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Synthesis of 4-Aryl-2-sulfenyl-2*H*-1-benzothiopyran Derivatives by Cyclization of [2-(1-Aryl-2-methoxyvinyl)phenylthio][methyl(or phenyl)thio]methyllithiums

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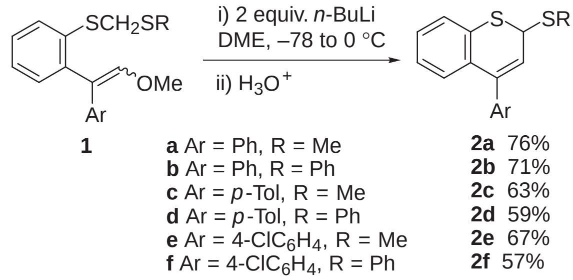
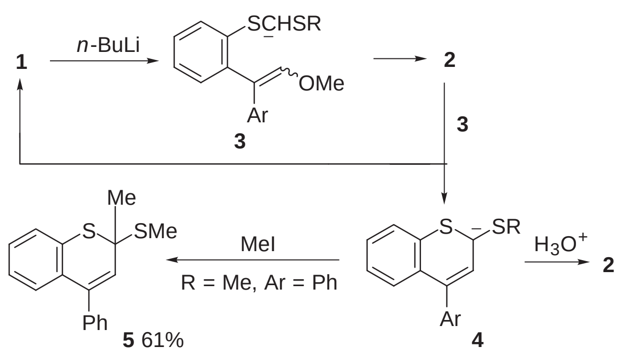
4-Aryl-2-methyl(or phenyl)thio-2*H*-1-benzothiopyrans have been prepared in satisfactory yields from the corresponding 1-(1-aryl-2-methoxyethenyl)-2-{[methyl(or phenyl)thiomethyl]thio}benzenes via lithiation of the carbon atom between the two sulfur atoms, followed by intramolecular cyclization with loss of lithium methoxide.

Compounds having a 2*H*-1-benzothiopyran skeleton are interesting from a biological point of view, because compounds with related skeletons exhibit a variety of biological activities.[1] However, only a few works on the synthesis of 2*H*-1-benzothiopyran derivatives have been reported to date.[2] Recently, Kaye and Nocanda reported a convenient Baylis–Hillman synthesis of 3-substituted 2*H*-1-benzothiopyrans.[2b] Accordingly, we became interested in developing a general method for the preparation of 2*H*-1-benzothiopyran derivatives. We now report a facile synthetic route to 4-aryl-2-sulfenyl-2*H*-1-benzothiopyrans **2**.[3]

Our procedure to construct the 2*H*-1-benzothiopyran skeleton is based on base-mediated cyclization of 1-(1-aryl-2-methoxyethenyl)-2-(sulfenylmethylthio)benzenes **1**,[4] which were easily prepared from readily available 2-mercaptobenzophenone[5,6] in two steps, as illustrated in Schemes 1 and 2. Thus, compounds **1** were treated with two molar amounts of butyllithium at −78 °C to generate the carbanions stabilized by two sulfur atoms **3**, and these carbanions were allowed to attack intramolecularly the α-carbon of the methoxyvinyl moiety by raising the reaction temperature to 0 °C to afford via the corresponding benzyl anion intermediates with loss of methoxide, products **2** in generally fair-to-good yields, as summarized in Scheme 1. The use of two molar amounts of butyllithium was essential for complete conversion. When the reaction was carried out using an equimolar amount of butyllithium, a low yield of **2** was obtained and a considerable amount of **1** was recovered.



Scheme 1.



Scheme 2.

