A New, Selective Method for Conversion of Alcohols to *Vicinal* Fluorohydrins

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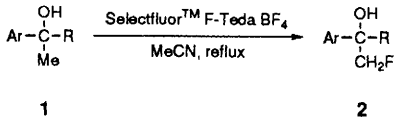
Aryl–alkyl substituted tertiary alcohols are efficiently converted directly to *vicinal* fluorohydrins in high yield by reaction with 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-Teda BF_4) in acetonitrile solution.

Selective fluorination of organic compounds has been a shared and important interest of organic chemists for the last three decades, mainly owing to the fact the fluorine-containing organic molecules possess enhanced biological activity.[1] Much effort has been made to finding generally acceptable, easy handling, non-toxic and inexpensive reagents and in developing new methods for selective introduction of a fluorine atom into organic molecules under mild reaction conditions, but the problem is still only partly solved.[2] Recently, a variety of *N*-fluoro compounds have been introduced as electrophilic fluorinating reagents,[3] among them 'Banks reagents', based on *N*-fluoroquinuclidinium salts,[4] which seem to be very close to resolving this complicated task, particularly when very recently this family of reagents has been enriched with 1-alkyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane salts[5] which are already commercially available as Selectfluor™ reagents.[6]

Almost without exception, all the electrophilic fluorinating agents are also strong oxidants. This fact can cause significant competition between fluorofunctionalisation and oxidation of the organic molecule substrate, especially when oxidisable functional groups or heteroatoms are involved in the reaction.[7] The hydroxy functional group, and particularly the hydroxyalkyl functional block, often present in bioactive molecules, could be undesirable side reactions centres, but in some cases also excellent precursors for the selective introduction of a fluorine atom in organic molecules, as we have shown recently.[8] We now report the reactions of aryl–alkyl substituted alcohols with 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-Teda BF_4).

In a typical experiment 390 mg (1.1 mmol) of F-Teda BF_4 was added to 10 ml of a 0.1 molar solution of a tertiary aryl-alkyl substituted alcohol **1** in acetonitrile and the reaction solution kept under reflux for half an hour, then cooled to room temp., diluted with 50 ml of CH_2Cl_2, washed with saturated $NaHCO_3$ (25 ml) and water (2 × 25 ml), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The isolated crude reaction mixture was analysed by ^1H and ^{19}F NMR spectroscopy, and the products isolated by column or TL chromatography and identified on the basis of their spectroscopic data [^1H and ^{19}F NMR, IR, MS and high resolution mass spectrometry (HRMS)]. Under these reaction conditions 2-phenylpropan-2-ol **1a** was unexpectedly converted to *vicinal* fluorohydrin *i.e.* 1-fluoro-2-phenyl-propan-2-ol **2a** in excellent yield (90%). In order to evaluate this reaction more fully, which could open an elegant way for the direct introduction of a fluorine atom *vicinal* to a hydroxy group and so to constructing a functional block often present in bioactive molecules, we first examined, the effect of structure variations of the aryl part of molecule **1**, following our recent experience that the structure of this part of the molecule has a crucial role on the course of the reaction of aryl–alkyl substituted alcohols with various fluorinating agents.[8] We found that introduction of an additional phenyl group *geminal* to the OH group even improved the yield of *vicinal* fluorohydrin formation, which in the case of 1,1-diphenylethanol **1b** was 95%, while the activation of the phenyl group with a *para*-methoxy substituent had no substantial effect on the course of the reaction. 1-(4-Methoxyphenyl)-1-phenylethanol **1c** was readily converted to the corresponding vicinal fluorohydrin **2c** in 83% yield and less than 5% of benzene ring fluorination was observed. On the other hand, by deactivation of the benzene ring with a *meta*-trifluoromethyl group the conversion of 1-(3-trifluoromethylphenyl)-1-phenylethanol **1d** to 1-(3-trifluoromethyl phenyl)-1-phenyl-2-fluoroethanol **2d** was almost quantitative. Finally, we found that by the exchange of the benzene ring in the aryl–alkyl substituted alcohol molecule by some of its polynuclear analogues, a good yield of *vicinal* fluorohydrins also could be obtained after treatment with F-Teda BF_4. 2-(2-Fluorenyl)propan-2-ol **1e** and 2-(2-phenanthryl)propan-2-ol **1f** were converted to 1-fluoro-2-(2-fluorenyl)propan-2-ol **2e** and 1-fluoro-2(2-phenanthryl)propan-2-ol **2f** in 78 and 66% yield, respectively, and 9-methyl-9-hydroxyfluorene **3** to 9-fluoromethyl-9-hydroxyfluorene **4** in 85% yield (Table 1, Scheme 1).

