Cyclohexenyl Intermediates in Acid-Catalyzed Cyclization of 2-Alkenyl-1-methylcyclohexanols

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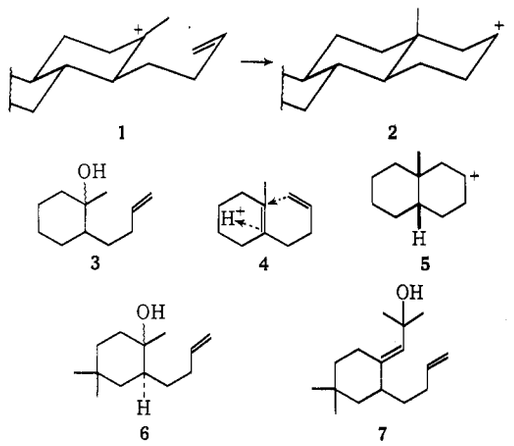
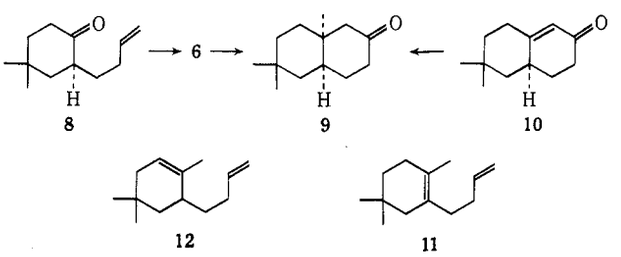
Recent results from our laboratory[1] have indicated that intramolecular attack of an olefinic double bond on a conformationally rigid cyclohexyl cation (*e.g.*, **1** → **2**) will proceed with high selectivity to give trans-fused products. This result suggested that cyclizations of alkenyl-substituted 1-methylcyclohexanols which lead to significant amounts of cis-fused products[2] may not involve cyclization through a cyclohexyl cation as the principal intermediate, since this should lead to selective formation of trans-fused products.[1] The predominant formation of cis-fused products may be rationalized, as pointed out by Stork,[3] if the cyclization involves elimination to a cyclohexene followed by concerted protonation–cyclization (**3** → **4** → **5**).

Although some evidence to support such an interpretation has been available,[2-4] previous mechanistic studies involved systems with conformationally mobile cyclohexane rings. Thus, we felt it imperative that the cyclization of alcohol **6** should be examined for comparison with previous results with alcohol **7**.[1]



Treatment of the previously prepared ketone **8**[1] with an excess of methylmagnesium iodide gave a 3:1 mixture of epimeric alcohols of structure **6**.[5] Although the two epimers could be separated by thin layer chromatography, the mixture was used in most of the cyclization studies, since cyclization of the mixture or of either of the individual isomers gave identical stereochemical results. Cyclization to bicyclic formates was readily effected in 95% yield by treatment with anhydrous formic acid at room temperature for 60 min. Reductive cleavage of the formate ester with lithium aluminum hydride followed by oxidation with Jones reagent[6] and bulb-to-bulb distillation gave bicyclic ketone **9**. The structure of this ketone was confirmed by spectral comparison with authentic material prepared by copper-catalyzed addition of methylmagnesium iodide to octalone **10**.[1,7] Close examination of the 100-MHz nmr spectrum of the cyclization ketone indicated the presence of 5–10% of the isomeric trans-fused ketone.[8]

Evidence concerning the cyclization mechanism was obtained by conducting the cyclization in deuterioformic acid. Mass spectral analysis of the ketonic products derived from this cyclization showed that 86% of the product had incorporated one or more deuterium atoms (49% d_1, 26% d_2, and 11% d_3). This result proves that cyclohexenes such as **11** and **12** must be involved in the cyclization of alcohol **6**. Concerted protonation–cyclization of either **11** or **12** by a trans-antiparallel mechanism can lead only to cis-fused products.



The above results confirm previous conclusions[4] that dehydration of 1-methylcyclohexanols is rapid relative to the cyclization reaction and that monocyclic dienes, not the monocyclic alcohols, are the primary precursors of bicyclic material. The large preponderance of cis-fused products obtained from the cyclization of alcohol **6** suggests that the major pathway for cyclization of the monocyclic dienes is by concerted protonation–cyclization rather than protonation to a cyclohexyl cation intermediate.[9]

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were obtained with Varian Associates T-60 or HA-100 spectrometers. Chemical shifts (δ) are reported in parts per million downfield with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperatures of the oven during the distillation.

