



Synthesis of substituted 2-mercaptobenzaldehydes and 2-substituted benzo[*b*]thiophenes

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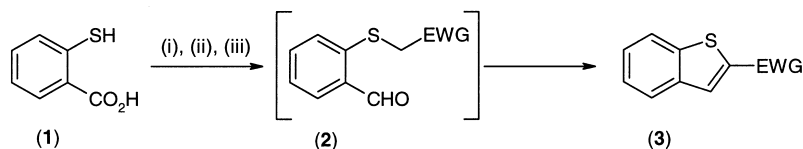
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Abstract

Simple and rapid single-pot preparations of substituted 2-mercaptobenzaldehydes **5** and 2-substituted benzo[*b*]thiophenes **3** based on *ortho*-lithiation methodology are described. © 2000 Elsevier Science Ltd. All rights reserved.

The literature describes several methods for the preparation of 2-substituted benzo[*b*]thiophenes **3**.¹ Most notably, the method of Hsiao et al.² gives benzo[*b*]thiophenes **3** from 2-mercaptobenzoic acids **1** via reduction, in situ *S*-alkylation and re-oxidation to benzaldehyde **2**, which undergoes cyclisation as shown in Scheme 1.

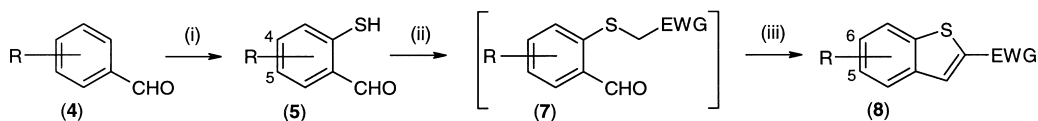


Scheme 1. *Reagents:* (i) LiAlH_4 ; (ii) XCH_2EWG ; (iii) $\text{SO}_3 \cdot \text{C}_5\text{H}_5\text{N}$, $(\text{CH}_3)_2\text{SO}$, NEt_3 , $\text{EWG} = \text{CO}_2\text{Et}$, CN , COPh , COMe

Hsiao's route is amenable to the efficient preparation of 2-substituted benzo[*b*]thiophenes **3** in 60–70% overall yield (for three steps); however, this methodology suffers from two drawbacks. These relate to the limited commercial availability of substituted 2-mercaptobenzoic acids **1** while the use of lithium aluminium hydride further limits the versatility and synthetic scope of the sequence. We have now developed an alternative, general and rapid 'one-pot' synthesis of both 2-substituted benzo[*b*]thiophenes **3** and 2-mercaptobenzaldehydes **5** from readily available benzaldehydes.

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The process which is outlined in Scheme 2, exploits the α -amino alkoxide-mediated *ortho*-lithiation of benzaldehydes devised by Comins,³ circumventing the redox sequence used by Hsaio and avoiding the use of LiAlH_4 .



Scheme 2. Reagents: (i) $\text{LiN}(\text{Me})(\text{CH}_2)_2\text{N}(\text{Me})_2$, THF, *n*-BuLi, S_8 , HCl; (ii) **6** (see Table 2), K_2CO_3 , THF

Elemental sulfur has frequently been used as an electrophile to quench *ortho*-lithiated intermediates to give aryl thiols.⁴ In the sequence shown in Scheme 2, the corresponding substituted 2-mercaptobenzaldehydes **5a–e** were isolated in moderate yield and with reasonable levels of purity (Table 1). Thiols **5** are quite unstable and attempts to carry out a rigorous purification resulted in extensive decomposition.^{2,5} Direct *S*-alkylation of intermediate thiol **5** with activated electrophiles **6a–d** (Table 2) and in situ aldol condensation gave the target 2-substituted benzo[*b*]thiophenes **8a–j** as shown in Scheme 2 and Table 3. In the case of **8j**, the intermediate benzaldehyde **7j** was isolated in 20% yield and cyclised (using Hsaio's conditions²) to give **8j** in 15% overall yield from **4b**.

Table 1
Yields for 2-mercaptobenzaldehydes **5a–e**

Aldehyde	R	Yield 5 , % (% ^a)
4a	H	5a , 72 (82 %)
4b	4-Me	5b , 78 (85 %)
4c	4-MeO	5c , 80 (94 %)
4d	4-Cl	5d , 72 (79 %)
4e	4,5-fused benzo	5e , 94 (89 %)

^a Estimated purity (by ^1H NMR) of the crude product.

