Journal of Organometallic Chemistry, 366 (1989) 1–9
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09710

Metalation reactions

XIII *. The reactions of electrophiles with the dilithiated species 1-(α-lithiomethyl)-2-[(α-lithiomethyl)thio]benzene

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(Received October 31st, 1988)

Abstract

Direct dimetalation of 1-methyl-2-(methylthio)benzene (**1**) gives the dilithiated species (**2**) in good yield, which can be used to introduce substituents into the thiomethyl and methyl groups. Species **2** can react also with a variety of dichlorosilanes and dichlorostannanes, and with sulphur chloride, to yield derivatives of 1,3-benzothiasilin, 1,3-benzothiastannin and 1,3-benzodithiin respectively. Reaction of **2** with tetrachlorosilane yields a spirocyclic silicon compound, while reaction with benzoyl chloride yields a derivative of 1-benzothiopyran.

Introduction

We have previously shown that aromatic thioethers undergo direct dimetalation to yield stable dilithiated compounds [1–3]. This raised the possibility of treating such compounds with electrophiles in order to introduce two substituents on the ring or to give new heterocyclic compounds. We also showed [4] that 1-methyl-2-(methylthio)benzene (**1**) can be metalated either at the methyl or thiomethyl carbon atom depending on the reaction conditions.

In the present work we used compound **1**, in order to examine its dimetalation and identify the dimetalated product; we then used the dimetalated species to check the possibility of introducing functionality into **1** by a one-pot treatment with two electrophiles, and also investigated a possible new synthesis of six-membered heterocyclic compounds containing one or two heteroatoms.

Results and discussion

Compound **1**, which can be made by methylation of the commercially available 2-methylbenzenethiol, was treated in hexane with two equivalents of n-butyllithium

* For Part XII see ref. 3.

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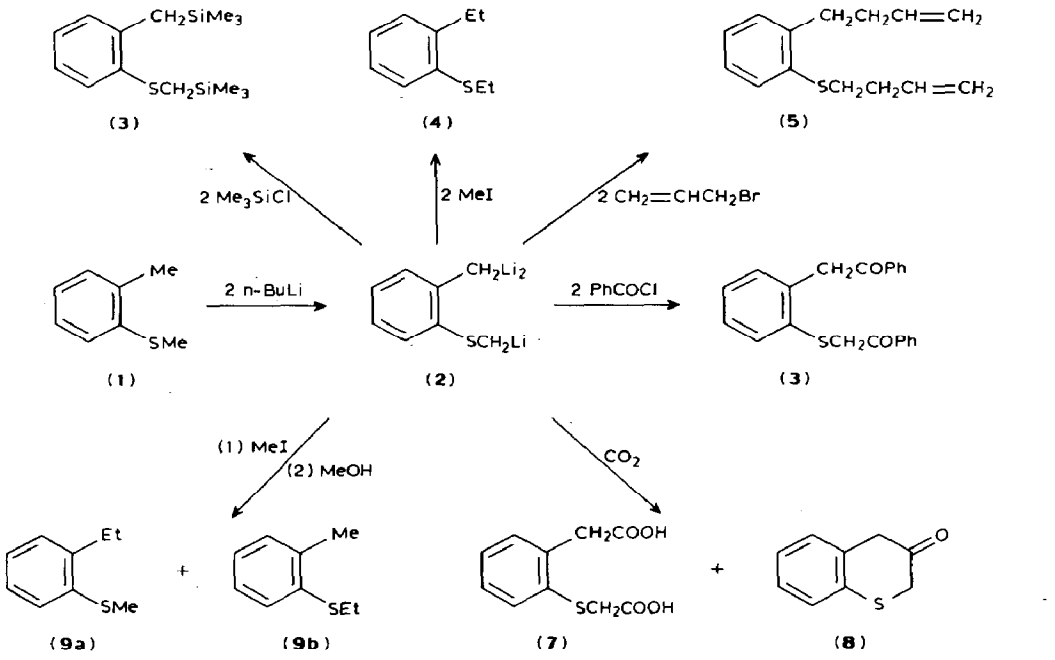
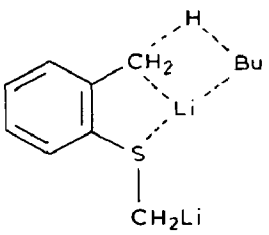


