Tetrahedron Letters No. 41, pp 3653 - 3656, 1974. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF CYCLOBUTANONES
USING METHYL METHYLTHIOMETHYL SULFOXIDE

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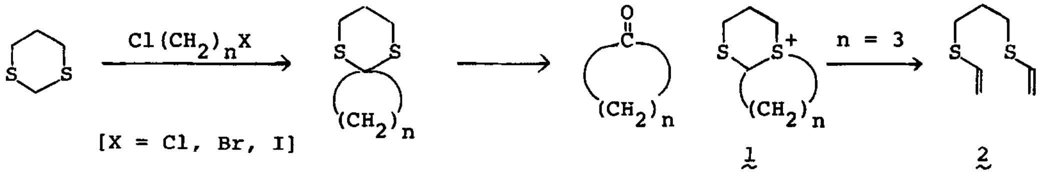
(Received in Japan 1 August 1974; received in UK for publication 3 September 1974)

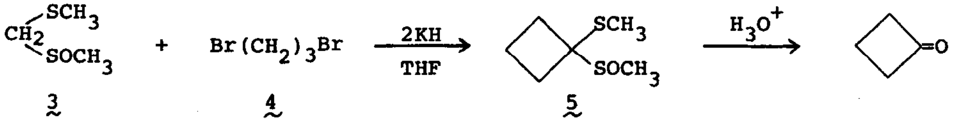
An elegant synthesis of cyclic ketones by the reaction of 1,3-dithiane with α,ω-dihaloalkanes has been developed by Seebach and Corey.[1] To practice this synthesis, however, the use of ω-chloroalkyl bromide (or iodide) or an excessive amount of α,ω-dichloroalkane is necessitated to avoid the undesirable formation of disubstituted products. The use of α,ω-dibromoalkanes appeared to be also impractical because of the formation of cyclic sulfonium salts (**1**). Treatment of **1** (n = 3) with a base gave 1,3-bis(vinylthio)propane (**2**) (scheme 1).

Scheme 1

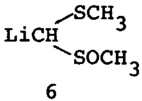


We have found that the reaction of methyl methylthiomethyl sulfoxide (**3**)[2] with α,ω-dibromoalkanes in the presence of a base results in the exclusive formation of cyclic ketone dimethyl dithioacetal S-oxides, and this letter describes a convenient two-step synthesis of cyclobutanone derivatives from 1,3-dibromo(or tosyloxy)alkanes which can be prepared from easily accessible 1,3-diols.

Scheme 2



Methyl methylthiomethyl sulfoxide (3, 1.044 g, 8.42 mmol)[3] was treated with 1.89 g (2.80 equiv) of potassium hydride (50% content, dispersed in mineral oil) in tetrahydrofuran (THF) at 0° for 1 hr. 1,3-Dibromopropane (4, 2.070 g, 10.25 mmol) was added dropwise during 10 min and the mixture was kept stirring at 0° for 1 hr and then at room temperature for 17 hr. After addition of methylene chloride (100 ml), the solid deposited was filtered off. Evaporation of the solvent left an oil which was subjected to column chromatography (on silica gel, eluted with methylene chloride, ether, and methanol) to afford, together with the recovery of 3 (199 mg), 1.081 g (97%, based on the unrecovered 3) of cyclobutanone dimethyl dithioacetal S-oxide (5) as a pale yellow oil[4]; IR (neat): 1052 cm^{-1}; NMR ($CDCl_3$): δ 1.5 - 3.1 (6H, m), 2.13 (3H, s), and 2.47 (3H, s). The dithioacetal S-oxide (5) was also formed in 45% yield (78%, based on the unrecovered 3) by the reaction of 1.3 mol-equiv of 4 with the lithio derivative (6)[5] of 3 in THF at -10° - room temperature.[6] Interestingly, the use of 2.02 mol-equiv of 6 increased the yield of 5 up to 70%. Similarly, 1,3-ditosyloxypropane gave 5 in 91% yield.

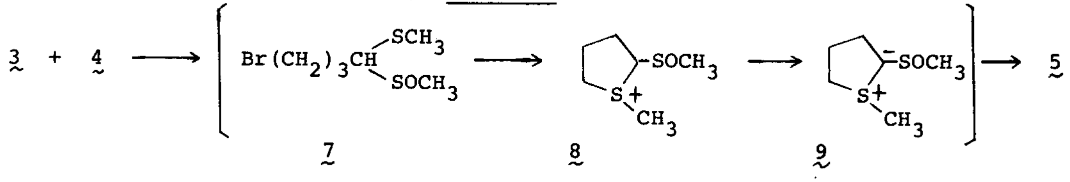


$LiCH(SCH_3)(SOCH_3)$

6

It is remarkable that the monosubstituted product (7) and disubstituted product were not obtained in the present cyclization reaction. This unexpected result may be accounted for by the following reaction scheme involving an intermediacy of a cyclic sulfonium salt (8).

