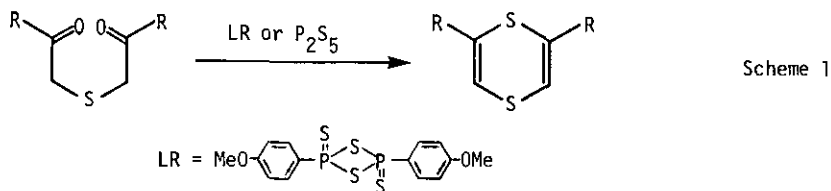


REACTION OF BIS(3,3-DIMETHYL-2-OXOBUTYL) SULFIDE WITH LAWESSON'S REAGENT. FORMATION OF 1,4-DI-t-BUTYL-2,5,7-TRITHIA[2.2.1]HEPTANE AND 2,5- AND 2,6-DI-t-BUTYL-1,4-DITHIINS

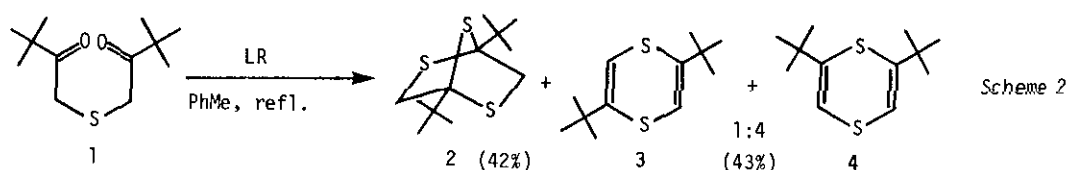
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Abstract — Treatment of bis(3,3-dimethyl-2-oxobutyl) sulfide (1) with Lawesson's reagent (3 equiv.) in refluxing toluene for 2 h affords 1,4-di-t-butyl-2,5,7-trithia[2.2.1]heptane (2) in 42% yield and 2,5- and 2,6-di-t-butyl-1,4-dithiins (3 and 4) in 43% yields in the 1:4 ratio.

We have previously developed a convenient synthesis of 2,6-disubstituted 1,4-dithiins which involves treatment of readily accessible diketo sulfides with Lawesson's reagent (LR) or with phosphorus pentasulfide (Scheme 1).¹

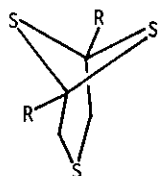


We now report that application of this method to sterically crowded bis(3,3-dimethyl-2-oxobutyl) sulfide (1) brings about the anomalous reaction which affords 1,4-di-t-butyl-2,5,7-trithiabicyclo[2.2.1]heptane (2) in addition to 2,5- and 2,6-di-t-butyl-1,4-dithiins (3 and 4) (Scheme 2).



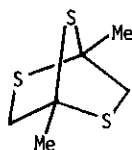
Diketo sulfide 1 is easily obtainable from pinacolone according to the literature method.² A mixture of 1 and LR (3 equiv.)³ in toluene was refluxed for 2 h under nitrogen. Chromatographic work-up of the reaction mixture gave 2 in 42% yield and a mixture of 3 and 4 in 43% yield in the 1:4 ratio. The ratio of 3 and 4 was determined by ¹H nmr analysis, and re-chromatography of the mixture allowed to isolate 3 and 4 in pure form.

The structure of 2 was determined in the following ways. Elemental analysis coupled to molecular weight determination by ms (M⁺, 262) reveals that the compound has a molecular formula of C₁₂H₂₂S₃. ¹H Nmr spectrum of 2 in CDCl₃ shows the presence of two equivalent methylenes (δ, 3.75; singlet) and t-butyls (δ, 1.34; singlet). ¹³C Nmr spectrum shows the presence of two equivalent quaternary carbons in addition to methylenes and t-butyls. Two structures 2 and 5 satisfy the observed nmr spectral data. Differentiation of these two structures by spectroscopic means seems to be difficult. Actually there had been considerable discussion about the structure of the product C₆H₁₀S₃ that is obtained by reaction of chloroacetone with hydrogen sulfide in ethanol saturated with hydrogen chloride; proposed structures for this compound involve 6 and 7.⁴⁻⁹ The correct structure was finally shown to be 7 by X-ray crystal structure analysis.¹⁰ Therefore, our compound was also analysed by X-ray single-crystal diffraction and unambiguously determined to be 2.¹¹