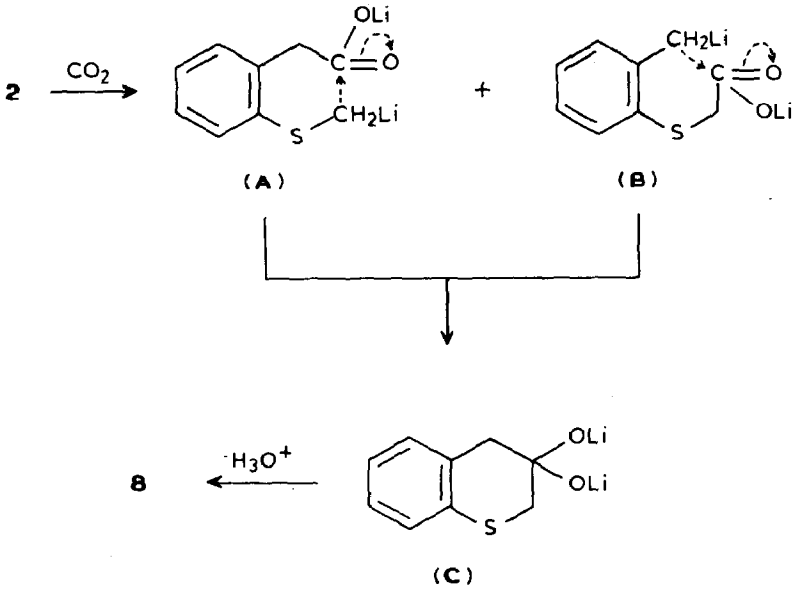
Scheme 1

(in hexane) in the presence of *N,N,N′,N′*-tetramethyl-1,2-ethanediamine (TMEDA). The lithium compound was then treated with two equivalents of chlorotrimethylsilane, and the resulting product, **3**, was identified by elemental analysis, ^{1}H NMR and mass spectroscopy. It was found that dimetalation of **1** yields the dilithiated compound **2**, the active sites being the methyl and the thiomethyl carbon atoms (Scheme 1).

It is noteworthy that when the methyl group is *meta* or *para* to the thiomethyl group, benzylic metalation does not occur [1,5]. With these substrates the second lithium atom replaces a ring hydrogen atom *ortho* to the thioether group. The benzylic metalation of **1** can be accounted for in terms of prior reaction of the thiomethyl group, which is facilitated by sulphur *d*-orbital participation [6]. The partially negative sulphur atom interacts with a second molecule of n-butyllithium, which is thus held in the appropriate position to deprotonate the benzylic group, as shown below:



This result just described showed that it was possible to introduce simultaneously in a one pot reaction two identical functional groups in strategic points of **1**, to give products not easily accessible by other routes, but requiring multistep procedures.



