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BASE-INDUCED RING CLOSURE OF BIS-DITHIOACETALS VIA AN APPARENT CARBENOID. A NOVEL ROUTE TO FUNCTIONALIZED CYCLOBUTANES AND CYCLOPENTANES

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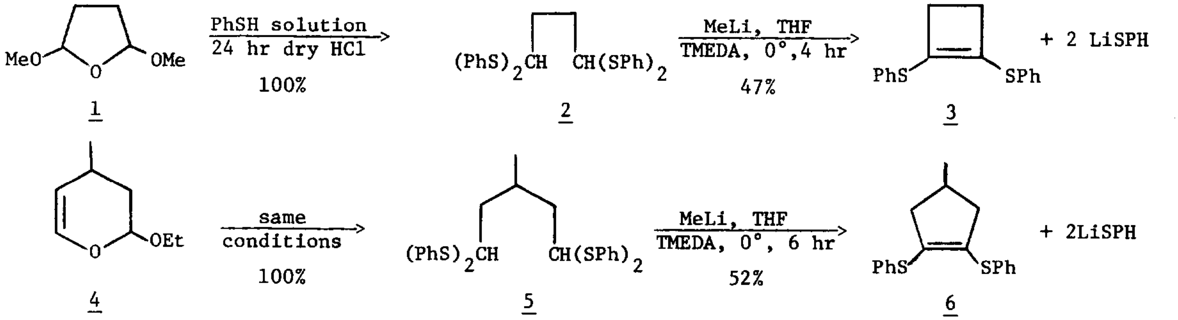
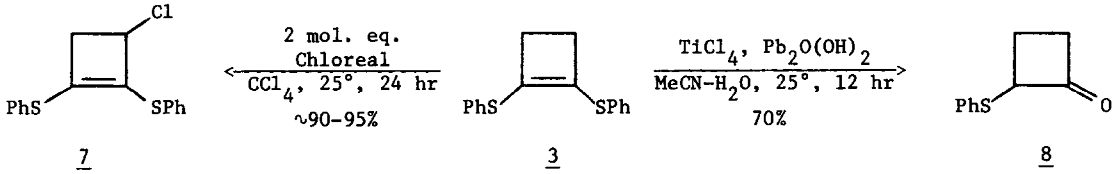
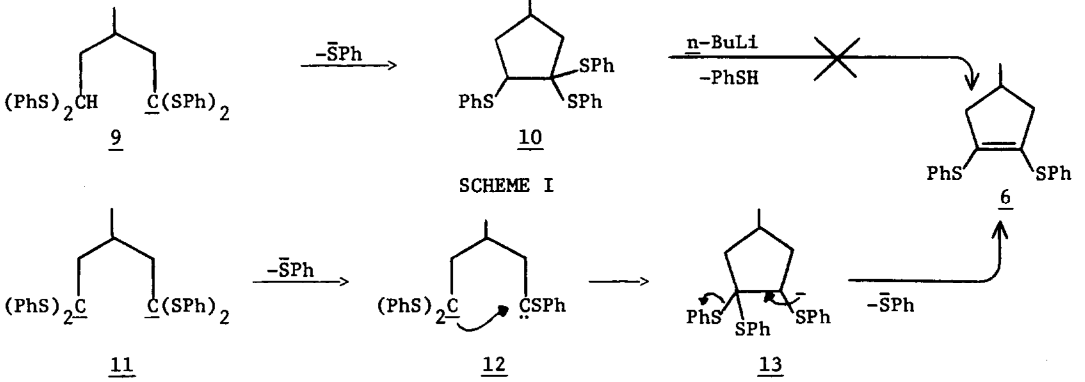
A recent report from this laboratory disclosed an extremely efficient preparation of cyclopropanone dithioketals by treatment of dithioacetals containing a 3-phenylthio substituent with methyllithium in tetrahydrofuran (THF) containing tetramethylethylenediamine (TMEDA) at 0°C.[1] We now report that remarkable ring closures to 4- and 5-membered rings occur when appropriate bis-dithioacetals are treated under the same conditions with four molar equivalents of methyllithium in THF containing four molar equivalents of TMEDA under argon; when two molar equivalents of methyllithium are used, the reaction is more sluggish. Treatment of 1,1,6,6-tetrakis(phenylthio)hexane[2] under the same conditions yields only ca. 5% of 1,2-bis(phenylthio)cyclohexene; the other products of this reaction are under investigation.[3]



The substrates, 2 and 5, are readily prepared from inexpensive, commercially available reactants.[5a,b] Because of the great synthetic versatility of sulfur in organic chemistry, a number of procedures for further elaboration of the cyclized products can be envisioned. Two of these have been demonstrated. Treatment of 3 with trichloroisocyanuric acid[6] (Chloreal) provides a high yield of slightly impure (7), the product of allylic chlorination;[7] this material which is too reactive to be purified by silica chromatography, should undergo useful transformations including hydrolysis to an enone. Hydrolysis of 3 in the presence of $TiCl_4$[8] provides a 70% yield of 2-(phenylthio)cyclobutanone (8), the starting material for Trost's synthesis of 2-oxygenated-3-sulfur-substituted-1,3-dienes;[9] one of the major attractions of this procedure is the great utility of α-(phenylthio)ketones[10] and, in the case of the 4-member ring, the presence of the phenylthio group has the added advantage of lowering the volatility and water-solubility of the cyclobutanone, thus improving its ease of handling. Even in its present unoptimized state, this procedure may be one of the most efficient methods for producing simple, usefully functionalized cyclobutanes.[11]



