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INTRAMOLECULAR SULFUR-YLIDE ADDITIONS TO KETONES. A CYCLOPENTANE ANNULATION[1]

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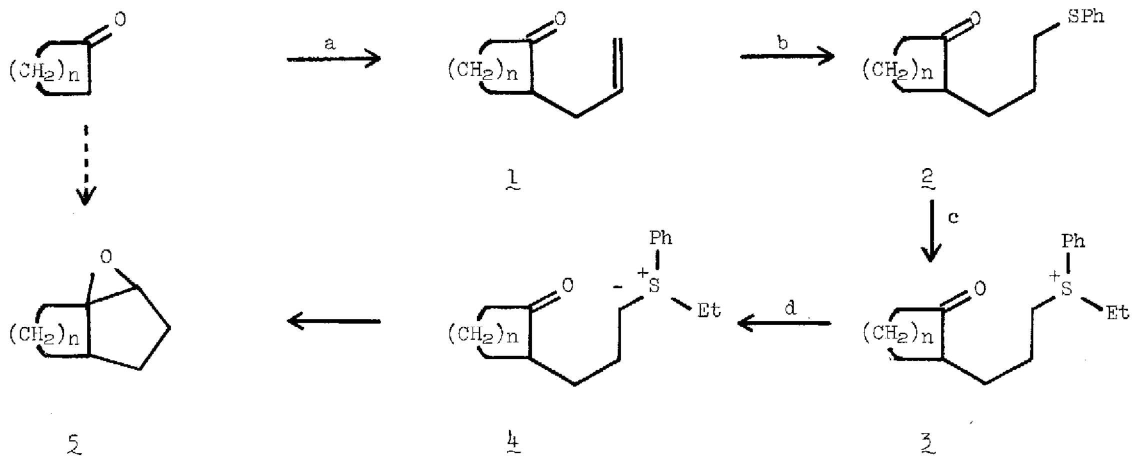
Summary: Various 2-(3'-phenylthiopropyl)cycloalkanones were prepared from the corresponding cyclic ketones and subjected to S-alkylation by triethyloxonium tetrafluoroborate followed by potassium *tert*-butoxide treatment to give bicyclic epoxides with new five-membered carbocycles. A related cyclization to a six-membered ring was also observed.

The reaction of sulfur ylides with aldehydes and ketones constitutes an important general method for the synthesis of epoxides by a process which generates a new carbon-carbon bond.[2] Intramolecular versions of this reaction are potentially useful for the construction of carbocyclic systems bearing the synthetically versatile epoxide function, but examples of this type of conversion are sparse.[3,4,5] In this contribution we describe a new cyclopentane annulation scheme which utilizes such an intramolecular sulfur-ylide reaction as the key transformation in the overall conversion **1** → **5** depicted below.[6] The stereochemical features of this process are also explored.

Scheme 1



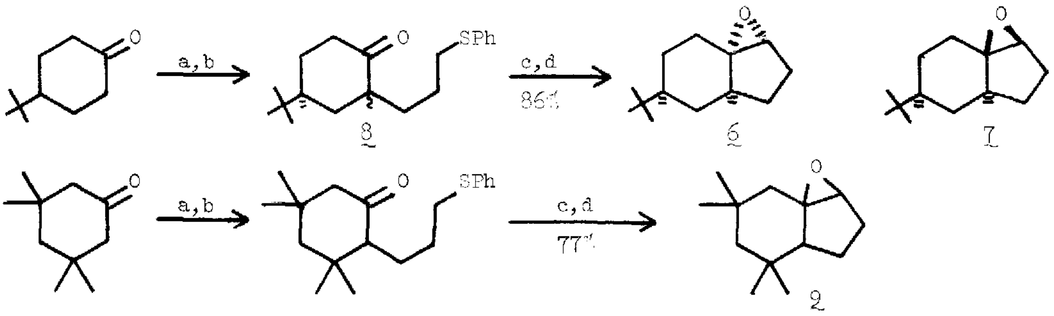
n	1 → 2	2 → 5	(cis:trans)
3	65%	67%	(100: -)
4	79%	66%	(94:6)
5	49%	62%	(47:53)

