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A NOVEL SYNTHESIS OF CYCLIC KETONES USING METHYL METHYLTHIOMETHYL SULFOXIDE

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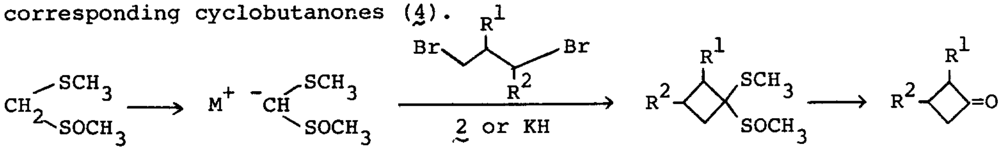
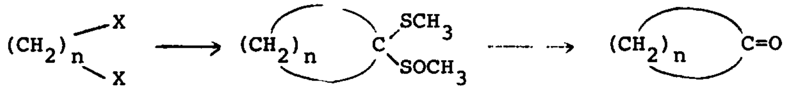
Our earlier paper[1] described a new method of making cyclobutanone derivatives, which consists of two processes, i.e., a one-step formation of cyclobutanone dimethyl dithioacetal S-oxide derivatives (3) by the reaction of 1,3-dibromo(or tosyloxy)alkanes with the carbanion (2), derived from methyl methylthiomethyl sulfoxide (1), and the subsequent acid-hydrolysis of 3 to the corresponding cyclobutanones (4).



1 2 3 4

The former cyclization reaction is remarkable in view of the one-step and high-yield formation of a strained four-membered ring from a 1,3-dibromoalkane without conducting under conditions of high dilution. We have further investigated on the application of this potential method to the preparation of other ring systems, and we now wish to report the scope and limitations for the general synthesis of cyclic ketones[2] from 1,ω-dihalo(tosyloxy)alkanes by the reaction with the carbanion (2), as well as the preparation of tetrahydro-γ-pyrone and 3-cyclopentenone.

For the reaction of a 1,ω-dihalo(or tosyloxy)alkane (5) and methyl methylthiomethyl sulfoxide (1), two types of procedures were employed: (a) After treating 1 with potassium hydride (2.2-2.8 equiv to 1) in tetrahydrofuran (THF), 5 was added dropwise and the resulting mixture was stirred at -10°-room temperature (designated as "Method A"), and (b) 5 was subjected to react with 2.0-2.5 mol-equiv of the carbanion (2, M = Li)[3] in THF at -70°-room temperature (designated as "Method B"). The products (6) were isolated by column-chromatography on silica gel or Florisil (eluted with methylene chloride and ethyl acetate).[4] The hydrolysis of 6 to the corresponding ketone (7) was easily achieved by treating with a small amount of 9N sulfuric acid in diethyl ether or ethanol at room temperature. The results were summarized in Table 1.



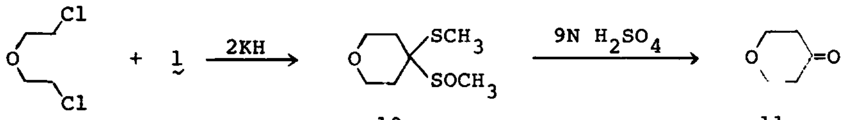
5 6 7

Table 1. The Yields (%) of 5 → 6 and 6 → 7.

	5 → 6			6 → 7[d]
	X = Br		X = TolSO$_3$	
	(Method A)	(Method B)	(Method B)	
n = 2	trace	33	78	--
n = 3	78	70	91	79
n = 4	80	80	84	92
n = 5	82	74	80	88[5]
n = 6	none[a]	none[b]	none[c]	--

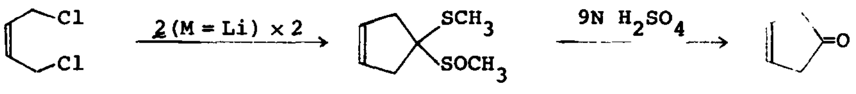
[a] 1,8-Bis(methylsulfinyl)-1,8-bis(methylthio)octane (8) and 1-methylsulfinyl-1-methylthio-7-bromoheptane (9) were obtained in 24% and 11% yields, respectively. [b] The yields of 8 and 9 were 20% and 22%, respectively. [c] The former product (8) was isolated in 23% yield. [d] Trapped as the corresponding 2,4-dinitrophenylhydrazone derivatives.

