SYNTHESIS WITH BIS(*o*-MERCAPTO)PHENYL SULFIDE: AN EASY ACCESS TO SULFUR-CONTAINING 16-MEMBERED HETEROCYCLES

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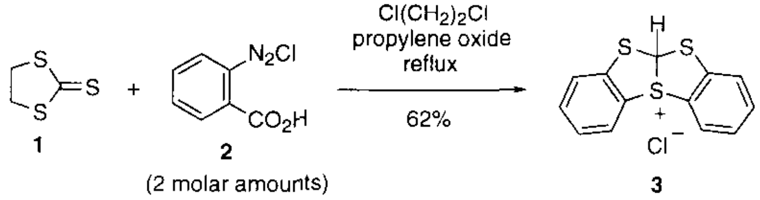
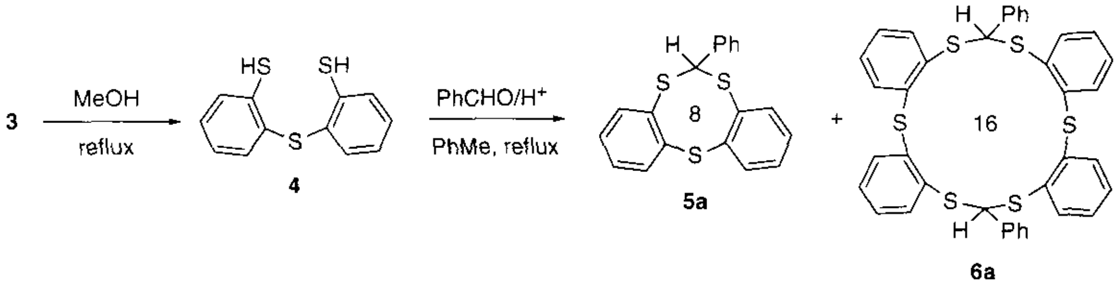
Abstract–Condensations of bis(*o*-mercaptophenyl) sulfide (**4**) with paraformaldehyde or diiodomethane in moderately concentrated solutions gave 28-49% yield of a 1:1 condensation product, dibenzotrithiocin (**5b**), and 6-10% yield of a 2:2 condensation product (**6b**) with a 16-membered ring, whereas condensation of **4** with diiodomethane in a dilute solution gave **5b** in 90% yield. Condensations of **4** with 1,1'-carbonyl- and 1,1'-thiocarbonyl-diimidazoles gave 2:2 condensation products (**6c**) and (**6d**) as the practically sole product in 79 and 57% yields, respectively, thus providing a convenient synthesis of 16-membered heterocycles containing 6 sulfur atoms in the ring.

Previously, we reported a convenient one-pot synthesis of a polycyclic sulfonium salt, 9a*H*-9,10-dithia-4b-thioniaindeno[1,2-*a*]indene chloride (**3**), which involved the reaction of ethylene trithiocarbonate (**1**) with benzyne, generated by thermolysis of two molar amounts of 2-carboxybenzenediazonium chloride (**2**).[1,2] Unexpectedly, heating the sulfonium salt (**3**) in refluxing methanol provided an easy access to bis(*o*-mercaptophenyl) sulfide (**4**),[3] which otherwise seemed to be difficult to prepare in a preparative scale.[4] *p*-Toluenesulfonic acid-catalyzed condensation of the dithiol (**4**) with benzaldehyde gave a dibenzotrithiocin derivative (**5a**) as the major product.[3] The reaction also gave a byproduct which was assumed to be a 2:2 condensation product (**6a**), which is probably composed of *cis*- and *trans*-isomers. Rigid structure elucidation of the compound was not examined at that occasion. Such condensation, if it takes place actually, would provide a useful synthetic method for sulfur-containing macrocycles.[5] We have then investigated the condensation of **4** with several reagents.

This paper is dedicated to Volume 50 Anniversary of HETEROCYCLES.





