Tetrahedron Letters, Vol. 33, No. 24, pp. 3439-3442, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Phenylthio Radical Catalyzed Rearrangement of Acetoxyalkenyl Epoxides to Acetoxyalkenyl Cyclopentanols

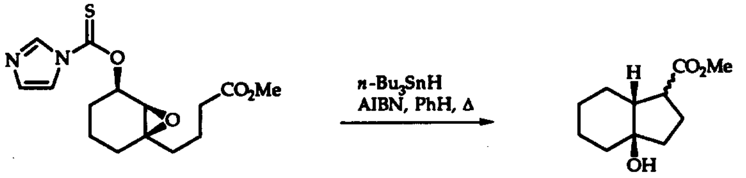
Viresh H. Rawal* and Venkat Krishnamurthy

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Key Words: phenylthio radical; enolacetate; radical catalyzed cyclization; epoxide fragmentation

Abstract: Exposure of cyclic acetoxyalkenyl epoxides to a catalytic amount of PhS• initiates a tandem radical induced epoxide fragmentation–H• abstraction–cyclization process that results in a net isomerization to bicyclic enolacetates.

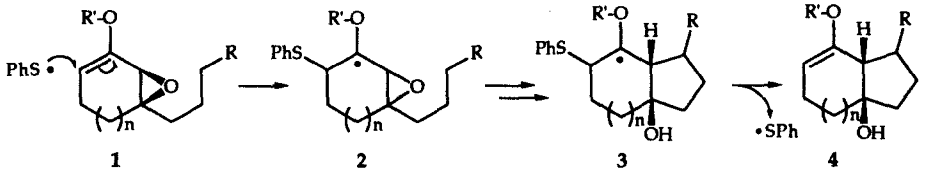
We recently reported a route to *cis*-fused bicyclic carbocycles which utilized a tandem radical-mediated epoxide fragmentation–H• abstraction–cyclization process, typified by the example in Equation 1.[1] The final step in this tandem process is a typical radical cyclization, where the cyclized species abstracts a hydrogen from *n*-Bu_3SnH. Consequently, this sequence suffers from the same drawbacks as other radical processes, in that the final radical site is reduced rather than functionalized.[2] We were interested in developing a method for carrying out the tandem processes whereby the originally present oxygen unit can be retained in the product.[3] Such products would be useful not only because of the versatility of oxygenated subunits, which allow further synthetic elaboration, but also because this oxygenation pattern is present in some biologically active natural products that are of interest to us. We report here a useful extension of our original work which addresses this issue. We describe a general two-step process for converting epoxyketones into bicyclic compounds, with retention of the oxygen moiety.



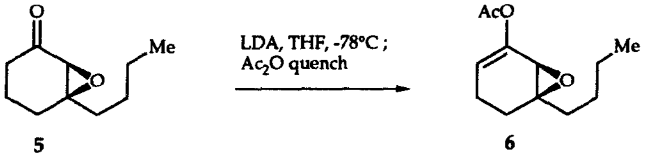
(Eq. 1)

We formulated our approach based on the well known reversible addition of thiyl radicals to olefins.[4,5] Addition of a thiyl radical to a suitably protected epoxyketone enolate 1 would generate the requisite oxiranyl carbinyl radical 2, which was expected to go through the tandem sequence that we had developed and generate radical 3.[1] In the absence of a good hydrogen donor, radical 3 was expected to produce enol 4 by expelling the initiator, PhS• (Scheme I).[6,7]

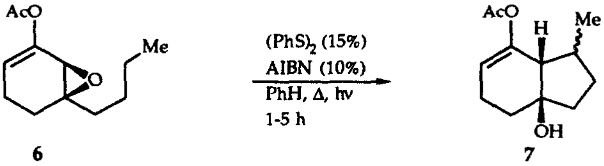
Scheme I



The general strategy was tested on acetyl protected epoxy enols (R' = Ac), which were prepared in good yield from the epoxyketones (e.g., 5 → 6) by kinetic deprotonation with LDA followed by quenching of the enolate with acetic anhydride.[8,9] The acetoxyalkenyl epoxides are stable enough to be purified by flash chromatography and handled using normal precautions, although they do undergo slow hydrolysis if left out at room temperature.

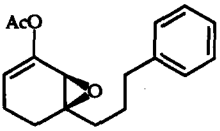
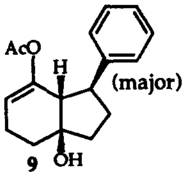
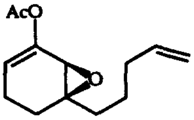
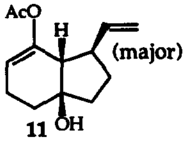
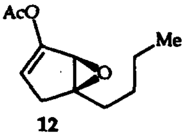
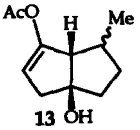
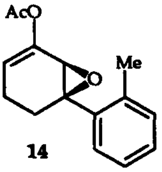
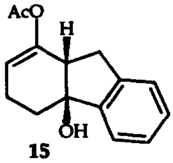
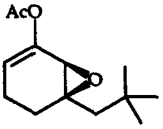
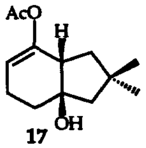