Versatility of this method is exemplified by the synthesis of tetrahydro-γ-pyrone (11).[6] The reaction of 1 with bis(2-chloroethyl) ether in the presence of potassium hydride (2.4 equiv) in THF afforded the dimethyl dithioacetal S-oxide (10) which was subjected to the acid-hydrolysis, followed by the fractional distillation to give 11 in an over-all yield of 66%.



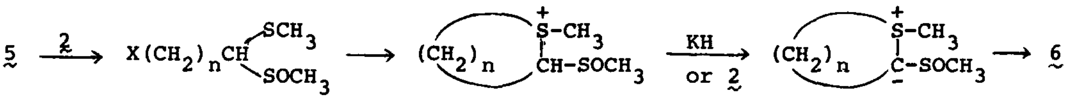
10 11

3-Cyclopentenone (14) could also be synthesized. According to the Method B, cis-1,4-dichloro-2-butene (12) gave 3-cyclopentenone dimethyl dithioacetal S-oxide (13, 75% yield)[7] which was smoothly converted into 14 (60% yield) on treatment with 9N sulfuric acid in acetone-water (9 : 1) at room temperature.[8]



12 13 14

The present method could be utilized favorably for the synthesis of four-, five-, and six-membered cyclic ketones as mentioned above, whereas the Dieckmann condensation method is suitable for the formation of five-, six-, and seven-membered cycloalkanone derivatives.[10] It should also be noted that a 1,ω-dihalo-(or tosyloxy)alkane (5) afforded the cyclic compound (6) in high yield by the reaction with more than two mol-equiv of the carbanion (2), indicating the involvement of a more acidic intermediate than 1. These facts seem to be in accord with the previously-proposed hypothesis that the present cyclization reaction may involve the formation of an intermediary sulfonium salt (18), followed by the Stevens-type rearrangement to 6.[11]



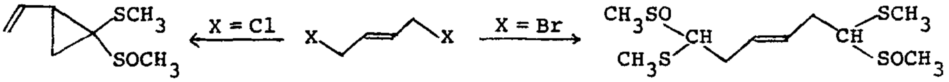
18 19

We are continuing our studies on the mechanism and further synthetic application of this intriguing cyclization.

REFERENCES AND REMARKS

1. K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 3653 (1974).
2. Two-step cyclization reaction of 1,ω-dihaloalkanes with 1,3-dithiane was reported: (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).

3. The carbanion (2, M = Li) was obtained by the addition of n-butyl lithium (n-hexane solution) to a solution of 1 in THF at about -10°.
4. Satisfactory elemental analyses and acceptable spectral data were obtained for all new compounds reported herein.
5. Direct transformation into diethyl acetal of cyclohexanone can be achieved on treatment of 6 (n = 5) with ethyl orthoformate in ethanol in the presence of conc. sulfuric acid.
6. G. R. Owen and C. B. Reese, *J. Chem. Soc.* (C), 2401 (1970).
7. In the reaction of 2 with 1,4-dihalo-2-butenes, it was found that the different kinds of products were formed, depending upon the nature of halogen atom and the geometry at the carbon-carbon double bond. Thus, trans-1,4-dichloro-2-butene (15, X = Cl) gave 2-vinylcyclopropanone dimethyl dithioacetal S-oxide (16, 75% yield) under the analogous condition to the Method B, while 1,6-bis(methylsulfinyl)-1,6-bis(methylthio)-3-hexene (17) was formed in 48% yield, together with a small amount of 16, by the reaction of trans-1,4-dibromo-2-butene (15, X = Br) with 2 (M = Li).



16 15 17

8. 2-Cyclopentenone (20) was also detected (6% yield) by gas-chromatographic analysis. The structures of 14 and 20 were confirmed by the comparison of their retention-times on gas chromatography and their mass spectra with those of the corresponding authentic specimens.[9]
9. H. M. Hess and H. C. Brown, *J. Org. Chem.*, **32**, 4138 (1967).
10. J. P. Schaefer and J. J. Bloomfield, *Org. Reactions,* **15**, 1 (1967).
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