Efficient Synthesis of 2,3-Disubstituted Benzo[*b*]thiophenes Starting from 2-Aminobenzophenone

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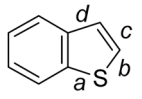
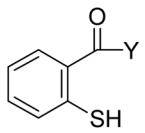
Benzo[*b*]thiophene derivatives have been reported to have many interesting biologically properties[1-6] and the synthesis and derivatization of the benzo[*b*]thiophene ring have drawn much interests.[1-11] The syntheses of the benzo[*b*]thiophene ring were usually accomplished by the formation of a fused thiophene ring starting from appropriate benzene derivatives through the formation of one bond '*a*', '*b*', '*c*', or '*d*', or the formation of two bonds '*a*' and '*b*', '*a*' and '*c*', or '*b*' and '*c*'.[1-6,8-11] The fused thiophene ring synthesis through the formation of '*b*' and '*c*' bonds would readily provide 2,3-disubstituted benzo[*b*]thiophene derivatives. For the thiophene ring synthesis through that two-bond formation, 2-mercaptobenzoyl derivatives **1** or their precursor compounds are necessary as starting materials. However, only a few 2-mercaptobenzoyl derivatives or their precursors are readily available.[5,12,13]



benzo[*b*]thiophene ring



1

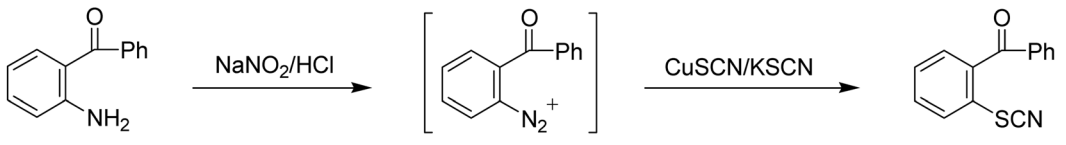
Here, we report an improved synthesis of 2-thiocyanatobenzophenone **2**, which can be served as a precursor of 2-mercaptobenzophenone, from 2-aminobenzophenone and the direct one-pot synthesis of 2,3-disubstituted benzo[*b*]-thiophenes from **2**.

2-Thiocyanatobenzophenone **2** was prepared from 2-aminobenzophenone by diazotization followed by Sandmeyer-type reaction.[12,14] The reported procedure for the synthesis of **2** consists of diazotization of 2-aminobenzophenone, the isolation of the diazonium compound as the fluoroborate salt, and then treatment with CuSCN/KSCN to give **2** in 18% yield.[12] We were able to improve the yield to 58% *via* a one-pot reaction from 2-aminobenzophenone without isolation of the diazonium salt (Scheme 1).

Hydrolysis of the compound **2** was attempted using NaOH or KOH as a base to obtain the corresponding thiophenol **3**, but the yield of **3** was very low and variable: the major isolated product was the disulfide **4**, resulting from the oxidation of the thiophenol **3**, even though much effort was exercised to exclude oxygen (Scheme 2).[13,15] Reduction of **4** with triphenylphosphine didn't give a satisfactory yield of **3** either[16]: tlc indicated that the reaction proceeded smoothly, but **3** appears to be re-oxidized to **4** during work-up process. Thus, we decided to carry out the hydrolysis and then alkylation reaction in a one-pot, without attempting the isolation of the hydrolyzed product, **3**.