The need for two molar amounts of butyllithium can be explained as follows (see, Scheme 2). The carbon atom between two sulfur atoms is first lithiated by butyllithium to generate the sulfur-stabilized carbanion **3**. This carbanion is cyclized to **2**, the 2-proton of which is removed upon reaction with **3** to generate benzothiopyran-2-yl carbanion **4**, and **3** reverts to **1**. Compound **1** is again converted into **2** by another butyllithium. The conversion of **2** into **4** may occur via the second equivalent of butyllithium. The carbanion **4** was protonated upon aqueous workup to give **2**. The existence of **4** in the reaction mixture was confirmed by the production of 2-methyl-2-methylthio-4-phenyl-2*H*-1-benzothiopyran (**5**). In other words, when the reaction between **1a** and two molar amounts of butyllithium was quenched with iodomethane, **5** was afforded in fair yield, as shown in Scheme 2. The formation of **5** was supported by its ^{1}H NMR spectrum, which has the signal for 3-H at δ 6.10. This value is very close to those of compounds **2**. If methylation occurred at the 4-position, the signal for 3-H would appear in further upfield.

In summary, we have demonstrated that a new type of 2*H*-1-benzothiopyran derivatives can be prepared conveniently. This synthesis may find some value in the synthesis of this type of heterocycles because of the ready availability of the starting materials and the ease of operations.

Experimental

{2-[(Methylthiomethyl)thio]phenyl}phenylmethanone. This compound was prepared by *S*-(methylthio)methylation of (2-mercaptophenyl)phenylmethanone[5] with chloromethyl methyl sulfide using NaH as a base in THF at 0 °C in 76% yield: a pale-yellow oil; R_f 0.41 (hexane–AcOEt 5:1); IR (neat) 1668 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.08 (3H, s), 3.92 (2H, s), 7.32–7.40 (2H, m), 7.44–7.50 (3H, m), 7.59 (1H, tt, $J = 7.3$ and 1.4 Hz), 7.62 (1H, d, $J = 7.3$ Hz), and 7.80 (2H, dd, $J = 8.3$ and 1.4 Hz). Calcd for $C_{15}H_{14}OS_2$: C, 65.66; H, 5.14; S, 23.37%. Found: C, 65.59; H, 5.24; S, 23.47%.

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1-(2-Methoxy-1-phenylethenyl)-2-[(methylthiomethyl)thio]benzene (1a). This compound was prepared by treatment of {2-[(methylthiomethyl)thio]}phenylmethanone with (methoxymethylene)triphenylphosphoran in THF at 0 °C in 66% yield: a pale-yellow oil; R_f 0.27 (hexane–Et_2O 8:1); *E*:*Z* = ca. 1:1; IR (neat) 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (1.5H, s), 2.06 (1.5H, s), 3.73 (1.5H, s), 3.80 (1.5H, s), 3.84 (1H, s), 3.88 (1H, s), 6.23 (0.5H, s, vinyl-H of *E*-isomer), 6.69 (0.5H, s, vinyl-H of *Z*-isomer), 7.11–7.43 (8.5H, m), and 7.50 (0.5H, dd, $J = 7.8$ and 0.9 Hz). Calcd for $C_{17}H_{18}OS_2$: C, 67.51; H, 6.00; S, 21.20%. Found: C, 67.37; H, 6.05; S, 21.27%.

Phenyl{2-[(phenylthiomethyl)thio]phenyl}methanone. This compound was prepared from (2-mercaptophenyl)phenylmethanone[5] and chloromethyl phenyl sulfide in a manner similar to that described for the preparation of {2-[(methylthiomethyl)thio]phenyl}phenylmethanone in 76% yield; a pale-yellow oil; R_f 0.15 (hexane–AcOEt 5:1); IR (neat) 1666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (2H, s), 7.18–7.26 (3H, m), 7.32–7.37 (3H, m), 7.39 (1H, dd, $J = 7.8$ and 1.8 Hz), 7.42–7.49 (3H, m), 7.57 (1H, ddd, $J = 7.8$, 7.3, and 1.4 Hz), 7.63 (1H, dd, $J = 7.8$ and 0.9 Hz), and 7.77 (2H, dd, $J = 8.2$ and 1.4 Hz). Calcd for $C_{20}H_{16}OS_2$: C, 71.39; H, 4.79; S, 19.06%. Found: C, 71.36; H, 4.92; S, 19.22%.