a. CH_2=$CHCH_2OH$, $(CH_3)_2C(OCH_3)_2$, H^+, Δ
b. PhSH, AIBN, Δ
c. $(C_2H_5)_3O^+ BF_4^-$
d. *t*-BuOK

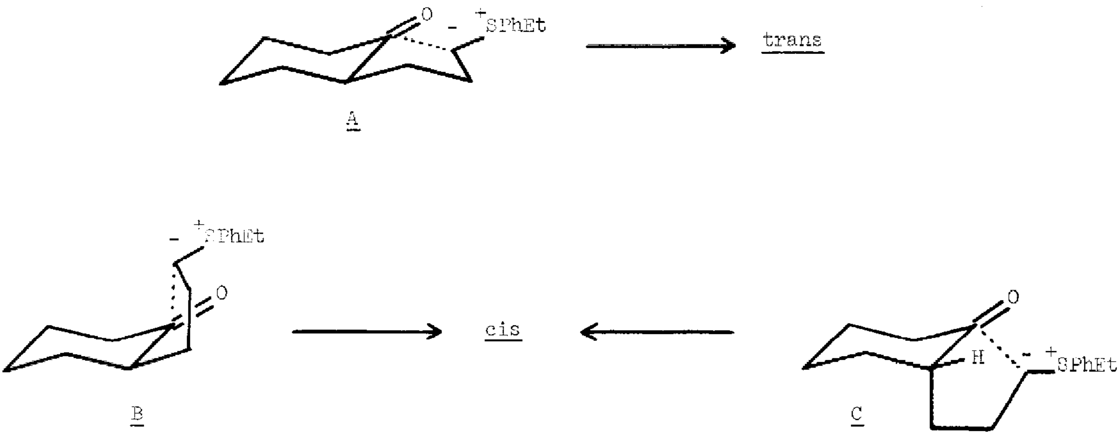
The 2-allylcycloalkanones (1) are readily obtained by alkylation of the corresponding cycloalkanones or, more conveniently, by an adaptation of the Claisen rearrangement in which an allyl vinyl ether is produced and thermally transformed in situ.[7] The regioselective addition of thiophenol under free-radical conditions proceeds smoothly to give the corresponding 2-(3'-phenylthiopropyl)cycloalkanones (2).[8] These materials are converted in turn to the sulfonium salts 3 by triethyloxonium tetrafluoroborate in CH_2Cl_2. The keto sulfonium salts 3 are potential precursors of the desired sulfur ylides 4 under strongly basic conditions, although the generation of an enolate anion and subsequent reaction (e.g., alkylation) of this species is also a reasonable possibility. In the actual event, exposure of the sulfonium salts 3 to potassium tert-butoxide in THF led to the desired epoxides 5 as summarized in Scheme 1. Characterization of the epoxide products was facilitated by $LiAlH_4$ reduction to the corresponding bridgehead alcohols.[9]

Annulation of cyclopentanone gave only the more stable cis-bicyclo[3.3.0]octane derivative. The product derived from cyclohexanone was also formed highly stereoselectively, the cis-isomer predominating over the trans compound by a 94:6 ratio. However, cycloheptanone led to a disappointing 47:53 ratio of cis to trans epoxides. Thus, the stereochemical outcome of the cyclization process depends significantly on the conformational flexibility of the cycloalkanone moiety.

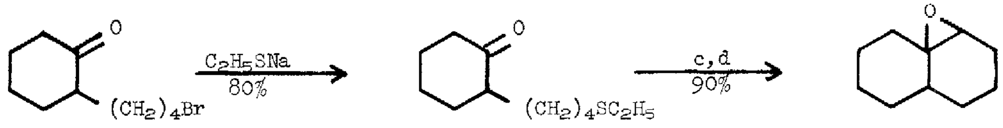
Two substituted cyclohexanones were also investigated as substrates for the annulation procedure. 4-tert-Butylcyclohexanone was converted by the standard sequence to an 85:15 mixture of epoxides 6 and 7. In this case, the cis and trans isomers of the phenylthioketone 8 were separated and individually subjected to alkylation and base cyclization. The production of the same mixture of epoxides from either precursor suggests that epimerization via enolate formation interconverts the two sulfonium salts faster than cyclization occurs. In a similar fashion, 3,3,5,5-tetramethylcyclohexanone was transformed to a 57:43 mixture of the cis and trans isomers of epoxide 9. Thus, substituents on the cyclohexanone ring are clearly capable of influencing the cyclization in a significant way.



