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Niobium Pentachloride Catalysed Ring Opening of Epoxides

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Abstract: Epoxide ring opening is a frequently required transformation in Organic Synthesis. In this paper we describe the application of $NbCl_5$ for this purpose using three different substrates. Chlorohydrins, 1,2-diols, products containing solvent residues as well as rearrangement products are obtained, depending on both the substrate structure and reaction conditions. Rationalizations to account for some of the results are suggested.

Keywords: Niobium pentachloride, Epoxides, 1,2-Diols, Chlorohydrins

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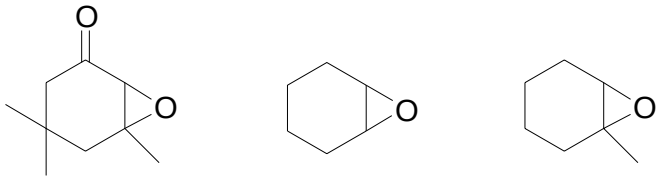
Introduction

Opening of epoxide rings has been a frequently required transformation in our studies on the synthesis of natural products [1]. Boron trifluoride etherate is the most commonly used Lewis acid for this purpose, but we decided to investigate the possibility of obtaining different products by using niobium pentachloride ($NbCl_5$), which is a stronger Lewis acid and is currently attaining increasing popularity as a reagent [2].

In preliminary experiments we found that the reaction of epoxides with $NbCl_5$ is very fast and follows different paths and mechanisms depending on the substrate structure and the reaction medium. We have now chosen three model substrates, compounds **1** – **3** (Figure 1), containing suitable structural variations, with the aim of comparing the results and, as much as possible, rationalize the observed

structure-result correlations and extend them to further more detailed studies. Thus, compounds **1** and **3** have a fully substituted carbon in the epoxide ring that could lead to a carbocation formation; compound **1** has, additionally, an efficient migrating group. Compound **2** cannot form a tertiary carbocation.

Figure 1. Substrates chosen for treatment with $NbCl_5$.

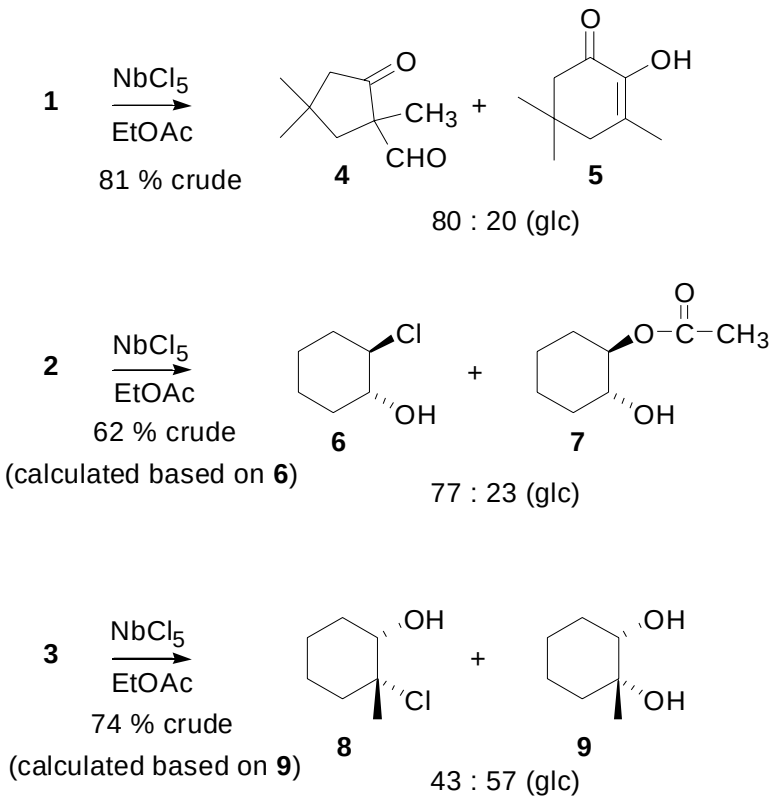


Results and Discussion

We first treated each of the three substrates with $NbCl_5$ dissolved in anhydrous ethyl acetate, at room temperature under N_2 atmosphere. Ethyl acetate dissolves $NbCl_5$ completely, giving a yellow solution. When the substrate, dissolved in ethyl acetate, was added to this solution, an instantaneous reaction took place, giving a solution that was quenched after 1.0 min with a 10 % aqueous citric acid solution [3].

