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A SIMPLE PREPARATION OF SULFUR-STABILIZED CYCLOPROPYL ANIONS VIA REDUCTIVE LITHIATION OF CYCLOPROPANONE DITHIOKETALS.

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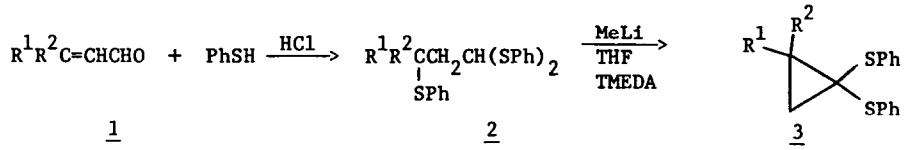
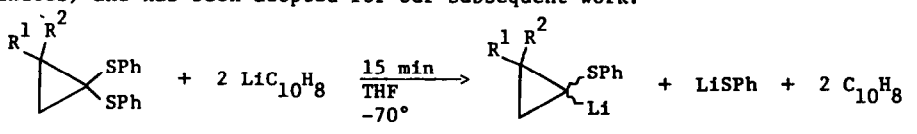
A new very simple method for the preparation of cyclopropanone dithioketals (3) in quantitative or nearly quantitative yields was recently reported from this laboratory.[1] It consists of the 1,3-elimination of thiophenol from a 1,1,3-tris(phenylthio)alkane (2); the latter are available in quantitative yield from conjugated enals, as shown in the example below, or in a similar fashion from other readily available precursors.[1]



1 2 3

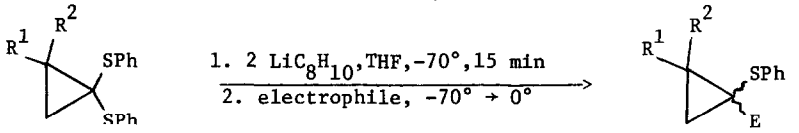
Other methods of preparation of cyclopropanone dithioketals are also known.[2]

The ready availability of such compounds would make them very attractive precursors of sulfur-stabilized cyclopropyl anions if a method of reductive metalation could be found. We have surveyed several likely possibilities, three of which were successful as judged by liquid chromatograms of the cyclopropyl phenyl sulfide formed by reductive lithiation of 3 (R^1=R^2=H) followed by quenching with water: 1) metal-thiophenoxy exchange with t-butyllithium in THF at 0°C (70% reduction);[3,6] 2) reduction with lithium metal in a mixture of ether and hexamethylphosphoric triamide (90% reduction); 3) reduction with two equivalents of lithium naphthalenide[8] in THF at -70° (100% reduction). The latter method is far superior in ease of operation, mildness of conditions, and speed (decolorization of the reagent occurs in less than 15 minutes) and has been adopted for our subsequent work.[9]



3 4

The results of the reductive lithiations followed by reactions of the anions with some electrophiles are summarized in the table.[11] The product yields are generally satisfactory for trapping with carbon dioxide and benzaldehyde. As found by Trost,[7] enolization becomes a problem with cyclic ketones and the problem is exacerbated by a methyl substituent on the cyclopropane ring. The yield of methylation product was decreased by losses sustained in the difficult HPLC separation required in that case.

Table 

R^1	R^2	Electrophile [a]	E	Yield, % [b]
H	H	CO_2	CO_2H	94
H	H	PhCHO	PhCHOH	71
H	H	Cyclohexanone	$(CH_2)_5$⌒COH	53
H	H	MeI	Me	49
Me	H	CO_2	CO_2H	86 [c]
Me	H	PhCHO	PhCHOH	76 [c]
Me	H	Cyclohexanone	$(CH_2)_5$⌒COH	21 [c]
Me	Me	CO_2	CO_2H	78
Me	Me	PhCHO	PhCHOH	53

[a] 1.1 molar eq. except in case of MeI in which 6 molar eq. were used. [b] After silica chromatography except in the case of carboxylic acids. [c] Two stereoisomers.[14]

The reductive lithiation is carried out as follows. To a solution containing 10 ml of THF and 4.2 ml (2.1 mmol) of a 0.50 M stock solution of lithium naphthalenide (prepared by stirring a mixture of equimolar quantities of lithium chips and naphthalene in THF at 25°C for 6 hr) at -70° was added 1.0 mmol of the thioketal dissolved in 3 ml of THF. After the solution had been stirred for 15 min, the electrophile was added and the solution was stirred for 5 min at -70° and for 3 hr at 25°. Standard extraction procedures yielded the product which, in the case of carbonation, was pure by ^{1}H NMR spectroscopy as well as by GLC analysis of the ester formed upon treatment with diazomethane; in other cases, the product had to be separated from naphthalene by silica chromatography using 5% ethyl acetate in hexane.

