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Improved Preparation of 3,4-Dimethoxythiophene

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3,4-Dimethoxythiophene **1**, together with some other dialkoxythiophenes, has recently received considerable attention as a building block for chemically or electrochemically generated conducting polymers [2]. The procedures described in the literature for the preparation of **1** commonly begin with the condensation of diethyl thiodiglycolate and diethyloxalate to give the 3,4-dihydroxythiophene dicarboxylic esters **2** [2], followed by the subsequent reaction steps quoted in Scheme 1. [3–5] The improvements reported in this communication concern the methylation of **2**, for which surprisingly low yields had been obtained, and the final decarboxylation. Compound **1** was described as a dark colored unstable liquid; pure **1**, however, is colourless and stable to air with a *m.p.* of 23–24 °C.

The dianion of **2** is a multident nucleophile susceptible to alkylation at the oxygen or at the C-2 carbon [6]. The proper choice for efficient *bis-O*-alkylation, following the HSAB [7] or allopolarization [8] principles, is a dipolar aprotic solvent, a soft cation and a hard leaving group. As a substitute for the dipolar aprotic solvent, the conditions of phase transfer catalysis in a solvent of low polarity may be even superior [9]. Accordingly, **2** is formed in high yield by the reaction of the potassium salt **3** with dimethyl sulfate and 2 mol% [18] crown-6 as a phase transfer catalyst in toluene.

For the decarboxylation of the diacid **6** several protocols have been recommended: heating of **6** with copper powder [4] or a quinoline solution of **6** with copper chromite [3, 10]. In our hands, simple heating of neat **6** at 250 °C was most suitable. The isolated yield of pure dimethoxythiophene is 65%. For a smooth decarboxylation it is essential that the diacid **6** is free of the hardly soluble mono potassium salt which is initially formed during acidification of the aqueous methanolic solution obtained by alkaline hydrolysis of **4.**

An unexpected side product is the ester **7** wich apparently is formed by an ether to ester methyl transfer. Furthermore, together with some amounts of the monodecarboxylated acid **8** the air-sensitive hydroxythiophene **9** is isolated which is the source of the reported instability of dimethoxythiophene 1 [5]. From this result it appears that the methyl transfer proceeds intermolecularly.

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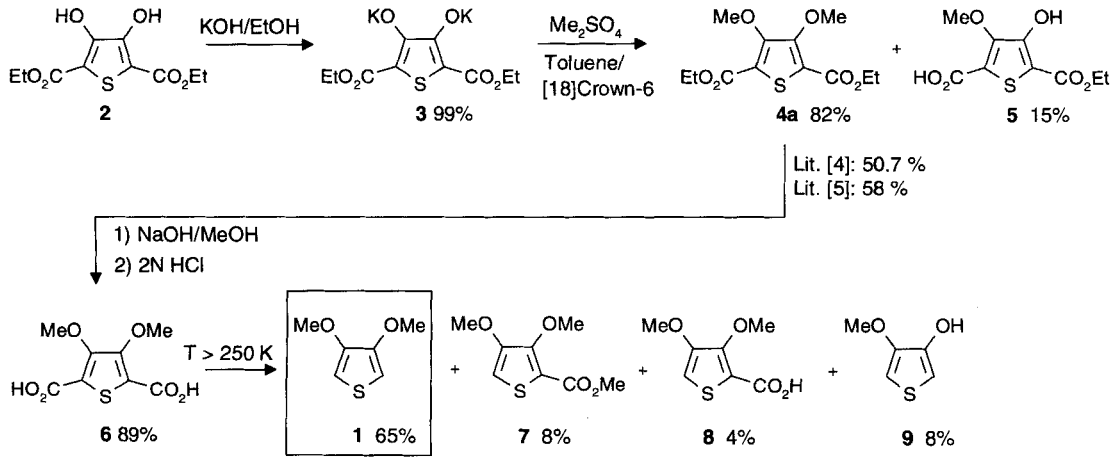

Scheme 1

Experimental

The following analytical instruments were used: Beckman Acculab 1 or 2 (IR); Hitachi U 2000 (UV/VIS); Bruker AW 80, Varian WM 250 or Bruker ARX 400 (80, 250 or 400 MHz ^{1}H NMR and ^{13}C spectra, using TMS as internal standard, in $CDCl_3$ unless otherwise noted). Varian MAT 112 S (EI-MS (70 eV)); Melting points (uncorrected) were determined with a Büchi 510 apparatus. Elemental analyses were performed by the analytical laboratory of the University of Regensburg. The starting material 3,4-dihydroxy-2,5-dicarbethoxythiophene (**2**) [3–5] was prepared by a literature procedure.