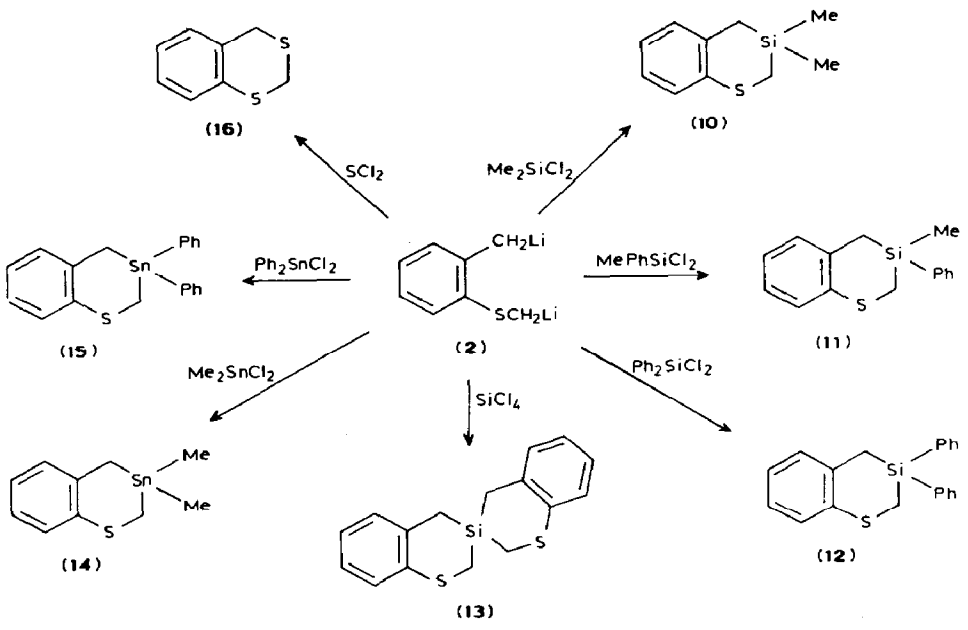
Scheme 2

Thus, treatment of **2** with two equivalents of methyl iodide, allyl bromide, or benzyl chloride gave the bifunctionalized derivatives **4**, **5**, or **6** (Scheme 1) in good yields (63–68%).

In contrast, an attempt to obtain the carboxylic acid **7** by treatment of **2** with dry ice gave unsatisfactory results; **7** was always obtained only in low yields (ca. 20%), and was always accompanied by the heterocyclic compound **8** (ca. 50%) even in the presence of a large excess of dry ice. The formation of **8** could be accounted for (Scheme 2) in terms of initial addition of carbon dioxide to one of the two reactive centres of **2**, to yield intermediates "**A**" or "**B**", followed by an intramolecular addition of the second active centre to the carboxylated salt to yield "**C**", which after hydrolysis gives the heterocyclic species **8**. This type of reaction usually occurs when a deficiency of carbon dioxide is used [7], and unusual behaviour in the present case can be attribute to the fact that intramolecular reaction of "**A**" or "**B**" yields **8** more rapidly than the intermolecular reaction with a second molecule of carbon dioxide to yield **7**.

Attempts to regioselectively introduce two different functional groups into **2** were unsuccessfull. Thus (Scheme 1) upon treatment of the dianion with an equivalent of methyl iodide followed by an excess of methanol, a equimolar mixture of the two possible isomers **9a** and **9b** was obtained.

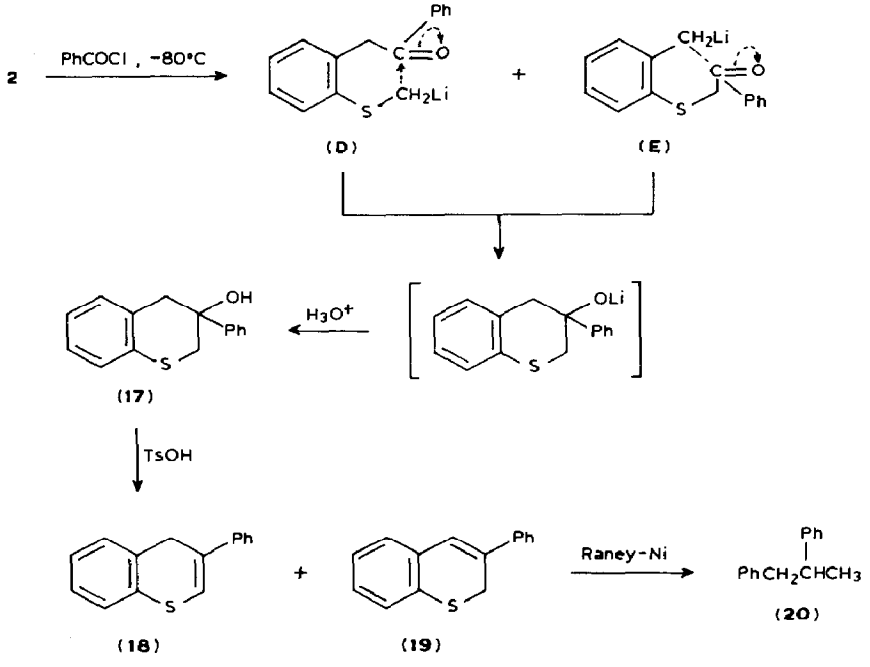
The results obtained up to this point suggested that we should also examine the reaction of **2** with a number of *gem*-dialogeno compounds in order to obtain benzo-condensed six-membered heterocycles containing two heteroatoms. Reaction of **2** with dimethyl-, methylphenyl- and diphenyl-dichlorosilane gave 1,3-benzothiasilinic derivatives (**10–12**) (Scheme 3). Dimethyl- and diphenyl-dichlorostannane likewise yielded 1,3-benzothiastannins (**14, 15**) and tetrachlorosilane gave the spiro compound **13**. The reaction with sulphur dichloride gave the expected 1,3-benzodi-



