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ONE-POT SYNTHESIS OF 2,3-DISUBSTITUTED BENZO[*b*]THIOPHENE DERIVATIVES FROM 2-MERCAPTOPHENYL KETONES

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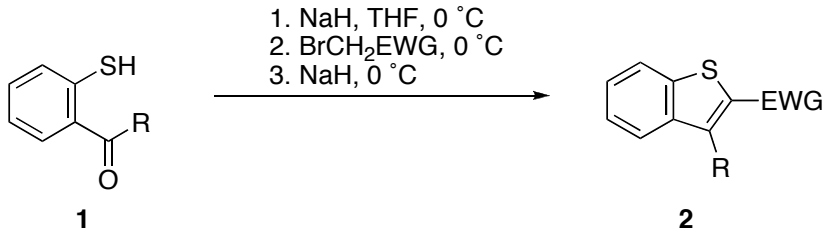
Abstract - 2-Mercaptophenyl ketones have been found to react with activated alkyl bromides ($BrCH_2EWG$'s), such as bromoacetates, bromoacetonitrile, and bromomethyl phenyl ketone, in the presence of two molar amounts of sodium hydride in THF at 0 ˚C to afford 2,3-disubstituted benzo[*b*]thiophenes in generally good to excellent yields.

The benzo[*b*]thiophene skeleton is found in many biologically active compounds.[1] Accordingly, we[2] and others[3] have been recently developing new methods for the preparation of this class of heterocycles. The synthesis of 3-aminobenzo[*b*]thiophene derivatives by reactions of 2-mercaptobenzonitriles with XCH_2EWG's (EWG = electron-withdrawing group) in the presence of an appropriate base has been reported previously.[4] 2-Mercaptobenzaldehydes have been reported to give 2-substituted benzo[*b*]thiophene derivatives under similar conditions.[5] However, the use of 2-mercaptophenyl ketones for the preparation of 2,3-disubstituted benzo[*b*]thiophenes has been extremely limited. The synthesis of 3-methyl-2-pivaloylbenzo[*b*]thiophene by treating 2-mercaptophenyl methyl ketone with bromomethyl *t*-butyl ketone in the presence of cesium carbonate at 70 ˚C for 3 d has been reported by Shen and Doherty.[6] We reasoned that preparation of 2,3-disubstituted benzo[*b*]thiophene derivatives under milder reaction conditions would be achieved by reactions of 2-mercaptophenyl ketones with $BrCH_2EWG$'s using an appropriate base. We have found that 2,3-disubstituted benzo[*b*]thiophene derivatives (**2**) can be prepared by treating 2-mercaptophenyl ketones (**1**) with $BrCH_2EWG$'s in the presence of two molar amounts of sodium hydride at 0 ˚C.

Our one-pot synthesis of 2,3-disubstituted benzo[*b*]thiophenes (**2**) from 2-mercaptophenyl ketones (**1**), which were readily prepared by treatment of 2-mercaptobenzoic acid with appropriate organolithiums, was conducted as illustrated in Scheme 1. Thus, treatment of the starting mercapto ketones (**1**) with an equimolar amount of sodium hydride in THF at 0 ˚C was followed by addition of activated alkyl bromides, such as bromoacetates, bromoacetonitrile, and bromomethyl phenyl ketone. The mixture was then subjected to further treatment with an additional equimolar amount of sodium hydride at the same

temperature. The usual aqueous workup and subsequent purification by preparative TLC on silica gel afforded the desired products (**2**). The results using five 2-mercaptophenyl ketones and four $BrCH_2EWG$'s are summarized in Table 1, which indicates that the yields are generally good to excellent. The lower yield of the product (**2b**) may be ascribed to the liability of the methoxycarbonyl function to saponification with sodium hydroxide, generated in the reaction mixture.



1 **2**

Scheme 1

Table 1: Preparation of 2,3-Disubstituted Benzo[*b*]thiophenes (**2**)

Entry	**1**	EWG	**2** (Yield/%)[a]
1	**1a** (R = *n*-Bu)	CO_2t-Bu	**2a** (86)
2	**1a**	CO_2Me	**2b** (40)
3	**1a**	CN	**2c** (95)
4	**1a**	COPh	**2d** (99)
5	**1b** (R = *t*-Bu)	CO_2t-Bu	**2e** (76)
6	**1b**	CN	**2f** (71)
7	**1c** (R = Ph)	CN	**2g** (82)
8	**1d** (R = 4-ClC_6H_4)	CO_2t-Bu	**2h** (83)
9	**1d**	CN	**2i** (87)
10	**1d**	COPh	**2j** (91)
11	**1e** (R = 4-$MeOC_6H_4$)	CO_2t-Bu	**2k** (75)

[a]Isolated yields.

