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SYNTHESIS OF 1-ARYL-1,3-DIHYDROBENZO[*c*]THIOPHENES BY ACID-MEDIATED CYCLIZATION OF 1-[ARYL(METHOXY)METHYL]-2-[(*tert*-BUTYLSULFANYL)METHYL]BENZENES

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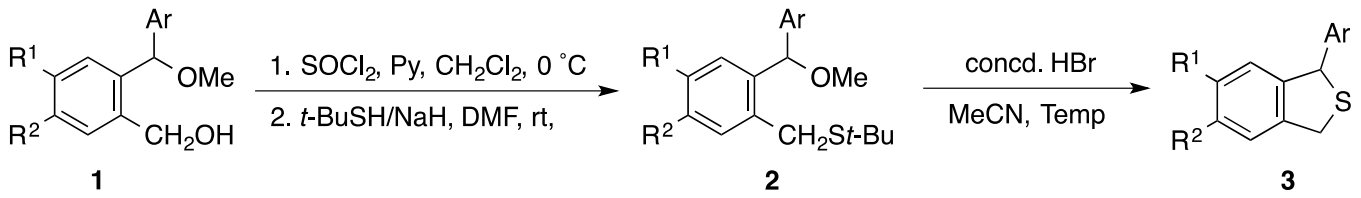
Abstract – A convenient method for the preparation of 1-aryl-1,3-dihydrobenzo[*c*]thiophenes has been developed using a three-step sequence starting from 2-[aryl(methoxy)methyl]benzyl alcohols. Thus, treatment of the starting materials with thionyl chloride gives the corresponding benzyl chlorides, which are allowed to react with sodium *tert*-butyl mercaptide to yield 1-[aryl(methoxy)methyl]-2-[(*tert*-butylsulfanyl)methyl]benzenes. Finally, these compounds undergo cyclization on treatment with concentrated hydrobromic acid to provide the desired products in reasonable yields.

The utilization of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides, derived by the oxidation of 1,3-dihydrobenzo[*c*]thiophenes, as the precursors for the generation of *o*-quinone dimethides have been reported.[1] Other synthetic applications utilizing 1,3-dihydrobenzo[*c*]thiophene derivatives have also been reported.[2] For example, the selective 1,1- and 1,3-bis(trialkylsilylation) of 1,3-dihydrobenzo[*c*]thiophene has been explored.[2b,c] The most common methods used for the preparation of 1,3-dihydrobenzo[*c*]thiophenes is base on the reaction of *o*-xylene α,α'-dihalides with disodium sulfide,[3] though an efficient method based on the Ga-promoted cycloaddition of alkynyl enynes have recently been reported.[4] However, as far as we are aware, few general methods for the preparation of 1-aryl-1,3-dihydrobenzo[*c*]thiophenes have been reported; Nishio demonstrated the formation of 3-phenyl-1,3-dihydrobenzo[*c*]thiophene by a Lawesson's reagent-mediated cyclization of [(2-hydroxymethyl)phenyl](phenyl)methanol.[5] In connection with our recent study, in which the preparation of *N,N*-disubstituted 1,3-dihydroisoindole-2-carbothioamides from 2-[aryl(methoxy)methyl]benzyl alcohols was demonstrated,[6] we were interested in developing an efficient

method to prepare 1-aryl-1,3-dihydrobenzo[*c*]thiophenes (**3**) from these benzyl alcohols (**1**). In this paper, we wish to report that compounds (**1**), which are easily prepared by the reaction of 2-[aryl(methoxy)methyl]phenyllithiums with 1-formylpiperidine followed by reduction,[6] can be transformed into **3** utilizing an easily operated three-step sequence under mild conditions. The present paper is the first report on the general synthesis of this class of 1,3-dihydrobenzo[*c*]thiophenes.

The procedure developed for the preparation of **3** from **1** is illustrated in Scheme 1. The starting materials (**1**) were easily prepared from 2-bromobenzaldehydes according to the methods reported previously by us.[6] These alcohols were readily converted into the corresponding 2-[aryl(methoxy)methyl]benzyl chlorides on treatment with thionyl chloride in dichloromethane in the presence of pyridine at room temperature. These chlorides were used directly in the next step without further purification after workup. Their *tert*-butylsulfanylation with *tert*-butyl mercaptide in DMF at room temperature proceeded smoothly and cleanly to give 1-[aryl(methoxy)methyl]-2-[(*tert*-butylsulfanyl)methyl]benzenes (**2**) in good yields as summarized in Table 1.



