A straightforward expeditious synthesis of 5-nitrobenzo[b]thiophene-2-carbaldehyde

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A high yielding one-pot synthesis of 5-nitrobenzo[b]thiophene-2-carbaldehyde is reported using the readily available, cheap starting material 2,5-dihydroxy-1,4-dithiane and 2-chloro-5-nitrobenzaldehyde.

Keywords: benzo[b]thiophene, benzo[b]thiophene-2-carbaldehyde, 2,5-dihydroxy-1,4-dithiane

Benzothiophenes are important heterocycles, both as biologically-active molecules and as luminescent components in organic materials.[1] Benzo[b]thiophene and its derivatives have useful medicinal properties.[2] They are also an important class of compounds which are used in the synthesis of pesticides and in general synthesis.[3,4]

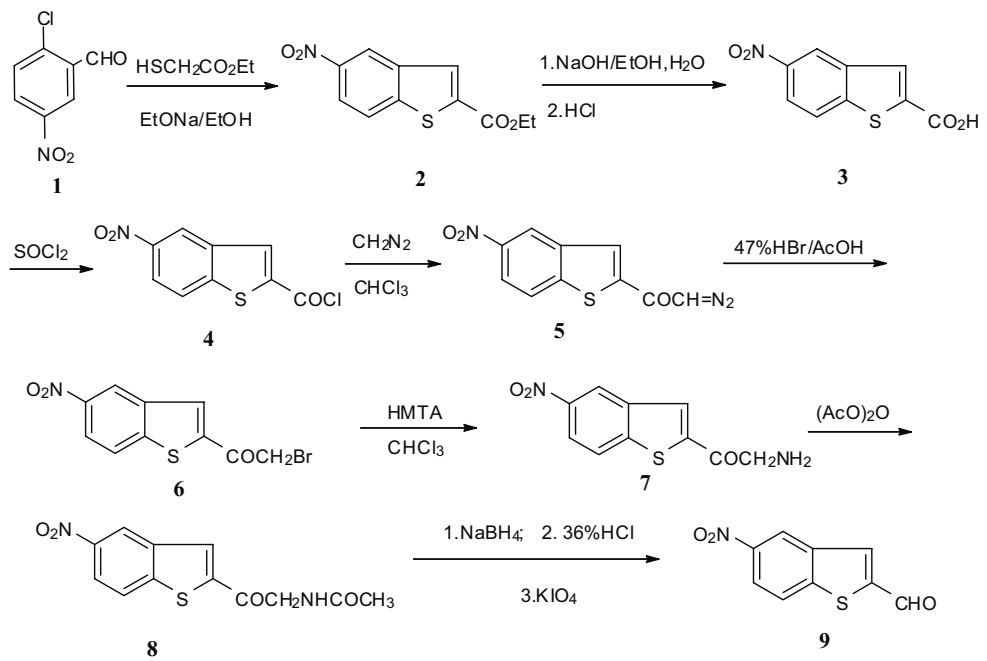
There is a wealth of patent literature on the use of the 2-carboxaldehydes of five-membered benzo-fused heterocycles in the preparation of lipoxygenase inhibitors,[5] antitumor agents,[6] and as psychotropic antagonists[7] among other drug classes. Thus considerable attention has been devoted to the synthesis of substituted benzo[b]thiophene-2-carbaldehydes. In connection with an ongoing project, we required an efficient synthesis of 5-nitrobenzo[b]thiophene-2-carbaldehyde **9** as an intermediate, which we now report.

The first synthesis of 5-nitrobenzo[b]thiophene-2-carbaldehyde **9** was reported by Rossi and Trave.[8] They described the preparation of benzo [b]thiophene-2-carbaldehyde **9** from 2-chloro-5-nitrobenzaldehyde **1** in nine steps (Scheme 1).

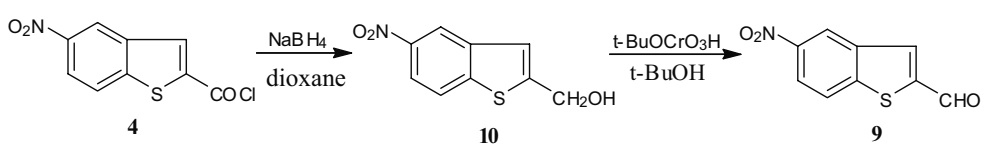
The preparation of 5-nitrobenzo[b]thiophene-2-carbaldehyde **3** has also been described by modification of the procedure which had been used previously to synthesise benzothiophene derivatives (Scheme 2).[9-11]

Since the approaches shown in Schemes 1 and 2 seemed long and tedious, we devised another route. We now report a convenient method of preparing 5-nitrobenzo[b]thiophene-2-carbaldehyde **3** is described starting from the reaction of 2-chloro-5-nitrobenzaldehyde **4,** with 2,5-dihydroxy-1,4-dithiane **13**, the dimer of mercaptoacetaldehyde, in presence of Et_3N as shown in Scheme 3.

Mercaptoacetaldehyde, commercially available only as its dimer, can be generated *in situ* from its dimer with presence of Et_3N.[12] Because of the electron-withdrawing effect of the nitro



Scheme 1



Scheme 2

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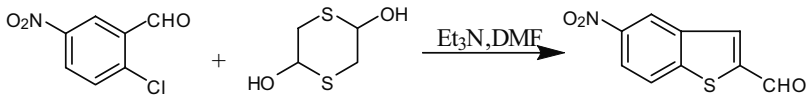

1 **11** **9**

Scheme 3

substituent at the para position of 2-chloro atom, the reaction involving the nucleophilic displacement by sulfur proceeds.

The synthesis does not require special conditions such as low temperatures and column chromatographic purification. The method involves readily available reagents and has been demonstrated to be reliable at multi-kilogram scale.

Experimental

Melting points were determined on a RY-1 hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-300 MHz/500 MHz instrument in $CDCl_3$, chemical shifts (δ) are given in part per million(ppm) relative to TMS as an internal standard. Elemental analyses were performed on Elementar Vario ELIII instrument. All reactions were monitored by TLC on silica gel 60F-254 glass plates (E.Merck).

Preparation of **9**: Triethylamine (106.3 g, 1.05 mol) was added dropwise to a solution of **1** (93.0 g, 0.5 mol) and **11** (39.9 g, 0.26 mol) in DMF (250 ml) at 10 °C over a 30 min period and then the reaction mixture was stirred at 35 °C for 8 h. The mixture was cooled to 0 °C, and the solid was collected and washed with water. The crude product was dissolved in THF, treated with active charcoal and the solution was filtered. Removing the solvent *in vacuo* yielded **9** (90.1 g, 87%). Recrystallisation from AcOH afforded the pure product as a yellowish solid. M.p. 201–203 °C, lit [8]. 202–204 °C, ^{1}H NMR: δ 10.19 (s,1H), 9.05 (d,1H,J = 2.2 Hz), 8.60 (s,1H), 8.36 (d, 1H, J = 9 Hz), 8.32 (d*d, J_1 = 2.2 Hz, J_2 = 9 Hz). Anal. Calcd for $C_9H_5NO_3S$: C, 52.17; H, 2.43; N, 6.76. Found: C, 52.23; H, 2.50; N, 6.73%.

Received 24 March 2009; accepted 14 April 2009
Paper 09/0511 doi: 10.3184/030823409X460669
Published online: 22 June 2009

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