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A FACILE SYNTHESIS OF 4-ARYL-1*H*-2-BENZOTHIOPYRAN-3-CARBOXYLIC ACID DERIVATIVES FROM *o*-BROMOBENZYL MERCAPTANS

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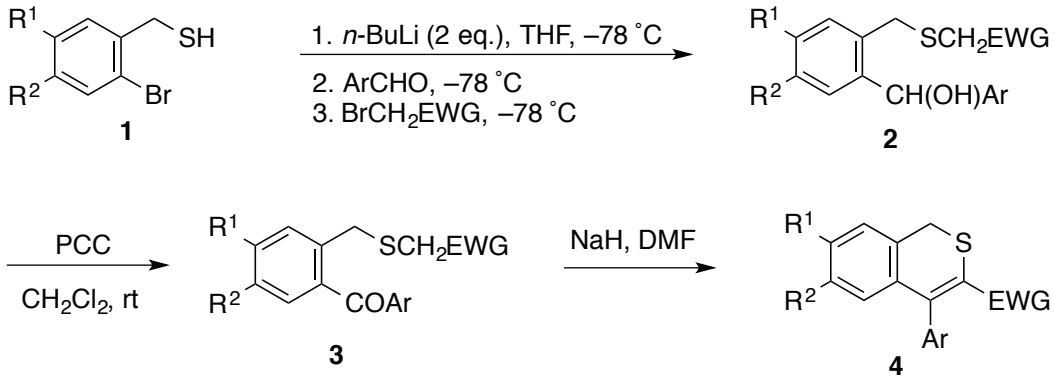
Abstract – The synthesis of 4-aryl-1*H*-2-benzothiopyran-3-carboxylic acid derivatives by a sodium hydride-mediated thiopyran ring formation of 2-[(2-aroylphenyl)methylsulfanyl]acetic acid derivatives is reported. The precursors were prepared by successive treatment of lithium *o*-lithiobenzyl mercaptides, which were generated by the reaction of *o*-bromobenzyl mercaptans with two equivalents of butyllithium, with aromatic aldehydes and 2-bromoacetonitrile or *tert*-butyl 2-bromoacetate, followed by oxidation of the resulting sulfanyl alcohols with pyridinium chlorochromate (PCC).

Some compounds having the 1*H*-2-benzothiopyran (isothiochromene) skeleton have been reported to exhibit biological activities.[1] 4-Substituted derivatives are usually prepared using the procedure of Padwa *et al*.,[2] which involves the reaction of 1*H*-2-benzothiopyran-4(3*H*)-one (isothiochroman-4-one) with Grignard reagents followed by dehydration with concentrated sulfuric acid. We recently reported that these derivatives have also been more conveniently formed through iodine-mediated cyclization of α-substituted *o*-[(*tert*-butylsulfanyl)methyl]styrenes, derived from α-substituted *o*-bromostyrenes using an easily operated four-step sequence.[3] However, only few methods for the preparation of 3,4-disubstituted 1*H*-2-benzothiopyrans have been recorded, though Spencer *et al*. have demonstrated the synthesis by the reaction of cyclopalladated compounds, derived from $Pd(dba)_2$ and *tert*-butyl *o*-iodobenzyl sulfide, with diphenylacetylene, ethyl 3-phenylpropynoate and phenylpropynal.[4] Accordingly, we decided to develop a facile method for the preparation of a new type of 3,4-disubstituted

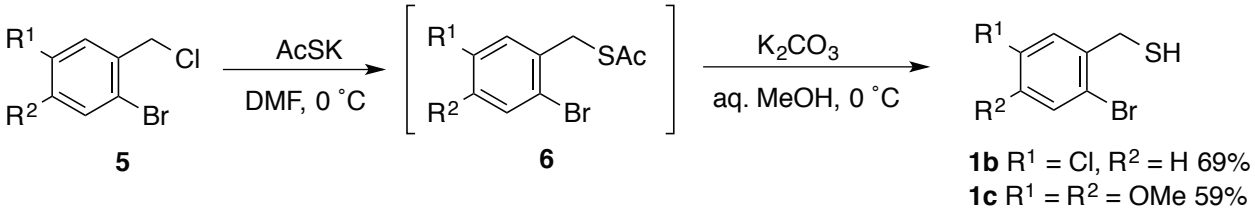
1*H*-2-benzothiopyrans from readily available starting materials. We envisioned that the successive reaction of lithium *o*-lithiobenzyl mercaptides with aromatic aldehydes and $BrCH_2EWGs$, followed by oxidation, could afford useful intermediates for base-mediated cyclization to the desired 1*H*-2-benzothiopyran derivatives. Herein, we wish to report the results of our investigation which offer a convenient method for the synthesis of 4-aryl-1*H*-2-benzothiopyran-3-carboxylic acid derivatives (**4**). Although there have been few reports on the synthesis of 1*H*-2-benzothiopyran derivatives like **4**, some 4-aryl-1*H*-2-benzothiopyran-3-carboxylic acid derivatives have been utilized as precursors for the preparation of anticholesteremics.[5] To the best of our knowledge, this is the first reports on the generation of lithium *o*-lithiobenzyl mercaptides and their utilization to the synthesis of heterocycles.



