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ONE POT CYCLIZATION OF EPOXYOLEFINS TO SUBSTITUTED CYCLOALKANOLS VIA FREE RADICALS

Carlo Bonini*
Dipartimento di Chimica, Università degli Studi della Basilicata,
Via N. Sauro 85, 85100 Potenza, ITALY.
Romano Di Fabio, Sandro Mecozzi and Giuliana Righi
Centro C.N.R. per lo Studio della Chimica delle Sostanze Naturali,
c/o Dipartimento di Chimica, Università " La Sapienza", P. le A. Moro 5,
00185 Roma, ITALY.

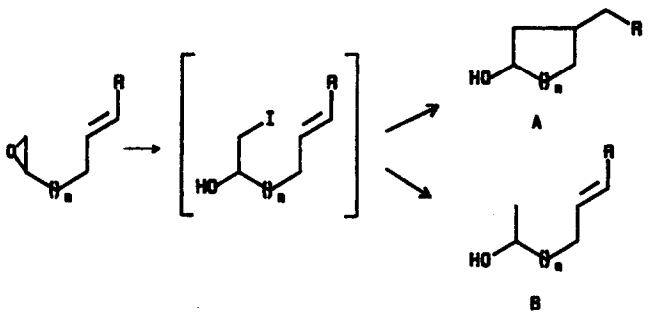
ABSTRACT: 1,2 epoxyolefins (γ or δ) provide functionalized carbocycles via regioselective oxirane ring opening to the corresponding iodohydrines and subsequent radical cyclization mediated by tributyltin hydride.

Cyclization of δ, ε unsaturated radicals is a common process which easily provides cyclopentyl or cyclohexyl rings.[1] Most employed methods to prepare the starting radicals involve the reaction of various functions such as halides, thioethers, selenides and sulphides, mainly with tributyltin hydride.[2] Other methods involve the reduction of unsaturated ketones or aldeydes via O-stannyl ketyl.[3] Some of the limitations proper to these procedures are mainly due: a) the loss of two functional groups in the cyclization process; b) the difficulty to obtain optically active carbocycles from an opportune chiral precursor. In consideration of the above, epoxides (which can be easily prepared in optically active form, see below) could represent an appropriate α hydroxy radical synthon, as also shown in a recent paper by Nugent.[4]

We have recently described [5,6] a general and efficient methodology for the chemo and regioselective reductive opening of 1,2 epoxides to the corresponding secondary alcohols. First the oxirane ring is opened regioselectively (with NaI or LiI in DME or with MgI_2 in benzene). In presence of an appropriate unsaturation the resulting iodohydrine could lead, via the radical generated by tributyltin hydride, to the carbocycle or to the reduction product (see figure 1). An appropriate choice of the reaction conditions (high dilution and slow addition of the tributyltin

hydride) would hopefully result in an increase of the cyclization products.

Figure 1



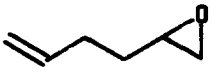
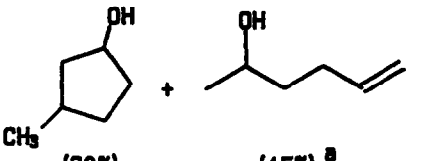
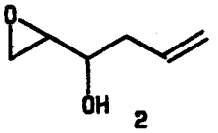
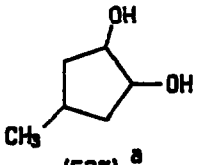
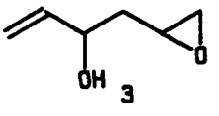
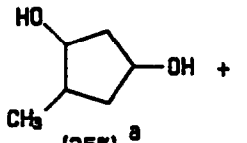
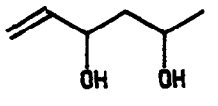
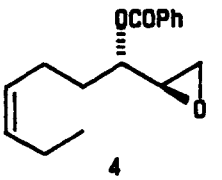
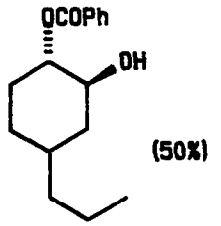
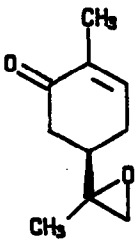
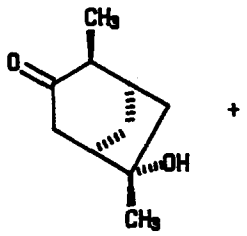
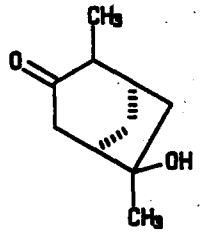
The results of the application of such methodology to a series of unsaturated epoxides are reported in Table 1.

