

Radical Annulation: A Method for Preparation of Carbocycles

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β -Acetylenic radicals, e.g., (6b) and (12), generated in three steps from epoxides or in two steps from α -halogenoketones, respectively, react with electron-deficient olefins to produce five-membered carbocycles by a process of conjugate addition and 5-*exo-digonal* closure.

Ring closure reactions involving radicals are attracting attention for use in organic synthesis and a fair number of examples are known in which such methods have been employed to make heterocycles.¹ However, comparatively little work has been reported on attempts to develop corresponding general methods for synthesis of carbocycles.² In principle, ring closure of acetylenic radicals, e.g., (1) \rightarrow (2), is likely to be very useful in this regard because the products (2) possess a double bond that permits further elaboration, such as cleavage to a ketone, (2) \rightarrow (3). We report a new route to carbocycles, that operates in the sense just described (equation 1) and employs readily available starting materials. The method, which is summarized in Scheme 1, involves formation of a β -acetylenic radical, e.g. (6b) in the presence of a Michael acceptor. Conjugate addition followed by 5-*exo-digonal* closure takes place to produce a carbocycle.

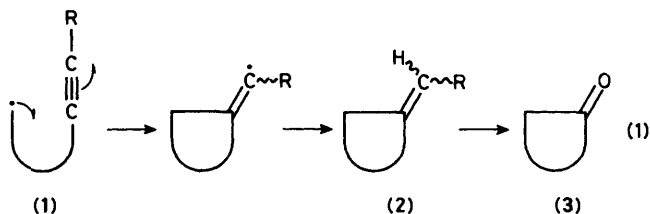
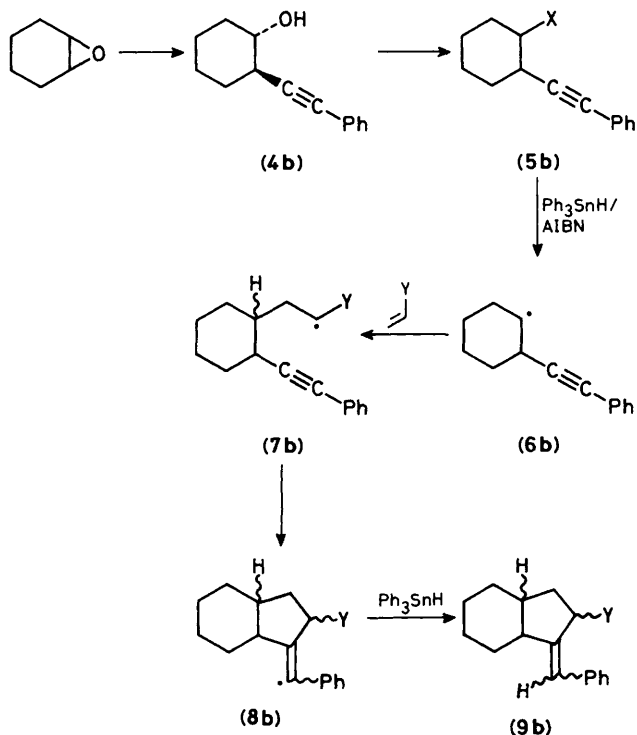
Treatment of cyclohexene oxide with lithium phenylacetylide according to a known procedure³ afforded the hydroxyacetylene (4b) in 96% yield. The oxygen function in this compound is not a suitable precursor to the desired radical (6b) (see Scheme 1) because the reaction shown in equation 2 takes place when the derived^{2a,4} thiocarbonylimidazolide (10) [80% from (4b)] is treated with triphenyltin hydride in the presence of AIBN (azobisisobutyronitrile) and with, or without, an excess of methyl acrylate (cf. Scheme 1). Evidently, a radical intermediate of the usual⁵ deoxygenation sequence is trapped intramolecularly.^{5,6} The structure of compound (11) was established by treatment with benzeneseleninic anhydride⁷ (C=S \rightarrow C=O) to give (80%) a γ -lactone identical with that obtained by benzylation[†] [lithium di-isopropylamide (LDA), PhCH₂Br], deprotonation (LDA), and reprotonation of *trans*-hexahydro-2(3*H*)-benzofuranone.