Condensation of **4** with formaldehyde was first investigated since this combination excludes the formation of an isomeric mixture, making separation and structure elucidation of the products much easier. Thus, to a 0.2 M solution of **4** in toluene were added paraformaldehyde $(HCHO)_n$ (1.1 equiv. as HCHO) and a catalytic amount of *p*-toluenesulfonic acid (TsOH), and the mixture was heated under reflux for 2 h. As expected, chromatographic purification of the mixture gave a 2:2 condensation product (**6b**) in 8% yield along with a 1:1 condensation product (**5b**) in 49% yield (Table 1; Entry 1). Although improvement of the yield of **6b** was attempted by heating a more concentrated solution of **4**, it was practically fruitless (Entry 2). In this case, even the yield of **5b** decreased because of the formation of much polymeric products. The use of diiodomethane as the condensation reagent in a dilute solution in the presence of Cs_2CO_3[6] gave **5b** as the sole product in 90% yield (Entry 3). When diiodomethane was allowed to react with **4** in a more concentrated solution, both **5b** and **6b** were formed in 47 and 10% yields, respectively (Entry 4). The lithium salt of **4** also reacted with diiodomethane under the same concentration to give **5b** and **6b** in 42 and 6% yields, respectively (Entry 5).

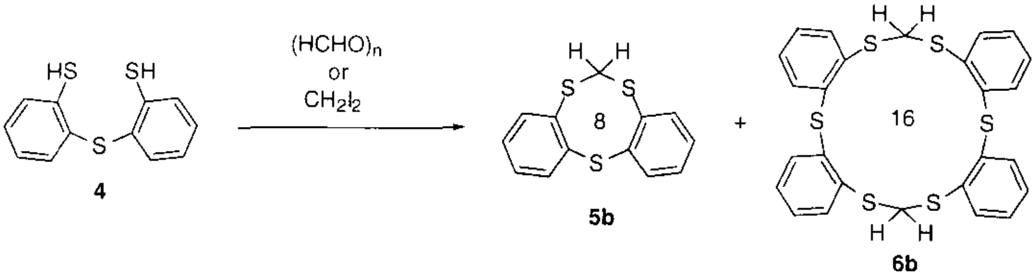
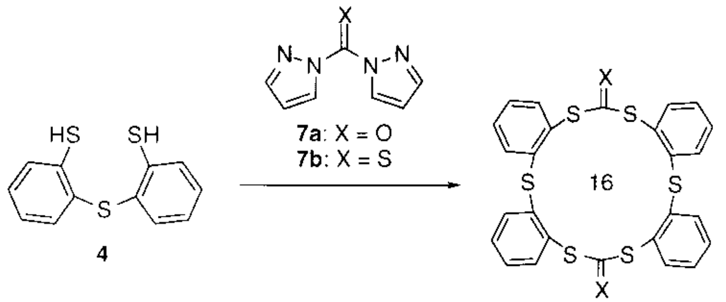


Table 1. Condensations of **4** with paraformaldehyde $(HCHO)_n$ and diiodomethane

Entry	Condensation reagent	Conditions	Yield (%)	
			5b	**6b**
1	$(HCHO)_n$	TsOH, PhMe, reflux, 2 h[a]	49	8
2	$(HCHO)_n$	TsOH, PhMe, reflux, 2.5 h[b]	28	10
3	CH_2I_2	Cs_2CO_3, DMF, 40–50 °C, 2 h.[c]	90	0
4	CH_2I_2	Cs_2CO_3, DMF, rt, 1 h[d]	47	10
5	CH_2I_2	BuLi, THF, rt, 3 h[e]	42	6

[a] A 0.2 M solution of **4** in PhMe (**4**:HCHO = 1:1.1) was used. [b] A 0.4 M solution of **4** in PhMe (**4**:HCHO = 1:1.1) was used. [c] A 0.008 M solution of **4** in DMF was used. [d] A 0.2 M solution of **4** in DMF was used. [e] A 0.2 M solution of **4** in THF was used.

Condensation of **4** with 1,1'-carbonyldiimidazole (**7a**) in refluxing THF gave the 16-membered ring 2:2 condensation product (**6c**) as the sole isolated product in 79% yield. Similarly, condensation of **4** with 1,1'-thiocarbonyldiimidazole (**7b**) gave the 16-membered ring compound (**6d**) in 57% yield. Both **6c** and **6d** are hardly soluble in common organic solvents at ambient temperature and thus their NMR spectra were determined in hot $CDCl_3$ (328 K) and DMSO-d_6 (353 K), respectively. Their MS spectra showed the correct M^+ peaks. Although it is well documented that condensation of 1,2-benzenedithiols with carbon disulfide affords 1,3-dibenzodithiole-2-thiones,[7] the condensation of **4** with carbon disulfide did not proceed even under forcing conditions. No formation of the 8-membered ring compounds (**8**) was observed in the both cases. Thus, the above reactions provide a convenient synthesis of the 16-membered heterocycles containing 6 sulfur atoms in the ring.[5] Treatment of **6d** with $Hg(OAc)_2$ in a mixture of AcOH and CH_2Cl_2 gave **6c** in 51% yield. Attempted reduction of **6c** to **6b** with Et_3SiH in refluxing CF_3CO_2H failed; **6c** was recovered quantitatively.