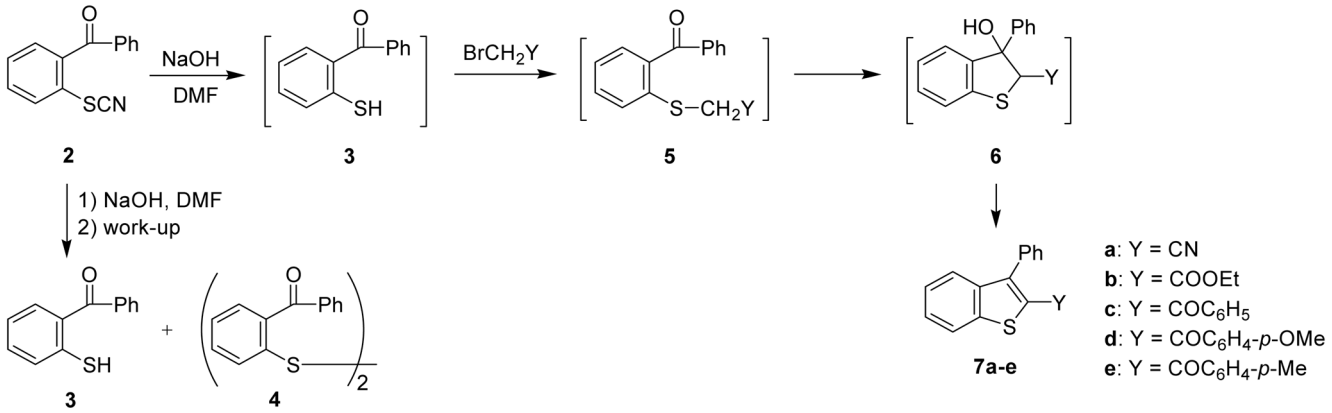
A hydrolysis reaction mixture obtained from stirring a solution of the thiocyanatobenzophenone **2** and NaOH in DMF/water was treated with alkyl bromide ($BrCH_2Y$: Y = CN, CO_2Et, COPh, COPh-4-OMe, or COPh-4-Me), stirred at 35 °C for 3-5 h and then quenched with 10% aq HCl. Work-up of the reaction mixture gave the corresponding benzo[*b*]thiophene derivatives **7**. The *S*-alkylated product **5** could not be isolated, implying that four steps to give **7** from **2**, hydrolysis, *S*-alkylation, cyclization, and then dehydration, occur consecutively in one-pot (Scheme 2). The yields of **7** were in the range of 50-80% based on the starting material **2**. Considering that four steps are involved in the transformation of **2** to **7**, it is certain that the reactions are quite efficient and convenient. 2,3-Disubstituted benzo[*b*]-thiophenes **7a-e** synthesized in this study are either new (**7e**) or have previously been prepared individually by a specific and/or complicated method from not-readily available starting materials.[6,17-19]

In conclusion, 2-thiocyanatobenzophenone **2** was easily prepared in moderate yield from readily available 2-aminobenzophenone *via* diazotization followed by reaction with CuSCN/KSCN. Treatment of **2** with NaOH and then alkyl halide in DMF-water provided 2,3-disubstituted benzo[*b*]-thiophenes **7a-e** in good yields: hydrolysis of **2** to thiol,



2 (58 %)

Scheme 1. Synthesis of 2-thiocyanatobenzophenone **2**.



Scheme 2. Synthesis of 2,3-disubstituted benzo[*b*]thiophenes starting from 2-thiocyanatobenzophenone.

alkylation of the thiol, and then ring-closure/dehydration through Aldol-type condensation reaction occur consecutively in one-pot. We believe that our synthetic method described here provides a general, cheap, and efficient route for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using tetramethylsilane (in $CDCl_3$) as an internal standard.

Preparation of 2-thiocyanatobenzophenone 2. The literature procedure[12,14] was followed with slight modification. A solution of sodium nitrite (0.77 g, 11 mmol) in water (2 mL) was added slowly over 15 min to a mixture of 2-aminobenzophenone (2.00 g, 10.1 mmol), conc. HCl (3.0 mL), and water (30.0 mL) at 0 °C and the reaction mixture was stirred for additional 20 min at 0 °C under N_2 atmosphere. This reaction mixture was added slowly to a solution of CuSCN (2.0 g, 16 mmol) and KSCN (19.5 g, 0.201 mol) in water (20 mL) at 0 °C and then the mixture was stirred at room temperature for 1 h and then at 60 °C for 30 min under N_2 atmosphere. The mixture was cooled to room temperature and the solid was collected by filtration. The solid was dried, and then extracted three times with boiling petroleum ether (3 × 40 mL). The extracts were concentrated and the residue was purified by silica gel column chromatography eluting with 20:1 hexane-ethyl acetate to provide 1.39 g (58%) of 2-thiocyanatobenzophenone **2**: mp 83 °C (lit.[12] 82-82.5 °C); ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1H, J = 8.0 Hz), 7.78-7.73 (m, 3H), 7.69-7.62 (m, 2H), 7.52 (t, 2H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.6 Hz); IR (KBr) 2154, 1635, 1586, 1438, 1322, 1313, 1273, 737, 730, 696 cm^{-1}.