When alcohol (4b) was first converted into bromide (5b; X = Br) (50%), then the desired radical (6b) was formed under the experimental conditions described below. It underwent conjugate addition to methyl acrylate, (6b) \rightarrow (7b; Y = CO₂Me) and 5-*exo*-closure then took place, the bicyclic product (9b; Y = CO₂Me) being isolated in 38% yield as a mixture of isomers. The reaction sequence is a general one: it was tried with a number of epoxides and three different Michael acceptors. Our results are collected in Table 1.

Each hydroxyacetylene was made in good yield by adding the appropriate epoxide to a cold (-78 °C) solution of a

lithium acetylide and boron trifluoride-diethyl ether.³ Conversion into the derived bromide [(PhO)₃P · Br₂,⁹ Et₂O, room temp., 12 h] proceeded in 41–61% yield. The stereochemistry of bromide (5b; X = Br) was cleanly *cis* from its ¹H n.m.r. spectrum; probably, all the other bromides were likewise formed with Walden inversion. The main by-product generated with each bromide was the corresponding non-conjugated enyne, except in the case of (4f) \rightarrow (5f), where the conjugated isomer was formed.

The radical annulations were each carried out (under argon) by the same method. Benzene solutions of triphenyltin hydride (1.2–1.5 mmol per mmol bromide, 0.07–0.15 M) and of AIBN (0.05–0.1 mmol per mmol bromide, ca. 0.008 M) were added simultaneously over 10 h by syringe pump to a refluxing benzene solution (0.015–0.025 M) of the bromide (0.5–1.0 mmol) and the Michael acceptor (a 15-fold excess).



† The stereochemistry assigned at C(3) in (11) is tentative because the stereochemical assignment for the benzylation and protonation are not based on a *close* analogy (cf. ref. 8) and could not be proven by nuclear Overhauser enhancement experiments.

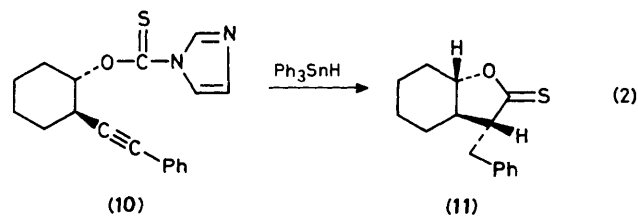
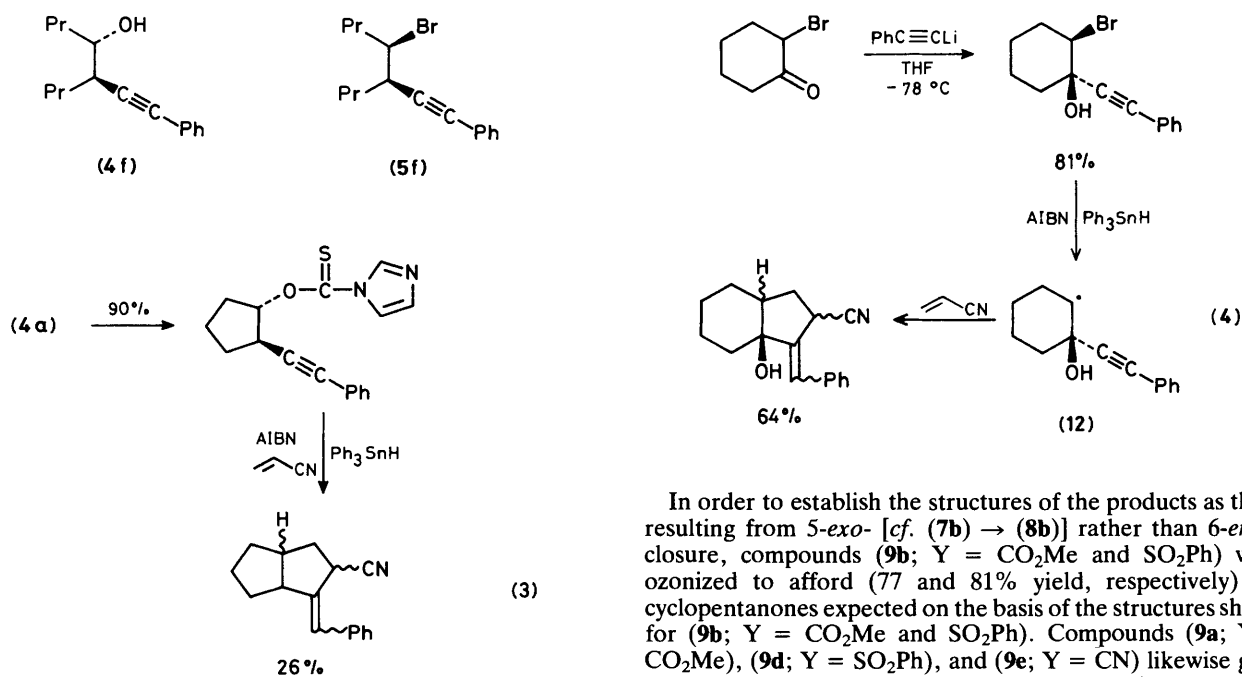


