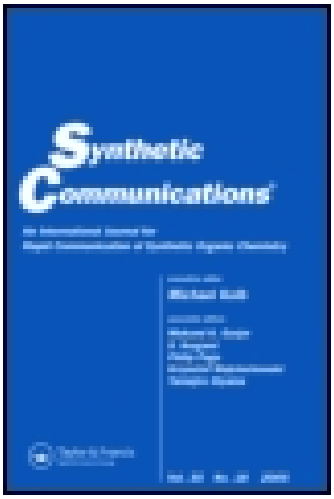

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Two Efficient and Practical Syntheses of Methyl 4-Mercaptobenzoate

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TWO EFFICIENT AND PRACTICAL SYNTHESES OF METHYL 4-MERCAPTOBENZOATE

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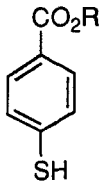
Abstract: *Two efficient syntheses of methyl 4-mercaptobenzoate are described, one utilizing the dianion of 4-bromothiophenol, the other a S_NAr reaction starting with 4-fluorobenzonitrile.*

As part of our program aimed at the synthesis of novel leukotriene antagonists we required access to kilogram quantities of methyl 4-mercaptobenzoate **1**.



1 R = Me
2 R = H

A search of the literature for preparations of **1** or its free acid **2** revealed that, from a process development standpoint, existing routes were unattractive

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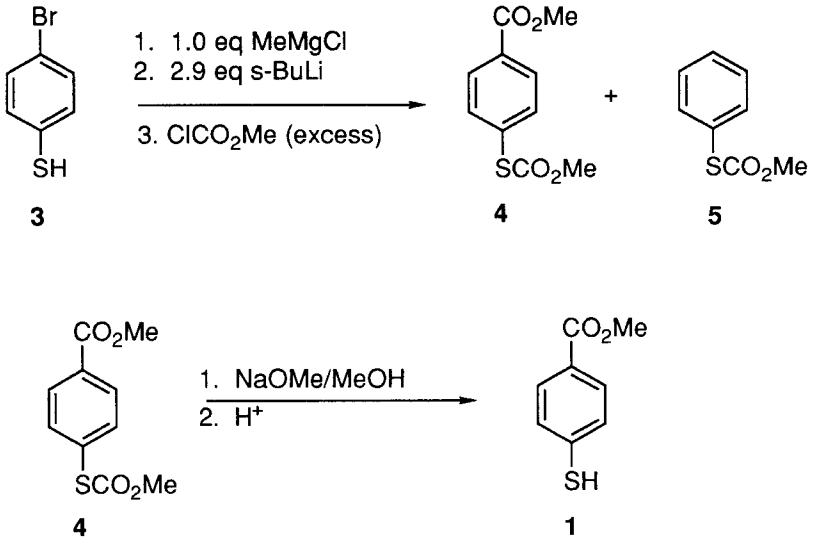
because they were inefficient or posed safety problems.[1a-i] We now report two convenient routes to **1** that utilize commercially available starting materials and are suitable for preparative scale.