Scheme 1

Our process for the preparation of **4** from *o*-bromobenzyl mercaptans (**1**) is illustrated in Scheme 1. Initial studies were carried out using commercially available *o*-bromobenzyl mercaptan (**1a**). Thus, compound (**1a**) was treated with two equivalents of butyllithium in THF at –78 ˚C to generate lithium *o*-lithiobenzyl mercaptide, which was allowed to react with aromatic aldehydes and then $BrCH_2EWGs$ at the same temperature. After aqueous workup and the subsequent purification using column chromatography on silica gel, sulfanyl alcohols (**2**) were obtained. The scope of the procedure was investigated using several aromatic aldehydes and two $BrCH_2EWGs$ (EWG = CO_2t-Bu and CN) (Table 1, Entries 1-7). The results show that relatively good yields of sulfanyl alcohols (**2**) were obtained in general from aromatic aldehydes including electron-neutral (Entries 1 and 2), electron-deficient (Entries 4 and 5), electron-rich aromatic (Entries 3 and 6) examples. 2-Naphthaldehyde was also usable in the reaction (Entry 7). Then, *o*-bromobenzyl mercaptans bearing substituent(s) on the benzene nucleus (**1b**) and (**1c**), which were unknown compounds but could be easily prepared from *o*-bromobenzyl chlorides (**5b**) and (**5c**) *via* the formation of *S*-(*o*-bromobenzyl) thioacetates (**6b**) and (**6c**), respectively (Scheme 2), were also used in the present transformation. Unfortunately, however, the yields of the corresponding desired sulfanyl alcohols

(**2h-j**) from these mercaptans were somewhat lower (Entries 8-10) than those from **1a**, though the reason(s) for these results is not clear yet.



Scheme 2

These sulfanyl alcohols (**2**) were then transformed into the corresponding sulfanyl ketones (**3**) in good yields on treatment with pyridinium chlorochromate (PCC) in dichloromethane at room temperature. The yields of **3** are also compiled in Table 1.

Table 1. Preparation of sulfanyl ketone precursors (**3**)

Entry	**1**	R^1	R^2	Ar in ArCHO	EWG	**2**	Yield/%[a]	**3**	Yield/%[a]
1	**1a**	H	H	Ph	CO_2t-Bu	**2a**	79	**3a**	82
2	**1a**	H	H	Ph	CN	**2b**	68	**3b**	84
3	**1a**	H	H	*o*-Tol	CN	**2c**	67	**3c**	91
4	**1a**	H	H	4-ClC_6H_4	CO_2t-Bu	**2d**	60	**3d**	76
5	**1a**	H	H	4-ClC_6H_4	CN	**2e**	62	**3e**	84
6	**1a**	H	H	4-$MeOC_6H_4$	CN	**2f**	68	**3f**	83
7	**1a**	H	H	naphthalen-2-yl	CN	**2g**	62	**3g**	88
8	**1b**	Cl	H	Ph	CO_2t-Bu	**2h**	49	**3h**	88
9	**1b**	Cl	H	Ph	CN	**2i**	47	**3i**	89
10	**1c**	MeO	MeO	Ph	CN	**2j**	50	**3j**	84

[a] Yields of isolated products.

Table 2. Preparation of 3,4-disubstituted 1*H*-2-benzothiopyran (**4**)

Entry	**3**	R^1	R^2	Ar	EWG	Temp	**4**	Yield/%[a]
1	**3a**	H	H	Ph	CO_2t-Bu	rt	**4a**	59
2	**3b**	H	H	Ph	CN	0 ˚C	**4b**	81
3	**3c**	H	H	*o*-Tol	CN	0 ˚C	**4c**	88
4	**3d**	H	H	4-ClC_6H_4	CO_2t-Bu	rt	**4d**	62
5	**3e**	H	H	4-ClC_6H_4	CN	0 ˚C	**4e**	71
6	**3f**	H	H	4-$MeOC_6H_4$	CN	0 ˚C	**4f**	76
7	**3g**	H	H	naphthalen-2-yl	CN	0 ˚C	**4g**	79
8	**3h**	Cl	H	Ph	CO_2t-Bu	rt	**4h**	54
9	**3i**	Cl	H	Ph	CN	0 ˚C	**4i**	81
10	**3j**	MeO	MeO	Ph	CN	0 ˚C	**4j**	76

[a] Yields of isolated products.

Treatment of **3** with sodium hydride in DMF resulted in the formation of the desired 1*H*-2-benzothiopyran derivatives (**4**). However, it should be noted that reaction temperature of this step was dependent on EWGs. The cyclization of the precursors with a cyano substituent proceeded rapidly at 0 ˚C to afford the corresponding products in relatively good yields (Table 2, Entries 2, 3, 5-7, 9, and 10). However, the progress of cyclization of the precursors with a *tert*-butoxycarbonyl substituent was very sluggish at the temperature and room temperature was required for adequate progress and the yields of the corresponding products were only moderate (Entries 1, 4, and 8). These results may be due to the difference of electron-withdrawing properties between these EWGs.

