 95%); υ_{max} 3418 (OH) cm^{-1}; ^1H NMR: δ 3.75 (s, 3H), 3.85 (s,3H), 3.89 (s,3H) (2,3,4-OMe), 5.67 (s, 1H, OH), 6.49–6.60 (q_{AB}, 2H, J = 8 Hz), (5-H, 6-H). ^{13}C NMR: δ 146.9 (C4), 143.4 (C1), 142.3 (C2), 140.5 (C3), 108.7 (C6), 107.6 (C5), 61.1 (C7), 60.8 (C8), 56.6 (C9); MS: 184 (M^+); Anal. Calcd for $C_9H_{12}O_4$: C,58.69; H, 6.57. Found: C, 58.84; H, 6.69%

6-Formyl-2,3,4-trimethoxyphenol **3**: A mixture of phenol **2** (1.01 g, 5.4 mmol), anhydrous magnesium chloride (1 g, 10.5 mmol), triethylamine (1.5 mL, 10.8 mmol) and paraformaldehyde (0.5 g, 16.7 mmol) under nitrogen and in dry THF (50 mL) was heated under reflux for 4 h. The reaction mixture was cooled, acidified (5% HCl) and extracted with dichloromethane. The usual work up yielded an oil (1.03 g) which contained a mixture of phenol **2** (615 mg, 62%) and aldehyde **3** (382 mg, 33%); υ_{max} 1650 (CO) cm^{-1}; ^1H NMR: δ 3.75 (s,3H), 3.84 (s,3H), 3.89 (s,3H), (2,3,4-OMe), 6.73 (s,1H, 5-H), 9.72 (s, 1H, CHO), 10.93 (s, 1H, OH); ^{13}C NMR: δ 194.8(CHO), 151.7 (C1), 150.3 (C4), 143.3 (C3), 140.9 (C2), 115.2 (C6), 107.6 (C5), 61.1 (C7), 60.8 (C8), 56.4 (C9); MS: 212 (M^+). As we were unable to separate the phenol **2** and aldehyde **3**, an analytical sample of the aldehyde **3** could not be prepared.

2,3,4-Trimethoxy-6-methylphenol **4**: The mixture (1.03 g) of phenol **2** and aldehyde **3** was dissolved in ethanol (40 mL) and hydrogenated with Pd/C (270 mg, 10%) under hydrogen at 500 psi for 4 h. Work up followed by chromatographic purification over silica gel (eluant hexane) furnished phenol **4** (352 mg, 98%); υ_{max} 3418 (OH) cm^{-1}; ^1H NMR: δ 2.16 (s, 3H, Me), 3.75 (s, 3H), 3.89 (s, 3H) (2,3,4-OMe), 5.65 (s, 1H, OH), 6.40 (s, 1H, 5-H); ^{13}C NMR: δ 145.9 (C4), 141.1 (C1), 140 (C2), 139 (C3), 118.1 (C6), 109.5 (C5), 60.8 (C7), 61.1 (C8), 56.5 (C9), 15.4 (C10); MS: 198 (M^+); Anal. Calcd. For $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.76; H, 7.26%

2,3,4,5-Tetramethoxytoluene **5**: Freshly distilled dimethylsulfate (13 mL, 0.13 mmol) and sodium hydroxide (13 mL 10%) was added to a solution of the phenol **4** (352 mg, 1.77 mmol) in ethanol (100 mL). The resulting mixture was stirred at room temperature and then heated under reflux at 80 °C for 2 h. The reaction mixture was cooled, diluted with water and extracted with ether. The organic extract was washed, dried and evaporated under reduced pressure. Preparative TLC of the residue on silica gel (eluant hexane-chloroform 6:4) yielded the target compound **5** (274 mg, 73%); ^1H NMR: δ 2.17 (s, 3H, Me), 3.73 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H) (2,3,4,5-OMe), 6.39 (s, 1H, 5-H); ^{13}C NMR: δ 149.1 (C4), 147 (C2), 145.5 (C1), 140.9 (C3), 125.8 (C6), 108.4 (C5), 61.1 and 61.6 (C7, C8), 60.5 (C11), 56.1 (C9), 15.8 (C10); MS: 212 (M^+); Anal.Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.41; H, 7.69%

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