Tetrahedron Letters No. 33, pp 2991 - 2994.

0040-4039/78/0808-2991$02.00/0

A CONVENIENT ROUTE TO CYCLOPROPANONE DITHIOKETALS. THE THIOPHENOXIDE ANION AS A NUCLEOFUGAL LEAVING GROUP

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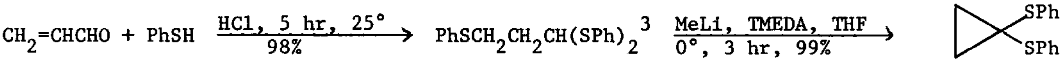
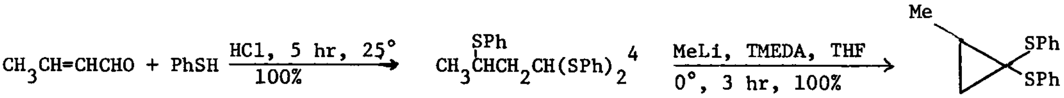
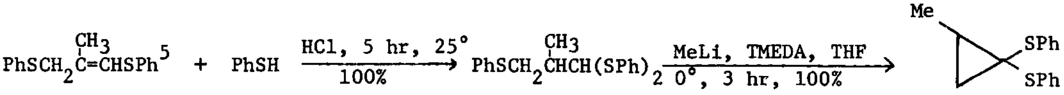
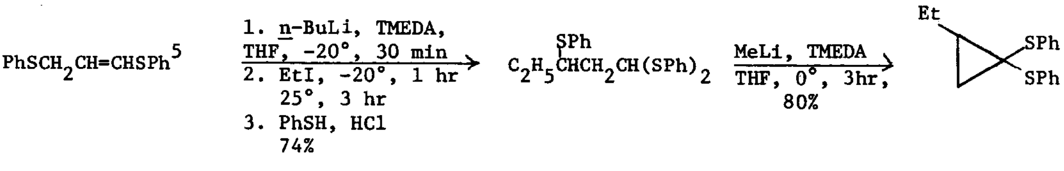
Cyclopropanone dithioketals are available from a variety of routes but many of these suffer from lack of generality, excessive length, and/or low yields.[1] We now describe a new high-yield procedure of some generality. The key feature is the elimination of thiophenol from a 1,1,3-tris(phenylthio)alkane induced by one molar equivalent of methyllithium in tetrahydrofuran (THF) containing two molar equivalents of tetramethylethylenediamine (TMEDA). The yields in this ring closure are not only high and in many cases quantitative as indicated by eq 1-5, but the reactions are remarkably clean; the pure product[2] is frequently obtained by evaporation of the ether extract after aqueous work-up. Furthermore, the method is rather flexible in that the substrates for the ring closures can be obtained by the treatment of a variety of compound types with benzenethiol and dry HCl; several examples are given.

(1) 

(2) 

(3) 

(4) 

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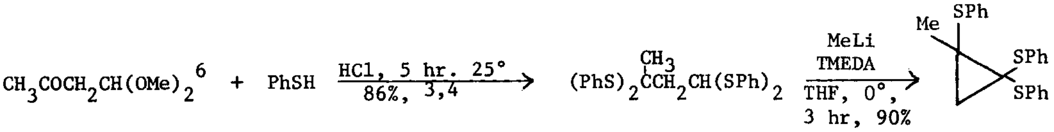

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The simplest mechanistic picture is the formation of the anion 2 followed by an intramolecular nucleophilic displacement of thiophenoxide ion. However, the behavior of thiophenoxide ion as a leaving group in an SN2 displacement is apparently unprecedented. Furthermore, the production of 1 (eq 5) proceeds in quite satisfactory yield despite the necessity for attack by a bulky nucleophile on a highly congested carbon atom. An alternative and quite credible mechanism involves the loss of thiophenoxide from 2 and intramolecualr capture of the resulting carbene (3) by the thioether group to yield the 4-member ring ylide 4, which by Stevens rearrangement would be expected to yield the cyclopropane 5 (eq 6)[7]. There is ample precedent[8] for the loss of thiophenoxide from sulfur stabilized anions, including thioacetal anions[8b], to produce carbenes. Furthermore, it has been shown[9] that 3-(phenylthio)carbenes do indeed yield cyclopropanes, apparently by way of 4-member-ring ylides.