In conclusion, 4-aryl-1*H*-2-benzothiopyran-3-carboxylic acid derivatives have synthesized concisely from *o*-bromobenzyl mercaptans. As the features of the present method are the readily availability of the starting materials and the ease of experimental manipulations, it may be of value in organic synthesis.

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 and ^{13}C NMR spectra were recorded in $CDCl_3$ 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 Thermo Scientific Exactive spectrometer. 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. 1-Bromo-4-chloro-2-(chloromethyl)benzene[6] and 1-bromo-2-(chloromethyl)-4,5-dimethoxybenzene[7] were prepared by the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of (2-Bromophenyl)methanethiols (1). (2-Bromo-5-chlorophenyl)methanethiol (1b). To a stirred solution of AcSK (0.23 g, 2.0 mmol) in DMF at 0 ˚C was added a solution of 1-bromo-4-chloro-2-(chloromethyl)benzene (0.48 g, 2.0 mmol) in DMF (6 mL) dropwise and stirring was continued for 15 min at the same temperature before addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with AcOEt (3 × 15 mL), and the combined extracts were washed with H_2O (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual crude thioacetate was dissolved in MeOH (8 mL) and the solution was cooled to 0 ˚C. To this solution, a solution of K_2CO_3 (0.28 g, 2.0 mmol) in H_2O (2 mL) was added under stirring and it was continued for 20 min. After addition of saturated aqueous NH_4Cl (20 mL), most of MeOH was evaporated and the resulting mixture was worked up as described above. The residue was purified by column

chromatography on SiO_2 to afford **1b** (0.33 g, 69%); a colorless oil; R_f 0.49 (hexane); IR (neat) 2569 cm^{-1}; ^1H NMR δ 2.00 (t, *J* = 8.6 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 2H), 7.09 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.38 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 29.3, 121.4, 128.8, 129.9, 133.7, 134.1, 142.2. HR-MS (DART, negative). Calcd for C_7H_5BrClS (M–H): 234.8984. Found: *m/z* 234.8993.

(2-Bromo-4,5-dimethoxyphenyl)methanethiol (1c): yield: 59%; a white solid; mp 41–42 ˚C (pentane); IR (KBr) 2537, 1602 cm^{-1}; ^1H NMR δ 1.98 (t, *J* = 8.0 Hz, 1H), 3.78 (d, *J* = 8.0 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.88 (s, 1H), 7.00 (s, 1H); ^{13}C NMR δ 29.4, 56.1, 56.2, 112.4, 113.4, 115.6, 132.4, 148.66, 148.69. HR-MS (DART, negative). Calcd for $C_9H_{10}BrO_2S$ (M–H): 260.9585. Found: *m/z* 260.9587.

Typical Procedure for the Preparation of Sulfanyl Alcohols (2). 1,1-Dimethylethyl 2-[({2-[Hydroxy(phenyl)methyl]phenyl}methyl)sulfanyl]acetate (2a). To a stirred solution of **1a** (0.41 g, 2.0 mmol) in THF (12 ml) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 4.0 mmol) dropwise. After 5 min, PhCHO (0.11 g, 1.0 mmol) and $BrCH_2CO_2t$-Bu (0.20 g, 1.0 mmol) were successively added and stirring was continued for an additional 10 min before addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with AcOEt (3 × 15 mL), and the combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **2a** (0.54 g, 79%); a colorless oil; R_f 0.39 (AcOEt/hexane 1:6); IR (neat) 3446, 1723, 1601 cm^{-1}; ^1H NMR δ 1.45 (s, 9H), 3.03–3.10 (m, 3H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 6.28 (d, *J* = 2.3 Hz, 1H), 7.23–7.28 (m, 5H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 27.9, 33.8, 34.0, 72.0, 81.9, 126.7, 127.3, 127.6, 128.0, 128.3, 128.6, 130.8, 134.4, 142.5, 142.9, 169.6. HR-MS (DART, positive). Calcd for $C_{20}H_{28}NO_3S$ (M+NH_4): 362.1784. Found: *m/z* 362.1786.

2-[({2-[Hydroxy(phenyl)methyl]phenyl}methyl)sulfanyl]acetonitrile (2b): a colorless oil; R_f 0.34 (AcOEt/hexane 1:3); IR (neat) 3446, 2245, 1600 cm^{-1}; ^1H NMR δ 2.54 (s, 1H), 3.09 (d, *J* = 17.2 Hz, 1H), 3.14 (d, *J* = 17.2 Hz, 1H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 6.23 (s, 1H), 7.29–7.35 (m, 8H), 7.48 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 16.5, 33.6, 72.5, 116.4, 126.8, 127.8, 128.0, 128.4, 128.5, 128.6, 130.7, 132.8, 142.0, 142.6. HR-MS (DART, positive). Calcd for $C_{16}H_{19}N_2OS$ (M+NH_4): 287.1213. Found: *m/z* 287.1211.