1-(2-Methoxy-1-phenylethenyl)-2-[(phenylthiomethyl)thio]benzene (1b). This compound was prepared from phenyl{2-[(phenylthiomethyl)thio]phenyl}methanone as described for the preparation of **1a** in 60% yield; a pale-yellow oil; R_f 0.48 (hexane–AcOEt 5:1); *E*:*Z* = ca. 1:1; IR (neat) 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (1.5H, s), 3.76 (1H, s), 4.18 (1H, s), 4.23 (1.5H, s), 6.20 (0.5H, s, vinyl-H of *E*-isomer), 6.65 (0.5H, s, vinyl-H of *Z*-isomer), 7.09–7.39 (13H, m), 7.46 (0.5H, d, $J = 8.2$ Hz), and 7.53 (0.5H, dd, $J = 7.8$ and 1.4 Hz). Calcd for $C_{22}H_{20}OS_2$: C, 72.49; H, 5.53; S, 17.59%. Found: C, 72.10; H, 5.56; S, 17.39%.

4-Methylphenyl{2-[(methylthiomethyl)thio]phenyl}methanone. This compound was prepared from 2-mercaptophenyl(4-methylphenyl)methanone[6] and chloromethyl methyl sulfide as described for the preparation of {2-[(methylthiomethyl)thio]phenyl}phenylmethanone in 64% yield; a pale-yellow oil; R_f 0.35 (hexane–THF 5:1); IR (neat) 1661 and 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (3H, s), 2.42 (3H, s), 3.91 (2H, s), 7.25 (2H, d, $J = 7.8$ Hz), 7.32–7.37 (2H, m), 7.46 (1H, ddd, $J = 7.8$, 6.9, and 2.3 Hz), 7.61 (1H, d, $J = 8.2$ Hz), and 7.70 (2H, d, $J = 7.8$ Hz). Calcd for $C_{16}H_{16}OS_2$: C, 66.63; H, 5.59; S, 22.23%. Found: C, 66.32; H, 5.61; S, 22.32%.

1-[1-(4-Methylphenyl)-2-methoxyethenyl]-2-[(methylthiomethyl)thio]benzene (1c). This compound was prepared from 4-methylphenyl{2-[(methylthiomethyl)thio]phenyl}methanone as described for the preparation of **1a** in 60% yield; a colorless oil; a mixture of stereoisomers (*E*:*Z* = ca. 6:4); R_f 0.42 (hexane–Et_2O 5:1); IR (neat) 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.06 and 2.08 (combined 3H, 2s), 2.30 (3H, s), 3.72, 3.79, 3.86, and 3.89 (combined 5H, 4s), 6.19 (0.6H, s, vinyl-H of *E*-isomer), 6.65 (0.4H, s, vinyl-H of *Z*-isomer), 7.01–7.07 (3H, m), 7.18–7.32 (4H, m), 7.42 (0.6H, d, $J = 8.2$ Hz), and 7.50 (0.4H, d, $J = 7.8$ Hz). Calcd for $C_{18}H_{20}OS_2$: C, 68.31; H, 6.37; S, 20.26%. Found: C, 68.36; H, 6.38; S, 22.16%.

4-Methylphenyl{2-[(phenylthiomethyl)thio]phenyl}methanone. This compound was prepared from 2-mercaptophenyl(4-methylphenyl)methanone[6] and chloromethyl phenyl sulfide as described for the preparation of {2-[(methylthiomethyl)thio]phenyl}phenylmethanone in 70% yield; a pale-yellow oil; R_f 0.33 (hexane–THF 10:1); IR (neat) 1661 and 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (3H, s), 4.27 (2H, s), 7.18–7.25 (5H, m), 7.32–7.38 (4H, m), 7.46 (1H, ddd, $J = 7.8$, 6.9, and 1.8 Hz), 7.62 (1H, d, $J = 7.8$ Hz), 7.67 (2H, d, $J = 8.2$ Hz). Calcd for $C_{21}H_{18}OS_2$: C, 71.96; H, 5.18; S, 18.30%. Found: C, 71.65; H, 5.31; S, 18.15%.