The results are summarized in Scheme 1. Isolated crude product (mixture) yields are given, together with an indication of the product taken as a base for the calculation, as well as the ratio, determined by GLC, between the products of each reaction. All products were isolated and characterized by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra.

Scheme 1. Results obtained on treatment of epoxides with $NbCl_5$ using ethyl acetate as solvent.

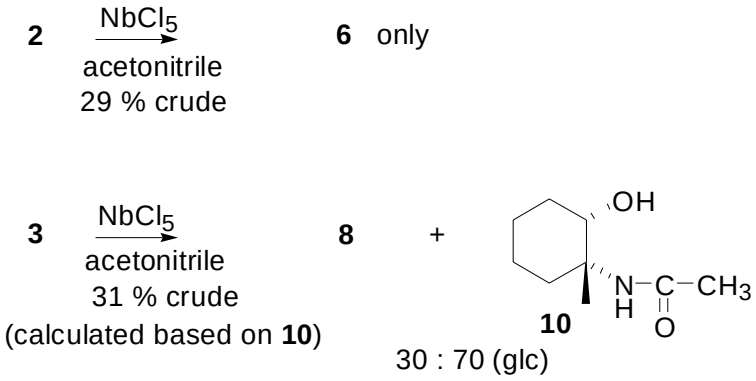


The formation of compounds **4** and **5** from substrate **1**, as well as the formation of compound **8** from **3** clearly show a preferential breakage of the epoxide bond to the more substituted carbon atom. The resulting tertiary carbocation from compound **1** (either incipient or fully formed) has undergone acyl group migration to form **4**, or H^+ elimination to give **5** [4]. The cation from compound **3**, having neither groups with high migratory aptitude nor a carbonyl group to favor the formation of a conjugated double bond through H^+ elimination, followed a different path, namely addition of Cl^- which, considering the stereochemistry of the product, apparently came directly from the catalyst residue still bonded to the epoxide oxygen. At this stage we cannot suggest a mechanism to account for the formation of compound **9**, which apparently was formed during the hydrolysis process. Its definite stereochemistry suggests the participation of the catalyst in the introduction of the OH group in the tertiary carbon atom.

Substrate **2** has no fully substituted carbon atom to favor the ring opening and thus reacted in a different way. The *trans* stereochemistry of both products suggests that the epoxide, activated by the Lewis acid, reacted through S_N2 mechanisms, the attack by Cl^- to form **6** or by the solvent to form **7** possibly playing an important role in the opening of the epoxide ring.

Changing the solvent for the reactions of compounds **2** and **3** resulted in meaningful differences (Scheme 2). Compound **2**, with $NbCl_5$ dissolved in acetonitrile, gave only the chlorohydrin **6**; the comparatively low yield (29 %) apparently being due to loss of product in the aqueous phase during extraction. More productive extraction methods are currently being investigated.

Scheme 2. Results obtained on treatment of epoxides with $NbCl_5$ using acetonitrile as solvent.



Compound **3**, under the same conditions, also gave a lower yield of crude product, but the structures of products **8** and **10** are consistent with the interpretation of ring opening by breaking the bond to the more substituted carbon atom, followed by incorporation of a nucleophile from the same face of the oxygen atom and the catalyst, thus suggesting that the nucleophile came from the catalyst.

The relative stereochemistry of compounds **6**, **7** and **9** was assigned based on their ^{1}H- and ^{13}C-NMR spectra, and careful comparison with literature data [5]. For compounds **8** and **10**, however, no literature data was available. Molecular mechanics studies [6] show that NOE experiments could lead to ambiguous results, but the coupling constants between the carbinolic hydrogen and the two neighboring hydrogens would be very different for the two possible isomers (*cis* or *trans*) of each compound (see Table 1).

Table 1. Calculated and experimental vicinal coupling constants for compounds **8** and **10**.