2-[({2-[Hydroxy(2-methylphenyl)methyl]phenyl}methyl)sulfanyl]acetonitrile (2c): a colorless oil; R_f 0.32 (AcOEt/hexane 1:3); IR (neat) 3429, 2245, 1603 cm^{-1}; ^1H NMR δ 2.21 (s, 3H), 2.49 (d, *J* = 4.6 Hz, 1H), 3.11 (d, *J* = 17.2 Hz, 1H), 3.17 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 6.37 (d, *J* = 4.6 Hz, 1H), 7.17 (dd, *J* = 8.6, 3.4 Hz, 1H), 7.21–7.31 (m, 6H), 7.38 (dd, *J* = 9.2, 3.4 Hz, 1H); ^{13}C NMR δ 16.4, 19.3, 33.6, 69.4, 116.4, 126.2, 126.3, 127.8, 128.0, 128.2, 128.4, 130.6, 130.7, 133.2, 135.6, 140.3, 141.2. HR-MS (DART, negative). Calcd for $C_{17}H_{16}NOS$ (M–H): 282.0953. Found: *m/z* 282.0956.

1,1-Dimethylethyl 2-[({2-[(4-Chlorophenyl)(hydroxy)methyl]phenyl}methyl)sulfanyl]acetate (2d): a colorless oil; R_f 0.40 (AcOEt/hexane 1:5); IR (neat) 3440, 1723 cm^{-1}; ^1H NMR δ 1.43 (s, 9H), 3.06 (s, 2H), 3.24 (br s, 1H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 6.25 (br s, 1H), 7.27–7.33 (m, 8H); ^{13}C NMR δ 27.9, 33.9, 34.0, 71.4, 82.0, 127.8, 128.0, 128.2, 128.4, 128.8, 130.9, 133.0, 134.5, 141.6, 142.2, 169.5. HR-MS (DART, positive). Calcd for $C_{20}H_{27}ClNO_3S$ (M+NH_4): 396.1395. Found: *m/z* 396.1382.

2-[({2-[(4-Chlorophenyl)(hydroxy)methyl]phenyl}methyl)sulfanyl]acetonitrile (2e): a colorless oil; R_f 0.32 (AcOEt/hexane 1:3); IR (neat) 3431, 2245 cm^{-1}; ^1H NMR δ 2.59 (br s, 1H), 3.07 (d, *J* = 17.8 Hz, 1H), 3.10 (d, *J* = 17.8 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.90 (d, *J* = 13.2 Hz, 1H), 6.13 (s, 1H), 7.18–7.25 (m, 7H), 7.32 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 16.5, 33.6, 71.8, 116.4, 128.18, 128.21, 128.5, 128.6, 128.7, 130.8, 132.9, 133.5, 141.1, 141.7. HR-MS (ESI, positive). Calcd for $C_{16}H_{14}ClNNaOS$ (M+Na): 326.0383. Found: *m/z* 326.0377.

2-[({2-[(Hydroxy)(4-methoxyphenyl)methyl]phenyl}methyl)sulfanyl]acetonitrile (2f): a colorless oil; R_f 0.24 (AcOEt/hexane 1:3); IR (neat) 3460, 2244, 1610 cm^{-1}; ^1H NMR δ 2.47 (s, 1H), 3.09 (d, *J* = 17.2 Hz, 1H), 3.13 (d, *J* = 17.2 Hz, 1H), 3.79 (s, 3H), 3.86 (d, *J* = 13.7 Hz, 1H), 3.91 (d, *J* = 13.7 Hz, 1H), 6.19 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 7.24–7.35 (m, 5H), 7.55 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 16.5, 33.6, 55.3, 72.1, 114.0, 116.5, 127.8, 127.9, 128.3, 128.4, 130.7, 132.6, 134.7, 142.2, 159.2. HR-MS (ESI, positive). Calcd for $C_{17}H_{17}NNaO_2S$ (M+Na): 322.0878. Found: *m/z* 322.0871.

2-[({2-[(Hydroxy)(naphthalen-2-yl)methyl]phenyl}methyl)sulfanyl]acetonitrile (2g): a colorless oil; R_f 0.23 (AcOEt/hexane 1:3); IR (neat) 3441, 2245, 1601 cm^{-1}; ^1H NMR δ 2.71 (s, 1H), 3.19 (d, *J* = 17.2 Hz, 1H), 3.14 (d, *J* = 17.2 Hz, 1H), 3.95 (d, *J* = 13.7 Hz, 1H), 3.99 (d, *J* = 13.7 Hz, 1H), 6.38 (s, 1H), 7.29–7.32 (m, 3H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.46–7.49 (m, 3H), 7.78–7.82 (m, 3H), 7.82 (s, 1H); ^{13}C NMR δ 16.5, 33.6, 72.5, 116.4, 124.9, 125.4, 126.1, 126.3, 127.6, 128.0, 128.1, 128.4, 128.5, 128.6, 130.8, 132.9, 133.0, 133.2, 140.0, 141.8. HR-MS (ESI, positive). Calcd for $C_{20}H_{17}NNaOS$ (M+Na): 342.0929. Found: *m/z* 342.0926.

