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Alternative Synthesis of 1,2,3,4-Tetramethoxy-5-methylbenzene: A Key Intermediate for Preparing Coenzyme Q Homologs and Analogs

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Abstract: Preparation of 1,2,3,4-tetramethoxy-5-methylbenzene (1) through a new process from pyrogallol is described. In the preparation, a modified mild brominating agent was employed, and a simple introduction of methyl group into aromatic ring through chloromethylation of the corresponding substrate (4), followed by reductive dehalogenation, was achieved successfully with good yields.

Keywords: CoEnzyme Q, chloromethylation, pyrallol chemistry

1,2,3,4-Tetramethoxy-5-methylbenzene (**1**) is a key intermediate for the synthesis of coenzyme Q (Ubiquinone) homologs and analogs, which show a diversity of biological activities and can be developed for use as pharmaceuticals, cosmetics, nutritional supplements, and so forth.[1,2] There are several methods[2] to prepare the title compound. With reference to a classic synthesis starting from the abundant and inexpensive pyrogallol, which had been reported by Syper and his coworkers,[2b] we proposed an alternative method to synthesize the compound. Herein, we present the new process.

Our first attempts to obtain the compound 2 in a one-pot reaction[2b] from pyrogallol with dimethyl sulfate and K_2CO_3 in acetone resulted in very poor

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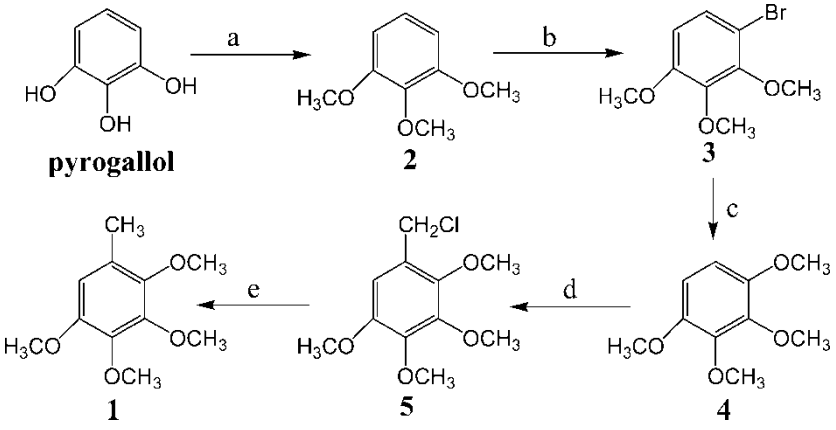
yield (<10%). However, the yield reached about 90% when the etherification was carried out in and aqueous solution. Bromination[2b] of the ether **2** with Br_2 in methylene chloride (DCM) at −10 °C produced the compound **3** with high yield (>90%), but use of Br_2 and the workup were inconvenient because of the irritation and corrosion of Br_2 and the released hydrogen bromide gas. So, we attempted to develop the $NaBr–H_2O_2$ system as the brominating agent in acetic acid–water for this transformation with high yield. The type of this reaction became very environmentally friendly. The bromide 3 was treated[3] in the $CH_3ONa–CH_3OH$ system in the presence of cuprous salts and dimethyl formamide (DMF), and readily provided the compound **4** with high yield.

REAGENTS AND CONDITIONS

(a) $(CH_3)_2SO_4$, 30% aq. NaOH, H_2O; (b) NaBr, 30%H_2O_2, HOAc, rt; (c) CH_3ONa, CH_3OH, CuCl, DMF; (d) (HCHO)n, conc. HCl, hexane, rt; (e) Mg, C_2H_5OH, 40–45 °C (Scheme 1).

The chloromethylation[4] of the ether 4 using paraformaldehyde and conc. HCl with benzene, chloroform, or DCM as cosolvents gave the compound **5** in moderate yields (about 70%). In addition, bis-chloromethylation occurred heavily. When we used hexane instead of these cosolvents to extract the product **5** from the reaction system once it formed, the yield reached about 90%. In the final step, the reductive dehalogenation[5] of the benzyl chloride **5** was accomplished in ethanol with magnesium particles, and the title compound (1) was obtained with high yield while no by-product was observed.

In conclusion, the modification of the brominating reaction and the method of introducing a methyl group into the aromatic ring were



Scheme 1.

developed, and this method not only has a shorter route but also is less expensive, more practical, and environmentally friendly.

EXPERIMENTAL

All reactions were monitored by TLC, and TLC was performed on silica gel GF_{254} with mixed solvents (hexane/ethyl acetate, 9 : 1) as developer. Organic extracts were dried over anhydrous $MgSO_4$. ^1H NMR spectra were measured at 400 MHz ($CDCl_3$/TMS) on a Varian-Inova 400 spectrometer, and chemical shifts are reported in parts per million (ppm) (δ) relative to TMS as internal standard. Mass spectra (ESI) were determined on API3000 spectrometer and reported as m/z. Melting points were uncorrected.

