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# Novel ring-opening of epoxides and oxetanes with $POCl_3$ or $PCl_3$ in the presence of DMAP

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**Abstract**—Efficient synthesis of chlorohydrins by cleavage of oxiranes and oxetanes using $POCl_3$ or $PCl_3$ in the presence of DMAP (4-*N*,*N*-dimethylaminopyridine) has been studied. 

There is a continued interest in the regioselective ring-opening of oxiranes and oxetanes to the corresponding 1,2 and 1,3 halohydrins. Although a variety of new and mild procedures to make this transformation have been reported, most of them have some limitations.[1] Methods based upon hydrogen chloride are not considered appropriate because of the formation of some unwanted byproducts and low regioselectivities.[2]

Ring-opening of asymmetrically substituted oxiranes had been reported with chlorosilanes,[3] haloborane reagents,[4] $Br_2/PPh_3$,[5] $Me_3SiBr$,[6] Py·HCl,[7] Lewis acid metal halides,[8] complex halide metal salts,[9] $n$-$Bu_4N^+Br^-/Mg(NO_3)_2$,[10] and elemental $I_2$ and $Br_2$ in the presence of catalysts.[11] However, some of these methods are not always fully satisfactory and suffer from disadvantages such as acidity, handling and in situ preparation of reagent or relative long reaction times. Besides, not all the above-mentioned methodologies are suitable to give chlorohydrins, due to the reactivity order of the three halides: $I^->Br^->Cl^-$.[1]

We have examined this reaction and report the opening of symmetric and asymmetric epoxides and oxetanes (see Table 1, entries 1–14), with $POCl_3$ or $PCl_3$ in the presence of DMAP in dichloromethane in high yields (70–85%) under mild conditions, at rt over 30–45 min even when sensitive functional groups are present in the molecules. Nevertheless, cyclohexene oxide, **4** (entries 10–12) was treated under milder conditions (−78°C, entry 12) to obtain the 2-choro-cyclohexanol, otherwise the 1,2-dichlorocyclohexane was recovered.[13]

The attack of the chloride ion in the asymmetric rings proceeds on the carbon atom with the most favorable electronic effects (substrates **1** and **2**) or on the less hindered carbon atom (substrates **3** and **6**). The higher regioselectivities were obtained using $POCl_3$.[14]

Besides, we observed that (*R*)-(+)-styrene oxide reacts enantioselectively with inversion of configuration on the stereogenic center yielding (*S*)-(+)-2-chloro-2-phenylethanol, 98% e.e. by HPLC analysis, $[\alpha]_D = +116.1$ ($c=1$, $CHCl_3$), meanwhile Kotsuki et al. report $[\alpha]_D = +30.7$ ($c=1$, $CHCl_3$), 18% e.e. by HPLC analysis.[15]

Based on the results we observed a rigorously $S_N2$ type mechanism. The reaction occurred by nucleophilic attack of the chloride ion which is formed by the reaction between DMAP and phosphorus atom of $POCl_3$ or $PCl_3$, leading to a complex, which was observed by NMR.[16]

On behalf of our interest in halohydrins, this work is still in progress in our laboratory.

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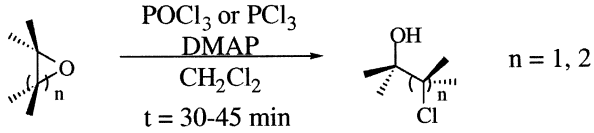
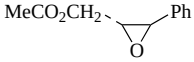
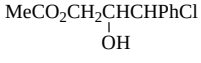
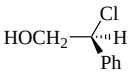
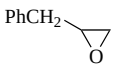
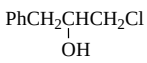
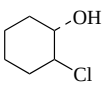
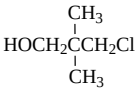
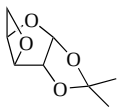
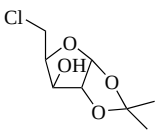
**Table 1.** Ring-opening reaction with different reagents and conditions




| Entry | | Substrate | Major regioisomer | Reagents and conditions[a] | Regioselectivity (%)[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **1** |  |  | $POCl_3$ (3:3)/rt | 100 | 73 |
| 2 | **1** | | | $POCl_3$ (1:1)/rt | 87 | 79 |
| 3 | **1** | | | $PCl_3$ (3:3)/rt | 86 | 75 |
| 4 | **1** | | | $PCl_3$ (1:1)/rt | 66 | 73 |
| 5 | **2**[d] |  (*R*)-(+) |  (*S*)-(+) | $POCl_3$ (3:3)/rt | 100 | 80 |
| 6 | **2**[d] | | | $POCl_3$ (1:1)/rt | 100 | 85 |
| 7 | **3** |  |  | $POCl_3$ (3:3)/rt | 84 | 80 |
| 8 | **3** | | | $POCl_3$ (1:1)/rt | 84 | 70 |
| 9 | **3** | | | $PCl_3$ (1:1)/rt | 83 | 80 |
| 10 | **4** |  |  | $POCl_3$ (3:3)/rt | – | [e] |
| 11 | **4** | | | $POCl_3$ (3:3)/−40°C | – | [e] |
| 12 | **4** | | | $PCl_3$ (1:1)/−78°C | – | 85 |
| 13 | **5** |  |  | $POCl_3$ (3:3)/rt | – | 80 |
| 14 | **6**[12] |  |  | $POCl_3$ (3:3)/rt | 100 | 77 |

[a] The epoxide or oxetane (1 equiv.) reacts with DMAP (1–3 equiv.) and $PCl_3$ or $POCl_3$ (1–3 equiv.) at the indicated temperature in each entry.
[b] Regioselectivity was measured by GC and NMR.
[c] Isolated yield after column chromatography on silica gel.
[d] The stereochemical outcome was determined by optical rotation and HPLC (Chiralcel OD).
[e] 1,2-Dichlorocyclohexane was the main product (80% yield).

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12. 3,5-Anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose, **6**, was synthesized from diacetone-α-D-glucose, $[\alpha]_D = +11.24$ ($c = 1$, $CHCl_3$), and compare with literature ($[\alpha]_D = +12.0$ ($c = 0.80$, $CHCl_3$)). Cooke, N. G.; Jones, D. A.; Whiting, A. *Tetrahedron* **1992**, *48*, 9553–9560.
13. *General procedure*: In a two-necked flask provided with a thermometer and a magnetic stirrer, under argon, the epoxide or the oxetane (**1**–**6**, 1 mmol) and DMAP (1–3 mmol) were dissolved in dry $CH_2Cl_2$ (30 mL). To the mixture was added dropwise $POCl_3$ or $PCl_3$ (1–3 mmol) in dry $CH_2Cl_2$ (5 mL). The reaction mixture was stirred until no more epoxide or oxetane (**1**–**6**) was detected by TLC (ca. 30–45 min). Finally, the reaction mixture was neutralized and extracted with $CH_2Cl_2$ (3×25 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude products were purified by flash chromatography.
14. The regiochemistry on the opening of *trans*-cinnamyl-acetate, **1** (entries 1–4) has been unequivocally established by the exclusive formation of both regioisomers.
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16. $^1H$ NMR spectra of the complex show signals at 8.21 and 8.70, compared to 6.47 and 7.79 for free DMAP, and $^{31}P$ NMR spectra shows a signal at 10.01 ppm, compared to 5.00 for free $POCl_3$.