General procedure: to a stirred solution of the epoxide in benzene (0.02 M) under argon atmosphere was added MgI_2 (1,2 eq) freshly prepared in ether; than the solution was refluxed and, by using a syring pump over a period of 2-6 h, it was added of a benzene solution of tributyltin hydride (1.2 eq, 0.02 M) with a catalytic amount of AIBN. After monitoring the reaction by TLC, the solution was evaporated in vacuo and the usual work up to eliminate most of the tin residues was carried out. The reaction mixture was checked by GC and chromatographed on a silica gel column in order to isolate pure products.

As shown in Table 1 the procedure is characterized by general application on different substrates, with good chemoselectivity and reasonable yields (considering the two steps sequence) although a minor formation of the reductive products for compounds 1 and 3 occurs.[7] In all the cases we observed a highly regioselective opening of the epoxy ring which allows a useful prediction of the cyclization products.[8]

Epoxycarvone 5 (an unseparable mixture of the two diastereoisomers obtained by epoxidation of (R)- Carvone) accounts for a particularly interesting case. The cyclization process cleanly provides a bicyclo [3.2.1] octanone system and the 50% of the reaction products proved to be the single optically pure diastereoisomer 6[9] (as demonstrated by careful ^{1}H-NMR and ^{13}C-NMR experiments, as COSY and NOE). This product showed to be

TABLE 1

Starting epoxides	Products (yields)
 1	 (30%) + (15%) [a]
 2	 (53%) [a]
 3	 (35%) [a] +  (12%)
 4	 (50%)
 5	 6 (40%) +  (40%)

a. yields on isolated products showed to be lower due to their volatility: yields obtained by GC are in the range 80-90%.

the most sterically favoured one, arising from the radical α to the carbonyl function.[10]

The further example of chiral epoxide 4[11,12]demonstrates the application advantages provided by the use of the oxirane ring as a radical precursor.

Work is in progress to extend such methodology to conjugated (EWG) olefins in order to better control the stereochemistry of the cyclization products, as well as to explore the behaviour of 2,3 epoxy alcohols or esters under similar reduction or cyclization conditions.[13]

REFERENCES AND NOTES

1. " Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds." Bernd Giese, Pergamon Press, New York, 1986.

2. See for recent reviews: Curran, D. P., Synthesis,1988, 417 and 489.

3. For recent methods: a. Yadav, V. and Fallis, A. G., Tetrahedron Lett., 1989, 30, 3283, and references therein; b) Enholm, E. J. and Prasad, G., Tetrahedron Lett., 1989,30, 4939 and references therein.

4. Nugent, W. A. and RajanBabu, T. V., J. Am. Chem. Soc., 1988,110, 8561.

5. Bonini, C. and Di Fabio, R., Tetrahedron Lett., 1988, 29, 819.

6. Bonini, C.; Di Fabio R.; Sotgiu, G., and Cavagnero, S., Tetrahedron Symposia in Print n. 38, " Strain Assisted Syntheses, 1989, 45, 2895.

7. We obsverved a substantial diminuishing of the reduction products using longer reaction times but the reactions have not yet been optimized.

8. Our method is complementary to that described in ref.4, due to the reversed regioselective opening of the oxirane rings.

9. Compound 6:$[\alpha]_D$ = + 28.9°, in $CHCl_3$, c= 1.64%.

10. This rapid preparation of such bicyclo [3.2.1] octane system resembles the one already described in the cyclization of oxathiolanones (ref.3a).

11. 1,2 chiral epoxyalcohols are readily available both by kinetic resolution of secondary epoxy alcohols :a) Gao, Y.; Hanson, R. M.; Klunder, J.M .; Ko, S. Y.; Masamune, H. and Sharpless, K. B., J. Am. Chem. Soc., 1987, 109, 5765; or by isomerization of primary chiral 2,3 epoxy alcohols : b) Palazon, J. ; Anorbe, B. and Martin, V. S.,Tetrahedron Lett. 1986, 26, 4987 and references therein.

12. The chiral epoxide 4 was prepared from trans-2, cis-6 nonadienol and following the procedure described in ref. 11b. for compound 4 $[\alpha]_D$ = - 25.9°, in CH_2Cl_2, c= 6.6%.

13. All the products gave satisfactory ^{1}H-NMR, ^{13}C-MR, GC/MS and analytical data. We thank Prof. Rosa Lanzetta for helpful discussion.

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