Preparation of 2,3-disubstituted benzo[*b*]thiophenes 7a-e. A solution of 2-thiocyanatobenzophenone **2** (0.20 g, 0.84 mmol) in DMF (3 mL) was added slowly to a solution of NaOH (0.334 g, 8.4 mmol) in water (3 mL) under N_2 atmosphere and the reaction mixture was stirred at 35 °C for 3 h. To this mixture was added slowly alkyl bromide (1.7 mmol) $BrCH_2Y$ (Y = CN, CO_2Et, COPh, COPh-4-OMe, or COPh-4-Me) dissolved in DMF (2 mL). The reaction mixture was stirred at 35 °C for 3-5 h and then quenched by neutralization with 10% aq HCl. Saturated aq NH_4Cl solution (15 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, concentrated, and then purified by silica gel column chromatography eluting with 20:1 hexane-ethyl acetate to provide the corresponding 2,3-disubstituted benzo[*b*]thiophene **7**.

2-Cyano-3-phenylbenzo[*b*]thiophene **7a**: yield 59%; mp 88 °C (lit.[17] 78-81 °C); ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 8.4 Hz), 7.64-7.49 (m, 6H), 7.47 (t, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 148.32, 140.98, 136.58, 132.15, 129.30, 129.20, 128.99, 127.92, 125.65, 124.94, 122.57, 114.68, 105.86; IR (KBr) 2209, 1487, 1443, 1354, 1262, 1111, 770, 733, 694 cm^{-1}.

Ethyl 3-phenylbenzo[*b*]thiophene-2-carboxylate **7b**: yield 50%; mp 60-61 °C (lit.[18] 63-65 °C); ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.53-7.45 (m, 4H), 7.43-7.39 (m, 2H), 7.36 (t, 1H, J = 7.6 Hz), 4.25 (q, 2H, J = 7.6 Hz), 1.21 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 162.47, 143.63, 140.27, 140.03, 134.59, 129.57, 128.55, 127.87, 126.99, 125.15, 124.64, 122.35, 61.20, 13.99 (one carbon is missing due to overlap); IR (KBr) 1723, 1714, 1531, 1489, 1274, 1230, 1176, 758, 736, 697 cm^{-1}.

2-Benzoyl-3-phenylbenzo[*b*]thiophene **7c**: yield 73%; mp 104-105 °C (lit.[19] 105-106 °C); ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.61 (dd, 2H, J = 8.0, 1.2 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.34-7.13 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 191.45, 141.27, 140.60, 139.12, 137.61, 137.37, 134.19, 132.23, 130.18, 129.49, 128.10, 127.85, 127.68 126.81, 124.95, 124.92, 122.56; IR (KBr) 1626, 1598, 1517, 1444, 1349, 1289, 735, 725, 703 cm^{-1}.

2-(4-Methoxybenzoyl)-3-phenylbenzo[*b*]thiophene **7d**: yield 78%; mp 95-97 °C (lit.[6] 94-95 °C); ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.40 (t, 1H, J = 8.0 Hz), 7.32 (dd, 2H, J = 8.0, 1.6 Hz), 7.29-7.20 (m, 3H), 6.67 (d, 2H, J = 8.0 Hz), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.08, 163.16, 140.38, 140.15, 139.08, 137.72, 134.46, 132.22, 130.17, 130.14, 128.28, 127.89, 126.51 124.93,

124.73, 122.60, 113.17, 55.37; IR (KBr) 1629, 1592, 1283, 1252, 1165, 1107, 1031, 700 cm^{-1}.

2-(4-Methylbenzoyl)-3-phenylbenzo[*b*]thiophene **7e**: yield 80%; mp 86-87 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.56 (d, 2H, J = 8.0 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.31 (dd, 2H, J = 8.0, 1.6 Hz), 7.28-7.20 (m, 3H), 6.98 (d, 2H, J = 8.0 Hz), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.22, 143.32, 140.80, 140.52, 139.17, 137.66, 134.82, 134.40, 130.19, 129.90, 128.54, 128.22, 127.81, 126.68, 124.95, 124.89, 122.62, 21.58; IR (KBr) 1624, 1604, 1518, 1484, 1351, 1286, 1105, 938, 778, 748, 735 cm^{-1}. Anal: Calcd for $C_{22}H_{16}OS$: C, 80.45; H, 4.91; S, 9.76. Found: C, 80.59; H, 4.89; S, 9.59.

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