Nucleophilic Fluorination by Selective Ring Opening of α-Halooxiranes†

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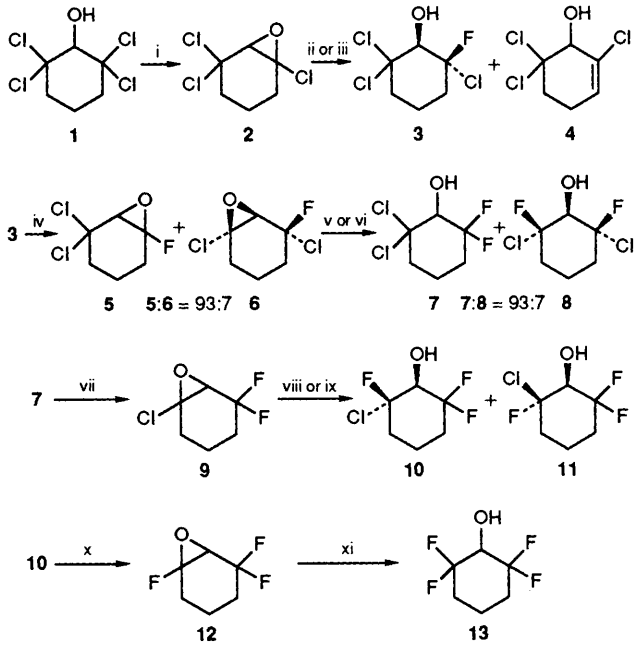
Reaction of 1,3,3-trihalo-7-oxabicyclo[4.1.0]heptanes with boron trifluoride–ether or HF·pyridine resulted in the regio- and stereo-selective formation in high yield of the corresponding *cis*-fluorohydrins; using a succession of cyclisations followed by ring-opening reactions by fluoride afforded an iterative preparation of unknown 2,2,6,6-tetrafluorocyclohexanol **13** starting from the chlorinated analogue **1**.

Owing to the interesting biological, chemical and physical properties of organofluorine compounds, considerable effort has been made to discover methodologies for selective fluorination.[1] The preparation of fluorohydrins by ring opening of oxiranes is one of the most common and most selective reactions for introducing a fluorine atom into molecules such as steroids, amino acids, carbohydrates and prostaglandins.[2] The use of anhydrous hydrogen fluoride is dangerous and highly toxic. In addition, because of its high reactivity it often affords polymers[3] or rearrangement products. Thus, various reagents[4] such as KF, KHF_2, CsF, KHF_2–AlF_3, Bu^n_4NF, $Bu^n_4N^+\cdot H_2F_3^-$, $Bu^n_4PF\cdot HF$ or SiF_4, various amine·HF adducts[5] such as pyridine poly-hydrofluoride (HF·pyridine), $Et_3N\cdot 3HF$ and $Pr^i_2NH\cdot 3HF$ have been used successfully as alternatives and these reagents can have different selectivities with the same oxirane.

In the present paper we describe an easy regio- and stereo-selective method for fluorination of α-chloro- and α-fluoro-epoxycyclohexanes using as the reagent an unexpected fluorinating agent, boron trifluoride–ether ($BF_3\cdot Et_2O$) and we compare it with the classic Olah's reagent (HF·pyridine). A few cases of nucleophilic fluorination with $BF_3\cdot Et_2O$ are mentioned with oxiranes, and most of fluorohydrins are obtained in the field of steroidic oxiranes.[6]

By a simple cyclisation of the available 2,2,6,6-tetrachlorocyclohexanol **1** with aqueous NaOH,[7] the 1,3,3-trichloro-7-oxabicyclo[4.1.0]heptane **2** was obtained in 96% yield.‡ When treated with HF·pyridine at −35 °C, the chlorooxirane **2** reacted quantitatively to yield a mixture of products, the *cis*-fluorohydrin **3** and the allylic alcohol **4** in ratio **3**:**4** = 85:15 (determination by ^{1}H NMR spectroscopy). The *cis*- fluorohydrin **3** can be isolated by chemical purification.§ When the same reaction is carried out at 0 °C, the ratio between the alcohols **3** and **4** is 76:24, the increase in temperature leads to an increased formation of the elimination product (Scheme 1).