1-[1-(4-Methylphenyl)-2-methoxyethenyl]-2-[(phenylthiomethyl)thio]benzene (1d). This compound was prepared from 4-methylphenyl{2-[(phenylthiomethyl)thio]phenyl}methanone as described for the preparation of **1a** in 57% yield; a colorless oil; a mixture of stereoisomers (*E*:*Z* = 4:6); R_f 0.30 (hexane–Et_2O 10:1); IR (neat) 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.67 (1.8H, s), 3.74 (1.2H, s), 4.18 (1.2H, s), 4.23 (0.8H, s), 6.16 (0.4H, s, vinyl-H of *E*-isomer), 6.61 (0.6H, s, vinyl-H of *Z*-isomer), 6.99–7.06 (3H, m), 7.17–7.35 (9H, m), 7.45 (0.4H, d, $J = 7.8$ Hz), and 7.52 (0.6H, dd, $J = 7.3$ and 1.8 Hz). Calcd for $C_{23}H_{22}OS_2$: C, 72.97; H, 5.86; S, 16.94%. Found: C, 72.95; H, 6.01; S, 16.93%.

4-Chlorophenyl{2-[(methylthiomethyl)thio]phenyl}methanone. This compound was prepared from 4-chlorophenyl(2-mercaptophenyl)methanone[6] and chloromethyl methyl sulfide as described for the preparation of {2-[(methylthiomethyl)thio]phenyl}phenylmethanone in 68% yield; a pale-yellow oil; R_f 0.28 (hexane–THF 5:1); IR (neat) 1666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (3H, s), 3.92 (2H, s), 7.35–7.37 (2H, m), 7.43 (2H, d, $J = 8.7$ Hz), 7.46–7.52 (1H, m), 7.62 (1H, d, $J = 7.8$ Hz), and 7.74 (2H, d, $J = 8.7$ Hz). Calcd for $C_{15}H_{13}ClOS_2$: C, 58.33; H, 4.24; S, 20.76%. Found: C, 58.31; H, 4.51; S, 20.89%.

1-[1-(4-Chlorophenyl)-2-methoxyethenyl]-2-[(methylthiomethyl)thio]benzene (1e). This compound was prepared from 4-chlorophenyl-2-{[(methylthiomethyl)thio]phenyl}methanone as described for the preparation of **1a** in 57% yield; a pale-yellow oil; R_f 0.24 (hexane–CH_2Cl_2 2:1); a mixture of stereoisomers (*E*:*Z* = ca. 7:3); IR (neat) 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 and 2.07 (combined 3H, 2s), 3.73, 3.81, 3.86, and 3.89 (combined 5H, 4s), 6.23 (0.7H, s, vinyl-H of *E*-isomer), 6.67 (0.3H, s, vinyl-H of *Z*-isomer), 7.05 (0.6H, d, $J = 8.7$ Hz), 7.16–7.27 (3.8H, m), 7.29–7.35 (2.6H, m), 7.42 (0.7H, d, $J = 7.8$ Hz), and 7.50 (0.3H, dd, $J = 7.8$ and 1.4 Hz). Calcd for $C_{17}H_{17}ClOS_2$: C, 60.61; H, 5.09; S, 19.04%. Found: C, 60.52; H, 5.11; S, 19.72%.

4-Chlorophenyl{2-[(phenylthiomethyl)thio]phenyl}methanone. This compound was prepared from 4-chlorophenyl(2-mercaptophenyl)methanone[6] and chloromethyl phenyl sulfide as described for the preparation of {2-[(methylthiomethyl)thio]phenyl}phenylmethanone in 67% yield; a pale-yellow oil; R_f 0.28 (hexane–THF 5:1); IR (neat) 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (2H, s), 7.20–7.50 (10H, m), 7.62 (1H, d, $J = 7.7$ Hz), and 7.69 (2H, d, $J = 8.4$ Hz). Calcd for $C_{20}H_{15}ClOS_2$: C, 64.76; H, 4.08; S, 17.29%. Found: C, 64.50; H, 4.09; S, 17.13%.