Table 2
Electrophiles **6** ($\text{X}-\text{CH}_2^-$ EWG)

	X	EWG		X	EWG
a	Cl	COMe	c	Br	CO_2Et
b	Cl	COPh	d	Cl	CN

In summary, we have described a 'one-pot' procedure for the preparation of a range of 2-substituted benzo[*b*]thiophenes **8**. Although the overall yields of 2-substituted benzo[*b*]thiophenes **8a–j** are, in general, lower than those reported by Hsaio et al. our approach is more versatile and more direct. In addition, the chemistry described in this paper also provides a viable route for the synthesis of the labile 2-mercaptobenzaldehydes **5a–e**.

Table 3
Yields for benzo[*b*]thiophenes **8a–j** from reaction of 2-mercaptobenzaldehydes **5** with electrophiles **6a–e**

2-Mercaptobenzaldehyde	Yield 8 , % ^a	R	EWG
5a	8a , 38	H	COMe
5b	8b , 50	6-Me	COMe
5c	8c , 42	6-MeO	COMe
5c	8d , 32	6-MeO	COPh
5c	8e , 26	6-MeO	CO ₂ Et
5c	8f , 27	6-MeO	CN
5d	8g , 30	6-Cl	COMe
5e	8h , 26	5,6-fused benzo	COMe
5b	8j , 20 ^b (15 ^c)	6-Me	CN

^a From aldehyde **4**

^b Yield of isolated aldehyde intermediate **7j**

^c Overall yield of benzo[*b*]thiophene **8j** (from **4b**)

General method of preparation for substituted 2-mercaptobenzaldehydes 5a–e: *n*-Butyl lithium (2.5 M in hexanes, 8.4 cm³, 21 mmol) was added to a solution of *N,N,N'*-trimethylethylenediamine (2.25 g, 2.5 cm³, 22 mmol) in anhydrous tetrahydrofuran (60 cm³) at –20°C under argon and the mixture was stirred for 15 min. Neat aldehyde **4** (20 mmol) was added and the mixture stirred at –20°C for 24 h. The reaction mixture was then cooled to –40°C and treated with sulfur (1.67 g, 52 mmol). After stirring for a further 3 h at –20°C, the mixture was quenched with 2 M hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water, then brine, dried (MgSO₄) and the solvents evaporated to yield the corresponding thiol as a yellow oil which could be stored at –10°C under argon. Routinely, the thiol was used immediately without purification.

2-Mercapto-4-methoxybenzaldehyde 5c: Isolated as a yellow oil; δ_{H} (250 MHz, CDCl₃) 3.81 (3H, s, ArOCH₃), 6.26 (1H, s, ArSH), 6.84 (2H, m, ArH), 7.60 (1H, d, *J* = 8.04, ArH), 9.45 (1H, s, ArCHO); *m/z* 168 (M⁺, 100%), 134 (M⁺–34); HRMS for C₈H₈O₂S (M⁺) calcd: 168.0245; found: 168.0244.

*General method of preparation for benzo[*b*]thiophenes 8a–j:* A mixture of 2-mercaptobenzaldehyde **5** (1.3 mmol) and potassium carbonate (1.3 mmol) in anhydrous tetrahydrofuran (4 cm³) was treated with the required alkylating agent **6** (2.6 mmol) and shaken for 24 h. The solution was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water then brine, dried (MgSO₄) and the solvents removed in vacuo to yield the crude product.

Alternatively, following the preparation of 2-mercaptobenzaldehydes **4**, the intermediate thiolate mixture (after stirring for 3 h at –20°C and prior to quenching) was treated directly with 2 equivalents of the alkylating agent **6** to afford the benzo[*b*]thiophenes **8** in a ‘one-pot’ operation. Chromatography over silica (MERCK 15111) with dichloromethane/hexane gave the benzo[*b*]thiophenes **8** as yellow crystalline solids.

*2-Acetyl-6-methoxybenzo[*b*]thiophene 8c:* Isolated as a yellow crystalline solid, m.p. 124–125°C (EtOH); ν_{max} (Nujol mull)/cm^{–1} 1680 (C=O); δ_{H} (400 MHz, CDCl₃) 2.68 (3H, s, ArCOCH₃), 3.92 (3H, s, ArOCH₃), 6.98 (1H, dd, *J* = 2.28 and 8.82, ArH), 7.28 (1H, d, *J* = 2.30, ArH), 7.83 (1H, d,

$J=8.81$, ArH), 7.94 (1H, s, ArH); m/z 206 (M^+ , 80%), 191 (M^+-15 , 100%); HRMS for $C_{11}H_{10}O_2S$ (M^+) calcd: 206.0402; found: 206.0406.

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