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Preparation of chiral sugar-derived fluorides using new nucleophilic fluorinating reagents

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In dedication to Professor Antonio Togni, the winner of the ACS Award for Creative Work in Fluorine Chemistry.

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ABSTRACT

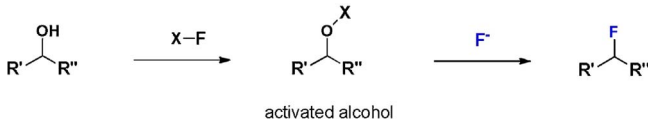
New fluorinating reagents, composed of (*S*)-2-(diphenylmethyl)pyrrolidine and 1,1,3,3,3-pentafluoropropene/hexafluoropropene, have been found to be an effective system for nucleophilic deoxyfluorination. Regio- and stereoselectivity of deoxyfluorination of sugar-derived allylic, benzylic and propargylic alcohols with new reagents have been studied.

1. Introduction

The replacement of a hydroxyl group by fluorine atom causes a minor change in the steric arrangement of the molecule but such modification has profound impact on the stereoelectronic properties and hence on the chemical properties [1]. As a result, fluorinated compounds have attracted much interest in the areas of pharmaceutical, medicinal and materials sciences due to their unique changes in properties (including biological activity) exerted by small atom of fluorine [2]. Fluorine containing compounds have been also considered as one of the most valuable building blocks in the organic synthesis. This is because their incorporation/attachment into larger species give access to a new classes of organic molecules [3].

Fluorination of carbohydrates is a quite common method to gain an information regarding catalytic mechanism of various enzymatic transformations [4]. Fluorinated carbohydrate analogues are often better enzyme inhibitors compared to the un-fluorinated analogues [5]. Among others, polyfluorinated sugars have become an interesting issue of studies related to hydrophobicity effect, in which the hydrophobic domains are created by replacement of CHOH groups on carbohydrate ring with CF_2 groups [6] and/or by introduction of CF_3 group into carbohydrate molecules [7].

A well-known procedure for preparation of alkyl fluorides, including fluorinated carbohydrates, is the nucleophilic substitution (S_N). The important strategy in this context is deoxyfluorination reaction (Scheme 1). There are several examples of nucleophilic reagents employed to construct the C-F bond, including bis(2-methoxyethyl) aminosulfur trifluoride (Deoxo-Fluor™) [8], aminodifluorosulfinium salts (XtalFluor-E, XtalFluor-M) [9], diethylaminosulfur trifluoride (DAST) and fluoroamino-reagents such as: 1,1,2,3,3,3-hexafluoropropyl-*N,N*-diethylamine [10] (Ishikawa reagent), (2-chloro-1,1,2-trifluoroethyl)-*N,N*-diethylamine (Yarovenko's reagent) [11] and 1,1,2,2-tetrafluoroethyl-*N,N*-dimethylamine (Petrov reagent) [12].



Scheme 1. Deoxyfluorination reaction.

In this paper we would like to focus our attention on the synthesis of new fluorinating reagents obtained from cyclic pyrrolidine derivative and two fluorinated olefins: hexafluoropropene and 1,1,3,3,3-pentafluoropropene. We report here the results of the regio- and diastereoselectivity of fluorination reaction of several secondary alcohols obtained from 2,3-*O*-isopropylideneglyceraldehyde. These alcohols are widely used in the organic synthesis, including synthesis of unusual amino acids [13a] or biologically active alkaloids [13d]. Also, propargylic and allylic fluorides in racemic or enantioenriched form are used for diverse academic and industrial applications [3].

In general, the obtained fluorinated analogues prepared in the course of these studies are new, not known in literature, and can be employed as valuable building blocks in the synthesis of a larger systems.

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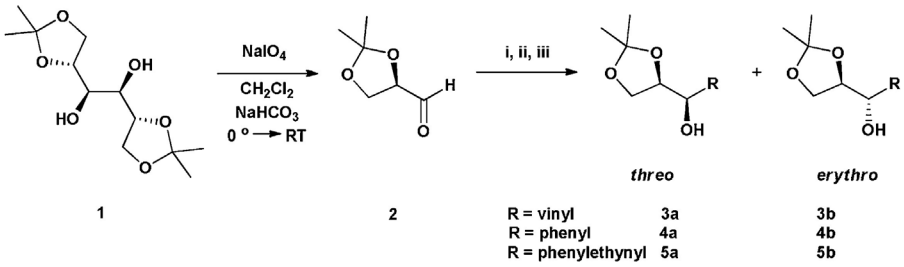


Scheme 2. Reagents and conditions (i) $CH_2CHMgBr$, THF, RT; (ii) PhMgBr, THF, RT; (iii) PhCCH, *n*-BuLi, THF, −78 °C.

Table 1
Preparation of alcohols *via* Grignard reactions.

Alcohols	Ratio[a]	Yield[b] [%]
3a/3b	47:53	53
4a/4b	44:56	50
5a/5b	40:60	54
6a/6b	44:56	82

[a] Determined by ^{1}H NMR spectroscopy for isolated mixtures of alcohols.
[b] Determined after product isolation.

