Notes

Ferric Chloride in Ether. A Convenient Reagent for the Conversion of Epoxides into Chlorohydrins

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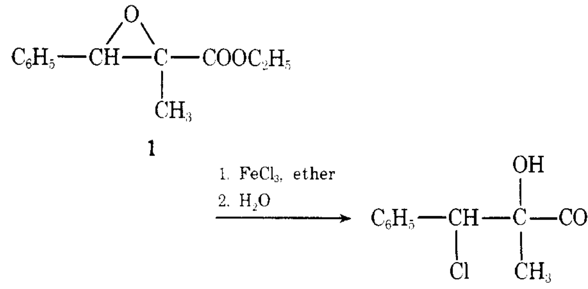
During a study of the photochemistry of glycidic esters in the presence of metallic salts, a reaction of ethyl (*Z*)-2-methyl-3-phenylglycidate (*Z*-1) with an equimolar amount of $FeCl_3$ in ether was observed to take place rapidly at room temperature in the dark. After 2 min the ether solution was washed with water and found to give a mixture of *threo*- and *erythro*-ethyl 2-methyl-3-chloro-3-phenyllactate (**2**) in 82% yield,[1] uncontaminated by starting material or rearrangement products.



1 **2**

The reaction was stereoselective, yielding predominantly the product of back-side attack onto the benzylic carbon–oxygen bond. Thus, the ratio of *threo*- to *erythro*-**2** was 3.5:1 from *Z*-**1**, while it was 0.62:1 from *E*-**1** under the same conditions.

It is well known that the reaction of Lewis acids with epoxides may follow several paths: isomerization to carbonyl products, isomerization to allylic alcohols or derivatives, or reaction with nucleophiles.[2] In this last category, the formation of fluorohydrins and bromohydrins in reactions with boron trifluoride and magnesium bromide, respectively, are examples where the nucleophile is derived from the Lewis acid itself, but there are very few examples of chlorohydrins having been prepared by reaction of an epoxide with a metal chloride, and only one where ferric chloride was used for this conversion.[3] There, ethylene and propylene oxides were shown to give their chlorohydrins in 23 and 34% yield, respectively.

Before checking on the generality of the reaction of $FeCl_3$ in ether with other epoxides, the published reactions were repeated with similar results, and their complexity was confirmed by a GLC analysis which disclosed the presence of at least 28 products in the reaction with ethylene oxide. These were not investigated further.

Other examples of epoxides which were investigated are shown in Table I.

Cyclohexene oxide (**3**) yielded 2-chlorocyclohexanol which had NMR and ir spectra practically superimposable on those of the trans isomer obtained by hydrogen chloride treatment.[4] The trace of cis isomer was detected by GLC.

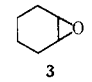
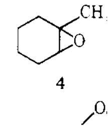
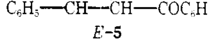
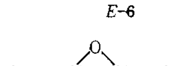
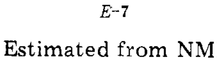
1-Methylcyclohexene oxide (**4**) was studied in order to compare its reaction with $FeCl_3$ to that with $MgBr_2$ which yielded carbonyl products exclusively, without any bromohydrins.[5] We found that although **4** reacted with $FeCl_3$ in ether to produce small amounts of aldehyde and ketonic materials (from NMR and ir analysis), a good yield of trans chlorohydrin was obtained. This product as well as that obtained by reaction of **4** with HCl was free from the cis isomer (GLC analysis).[6]

The stereoselectivity was not as good in the reaction of epoxides which were not part of a fused bicyclic system. Thus chalcone oxide [(*E*)-2-phenyl-3-benzoyloxirane, **5**] yielded a mixture of chlorohydrins which was nearly 50% produced by cis opening.[7] The major by-product of the reaction was 2-benzoylphenylacetaldehyde, the usual rearrangement product of this epoxide.[8] We note that in this case both the yield of chlorohydrins and the stereoselectivity of the reaction were not as high as reported in the treatment with $SnCl_4$.[8]

Ethyl (*E*)-2-phenylglycidate (**6**) reacted almost identically with $FeCl_3$ in ether and with HCl in ether, in terms of yield and stereoselectivity.