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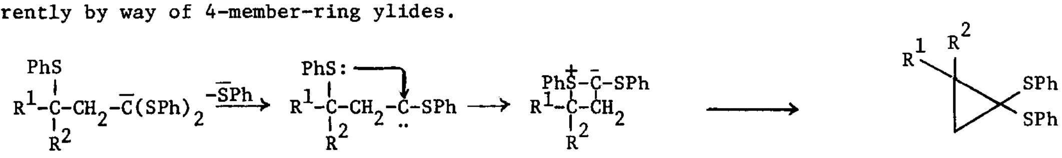
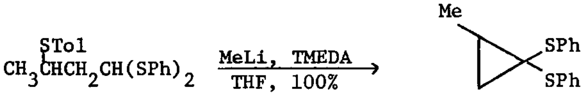


2 3 4 5

The SN2 mechanism predicts the loss of the 3-phenylthio group whereas the carbene mechanism predicts the loss of one of the 1-phenylthio groups. 1,1-bis(Phenylthio)-3-(p-tolylthio)butane (6) was prepared by the β-addition of p-thiocresol to crotonaldehyde, in the presence of triethylamine (yield 71%), and treatment of the 3-(p-tolylthio)butanal with PhSH and HCl (95% yield). When 6 was treated under the standard ring closure conditions, the cyclopropane, produced in quantitative yield, was identical to that formed in eq 2 and 3. Thus, the tolylthio group is cleanly lost and the ring closure is revealed as an apparently unique example of an SN2 reaction in which thiophenoxide is the leaving group.



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No more than trace amounts of 4- and 5-member rings were formed when the appropriate substrates[10] were submitted to the ring-closure conditions.

The synthetic methods reported here nicely complement those[1] in which one of the cyclopropyl carbon atoms is added during the construction of the 3-member ring. It may very well supplant those[11] more cumbersome and lower yield methods which proceed from α,β-unsaturated aldehydes, provided that phenylthioacetals are desired. It is doubtful if the product (**1**) of eq 5 could be prepared satisfactorily from any of the extant procedures. The finding that thiophenoxide can be efficiently displaced during 3-member ring formation may have implications with regard to cyclopropane construction in which anions other than those of thioacetals may behave as the nucleophile; this concept is under exploration.

Braun and Seebach[1] have demonstrated a number of interesting ring-opening reactions of cyclopropanone dithioketals and other uses for these compounds as synthetic intermediates can be envisioned. Perhaps the most important of these is the conversion of these products to the lithio derivatives of cyclopropyl phenyl sulfides, a class of intermediates with great actual[12] and potential[13] synthetic utility; this conversion has been brought to practice and will be reported shortly. Given the ease with which phenylthio groups are reductively removed, the present procedure may also be a considerably more satisfactory method of converting enals to cyclopropanes, via connection of the 1- and 3-carbon atoms, than the recently reported, lengthier procedures which result in an inseparable mixture of the cyclopropane with its open-chain reduction product.[14]

Acknowledgements. We wish to thank Mr. Glen Herman for recording the mass spectra, the National Institutes of Health for support of this work (GM 22760), and the Chemistry Department of the University of North Carolina at Chapel Hill for its hospitality to T.C. while he was on leave there during the writing of this paper.

References and Notes

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2. All products were characterized by ^{1}H NMR, infrared, and mass spectroscopy. Elemental compositions were determined for all new compounds either by combustion analysis or exact mass determination.
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4. The first observation of such ring closures was made by Dr. D. W. Shull when this thioacetal was treated with methyllithium in order to exchange the thioacetal proton for a deuteron. The preparation of both labeled and unlabeled thioacetals is described in: T. Cohen, A. J. Mura, Jr., D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, J. Org. Chem., 41, 3218 (1976).
5. These compounds are prepared in over 90% yield from commercially available allyl or methallyl phenyl sulfide: T. Cohen, D. A. Bennett, and A. J. Mura, Jr., J. Org. Chem., 41, 2506 (1976).
6. Aldrich Chemical Company.
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8. (a) D. Seebach, Chem. Ber., 105, 487 (1972) and references there cited; (b) I. Kuwajima, H. Shinozaki and S. Hayakawa, Chem. Lett., 197 (1973); T. Cohen and W. M. Daniewski, unpublished observations; P. Beak and J. W. Worley, J. Am. Chem. Soc., 94, 597 (1972); L. Léger and M. Saquet, Bull. Soc. Chim. France, 657 (1975).
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14. T. Shono, Y. Matsumura, S. Kashimura and H. Kyutoku, Tetrahedron Lett., 1205 (1978); Y-H. Chang, D. E. Campbell, and H. W. Pinnick, ibid, 3337 (1977).

(Received in USA 15 May 1978; received in UK for publication 20 June 1978)