Scheme 3

thiin (**15**), but in order to avoid other reaction paths [3] a low temperature (ca. −80 °C) was required for this coupling.

Both lithiated centres of **2** can react with the same carbon atom C(1) of an acyl halide to yield 1-benzothiopyranic derivatives. Thus (Scheme 4) treatment of **2** at



Scheme 4

−80 °C with an equivalent of benzoyl chloride, followed by slow warming of the mixture to room temperature, gave the benzothiopyran compound **17**. The latter readily undergoes dehydration to yield **18** and traces of **19**. The formation of **17** can be explained in terms of an initial nucleophilic attack at one of the two active centres of the acylic carbon atom to give the two monolithiated species "**D**" and "**E**" [2] with these intermediates then giving the benzothiopyran compound by nucleophilic attack of the thiomethylic or benzylic carbanion on the carbonylic carbon.

Compounds **18** and **19** were identified by GC, GC/MS and analysis of the products from their desulphurisation with Ni-Raney, and from the ^{1}H NMR spectrum of the more abundant species. GLC analysis of the crude product showed two peaks in 95/5 ratio. GS/MS examination showed that the components give rise to the same molecular ion (M^+ 224). Desulphurisation of the mixture yields 1,2-diphenylpropane (**20**) as a single product. The more abundant product, **18**, after isolation, gave a ^{1}H NMR spectrum with a characteristic ArCH_2 signal at δ 4.20 and a signal at δ 6.59 which can be assigned to an SCH proton.These values are in accord with those reported for analogous compounds [8].

Experimental

General

Commercially available reagent-grade starting materials and solvents were used. Solutions of n-butyllithium in hexane were obtained from Janssen Chimica and are analyzed by the Gilman double titration method before use [9]. TMEDA was obtained from the Aldrich Chemical Company and distilled from calcium hydride before use. Hexane was distilled from lithium aluminum hydride. Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck.

Melting points were determined with a Kofler hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer for potassium bromide mulls or neat liquids between sodium chloride plates. ^{1}H NMR spectra were recorded on a Varian EM 360A spectrometer with tetramethylsilane as internal reference. Analyses by GLC were carried out with a Carlo Erba Fractovap 4200 Gas Chromatograph equipped with a flame ionization detector and a 5 m Apiezon L capillary column. Mass spectra were determined with a "Hitachi" Perkin–Elmer RMU-6D spectrometer, by use of the direct-inlet system. The GC/MS analyses were performed with a Finnigan 1020 GC/MS instrument fitted with a capillary column. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser.

Starting materials

1-Methyl-2-(methylthio)benzene (**1**) was prepared by published methods [10]. Iodomethane, allyl bromide, benzoyl chloride, chlorotrimethylsilane, dimethyl-, methylphenyl- and diphenyl-dichlorosilane, tetrachlorosilane, dimethyl- and diphenyl-dichlorostannane, and sulphur chloride were purchased from Janssen Chimica and used without further purification.

Authentic samples

1-Ethyl-2-(methylthio)- (**9a**) and 1-(ethylthio)-2-methylbenzene (**9b**), 2-[(carboxymethyl)thio]benzeneacetic acid (**7**), 2*H*-1-benzothiopyran-3(4*H*)-one (**8**) and 1,2-diphenylpropane (**20**) were prepared by published procedures [11–14].