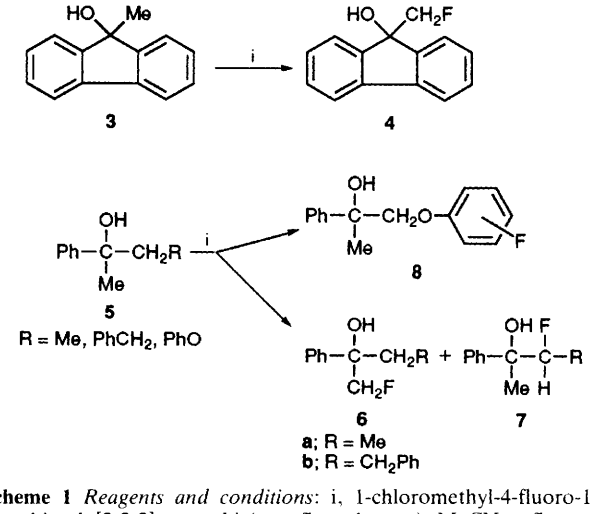
We studied further the regioselectivity of the reaction and found that in the case of 2-phenylbutan-2-ol (**5**, R = Me) a pair of regioisomers was formed with a considerable excess of 2-phenyl-3-fluorobutan-2-ol (**7a**, *erythro* : *threo* 1 : 6) over



1 **2**

Table 1

	Ar	R	Yields† (%) of **2**
1a	Ph	Me	**2a** 90 (85)
1b	Ph	Ph	**2b** 95 (89)
1c	Ph	4-OMe-C_6H_4	**2c** 83 (77)
1d	Ph	3-CF_3-C_6H_4	**2d** 95 (90)
1e	2-Fluorenyl	Me	**2e** 78 (68)
1f	2-Phenanthryl	Me	**2f** 66 (55)



Scheme 1 *Reagents and conditions*: i, 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate), MeCN, reflux

1-fluoro-2-phenylbutan-2-ol (**6a**, **7a** : **6a** = 1.8 : 1, overall yield 87%), while in the case of 2,4-diphenylbutan-2-ol (**5**, R = $PhCH_2$) the formation of equimolar amounts of both isomers was observed with an overall yield of 85% with 1 : 6 ratio of *erythro–threo* isomers in **7b**. On the other hand, the introduction of a phenoxy group *vicinal* to the OH group after the treatment of 1-phenoxy-2-phenylpropan-2-ol (**5**, R = PhO) with F-Teda BF_4 resulted only in phenoxy benzene ring fluorofunctionalisation **8**, with the *ortho* derivative predominant over the *para* isomer (*o* : *p* 1.8 : 1). Finally, we also found that in the case of secondary and primary alcohols the oxidation of the molecule is the predominant process in the reaction. Under mentioned reaction conditions 1-phenyl ethanol or benzyl alcohols were readily oxidized to acetophenone or benzaldehyde with F-Teda BF_4. These facts should be considered as the limitations of the method.

The present report opens new possibilities for the formation of *vicinal* fluorohydrins with some advantages in comparison to some other routes (epoxide opening by HF[9] or KHF_2–AlF_3,[10] fluorination of a double bond in the presence of water[3b] or with HOF[11]) for the construction of this functional block carrying potential bioactivity.‡ In order to expand the scope of the method, the mechanistic elucidation and the examination of the reaction with some other hydroxyalkyl molecules is in progress.

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Footnotes

† The yields were determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene as additional standard and calculated on starting material. The yields in parentheses are referred to isolated pure compounds.

‡ In all cited reports, except in 3(*b*), the opposite regioselectivity of *vicinal* fluorohydrins formation as reported in this present paper was observed.

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