1-[1-(4-Chlorophenyl)-2-methoxyethenyl]-2-[(phenylthiomethyl)thio]benzene (1f). This compound was prepared from 4-chlorophenyl{2-[(phenylthiomethyl)thio]phenyl}methanone as described for the preparation of **1a** in 59% yield; a pale-yellow oil; a mixture of stereoisomers (*E*:*Z* = ca. 1:1); R_f 0.28 (hexane–CH_2Cl_2 3:1); IR (neat) 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (1.5H, s), 3.76 (1.5H, s), 4.19 (1H, s), 4.23 (1H, s), 6.19 (0.5H, s, vinyl-H of *E*-isomer), 6.62 (0.5H, s, vinyl-H of *Z*-isomer), 7.00 (1H, d, $J = 8.8$ Hz), 7.15–7.34 (11H, m), and 7.44 (0.5H, d, $J = 7.3$ Hz), and 7.51 (0.5H, dd, $J = 7.7$ and 1.4 Hz). Calcd for $C_{22}H_{19}ClOS_2$: C, 66.23; H, 4.80; S, 16.07%. Found: C, 66.22; H, 4.86; S, 15.97%.

Typical Procedure for the Preparation of 2. 2-Methylthio-4-phenyl-2*H*-1-benzothiopyran (2a). To a stirred solution of **1a**

(0.14 g, 0.48 mmol) in DME (6 mL) at −78 °C was added *n*-BuLi (1.55 M in hexane; 1.0 mmol) (1 M = 1 mol dm^{-3}) dropwise. After 5 min, the temperature was gradually raised to 0 °C before the reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The usual workup followed by purification using preparative TLC on silica gel (hexane–AcOEt 50:1) gave **2a** (96 mg, 75%); a pale-pink solid; mp 91–92 °C (hexane–Et_2O); IR (KBr disk) 1464 and 1348 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (3H, s), 4.74 (1H, d, $J = 7.3$ Hz), 6.10 (1H, d, $J = 7.3$ Hz), 7.05–7.10 (2H, m), 7.20 (1H, ddd, $J = 7.8$, 6.0, and 2.3 Hz), 7.30–7.33 (2H, m), and 7.36–7.40 (4H, m); MS (EI) m/z (%) 270 (M$^+$, 0.26), 269 (0.57), and 223 (100). Calcd for $C_{16}H_{14}S_2$: C, 71.07; H, 5.22; S, 23.72%. Found: C, 70.95; H, 5.23; S, 23.65%.

4-Phenyl-2-phenylthio-2*H*-1-benzothiopyran (2b): A pale-pink solid; mp 102–103 °C (hexane–Et_2O) (lit.,[7] 101 °C). Spectral data (IR and ^{1}H NMR) were identical to those reported previously.[7]

4-(4-Methylphenyl)-2-methylthio-2*H*-1-benzothiopyran (2c): A reddish-brown oil; R_f 0.33 (hexane–AcOEt 50:1); IR (neat) 1510, 1463, 1431, and 1346 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (3H, s), 2.40 (3H, s), 4.73 (1H, d, $J = 7.3$ Hz), 6.09 (1H, d, $J = 7.3$ Hz), 7.05–7.09 (2H, m), 7.18–7.22 (5H, m), and 7.38 (1H, d, $J = 7.8$ Hz); MS (EI) m/z (%) 284 (M$^+$, 0.02), 283 (0.06), and 237 (100). Calcd for $C_{17}H_{16}S_2$: C, 71.78; H, 5.67; S, 22.55%. Found: C, 71.61; H, 5.70; S, 22.22%.