1,1-Dimethylethyl 2-[({5-Chloro-2-[(hydroxy)(phenyl)methyl]phenyl}methyl)sulfanyl]acetate (2h): a colorless oil; R_f 0.27 (AcOEt/hexane 1:5); IR (neat) 3436, 1723 cm^{-1}; ^1H NMR δ 1.44 (s, 9H), 3.06 (s, 2H), 3.10 (d, *J* = 2.9 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.85 (d, *J* = 13.7 Hz, 1H), 6.23 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.26–7.35 (m, 7H); ^{13}C NMR δ 27.9, 33.4, 34.0, 71.5, 82.1, 126.6, 127.6, 128.0, 128.5, 130.1, 130.4, 133.2, 136.5, 141.1, 142.5, 169.5. HR-MS (ESI, positive). Calcd for $C_{20}H_{23}ClNaO_3S$ (M+Na): 401.0954. Found: *m/z* 401.0947.

2-[({5-Chloro-2-[(hydroxy)(phenyl)methyl]phenyl}methyl)sulfanyl]acetonitrile (2i): a colorless oil; R_f 0.34 (AcOEt/hexane 1:3); IR (neat) 3445, 2246 cm^{-1}; ^1H NMR δ 2.51 (d, *J* = 3.4 Hz, 1H), 3.14 (d, *J* =

17.2 Hz, 1H), 3.18 (d, *J* = 17.2 Hz, 1H), 3.85 (d, *J* = 13.8 Hz, 1H), 3.89 (d, *J* = 13.8 Hz, 1H), 6.18 (d, *J* =3.4 Hz, 1H), 7.30–7.37 (m, 7H), 7.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 16.7, 33.2, 72.2, 116.2, 126.9, 128.1, 128.4, 128.8, 129.7, 130.3, 133.7, 134.9, 140.5, 142.1. HR-MS (DART, positive). Calcd for $C_{16}H_{14}ClKNOS$ (M+K): 342.0122. Found: *m/z* 342.0116.

2-[({2-[(Hydroxy)(phenyl)methyl]-4,5-dimethoxyphenyl}methyl)sulfanyl]acetonitrile (2j): a pale-yellow solid; mp 85–86 ˚C (hexane/CH_2Cl_2); IR (neat) 3508, 2243, 1607 cm^{-1}; ^{1}H NMR δ 2.51 (br s, 1H), 3.11 (d, *J* = 17.2 Hz, 1H), 3.16 (d, *J* = 17.2 Hz, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 3.91 (s, 2H), 6.19 (br s, 1H), 6.84 (s, 1H), 7.01 (s, 1H), 7.28–7.35 (m, 5H); ^{13}C NMR δ 16.4, 33.4, 55.9, 56.0, 72.1, 111.3, 113.6, 116.5, 124.6, 126.7, 127.7, 128.6, 134.6, 142.9, 148.2, 148.8. HR-MS (DART, positive). Calcd for $C_{18}H_{20}NO_3S$ (M+H): 330.1164. Found: *m/z* 330.1421.

Typical Procedure for the Preparation of Sulfanyl Ketones (3). 1,1-Dimethylethyl 2-{[(2-Benzoylphenyl)methyl]sulfanyl}acetate (3a). A mixture of **2a** (0.32 g, 0.93 mmol) and PCC (0.24 g, 1.1 mmol) in CH_2Cl_2 (12 mL) containing Celite 400 (1.2 g) was stirred at rt until disappearance of **2a** had been confirmed by TLC analyses on SiO_2. The mixture was filtered under reduced pressure and filtrate was concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **3a** (0.26 g, 82%); a colorless oil; R_f 0.51 (Et_2O/hexane 1:3); IR (neat) 1733, 1661 cm^{-1}; ^{1}H NMR δ 1.44 (s, 9H), 2.95 (s, 2H), 4.01 (s, 2H), 7.31–7.35 (m, 2H), 7.44–7.47 (m, 4H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 27.9, 33.5, 34.2, 81.5, 126.6, 128.3, 129.7, 130.2, 130.3, 131.1, 133.1, 137.6, 137.7, 138.3, 169.4, 197.9. HR-MS (DART, positive). Calcd for $C_{20}H_{23}O_3S$ (M+H): 343.1368. Found: *m/z* 343.1366.

2-{[(2-Benzoylphenyl)methyl]sulfanyl}acetonitrile (3b): a colorless oil; R_f 0.29 (Et_2O/hexane 1:2); IR (neat) 2244, 1661 cm^{-1}; ^{1}H NMR δ 3.13 (s, 2H), 4.09 (s, 2H), 7.28–7.46 (m, 6H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 16.6, 33.9, 116.3, 127.3, 128.5, 130.2, 130.3, 130.8, 131.1, 133.3, 136.4, 137.5, 137.9, 197.7. HR-MS (DART, positive). Calcd for $C_{16}H_{14}NOS$ (M+H): 268.0796. Found: *m/z* 268.0791.

2-({[2-(2-Methylbenzoyl)phenyl]methyl}sulfanyl)acetonitrile (3c): a colorless oil; R_f 0.31 (Et_2O/hexane 1:2); IR (neat) 2244, 1661 cm^{-1}; ^{1}H NMR δ 2.49 (s, 3H), 3.21 (s, 2H), 4.24 (s, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.32–7.46 (m, 6H), 7.55 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 16.7, 20.6, 34.3, 116.4, 125.4, 127.6, 130.4, 131.2, 131.38, 131.41, 131.5, 131.9, 136.9, 138.2, 138.3, 138.5, 199.8. HR-MS (DART, positive). Calcd for $C_{17}H_{16}NOS$ (M+H): 282.0952. Found: *m/z* 282.0938.