Trimethyl[[[2-[(trimethylsilyl)methyl]thio]phenyl]methyl]silane (3)

To a vigorously stirred solution of **1** (5 g, 36 mmol), anhydrous TMEDA (9.2 g, 79 mmol) and anhydrous hexane (100 ml) cooled to 0 °C a 1.2 *M* solution of n-butyllithium in hexane (65.8 ml, 79 mmol) were gradually added under nitrogen, and stirring was continued at room temperature for 12 h. The resulting solution of **2** was then cooled to 0 °C and treated dropwise with chlorotrimethylsilane (7.8 g, 72 mmol). The mixture was then allowed to warm, left at room temperature for 12 h with stirring and poured into water, and the pH was adjusted to 5–6 by addition of 10% hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether. The organic solutions were combined, dried (Na_2SO_4), and concentrated. The crude product was purified by flash-chromatography with hexane as eluent. Yield 71% b.p. 60–61 °C/12 mmHg; n_D^{29} 1.5310; ^{1}H NMR ($CDCl_3$): δ 0.3 (s, 18H, SiC*H*$_3$), 2.10 (s, 2H, SC*H*$_2$), 2.20 (s, 2H, ArC*H*$_2$), 6.90 (m, 4H, arom-*H*); MS, *m/z* 282 (M^+). Elemental analysis: Found: C, 59.38; H, 9.34; S, 11.17. $C_{14}H_{26}SSi_2$ (282.53) calcd.: C, 59.51; H, 9.28; S, 11.35%.

The following compounds were obtained analogously, from **1** and iodomethane, allyl bromide, benzoyl chloride, dimethyl-, methylphenyl- and diphenyl-dichlorosilane, tetrachlorosilane, dimethyl- and diphenyl-dichlorostannane and sulphur chloride.

1-Ethyl-2-(ethylthio)benzene (4). Yield 65%; b.p. 113–115 °C/25 mmHg; n_D^{29} 1.5570; ^{1}H NMR ($CDCl_3$): δ 1.22 (m, 6H, C*H*$_3$), 2.60 (m, 4H, C*H*$_2$), 7.10 (m, 4H, arom-*H*); MS, *m/z* 166 (M^+). Elemental analysis: Found: C, 72.10; H, 8.31; S, 19.07. $C_{10}H_{14}S$ (166.27) calcd.: C, 72.23; H, 8.49; S, 19.28%.

1-(3-Butenyl)-2-(3-butenylthio)benzene (5). Yield 68%; b.p. 150–152 °C/45 mmHg; n_D^{29} 1.5537; ^{1}H NMR ($CDCl_3$); δ 2.15 (m, 4H, CH=C*H*$_2$), 2.80 (m, 2H, SC*H*$_2$), 3.30 (m, 2H, ArC*H*$_2$), 5.0 (m, 4H, C*H*$_2$–CH=C*H*$_2$), 5.70 (m, 2H, C*H*=CH$_2$), 7.10 (m, 4H, arom-*H*); MS, *m/z* (218 (M^+). Elemental analysis: Found: C, 76.88; H, 8.23; S, 16.50. $C_{14}H_{18}S$ (218.34) calcd.: C, 77.01; H, 8.31; S, 14.68%.

2-[2-[[benzoyl]methyl]thio]phenyl]-1-phenylethanone (6). The reaction was carried out at −80 °C. Yield 63%; flash-chromatography (20/1 hexane/ethyl acetate); b.p. 85–86 °C/2 mmHg; n_D^{28} 1.5020; IR (neat): 1725, 1710 cm^{-1} ν(C=O); ^{1}H NMR ($CDCl_3$): δ 4.20 (s, 2H, SC*H*$_2$), 4.40 (s, 2H, ArC*H*$_2$), 7.60 (m, 14H, arom-*H*); MS, *m/z* 346 (M^+). Elemental analysis: Found: C, 76.12; H, 5.16; S, 9.11. $C_{22}H_{18}O_2S$ (346.42) calcd.: C, 76.27; H, 5.24; S, 9.25%.

3,3-Dimethyl-1,3-benzothiasilin (10). This was made from 36 mmol of **1** and 18 mmol of dichlorodimethylsilane. Yield 75%; flash-chromatography (light petroleum); b.p. 97–99 °C/28 mmHg; n_D^{28} 1.5570; ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 6H, SiC*H*$_3$) 1.70 (s, 2H, SC*H*$_2$), 1.92 (s, 2H, ArC*H*$_2$), 6.73 (m, 4H, arom-*H*); MS, *m/z* 194 (M^+). Elemental analysis: Found: C, 61.68; H 7.17; S, 16.32. $C_{10}H_{14}SSi$ (194.33) calcd.: C, 61.80; H, 7.26; S, 16.50%.