When a benzene solution of acetoxyalkenyl epoxide 6 (0.05 M) containing a catalytic amount of AIBN and diphenyl disulfide was irradiated with a sunlamp, a clean conversion to the expected bicyclic product, 7, was observed. The product, isolated in 73% yield, was a 3:2 mixture of diastereomers. The methyl group was assigned the β orientation in the major isomer, based on NMR experiments. An examination of the different reaction parameters allows us to make the following observations. The reaction generally proceeded faster and more cleanly when using a Hanovia apparatus (450 watt medium pressure Hg lamp) than with a sunlamp. Likewise, better results were obtained when a higher mol% of diphenyl disulfide was used. The reaction was relatively insensitive to substrate concentration, as comparable results were obtained at 0.01M and 1.0M concentration. Curiously, both AIBN and light were essential for success in this process. No reaction occurred at reflux in the absence of light, and a slow, messy reaction took place without AIBN.



We have examined the radical catalyzed fragmentation–cyclization of some related systems and our results are summarized in the Table. The diastereoselectivity was higher for compounds with side chains having radical stabilizing groups. Cyclization of the phenyl containing side chain afforded, after chromatographic purification, a good yield of essentially one isomer of the bicyclic product (Entry 1, >13:1 by GC).[10] The stereochemistry of the phenyl group was assigned using NMR experiments. The vinyl side chain precursor, shown in Entry 2, gave a 4:1 mixture of the expected cyclization product, with none of the product resulting from direct cyclization of the alkoxy radical onto the alkene.[11] Entry 5 shows the synthesis of an interesting benzo-fused hydrindane skeleton.

Table – Fragmentation-Cyclization of Acetoxyalkenyl Epoxides

Entry	Substrate	Method	Product	Ratio	Yield(%)[a]
1	 8	A	 9 (major)	13:1[b] (19:1)[c]	82
2	 10	B	 11 (major)	4:1[c]	60
3	 12	B	 13	3:2[c]	70
4	 14	B	 15		60
5	 16	B	 17		28

[a]Isolated Yields. [b]Ratio determined by GC. [c]Ratio of isolated products. All diastereomers are separable by flash chromatography or MPLC.

Method A: 275 W sunlamp. Method B: 450 W medium pressure Hg lamp.

Overall, the present method offers several advantages over our original method.[1] The reaction avoids the use of n-Bu$_3$SnH and relies, instead, on a catalytic amount of diphenyl disulphide as the radical source. The absence of a H• source minimizes reduction as a competing side-reaction during the tandem sequence, resulting in higher yields. The most important advantage of the present method is that it retains, in a masked form, the carbonyl group, which is a valuable handle for further transformations on the molecule. Further studies on this reaction and its application to the synthesis of complex targets will be published in due course.[2]

Acknowledgment: This work was supported in part by the American Heart Association and the American Cancer Society. V. H. R. thanks the American Cancer Society for a Junior Faculty Research Award.

References and Notes

1. Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181, and references cited therein.
2. We have also developed an atom transfer mediated process for carrying out these tandem processes: V. H. Rawal and S. Iwasa, *manuscript submitted for publication*.
3. General reviews on free radical chemistry: (a) Beckwith, A. L. J.; Ingold, K. U. In *Free Radical Rearrangements*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 161. (b) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. (c) Giese, B. *Radicals in Organic Synthesis: Formation of C-C Bonds*, Pergamon Press: New York, 1986. (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (e) Curran, D. P. *Synthesis* **1988**, 417, and 489.
4. (a) Kice, J. L. In *Free Radicals*; Kochi, J. K., Ed.; Vol. 2, Wiley: New York, 1973; Chapter 24. (b) Abell, P. I. *ibid*; Chapter 13.
5. For recent applications of this reversible addition, see: (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (c) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1989**, *30*, 5845. (d) Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989**, *45*, 2969. (e) Singleton, D. A.; Church, K. M.; Lucero, M. J. *Tetrahedron Lett.* **1990**, *31*, 5551. (f) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (g) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100.
6. Feldman and coworkers at Penn State had independently discovered similar reactivity with an acyclic vinyl epoxide (personal communication).
7. Recently, Kim et al. also extended the usefulness of the tandem process by exploiting the reversible addition of $R_3Sn\bullet$ to alkenes: Kim, S.; Lee, S.; Koh, J. *J. Am. Chem. Soc.* **1991**, *113*, 5106.
8. Wender has prepared and studied the reactivity of the corresponding silyloxyalkenyl epoxides: Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.
9. Groups besides the acetyl should also prove useful. For example, the enol-triflate offers the possibility of carrying out palladium mediated coupling after the tandem process.
10. The higher selectivity may result from reversibility in the cyclization step: (a) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553. (b) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081. (b) Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911.
11. (a) Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1988**, 294. (b) Gash, R. C.; Mac Corquodale, F.; Walton, J. C. *Tetrahedron* **1989**, *45*, 5531.

(Received in USA 24 February 1992)