Compound 1

The mixture of the benzyl chloride **5** (4.93 g, 0.02 mol) and magnesium particles (0.72 g, 0.03 mol) in ethanol (20 ml) was stirred at 40–45°C for 2 h. Water (20 ml) and hexane (100 ml) were added and then filtered. The two layers of the filtrate were separated. The aqueous layer was extracted with hexane (2 × 50 ml) again. The organic layer and the extracts were combined, washed with brine, dried, and evaporated in vacuo to give the title compound (**1**) as colorless oil[2a] in 94% yield (4.0 g). $R_f = 0.51$, ^1H NMR: δ 3.92 (s, 3H), δ 3.86 (s, 3H), δ 3.80 (s, 3H), δ 3.78 (s, 3H), δ 2.22 (s, 3H), δ 6.44 (s, 3H). MS (m/e): 212 (M^+).

Compound 2

To a stirred mixture of pyrogallol (12.6 g, 0.1 mol) and Me_2SO_4 (50.4 g, 0.4 mol) in water (150 ml) was added dropwise 30% aq. NaOH solution (106.0 g, corresponding to NaOH 32.0 g, 0.4 mol) at 30–35 °C for 1 h under an N_2 atmosphere. After the addition, the reaction mixture was refluxed for another 2 h. Then the mixture was cooled to below 20 °C and filtered, and the cookie was washed with water and dried to give the crude compound 2 in 90% yield (15.1 g). Recrystallization from CH_3OH–H_2O (2 : 1) gave needle crystals. $R_f = 0.4$, mp 42–43 °C. ^1H NMR: δ 3.86 (s, 9H), δ 6.58 (d, 2H, $J = 8.4$ Hz), δ 6.99 (t, H, $J = 8.4$ Hz). MS (m/e): 168 (M^+).

Compound 3

To a stirred mixture of the ether 2 (16.8 g, 0.1 mol) and NaBr (10.3 g, 0.1 mol) in acetic acid (20 ml) was added dropwise 30% H_2O_2 (12 ml, corresponding

to H_2O_2 0.108 mol, roughly) for 2 h at room temperature. Then, water (20 ml) and hexane (80 ml) were added, and the stirring was continued for 1 min. The two layers were separated, and the aqueous layer was extracted with hexane (2×50 ml) again. The organic layer and the extracts were combined, washed with water, dried, and evaporated in vacuo to afford the slightly yellow oil[6] in 97% yield (23.2 g). R_f =0.46, ^{1}H NMR: δ 3.85 (s, 3H), δ 3.88 (s, 3H), δ 3.90 (s, 3H), δ 6.58 (d, H, $J = 9.2$ Hz), δ 7.20 (d, H, $J = 9.2$ Hz). MS (m/e): 247 (M^+).

Compound 4

Freshly cut sodium (5.75 g, 0.25 mol) was dissolved in dry methanol (80 ml). Afterward, most of the methanol was distillated off. Under an N_2 atmosphere, CuCl (0.2 g, 0.002 mol) and the mixture of the bromide 3 (23.9 g, 0.1 mol) and DMF (8 ml) were added in sequence. The mixture was stirred at 110°C for 9 h. Then, 150 ml of water was added, and the mixture was refluxed for another 30 min. The mixture was cooled and filtered. The filtrate and the cookie were separated. The filtrate was extracted with hexane (2×100 ml) again. The extracts were dried and evaporated in vacuo. The residue and the cookie were combined and recrystallized from CH_3OH to give the compound **4** as a white crystal in 90% yield (18.0 g). $R_f = 0.3$, mp 87–87.5°C (lit.:[7] 87–87.5°C). ^{1}H NMR: δ 3.82 (s, 6H), δ 3.90 (s, 6H), δ 6.58 (s, 2H). MS (m/e): 198 (M^+).

Compound 5

To a stirred mixture of the ether **4** (10.0 g, 0.05 mol) and paraformaldehyde (1.5 g, 0.05 mol) in hexane (100 ml) was added dropwise conc. HCl (50 ml) at room temperature. After the solid was dissolved completely, the mixture was stirred for another 30 min and then stood still. The two layers were separated. The aqueous layer was extracted with hexane (2×50 ml) again. The organic layer and the extracts were combined, washed with brine, dried, and evaporated in vacuo. Silica gel chromatography of the residue provided the benzyl chloride **5** as colorless oil in 90% yield (11.1 g). $R_f = 0.42$, ^{1}H NMR: δ 3.85 (s, 3H), δ 3.90 (s, 6H), δ 3.93 (s, 3H), δ 4.61 (s, 2H), δ 6.65 (s, H). MS (m/e): 246 (M^+).

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