3-Methyl-3-phenyl-1,3-benzothiasilin (11). This was made from 36 mmol of **1** and 18 mmol of dichloromethylphenylsilane. Yield 70%; flash-chromatography (40/1 hexane/chloroform); b.p. 130–131 °C/6 mmHg; n_D^{28} 1.5733; ^{1}H NMR ($CDCl_3$): δ 0.23 (s, 3H, SiC*H*$_3$), 1.75 (s, 2H, SC*H*$_2$), 1.86 (s, 2H, ArC*H*$_2$), 7.00 (m, 9H, arom-*H*); MS, *m/z* 256 (M^+). Elemental analysis: Found: C, 70.11; H, 6.14; S, 12.33. $C_{15}H_{16}SSi$ (256.4) calcd.: C, 70.26; H, 6.29; S, 12.50%.

3,3-Diphenyl-1,3-benzothiasilin (12). This compound was made from 36 mmol of **1** and 18 mmol of dichlorodiphenylsilane. Yield 78%; flash-chromatography (50/1

hexane/chloroform); m.p. 207–208 °C; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 2H, SCH_2), 2.30 (s, 2H, $ArCH_2$), 7.32 (m, 14H, arom-*H*); MS, *m/z* 318 (M^+). Elemental analysis: Found: C, 75.55; H, 5.61; S, 9.92. $C_{20}H_{18}SSi$ (318.46) calcd.: C, 75.42; H, 5.70; S., 10.07%.

3,3'-Spirobi[1,3-benzothiasilin] (13). This was made from 36 mmol of **1** and 9 mmol of tetrachlorosilane. Yield 62%; flash-chromatography (light petroleum); m.p. 88–89 °C; ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 4H, SCH_2), 2.45 (s, 4H, $ArCH_2$), 6.80 (m, 8H, arom-*H*); MS, *m/z* 300 (M^+). Elemental analysis: Found: C, 63.82; H, 5.31; S, 21.18. $C_{16}H_{16}S_2Si$ (300.47) calcd.: C, 63.95; H, 5.37; S, 21.34%.

3,3-Dimethyl-1,3-benzothiastannin (14). This was made from 36 mmol of **1** and 18 mmol of dichlorodimethylstannane. Yield 61%; flash-chromatography (light petroleum); m.p. 120 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 6H, CH_3), 2.32 (s, 2H, SCH_2), 2.43 (s, 2H, $ArCH_2$), 7.15 (m, 4H, arom-*H*).MS, *m/z* 285 (M^+). Elemental analysis: Found: C, 42.25; H, 5.05; S, 11.08. $C_{10}H_{14}SSn$ (284.97) calcd.: C, 42.14; H, 4.95; S, 11.26%.

3,3-Diphenyl-1,3-benzothiastannin (15). This was made from 36 mmol of **1** and 18 mmol of dichlorodiphenylstannane. Yield 56%; flash-chromatography (40/1 light petroleum/diethyl ether); m.p. 212–214 °C; ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 2H, SCH_2), 2.25 (s, 2H, $ArCH_2$), 7.15 (m, 14H, arom-*H*). MS, *m/z* 409 (M^+). Elemental analysis: Found: C, 58.89; H, 4.52; S, 7.65. $C_{20}H_{18}SSn$ (409.1) calcd.: C, 58.71; H, 4.43; S, 7.84%.

4H-1,3-Benzodithiin (16). This was made from 36 mmol of **1** and 18 mmol of sulphur chloride, and the reaction was carried out at −90 °C. Yield 64%. Flash-chromatography (3/1 hexane/diethyl ether); n_D^{28} 1.6240; ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 2H, SCH_2S), 4.30 (s, 2H, $ArCH_2$), 7.30 (m, 4H, arom-*H*). MS, *m/z* 168 (M^+). Elemental analysis: Found: C, 57.21; H, 4.88; S, 38.03. $C_8H_8S_2$ (168.26) calcd.: C, 57.10; H, 4.79; S, 38.11%.