ROUTE 1

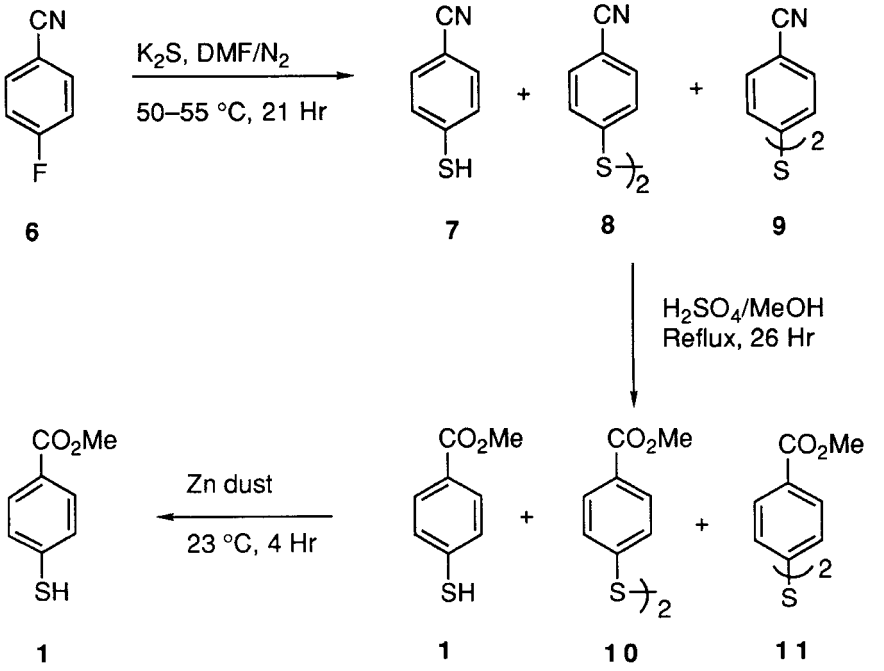


The first method of preparation (Route 1) is based on a modification of an approach to 4-mercaptobenzoic acid **2** first described by Gilman.[1d] Gilman's method required treatment of 4-bromothiophenol **3** with excess n-butyllithium in refluxing ether to effect dianion formation. Subsequent carbon dioxide quench produced crude 4-mercaptobenzoic acid in 74% yield. Our method differs by first effecting a clean deprotonation of the thiol prior to the metal halogen exchange.[2a-c] Thus, initial treatment of 4-bromothiophenol with 1 equivalent of methyl magnesium chloride in THF formed a soluble thiolate anion. Subsequent treatment with 2.9 equivalents of s-BuLi at a temperature below 15 °C produced a two phase mixture with the dianion[3] residing principally in the lower phase.

We then substituted methyl chloroformate for carbon dioxide as the electrophilic quench. On a large scale the addition of solid carbon dioxide[4] to the dianion was unwieldy and produced a rapid and large exotherm which was difficult to control. Methyl chloroformate, as a liquid electrophile, mixed more efficiently with the dianion and produced a less dramatic exotherm. By using an inverse addition of the dianion to methyl chloroformate, we easily controlled the accompanying exotherm. Thus, the dianion was quenched by transferring the lower phase into an excess of methyl chloroformate at -20 °C. Use of only the bottom layer for the quench increased the throughput of the reaction by 33% without sacrificing yield. The resultant quench produced a mixture of the desired product **4** and O-methyl-S-phenyl carbonothioate **5** in a ratio of 95:5 [peak area ratio (PAR) by HPLC, 74% wt/wt assay of **4**]. Crystallization of the crude product mixture from 2-propanol afforded pure **4**. A facile selective hydrolysis of **4** with sodium methoxide in MeOH at 10 °C afforded **1** in sufficient purity to be used without further purification (95% PAR by HPLC) in an overall yield of 70%[5] from 4-bromothiophenol.

For Route 2 our strategy was to effect an S_NAr reaction between a thionucleophile and either 4-halo or 4-nitrobenzoic acid or their methyl esters.[6a-e] However, heating these substrates with a variety of thionucleophiles up to temperatures of 150 °C returned only unreacted starting materials or gave the corresponding hydrolysis products.[7] When we extended our study to 4-halobenzonitriles, we found that 4-fluorobenzonitrile **6** reacted with 1.1 equivalent of anhydrous K_2S or Na_2S in DMF at 55 °C to give 4-mercaptobenzonitrile **7** along with varying amounts of the disulfide, 4,4'-dithiobis[benzonitrile] **8**[8] and the sulfide, 4,4'-thiobis[benzonitrile] **9** (10%). Efforts to reduce the amount of disulfide were unsuccessful; however, this did not prove to be a problem as the

ROUTE 2



final reduction step converts it to the desired product. The mixture was then hydrolyzed by refluxing with H_2SO_4/MeOH for 24 hours to form the corresponding methyl ester mixture. A subsequent *in situ* reduction with 2.0 equivalents of zinc resulted in a facile cleavage of the disulfide to produce **1** in 63% overall yield[5] from 4-fluorobenzonitrile of sufficient purity (92% w/w assay) to use in our synthetic sequence.