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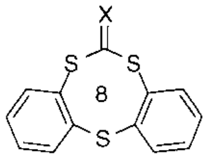
7a: X = O
7b: X = S

6c: X = O, 79%
6d: X = S, 57%

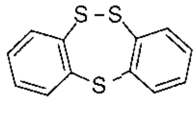


8 (X = O or S)

$$\mathbf{6d} \xrightarrow[\text{AcOH/CH}_2\text{Cl}_2]{\text{Hg(OAc)}_2} \mathbf{6c}$$

$$51\%$$

Treatment of **4** with bromine gave polymeric products quantitatively which are practically insoluble in any organic solvents. No expected products, such as **9**,[8] was formed.



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EXPERIMENTAL

Melting points were determined on a MEL-TEMP capillary tube apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were determined on a Bruker AM-400 and a Bruker ARX400 spectrometers with tetramethylsilane as the internal standard. IR spectra are determined on a Hitachi 270-50 spectrophotometer. MS spectra were obtained at 70 eV in the EI mode on a JEOL JMS-DX303 spectrometer. Column chromatography was performed with Merck Kieselgel 60 (70-230 mesh). HPLC was performed on a Japan Analytical Industry LC-908.

Condensation of 4 with Formaldehyde. *a) In a 0.2 M solution.* A mixture of 250 mg (1 mmol) of **4**, 33 mg (1.1 mmol as HCHO) of paraformaldehyde, and a catalytic amount (20 mg) of *p*-toluenesulfonic acid in 5 mL of toluene was heated under reflux for 2 h. The mixture was diluted with toluene, washed with saturated aqueous $NaHCO_3$ and then with water, dried over $MgSO_4$, and evaporated. The resulting residue was chromatographed on a column of silica gel (40 g). The column was eluted with a mixture of hexane and AcOEt (3:1) to give 128 mg (49%) of dibenzo[*d,g*][1,3,6]trithiocin (**5b**), mp 156-157 °C (lit.,[2] mp 156.5-157.0 °C), and unidentified products in small amounts. The column was further eluted with $CHCl_3$ to give 22 mg (8%) of 1,2;4,5;9,10;12,13-tetrabenzo-3,6,8,11,14,16-hexathiacyclohexadeca-1,4,9,12-tetraene (**6b**). *b) In a 0.4 M solution.* A mixture of 250 mg (1 mmol) of **4**, 33 mg (1.1 mmol as HCHO) of paraformaldehyde, and a catalytic amount (20 mg) of *p*-toluenesulfonic acid in 2.5 mL of toluene was heated under reflux for 2.5 h. The mixture was treated as described above to give 74 mg (28%) of **5b** and 27 mg (10%) of **6b** (in this case, purification by column chromatography and then by HPLC was required for isolation of pure **6b**). **6b**: mp 271.0-

272.5 °C (decomp); colorless crystals (from $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.39 (4H,s), 6.97 (4H, dd, J = 7.6/1.3 Hz), 7.08 (4H, dt, J = 7.6/1.3 Hz), 7.18 (4H, dt, J = 7.6/1.3 Hz), 7.40 (4H, dd, J = 7.6/1.3 Hz); ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 39.14, 127.77, 127.84, 131.51, 131.54, 136.95, 137.15; MS (EI): *m/z* 524 (M^+), 262, 216, 184, 153 (100%). Anal. Calcd for $C_{26}H_{20}S_6$: C, 59.50; H, 3.84. Found: C, 59.27; H, 3.68.