Reaction of 2 with carbon dioxide

The solution of **2**, obtained as previously above was poured on to ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate and then with diethyl ether. The aqueous layer was separated, washed with diethyl ether, acidified with cold concentrated hydrochloric acid, and extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The product, identified as 2-[(carboxymethyl)-thio]benzeneacetic acid (**7**), by comparison with an authentic sample, was recrystallized from toluene; yield 18%; m.p. 185–186 °C; (lit. [13] m.p. 186 °C).

The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The product was purified by flash-chromatography with hexane as eluent, and identified as 2H-1-benzothiopyran-3(4H)-one (**8**) by comparison with an authentic sample. Yield 51%; b.p. 111–112 °C/5 mmHg; (lit. [13] b.p. 83 °C/0.4 mmHg).

Sequential, one-pot introduction of two different electrophiles

To a vigorously stirred solution of **2**, iodomethane (5.1 g, 36 mmol) was gradually added at 0 °C. When the addition was complete the mixture was allowed to warm to room temperature and kept there for 12 h with stirring. It was then treated at 0 °C with an excess of methanol, and work-up was then as described for **3**. GC

examination of the ethereal solution showed four peaks, with retention times identical to those of authentic samples of **1, 4, 9a, 9b**, in the ratio 10/15/36/39.

3,4-Dihydro-3-hydroxy-3-phenyl-2H-1-benzothiopyran (17). To a vigorously stirred solution of **2** cooled to −80 °C, a solution of benzoyl chloride (5 g, 36 mmol) in anhydrous diethyl ether (20 ml) was gradually added under nitrogen. The mixture was stirred at −80 °C for 3 h, then allowed to warm to room temperature, stirred for 20 h, and poured into water. The pH was adjusted to 4–5 with 10% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether. The organic solutions were combined, dried (Na_2SO_4), and evaporated. The crude product was purified by flash-chromatography with hexane/ethyl acetate (5/1) as eluent. Yield 58%; n_D^{28} 1.6197; IR (neat): 3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 3.50 (s, 2H, SCH_2), 4.15 (s, 2H, $ArCH_2$), 7.50 (m, 9H, arom-*H*); MS, *m/z* 242 (M^+). Elemental analysis: Found: C, 74.18; H, 5.77; S, 13.11. $C_{15}H_{14}OS$ (242.32) calcd.: C, 74.34; H, 5.82; S, 13.23%.

3-Phenyl-4H-1-benzothiopyran (18) and 3-Phenyl-2H-1-benzothiopyran (19). A solution of **17** (2.4 g, 10 mmol) in anhydrous benzene (10 ml) containing *p*-toluensulfonic acid (0.1 g) was refluxed with stirring for 3 h, poured into water. After extraction with diethyl ether, the extracts were washed with water, dried ($CaCl_2$), and evaporated. GC analysis of the crude oil showed of the presence of two isomeric products in a ratio of 95/5. GC–MS showed that the two products gave the same molecular ion M^+ 224.

A solution of the mixture (0.5 g, 2.2 mmol) in 95% ethanol (3 ml) was refluxed for 2 h with Raney nickel (0.5 g) [15]. The mixture was then filtered and poured into water. After extraction with diethyl ether the extract was dried (Na_2SO_4) and evaporated, to give only 1,2-diphenylpropane (**23**) in almost quantitative yield. The product was identified by comparison with an authentic sample; b.p. 130–131 °C/6 mmHg; n_D^{26} 1.5598 (lit. [14] b.p. 160 °C/25 mmHg, n_D^{25} 1.5593).

The major component was isolated by flash-chromatography with hexane as eluent and identified as **18**; n_D^{28} 1.6039; ^1H NMR ($CDCl_3$): δ 4.20 (s, 2H, $ArCH_2$), 6.59 (s, 1H, SC*H*), 7.62 (m, 9H, arom-*H*); MS, *m/z* 224 (M^+). Elemental analysis: Found: C, 80.17; H, 5.33; S, 14.13. $C_{15}H_{12}S$ (234.31) calcd.: C, 80.31; H, 5.39; S, 14.29%.

Acknowledgement

We acknowledge financial support from C.N.R. and from M.P.I., Italy.

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