Table 1.

(4)	(5)	(9)
Yield of (4) from epoxide (%)	Yield of (5) from alcohol (%)	Yield of (9) in annulation (%) ^a
(4a) R = Ph; n = 0	(98)	(5a) X = Br
(4b) R = Ph; n = 1	(96)	(5b) X = Br
(4c) [≡(4b)] R = Ph; n = 1	(96)	(5c) X = SePh
(4d) R = Ph; n = 2	(81)	(5d) X = Br
(4e) R = n-C ₅ H ₁₁ n = 1	(≥69)	(5e) X = Br
(4f)	(87) ^d	(5f)
		(44) $\begin{cases} Y = \text{CO}_2\text{Me} & (31) \\ Y = \text{CN} & (38) \\ Y = \text{SO}_2\text{Ph} & (28) \end{cases}$
		(50) $\begin{cases} Y = \text{CO}_2\text{Me} & (38) \\ Y = \text{CN} & (56) \\ Y = \text{SO}_2\text{Ph} & (52) \end{cases}$
		(100) ^b $\begin{cases} Y = \text{CO}_2\text{Me} & (35) \\ Y = \text{CN} & (30) \end{cases}$
		(61) $\begin{cases} Y = \text{CO}_2\text{Me} & (44) \\ Y = \text{CN} & (53) \\ Y = \text{SO}_2\text{Ph} & (38) \end{cases}$
		(41) Y = CN ^c (34)
		(60) $\begin{cases} Y = \text{CO}_2\text{Me} & (40) \\ Y = \text{CN} & (46) \\ Y = \text{SO}_2\text{Ph} & (20) \end{cases}$

^a All annulation products are isomer mixtures not separable by t.l.c. ^b Prepared by treatment of (4c) with PhSeSePh and Bu₃P in tetrahydrofuran: M. Sevrin and A. Krief, *J. Chem. Soc., Chem. Commun.*, 1980, 656; P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485. Yield before correction for recovered alcohol is 76%. ^c Other Y substituents have not been examined. ^d Prepared from *cis*-epoxide.



At the end of the addition, refluxing was continued for an arbitrary period of 2 h. Evaporation of the solvent, removal of triphenyltin bromide by shaking the residue with diethyl ether and aqueous potassium fluoride,¹⁰ and flash chromatography over silica gel gave the products in the yields indicated.