Scheme 1

Table 1. Preparation of 1,3-dihydrobenzo[*c*]thiophenes (**3**)

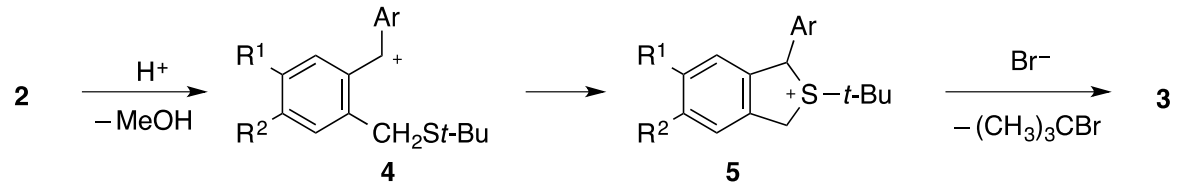
Entry	**2**	Yield/%[a]	Temp	**3**	Yield/%[a]
1	**2a** (R^1 = R^2 = H, Ar = Ph)	85	rt	**3a**	77
2	**2b** (R^1 = R^2 = H, Ar = 4-ClC_6H_4)	87	rt	**3b**	76
3	**2c** (R^1 = R^2 = H, Ar = 4-$MeOC_6H_4$)	79	rt	**3c**	74
4	**2d** [R^1 = R^2 = H, Ar = 3,4-$(MeO)_2C_6H_3$]	86	0 ˚C	**3d**	85
5	**2e** (R^1 = R^2 = H, Ar = 4-PhC_6H_4)	79	rt	**3e**	90
6	**2f** (R^1 = Cl, R^2 = H, Ar = Ph)	85	40 ˚C	**3f**	85
7	**2g** (R^1 = Cl, R^2 = H, Ar = 4-$MeOC_6H_4$)	92	rt	**3g**	86
8	**2h** (R^1 = OMe, R^2 = H, Ar = Ph)	92	0 ˚C	**3h**	76
9	**2i** (R^1 = R^2 = OMe, Ar = Ph)	83	0 ˚C	**3i**	83
10	**2j** (R^1 = R^2 = OMe, Ar = 4-ClC_6H_4)	92	rt	**3j**	88

[a] Yields of isolated products.

The *tert*-butylsulfanyl derivatives (**2**), thus obtained, were treated with an equimolar amount of concentrated hydrobromic acid at the temperatures listed in Table 1. An equimolar amount of the acid was required for complete consumption of **2**. The cyclization proceeded uneventfully to give, after aqueous workup and subsequent purification by column chromatography on silica gel or recrystallization,

the desired 1-aryl-1,3-dihydrobenzo[*c*]thiophenes (**3**) in fair to good yields, as compiled in Table 1 as well. As expected, the substitution of electron-donating methoxy group(s) on the benzene rings lowered the reaction temperature and that of electron-withdrawing chlorine raised it. The reaction of **2f** was conducted at 40 ˚C to give the corresponding desired product (**3f**) in 85% yield (Entry 6).

Mechanistically, this cyclization process for the formation of 1-aryl-1,3-dihydrobenzo[*c*]thiophenes (**3**) from 1-[aryl(methoxy)methyl]-2-[(*tert*-butylsulfanyl)methyl]benzenes (**2**) appears to proceed as illustrated in Scheme 2. Thus, treatment of **2** with hydrobromic acid generates a benzyl cation intermediate (**4**) with a loss of methanol from the corresponding alkyloxonium ion. Trapping of the cation center by the lone pair of sulfur atom produces the sulfonium ion intermediate (**5**), from which removal of *tert*-butyl cation as *tert*-butyl bromide gives **3**.



Scheme 2

In conclusion, we have demonstrated that 1-aryl-1,3-dihydrobenzo[*c*]thiophenes can be conveniently synthesized from 2-[aryl(methoxy)methyl]benzyl alcohols, which are difficult to prepared by previous methods, in three steps utilizing hydrobromic acid mediated cyclization of 1-[aryl(methoxy)methyl]-2-[(*tert*-butylsulfanyl)methyl]benzenes. The starting materials are readily prepared *via* the reaction of 2-[aryl(methoxy)methyl]phenyllithiums with 1-formylpiperidine. The ease of operations makes also the present method attractive. Further investigation on developing methods for the preparation of other heterocyclic compounds utilizing the reactions of these lithium compounds is under way in our laboratory.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a JEOL JMS-T100GCV spectrometer (EI, TOF; 70eV) or a Thermo Scientific Exactive spectrometer (DART, positive). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed

using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. (2-Bromophenyl)(3,4-dimethoxyphenyl)methanol,[7] 1-bromo-2-[methoxy(phenyl)methyl]benzene,[8] and [2-[aryl(methoxy)methyl]phenylmethanols (**1a-c**, **1g**, **1h)**, and (**1i**)[6] were prepared according to the reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