Finally, (*E*)-stilbene oxide (**7**) gave quantitative isomer-

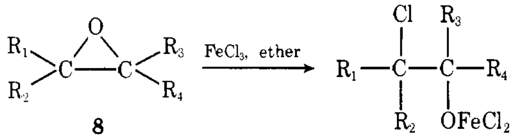
Table I. Reaction of Ferric Chloride in Ether with Selected Epoxides

Substrate	Registry no.	Yield of chlorohydrin (isolated)	% cis opening
 3	279-49-2	78 (6628-80-4)[b]	6 (17002-09-4)[b]
 4	1713-33-3	74 (60537-96-4)[b]	0
 *E*-5	7570-86-7	55 (22464-01-3)[b]	50 (22464-02-4)[b]
 *E*-6	2272-55-1	64[a] (60537-97-5)[b]	33 (60537-98-6)[b]
 *E*-7	1439-07-2	0	

[a] Estimated from NMR. [b] Registry no.

ization to diphenylacetaldehyde, even though an independent treatment of the expected chlorohydrin showed it to be stable under the reaction conditions. In this case, it is likely that the phenyl migration took place concertedly with the epoxide ring opening, or (less probably) from an organoiron derivative of the chlorohydrin itself.[9]

In all this work, we made no attempts to characterize the intermediate organoiron compounds produced in the reactions, which we formulate as 8 by analogy with the reaction of other metal halides with epoxides.[2]



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Ether seemed to be the solvent of choice since **1** did not react with $FeCl_3$ in chlorobenzene, toluene, dimethyl sulfoxide, or when no solvent was used. In carbon tetrachloride, there was only 50% conversion after 25 min, while in acetonitrile the conversion was very slow, yielding 30% of **2** after 16 h. In methanol, the solvent participated in the reaction, and *Z*-**1** gave *threo*-3-methoxy-3-phenyllactate stereospecifically in 30% yield after 20 h. Under the same conditions, there was no reaction with the *E* isomer. Benzene gave mixed results: $FeCl_3$ is appreciably soluble in this solvent, and the conversion of *Z*-**1** to **2** took place readily with good stereoselectivity (66% threo). However, **4** did not yield any chlorohydrins in these conditions, and instead isomerized quantitatively into 2-methylcyclohexanone, a reaction reminiscent of that described with $MgBr_2$ in ether.[5]

The high solubility of $FeCl_3$ in ether containing hydrogen chloride has been used for the selective extraction of this salt from aqueous solutions,[10] and the crystalline mono- and dietherates of $HFeCl_4$ were prepared from such ether solutions.[11] Similarly, the preparation of a mono-[11,12] and a dietherate[11] of $FeCl_3$ itself has been claimed, but the physical properties of these compounds were barely described. However, the monoetherate obtained by concentration of a solution of $FeCl_3$ in ether was reported to be soluble in benzene.[12] We therefore attempted to use such a solution for preparing **2** from **1**. Here the conversion took place smoothly at room temperature, but without stereoselectivity.

The reaction of **4** with ferric chloride etherate in benzene yielded a mixture of the isomeric 1-methylcyclopentanecarboxaldehyde (33%) and 2-methylcyclohexanone (66%), while it gave a mixture of the chlorohydrin (50%), the aldehyde (26%), and the ketone (24%) with ferric chloride etherate in carbon tetrachloride.

We also observed that benzene provided no improvement over ether in the reaction of **7** with ferric chloride etherate. Complete rearrangement to diphenylacetaldehyde also took place.

Finally, the superior solvent power of isopropyl ether over ethyl ether for $FeCl_3$[12] suggested the use of that solvent as a possible improvement in the procedure. However, when treated with $FeCl_3$ in isopropyl ether, *Z*-**1** could be recovered quantitatively.

In conclusion, although $FeCl_3$ or its etherate(s) may be occasionaly used in other solvents, no combination proved superior to $FeCl_3$ in ether, which is a very convenient, if not general, reagent for synthesizing chlorohydrins from epoxides.[14]

Experimental Section

Representative Reaction of an Epoxide with Ferric Chloride in Ether. Anhydrous $FeCl_3$ (150 mg, 0.73 mmol) was dissolved in 50 ml of anhydrous ether. The reaction was exothermic, and produced an orange solution, to which 150 mg (0.73 mmol) of **1** was added. After 2 min of stirring, the green-black solution was diluted with 25 ml of ether and washed with two 50-ml portions of water. The aqueous extracts were combined and extracted with 50 ml of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated under vacuum, and yielded 145 mg (0.60 mmol, 82% yield) of a slightly yellow liquid which crystallized slowly. The solid melted at 45–70 °C: mass spectrum *m/e* 242 (M^+), 206, 190, 11/, 116, 115, 105, and 91; NMR ($CDCl_3$) 1.15 (t, $J = 7$ Hz, 3 H), 1.60 (s, 3 H), 4.05 (q, $J = 7$ Hz, 2 H), and 5.07 ppm (s, 1 H) for the erythro (22.5%), and 1.18 (s, 3), 1.32 (t, $J = 7$ Hz, 3 H), 4.30 (q, $J = 7$ Hz, 2 H), and 5.12 ppm (s, 1 H) for the threo isomer (77.5%). The aromatic signals were centered at 7.32 ppm (m, 5 H), and the hydroxyls at 3.30 ppm (disappearing in the presence of D_2O) for both diastereoisomers.[18]

Registry No.—*E*-**1**, 7141-24-4; *z*-**1**, 7042-28-6; *threo*-**2**, 59069-85-1; *erythro*-**2**, 59069-84-0; $FeCl_3$, 7705-08-0.