Ring closure of the monoanion (9) of the bis-thioacetal (5) to 10 by displacement of thiophenoxide ion (Scheme I) is ruled out as a first step by the finding[1] that 4- and 5-member rings are produced in only trace quantities from 4- and 5-phenylthio-substituted thioacetals and by the stability to the reaction conditions of 10, prepared by HCl-catalyzed addition of thiophenol to 6. A reasonable mechanism (Scheme II) involves loss of thiophenoxide ion from the dianion 11, extremely rapid ring-closure (possibly concerted with the loss of thiophenoxide ion) of the resulting carbene-anion 12, and expulsion of thiophenoxide from the ring-closed anion 13.



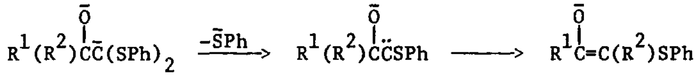
SCHEME I

SCHEME II

An analogy is the extensively studied[12,13] coupling of the tris(phenylthio)methyl anion (14), which is believed to proceed by loss of thiophenoxide ion in an unfavorable equilibrium and reaction of the resulting carbene with its anionic precursor with subsequent loss of thiophenoxide ion. A similar reaction occurs when groups other than phenyl are attached to sulfur.[14] Finally, an analogous intermolecular coupling has been observed with the anions of thioacetals, albeit those of benzaldehyde.[13,15,16]

$$(PhS)_3\bar{C} \xleftarrow{\rightarrow} Ph\bar{S} + (PhS)_2C: \xrightarrow{\underline{14}} (PhS)_2\bar{C}C(SPh)_3 \xrightarrow{-Ph\bar{S}} (PhS)_2C{=}C(SPh)_2$$

14

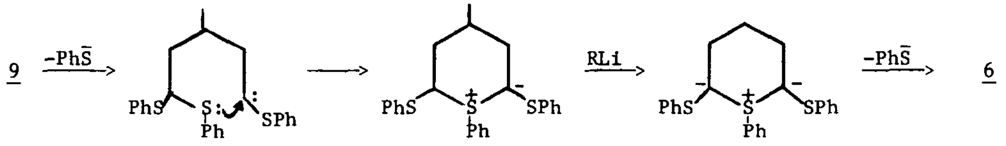


$$R^1(R^2)\overset{\bar{O}}{C}\bar{C}(SPh)_2 \xrightarrow{-\bar{S}Ph} R^1(R^2)\overset{\bar{O}}{C}\ddot{C}SPh \longrightarrow R^1\overset{\bar{O}}{C}{=}C(R^2)SPh$$

15 16 17

A possibly closer analogy for the carbene-forming step is the apparent loss of thiophenoxide from the dianion 15 to form a presumed carbene 16 which, by hydride or alkyl migration, leads to the enolate 17.[17] It is of interest that the two cases of the apparent formation of a carbene, which is stabilized by a single thio group and generated by loss of thiophenoxide, may both occur in dianions, thereby allowing rapid intramolecular carbene capture.

An alternative mechanism involves loss of thiophenol from the monoanion 9 to yield carbene 18, attack of sulfur on the carbenoid carbon atom, deprotonation of the resulting ylide 19 by methyllithium, and collapse of the resulting anion-ylide (20) to 6, possibly via 12 and 13. Other variations in the timing of events are also possible; for example, a thioacetal sulfur atom of 12 could attack the carbene carbon atom leading to 20.



18 19 20

When the reaction in which 5 was being converted to 6 was quenched with D_2O at approximately one third completion, most of the recovered starting material was found to be monodeuterated. This result is consistent with any of these mechanisms provided that in the dianion mechanisms, removal of the second proton is the rate determining step.

These highly unusual ring closures by 1,4- and 1,5-elimination of thiophenol may be capable of considerable variation. Further study is in progress.

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References and Notes

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2. This substance was prepared in 81% yield by the reaction of 1,4-diiodobutane with the cuprate[4] of the lithio derivative of bis(phenylthio)methane at -78° for 3 hr.

3. All products were characterized by ^{1}H NMR, IR, and mass spectroscopy. Elemental compositions were determined for new compounds by combustion analysis or exact mass determination.

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5. (a) Compounds 1 and 4 are available from Aldrich. The desmethyl analogue of 4 is also offered by Aldrich. (b) The conversion of 1 to 2 was carried out previously in this laboratory;[5c] a bisdithioacetal had previously been prepared from 1 by the use of propane-1,3-dithiol by D. Seebach, N. R. Jones, and E. J. Corey, J. Org. Chem., 33, 300 (1968). (c) A. J. Mura, Jr., Ph.D. Thesis, University of Pittsburgh, 1977.

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