2-(3-Butenyl)-1,4,4-trimethylcyclohexanol (6).—To 7 ml of a solution of 1.4 *M* methylmagnesium iodide in ether, diluted with

(1) K. E. Harding, R. C. Ligon, T. Wu, and L. Rode, *J. Amer. Chem. Soc.*, **94**, 6245 (1972).

(2) Examples of this type include (a) P. T. Lansbury, P. C. Briggs, T. R. Demmin, and G. E. DuBois, *J. Amer. Chem. Soc.*, **93**, 1311 (1971); (b) P. T. Lansbury and G. E. DuBois, *Chem. Commun.*, 1107 (1971); (c) R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Amer. Chem. Soc.*, **94**, 2056 (1972).

(3) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); G. Stork and H. Conroy, *ibid.*, **73**, 4748 (1951).

(4) (a) D. C. Hibbitt and R. P. Linstead, *J. Chem. Soc.*, 470 (1936). (b) Unpublished observations of W. S. Johnson and H. D. Doshan; see H. D. Doshan, Ph.D. Thesis, Stanford University, 1968.

(5) The major isomer is assumed to be the alcohol with an axial hydroxyl group resulting from preferential equatorial attack of the Grignard reagent.

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(7) K. E. Harding, R. C. Ligon, and C. Tseng, *J. Org. Chem.*, in press.

(8) Ketone **9** or related ketones have potential utility as synthons for the D–E ring system of pentacyclic triterpenes. *Cf.*, *inter alia*, E. E. Van Tamelen, M. P. Seiler, and W. Wierenga, *J. Amer. Chem. Soc.*, **94**, 8229 (1973); C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971); J. D. Metzger, M. W. Baker, and R. J. Morris, *J. Org. Chem.*, **37**, 789 (1972).

(9) For a discussion of the relevance of this conclusion to other cyclizations of 1-methylcyclohexanols[2] see K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973).

7 ml of anhydrous ether, was added 300 mg of 2-(3-butenyl)-4,4-dimethylcyclohexanone (**8**) in 5 ml of anhydrous ether. The reaction was stirred at room temperature under a nitrogen atmosphere for 24 hr, then poured into a dilute, ice-cold acetic acid solution. The aqueous portion was extracted five times with ether. The combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 273 mg of crude alcohol. Evaporative distillation (0.3 mm, 70°) provided 254 mg of a 3:1 mixture of axial and equatorial alcohols. The alcohols could be separated by preparative thin layer chromatography.

The major isomer had nmr (CCl_4, 100 MHz) δ 0.84 and 0.90 (s, 3 H each, geminal methyls), 1.13 (s, 3 H, C-1 methyl), 4.84–5.08 (m, 2 H, $-CH=CH_2$), and 5.52–6.00 ppm (m, 1 H, $-CH=CH_2$); ir (film) 3450, 1640, and 915 cm^{-1}.

The minor isomer had nmr (CCl_4, 100 MHz) δ 0.90 and 0.92 (s, 3 H each, geminal methyls), 0.99 (s, 3 H, C-1 methyl), 4.82–5.10 (m, 2 H, $-CH=CH_2$), and 5.57–6.00 ppm (m, 1 H, $-CH=CH_2$); ir (film) 3375, 1635, and 920 cm^{-1}.

Cyclization Studies. A. Cyclization with Formic Acid.—A 60-mg sample of the mixture of alcohols described above was dissolved in 6 ml of anhydrous formic acid and stirred at room temperature for 3 hr. The solution was poured into water and extracted four times with ether. The combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 57 mg of product.

The crude material was hydrolyzed by addition to a stirred solution of lithium aluminum hydride in ether and stirring for 30 min. Then 2 ml of methanol and 2 ml of 10% sodium hydroxide solution were added carefully. The mixture was stirred for 5 min, filtered, and concentrated. The crude material was oxidized in the normal manner with Jones reagent in acetone.[6] Evaporative distillation (0.25 mm, 72°) gave 28 mg of ketonic product: nmr (CCl_4, 100 MHz) δ 0.93 (d, J = ~1 Hz, 3 H, C-9 methyl),[10] 0.96 and 0.97 ppm (s, 3 H each, geminal methyls); ir (film) 1700 cm^{-1}. Analysis by gas chromatography on SE-30 or Carbowax columns showed only one significant peak.

Careful examination of the nmr spectrum showed a small peak at δ 0.74 ppm. This peak can be attributed to the C-9 methyl of *trans*-6,6,9-trimethyl-2-decalone.[10]

Cyclization of either of the individual isomers of alcohol **6** gave results indistinguishable from cyclization of the mixture.

