Tetrahedron Letters Vol. 21, pp 4811 - 4814 0040-4039/80/1208-4811$02.00/0
©Pergamon Press Ltd. 1980. Printed in Great Britain

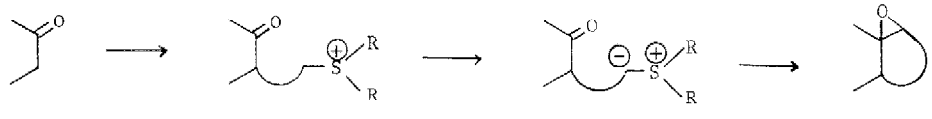
Epoxyannulation II: Cyclization of ω-Ketosulfonium Salts

M. E. Garst* and A. T. Johnson[1]
Department of Chemistry
University of California, San Diego
La Jolla, California 92093

Abstract: Treatment of 1,5 or 1,6 ketosulfonium salts with potassium t-butoxide has yielded cyclic epoxides of high stereochemical purity in good yield.

Sulfur ylide reactions provide many useful synthetic transformations, including the conversion of enones to cyclopropyl carbonyls and of ketones or aldehydes to epoxides. Intramolecular variants could be valuable ring forming reactions but have not been investigated in detail (Scheme 1).[2-5]

Scheme I:

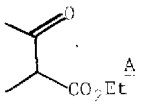
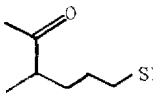
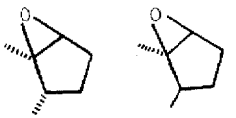
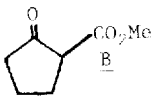
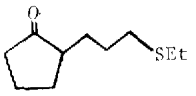
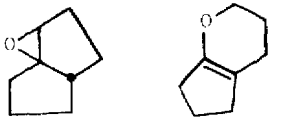
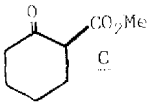
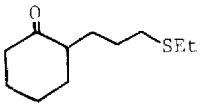
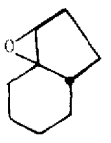
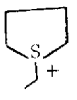
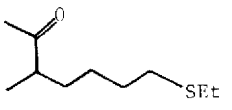
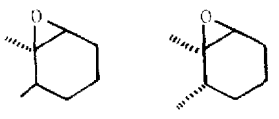
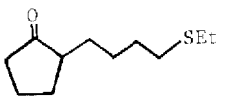
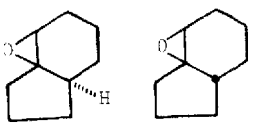
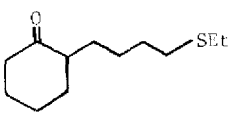
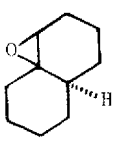
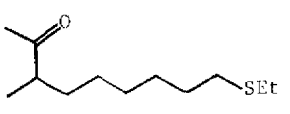
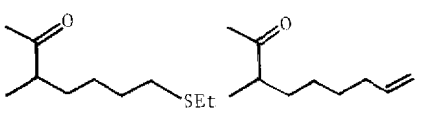


Several initial concerns about the reaction in Scheme I are apparent. First, can one generate a sulfonium ylide in the presence of a ketone or will the ketone enolate displace the sulfonium salt, a reaction reported for other ketones with ω leaving groups? Will the desired ylide be formed to the exclusion of other ylides? Will ring closure occur rather than other ylide reactions? Finally, if the desired reaction does occur will the process be stereoselective enough to be of synthetic utility? We are pleased to report that these intramolecular epoxidations yield five- and six-membered rings stereoselectively in high chemical yield.

Several ω-ketosulfonium salts have been prepared and treated with potassium t-butoxide at ambient temperatures in THF to yield cyclic epoxides with considerable stereoselectivity (Table I). In some instances this sequence complements our previously reported epoxyannulation sequence.[2] Of the compounds investigated only keto-ylides leading to a medium-sized ring have completely failed to undergo reaction.

The epoxide structures in Table I have been assigned by the normal spectroscopic techniques. The epoxide stereochemistry has been assigned by reduction to tertiary alcohol which

Table I

Entry	Ketoester	Alkylating Agent	Ketosulfide (% Yield)[13]	Epoxide(s) (Ratio; % Yield)[13,14]
1.	 A	$I(CH_2)_3SEt$ D	 (83%)	 (79:21; ca.80%)
2.	 B	D	 (37%)	 (1:1; 90%)
3.	 C	D	 (51%)	 (89%)
4.	A	 E BF_4^-	 (55%)	 (88:12; 59%)
5.	B	E	 (69%)	 (26:74; 73%)
6.	C	E	 (65%)	 (67%)
7.	A	$I(CH_2)_6SEt$		

was then compared with an authentic sample prepared either by ozonolysis of the appropriate hydrocarbon,[6] or by methyl magnesium bromide addition to the α-methyl ketone.[7] One epoxide (entry 2) was assigned cis based on steric considerations. The side product structure (entry 2) was assigned by comparison with the published spectral data.[8,9]