The further treatment with sodium hydride proved to be essential for the satisfactory production of **2**. For example, the treatment of **1c** with bromoacetonitrile in the presence of an equimolar amount of sodium hydride resulted in the formation of the desired (**2g**) in 29% yield, accompanied by 3-hydroxy-3-phenyl-2,3-dihydrobenzo[*b*]thiophene-2-carbonitrile (**3**) in 49% yield, even at an elevated temperature and after a prolonged reaction time (see Experimental), as shown in Scheme 2. Although compound **3** was shown to be one of the possible two diastereomers, its explicit stereochemistry could not been determined.

In summary, we have shown that the reaction of 2-mercaptophenyl ketones with activated alkyl bromides, such as bromoacetates, bromoacetonitrile, and bromomethyl phenyl ketone, in the presence of sodium hydride gives 2,3-disubstituted benzo[*b*]thiophene derivatives. This preparation may be of value in heterocyclic synthesis because of the ready availability of the starting materials as well as simple

manipulations.

Scheme 2

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. *J* values are given in Hz. Low-resolution mass spectra (EI) were recorded on a JEOL JMS-AX505 HA spectrometer. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}.

Starting Materials. 2-Mercaptophenyl ketones (**1a**),[2] (**1b**),[2] (**1c**),[7] (**1d**),[8] and (**1e**)[8] were prepared by the appropriate reported procedures. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 2,3-Disubstituted Benzo[*b*]thiophene Derivatives (2). 1,1-Dimethylethyl 3-Butylbenzo[*b*]thiophene-2-carboxylate (2a). To a stirred suspension of NaH (60% in oil; 68 mg, 1.7 mmol) in THF (5 mL) at 0 ˚C was added a solution of **1a** (0.34 g, 1.7 mmol) in THF (2 mL). After 15 min, 1,1-dimethylethyl bromoacetate (0.33 g, 1.7 mmol) was added, and stirring was continued for additional 30 min at the same temperature. The resulting mixture was then treated with the second portion of NaH (60% in oil; 68 mg, 1.7 mmol) and further stirred for 30 min before saturated aqueous NH_4Cl (10 mL) was added. The resulting mixture was extracted with Et_2O three times (10 mL each), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to give **2a** (0.39 g, 86%); a colorless oil; R_f 0.82 (1:3 AcOEt–hexane); IR (neat) 3061, 1709 cm^{-1}; ^{1}H NMR δ 0.96 (3H, t, *J* 7.3), 1.46 (2H, sextet, *J* 7.3), 1.61–1.68 (11H, m including s at 1.62), 3.25 (2H, t, *J* 7.8), 7.39 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.43 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.80–7.83 (2H, m); MS *m*/*z* 290 (M^+, 29), 234 (100). Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64. Found: C, 70.28; H, 7.75.

Methyl 3-Butylbenzo[*b*]thiophene-2-carboxylate (2b): a colorless oil; R_f 0.60 (1:5 Et_2O–hexane); IR (neat) 3061, 1715 cm^{-1}; ^{1}H NMR δ 0.96 (3H, t, *J* 7.3), 1.47 (2H, sextet, *J* 7.3), 1.62–1.69 (2H, m), 3.30 (2H, t, *J* 7.8), 3.93 (3H, s), 7.42 (1H, ddd, *J* 8.2, 6.9, 0.9), 7.46 (1H, ddd, *J* 8.2, 6.9, 1.4), 7.83–7.87 (2H, m); MS *m*/*z* 248 (M^+, 85), 206 (100). Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.54; H, 6.51.

3-Butylbenzo[*b*]thiophene-2-carbonitrile (2c): a yellow oil; R_f 0.64 (1:5 AcOEt–hexane); IR (neat) 3061, 2214 cm^{-1}; ^{1}H NMR δ 0.97 (3H, t, *J* 7.3), 1.45 (2H, sextet, *J* 7.3), 1.69–1.77 (2H, m), 3.08 (2H, t, *J* 7.8), 7.48 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.52 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.84 (2H, dd, *J* 7.8, 1.4); MS *m/z* 215 (M$^+$, 35), 172 (100). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.09; N, 6.51. Found: C, 72.26; H, 6.10; N, 6.30.