1-Bromo-2-[(3,4-dimethoxyphenyl)(methoxy)methyl]benzene. This compound was prepared from (2-bromophenyl)(3,4-dimethoxyphenyl)methanol according to the procedure for the preparation of 1-bromo-2-[methoxy(phenyl)methyl]benzene.[8] Yield: 86%; a pale-yellow oil; R_f 0.35 (AcOEt/hexane 1:5); IR (neat) 1604 cm^{-1}; ^1H NMR δ 3.39 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 5.60 (s, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.90 (dd, J = 8.6, 1.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 7.13 (ddd, J = 8.0, 7.4, 1.1 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.52 (dd, J = 7.4, 1.1 Hz, 1H), 7.54 (dd, J = 8.0, 1.1 Hz, 1H). HR-MS (EI). Calcd for $C_{16}H_{17}BrO_3$ (M): 336.0361. Found: *m/z* 336.0367.

(Biphenyl-4-yl)(2-bromophenyl)methanol.[9] This compound was prepared from (biphenyl-4-yl)magnesium bromide and 2-bromobenzaldehyde according to the procedure for the preparation of (2-bromophenyl)(3,4-dimethoxyphenyl)methanol.[7] Yield: 95%; a colorless viscous oil; R_f 0.31 (AcOEt/hexane 1:7); IR (neat) 3366 cm^{-1}; ^1H NMR δ 2.39 (d, J = 3.4 Hz, 1H), 6.26 (d, J = 3.4 Hz, 1H), 7.17 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H), 7.34 (tt, J = 7.4, 1.1 Hz, 1H), 7.38 (td, J = 7.4, 1.1 Hz, 1H), 7.43 (t, J = 8.0, 7.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.55–7.58 (m, 5H), 7.65 (dd, J = 8.0, 1.7 Hz, 1H).

1-[(Biphenyl-4-yl)(methoxy)methyl]-2-bromobenzene. This compound was prepared from (biphenyl-4-yl)(2-bromophenyl)methanol according to the procedure for the preparation of 1-bromo-2-[methoxy(phenyl)methyl]benzene.[8] Yield: 94%; a colorless viscous oil; R_f 0.35 (AcOEt/hexane 1:2); IR (neat) 1091 cm^{-1}; ^1H NMR δ 3.43 (s, 3H), 5.72 (s, 1H), 7.15 (td, J = 7.4 Hz, 1H), 7.33 (tt, J = 7.4, 1.1 Hz, 1H), 7.36 (tt, J = 7.4, 1.1 Hz, 1H), 7.42 (dd, J = 8.0, 7.4 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.54–7.59 (m, 6H). HR-MS (EI). Calcd for $C_{20}H_{17}BrO$ (M): 352.0463. Found: *m/z* 352.0480.

(2-Bromo-4,5-dimethoxyphenyl)(4-chlorophenyl)methanol. This compound was prepared from 4-chlorophenylmagnesium bromide and 2-bromo-4,5-dimethoxybenzaldehyde according to the procedure for the preparation of (2-bromophenyl)(3,4-dimethoxyphenyl)methanol[7] in 89% yield; a white solid; mp 123–125 ˚C (hexane/CH_2Cl_2); IR (KBr) 3492, 1603 cm^{-1}; ^1H NMR δ 2.35 (d, J = 3.4 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.13 (d, J = 3.4 Hz, 1H), 7.00 (s, 1H), 7.02 (s, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{15}H_{14}BrClO_3$: C, 50.38; H, 3.95. Found: C, 50.25; H, 3.87.

1-Bromo-2-[(4-chlorophenyl)(methoxy)methyl]-4,5-dimethoxybenzene. This compound was prepared from (2-bromo-4,5-dimethoxyphenyl)(4-chlorophenyl)methanol according to the procedure for the preparation of 1-bromo-2-[methoxy(phenyl)methyl]benzene[8] in 83% yield; a white solid; mp 88–90 ˚C

(hexane/CH_2Cl_2); IR (KBr) 1602 cm^{-1}; ^1H NMR δ 3.38 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.59 (s, 1H), 6.95 (s, 1H), 7.00 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H). Anal. Calcd for $C_{16}H_{16}BrClO_3$: C, 51.71; H, 4.34. Found: C, 51.62; H, 4.28.