Trost has prepared the parent lithium derivative 4 (R^1=R^2=H) quantitatively by deprotonation at 0°C for 2 hr with n-butyllithium of cyclopropyl phenyl sulfide which was obtained in 71% yield by a 2-step procedure starting from 1-bromo-3-chloropropane. For many purposes, generation by the sequence 1→4 (R^1=R^2=H) may be preferable because of the quantitative yield in all steps, the lower price of starting materials, the ease and speed of the reactions, and the mild conditions of the lithiation step. In some cases, however, the byproducts in the present procedure may be objectionable.

In the case of 2-methylcyclopropyl phenyl sulfide, removal of the proton was found by Trost[7] to be far slower and incomplete. On the other hand, the present procedure yields the anion 4 (R^1=Me; R^2=H) just as readily as the unsubstituted one. In order to determine if greater steric hindrance would be detrimental, the gem-dimethylcyclopropanone dithioketal (3; R^1=R^2=Me) was prepared in quantitative yield from 2 and was found to undergo reductive lithiation about as rapidly as the unsubstituted isomer.

The anion of cyclopropyl phenyl sulfide (4; R^1=R^2=H) has been imaginatively exploited by Trost[12] in a variety of new synthetic techniques and many other uses can be envisioned.[13] Some of this technology may now be vastly extended by the use of any of a great variety of conceivable ring substituted anions. We are investigating a number of these possibilities as well as the use of reductive lithiation for the production of other sulfur-stabilized anions.

Acknowledgements. We thank Messrs. Glen Herman and Daniel Ouellette for recording the mass spectra and the National Institutes of Health for support of this work (GM 22760).

References and Notes

1. T. Cohen and W. M. Daniewski, Tetrahedron Lett., 2991 (1978).
2. M. Braun and D. Seebach, Chem. Ber., 109, 669 (1976) and references cited therein.
3. Metal-halogen exchange is quite common and has been used to prepare cyclopropyllithium.[4] Metal-thiophenoxy exchange has been used in certain cases in which the carbanion produced is highly stabilized.[5]
4. J. P. Marino and L. J. Browne, J. Org. Chem., 41, 3629 (1976). See also: E. J. Corey and P. Ulrich, Tetrahedron Lett., 3685 (1975).

5. L. Brandsma, Rec. Trav. Chim. Pays-Bas, 83, 307 (1964); G. A. Wildchut, H. J. T. Bos, L. Brandsma, and J. F. Arens, Monatsh. Chem., 98, 1043 (1967); D. Seebach, Angew. Chem., Intern. Ed. Engl., 6, 442 (1967).

6. The anion was also trapped by 2-methylcyclohexanone to give a 50% yield of the adduct[7].

7. B. M. Trost, D. E. Keeley, H. C. Arndt, J. H. Rigby, and M. J. Bogdanowicz, J. Am. Chem. Soc., 99, 3080 (1977).

8. N. L. Holy, Chem. Rev., 74, 243 (1974).

9. The idea of using lithium naphthalenide grew out of a conversation between T.C. and Dr. William Kitching of Queensland University. While this reagent was being investigated (our success in this endeavor was mentioned briefly in our prior paper[1]), a report appeared describing the reductive lithiation of n-alkyl phenyl thioethers by lithium naphthalenide at -55°C to -20°C.[10]

10. C. G. Screttas and M. Micha-Screttas, J. Org. Chem., 43, 1064 (1978).

11. New compounds were characterized by ^{1}H NMR, IR, and mass spectroscopy and by their exact masses as determined by high resolution mass spectroscopy.

12. B. M. Trost, Acc. Chem. Res., 7, 85 (1974); B. M. Trost and D. E. Keeley, J. Am. Chem. Soc., 98, 248 (1976); B. M. Trost, D. E. Keeley, H. C. Arndt, and M. J. Bogdanowicz, ibid., 99, 3088 (1977); B. M. Trost and J. H. Rigby, J. Org. Chem., 43, 2938 (1978).

13. Useful synthetic techniques utilizing cyclopropyl anions or cuprates have recently been presented: J. P. Marino and L. J. Browne, J. Org. Chem., 41, 3629 (1976); J. P. Marino and L.J. Browne, Tetrahedron Lett., 3245 (1976); E. Piers, C. K. Lau, and I. Nagakura, ibid., 3233 (1976); E. Piers and I. Nagakura, ibid., 3237 (1976).

14. In the case of carbonation, glc analysis of the methyl esters indicated that the two isomers were present in a ratio of 3:2; however, the configurations were not determined. In the other two cases, isomer ratios were not determined.

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