In order to establish the structures of the products as those resulting from 5-*exo*- [cf. (7b) \rightarrow (8b)] rather than 6-*endo*-closure, compounds (9b; Y = CO₂Me and SO₂Ph) were ozonized to afford (77 and 81% yield, respectively) the cyclopentanones expected on the basis of the structures shown for (9b; Y = CO₂Me and SO₂Ph). Compounds (9a; Y = CO₂Me), (9d; Y = SO₂Ph), and (9e; Y = CN) likewise gave cyclopentanones (59, 84, and 44%, respectively) and, in these cases, the total ozonolysis products were examined by ¹H n.m.r. spectroscopy (400 MHz). Aldehydes generated by ozonolysis of 6-*endo* cyclization products should have formyl proton resonances that appear as doublets. No such signals were detected. On the basis of these results, and analogies reported in the literature,¹¹ we assign structures to all the

other cyclization products shown in Table 1. The ozonolysis experiments also serve to establish the feasibility, in the present case, of the transformation (2) \rightarrow (3), equation 1.

Several related annulations were also examined. Table 1 shows that phenyl selenides, such as (5c; X = SePh), can be used, and we observed that, in geometrically favourable cases, even thiocarbonylimidazolides will undergo radical annulation (equation 3). Finally, 2-bromocyclohexanone was found to be an excellent starting material because it reacted efficiently in the sense of equation 4.¹²

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References

- 1 D. J. Hart, *Science*, 1984, **223**, 883 and references therein; J.-M. Surzur, in 'Reactive Intermediates,' ed. R. A. Abramovitch, Plenum Press, New York, 1982, Vol. 2, p. 121; G. A. Kraus and K. Landgrebe, *Tetrahedron Lett.*, 1984, **25**, 3939; R. Leardini, G. F. Pedulli, A. Tundo, and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1984, 1320.
- 2 For use of ω -acetylenic radicals see: (a) D. L. J. Clive, P. L. Beaulieu, and L. Set, *J. Org. Chem.*, 1984, **49**, 1313; (b) G. Büchi, H. Wüest, *J. Org. Chem.*, 1979, **44**, 546; (c) G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, 1983, **105**, 3720. For use of ω -olefinic radicals see: (d) P. Bakuzis, O. O. S. Campos, and M. L. F. Bakuzis, *J. Org. Chem.*, 1976, **41**, 3261; (e) G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, 1982, **104**, 2321; (f) C.-P. Chuang and D. J. Hart, *J. Org. Chem.*, 1983, **48**, 1782; (g) S. Danishefsky, S. Chackalamannil, and B.-J. Uang, *J. Org. Chem.*, 1982, **47**, 2231; (h) N. N. Marinovic and H. Ramanathan, *Tetrahedron Lett.*, 1983, **24**, 1871.
- 3 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391; M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 3693.
- 4 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.
- 5 See W. Hartwig, *Tetrahedron*, 1983, **39**, 2609.
- 6 Cf. P. J. Barker and A. L. J. Beckwith, *J. Chem. Soc., Chem. Commun.*, 1984, 683.
- 7 D. H. R. Barton, N. J. Cussans, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 1978, 393.
- 8 R. S. Reeve, B. G. Ramsay, and R. Y. Moir, *Tetrahedron Lett.*, 1973, 1529. Cf. P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 1974, **39**, 120.
- 9 D. K. Black, S. R. Landor, A. N. Patel, and P. F. Whiter, *J. Chem. Soc. (C)*, 1967, 2260.
- 10 J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.
- 11 J. K. Crandall and D. J. Keyton, *Tetrahedron Lett.*, 1969, 1653; T. Ohnuki, M. Yoshida, and O. Simamura, *Chem. Lett.*, 1972, 797; J. K. Crandall and W. J. Michaely, *J. Org. Chem.*, 1984, **49**, 4244; M. D. Bachi, F. Frolow, and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841.
- 12 The stereochemistry is assigned by analogy: A. Marcou, W. Chodkiewicz, and P. Cadiot, *Bull. Soc. Chim. Fr.*, 1967, **15**, 2429; P. A. Wender, D. A. Holt, and S. M. Sieburth, *J. Am. Chem. Soc.*, 1983, **105**, 3349.