[2-[Aryl(methoxy)methyl]phenylmethanols (1) Other Than 1a-c, g–i. These compounds were prepared from the respective 1-bromo-2-[aryl(methoxy)methyl]benzenes according to the sequence used for the preparation of **1a**,[6] *via* 2-[aryl(methoxy)methyl]benzaldehydes**.** The physical, spectral, and analytical data for new compounds follow.

2-[(3,4-Dimethoxyphenyl)(methoxy)methyl]benzaldehyde: yield: 92%; a colorless oil; R_f 0.30 (AcOEt/hexane 1:4); IR (neat) 2835, 2747, 1696 cm^{-1}; ^1H NMR δ 3.39 (s, 3H), 3.846 (s, 3H), 3.848 (s, 3H), 6.10 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 7.47 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.61 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 10.23 (s, 1H). HR-MS (EI). Calcd for $C_{17}H_{18}O_4$ (M): 286.1205. Found: *m/z* 286.1260.

2-[(3,4-Dimethoxyphenyl)(methoxy)methyl]phenylmethanol (1d): yield: 95%; a colorless oil; R_f 0.40 (AcOEt/hexane 1:1); IR (neat) 3475, 1603 cm^{-1}; ^1H NMR δ 2.59 (t, *J* = 6.3 Hz, 1H), 3.42 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.54–4.58 (m, 1H), 4.62–4.65 (m, 1H), 5.50 (s, 1H), 6.83 (s, 2H), 6.91 (s, 1H), 7.23–7.33 (m, 3H), 7.40 (d, *J* = 7.4 Hz, 1H). HR-MS (EI). Calcd for $C_{17}H_{20}O_4$ (M): 288.1362. Found: *m/z* 288.1355.

2-[(Biphenyl-4-yl)(methoxy)methyl]benzaldehyde: yield: 93%; a colorless viscous oil; R_f 0.33 (AcOEt/hexane 1:8); IR (neat) 2822, 2742, 1697 cm^{-1}; ^1H NMR δ 3.43 (s, 3H), 6.23 (s, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.65 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 10.25 (s, 1H). HR-MS (EI). Calcd for $C_{21}H_{18}O_2$ (M): 302.1307. Found: *m/z* 302.1306.

2-[(Biphenyl-4-yl)(methoxy)methyl]phenylmethanol (1e): yield: 94%; a colorless viscous oil; R_f 0.43 (AcOEt/hexane 1:2); IR (neat) 3400, 1600 cm^{-1}; ^1H NMR δ 2.66 (t, *J* = 6.3 Hz, 1H), 3.46 (s, 3H), 4.56–4.65 (m, 2H), 5.60 (s, 1H), 7.32–7.36 (m, 4H), 7.40–7.46 (m, 5H), 7.58–7.60 (m, 4H). HR-MS (EI). Calcd for $C_{21}H_{20}O_2$ (M): 304.1463. Found: *m/z* 352.1468.

4-Chloro-2-[methoxy(phenyl)methyl]benzaldehyde: yield: 63%; a colorless oil; R_f 0.30 (AcOEt/hexane 1:7); IR (neat) 2823, 2743, 1701 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 6.12 (s, 1H), 7.26–7.36 (m, 5H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.72 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 10.16 (s, 1H). HR-MS (EI). Calcd for $C_{15}H_{13}ClO_2$ (M): 260.0604. Found: *m/z* 260.0613.

{4-Chloro-2-[methoxy(phenyl)methyl]phenyl}methanol (1f): yield: 89%; a colorless oil; R_f 0.33 (AcOEt/hexane 1:3); IR (neat) 3399 cm^{-1}; ^1H NMR δ 2.32 (t, *J* = 6.3 Hz, 1H), 3.41 (s, 3H), 4.48–4.52 (m, 1H), 4.55–4.59 (m, 1H), 5.48 (s, 1H), 7.27–7.38 (m, 8H). HR-MS (EI). Calcd for $C_{15}H_{15}ClO_2$ (M): 262.0761. Found: *m/z* 262.0748.

2-[(4-Chlorophenyl)(methoxy)methyl]-4,5-dimethoxybenzaldehyde: yield: 86%; a white solid; mp 73–75 ˚C (hexane/CH_2Cl_2); IR (KBr) 2853, 2720, 1692 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 6.12 (s, 1H), 7.14 (s, 1H), 7.28 (s, 4H), 7.35 (s, 1H), 10.12 (s, 1H). Anal. Calcd for $C_{17}H_{17}ClO_4$: C, 63.66; H, 5.34. Found: C, 63.52; H, 5.29.