Compound	Compound **8**		Compound **10**	
Coupling constant	J_1 (Hz)	J_2 (Hz)	J_1 (Hz)	J_2 (Hz)
Calculated for *trans* isomer:	2.7	4.3	3.0	6.4
Calculated for *cis* isomer:	10.6	4.4	11.0	4.4
Experimental values:	9.5	4.3	10.7	4.8

The good agreement between the experimental J values and the calculated values for the *cis* isomer of both compounds, as well as the absence of values around 10 Hz in the calculated J values for the *trans* isomers, clearly establish that compounds **8** and **10** should have a *cis* relative stereochemistry as depicted in Schemes 1 and 2.

Acknowledgments

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Experimental

General

NMR spectra were measured using a Bruker DPX-300 instrument (300 MHz for ^{1}H-NMR and 75 MHz for the ^{13}C-NMR); deuteriochloroform was used as solvent and tetramethylsilane as an internal standard. GC-MS spectra were obtained by EI ionization at 70 eV on a HP-5988-A spectrometer. IR spectra were measured with a Perkin-Elmer 1600 FT spectrometer. TLC was performed on plates precoated with silica gel 60 F_{254} plates (0.25 mm thick, Merck), and for column chromatography, silica gel 60 (70-230 mesh, Merck) was used. Analytical gas chromatography (GLC) separations were performed on a Varian GC 3400 instrument with a fused silica capillary column (30 m length x 0.25 mm i.d.) coated with DB 1701 (phase thickness 0.25 μm) operating at temperatures in the range 50-200ºC.

Preparation of substrates

(±) – 4,4,6-Trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (**1**).

Prepared as described in the literature [7]; ^{1}H-NMR: δ 2.93 (dd, 1H, J_1=1.1, J_2=0.9 Hz); 2.51 (dd, 1H, J_1=13.4, J_2=0.9 Hz); 1.97 (dt, 1H, J_1=15.0, J_2=J_3=0.9 Hz); 1.69 (ddd, 1H, J_1=13.4, J_2=2.2, J_3=1.1 Hz); 1.59 (dd, 1H, J_1=15.0, J_2=2.2 Hz); 1.30 (s, 3H); 0.9 (s, 3H); 0.8 (s, 3H); ^{13}C-NMR: δ 207.68 (C=O); 64.05 (C); 61.17 (CH); 47.77 (CH_2); 42.51 (CH_2); 35.92 (C); 30.61 (CH_3); 27.61 (CH_3); 23.82 (CH_3); IR

(film)ν_{max} 2952; 2930; 2870; 1717; 1465; 1153 cm^{-1}; MS *m*/*z* (rel. intensity)(%): 154 [M^+] (4); 139 (24); 111 (10); 97 (24); 83 (100); 69 (60); 55 (48); 41 (35).

7-Oxa-bicyclo[4.1.0]heptane (**2**) [8]**.**

To an ice-cooled solution of cyclohexene (1.48 g, 18.1 mmol) in methylene chloride (28 mL) was added a solution of *m*-chloroperbenzoic acid (5.0 g of 85 % MCPBA, 29 mmol) in methylene chloride (70 mL) from a dropping funnel (50 min). The ice bath was removed and the stirring was continued for 1.5 h at room temperature. The resulting mixture was treated with 10 % aqueous sodium sulfite solution (140 mL) and stirred for 1 h to remove excess of peracid. The organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed in succession with 5 % sodium bicarbonate and saturated brine and then dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was distilled (Kugelrohr) at 25 ºC (0.5 mmHg). Yield 1.15 g (65%); ^{1}H-NMR: δ 3.11 (br. s, 1H); 3.10 (br. s, 1H); 1.94 (m, 2H); 1.81 (m, 2H); 1.43 (m, 2H); 1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.09 (CH); 24.53 (CH_2); 19.52 (CH_2); IR (film) ν_{max} 2977; 2932; 2890; 1439; 1261; 1112; 1072 cm^{-1}; MS *m*/*z* (rel. intensity) (%) 97 [$(M-1)^+$] (14); 83 (100); 70 (22); 69 (30); 55 (41); 54 (44); 41 (65); 39 (50).

(±)-1-Methyl-7-oxa-bicyclo[4.1.0]heptane (**3**).