(3-Butylbenzo[*b*]thiophen-2-yl)(phenyl)methanone (2d): a yellow oil; R_f 0.51 (1:5 AcOEt–hexane); IR (neat) 3059, 1643 cm^{-1}; ^{1}H NMR δ 0.90 (3H, t, *J* 7.3), 1.38 (2H, sextet, *J* 7.3), 1.63–1.69 (2H, m), 3.09 (2H, t, *J* 7.8), 7.44–7.50 (4H, m), 7.60 (1H, tt, *J* 7.3, 1.4), 7.85 (1H, dd, *J* 7.3, 1.4), 7.88–7.91 (3H, m); MS *m/z* 294 (M$^+$, 27), 251 (100). Anal. Calcd for $C_{19}H_{18}OS$: C, 77.51; H, 6.16. Found: C, 77.33; H, 6.21.

1,1-Dimethylethyl 3-(1,1-Dimethylethyl)benzo[*b*]thiophene-2-carboxylate (2e): white powder; mp 123–125 °C (hexane–Et_2O); IR (KBr disk) 3063, 1722 cm^{-1}; ^{1}H NMR δ 1.06 (9H, s), 1.44 (9H, s), 7.08–7.11 (2H, m), 7.21 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.26 (1H, dd, *J* 7.8, 1.4); MS *m/z* 290 (M$^+$, 26), 234 (100). Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64. Found: C, 70.30; H, 7.69.

3-(1,1-Dimethylethyl)benzo[*b*]thiophene-2-carbonitrile (2f): pale-yellow powder; mp 72–74 °C (hexane–Et_2O); IR (KBr disk) 3060, 2208 cm^{-1}; ^{1}H NMR δ 1.70 (9H, s), 7.43 (1H, ddd, *J* 8.2, 7.3, 1.4), 7.48 (1H, ddd, *J* 8.2, 7.3, 1.4), 7.81 (1H, d, *J* 8.2), 8.19 (1H, d, *J* 8.2); MS *m/z* 215 (M$^+$, 29), 200 (100). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.09; N, 6.51. Found: C, 72.39; H, 6.26; N, 6.68.

3-Phenylbenzo[*b*]thiophene-2-carbonitrile (2g): white powder; mp 79–81 °C (hexane–Et_2O) (lit.,[9] 78–81 °C). The IR and ^{1}H NMR data for this product were identical to those reported previously.[9]

1,1-Dimethylethyl 3-(4-Chlorophenyl)benzo[*b*]thiophene-2-carboxylate (2h): white powder; mp 148–150 °C (hexane–Et_2O); IR (KBr disk) 3061, 1690 cm^{-1}; ^{1}H NMR δ 1.40 (9H, s), 7.32 (2H, d, *J* 8.2), 7.34 (1H, ddd, *J* 7.8, 7.3, 1.4), 7.45–7.48 (4H, m), 7.87 (1H, dd, *J* 7.8, 1.4); MS *m/z* 344 (M$^+$, 23), 288 (100). Anal. Calcd for $C_{19}H_{17}ClO_2S$: C, 66.17; H, 4.97. Found: C, 66.14; H, 4.99.

3-(4-Chlorophenyl)benzo[*b*]thiophene-2-carbonitrile (2i): white powder; mp 162–163 °C (hexane–Et_2O); IR (KBr disk) 3072, 2216 cm^{-1}; ^{1}H NMR δ 7.49 (1H, dd, *J* 8.2, 7.3), 7.54–7.60 (5H, m), 7.81 (1H, d, *J* 8.2), 7.91 (1H, d, *J* 8.2); MS *m/z* 269 (M$^+$, 100). Anal. Calcd for $C_{15}H_8ClNS$: C, 66.79; H, 2.99; N, 5.19. Found: C, 66.64; H, 2.93; N, 5.05.

[3-(4-Chlorophenyl)benzo[*b*]thiophen-2-yl](phenyl)methanone (2j): pale-yellow powder; mp 89–91 °C (hexane–Et_2O); IR (KBr disk) 3061, 1645 cm^{-1}; ^{1}H NMR δ 7.21–7.24 (6H, m), 7.40 (1H, t, *J* 7.3), 7.43 (1H, dd, *J* 8.2, 7.3), 7.52 (1H, dd, *J* 8.2, 7.3), 7.63 (2H, dd, *J* 8.2, 0.9), 7.71 (1H, d, *J* 8.2), 7.95 (1H, d, *J* 8.2); MS *m/z* 348 (M$^+$, 100). Anal. Calcd for $C_{21}H_{13}ClOS$: C, 72.30; H, 3.76; S, 9.19. Found: C, 72.23; H, 3.88; S, 9.46.