{2-[(4-Chlorophenyl)(methoxy)methyl]-4,5-dimethoxyphenyl}methanol (1j): yield: 91%; a colorless oil; R_f 0.39 (AcOEt/hexane 1:2); IR (neat) 3483, 1608, 1097 cm^{-1}; ^1H NMR δ 2.29 (t, J = 6.3 Hz, 1H), 3.40 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 4.49–4.57 (m, 2H), 5.48 (s, 1H), 6.78 (s, 1H), 6.93 (s, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H). HR-MS (EI). Calcd for $C_{17}H_{19}ClO_4$ (M): 322.0972. Found: *m/z* 322.0975.

Typical Procedure for the Preparation of Sulfides (2). 1-{[(1,1-Dimethylethyl)sulfanyl]methyl}-2-[methoxy(phenyl)methyl]benzene (2a). To a stirred solution of 2-[methoxy(phenyl)methyl]phenylmethanol (**1a**) (0.80 g, 3.4 mmol) and pyridine (0.27 g, 3.4 mmol) in CH_2Cl_2 (15 mL) at 0 ˚C was added $SOCl_2$ (0.41 g, 3.4 mmol) dropwise. After 30 min, saturated aqueous $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were washed with 1% aqueous HCl (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation to give a residue. The crude 1-(chloromethyl)-2-[methoxy(phenyl)methyl]benzene was dissolved in DMF (10 mL) and was added to a stirring solution of *tert*-BuSNa, generated *in situ* by treating *tert*-BuSH (0.31 g, 3.4 mmol) with NaH (60% in mineral oil; 0.14 g, 3.4 mmol) in DMF (15 mL) at 0 ˚C. The temperature was warmed to rt and stirring was continued overnight. Saturated aqueous NH_4Cl and water (25 mL each) were added and the mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to afford **2a** (0.60 g, 59%); a colorless oil; R_f 0.30 (CH_2Cl_2/hexane 1:2); IR (neat) 1601, 1095 cm^{-1}; ^1H NMR δ 1.38 (s, 9H), 3.42 (s, 3H), 3.69 (d, J = 11.5 Hz, 1H), 3.75 (d, J = 11.5 Hz, 1H), 5.74 (s, 1H), 7.21–7.27 (m, 3H), 7.31–7.35 (m, 5H), 7.40 (dd, J = 7.4, 1.1 Hz, 1H). HR-MS (EI). Calcd for $C_{19}H_{24}OS$ (M): 300.1548. Found: *m/z* 300.1562.

1-[(4-Chlorophenyl)(methoxy)methyl]-2-{[(1,1-dimethylethyl)sulfanyl]methyl}benzene (2b): a colorless oil; R_f 0.44 (AcOEt/hexane 1:7); IR (neat) 1090 cm^{-1}; ^1H NMR δ 1.37 (s, 9H), 3.40 (s, 3H), 3.65 (d, J =11.5 Hz, 1H), 3.76 (d, J = 11.5 Hz, 1H), 5.70 (s, 1H), 7.24–7.35 (m, 8H). Anal. Calcd for $C_{19}H_{23}ClOS$: C, 68.14; H, 6.92. Found: C, 68.07; H, 7.06.

1-{[(1,1-Dimethylethyl)sulfanyl]methyl}2-[methoxy(4-methoxyphenyl)methyl]benzene (2c): a pale-yellow oil; R_f 0.36 (CH_2Cl_2/hexane 1:1); IR (neat) 1611, 1249, 1091 cm^{-1}; ^1H NMR δ 1.37 (s, 9H), 3,40 (s, 3H), 3.79 (s, 3H), 3.66 (d, J = 11.5 Hz, 1H), 3.71 (d, J = 11.5 Hz, 1H), 5.69 (s, 1H), 6.85 (d, J =

8.6 Hz, 2H), 7.21–7.31 (m, 5H), 7.45 (d, *J* = 7.4 Hz, 1H). HR-MS (EI). Calcd for $C_{20}H_{26}O_2S$ (M): 330.1654. Found: *m/z* 330.1648.

1-[(3,4-Dimethoxyphenyl)(methoxy)methyl]-2-{[(1,1-dimethylethyl)sulfanyl]methyl}benzene (2d): a colorless oil; R_f 0.38 (AcOEt/hexane 1:5); IR (neat) 1606 cm^{-1}; ^1H NMR δ 1.38 (s, 9H), 3.41 (s, 3H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 5.68 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.93 (d, *J* = 1.7 Hz, 1H), 7.21–7.27 (m, 2H), 7.32 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.41 (dd, *J* = 7.4, 1.7 Hz, 1H). HR-MS (EI). Calcd for $C_{21}H_{28}O_3S$ (M): 360.1759. Found: *m/z* 360.1761.