The same procedure as described for compound **2** was used, starting from 1-methylcyclohexene (1.74 g, 18.1 mmol). Yield 1.50 g (74%); ^{1}H-NMR: δ 2.86 (t, 1H); 1.69 (m, 4H); 1.21 (s, 3H); 1.12 (m, 4H); ^{13}C NMR: δ 59.53 (CH); 57.49 (C); 29.92 (CH_2); 24.80 (CH_2); 23.99 (CH_2); 20.08 (CH_2); 19.70 (CH_2); IR (film) ν_{max} 2977; 2961; 2931; 1434; 1214; 1114; 1070 cm^{-1}; MS *m*/*z* (rel. intensity) (%) 112 [M^+] (3); 111 (5); 97 (88); 69 (29); 67 (22); 55 (49); 43 (100); 41(46).

General Procedure for the Reactions of Epoxides with $NbCl_5$.

A solution of the epoxide **1**, **2** or **3** (1.0 mmol) in 1.0 mL of anhydrous solvent (ethyl acetate or acetonitrile) was added to a solution of niobium pentachloride (0.135 g, 0.5 mmol) in 1.0 mL of anhydrous solvent (ethyl acetate or acetonitrile), maintained at room temperature under nitrogen atmosphere. After 1.0 min, the reaction mixture was quenched with a 10% aqueous citric acid solution (2.0 mL). The mixture was diluted with water and ethyl acetate, the organic layer was separated and washed with 5% aqueous sodium bicarbonate, saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the products were purified by column chromatography through silica gel using a mixture of hexane and ethyl acetate (8:2) as eluent.

Characterization of the products

(±)-1,4,4-Trimethyl-2-oxo-cyclopentanecarbaldehyde (**4**):^{1}H-NMR δ 9.48 (s, 1H); 2.59 (dd, 1H, J_1=13.7, J_2=1 Hz); 2.27 (d, 1H, J_1=17.2 Hz); 2.17 (dd, 1H, J_1=17.2, J_2=1 Hz); 1.61 (d, 1H, J_1=13.7 Hz); 1.3 (s,

3H); 1.17 (s, 3H); 1.03 (s, 3H); ^{13}C-NMR δ 215.28 (C=O); 198.68 (C=O); 63.06 (C); 53.14 (CH_2); 44.22 (CH_2); 33.80 (C); 29.63 (CH_3); 28.92 (CH_3); 21.22 (CH_3); IR (film) ν_{max} 2956; 2868; 2712; 1730; 1714; 1453; 1370; 1149cm^{-1}; MS *m/z* (rel. intensity) (%) 139 [$(M-15)^+$] (21); 126 (13); 111 (23); 97 (22); 83 (100); 69 (47); 55 (40); 41 (49).

3,5,5-Trimethyl-cyclohexane-1,2-dione (**5**): ^{1}H-NMR: δ 6.02 (br. s, 1H); 2.35 (s, 2H); 2.25 (s, 2H); 1.88 (s, 3H); 1.06 (s, 6H); ^{13}C-NMR: δ 194.08 (C=O); 143.03 (C); 127.87 (C); 49.31 (CH_2); 44.66 (CH_2); 33.45 (CH_3); 28.36 (CH_3); 17.09 (CH_3); IR (film) ν_{max} 3402; 2947; 2876; 1666; 1640; 1405; 1173 cm^{-1}; MS *m/z* (rel. intensity) (%) 154 [M^+] (56); 126 (9); 111 (24); 98 (42); 70 (100); 55 (51); 41 (52); 27 (21).

(±)-trans-2-Chloro-cyclohexanol (**6**): ^{1}H-NMR: δ 3.70 (ddd, 1H, J_1=11.4, J_2=9.2, J_3=4.4 Hz), 3.49 (m, 1H), 2.58 (br. s, 1H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.75-1.50 (m, 3H), 1.35-1.15 (m, 3H); ^{13}C-NMR: δ 75.36 (CH), 67.55 (CH), 35.16 (CH_2), 33.11 (CH_2), 25.67 (CH_2), 23.98 (CH_2); IR (film) ν_{max} 3411, 2916, 1451, 1083, 961, 737 cm^{-1}; MS *m/z* (rel. intensity) (%) 134 [M^+] (36), 99 (61); 98 (100); 81 (93); 79 (34); 70 (39) 57 (22); 41 (30).