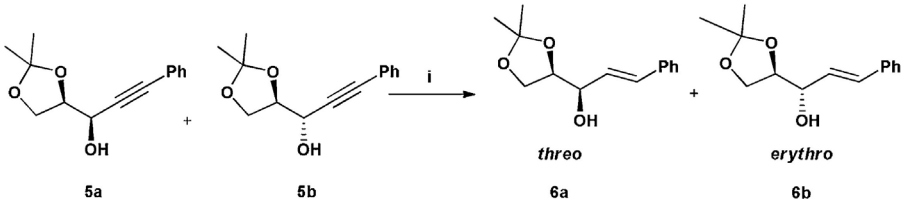
2. Results and discussion

Our synthesis have started from easy to be handled 1,2:5,6-di-*O*-isopropylidene-D-mannitol **1** and, as a result of an oxidative cleavage of diol, (*R*)-2,3-*O*-isopropylideneglyceraldehyde **2** has been obtained. This molecule is synthetically useful chiral starting material for the construction of optically active organic compounds. As shown in Scheme 2, the chiral alcohols have been simply prepared, by treatment of **2** with corresponding Grignard reagents (**3a–4a**, **3b–4b**) or lithium phenylacetylene (**5a**, **5b**), with good yields (Table 1).

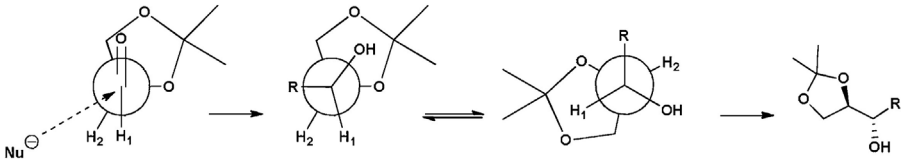
The mixture of two propargylic derivatives (**5a**/**5b**) has been subsequently transformed by reduction using $LiAlH_4$ to the corresponding allylic alcohols **6a**/**6b** (Scheme 3) with 44/56 (*threo*/*erythro*) ratio (82% yield).

Diastereoselectivity (Table 1) of Grignard reaction has been determined by analysis of the ^{1}H NMR spectra and can be understood by the concept of Felkin–Ahn model (Scheme 4). The absolute configuration of the newly created stereogenic centers of compounds **3a**/**3b**–**6a**/**6b** has been established on the basis of appropriate values of coupling constant (J_{H1-H2}) and compared with literature data [13]. In each of these reactions, the *erythro*-stereoisomers has been formed predominantly.

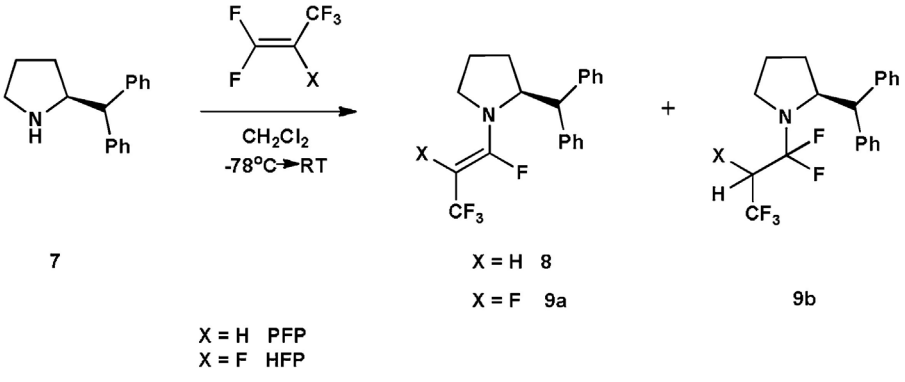
Next step, the synthesis of fluorinating reagents has employed the reactions of chiral secondary amine, cyclic pyrrolidine derivative **7**, with commercially available fluorinated olefins 1,1,3,3,3-pentafluoropropene (PFP) or hexafluoropropene (HFP). (*S*)-2-(Diphenylmethyl)-pyrrolidine **7** has been obtained from l-proline, according to the described procedure [14]. The reaction, in the case of PFP, has given the tetrafluorinated enamine **8** (Scheme 5) with a 73% yield (determined by ^{19}F NMR spectrum) [15]. Analogous reaction of chiral amine **7** with HFP has given a mixture of enamine and fluorinated tertiary amine **9a**/**9b** with a 65% total yield (the ratio of enamine/amine **9a**/**9b** was 1:32) (Scheme 5) [15]. The crude reaction enamine–amine mixtures **9a**/**9b**, after the previous ^{19}F NMR analysis, were directly used to fluorination without further purification and separation.



Scheme 3. Reagents and conditions (i) $LiAlH_4$, Et_2O, 0 °C, 3.5 h.



Scheme 4. Diastereoselectivity of Grignard reaction.



Scheme 5. Formation of fluorinating reagents.