B. Cyclization in Deuterioformic Acid.—A 31-mg sample of alcohol **6** was dissolved in 1 ml of deuterioformic acid. The mixture was stirred for 4 hr, and the product was isolated and converted into the trimethyldecalone in the manner described above. The mass spectrum of the product showed *m/e* (rel intensity) 194 (P, 22.5), 195 (P + 1, 100), 196 (P + 2, 41.9), and 197 (P + 3, 17.3). Correction for natural isotopic abundances indicates deuterium incorporation in 86% of the product (49% d_1, 26% d_2, and 11% d_3).

***cis*-6,6,9-Trimethyl-2-decalone (9).**—A mixture of 50 mg of cuprous bromide and 0.7 ml of 1.4 M methylmagnesium iodide in ether was diluted to 5 ml with anhydrous ether. Then 110 mg (0.625 mmol) of 6,6-dimethyl-$\Delta^{1,9}$-2-decalone (**10**) in 5 ml of ether was added. The reaction was stirred at room temperature for 2 hr and poured onto an ice–acetic acid mixture. The aqueous portion was extracted five times with ether, and the combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 96 mg of crude product. Preparative tlc and evaporative distillation (0.25 mm) gave 61 mg of authentic *cis*-6,6,9-trimethyl-2-decalone. *Anal.* Calcd for $C_{13}H_{22}O$: *m/e* 194.16719 (M^+). Found: *m/e* 194.16706. The ir and nmr spectra were identical with those obtained from material prepared by cyclization.

Acknowledgment.—We thank the Robert A. Welch Foundation and the National Institute of Arthritis and Metabolic Diseases for support of this research.

Registry No.—*cis*-**6**, 42271-36-3; *trans*-**6**, 42271-37-4; **8**, 38481-13-9; **9**, 42271-39-6; **10**, 4044-27-3.

(10) The C-9 methyl groups of *cis*- and *trans*-9-methyl-2-decalone show absorption at δ 0.97 and 0.78 ppm, respectively.[11] The C-9 methyl of *cis*-9-methyl-2-decalone has also been observed as a doublet.[12]

(11) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965).

(12) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965).

Lithium Dimethylcuprate Reaction with Oxygen-Substituted Epoxides[1]

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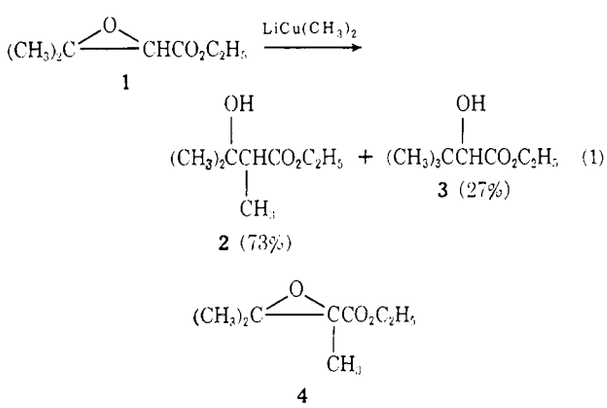
Recent work[2-4] has shown that lithium dimethylcuprate is superior to other organometallic reagents for the nucleophilic opening of epoxides. It was of interest to determine whether adjacent oxygen functions would exert a directive influence on the course of this reaction of the sort observed, *e.g.*, in the Simmons–Smith methylenation. We report here the results obtained with various substituted epoxides.

Johnson and coworkers[2] have reported that the reaction of lithium dimethylcuprate with ethyl 2,3-epoxybutyrate gives α-methylated product in good yield. We have extended this study to include the more highly substituted glycidic esters **1** and **4**. As shown in eq 1,



the reaction of **1** (overall yield 68%) shows only low regioselectivity, even though the formation of **3** formally requires substitution at a tertiary center. Interestingly, **4**, in which both epoxy centers are tertiary, failed to react at all with the organocopper reagent even under more forcing conditions. These results are difficult to interpret mechanistically, but indicate that the degree of selectivity observed in the simpler system[2] will not prove to be a generally useful feature of the reaction of glycidic esters.

As examples of other oxygen-substituted epoxides, 3-hydroxycyclohexene oxide and its derivative methyl ether and acetate were also subjected to lithium dimethylcuprate treatment. The cis and trans alcohols (**5** and **8**) both gave rapid gas evolution (methane) followed by slower attack of the oxirane ring; the reaction must therefore involve an intermediate O-metalated species. As shown in eq 2 and 3, these reactions exhibit completely stereospecific anti opening of the oxirane ring, with moderate regioselectivity suggesting preferred diaxial opening through the half-chair con-

(1) Support in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(2) R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 3813 (1970).

(3) R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 4979 (1970).

(4) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).