1,1-Dimethylethyl 3-(4-Methoxyphenyl)benzo[*b*]thiophene-2-carboxylate (2k): white powder; mp 121–123 °C (hexane–Et_2O); IR (KBr disk) 3061, 1713 cm^{-1}; ^{1}H NMR δ 1.40 (9H, s), 3.88 (3H, s), 7.01

(2H, d, *J* 8.7), 7.30–7.34 (3H, m), 7.44 (1H, dd, *J* 8.2, 7.3), 7.52 (1H, d, *J* 8.2), 7.85 (1H, d, *J* 8.2); MS *m/z* 340 (M^+, 29), 284 (100). Anal. Calcd for $C_{20}H_{20}O_2S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.55; H, 5.97; S, 9.59.

Reaction of 1c with $BrCH_2CN$ in the Presence of an Equimolar Amount of NaH. To a stirred suspension of NaH (60% in oil; 0.12 g, 2.9 mmol) in THF (5 mL) at 0 ˚C was added dropwise a solution of **1d** (0.63 g, 2.9 mmol) in THF (3 mL). After 15 min, $BrCH_2CN$ (0.35g, 2.9 mmol) was added, and the temperature was allowed to warm to rt; stirring was continued overnight. The reaction mixture was worked up in a manner similar to that described for the preparation of **2a**, and the crude product was purified by preparative TLC on silica gel to give **2g** (0.20 g, 29%), along with 3-hydroxy-3-phenyl-2,3-dihydrobenzo[*b*]thiophene-2-carbonitrile (**3**) (0.36 g, 49%): white powder; mp 122–124 ˚C (hexane–Et_2O); IR (KBr disk) 3417, 2249 cm^{-1}; ^1H NMR δ 2.99 (1H, s), 4.65 (1H, s), 7.06 (1H, dd, *J* 7.8, 0.9), 7.20 (1H, ddd, *J* 7.8, 7.3, 0.9), 7.33 (1H, *J* 7.8), 7.38 (1H, ddd, *J* 7.8, 7.3, 0.9), 7.40–7.44 (3H, m), 7.52 (2H, dd, *J* 7.8, 1.8). $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53. Found: C, 70.92; H, 4.47; N, 5.33.

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REFERENCES AND NOTES

1. (a) R. Romagnoli, P. Giovanni Baraldi, M. Dora Carrion, C. Lopez Cara, D. Preti, F. Fruttarolo, M. Giovanna Pavani, M. Aghazadeh Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, J. Balzarini, J. A. Hadfield, A. Brancale, and E. Hamel, *J. Med. Chem.*, 2007, **50**, 2273. (b) D. J. Witter, S. Belvedere, L. Chen. J. P. Secrist, R. T. Mosley, and T. A. Miller, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4562. (c) J. Fournier dit Chabert, B. Marquez, L. Neville, L. Joucla, S. Broussous, P. Bouhours, E. David, S. Pellet-Rostaing, B. Marquet, N. Moreau, and M. Lemaire, *Bioorg. Med. Chem.*, 2007, **15**, 4482. See also pertinent references cited in ref. 2.
2. K. Kobayashi, D. Nakamura, K. Miyamoto, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 1780.
3. Y. Wang and D. J. Burton, *J. Fluorine Chem.*, 2007, **128**, 1052. See also pertinent references cited in ref. 2.
4. (a) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc., C,* 1971, 3903. (b) A. Genevois-Borella, M. Vuilhorgne, and S. Mignani, *Heterocycles*, 2002, **57**, 317.
5. (a) L. K. A. Rahman and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. 1,* 1983, 2973. b) T. Gallagher, D. A. Pardoe, and R. A. Porter, *Tetrahedron Lett.*, 2000, **41**, 5415.

6. D. Shen and J. B. Doherty, PCT Int. Patent, 2005, 020917 (*Chem. Abstr.*, 2005, **142**, 297979).
7. S. W. McCombie, J. R. Tagat, W. A. Metz, D. Nazareno, and M. S. Puar, *Tetrahedron,* 1993, **49**, 8073.
8. K. Kobayashi, H. Umakoshi, A. Matsunaga, M. Tanmatsu, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2095.
9. K. Emayan, R. F. English, P. A. Koutentis, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1,* 1997, 3345.