Scheme 3

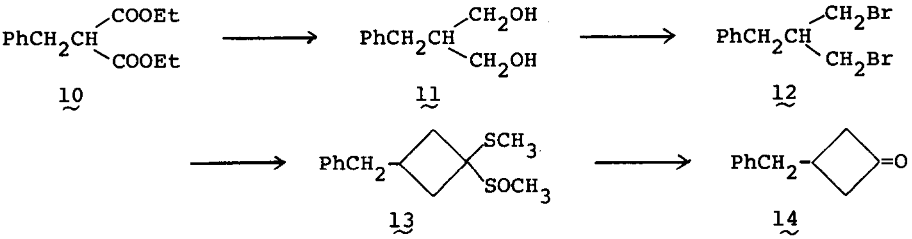


The easy production of the four-membered ring which is otherwise difficult to be formed,[8] may be rationalized by assuming an intermediary formation of five-membered cyclic sulfonium salt (8) which is finally converted into 5 by the Stevens-type rearrangement[9] as depicted in Scheme 3. Conceivably, methylthio group in 3 facilitates the formation of the sulfonium salt (8) and methylsulfinyl group governs the direction of the rearrangement (9 → 5) by assisting the formation of the carbanion (9).[10]

Since dithioacetal S-oxide groups can be transformed into the corresponding carbonyl groups by the acid-catalyzed hydrolysis,[2,7] this one-step cyclization provides a synthetic route to cyclobutanone derivatives. In fact, the hydrolysis of **5** was easily achieved. To a solution containing **5** (482 mg) in ethanol (3 ml), was added 8 drops of 9<u>N</u> sulfuric acid and the solution was stirred at room temperature for 18 hr and at 45° for 5 hr to give cyclobutanone (79% yield), which was identified as its 2,4-dinitrophenylhydrazone; mp 146.5 - 148° (lit.[11] mp 146°).

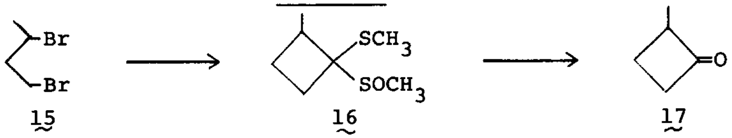
A simple and convenient method of synthesizing 3-substituted cyclobutanones is given by the combination of the malonic acid synthesis[12] and the present cyclization reaction. Thus, the reaction of 2-benzyl-1,3-dibromopropane (**12**), synthesized starting from diethyl benzylmalonate (**10**),[13] with **6** (2.31 mol-equiv) in THF afforded 3-benzylcyclobutanone dimethyl dithioacetal S-oxide (**13**) in 76.5% yield (Scheme 4).[15] The hydrolysis of **13** was effected with 9<u>N</u> sulfuric acid in refluxing ether to yield 3-benzylcyclobutanone (**14**) in 89% yield.

Scheme 4



This method is also applicable to the synthesis of 2-substituted cyclobutanones. The reaction of 1,3-dibromobutane (**15**) with **6** (2.42 mol-equiv) furnished 2-methylcyclobutanone dimethyl dithioacetal S-oxide (**16**, 80%), which was easily converted into 2-methylcyclobutanone (**17**, 77%) by the acid-hydrolysis.

Scheme 5



Further synthetic application of this type of cyclization to five- or six-membered ring compounds is the subject of an on-going study.

REFERENCES AND REMARKS

1. a) E. J. Corey and D. Seebach, Angew. Chem. Int. Ed. Engl., **4**, 1075, 1077 (1965); b) D. Seebach, N. R. Jones, and E. J. Corey, J. Org. Chem., **33**, 300 (1968); c) D. Seebach and A. K. Beck, Org. Syn., **51**, 76 (1971).
2. We have reported new methods of synthesizing labile aldehydes, phenylacetic acid derivatives, α-hydroxyaldehydes, and α-amino acids by using 3. K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 3151 (1971), 1383, 2681 (1972); J. Amer. Chem. Soc., **96**, 1960 (1974).
3. This reagent is now commercially available. Since 3 is hygroscopic, it need be dried over molecular sieves (Linde type 3A or 4A) prior to use.
4. The oxidation of 5 with hydrogen peroxide in methanol catalyzed by Na_2WO_4 afforded cyclobutanone dimethyl dithioacetal S,S,S',S'-tetraoxide, mp 141.5 - 142°; IR (KBr): 1295, 1140, 1110, 945, 771, and 505 cm^{-1}, NMR ($CDCl_3$): δ 2.0 - 2.6 (4H, m), 2.7 - 3.1 (4H, m), and 3.15 (6H, s). Anal. Calcd for $C_6H_{12}O_4S_2$: C, 33.94; H, 5.70; S, 30.21. Found: C, 33.99; H. 5.66; S, 30.27.
5. The lithio derivative (6) was obtained from 3 by the action of n-butyl lithium.
6. The reaction of the lithio derivative of ethyl ethylthiomethyl sulfoxide with 1,3-dibromopropane (1.3 mol-equiv) was reported to result in the formation of 4-bromobutyraldehyde diethyl dithioacetal S-oxide.[7]
7. J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, Tetrahedron Lett., 3267 (1973).
8. W. H. Perkin, J. Chem. Soc., 1347 (1929).
9. A. R. Lepley and A. G. Giumanini in "Mechanisms of Molecular Migrations", Vol. 3, B. S. Thyagarajan Ed., Wiley-Interscience, New York, N. Y., 1971, pp 297 - 440.
10. We are now investigating the detailed mechanism of this cyclization reaction.
11. N. J. Demjanov and M. Dozarenko, Ber., **55**, 2739 (1932).
12. A. C. Cope, H. L. Holmes, and H. O. House, Org. React., **9**, 107 (1957).
13. The reduction of diethyl benzylmalonate (10) with $LiAlH_4$ yielded 2-benzylpropane-1,3-diol (11) in almost quantitative yield, which was treated with carbon tetrabromide (2 mol-equiv) and triphenylphosphine (2 mol-equiv) in acetonitrile to give 2-benzyl-1,3-dibromopropane (12) in 79% yield.[14]
14. E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, J. Amer. Chem. Soc., **92**, 2139 (1970).
15. The use of 3 (1 mol-equiv) and potassium hydride (2 equiv) failed to afford 13 in satisfactory yield in this particular case.