Action of boron trifluoride–ether on α-chlorooxiranes is reported to afford rearrangement products but not to yield to *gem*-fluorochloroalcohols.[8] When the α-chlorooxirane **2** (5 mmol) was treated with 0.53 equiv. of $BF_3\cdot Et_2O$ in 7 ml of



Scheme 1 *Reagents and conditions*: i, 3 mol dm^{-3} NaOH, 75 min, room temp., 96.5%; ii, HF·pyridine, −35 °C then room temp., 210 min, ratio **3**:**4** = 85:15 (^{1}H NMR), 99%; iii, 0.53 equiv. $BF_3\cdot Et_2O$, 3 h, 1,2-dichloroethane at reflux, then H_2O at 80 °C, **3**, 92%; iv, 3 mol dm^{-3} NaOH, 75 min, room temp., 96%, **5**:**6** = 93:7 (^{1}H NMR, GC); v, HF·pyridine, 80 min, 0 °C then room temp., **7**:**8** = 93:7 (GC), total yield 86%; vi, 0.53 equiv. $BF_3\cdot Et_2O$, 1,2-dichloroethane at reflux, 105 min then H_2O, **7**:**8** = 93:7 (GC), total yield 82%; vii, 3 mol dm^{-3} NaOH, 75 min, room temp., 87%, viii, HF·pyridine, 80 min, 0 °C then room temp., **10**:**11** = 83:17 (isolated products), total yield 83.5%; ix, 0.55 equiv. $BF_3\cdot Et_2O$, 1,2-dichloroethane at reflux, 90 min then H_2O, **10**, 82.5%; x, 3 mol dm^{-3} NaOH, 75 min, room temp., 62%; xi, HF·pyridine, THF, 70 min, 0 °C then room temp., 49%

† Taken in part from the PhD Thesis, B. Leblond, Rouen, April 1991. All new compounds gave satisfactory analytical and spectroscopic data consistent with the assigned structures.

‡ Unlike most α-chlorooxiranes, the oxirane **2** was particularly stable and can be distilled under reduced pressure without thermal rearrangement.

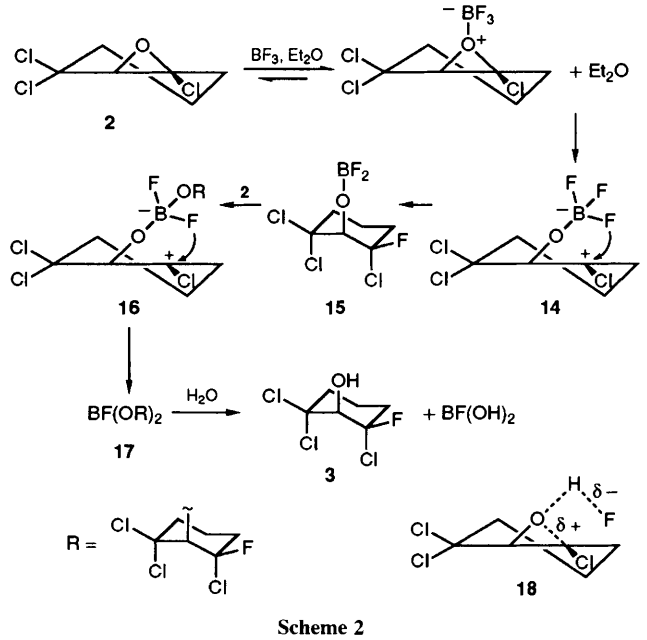
§ Action at room temp. in diethyl ether of 1.2 equiv. of morpholine on the crude fluorohydrin **3** yields a morpholinium salt. Recrystallisation followed by hydrolysis (HCl 10%) of the morpholinium salt gave pure fluorohydrin **3**.