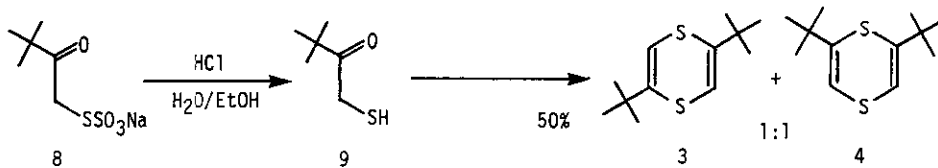
5 : R = t-Bu

6 : R = Me



7

Both 3^{12,13} and 4¹⁴ are known compounds and were identified by comparison with those prepared independently. It was reported that treatment of a mercapto ketone 9 with an acid catalyst affords 2,5-di-t-butyl-1,4-dithiin (3) as the sole product.^{12,13} Unexpectedly, however, when 9, prepared in situ by acid-catalyzed hydrolysis of the Bunte salt 8, was heated with alcoholic hydrogen chloride, a mixture of 3 and 4 was formed in 50% yield in the about 1:1 ratio. The formation of 4 may be explained by acid-catalysed isomerization of 3. It is known that treatment of 3 with aluminum chloride affords a mixture of 3 and 4.¹³

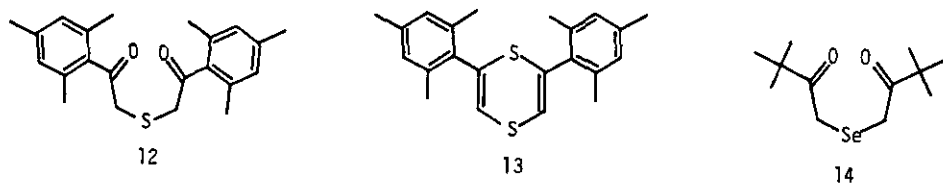


It is known that heating **9** with hydrochloric acid affords the bicyclic compound **10** in good yield, while the dithiin **3** is obtained in low yield when hydrogen chloride was bubbled into a refluxing solution of **9** in ether.¹² In the light of this observation and also of the formation of **7** by reaction of chloroacetone with hydrogen sulfide, the following seems to be probable as the mechanism of the formation of **2**; two molecules of a mercapto thioketone **11** or its synthetic equivalent are first formed from **1** by reaction with LR, and then self-condensation of **11** should lead to **2**.

The dithiin **4** must be formed from **1** in the usual manner,¹ and its isomer **3** may be formed either by isomerization of **4** or from **2** by loss of hydrogen sulfide.¹⁵



Although the diketo sulfide **12** is also sterically crowded, treatment of **12** with LR in refluxing toluene cleanly afforded the dithiin **13** in 80% yield. On the other hand, the reaction of sterically crowded diketo selenide **14** with LR gave an intractable complex mixture.



EXPERIMENTAL

Melting points were determined on a MEL-TEMP capillary tube melting point apparatus and are uncorrected. ^1H Nmr spectra were taken on a JEOL PMX-60 or on a JEOL FX-90Q spectrometer. ^{13}C Nmr spectra were recorded on a JEOL FX-90Q spectrometer. Mass spectra (ms) were determined on a JEOL JMS-D300 spectrometer. Column chromatography was conducted using E. Merck silica gel 60 (70-230 mesh).

Reaction of 1 with LR. A mixture of 1.46 g (6.3 mmol) of 1^2 and 7.7 g (19 mmol) of LR^3 in 100 ml of toluene was refluxed for 2 h under nitrogen. The mixture was cooled and the resulting precipitate was removed by filtration. The filtrate was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave 4.7 g of a viscous oil. ^1H Nmr analysis of the oil revealed that it contains 2,5- and 2,6-di-*t*-butyl-1,4-dithiins (3 and 4) in the ratio of about 1:4. The oil was chromatographed on a column of silica gel (200 g). Elution with hexane gave 710 mg (43%) of a mixture of 3 and 4 . The first-eluted part (350 mg) of the above oily mixture was re-chromatographed on a column of silica gel. Careful elution with hexane gave 50 mg of nearly pure crystalline 3 , a mixture of 3 and 4 , and 120 mg of pure oil of 4 in this order. Recrystallization of the crude 3 from methanol afforded pure material, mp 77.5-78 °C (lit.,¹² mp 80 °C). Further elution of the original column with carbon tetrachloride gave 700 mg (42%) of 1,4-di-*t*-butyl-2,5,7-trithiabicyclo[2.2.1]heptane (2), mp 86-86.5 °C, colorless needles from methanol.

2 : ^1H Nmr (CDCl_3) δ 1.34 (18H, s, Me), 3.75 (4H, s, CH_2); ^{13}C nmr (CDCl_3) δ 29.3 (q, Me), 36.9 (s, quaternary carbon of *t*-butyl), 52.9 (t, CH_2), 88.7 (s, bridge-head carbon); ms m/z 262 (M^+), 216, 215, 205, 201, 183, 147, 57 (base peak).

Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{S}_3$: C, 54.91; H, 8.45; S, 36.64. Found: C, 54.63; H, 8.25; S, 36.44.

3 : ^1H Nmr (CDCl_3) δ 1.20 (18H, s, Me), 5.93 (2H, s, dithiin ring).

4 : ^1H Nmr (CDCl_3) δ 1.23 (18H, s, Me), 6.10 (2H, s, dithiin ring); ^{13}C nmr (CDCl_3) δ 29.8 (q, Me), 38.4 (s, quaternary carbon of *t*-butyl), 116.7 (d, dithiin ring carbon carrying hydrogen), 151.7 (s, dithiin ring carbon carrying *t*-butyl).

Independent Synthesis of 3 and 4. A mixture of 1.80 g (10 mmol) of 1-bromo-3,3-dimethyl-2-butanone and 2.79 g (18 mmol) of sodium thiosulfate in 3.5 ml of water was stirred for 0.5 h at room temperature and then heated at 60 °C for 0.5 h.

The mixture was evaporated under reduced pressure. The residue was recrystallized from ethanol twice to give 0.89 g (31%) of sodium 3,3-dimethyl-2-oxobutyl thio-sulfate trihydrate (8), mp 91-92 °C; ^1H nmr (DMSO- d_6) δ 1.12 (9H, s, Me), 4.09 (2H, s, CH_2), 4.50 (ca. 6H, broad s, H_2O).

A mixture of 1.56 g (6.7 mmol) of 8, 3.8 ml of 12M hydrochloric acid, and 2 ml of ethanol was refluxed for 5.5 h. The mixture was diluted with water and extracted with ether. The extracts were washed with water, aqueous sodium bicarbonate, and water and dried over anhydrous sodium sulfate. The oily residue, obtained after evaporation of the ether, was subjected to silica gel column chromatography. Elution with hexane gave 150 mg of crystalline 3 contaminated with 4, 90 mg of an oily mixture of 3 and 4, and 60 mg of pure oil of 4. The total yield of 3 and 4 amounts to 50% and the ratio of 3 and 4 in the crude mixture, determined by ^1H nmr analysis, is 1:1. Recrystallization of the crude 3 from methanol gave pure material, mp 77-78 °C (lit.,¹² mp 80 °C).

2,6-Dimesityl-1,4-dithiin (13). To an ice-cooled and stirred solution of 1.26 g (6.4 mmol) of chloromethyl mesityl ketone¹⁶ in 22 ml of acetone was added a solution of 0.75 g (3.1 mmol) of sodium sulfide nonahydrate in 2 ml of water. After completion of the addition, acetone (40 ml) was added and stirring was continued for 5.5 h at room temperature. The mixture was diluted with water and extracted with dichloromethane. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on a column of silica gel. Elution with benzene gave 0.32 g (26%) of the starting material and 0.70 g (64%) of bis(2-mesityl-2-oxoethyl) sulfide (12), mp 133.5-135 °C; ^1H nmr (CDCl_3) δ 2.21 (6H, s, Me), 2.33 (12H, s, Me), 3.94 (4H, s, CH_2), 7.54 (4H, s, benzene ring). Exact ms: Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2\text{S}$, 354.1653; Found, 354.1622.

A mixture of 177 mg (0.5 mmol) of 12 and 600 mg (1.5 mmol) of LR in 15 ml of toluene was refluxed for 1 h under nitrogen. The mixture was cooled and the resulting precipitate was removed by filtration. The filtrate was evaporated and the residue was chromatographed on a column of silica gel. Elution with carbon tetrachloride gave 141 mg (80%) of 2,6-dimesityl-1,4-dithiin (13), mp 168-169 °C, yellowish brown crystals from hexane; ^1H nmr (CDCl_3) δ 2.15 (6H, s, Me), 2.27 (12H, s, Me), 6.39 (2H, s, dithiin ring), 7.24 (4H, s, benzene ring). Exact ms: Calcd for $\text{C}_{22}\text{H}_{24}\text{S}_2$, 352.1319; Found, 352.1298.

Reaction of 14 with LR. A mixture of 230 mg (0.8 mmol) of 14¹⁷ and 1.0 g (2.4 mmol) of LR in 15 ml of toluene was refluxed for 2.5 h under nitrogen. Analysis of the reaction mixture by tlc showed that a very complex reaction occurred. The mixture was not examined further.

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Received, 14th October, 1988