Other 4-halobenzonitriles were examined as substrates for this S_NAr reaction and as expected, the reactivity was found to decrease in the order of F>Cl>Br. Anhydrous Na_2S could also be used effectively as the nucleophile; however, it is more expensive and less available in bulk quantities.

In summary, two new routes to methyl 4-mercaptobenzoate **1** have been developed, both of which are practical methods for the preparation of multi-kilo quantities.

Experimental Section

s-Butyllithium was obtained from FMC Corporation and titrated before use against 2,5-dimethoxybenzyl alcohol.[10] 4-Bromothiophenol **3** was obtained from Lancaster Chemical Company, 4-fluorobenzonitrile **6** from Wychem, Ltd., zinc dust (300 mesh) from Fisher Scientific Company and potassium sulfide from Alfa Johnson Matthey; all were used without further purification. Reagent grade THF was dried over 4Å molecular sieves. All other solvents and reagents were used as obtained from commercial sources. All reactions were done under N_2 atmosphere. Infrared (FT) spectra were measured on a Nicolet 20SBX. ^1H NMR spectra were taken on a Bruker AM-300 or AM-400 spectrometer. ^{13}C NMR spectra were obtained on a Bruker AM-400. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. HPLC for Route 1 was performed on a C-18 μ-Bondapak column with a mobile phase of CH_3CN-H_2O-H_3PO_4 (65:35:0.1) at 230 nm detection; HPLC for Route 2 was performed on a Beckman ODS column using CH_3CN-H_2O-AcOH(50:50:0.1) at 225 nm detection. The analyses by HPLC are expressed by peak area ratio (PAR) for individual components.

Route 1

Methyl 4-[(methoxycarbonyl)thio]benzoate (4). A solution of methyl magnesium chloride (0.27 mol, 3 M in THF) was added dropwise at 0 °C to a solution of 4-bromothiophenol (**3**, 50 g , 98% purity, 0.26 mol) in THF (250 mL) under a nitrogen atmosphere at such a rate that the temperature did not exceed 15 °C. The reaction mixture was re-cooled to 0 °C and s-butyllithium (340 mL,

2.28 M in cyclohexane/heptane, 0.78 mol) was added at such a rate that the temperature did not exceed 15 °C. The layers were allowed to separate and the bottom phase added to cooled (-15 °C) methyl chloroformate (170 mL) at such a rate that the temperature did not exceed 10 °C. The reaction mixture was warmed to ambient temperature over 3 h, then re-cooled to 0 °C. After acidifying with 10% HCl, the mixture was extracted with toluene. The organic layers were washed with water and saturated brine solution and evaporated *in vacuo* to afford 64.3 g of a yellow oil containing methyl 4-[(methoxycarbonyl)thio]benzoate **4** and carbonothioate by-product **5** in the ratio of 94.5:5.5 (PAR by HPLC, 71.4% wt/wt assay, 74.0% corrected yield of **4**). The oil could be crystallized from isopropanol (70 mL) to afford 33.8 g of a white solid, mp 45–47 °C;[11] IR (KBr) 3417, 1724, 1717, 1597, 1292, 1280, 1186, 1149, 1109, 851, 814, 760 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 8.06–8.04 (dd, 2 H, J = 8.4, 1.8 Hz), 7.62-7.60 (dd, 2H, J = 8.4, 1.8 Hz), 3.93 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.4, 166.2, 134.0, 133.5, 130.9, 130.0, 54.6, 52.2; MS (CI) *m/e* 227 $(M + H)^+$, 211, 195, 183; Anal. Calcd. for $C_{10}H_{10}O_4S$: C, 53.09; H, 4.46; S, 14.17. Found: C, 53.08; H, 4.54; S, 14.47.