4-(4-Methylphenyl)-2-phenylthio-2*H*-1-benzothiopyran (2d): A pale-pink solid; mp 134–135 °C (hexane–Et_2O); IR (KBr disk) 1606, 1508, 1472, and 1437 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s), 5.04 (1H, d, $J = 7.3$ Hz), 6.14 (1H, d, $J = 7.3$ Hz), 7.02 (1H, dd, $J = 8.2$ and 1.4 Hz), 7.04 (1H, td, $J = 7.3$ and 1.4 Hz), 7.16–7.22 (5H, m), 7.25–7.27 (3H, m), 7.37 (1H, d, $J = 7.3$ Hz), and 7.49–7.51 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.20, 48.87, 120.39, 125.57, 128.14, 128.22, 128.41, 128.60, 128.65, 128.93, 129.05, 130.12, 132.77, 134.57 (two overlapped C's), 137.26, 137.65, and 141.53; MS (CI) m/z (%) 347 [(M + 1)$^+$, 34] and 237 (100). Calcd for $C_{22}H_{18}S_2$: C, 76.26; H, 5.24; S, 18.51%. Found: C, 76.01; H, 5.51; S, 18.46%.

4-(4-Chlorophenyl)-2-methylthio-2*H*-1-benzothiopyran (2e): A reddish-brown oil; R_f 0.29 (hexane–Et_2O 5:1); IR (neat) 1487, 1433, and 1348 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (3H, s), 4.73 (1H, d, $J = 7.3$ Hz), 6.09 (1H, d, $J = 7.3$ Hz), 7.02 (1H, d, $J = 7.8$ Hz), 7.09 (1H, dd, $J = 7.8$ and 7.3 Hz), 7.21 (1H, dd, $J = 7.8$ and 7.3 Hz), 7.25 (2H, d, $J = 7.8$ Hz), 7.36 (2H, d, $J = 7.8$ Hz), and 7.39 (1H, d, $J = 7.8$ Hz); MS (EI) m/z (%) 304 (M$^+$, 0.03), 303 (0.09), and 257 (100). Calcd for $C_{16}H_{13}ClS_2$: C, 63.04; H, 4.30; S, 21.04%. Found: C, 62.83; H, 4.41; S, 20.82%.

4-(4-Chlorophenyl)-2-phenylthio-2*H*-1-benzothiopyran (2f): A pale-pink solid; mp 123–125 °C (hexane–Et_2O); IR (KBr disk) 1582, 1486, and 1437 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (1H, d, $J = 7.8$ Hz), 6.14 (1H, d, $J = 7.8$ Hz), 6.95 (1H, d, $J = 7.8$ Hz), 7.05 (1H, dd, $J = 7.8$ and 7.3 Hz), 7.19–7.22 (3H, m), 7.24–7.27 (3H, m), 7.34–7.38 (3H, m), and 7.48–7.50 (2H, m); MS (CI) m/z (%) 367 [(M + 1)$^+$, 27] and 257 (100). Calcd for $C_{21}H_{15}ClS_2$: C, 68.74; H, 4.12; S, 17.48%. Found: C, 68.72; H, 4.13; S, 17.48%.

2-Methyl-2-methylthio-4-phenyl-2*H*-1-benzothiopyran (5). After **1a** was treated with 2 molar amounts of *n*-BuLi in a manner similar to that described above for the preparation of **2a**, MeI (2 molar amounts) was added. After 30 min, similar workup as described above followed by purification of the crude product by preparative TLC on silica gel gave **2b**: a reddish-brown oil; R_f 0.31 (hexane–CH_2Cl_2 3:1); IR (neat) 1602, 1598, 1492, 1469, 1443, 1433, and 1367 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (3H, s), 2.42 (3H, s), 6.10 (1H, s), 7.03–7.06 (1H, m), 7.14–7.17 (2H, m), 7.18–7.22 (3H, m), and 7.26–7.29 (3H, m); MS (EI) m/z (%) 284 (M$^+$, 9.9) and 269 (100). Calcd for $C_{17}H_{16}S_2$: C, 71.78; H, 5.67; S, 22.55%. Found: C, 71.86; H, 5.54; S, 22.48%.

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