Diethyl 3,4-dihydroxy-2,5-dicarboxylate, dipotassium salt (**3**)

A mixture of 2,5-dicarbethoxy-3,4-dihydroxythiophene **2** (115 g, 0.44 mol) in 99% ethanol (1.5 l) and KOH (74.0 g, 1.32 mol) in 99% ethanol (1.5 l) is refluxed (1 h). After cooling to r. t. the resulting yellow dipotassium salt is filtered off and washed with 99% ethanol and ether. **3** is dried overnight in air, and finally at 90–100 °C in an oven. 148 g (99%) bright yellow powder, *m.p.* > 240 °C. – IR (KBr): ν = 2950, 2955, 2905 (C-H); 1665, 1635 (C=O) cm^{-1}. – UV/VIS (water): λ (ε) = 302 (10765); 375 (6367).

Diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**4**) and *Ethyl 3-hydroxy-4-methoxythiophene-2-carboxy-5-carboxylate* (**5**)

The dipotassium salt **3** (100 g, 0.30 mol), [18]crown-6 (1.74 g, 2 mol %) and dry toluene (1.5 l) are placed in a 2–l three necked round bottomed flask fitted with a mechanical stirrer and a reflux condenser. Dimethylsulfate (56.6 ml, 0.60 mol) is added, and the vigorously stirred suspension is heated at reflux (48 h). After cooling to r. t. and removal of $NaCH_3SO_4$ by filtration the resulting organic solution is extracted with 2 N NaOH (3×500 ml) and water (1× 500 ml), dried ($MgSO_4$) and concentrated under reduced pressure. 70.6 g (82%) of **4** crystallized from methanol in bright yellow needles, which are used without further purification, *m.p.* 52–53 °C (MeOH, Lit. [4]: 52–53 °C). – IR (KBr): ν = 2980, 2960, 2920 (C-H aliph.); 1710, 1690 (C=O); 1555 (C=C arom.); 1290, 1270 (C-O val.) cm^{-1}. – UV/VIS (ethanol): λ (ε) = 280 (26000). – ^{1}H NMR (250 MHz): δ = 1.38 (t, J = 7 Hz, 6H, 2 $CO_2CH_2CH_3$); 4.01 (s, 6H, 2 OCH_3); 4.35 (q, J = 7 Hz, 4H, 2 $CO_2CH_2CH_3$);
On acidification of the alkaline aqueous washings to pH = 2 with 2N HCl 11.1 g (15%) of **5** precipitates as a colourless powder, *m.p.* 185–186 °C. – IR (KBr): ν = 3300 (OH, alcohol); 3200–2400 (OH, acid); 1660, 1680 (C=O) cm^{-1}. – ^{1}H-NMR (250 MHz; aceton-d_6): δ = 1.37(t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$); 4.03 (s, 3H, OCH_3); 4.41 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$); 9.42–10.14 (s, 2H, OH, CO_2H). – MS (EI): m/z(%) = 246 (M^+, 30); $[M-C_2H_5OH]^+$ 200 (71); $[200-OH]^+$ 183 (13); $[200-CO]^+$ 172 (100); $[172-CH_2O]^+$ 142 (30); 98 (12); 89 (14); 86 (25); 85 (19); 72 (17); 69 (45); 59 (14); 58 (12); 57 (13); 53 (12); 45 (63). – $C_9H_{10}O_6S$ (246.2): calcd. C: 43.90; H: 4.09; found C: 43.85; H: 4.11.

3,4-Dimethoxythiophene 2,5-dicarboxylic acid (**6**)

A mixture of **4** (50.0 g, 0.17 mol) in methanol (700 ml) and 1M aqueous NaOH (700 ml) is refluxed (3 h). After cooling and acidification with 2N HCl to pH 2 the resulting precipitate of **8** is stirred in the acid medium for 2 hours and then filtered with suction, washed with water and ether, and dried in air. The colourless powder, 35.8 g (89%), is used without further purification, *m.p.* > 260 °C (dec.) (Lit. [4] 260 °C). – IR (KBr): ν = 3400–2200 (OH); 1670 (C=O); 1555, 1500 (C=C arom.) cm^{-1}. – ^{1}H NMR (250 MHz; DMSO-d_6): δ = 3.92 (s, 6H, 2 OCH_3); 13–14 (s, 2H, 2 CO_2H);

3,4-Dimethoxythiophen (**1**)

