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ISOMERIZATION OF EPOXIDES TO ALLYLIC ALCOHOLS USING METHYLMAGNESIUM N-CYCLOHEXYLISOPROPYLAMIDE

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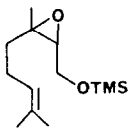
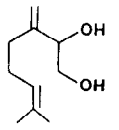
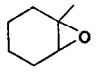
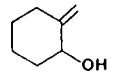
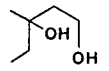
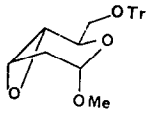
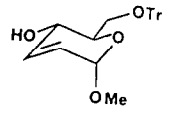
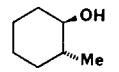
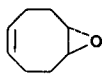
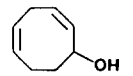
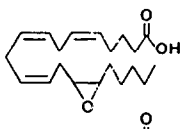
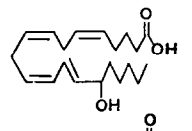
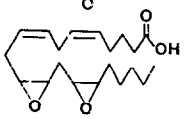
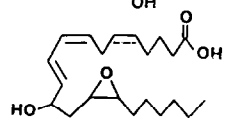
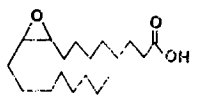
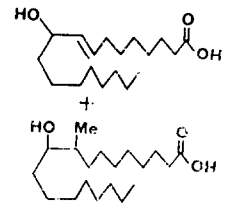
Summary: The scope of methylmagnesium N-cyclohexylisopropylamide promoted isomerizations of epoxides to allylic alcohols is described.

The isomerization of epoxides to allylic alcohols (eq. 1) is a common and preparatively useful functional group interchange[1]. In recent years, refinements in both selectivity and regiochemical control have been achieved by exploiting strong, non-nucleophilic bases that incorporate cations with a high affinity for the oxirane oxygen[2]. However, attempts in these laboratories to transform a sensitive, polyfunctional epoxide to the corresponding allylic alcohol using available methods resulted in low yields or refractory mixtures. Motivated by the initial observations of Corey et al.[3], we investigated various magnesium amides as an alternative and report herein the application[4] of methylmagnesium N-cyclohexylisopropylamide (MMA) for the isomerization of epoxides to allylic alcohols.

(1)

MMA is prepared by adding n-butyllithium (1 equiv) to a 0°C solution of N-cyclohexylisopropylamine in anhydrous toluene (0.85 M). After 15 min, methylmagnesium bromide (1 equiv, 3 M in Et_2O) is introduced dropwise. Stirring is continued for another 30-45 min during which time a white precipitate develops. Although the nature of the reagent and its state of aggregation are unknown, the formation of allylic alcohols from epoxides is assumed to proceed by a ß-elimination pathway in analogy with related systems[1].

Table. Reaction of Epoxides with MMA.

Entry	Epoxide	Temp (°C)	Time (hr)	Product	Isolated Yield (%)
1		0	7.5		96[a]
2		0	20		85[b]
3		0	7		50[b]
4		0	1.5		94 (mp 153-154°C)
5		24	16		42
6		24[c]	13		43
7		0	3		51
8		0	1.5		37
9		24[c]	20		45[d] 45[d]

a: isolated according to ref. 2b; b: characterized as the benzoate; c: added at 0°C; d: mixture of regioisomers.

The epoxide in toluene is added to a 3-4 fold excess of MMA (final MMA concentration 0.55 M) at 0°C and the mixture maintained under the conditions summarized in the Table. Proton abstraction from a methyl group is greatly preferred over that from a methylene in acyclic[2b] (entry 1) and cyclic (entry 2) systems. However, in some cases like a 1,1-disubstituted epoxide (entry 3) and a simple cyclic epoxide (entry 5), nucleophilic addition of methyl from MMA is the major result. In contrast, the more sterically biased pyranoside [5-7] in entry 4 isomerizes exclusively to allylic alcohol. It is noteworthy that, unlike lithium amides[8], MMA converts 5,6-epoxycyclooctene (entry 6) to 2,5-cyclooctadien-1-ol without significant ketone or conjugate diene formation. Exposure of 14,15-epoxyeicosatrienoic acid (entry 7) to MMA affords 15-hydroxyeicosatetraenoic acid (HETE). The yield of 15-HETE decreases dramatically if THF or toluene/HMPA (2:1) is the solvent[9,10]. Abstraction of an allylic proton in a related bis-epoxide (entry 8) also leads to a conjugated E,Z-dienol.