The preparation of the ketosulfonium salts has been completed by one of two general approaches. Entries 1-3 and 7 were prepared by the standard alkylation of a β-ketoester enolate with the appropriate ω-halosulfide followed by decarboxylation and S-ethylation with triethyl oxonium fluoborate. Entries 4-6 were prepared by treatment of the β-ketoester enolate with S-ethyl tetrahydrothiophonium fluoborate.[10] S-Ethyl salts yield de-ethylated sulfides and ethylated β-ketoesters. Both of these reactions are predicted from Eliel's study of cyclic onium salts.[10]

The stereochemical outcome of this cyclization sequence closely parallels that of other irreversible nucleophilic carbonyl addition reactions. That is, Grignard addition to 2-substituted cyclopentanones occurs to form a cis product while addition to a cyclohexanone yields a trans product.[7] Formation of a fused cyclopentyl ring often provides the cis ring juncture in other annulation reactions.[5]

The over-all reaction sequence is efficient and normally free of side products with two exceptions. First, the strained five-five system yields a product derived from enolate displacement of the sulfonium leaving group. This example is the only indication of any non-ylide derived product. Competition from enolate anions might have been predicted to be more serious than observed in this instance. Secondly, it appears that medium-sized rings and large rings are inaccessible by this chemistry using unstablized sulfur ylides attached to confirmationally mobile methylene chains. Ylide β-elimination is the only product observed with a cyclooctene oxide precursor (entry 7). A ketosulfonium salt which would provide a dimethyl-cycloundeceneoxide gives about 10% of epoxides with undefined stereochemistry.[11]

The real advantages in this epoxyannulation are the stereoselectivity of the cyclization process and the use of ketonic electrophiles. Other procedures for cyclic epoxide formation (i.e., olefin epoxidation) are much less stereoselective in cases such as entries 1 and 4.[12] The less electrophilic acyclic ketone is suitable for this epoxyannulation in contrast with a related reaction we have reported.[2] This work clearly establishes intramolecular sulfur ylide reactions as a useful method of ring formation.

We are continuing to investigate variations and applications of expoyannulation.

Acknowledgement. We are grateful to Professor J. K. Crandall for useful exchange of information during the preparation of this manuscript. Research Corporation and American Cancer Society Institutional Grant IN 93H provided support for this work. Support of the mass spectral facility was provided by NIH Grant RR 00708.

References

1. Undergraduate research participant, 1979-80.

2. Garst, M. E., J. Org. Chem., 1979, 44, 1578.

3. Newman, M. S. and Lee, L.-F., J. Org. Chem., 1974, 39, 1446.

4. Cazeau, P., Tétrahedron Lett., 1977, 1493 reported the formation of 2,3-diphenylcyclopentene oxide of unknown stereochemistry by this reaction process.

5. Professor J. K. Crandall, H. S. Magaha, R. K. Widener, and G. A. Tharp (see accompanying paper) have independently investigated this reaction. We are grateful to them for exchanging information.

6. Varkony, H., Pass, S. and Mazur, Y., J. C. S. Chem. Comm., 1974, 437.

7. Still, W. C. and Mac Donald, T. L., J. Am. Chem. Soc., 1975, 97, 5280 and Laemmle, J., Ashby, E. C. and Roling, P. V., J. Org. Chem., 1973, 38, 2526-34.

8. Etheridge, S. J., J. Org. Chem., 1966, 31, 1990.

9. The amount of this side product has varied from 10-50% in individual runs. Crandall et. al. have not observed this enolate displacement product, suggesting the phenyl sulfonium salt offers some advantage in cyclopentane formation.

10. Eliel, E., Hutchins, R. O., Mebane, R. and Willer, R. L., J. Org. Chem., 1976, 41, 1052.

11. Functionalized cycloheptane oxides have been prepared stereoselectively in modest yield by the cyclization of appropriate 1,7-ketosulfonium salts. These reactions will be reported in another context in due course (W. McBride and A. T. Johnson, work in progress).

12. Mc Curry, P. M., Jr., Ph.D. Thesis, 1970, Columbia University, University Microfilms #71-6225.

13. All yields are isolated for structures shown except for entry 2. All compounds have been characterized by ir, nmr, and high resolution mass spectra. Entry 2 was characterized as a mixture by nmr and ir and individually by gc-mass spectra.

14. Typical procedure: A 1 molar solution of the ketosulfide in CH_2Cl_2 was treated with 1.1 equiv. of triethyl oxonium tetrafluoborate. The solution was stirred for 12 hr and then concentrated to a viscous oil. This oil was suspended in anhydrous THF and treated with 1.5 equiv. of potassium t-butoxide. After 12 hr this solution was partitioned between pentane and brine. The pentane layer was dried over Na_2SO_4, filtered, and evaporated to leave the epoxides.

(Received in USA 15 August 1980)