(±)-trans-2-Hydroxy-cyclohexyl acetate (**7**): ^{1}H-NMR: δ 4.57 (ddd, 1H, J_1=10.2, J_2=9.0, J_3=4.7 Hz), 3.54 (ddd, 1H, J_1=10.4, J_2=8.8, J_3=4.5 Hz), 2.78 (br. s, 1H), 2.08 (s, 3H), 2.02 (m, 2H), 1.71 (m, 2H), 1.31 (m, 4H); ^{13}C-NMR: δ 171.27 (C=O), 77.92 (CH), 72.32 (CH), 32.89 (CH_2), 29.80 (CH_2), 23.68 (CH_2), 23.60 (CH_2), 21.16 (CH_3); IR (film) ν_{max} 3441, 2947, 2857, 1730, 1451, 1375, 1248 cm^{-1}; MS *m/z* (rel. intensity) (%) 158 [$(M-60)^+$] (63); 83 (24); 79 (29); 70 (53); 57 (22); 43 (100); 41 (31); 28 (12).

(±)-cis-2-Chloro-2-methyl-cyclohexanol (**8**): ^{1}H-NMR: δ 3.77 (dd, 1H, J_1=9.5 and J_2=4.3); 2.57 (s, 1H); 2.11 (m, 1H); 1.91 (m, 2H); 1.67 (m, 2H); 1.57 (s, 3H); 1.40 (m, 3H); ^{13}C-NMR: δ 77.10 (CH); 76.35 (C); 40.68 (CH_2); 30.14 (CH_2); 23.26 (CH_2); 23.18 (CH_2); 22.80 (CH_3); IR (film) ν_{max} 3456; 2932; 2872; 1451; 1375; 1248; 1084; 1041 cm^{-1}; MS *m/z* (rel. intensity) (%) 112 [$(M-36)^+$] (5); 84 (3); 68 (10); 56 (13); 55 (16); 41 (21); 32 (25); 28 (100).

(±)-cis-1-Methyl-cyclohexane-1,2-diol (**9**): ^{1}H-NMR: δ 3.49 (m, 1H); 1.86 (m, 1H); 1.74 (m, 3H); 1.62 (m, 1H); 1.33 (m, 3H); 1.20 (s, 3H); ^{13}C-NMR: δ 77.26 (CH); 73.88 (C); 38.64 (CH_2); 31.02 (CH_2); 24.00 (CH_2); 23.28 (CH_2); 19.69 (CH_3); IR (film) ν_{max} 3381; 2947; 2857; 1451; 1079; 1050 cm^{-1}; MS *m/z* (rel. intensity) (%) 84 [$(M-46)^+$] (44); 51 (28); 49 (88); 47 (18); 37 (6); 35 (16); 32 (28); 28 (100).

(±)-cis-N-(2-Hydroxy-1-methyl-cyclohexyl)acetamide (**10**): ^{1}H-NMR: δ 5.49 (br. s, 1H); 3.65 (dd, 1H, J_1= 10.7 and J_2=4.7 Hz); 2.00 (s, 3H); 1.4 (s, 3H); 1.91-1.50 (m, 4H); 1.35 (s, 3H); 1.40-1.25 (m, 4H); ^{13}C-NMR:δ 171.43 (C=O); 75.95 (CH); 59.82 (C); 38.70 (CH_2); 31.04 (CH_2); 24.29 (CH_3); 23.85 (CH_2); 21.55 (CH_2); 16.47 (CH_3); IR (film) ν_{max} 3312; 2917; 1650; 1370; 1633; 1077; 734 cm^{-1}; MS *m/z* (rel. intensity) (%) 128 [(**M**-43)$^+$] (7); 112 (78); 86 (26); 84 (13); 70 (86); 60 (47); 43 (100); 42 (68).

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3. In tests carried out with each of the three substrates, TLCs of reaction mixtures quenched after 1.0 min, 2.0 min and 5.0 min were identical.
4. The formation of **5** from **1** could also be explained by a hydrogen migration. In this case, however, we should expect the formation of a corresponding compound from **3**.
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8. This compound is commercially available. See also the literature NMR data in Pouchert, C.J. *The Aldrich Library of NMR Spectra*, 2nd ed., Aldrich Chemical Co.:Wisconsin, **1983**, Vol. I; p. 196.

Sample availability: Samples of compounds **4-10** are available from MDPI. Additional samples of compound **4** are available from the authors.