Methyl 4-mercaptobenzoate (1). To a cooled (10 °C) solution of **4** (15 g, 66.4 mmol) in MeOH (60 mL) at 5-10 °C was added sodium methoxide (23 mL, 25% solution in MeOH) over 5 min. After stirring 10 min, the reaction was complete. The mixture was acidified with 10% HCl and the resultant white solid was filtered, washed with water (35mL) and dried *in vacuo* to afford 10.4 g of **1** (93% uncorrected yield, 95.0% PAR by HPLC). IR (KBr) 3417, 2949, 2580, 1713, 1596, 1279, 1113, 1149, 758 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.90–7.88 (d, 2 H, J = 2.1 Hz), 7.30-7.28 (d, 2H, J = 2.1 Hz), 3.93 (s, 3 H), 3.60 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.3, 1127.8 (d), 129.9 (d), 126.7, 166.3, 51.8 (q).

Route 2

4-Mercaptobenzonitrile (7). Anhydrous potassium sulfide (50.0 g, 44% purity, 0.20 mole) was added to a solution of 4-fluorobenzonitrile (21.2 g, 0.18 mole) in DMF (250 mL) in one portion under a nitrogen atmosphere at ambient temperature. The resulting mixture was allowed to warm to 50-55 °C over a period of 15 min and stirred at this temperature for 21 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (300 mL), water (100 mL), and acidified with 10% HCl to pH 3. The suspended solid between the two layers (inorganic sulfur and its derivatives) was removed by filtration. The organic layer was separated, washed sequentially with water and brine, evaporated in vacuum to give 33.0 g of a mixture of mercaptobenzonitrile **7**, 4,4'-dithiobis[benzonitrile] **8** and 4,4'-thiobis[benzonitrile] **9** (5.0, 73.0,[10] and 9.5% PAR by HPLC respectively).

Methyl 4-mercaptobenzoate (1). Concentrated H_2SO_4 (200 mL) was added to a suspension of the crude mixture of nitriles **7-9** (32.5 g) in MeOH (800 mL) over 20 min under nitrogen atmosphere. The subsequent exotherm raised the reaction temperature to 50 °C The mixture was heated to reflux for 26 h and cooled to ambient temperature. Zinc dust (24 g, 0.36 moles) was added in three portions over 15 minutes and stirred vigorously for 4 h. The excess zinc and insoluble 4,4'-thiobis[methyl benzoate] **11** were removed by filtration. The clear filtrate was concentrated to 2/3 of its original volume, then quenched with ice water (600 mL). The resultant white solid was filtered, washed with cold water and dried in vacuum to afford 20.8 g (92% wt/wt assay) of **1**. The ^1H and ^{13}C NMR of **1** were identical to the product isolated in route 1. Overall corrected yield from 4-fluorobenzonitrile is 63%.

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3. The formation of both the thiolate anion and the dianion of 4-bromothiophenol was monitored by the addition of methyl iodide to HPLC samples and subsequent comparison with known standards.

4. We found that a quench of the dianion formed by Route 1 with solid carbon dioxide (Dry Ice) gave higher yields of 4-mercaptobenzoic acid than did a quench with gaseous carbon dioxide (84% vs. 25% on a 10g scale). See Gilman, H.; Van Ess, P. R. *J. Am. Chem. Soc.* **1933**, *55*, 1258 for a discussion on the necessity for a high local concentration of carbon dioxide.

5. Yield is unoptimized.

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7. Nucleophiles examined were: $NaSH{\bullet}xH_2O$, $Na_2S{\bullet}H_2O$, $NaSCH_3$, $Na_2S_2O_3$, Na_2S, $H_2N(C{=}S)NH_2$, $KS(C{=}S)OEt$, $K_2S_2O_3$, K_2S.

8. 4-Mercaptobenzonitrile rapidly oxidizes to 4,4'-dithiobis[benzonitrile] during work-up and on standing.

9. The reaction was examined at various temperatures. At lower temperature (35–40 °C) the reaction was not complete after 40 h; at higher temperature (80–85 °C), the reaction was faster; however, more undesired sulfide formed.

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11. The crude solid could alternatively be crystallized by trituration with chilled hexane (0 °C). Neither method of purification has been optimized.

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