Supplementary Material for

CONVENIENT AND EFFICIENT SYNTHESIS OF 2-METHYL-5-NITROBENZO[B]THIOPHENE AND ITS DERIVATIVES

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EXPERIMENTAL

All reactions were carried out under argon atmosphere. Solvents were dried by the usual methods and then distilled prior to use. Sublimation was performed in a cylinder round-bottom flask equipped with a magnetic bar. NMR spectra were obtained at 300 MHz for ^1H NMR and at 75 MHz for ^{13}C NMR with chemical shift values in the spectra being referenced to the solvent. Elemental analyses were carried out with a Perkin–Elmer CHN analyser (2400 series II).

Scheme S1. Four step synthesis of 2-methyl-5-nitrobenzo[b]thiophene (3).

Ethyl 5-nitrobenzo[b]thiophene-2-carboxylate (1). *t*-BuOK (14 g, 125 mmol) was dissolved in cooled absolute EtOH (150 mL) and to the formed solution ethyl mercaptoacetate (15.6 g, 130 mmol) was added in one portion. After 15 min of stirring at rt 2-chloro-5-nitrobenzaldehyde (20 g, 108 mmol) was added in portions keeping the temperature below 50 °C. The formed suspension was stirred at rt for 1 h and refluxed for 30 min. 50 mL of water was added at this point, and the reaction mixture was allowed to cool to 4 °C. Filtration of the residue followed by washings with water and cold EtOH gave 26.8 g (99 %) of light-yellow powder: mp 165-166 °C (lit.^[S1] 165 °C); ¹H NMR (300 MHz, CDCl₃) δ 1.45 (t, 3H, *J* = 7.1 Hz), 4.46 (q, 2H, *J* = 7.1 Hz), 8.00 (d, 1H, *J* = 9.0 Hz), 8.19 (s, 1H), 8.31 (dd, 1H, *J* = 9.0 Hz, *J* = 1.8 Hz), 8.78 (d, 1H, *J* = 1.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 14.3, 62.2, 120.8, 121.1, 123.6, 130.4, 137.8, 138.4, 145.9, 147.3, 161.8 (lit.^[S1] ¹H NMR).

2-(Chloromethyl)-5-nitrobenzo[b]thiophene (2). To a suspension of LiAlH₄ (4 g, 105 mmol) in absolute THF (250 mL) ethyl 5-nitrobenzo[b]thiophene-2-carboxylate (26.4 g, 105 mmol) was added in portions keeping the temperature of the reaction mixture below -35 °C. After 3 h of stirring at this temperature TLC analysis showed no starting material. H₂O (11.3 g, 630 mmol) was added, and the mixture was allowed to warm to rt. After 10 min of refluxing the residue was filtered off and additionally washed with hot ethyl acetate. Evaporation of the combined filtrate gave 20.7 g of crude intermediate alcohol as yellow solid. The obtained product was added to 90 g of SOCl₂ at -15 °C in one portion. The stirred reaction mixture was slowly allowed to warm up and kept at rt for 9 h. Excess of SOCl₂ was evaporated and the residue was filtered through a silica plug in methylene chloride. After evaporation of the solvent the crude target compound was sublimed in vacuo (110-120 °C / 1 mm) to give 21.5 g (90% for two steps) of yellow crystalline solid: mp 111-112 °C (lit.^[17] 110-112 °C); ¹H NMR (300 MHz, CDCl₃) δ 4.88 (s, 2H), 7.43 (s, 1H), 7.88 (d, 1H, *J* = 8.9 Hz), 8.16 (dd, 1H, *J* = 8.9 Hz, *J* = 2.0 Hz), 8.58 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 40.4, 119.1, 119.3, 123.0, 124.2, 138.8, 144.9, 145.7, 146.1; anal. calcd for C₉H₆ClNO₂S: C, 47.48; H, 2.66; N, 6.15; Cl, 15.57; S, 14.08; found: C, 47.22; H, 2.71; N, 6.03; Cl, 15.21; S, 14.23.

2-Methyl-5-nitrobenzo[b]thiophene (3). NaI (14.1 g, 94 mmol) was added to a solution of 2-(chloromethyl)-5-nitrobenzo[b]thiophene (19.6 g, 86 mmol) in absolute THF (250 mL). After stirring at rt the mixture was set to reflux, and NaBH₃CN (10 g, 159 mmol) was added in 3 portions (every 5 hours). After a total of 18 h of reflux TLC analysis showed no intermediate iodide in the reaction mixture. THF was evaporated, and the solid residue was dissolved in water and methylene chloride. The aqueous layer was additionally extracted with methylene chloride, and the combined organic extracts were washed with brine, dried with anhydrous sodium sulfate and then filtered through a silica plug. Evaporation of the solvent gave crude product that was sublimed in vacuo (115-125 °C / 1 mm) to give 16.2 g (98%) of yellow crystalline solid: mp 107-109 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.62 (s, 3H), 7.08 (s, 1H), 7.78 (d, 1H, *J* = 8.8 Hz), 8.06 (dd, 1H, *J* = 8.8 Hz, *J* = 1.6 Hz), 8.47 (d, 1H, *J* = 1.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 16.1, 117.6, 117.8, 122.1, 122.2, 140.0, 144.9, 145.3, 145.6; anal. calcd for C₉H₇NO₂S: C, 55.95; H, 3.65; N, 7.25; S, 16.59; found: C, 56.00; H, 3.56; N, 7.20; S, 16.49.

Scheme S2. Synthetic modifications of 2-methyl-5-nitrobenzo[b]thiophene (3).