1-[(Biphenyl-4-yl)(methoxy)methyl]-2-{[(1,1-dimethylethyl)sulfanyl]methyl}benzene (2e): a white solid; mp 72–74 ˚C (hexane/CH_2Cl_2); IR (KBr) 1600 cm^{-1}; ^1H NMR δ 1.39 (s, 9H), 3.46 (s, 3H), 3.72 (d, *J* = 11.5 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 5.79 (s, 1H), 7.25 (td, *J* = 7.4, 1.1 Hz, 1H), 7.29 (td, *J* = 7.4, 1.7 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.41–7.47 (m, 5H), 7.55–7.58 (m, 4H). Anal. Calcd for $C_{25}H_{28}OS$: C, 79.74; H, 7.50; S, 8.51. Found: C, 79.84; H, 7.78; S, 8.45.

4-Chloro-1-{[(1,1-dimethylethyl)sulfanyl]methyl}-2-[methoxy(phenyl)methyl]benzene (2f): a colorless oil; R_f 0.30 (AcOEt/hexane 1:5); IR (neat) 1096 cm^{-1}; ^1H NMR δ 1.35 (s, 9H), 3.41 (s, 3H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.67 (d, *J* = 11.5 Hz, 1H), 5.66 (s, 1H), 7.19 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.25–7.35 (m, 6H), 7.45 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for $C_{19}H_{23}ClOS$: C, 68.14; H, 6.92. Found: C, 68.35; H, 6.67.

4-Chloro-1-{[(1,1-dimethylethyl)sulfanyl]methyl}-2-[methoxy(4-methoxyphenyl)methyl]benzene (2g): a colorless oil; R_f 0.50 (AcOEt/hexane 1:10); IR (neat) 1611, 1250, 1094 cm^{-1}; ^1H NMR δ 1.35 (s, 9H), 3.39 (s, 3H), 3.59 (d, *J* = 12.0 Hz, 1H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 5.61 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.19 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H). HR-MS (EI). Calcd for $C_{20}H_{25}ClO_2S$ (M): 364.1264. Found: *m/z* 364.1270.

1-{[(1,1-Dimethylethyl)sulfanyl]methyl}-4-methoxy-2-[methoxy(phenyl)methyl]benzene (2h): a white solid; mp 72–75 ˚C (hexane/CH_2Cl_2); IR (KBr) 1612, 1284, 1084 cm^{-1}; ^1H NMR δ 1.37 (s, 9H), 3.43 (s, 3H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 3.78 (s, 3H), 5.71 (s, 1H), 6.77 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.02 (d, *J* = 2.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.31–7.35 (m, 5H). Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93. Found: C, 72.44; H, 3.12.

1-{[(1,1-Dimethylethyl)sulfanyl]methyl}-4,5-dimethoxy-2-[methoxy(phenyl)methyl]benzene (2i): a colorless oil; R_f 0.24 (AcOEt/hexane 1:7); IR (neat) 1607, 1514, 1097 cm^{-1}; ^1H NMR δ 1.38 (s, 9H), 3.42 (s, 3H), 3.66 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 5.66 (s, 1H), 6.83 (s, 1H), 6.93 (s, 1H), 7.24–7.35 (m, 5H). HR-MS (EI). Calcd for $C_{21}H_{28}O_3S$ (M): 360.1759. Found: *m/z* 360.1762.

1-[(4-Chlorophenyl)(methoxy)methyl]-2-{[(1,1-dimethylethyl)sulfanyl]methyl}-4,5-dimethoxybenzene (2j): a white solid; mp 122–124 ˚C (hexane/CH_2Cl_2); IR (KBr) 1609, 1506, 1094 cm^{-1}; ^1H NMR δ 1.37

(s, 9H), 3.40 (s, 3H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.70 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 5.62 (s, 1H), 6.83 (s, 1H), 6.85 (s, 1H), 7.26–7.30 (m, 4H). Anal. Calcd for $C_{21}H_{27}ClO_3S$: C, 63.86; H, 6.89; S, 8.12. Found: C, 63.85; H, 7.13; S, 8.25.

General Procedure for the Preparation of 1,3-Dihydrobenzo[*c*]thiophenes (3). To a stirred solution of **2** (1.0 mmol) in MeCN (10 mL) at 0 ˚C was added dropwise concentrated HBr (0.19 g, 1.0 mmol). Stirring was continued at the temperature indicated in Table 1 until consumption of the starting material had been confirmed by TLC (SiO_2; CH_2Cl_2/hexane 1:5) or ^{1}H NMR. Saturated aqueous $NaHCO_3$ (20 mL) was added and the organic solvent was evaporated. The resulting mixture was extracted with AcOEt (3 × 15 mL) and combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to afford **3**.