Condensation of 4 with Diiodomethane. *a) In a dilute solution in the presence of Cs_2CO_3.* A mixture of 250 mg (1 mmol) of **4**, 268 mg (1 mmol) of diiodomethane, and 358 mg (1.1 mmol) of Cs_2CO_3 in 120 mL of DMF was heated at 40-50 °C for 2 h. The mixture was evaporated under reduced pressure. The residue was stirred with CH_2Cl_2 and water. The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated. The residue was recrystallized from cyclohexane to give 235 mg (90%) of **5b**. *b) In a concentrated solution in the presence of Cs_2CO_3.* A mixture of 250 mg (1 mmol) of **4**, 268 mg (1 mmol) of diiodomethane, and 358 mg (1.1 mmol) of Cs_2CO_3 in 5 mL of DMF was stirred at rt for 1 h. The mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel and then by HPLC to give 124 mg (47%) of **5b** and 25 mg (10%) of **6b**. *c) Use of the lithium salt of 4.* A 1.53 M solution of BuLi in hexane (1.5 mL, 2.3 mmol) was added to a solution of 250 mg (1 mmol) of **4** in 5 mL of THF at 0 °C, which was followed by addition of 0.10 mL (1.2 mmol) of diiodomethane at the same temperature. The resulting mixture was stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel and then by HPLC to give 110 mg (42%) of **5b** and 15 mg (6%) of **6b**.

3,4;6,7;11,12;14,15-Tetrabenzo-2,5,8,10,13,16-hexathiacyclohexadeca-3,6,11,14-tetraene-1,9-dione (6c). A mixture of 251 mg (1 mol) of **4** and 178 mg (1.1 mmol) of 1,1'-carbonyldiimidazole (Merck) in 10 mL of THF was heated under reflux for 3 h. The mixture was evaporated and the residue was chromatographed on a column of silica gel (50 g). The column was eluted with a mixture of hexane and CH_2Cl_2 (1:1) to give 219 mg (79%) of **6c**: mp 264.0-267.0 °C (decomp); colorless crystals (from $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 328 K, 400 MHz): δ 7.19 (4H, dd, J = 7.5/1.6 Hz), 7.27 (4H, dt, J = 7.5/1.6 Hz), 7.34 (4H, dt, J = 7.5/1.6 Hz), 7.59 (4H, dd, J = 7.5/1.6 Hz); ^{13}C-NMR ($CDCl_3$, 328 K, 100.6 MHz): δ 127.94, 129.14, 131.52, 132.43, 137.41, 143.48, 186.07; IR (KBr): 1711, 1655 (C=O) cm^{-1}; MS (EI): *m/z* 552 (M^+), 524, 248 (100%), 216, 184. Anal. Calcd for $C_{26}H_{16}O_2S_6$: C, 56.49; H, 2.92. Found: C, 56.29; H, 2.79.

3,4;6,7;11,12;14,15-Tetrabenzo-2,5,8,10,13,16-hexathiacyclohexadeca-3,6,11,14-tetraene-1,9-dithione (6d). A mixture of 500 mg (2 mol) of **4** and 415 mg (2.3 mmol) of 1,1'-thiocarbonyldiimidazole (Aldrich) in 20 mL of THF was heated under reflux for 4 h. The mixture was allowed to stand at rt overnight and the resulting crystalline precipitate was collected by filtration to give 336 mg (57%) of **6d**: mp 305.0-305.5 °C (decomp); yellow crystals (from PhCl); ^{1}H-NMR (DMSO-d_6, 353 K, 400 MHz): δ 7.21 (4H, br d, J = 7.6 Hz), 7.39 (4H, dt, J = 7.6/1.3 Hz), 7.47 (4H, dt, J = 7.6/1.3 Hz), 7.60 (4H, dd, J = 7.6/1.3 Hz); ^{13}C-NMR (DMSO-d_6, 353 K, 100.6 MHz): δ 128.22, 130.52, 131.64, 132.12, 136.74, 141.87, 220.51; IR (KBr): 1058, 1029 (C=S) cm^{-1}; MS (EI): m/z 584 (M$^+$), 216 (100%). Anal.Calcd for $C_{26}H_{16}S_8$: C, 53.39; H, 2.76. Found: C, 53.55; H, 2.76.

Conversion of 6d to 6c. A suspension of 100 mg (0.17 mmol) of **6d** and 218 mg (0.68 mmol) of $Hg(OAc)_2$ in a mixture of AcOH (20 mL) and CH_2Cl_2 (5 mL) was stirred for 9 h at rt. The insoluble materials were collected by filtration and heated with $CHCl_3$ (200 mL), and then the insoluble inorganic materials were removed by filtration. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (40 g). The column was eluted with a mixture of hexane and $CHCl_3$ (2:3) to give 48 mg (51%) of **6c** and 31 mg of an unidentified product, mp 258-260 °C.

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