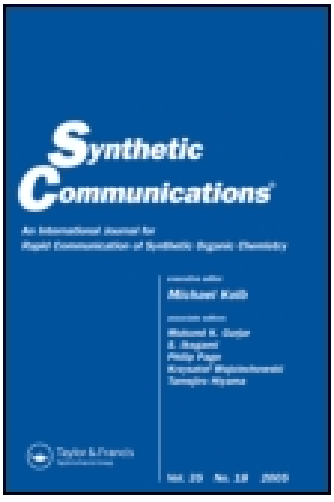

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Practical Synthesis of 2,3,4,5-Tetramethoxytoluene

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Practical Synthesis of 2,3,4,5-Tetramethoxytoluene

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Abstract: The title compound, a key material for synthesis of coenzyme Q_{10}, was effectively prepared in high yield by a reaction sequence starting from 3,4,5-trimethoxybenzadehyde via Wolff–Kishner reduction, Vilsmeier–Haack reaction, Dakin reaction, and methylation.

Keywords: Coenzyme Q_{10}, Dakin reaction, methylation, 2,3,4,5-tetramethoxytoluene, 3,4,5-trimethoxybenzadehyde, Vilsmeier–Haack reaction, Wolff–Kishner reduction

Coenzyme Q_{10} **1** performs an important role in many physiological electron-transfer processes for respiration as a redox carrier. The compound plays a good treatment effect on various heart-related diseases as a drug or dietary supplement sold in many countries, and there is an increasing market demand.[1] In the past thirty years, the synthesis of coenzyme Q_{10} has received special attention and remains interesting. Organic chemists have brought forward many total and semisynthetic methods for stereoselective and cost-efficient preparation of coenzyme Q_{10}. In general there may be considered to be two strategies, one from 2,3,4,5-tetramethoxytoluene **2** as starting material[1–9] and the other from 2,3-dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q_0, **3**) as starting material.[10–16] Likewise, **2** is a valuable material for synthesis of idebenone.[17] Several synthetic methods were reported for preparation of **3** via 3,4,5-trimethoxytoluene **5**[18–20]; however, a more practical process for preparation of **2** has rarely been

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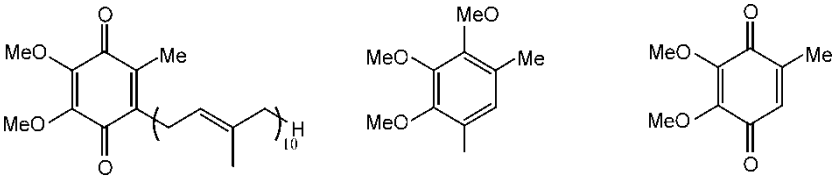
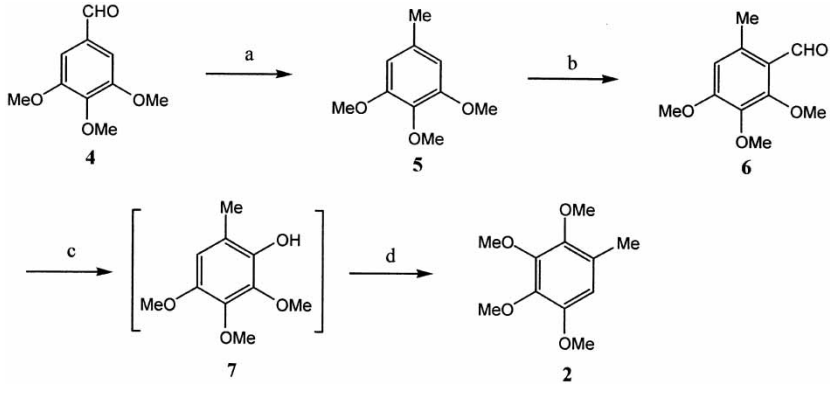
investigated. The reported method uses expensive reagent and severe reaction conditions and is unfavorable for large-scale production of **2**, in particular during the trimethoxylation of 2,3,6-tribromo-4-methylphenol in the presence of CuCN.[8,9]



1 **2** **3**

In the face of the increasing commercial demand for coenzyme Q_{10}, to develop an industrial route to **2** becomes an urgent matter. Because an improved technique has been successfully applied for the large-scale manufacture of 3,4,5-trimethoxybenzadehyde **4** in China to make it an inexpensive reagent (commercial price of **4** ca. \$10/kg in China),[21] there is an actual possibility of producing **2** from **4** to avoid the difficult reaction conditions. Herein we propose a novel and practical synthesis of **2** from **4** via Wolff–Kishner reduction, Vilsmeier–Haack reaction, Dakin reaction, and methylation to give an overall yield of 76.5% (Scheme 1).

The most direct method to reduce aldehyde **4** to toluene **5** is by the Wolff–Kishner reduction. We speculate that the electron-donating effect of three methoxy groups at **4** is more propitious for the reduction of the aldehyde. Actually, treatment of **4** under Wolff–Kishner conditions (NH_2NH_2, glycol, KOH) provided **5** in nearly quantitative yield. The reaction could be performed at the temperature of 120°C rather than a usual



Scheme 1. Reagents and conditions: (a) NH_2NH_2, glycol, KOH, 70°C/3 h, 120°C/3 h, 97%; (b) $POCl_3$ DMF, 65°C, 5 h, 95%; (c) 50% H_2O_2, H_2SO_4, 15°C, 0.5 h; (d) Me_2SO_4, NaOH, 55°C, 83% from **6**.