References and Notes

(1) These chlorohydrins were characterized in another study: J. Kagan, D. A. Agdeppa, Jr., D. A. Mayers, S. P. Singh, M. J. Walters, and R. D. Wintermute, *J. Org. Chem.*, **41**, 2355 (1976).

(2) General references may be found in (a) F. Johnson in "Friedel-Crafts and Related Reactions", Vol. IV, G. A Olah, Ed., Interscience, New York, N.Y., 1965, p 1; (b) M. S. Malinovskii, "Epoxides and Their Derivatives", Israel Program for Scientific Translation, 1965; (c) G. Dittus in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 6/3, Georg Thieme Verlag, Stuttgart, 1955, p 437.

(3) A. B. Borkovec, *J. Org. Chem.*, **23**, 826 (1958).

(4) P. J. Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

(5) S. M. Naqvi, J. P. Horwitz, and R. Filler, *J. Am. Chem. Soc.*, **79**, 6283 (1957).

(6) The synthesis of both chlorohydrins was described by H. Bodot, J. Jullien, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 1097 (1958). The trans isomer obtained by reaction of **4** with HCl in ether was believed to contain 45% of the cis isomer. This came from rate studies in the reaction of this product with base, assumed to convert the trans isomer quantitatively into **4**. Our GLC analysis showed the product of the HCl treatment to be pure trans, but its complete conversion into **4** in the presence of base was more sluggish than anticipated, thereby accounting for the discrepancy. The synthesis of the cis isomer was accomplished by these authors by reducing 2-chloro-2-methylcyclohexanone with $LiAlH_4$. We did not repeat this reaction and cannot confirm whether 19% of the trans isomer was indeed formed along with the cis chlorohydrin which melted at 19 °C. The reduction with $NaBH_4$ in ethanol yielded the cis isomer which contained ca. 7% of trans (GLC analysis), but the dehydrochlorination of this cis isomer (mostly to 2-methylcyclohexanone) took place at an appreciable rate under the published conditions, thus also invalidating this type of analysis. Our recrystallized cis chlorohydrin melted at 27 °C.

(7) We encountered some difficulties in the characterization of one of the chlorohydrins. Although pure by all spectroscopic criteria, it melted sharply at 90 °C, when 72 and 107 °C are the values reported for the two diastereoisomeric 1-benzoyl-2-chloro-2-phenylethanols.[8a] We later found that 90 °C was the melting point for a different crystalline modification of the compound which usually melts at 107 °C.

(8) (a) H. O. House, *J. Org. Chem.*, **21**, 1306 (1956); (b) *J. Am. Chem. Soc.*, **76**, 1235 (1954), and references cite, therein.

(9) H. O. House, *J. Am. Chem. Soc.*, **77**, 3070, 5083 (1955).

(10) C. Duval in "Nouveau Traite de Chimie Minerale", P. Pascal, Ed., Masson et Cie, Paris, 1959, p 14.

(11) F. Klages, H. Meuresch, and W. Steppich, *Justus Liebigs Ann. Chem.*, **592**, 81 (1955).

(12) A. Forster, C. Cooper, and G. Yarrow, *J. Chem. Soc.*, **111**, 810 (1917).

(13) R. W. Dodson, G. J. Forney, and E. H. Swift, *J. Am. Chem. Soc.*, **58**, 2573 (1936).

(14) It is interesting to mention three other recent reports where $FeCl_3$ was also used for cleaving ethers. In one[15] $FeCl_3$ in acetic anhydride was shown to convert ethers into a mixture of acetates, while in the other $FeCl_3$ in dimethylformamide cleaved and oxidized the trimethylsilyl ethers of bicyclic cyclopropanols into β-chloro ketones.[16] Finally, the poorly defined $FeCl_3$–*n*-BuLi system was shown to deoxygenate epoxides into olefins.[17]

(15) B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).

(16) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2078 (1976).

(17) T. Fujisawa, K. Sugimoto, and H. Ohta, *Chem. Lett.*, 883 (1974).

(18) Our limited experience suggests that it is not necessary to have complete solution of the $FeCl_3$ in ether prior to its reaction with an epoxide. The reagent dissolves rapidly as the reaction proceeds, and the total volume of solvent necessary for larger scale reactions may therefore be kept small.

Synthesis of 5-(*tert*-Alkyl)resorcinols

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In connection with other work underway in these laboratories, a short and efficient method for the preparation of large