1,2-dichloroethane at reflux (210 min) followed by hydrolysis at 80 °C in H_2O and extraction with dichloromethane, the same *cis*-fluorohydrin **3** as previously was obtained in 92% yield without elimination product **4**. The *cis* configuration of **3** was proved by ^1H and ^{19}F NMR spectroscopy and finally confirmed by synthesis of the *trans* isomer by an alternative route.

During the reaction using $BF_3{\cdot}Et_2O$, the regio- and stereo-selectivities observed can be explained by an intramolecular transfer of fluoride (S_Ni attack) from a zwitterionic trifluoroborate **14**, which led to the difluoroborate **15**. The intermediate difluoroborate **15** has sufficient Lewis acid character to react with another molecule of α-chlorooxirane **2** and yield, *via* a similar second intramolecular transfer of fluoride from a zwitterionic difluorodiborate **16**, the monofluoroborate **17**. With HF·pyridine, a similar intramolecular transfer of fluoride may be envisaged from the intermediate **18** in which a monomer of HF is bound by a hydrogen bond to the epoxidic oxygen forming a fluorinating arm (Scheme 2).

At this point we decided to try successive sequences of cyclisation–fluorination that could lead finally to the unknown fluorinated analogue **13** from starting material **1** *via* interesting and useful intermediates.[9]

The *cis*-fluorohydrin **3** led essentially to the α-fluorooxirane **5** accompanied by a little of its regioisomer **6** in the ratio **5** : **6** = 93 : 7 (^1H NMR determination) by cyclisation with NaOH in the same conditions as specified previously.¶ Only loss of the chlorine atom was observed and mainly from the chlorofluorocarbon group first, owing to the necessity of the anticoplanarity of the hydroxy group and secondly to the leaving substituent and the mesomeric assistance given by the fluorine atom. However, it was not possible to separate the two regioisomers **5** and **6** by classical techniques, so the fluorination was carried out directly on this mixture. The same result was obtained by the two processes ($BF_3{\cdot}Et_2O$ or HF·pyridine) a mixture of the 2,2-difluoroalcohol **7** and its regioisomer **8** in the same ratio as the starting material **7** : **8** = 93 : 7, so the fluorination proceeded totally regio- and stereoselectively. Fortunately, the 2,2-difluoroalcohol **7** can be separated from its isomer **8** by flash chromatography. The fluorohydrin **7** was then regioselectively cyclised to give α-chlorooxirane **9** in 87% yield (Scheme 1).



Scheme 2

¶ Use of KOH in ethanol or aqueous LiOH at room temp. produced a similar ratio of the two regioisomers **5** and **6**.

The third fluorine atom introduction was totally diastereoselective using $BF_3{\cdot}Et_2O$ yielding the *trans*-chlorohydrin **10** in 82.5% yield from the oxirane **9**; with HF·pyridine a mixture of the same *trans*-chlorohydrin **10** and its diastereoisomer, the *cis*-chlorohydrin **11** in ratio **10** : **11** = 83 : 17 were obtained and separated by flash chromatography.

Finally, from the alcohol **10**, the 1,3,3-trifluoroepoxycyclohexane **12** was easily prepared by cyclisation with aqueous NaOH in 62% yield, a last fluorination using HF·pyridine gave the expected 2,2,6,6-tetrafluorocyclohexanol **13** in 49% non-optimised yield (Scheme 1).

In conclusion, we have shown that α-halogenoepoxycyclohexanes are easily transformed into fluorohydrins by using HF·pyridine at −35 °C and $BF_3{\cdot}Et_2O$ in 1,2-dichloroethane at reflux. The superiority of the second reagent is to be noted: the yield and selectivity are higher. Moreover, the fact that just 0.53 equiv. of this reagent and normal glass vessels are required are also advantageous factors for the utilisation of this process with such substrates.

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