The epoxide of oleic acid displays intermediate reactivity with respect to isomerization or nucleophilic addition. Treatment with MMA furnishes approximately equal amounts of allylic alcohol and methyl addition product (entry 9). The ethylmagnesium and isopropylmagnesium analogues of MMA behave similarly. On the other hand, phenylmagnesium N-cyclohexylisopropylamide gives rise to only allylic alcohol, albiet in low yield ($\sim$ 20%).

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References and Notes:

1. Reviews: J.K. Crandall, M. Apparu, Organic Reactions 29: 345-443 (1983); J.G. Smith, Synthesis, 629-656 (1984); A.S. Rao, S.K. Paknikar, J.G. Kirtane, Tetrahedron 39: 2323-2367 (1983).
2. For example, (a) A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, H. Nozaki, J. Amer. Chem. Soc. 96: 6513-6514 (1974); (b) S. Tanaka, A. Yasuda, H. Yamamoto, H. Nozaki, ibid. 97: 3252-3254 (1975); (c) H. Yamamoto, H. Nozaki, Angew. Chem. Int. Ed. Engl. 17: 169-175 (1978).
3. E.J. Corey, A. Marfat, J.R. Falck, J.O. Albright, J. Amer. Chem. Soc. 102: 1433-1435 (1980); E.J. Corey, P.B. Hopkins, J.E. Munroe, A. Marfat, S. Hashimoto, ibid. 102: 7986 (1980).
4. For the use of MMA in the enantiospecific synthesis of coriolic acid see, C.A. Moustakis, D.K. Weerasinghe, P. Mosset, J.R. Falck, C. Mioskowski, accompanying communication.

5. Y.-L. Yang, J.R. Falck, Tetrahedron Letters 23: 4305-4308 (1982).
6. Satisfactory spectral data (nmr, ir, mass spectroscopy) were obtained for all new compounds using chromatographically homogeneous samples.
7. Methyl 2,3-dideoxy-2,3-dehydro-6-O-trityl-α-D-glucopyranoside (entry 4): NMR (90 MHz, $CDCl_3$) δ 3.36 (ddd, J ∿ 7, 7, 9 Hz, 1H), 3.40 (s, 3H), 3.72 (dd, J ∿ 7, 11 Hz, 1H), 3.78 (dd, J ∿ 7, 11 Hz, 1H), 4.06 (br d, J ∿ 9 Hz, 1H), 4.80 (br s, 1H), 5.64 (dt, J ∿ 11, 1.5 Hz, 1H), 5.86 (d, J ∿ 11 Hz, 1H), 7.08-7.50 (m, 15H); mass spec (rel. intensity) m/e 402 (5), 370 (2), 325 (12), 293 (12), 273 (4), 259 (56), 243 (100), 225 (68), 215 (50); TLC, SiO_2, EtOAc/hexane 1:2, R_f ∿ 0.35. 2,5-cyclooctadien-1-ol (entry 6): NMR (300 MHz, $CDCl_3$) δ 1.35-1.49 (m, 2H), 1.79-1.95 (m, 2H), 2.83 (br t, J ∿ 4.4 Hz, 2H), 4.91 (dddt, J ∿ 6.2, 10.5, 5.5, 1, 1H), 5.36 (ddt, J ∿ 11.4, 6.2, 1.5 Hz, 1H), 5.51 (dt, J ∿ 11, 7.5 Hz, 1H), 5.62 (dt, J ∿ 11, 4.4 Hz, 1H), 5.67 (dt, J ∿ 11, 4.4 Hz, 1H).
8. J.K. Crandall, L.-H. Chang, J. Org. Chem. 32: 532-536 (1967).
9. For a detailed study of the effect of HMPA on the reactivity of epoxides with lithium amides see, M. Apparu, M. Barrelle, Tetrahedron 34: 1817-1822 (1978) and earlier papers.
10. Treatment of certain classes of epoxides with halomagnesium alkylamides in THF affords the corresponding β-amino alcohols, M.C. Carre, J.P. Houmounou, P. Caubere, Tetrahedron Letters 26: 3107-3110 (1985).

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