1-Phenyl-1,3-dihydrobenzo[*c*]thiophene (3a): a colorless oil; R_f 0.45 (CH_2Cl_2/hexane 1:5). The spectra data (IR, ^{1}H NMR) were identical to those reported previously.[5]

1-(4-Chlorophenyl)-1,3-dihydrobenzo[*c*]thiophene (3b): a colorless oil; R_f 0.58 (CH_2Cl_2/hexane 1:2); IR (neat) 1486 cm^{-1}; ^{1}H NMR δ 4.35 (d, *J* = 13.7 Hz, 1H), 4.42 (dd, *J* = 13.7, 2.3 Hz, 1H), 5.75 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.16–7.27 (m, 6H), 7.30 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 37.85, 57.12, 124.71, 125.46, 127.12, 127.23, 128.74, 129.67, 133.12, 140.53, 142.52, 143.62. HR-MS (EI). Calcd for $C_{14}H_{11}ClS$ (M): 246.0270. Found: *m/z* 246.0272. Anal. Calcd for $C_{14}H_{11}ClS$: C, 68.15; H, 4.49. Found: C, 68.02; H, 4.80.

1-(4-Methoxyphenyl)-1,3-dihydrobenzo[*c*]thiophene (3c): a white solid; mp 87–88 ˚C (hexane/CH_2Cl_2); IR (KBr) 1611, 1511, 1250, 1032 cm^{-1}; ^{1}H NMR δ 3.79 (s, 3H), 4.34 (d, *J* = 13.7 Hz, 1H), 4.41 (dd, *J* = 13.7, 2.3 Hz, 1H), 5.77 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.23 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 37.67, 55.25, 57.32, 113.93, 124.60, 125.51, 126.92, 126.95, 129.43, 135.91, 141.00, 144.36, 158.86. HR-MS (DART). Calcd for $C_{15}H_{15}OS$ (M+H): 243.0843. Found: *m/z* 243.0837. Anal. Calcd for $C_{15}H_{14}OS$: C, 74.35; H, 5.82. Found: C, 74.18; H, 5.89.

1-(3,4-Dimethoxyphenyl)-1,3-dihydrobenzo[*c*]thiophene (3d): a colorless viscous oil; R_f 0.38 (AcOEt/hexane 1:5); IR (neat) 1603, 1513, 1262, 1028 cm^{-1}; ^{1}H NMR δ 3.81 (s, 3H), 3.86 (s, 3H), 4.34 (d, *J* = 13.7 Hz, 1H), 4.40 (dd, *J* = 13.7, 1.7 Hz, 1H), 5.77 (s, 1H), 6.79–6.86 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.24 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 37.65, 55.83, 55.87, 57.79, 110.85, 111.37, 120.63, 124.62, 125.48, 126.95, 126.98, 136.06, 140.51, 144.15, 148.42, 149.10. HR-MS (EI). Calcd for $C_{16}H_{16}O_2S$ (M): 272.0871. Found: *m/z* 272.0876. Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.31; H, 6.07.

1-(Biphenyl-4yl)-1,3-dihydrobenzo[*c*]thiophene (3e): a white solid; mp 118–120 ˚C (hexane/CH_2Cl_2); IR (KBr) 1485, 1450 cm^{-1}; ^{1}H NMR δ 4.38 (d, *J* = 13.7 Hz, 1H), 4.47 (d, *J* = 13.7 Hz, 1H), 5.84 (s, 1H),

7.01 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.32–7.35 (m, 4H), 7.43 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 37.88, 57.48, 124.67, 125.62, 127.04, 127.06, 127.09, 127.24, 127.36, 128.69, 128.71, 140.28, 140.58, 140.71, 143.00, 143.91. HR-MS (EI). Calcd for $C_{20}H_{16}S$ (M): 288.0973. Found: *m/z* 288.0975. Anal. Calcd for $C_{20}H_{16}S$: C, 83.29; H, 5.59; S, 11.12. Found: C, 83.20; H, 5.70; S, 11.02.

6-Chloro-1-phenyl-1,3-dihydrobenzo[*c*]thiophene (3f): a colorless oil; R_f 0.50 (CH_2Cl_2/hexane 1:3); IR (neat) 1478, 1078 cm^{-1}; ^{1}H NMR δ 4.29 (d, *J* = 14.3 Hz, 1H), 4.38 (dd, *J* = 14.3, 2.3 Hz, 1H), 5.72 (s, 1H), 6.91 (s, 1H), 7.19–7.27 (m, 5H), 7.32 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 37.22, 57.45, 125.56, 125.61, 127.30, 127.71, 128.31, 128.75, 133.00, 139.14, 143.01, 146.17. HR-MS (EI). Calcd for $C_{14}H_{11}ClS$ (M): 246.0270. Found: *m/z* 246.0276. Anal. Calcd for $C_{14}H_{11}ClS$: C, 68.15; H, 4.49. Found: C, 68.03; H, 4.12.

