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Short Note

Benzo[*b*]thiophene-2-carbaldehyde

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Abstract: A novel expedient synthesis of benzo[*b*]thiophene-2-carbaldehyde **2** is reported. It is based on the one-pot sequential reaction of methylthiobenzene **1** with BuLi and DMF to give **2** in 80% isolated yield.

Keywords: benzo[*b*]thiophene-2-carbaldehyde; formylation; heterocyclization

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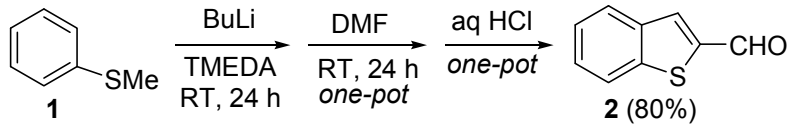
Benzo[*b*]thiophene-2-carbaldehyde **2** is a very important heterocycle derivative. It has been used as intermediate in organic synthesis for the preparation of a variety molecules [1–4], including biologically active compounds [5–10]. It is commonly prepared by formylation of benzo[*b*]thiophene with DMF [11] or other formylating agents [12,13] or by oxidation of benzo[*b*]thiophen-2-ylmethanol [14]. To the best of our knowledge, the only example of synthesis of **2** starting from an acyclic precursor is based on a 3-step procedure involving the reduction of 2-mercaptobenzoic acid followed by alkylation with bromoacetaldehyde dimethyl acetal and acid-promoted cyclization [15].

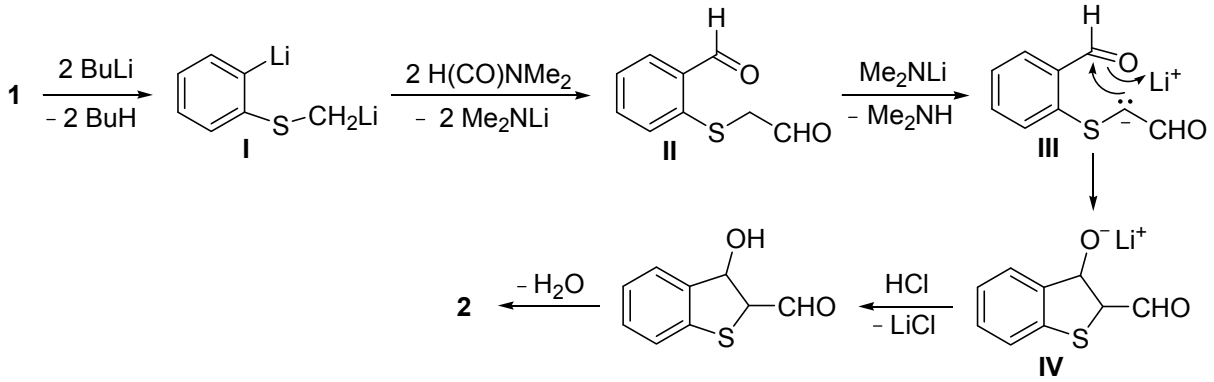
Here we report a simple and convenient method for the direct synthesis of **2** starting from unexpensive and commercially available methylthiobenzene **1**. The reaction of **1** with an excess of BuLi and tetramethylethylenediamine (TMEDA) at 0–25 °C, followed by the one-pot reaction with DMF at room temperature and quenching with aqueous HCl, led to **2** with an 80% isolated yield (Scheme 1).

Scheme 1. Synthesis of benzo[*b*]thiophene-2-carbaldehyde **2** from methylthiobenzene **1**.



Formation of **1** can be rationalized according to the mechanism shown in Scheme 2. Thus, TMEDA-promoted double lithiation of **1** (at the *ortho* position and on the thiomethyl group, leading to dilithiated intermediate **I**), followed by diformylation of **I** with DMF, affords dialdehyde intermediate **II**, whose intramolecular aldol-type condensation eventually affords **2**. Since Me_2NLi is formed from the formylation process leading to **II**, the condensation of **II** may occur through α-deprotonation to give intermediate **III**, followed by intramolecular nucleophilic attack of the carbanion moiety to the aldehydic group, to give aldolate **IV**. Protonation of the latter by HCl followed by dehydration with simultaneous aromatization finally leads to **2** (Scheme 2).

Scheme 2. Plausible reaction mechanism for the formation of benzo[*b*]thiophene-2-carbaldehyde **2** from methylthiobenzene **1**.



Experimental

Benzo[b]thiophene-2-carbaldehyde **2**: To a solution of methylthiobenzene **1** (1.0 g, 8.05 mmol) in hexane (30 mL) was added TMEDA (2.8 g, 24.1 mmol) under nitrogen and with stirring. The resulting stirred mixture was cooled at 0 °C for 10 min, and then a solution of BuLi in hexane (1.6 M; 15.1 mL, 24.2 mmol) was added dropwise at 0 °C under nitrogen. After additional stirring at 0 °C for 15 min and at RT for 24 h, the mixture was cooled with the aid of a cold water bath, and anhydrous DMF (2.1 mL, 27.4 mmol) was slowly added with vigorous stirring. The resulting mixture was allowed to stir under nitrogen at RT for 24 h. The reaction was quenched with aqueous HCl (1 M, 40 mL) and phases were separated. The organic phase was washed with 1 M HCl (2 × 20 mL), water (2 × 20 mL) and brine (20 mL) to give organic phase I. The collected acidic aqueous layers were extracted with Et_2O (3 × 80 mL), and the collected ethereal phases were washed with water (2 × 80 mL) and brine (80 mL) to give organic phase II. The collected organic phases I + II were then dried over Na_2SO_4. After filtration and elimination of the solvent by rotary evaporation, the product was recovered by column chropatography on silica gel (Merck, Darmstadt, Germany, 70–230 mesh) using as eluent pure hexane to 8:2 hexane/AcOEt. Yield: 1.05 g (80% based on starting **1**). Pale yellow solid, m.p. 27–28 °C. IR (film):

ν = 2826 (w), 1672 (s), 1593 (w), 1518 (m), 1432 (w), 1256 (w), 1225 (m), 1137 (m), 868 (w), 841 (w), 749 (m), 726 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.08 (s, 1 H, CHO), 7.99 (s, 1 H, =CH), 7.95–7.84 (m, 2 H, aromatic), 7.54–7.38 (m, 2 H, aromatic); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.1, 143.9, 143.1, 138.9, 133.7, 128.1, 126.3, 125.4, 123.4; GC-MS: *m/z* = 162 (100) [M^+], 161 (99), 134 (24), 133 (32), 108 (4), 89 (50), 63 (22); anal. calcd for C_9H_6OS (162.21): C, 66.64; H, 3.73; S, 19.77; found C, 66.71; H, 3.72; N, 19.74.

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Author Contributions

The authors contributed equally to this work.

Conflicts of Interest

The authors declare no conflict of interest.

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