1,1-Dimethylethyl 2-({[2-(4-Chlorobenzoyl)phenyl]methyl}sulfanyl)acetate (3d): a colorless oil; R_f 0.38 (Et_2O/hexane 1:5); IR (neat) 1732, 1662 cm^{-1}; ^{1}H NMR δ 1.44 (s, 9H), 2.94 (s, 2H), 4.01 (s, 2H), 7.29–7.32 (m, 2H), 7.42–7.45 (m, 4H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 27.9, 33.5, 34.2, 81.6, 126.7,

128.7, 129.5, 130.5, 131.2, 131.6, 136.1, 137.7, 137.8, 139.6, 169.3, 196.6. HR-MS (DART, positive). Calcd for $C_{20}H_{22}ClO_3S$ (M+H): 377.0978. Found: *m/z* 377.0961.

2-({[2-(4-Chlorobenzoyl)phenyl]methyl}sulfanyl)acetonitrile (3e): a colorless oil; R_f 0.34 (Et_2O/hexane 1:2); IR (neat) 2244, 1661 cm^{-1}; ^1H NMR δ 3.13 (s, 2H), 4.09 (s, 2H), 7.35–7.49 (m, 6H), 7.73 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 16.7, 33.9, 116.3, 127.3, 128.8, 130.1, 131.0, 131.2, 131.6, 135.8, 136.5, 137.5, 139.9, 196.4. HR-MS (DART, positive). Calcd for $C_{16}H_{13}ClNOS$ (M+H): 302.0406. Found: *m/z* 302.0392.

2-({[2-(4-Methoxybenzoyl)phenyl]methyl}sulfanyl)acetonitrile (3f): a colorless oil; R_f 0.32 (Et_2O/hexane 1:1); IR (neat) 2244, 1652 cm^{-1}; ^1H NMR δ 3.15 (s, 2H), 3.88 (s, 3H), 4.07 (s, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.37 (br s, 2H), 7.46 (br s, 2H), 7.79 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 16.6, 33.9, 55.5, 113.7, 116.4, 127.2, 129.7, 130.29, 130.34, 130.9, 132.6, 135.9, 138.6, 163.8, 196.2. HR-MS (DART, positive). Calcd for $C_{17}H_{16}NO_2S$ (M+H): 298.0901. Found: *m/z* 298.0893.

2-({[2-(Naphthalen-2-ylcarbonoyl)phenyl]methyl}sulfanyl)acetonitrile (3g): a colorless oil; R_f 0.42 (AcOEt/hexane 1:1); IR (neat) 2243, 1652 cm^{-1}; ^1H NMR δ 3.16 (s, 2H), 4.13 (s, 2H), 7.39–7.63 (m, 6H), 7.88–7.99 (m, 4H), 8.21 (s, 1H); ^{13}C NMR δ 16.7, 34.1, 116.4, 125.2, 126.9, 127.3, 127.8, 128.5, 128.8, 129.7, 130.3, 130.8, 131.1, 132.3, 132.7, 134.8, 135.7, 136.4, 138.2, 197.6. HR-MS (DART, positive). Calcd for $C_{20}H_{19}N_2OS$ ($M+NH_4$): 335.1213. Found: *m/z* 335.1197.

1,1-Dimethylethyl 2-{[(2-Benzoyl-5-chlorophenyl)methyl]sulfanyl}acetate (3h): a colorless oil; R_f 0.42 (Et_2O/hexane 1:5); IR (neat) 1729, 1667 cm^{-1}; ^1H NMR δ 1.44 (s, 9H), 2.97 (s, 2H), 3.98 (s, 2H), 7.27–7.30 (m, 2H), 7.45–7.48 (m, 3H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 27.9, 33.2, 34.2, 81.7, 126.7, 128.4, 130.1, 131.0, 131.1, 133.3, 136.3, 136.6, 137.5, 140.1, 169.2, 196.8. HR-MS (DART, positive). Calcd for $C_{20}H_{22}ClO_3S$ (M+H): 377.0978. Found: *m/z* 377.0961.

2-{[(2-Benzoyl-5-chlorophenyl)methyl]sulfanyl}acetonitrile (3i): a colorless oil; R_f 0.31 (Et_2O/hexane 1:2); IR (neat) 2244, 1661 cm^{-1}; ^1H NMR δ 3.20 (s, 2H), 4.08 (s, 2H), 7.35 (s, 2H), 7.46–7.50 (m, 3H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 16.8, 33.7, 116.1, 127.4, 128.6, 130.2, 130.9, 131.6, 133.6, 136.3, 136.9, 137.2, 138.8, 196.6. HR-MS (DART, positive). Calcd for $C_{16}H_{13}ClNOS$ (M+H): 302.0406. Found: *m/z* 302.0398.