3-Bromo-2-methyl-5-nitrobenzo[b]thiophene (4). Bromine (320 mg, 2 mmol) was added in one portion to a solution of 2-methyl-5-nitrobenzo[b]thiophene (250 mg, 1.3 mmol) in chloroform (15 mL). After stirring at 40 °C for 4 h TLC analysis showed no starting material in the reaction mixture. The solvent was evaporated and replaced by EtOH. The formed suspension was evaporated again and dried to give crude product that was sublimed in vacuo (160-175 °C / 1 mm) to give 343 mg (97%) of light-yellow crystalline solid: mp 173-174 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.60 (s, 3H), 7.84 (d, 1H, *J* = 8.8 Hz), 8.18 (dd, 1H, *J* = 8.8 Hz, *J* = 2.1 Hz), 8.58 (d, 1H, *J* = 2.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 15.7, 107.4, 118.2, 119.0, 122.8, 138.6, 139.3, 143.1, 145.9; anal. calcd for C₉H₆BrNO₂S: C, 39.73; H, 2.22; N, 5.15; Br, 29.36; S, 11.78; found: C, 39.76; H, 1.96; N, 5.12; Br, 29.46; S, 11.82.

1-(2-Methyl-5-nitrobenzo[b]thiophen-3-yl)-ethanone (5). AlCl₃ (580 mg, 4.4 mmol) was added in two portions to a cooled solution of 2-methyl-5-nitrobenzo[b]thiophene (250 mg, 1.3 mmol) and acetyl chloride (130 mg, 1.7 mmol) in methylene chloride (15 mL). After stirring at rt for 5 h TLC analysis showed no starting material in the reaction mixture. The solvent was evaporated, and the solid residue was consequently washed on filter with excess of water and aqueous NaHCO₃. After air-drying the crude product was sublimed in vacuo (155-175 °C / 1 mm) to give 300 mg (98%) of yellow crystalline solid: mp 154-155 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.69 (s, 3H), 2.85 (s, 3H), 7.83 (d, 1H, *J* = 8.8 Hz), 8.17 (dd, 1H, *J* = 8.8 Hz, *J* = 2.1 Hz), 9.13 (d, 1H, *J* = 2.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 17.4, 31.9, 118.9, 120.0, 122.0, 133.1, 138.6, 142.8, 146.2, 152.4, 194.6; anal. calcd for C₁₁H₉NO₃S: C, 56.16; H, 3.86; N, 5.95; S, 13.63; found: C, 56.27; H, 3.92; N, 6.06; S, 13.60.

2-Chloro-1-(2-methyl-5-nitrobenzo[b]thiophen-3-yl)-ethanone (6). AlCl₃ (580 mg, 4.4 mmol) was added in two portions to a cooled solution of 2-methyl-5-nitrobenzo[b]thiophene (250 mg, 1.3 mmol) and chloroacetyl chloride (200 mg, 1.8 mmol) in methylene chloride (15 mL). After stirring

at rt for 5 h TLC analysis showed no starting material in the reaction mixture. The solvent was evaporated, and the solid residue was consequently washed on filter with excess of water and aqueous NaHCO₃. After air-drying the crude product was sublimed in vacuo (190-210 °C / 1 mm) to give 310 mg (88%) of beige crystalline solid: mp 194-195 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.93 (s, 3H), 5.14 (s, 2H), 8.20 (dd, 1H, *J* = 8.8 Hz, *J* = 1.9 Hz), 8.27 (d, 1H, *J* = 8.8 Hz), 9.12 (d, 1H, *J* = 1.9 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 17.3, 50.4, 119.1, 119.2, 123.4, 129.5, 138.4, 142.8, 146.0, 155.2, 188.8; anal. calcd for C₁₁H₈ClNO₃S: C, 48.99; H, 2.99; N, 5.19; Cl, 13.14; S, 11.89; found: C, 48.85; H, 2.90; N, 5.13; Cl, 13.08; S, 11.83.

2-Methylbenzo[b]thiophen-5-amine (7). 300 mg of wet Ni Raney was added to a suspension of 2-methyl-5-nitrobenzo[b]thiophene (1 g, 5.2 mmol) in EtOH (25 mL). The reaction mixture was stirred under H₂ atmosphere at 65-70 °C until all organic precipitates had disappeared (10-12 h). TLC analysis showed no starting material or intermediates at this point. The formed transparent solution was filtered from Ni Raney and evaporated. The residue was dissolved in hot hexane and filtered. Evaporation gave 0.84 g (99%) of pure target amine as beige solid. The product might be crystallized from hexane at -20 °C as beige flakes: mp 56-57 °C (lit.^[S2] 56-58 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.57 (s, 3H), 3.58-3.70 (broad s, 2H), 6.70 (dd, 1H, *J* = 8.4 Hz, *J* = 2.1 Hz), 6.82 (s, 1H), 6.97 (d, 1H, *J* = 2.1 Hz), 7.52 (d, 1H, *J* = 8.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 16.2, 107.7, 113.7, 121.0, 122.4, 130.2, 141.7, 141.7, 143.5 (lit.^[S2] ¹H NMR); anal. calcd for C₉H₉NS: C, 66.22; H, 5.56; N, 8.58; S, 19.64; found: C, 66.05; H, 5.35; N, 8.54; S, 19.57.

REFERENCES

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Figure S1. ¹H NMR spectrum of compound **1** in CDCl₃.

Figure S2. ¹³C NMR spectrum of compound **1** in CDCl₃.

Figure S7. ¹H NMR spectrum of compound **4** in CDCl₃.

Figure S8. ¹³C NMR spectrum of compound **4** in CDCl₃.

Figure S9. ¹H NMR spectrum of compound **5** in CDCl₃.