2,5-Dicarboxy-3,4-dimethoxythiophene 6 (10.0 g, 43.1 mmol) is placed in a 100 ml round bottomed flask connected by a wide bent glass tube to a receiving flask with vaccum connection. The flask is heated to > 250 °C with a heating mantle und a heatgun (T > 250 °C). When the reaction starts the apparatus is evacuated (20–40 torr) and the receiver is cooled with liquid N_2. The yellow-brown viscous oil (5.92 g) in the receiver is taken up in ether (30 ml), extracted with 2N NaOH (3 × 20 ml) and water (1× 20 ml), dried ($MgSO_4$) and concentrated. The resulting yellow oil (5.30 g) is distilled over a short Vigreux column [*b.p.* 55–57 °C (0,05 bar)] to give 4.06 g (65%) of 1 as a colourless oil which solidifies to colourless crystalls, *m.p.* 23–24 °C (Lit. [3]: *b.p.* 110 °C (17 bar)). For the preparation of larger quantities batches up to 20 g with combined work-up are recommended. – IR (Film): ν = 3115 (C-H arom.); 3000–2820 (C-H aliph.); 1565, 1500 (C=C arom.); 1450, 1410 (C-H deform.) cm^{-1}; UV/VIS (ethanol): λ (ε) = 251 (7100); 221 (4300). – ^{1}H NMR (250 MHz): δ = 3.86 (s, 6H, 2 OCH_3); 6.19 (s, 2H, 2 H-arom.). – ^{13}C NMR (100 MHz): δ = 57,56 (OCH_3); 96,35 (α-C); 147,90 (β-C); MS (EI); m/z(%) = 144 (M^+, 100); $[M-CH_3]^+$ 129 (56); [129–CO] 101 (19); $[101-CH_3]^+$ 86 (14); 69 (13); 45 (39). – $C_6H_8O_2S$ (144.2): calcd. C: 49.97; H: 5.60; found C: 49.79; H: 5.54

Methyl 3,4-dimethoxythiophene-2-carboxylate (**7**)

The distillation residue of 1 is purified by kugelrohr distillation (100 °C, 0,05 bar) and recrystallization from MeOH: 0.72 g (8%) of 7, colourless crystals, *m.p.* 48–49 °C. – IR (KBr): ν = 3115 (C-H arom.); 3000–2820 (C-H aliph.); 1565, 1500 (C=C arom.); 1450, 1410 (C-H deform.) cm^{-1}. – ^{1}H NMR (400 MHz): δ = 3.85 (s, 3H, CO_2CH_3); 3.86 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 6.43 (s, 1H, H-arom.). – MS (EI): m/z (%) = 202 (M^+, 92); 173 (11); $[M-OCH_3]^+$ 171 (90); 169 (100); $[171-CH_3]^+$ 156 (19); $[156-CH_3]^+$ 141 (13); 59 (15); 45 (25); – $C_8H_{10}O_4S$ (202.3): calcd. C: 47.49; H: 4.99; found C: 47.39; H: 4.94.

2-Carboxy-3,4-dimethoxythiophene (**8**) and *3-Hydroxy-4-methoxythiophene* (**9**)

The aqueous alkaline extract obtained from the purification of 1 is acidified to pH 2–3 with 2N HCl is extracted with CH_2Cl_2 (3 × 50 ml). The extract is dried and concentrated to 10 ml, and a precipitate of 8 (0.32 g, 4%) is isolated by filtration to give colourless needles, *m.p.* 128–129 °C (MeOH). – $C_7H_8O_4S$ (188.3): calcd. C 44.67 H 4.28; found C 44.78 H 4.50.
IR (KBr): ν = 3300–2300 (OH); 3100 (C-H arom.); 3010–2820 (C-H aliph.); 1660 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz):

δ = 3.87 (s, 3H, OCH_3); 4.12 (s, 3H, OCH_3); 6.56 (s, 1H, H-arom.); 10–11 (s, 1H, CO_2H). – MS (EI): *m/z*(%) = 187 (M^+, 100); 170 (12); 169 (12); 159 (26); 155 (19); $[M-CO_2H]^+$ 143 (20); 141 (14); 115 (24); 101 (11); 85 (20); 69 (14); 45 (33). – $C_8H_{10}O_4S$ (188.3): calcd. C: 44.66; H: 4.29; found C: 44.78; H: 4.30.

From the filtrate, a brown, extremely smelling oil is obtained which on vacuum distillation (50 °C, 0,01 bar, kugelrohr) yields **9** as a bright yellow oil, 0.45 g (8%), which rapidly darkens on exposure to air.

IR (film): ν = 3400 (OH); 3120, 3080 (C-H arom.); 3010–2840 (C-H aliph.); 1570, 1500 (C=C arom.) cm^{-1}. – ^1H NMR (250 MHz): δ = 3.79 (s, 3H, OCH_3); 4.5–5.5 (s, 1H, OH); (2H, H-arom.). – MS (EI): *m/z* (%) = 130 (M^+, 100); 115 (75); 87 (15); 59 (17); 45 (33).

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