2-{[(2-Benzoyl-4,5-dimethoxyphenyl)methyl]sulfanyl}acetonitrile (3j): a white solid; mp 97–98 °C (hexane/CH_2Cl_2); IR (KBr) 2245, 1659 cm^{-1}; ^1H NMR δ 3.20 (s, 2H), 3.80 (s, 3H), 3.99 (s, 3H), 4.08 (s, 2H), 6.92 (s, 1H), 7.00 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 16.6, 33.9, 56.1, 56.2, 113.8 (2 overlapped Cs), 116.6, 128.4, 130.09, 130.13, 133.04 (2 overlapped Cs), 138.1, 147.4, 150.9, 196.9. HR-MS (DART, positive). Calcd for $C_{18}H_{18}NO_3S$ (M+H): 328.1007. Found: *m/z* 328.1000.

General Procedure for the Preparation of 1*H*-2-Benzothiopyrans (4). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in DMF (4 mL) at 0 ˚C was added a solution of **3** (1.0 mmol) in DMF (2 mL) dropwise and stirring was continued at the temperature indicated in Table 2 until consumption of the starting material had been confirmed by TLC analyses on SiO_2 (AcOEt/hexane 1:5). The resulting mixture was worked up as described for the preparation of **2** and the residual solid was recrystallized to give **4**.

1,1-Dimethylethyl 4-Phenyl-1*H*-2-benzothiopyran-3-carboxylate (4a): a white solid; mp 104–105 ˚C (hexane/CH_2Cl_2); IR (KBr) 1698, 1655 cm^{-1}; ^1H NMR δ 1.23 (s, 9H), 3.90 (s, 2H), 6.74 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.18–7.21 (m, 3H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.37–7.40 (m, 3H); ^{13}C NMR δ 27.5, 31.4, 82.1, 126.4, 127.2, 127.5, 127.8, 128.2, 128.3, 129.3, 129.5, 130.1, 135.4, 139.1, 140.5, 165.8. HR-MS (DART, positive). Calcd for $C_{20}H_{21}O_2S$ (M+H): 325.1262. Found: *m/z* 325.1256. Anal. Calcd for $C_{20}H_{20}O_2S$: C, 74.04; H, 6.21; S, 9.88. Found: C, 73.93; H, 6.15; S, 9.97.

4-Phenyl-1*H*-2-benzothiopyran-3-carbonitrile (4b): a pale-yellow solid; mp 116–117 ˚C (hexane/CH_2Cl_2); IR (KBr) 2209 cm^{-1}; ^1H NMR δ 3.98 (s, 2H), 6.87 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.36–7.39 (m, 3H), 7.45–7.48 (m, 3H); ^{13}C NMR δ 31.5, 103.4, 116.4, 126.8, 127.8, 128.6, 128.8, 129.3, 129.7, 130.5, 131.0, 133.8, 136.5, 151.2. HR-MS (DART). Calcd for $C_{16}H_{15}N_2S$ (M+NH_4): 267.0950. Found: *m/z* 267.0953. Anal. Calcd for $C_{16}H_{11}NS$: C, 77.08; H, 4.45; N, 5.62; S, 12.86. Found: C, 76.68; H, 4.41; N, 5.56; S, 12.94.

4-(2-Methylphenyl)-1*H*-2-benzothiopyran-3-carbonitrile (4c): a pale-yellow solid; mp 120–121 ˚C (hexane/CH_2Cl_2); IR (KBr) 2213 cm^{-1}; ^1H NMR δ 2.11 (s, 3H), 3.91 (d, *J* = 14.3 Hz, 1H), 4.07 (d, *J* = 14.3 Hz, 1H), 6.74 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.22–7.37 (m, 6H); ^{13}C NMR δ 19.5, 31.4, 104.6, 115.9, 126.3, 127.0, 127.5, 128.1, 129.3, 129.5, 129.8, 130.6, 131.0, 133.2, 136.0, 136.2, 150.9. HR-MS (DART, positive). Calcd for $C_{17}H_{14}NS$ (M+H): 264.0847. Found: *m/z* 264.0834.

1,1-Dimethylethyl 4-(4-Chlorophenyl)-1*H*-2-benzothiopyran-3-carboxylate (4d): a pale-yellow solid; mp 144–145 ˚C (hexane/CH_2Cl_2); IR (KBr) 1695 cm^{-1}; ^1H NMR δ 1.28 (s, 9H), 3.88 (s, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 7.11–7.16 (m, 3H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 27.6, 31.3, 82.4, 126.5, 127.3, 128.0, 128.4 (2 overlapped Cs), 129.5, 130.1, 130.9, 133.6, 135.0, 137.6, 139.3, 165.5. HR-MS (DART, positive). Calcd for $C_{20}H_{20}ClO_2S$ (M+H): 359.0872. Found: *m/z* 359.0858. Anal. Calcd for $C_{20}H_{19}ClO_2S$: C, 66.94; H, 5.34; S, 8.93. Found: C, 66.65; H, 4.98; S, 8.84.

