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

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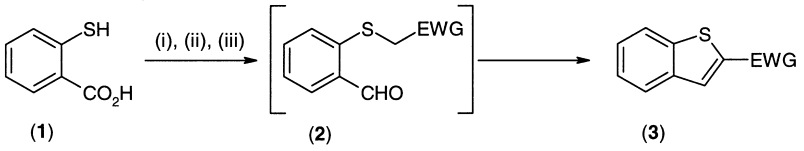
**Abstract**

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. 

The literature describes several methods for the preparation of 2-substituted benzo[*b*]thiophenes **3**.[1] Most notably, the method of Hsaio 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) $SO_3{\cdot}C_5H_5N$, $(CH_3)_2SO$, $NEt_3{\cdot}EWG{=}CO_2Et$, CN, COPh, COMe

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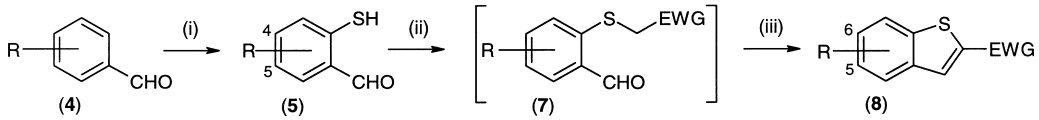
The process which is outlined in Scheme 2, exploits the α-amino alkoxide-mediated *ortho*-lithiation of benzaldehydes devised by Comins,[3] circumventing the redox sequence used by Hsaio and avoiding the use of $LiAlH_4$.




Scheme 2. *Reagents:* (i) $LiN(Me)(CH_2)_2N(Me)_2$, 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 conditions[2]) 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** ($X–CH_2^-$ 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 | $CO_2Et$ |
| **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 $cm^3$, 21 mmol) was added to a solution of *N*,*N*,*N*′-trimethylethylenediamine (2.25 g, 2.5 $cm^3$, 22 mmol) in anhydrous tetrahydrofuran (60 $cm^3$) 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 ($MgSO_4$) 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; $\delta_H$ (250 MHz, $CDCl_3$) 3.81 (3H, s, ArOC$H_3$), 6.26 (1H, s, ArS*H*), 6.84 (2H, m, Ar*H*), 7.60 (1H, d, $J = 8.04$, Ar*H*), 9.45 (1H, s, ArC*H*O); *m*/*z* 168 ($M^{\cdot+}$, 100%), 134 ($M^{\cdot+}$–34); HRMS for $C_8H_8O_2S$ ($M^+$) 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 $cm^3$) 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 ($MgSO_4$) 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); $\nu_{max}$ (Nujol mull)/$cm^{-1}$ 1680 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 2.68 (3H, s, ArCOC$H_3$), 3.92 (3H, s, ArOC$H_3$), 6.98 (1H, dd, $J = 2.28$ and 8.82, Ar*H*), 7.28 (1H, d, $J = 2.30$, Ar*H*), 7.83 (1H, d,

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

## References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