Highly Efficient, Regio- and Stereoselective Alcoholysis of Epoxides Catalyzed with Iron(III) Chloride

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Received 8 February 1994; revised 20 June 1994

An efficient, catalytic, simple and mild method for the conversion of epoxides into their corresponding β-alkoxy alcohols was performed in primary, secondary and tertiary alcohols and in the presence of catalytic amounts of ferric chloride. The β-alkoxy alcohols were obtained with high stereo- and regioselectivity and in good to excellent yields.

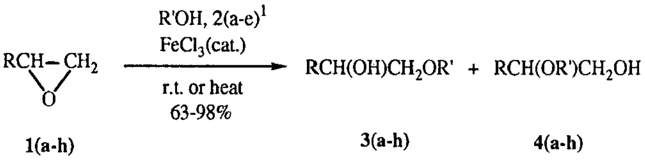
Epoxides[1] and β-alkoxy alcohols are important intermediates in organic synthesis. Easy oxidation of this latter functional group is a common method for the preparation of α-alkoxy ketones or α-alkoxy acids. β-Alkoxy alcohols are also present in some naturally occuring compounds.[2]

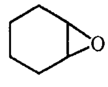
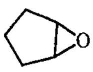
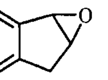
Alcoholysis of epoxides to β-alkoxy alcohols under mild and neutral conditions is very important in modern synthesis.[1] However, standard methods for nucleophilic opening of epoxides are not always satisfactory and suffer from disadvantages such as high acidity,[3,4] unsatisfactory regioselectivity,[4,5] inconvenient handling of the reagent,[6,7] non-catalytic nature of the reagent[8] and long reaction time.[6,8] Recently, the use of some one-electron transfer catalysts has also been reported for the alcoholysis of epoxides.[9]

Iron(III) has been extensively used as an efficient oxidant for different functional group transformations.[10] In this paper, we wish to report that catalytic amounts of iron(III) as anhydrous ferric chloride can bring about an efficient, smooth, regio- and stereoselective ring opening of epoxides in 1°, 2° and 3° alcohols.

Alcoholysis of different classes of epoxides such as cyclohexene and cyclopentene oxides, styrene and indene oxides, epichlorohydrin, allyl 2,3-epoxypropyl ether, 2,3-epoxypropyl isopropyl ether and 2,3-epoxypropylphenyl ether as examples of alicyclic, activated and deactivated epoxides were performed in primary, secondary and tertiary alcohols. Their corresponding β-alkoxy alcohols were obtained in good to excellent yields (Scheme, Table).

The Table shows the results obtained in the reaction of some representative epoxides with catalytic amounts of Fe(III) as anhydrous ferric chloride. The reactions of cyclohexene and cyclopentene oxide in all alcohols except *t*-BuOH were performed at room temperature (Table, entries 23–28). The reactions with cyclic compounds were completely stereoselective and the trans products were obtained in 63–85 % yields. In the case of unsymmetrical epoxides, the regiochemistry is strongly dependent on the nature of the substituent on the substrate. The reaction of those epoxides with an electron-donating group (Scheme, **1a,h**) occurs on that carbon atom which can effectively stabilize the developing positive charge. For those epoxides which are substituted with a deactivating group (Scheme, **1b–e**), the reactions are again charge controlled and nucleophilic attack occurs with high regioselectivity on the carbon atom away from the electron-withdrawing substituent.



	R or Epoxide
1a	Ph-
1b	ClCH$_2$-
1c	(CH$_3$)$_2$CHOCH$_2$-
1d	PhOCH$_2$-
1e	CH$_2$=CHCH$_2$OCH$_2$-
1f	
1g	
1h	

[1]2a = MeOH; 2b = EtOH; 2c = ^{n}PrOH; 2d = ^{i}PrOH; 2e = ^{t}BuOH

Scheme

Fe(III) as ferric chloride has been reported to act as a one-electron transfer agent for carbon–oxygen bond cleavage in some benzylic ethers[10a] and in coupling reactions of some aromatic compounds.[10b] In both reactions, removal of one electron by Fe(III) and the formation of a radical cation may be the initial step of these reactions.

In our case, although the precise mechanism of the reaction is not clear, we propose that, on the basis of our previous results obtained from the reaction of epoxides with nucleophiles catalyzed by one-electron transfer catalysts such as Ce(IV)[9b–e] and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[9a] the formation of the radical cations (i) and (ii) as intermediates may account for the above features of the reaction (Fig. 1).

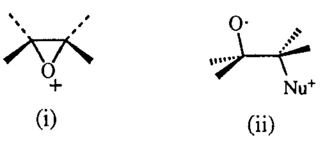


Figure 1

The formation of a radical in the reaction can be demonstrated by the addition of acrylamide as a radical trapping agent.[11] The catalytic nature of the reaction could be due to the regeneration of Fe(III) through a one-electron transfer between alkoxy radical cation (ii) and Fe(II).