4-(4-Chlorophenyl)-1*H*-2-benzothiopyran-3-carbonitrile (4e): a pale-yellow solid; mp 152–153 ˚C (hexane/CH_2Cl_2); IR (KBr) 2211 cm^{-1}; ^1H NMR δ 3.98 (s, 2H), 6.85 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 7.4 Hz,

2H); ^{13}C NMR δ 31.5, 104.0, 116.2, 127.0, 128.0, 128.6, 129.0, 130.5, 131.1, 131.2, 133.5, 134.92, 135.5, 149.9. HR-MS (ESI, positive). Calcd for $C_{16}H_{10}ClNNaS$ (M+Na): 306.0120. Found: *m/z* 306.0114. Anal. Calcd for $C_{16}H_{10}ClNS$: C, 67.72; H, 3.55; N, 4.94. Found: C, 67.60; H, 3.64; N, 4.74.

4-(4-Methoxyphenyl)-1*H*-2-benzothiopyran-3-carbonitrile (4f): a pale-yellow solid; mp 115–116 °C (hexane/CH_2Cl_2); IR (KBr) 2205, 1608 cm^{-1}; ^{1}H NMR δ 3.87 (s, 3H), 3.95 (s, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.19–7.23 (m, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 31.5, 55.3, 102.3, 114.0, 116.8, 126.8, 127.8, 128.7, 129.0, 130.88, 130.94, 131.1, 134.0, 151.2, 160.3. HR-MS (DART, positive). Calcd for $C_{17}H_{14}NOS$ (M+H): 280.0796. Found: *m/z* 280.0783. Anal. Calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01; S, 11.48. Found: C, 72.84; H, 4.67; N, 5.02; S, 11.24.

4-(Naphthalen-2-yl)-1*H*-2-benzothiopyran-3-carbonitrile (4g): a pale-yellow solid; mp 152–153 °C (hexane/CH_2Cl_2); IR (KBr) 2214 cm^{-1}; ^{1}H NMR δ 4.01 (s, 2H), 6.88 (d, *J* = 7.4 Hz, 1H), 7.17 (dd, *J* = 7.4, 6.9 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 7.37–7.42 (m, 2H), 7.55 (br s, 2H), 7.89–7.94 (m, 3H), 8.01 (s, 1H); ^{13}C NMR δ 31.6, 103.7, 116.5, 126.7, 126.9 (2 overlapped Cs), 127.1, 127.8, 127.9, 128.3, 128.4, 129.0, 129.5, 130.6, 131.0 (2 overlapped Cs), 133.0, 133.4, 133.9, 151.1. HR-MS (DART, positive). Calcd for $C_{20}H_{17}N_2S$ (M+NH_4): 317.1107. Found: *m/z* 317.1092. Anal. Calcd for $C_{20}H_{13}NS$: C, 80.24; H, 4.38; N, 4.68; S, 10.71. Found: C, 80.23; H, 4.27; N, 4.68; S, 10.50.

1,1-Dimethylethyl 7-Chloro-4-phenyl-1*H*-2-benzothiopyran-3-carboxylate (4h): a white solid; mp 105–106 °C (hexane); IR (KBr) 1690 cm^{-1}; ^{1}H NMR δ 1.16 (s, 9H), 3.78 (s, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.09–7.13 (m, 3H), 7.30–7.33 (m, 3H); ^{13}C NMR δ 27.5, 31.0, 82.3, 126.4, 127.3, 127.7, 128.1, 128.3, 129.4, 129.5, 131.7, 134.0, 134.8, 128.6, 139.7, 165.5. HR-MS (DART). Calcd for $C_{20}H_{20}ClO_2S$ (M+H): 359.0872. Found: *m/z* 359.0856.

7-Chloro-4-phenyl-1*H*-2-benzothiopyran-3-carbonitrile (4i): a pale-yellow solid; mp 120–121 °C (hexane/CH_2Cl_2); IR (KBr) 2214 cm^{-1}; ^{1}H NMR δ 3.97 (s, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 7.17 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.37 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.46–7.49 (m, 3H); ^{13}C NMR δ 31.2, 103.6, 116.1, 127.0, 128.0, 128.8, 129.5, 129.6, 130.1, 132.1, 132.4, 136.1, 136.6, 150.4. HR-MS (DART, positive). Calcd for $C_{16}H_{14}ClN_2S$ (M+NH_4): 301.0561. Found: *m/z* 301.0558. Anal. Calcd for $C_{16}H_{10}ClNS$: C, 67.72; H, 3.55; N, 4.94. Found: C, 67.40; H, 3.86; N, 4.91.

6,7-Dimethoxy-4-phenyl-1*H*-2-benzothiopyran-3-carbonitrile (4j): a pale-yellow solid; mp 150–151 °C (hexane/CH_2Cl_2); IR (KBr) 2209 cm^{-1}; ^{1}H NMR δ 3.59 (s, 3H), 3.92 (s, 2H), 3.93 (s, 3H), 6.34 (s, 1H), 6.73 (s, 1H), 7.39 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.45–7.48 (m, 3H); ^{13}C NMR δ 31.1, 55.9, 56.1, 100.2, 109.9, 112.3, 116.8, 124.2, 126.7, 128.6, 129.4, 129.7, 136.6, 148.1, 151.0, 151.2. HR-MS (DART, positive). Calcd for $C_{18}H_{16}NO_2S$ (M+H): 310.0901. Found: *m/z* 310.0893. Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.60; H, 4.98; N, 4.51.

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