200°C. The reaction of **4** under Clemmensen conditions only afforded **5** in 65% yield along with 3,4,5-trimethoxybenzyl alcohol as a by-product according to the literature.[19]

Similarly, the electron-donating effect of methoxy and methyl groups would induce a beneficial influence on the following Vilsmeier–Haack reaction and Dakin reaction. The Vilsmeier–Haack reaction was carried out by treating **5** with $POCl_3$ and dimethyl formamide (DMF) at 65°C for 5 h to give aldehyde **6** in 95% yield. DMF was employed as both reagent and solvent. Even though a low ratio of 1/1 (**5**/DMF, w/mL) was introduced, the reaction results were perfectly reproduced. The oxidation of **6** with 50% H_2O_2 was executed via Dakin reaction to provide **7** without separation; the organic solvent was removed and followed by methylation with Me_2SO_4 in H_2O and benzene in the presence of a phase-transfer catalyst to afford **2** directly in 83% yield based on **6** (both carried out in one pot). We found that 50% H_2O_2 was more efficient to facilitate the Dakin reaction than 30% H_2O_2.

EXPERIMENTAL

All reactions were monitored by TLC, and the spots were visualized with iodine vapor. Melting points were determined by the capillary method without correction. ^{1}H NMR spectra were recorded on Bruker Avance 500 instrument in $CDCl_3$, and the residual solvent peaks were used as internal standard. Mass spectra were recorded on Micromass GCT mass spectrometer with the electronic impacts (EI) at 70 eV.

3,4,5-Trimethoxytoluene (5)

3,4,5-Trimethoxybenzadehyde **4** (19.6 g, 0.10 mol), 98% hydrazine hydrate (15.3 g, 0.30 mol), and KOH (2.0 g, 0.036 mol) in glycol (200 mL) were heated at 70°C for 3 h, and then the mixture was further heated at 120°C for 3 h. The resulting mixture was extracted with petroleum ether (4 × 100 mL), and the combined extracts were washed with water (100 mL). The solution was dried over Na_2SO_4 and solvent was removed in vacuo to afford a yellowy solid **5** (17.6 g) in 97% yield. Mp 32.7–35.4°C. ^{1}H NMR (500 MHz): δ 6.30 (s, 2H, Ar*H*), 3.80 (s, 6H, OCH_3), 3.72 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). MS (m/z): 182 (M^+, 100), 167 (90), 152 (7), 139 (36), 124 (31).

2,3,4-Trimethoxy-6-methylbenzadehyde (6)

To a solution of **5** (18.2 g, 0.10 mol) in dry DMF (18.5 mL), $POCl_3$ (19.9 g, 0.13 mol) was added dropwise at 25°C over a period of 1 h under an N_2 atmosphere. Then the reaction mixture was intensely stirred at 65°C for

another 5 h. The resulting solution was poured into water (500 mL) and then neutralized 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 **6** (20.0 g) as a white solid in 95% yield. Mp 59.5–61.0°C; ^{1}H NMR (500 MHz): δ 9.83 (s, 1H, C*H*O), 7.14 (s, 2H, Ar*H*), 3.88 (s, 9H, OCH_3), 2.12 (s, 3H, CH_3). MS (m/z): 210 (M^+, 100), 195 (46), 177 (32), 162 (26), 134 (34).

2,3,4,5-Tetramethoxytoluene (2)

Freshly prepared **6** (21.0 g, 0.10 mol) and 98% H_2SO_4 (1.0 g, 0.01 mol) was dissolved in methanol (200 mL). To the solution, 50% H_2O_2 (7.6 g, 0.20 mol) was added dropwise at 10°C over a period of 30 min. The mixture was stirred at room temperature for additional 30 min. Then the excessive H_2O_2 was reductively removed by addition of 10% aqueous $NaHSO_3$. The solvent methanol was distilled out in vacuo, and water (200 mL), benzene (200 mL), Me_2SO_4 (64.0 g, 0.50 mol), and polyglycol-400 (3 g) were added to the residue. The reaction mixture was treated by slowly dropping 30% aqueous NaOH into it at 55°C over a period of 2.5 h. The pH value was carefully controlled within a range of 9.0–9.5 in course of the reaction. The organic layer was washed by 5% aqueous NaOH, dried over Na_2SO_4, and evaporated. Finally the concentrated residue was distilled in vacuo to afford the desired product **2** as a colorless liquid (17.6 g) in 83% yield based on **6**. Bp 118–120°C/160 Pa. ^{1}H NMR (500 MHz): δ 6.42 (s, 2H, Ar*H*), 3.79 (s, 12H, OCH_3), 2.22 (s, 3H, CH_3). MS (m/z): 212 (M^+, 78), 197 (100), 169 (17), 154 (38).

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