Table. Catalytic Ring-Opening Reaction of Epoxides with Iron(III) Chloride in Alcohols

Entry	Epoxide	R'OH	Product[a]	Time/Temp (h)(°C)	$FeCl_3$/ Epoxide (molar ratio)	Yield[b] (%)	Bp(°C)/Torr or n_D^{20}(°)	
							Found	Reported
1	**1a**	**2a**	**4a**	0.75/25	0.05	90	60/2	75/0.7[8,9,13-15]
2	**1a**	**2b**	**4a**	0.75/25	0.05	96	1.5143	1.5145[8,9]
3	**1a**	**2c**	**4a**	0.75/25	0.05	98	1.5106	1.5108[8,9]
4	**1a**	**2d**	**4a**	0.75/25	0.05	90	1.5075	1.5073[8,9]
5	**1a**	**2e**	**4a**	2/85	0.15	82	1.5130	1.5127[8,9]
6	**1b**	**2a**	**3b**	2.5/65	0.15	65	97–100/9	105/10[9,16]
7	**1b**	**2b**	**3b**	2/80	0.1	70	110–111/9	104–105/8[9,16]
8	**1b**	**2c**	**3b**	1/100	0.05	85	1.4377	1.4378[9,16,17]
9	**1b**	**2d**	**3b**	1/85	0.05	75	117–118/15	108–110/10[9,16,17]
10	**1b**	**2e**	**3b**	1/85	0.05	75	1.4434	1.4436[9]
11	**1c**	**2a**	**3c**	2.5/65	0.15	80	200–202	202–203[16]
12	**1c**	**2b**	**3c**	1.75/80	0.05	90	208–209	209[16,18]
13	**1c**	**2d**	**3c**	0.75/85	0.05	91	1.4196	1.4198[16]
14	**1d**	**2a**	**3d**	3/65	0.15	95	120–121/3	128/5[19]
15	**1d**	**2c**	**3d**	1.5/100	0.08	95	1.5042	1.5040[19]
16	**1d**	**2d**	**3d**	1/85	0.05	95	1.4972	1.4974[8,9]
17	**1d**	**2e**	**3d**	1.5/85	0.05	93	1.4950	1.4955[8,9]
18	**1e**	**2a**	**3e**	4/65	0.15	90	1.4462	1.4460[20]
19	**1e**	**2b**	**3e**	1.5/80	0.1	96	1.4375	1.4373[9]
20	**1e**	**2c**	**3e**	1.5/100	0.1	96	1.4380	1.4382[9]
21	**1e**	**2d**	**3e**	1/85	0.05	95	1.4364	1.4365[9]
22	**1e**	**2e**	**3e**	1.75/85	0.05	75	1.4580	1.4581[9]
23	**1f**	**2a**	*trans*-2-methoxy-cyclohexanol	2/25	0.05	75	100–101/60	107–111/65[21]
24	**1f**	**2b**	*trans*-2-ethoxy-cyclohexanol	2/25	0.05	80	72–75/11	80–85/15[21,22]
25	**1f**	**2c**	*trans*-2-propoxy-cyclohexanol	2.5/25	0.05	85	86–87/10	92–96/14[21]
26	**1f**	**2d**	*trans*-2-isopropoxy-cyclohexanol	3.5/25	0.05	70	80–81/16	89–93/18[21]
27	**1f**	**2e**	*trans*-2-*tert*-butoxy-cyclohexanol	2/85	0.15	63	90–92/15	86–91/14[21]
28	**1g**	**2a**	*trans*-2-methoxy-cyclopentanol	1/25	0.1	88	173	175[23]
29	**1h**	**2a**	*trans*-1-methoxy-indan-2-ol	0.5/25	0.1	85	146–147/11	146–148/11[24]

[a] The product was isolated and compared with authentic sample.

[b] Yields refer to isolated products.

Regeneration of Fe(III) from the reaction of hydroxyl radical and Fe(II) has been shown to occur very rapidly.[12]

In conclusion, the catalytic method described here appears to be an efficient, mild and simple method for the alcoholysis of epoxides in different classes of alcohols. In addition, the advantages such as high regio- and stereoselectivity, availability and nontoxicity of the reagent, ease of workup, high yield and relatively short reaction times make this method a useful addition to the present methodologies in organic synthesis.

Products were characterized by comparison of their physical data, IR, NMR and mass spectra, with those prepared in accordance with literature procedures. All yields refer to isolated products. IR spectra were recorded on a Perkin-Elmer IR-157 G and a Perkin-Elmer 781 spectrometer. NMR spectra were recorded on a Hitachi, R-2413, 60 MHz or Varian XL-100 spectrophotometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The purity determination of the substrates and monitoring of reactions were accomplished by TLC on silica gel Polygram SILG/UV 254 plates or GLC on a Shimadzu GC-8A instrument with a flame ionization detector using a column of 15% Carbowax 20M Chromosorb-W acid-washed 60–80 mesh. Chemicals were purchased from Fluka and Merck chemical companies. Products were separated and purified by different chromatography techniques. 2-Methoxy-2-phenylethanol and its α-naphthylurethane gave C,H (and N where appropriate) analysis ± 0.1%.

Catalytic Reaction of Styrene Oxide with Ferric Chloride in Methanol; Typical Procedure:

A mixture of styrene oxide (1.2 g, 10 mmol) and anhydr. $FeCl_3$ (81 mg, 0.5 mmol) in MeOH (50 mL) was stirred at r.t. for 45 min. The reaction was monitored by GLC. The solvent was removed under vacuum. Water (25 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The organic solution was dried ($MgSO_4$). Evaporation of the solvent followed by chromatography on a short column of silica gel gave the pure 2-methoxy-2-phenylethanol as a colorless liquid (1.37 g, 90%), bp 60 °C/0.2 mmHg (Lit.[13,14] 75 °C/0.7 mmHg).

^{1}H NMR (CCl_4/TMS): $\delta = 7.28$ (s, 5 H, Ph), 4.20 (dd, 1 H, $J = 7$, 5 Hz, CH), 3.5 (dd, 2 H, $J = 7$, 5 Hz, CH_2), 3.25 (s, 3 H, OMe), 2.70 (s, 1 H, OH).

Its α-naphthylurethane was obtained as fine colorless needles, mp 124.5–125 °C (Lit.,[13,14] 120 °C).

We would like to acknowledge the support of this work by the Shiraz University Research Council, and Dr. A. A. Jarahpoor for running the mass spectra.

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