6-Chloro-1-(4-methoxyphenyl)-1,3-dihydrobenzo[*c*]thiophene (3g): a white solid; mp 80–82 ˚C (hexane/CH_2Cl_2); IR (KBr) 1610, 1511, 1262, 1028 cm^{-1}; ^{1}H NMR δ 3.80 (s, 3H), 4.28 (d, *J* = 13.7 Hz, 1H), 4.44 (dd, *J* = 13.7, 2.3 Hz, 1H), 5.71 (s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.89 (br s, 1H), 7.19–7.22 (m, 4H); ^{13}C NMR δ 37.06, 55.29, 56.97, 114.12, 125.55, 125.57, 127.20, 129.48, 132.96, 134.94, 139.07, 146.51, 159.13. HR-MS (EI). Calcd for $C_{15}H_{13}ClOS$ (M): 276.0376. Found: *m/z* 276.0389. Anal. Calcd for $C_{15}H_{13}ClOS$: C, 65.09; H, 4.73; S, 11.58. Found: C, 64.98; H, 4.96; S, 11.82.

6-Methoxy-1-phenyl-1,3-dihydrobenzo[*c*]thiophene (3h): a pale-yellow solid; mp 37–39 ˚C (hexane); IR (KBr) 1607, 1494, 1273, 1030 cm^{-1}; ^{1}H NMR δ 3.67 (s, 3H), 4.25 (d, *J* = 13.2 Hz, 1H), 4.35 (dd, *J* = 13.2, 1.1 Hz, 1H), 5.72 (s, 1H), 6.44 (s, 1H), 6.79 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.21–7.34 (m, 5H); ^{13}C NMR δ 37.06, 55.35, 57.75, 110.28, 113.43, 125.02, 127.34, 128.21, 128.55, 132.64, 143.78, 145.53, 159.01. HR-MS (EI). Calcd for $C_{15}H_{14}OS$ (M): 242.0765. Found: *m/z* 242.0769. Anal. Calcd for $C_{15}H_{14}OS$: C, 74.35; H, 5.82. Found: C, 74.19; H, 5.81.

5,6-Dimethoxy-1-phenyl-1,3-dihydrobenzo[*c*]thiophene (3i): a yellow oil; R_f 0.31 (AcOEt/hexane 1:5); IR (neat) 1605, 1508, 1282, 1097 cm^{-1}; ^{1}H NMR δ 3.72 (s, 3H), 3.89 (s, 3H), 4.29 (d, *J* = 13.7 Hz, 1H), 4.41 (dd, *J* = 13.7, 2.9 Hz, 1H), 5.74 (s, 1H), 6.41 (s, 1H), 6.79 (s, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR δ 37.81, 55.86, 55.87, 57.85, 106.69, 107.59, 127.28, 128.02, 128.54, 132.24, 135.49, 141.16, 148.34, 148.38. HR-MS (EI). Calcd for $C_{16}H_{16}O_2S$ (M): 272.0871. Found: *m/z* 272.0869. Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.21; H, 5.97.

1-(4-Chlorophenyl)-5,6-dimethoxy-1,3-dihydrobenzo[*c*]thiophene (3j): a pale-yellow solid; mp 91–93 ˚C (hexane/CH_2Cl_2); IR (KBr) 1603, 1509, 1279, 1094 cm^{-1}; ^{1}H NMR δ 3.73 (s, 3H), 3.89 (s, 3H), 4.28 (d, *J* = 13.2 Hz, 1H), 4.39 (dd, *J* = 13.2, 2.3 Hz, 1H), 5.70 (s, 1H), 6.36 (s, 1H), 6.78 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H); ^{13}C NMRδ 37.90, 55.96, 55.98, 57.25, 106.83, 107.54, 128.76, 129.50, 132.29, 133.06, 135.13, 142.82, 148.56, 148.65. HR-MS (EI). Calcd for $C_{16}H_{15}ClO_2S$ (M): 306.0481.

Found: *m/z* 306.0489. Anal. Calcd for $C_{16}H_{15}ClO_2S$: C, 62.64; H, 4.93; S, 10.45. Found: C, 62.47; H, 5.03; S, 10.52.

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