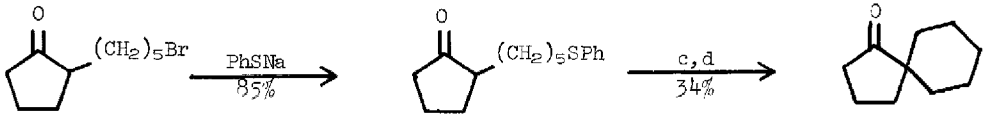
There are three potential modes for the initial cyclization phase of the cyclohexanone derivatives which can be depicted by structures A, B and C. If this step is irreversible, as is the case with bimolecular additions of dimethylsulfonium methylide to cyclohexanones,[10] then the stereochemistry of the epoxide product is determined by the relative facility of the three cyclization processes.[11] The results are consistent with such an interpretation. Reaction *via* A, in which an equatorial side-chain moiety attacks the carbonyl group from the equatorial direction, leads to a *trans* ring fusion. This process accounts for only a small amount of product with the unsubstituted system where the *cis* isomer predominates. *Cis* stereochemistry results from either cyclization mode B (axial attack of the carbonyl by an equatorially oriented side-chain) or C (equatorial approach of an axially situated side-chain), or possibly both B and C. The results with the 4-*tert*-butyl derivatives suggest that the pathway to *cis* epoxide proceeds *via* B, since C would have given a product isomeric with those observed. This is true even when the starting material initially possesses an axial side-chain as with the *trans* isomer of **8**. The preference for B over A appears to derive from the greater torsional and bond-angle strain during bond formation from the latter. With the more flexible cycloheptanone compound this difference disappears and cyclization is essentially stereorandom. Likewise, the presence of severe 1,3-diaxial interactions in the tetramethylcyclohexanone derivative destabilizes B allowing A to become competitive. In fact, with this species the *cis* epoxide may well arise by cyclization by mode C which avoids these 1,3-diaxial interactions.



Two attempts to extend the cyclization process to the generation of larger rings met with mixed success. Thus, reaction of the ethylthioketone **10** (prepared by reacting bromoketone **11**[12] with sodium ethylthiolate) under the usual conditions led to an 8:92 ratio of the *cis* and *trans* isomers of **12**.[13] Interestingly, cyclization to a six-membered ring shows the opposite stereoselectivity to that observed with five-ring formation, presumably because of the conformational flexibility of the longer side-chain which permits facile equatorial attack in a fashion analogous to A. In the case of system **13**, designed to give cyclization to a seven-membered ring, we observed intramolecular alkylation of the ketone enolate leading to spiroketone **14** as the only important volatile product.



11 10 12



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REFERENCES AND NOTES

1. Contribution number 3503. Support from Indiana University in the form of a Grant-in-Aid of Research is gratefully acknowledged.

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6. After completion of this work we learned of a related study by Garst and Johnson (see accompanying communication). We thank Professor Garst for the exchange of information and the agreement to publish simultaneously.

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9. All new compounds isolated in this study were characterized by consistent elemental analyses and spectral data. The general experimental procedure for the preparation of epoxides **5** is as follows: A solution of **2** and 1.1 equiv of $(C_2H_5)_3O^+ BF_4^-$ in CH_2Cl_2 was stirred overnight. The solvent was removed to give crude **3**. This material was dissolved in THF and added dropwise to 1.2 equiv of t-BuOK in THF at 0°. After several hours at 25°, the reaction mixture was hydrolyzed and worked up in the normal fashion. The crude product was purified by chromatography on silica gel.

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11. The stereochemistry of the sulfonium moiety is, of course, crucial for the epoxide-forming step, but epimerization to achieve the necessary trans relationship with respect to the alkoxide group is expected.

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13. The ethylthio derivative was used since the analogous phenylthio derivative gave a mixture of epoxide and ethyl phenyl sulfide which was difficult to separate without decomposition of the epoxide.

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