Selective monofluorination of diols using DFMBA†

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Selective monofluorination of 1,2- and 1,3-diols was achieved by reaction with DFMBA. The method is applicable for the synthesis of optically-active fluorohydrin derivatives.

Selective monofluorination of 1,2- or 1,3-diols is a useful methodology for the synthesis of fluorinated sugars,[1] nucleosides,[2] and optically-active fluorohydrins.[3] However, it is hard to selectively convert only one hydroxy group of diols to fluoride, leaving the other unchanged, because preventing the second deoxyfluorination reaction is usually difficult. Moreover, when 1,2- or 1,3-diols are treated with diethylaminosulfur trifluoride (DAST), the most typical deoxyfluorination reagent, or its analog deoxyfluor™, side reactions such as rearrangement[4] or cyclic sulfonate formation[5] competitively take place, and the expected fluorination products cannot usually be obtained in good yield. Recently, we reported that primary and anomeric hydroxy groups in sugars can be selectively converted to fluoride using *N,N*-diethyl-α,α-difluoro(*meta*-methylbenzyl)amine (DFMBA).[6] We wish to report here the selective monofluorination of diols using

† Electronic Supplementary Information (ESI) available: Experimental details and characterisation data for the compounds prepared. See http://www.rsc.org/suppdata/cc/b5/b502471d/

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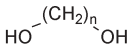
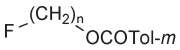
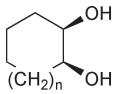
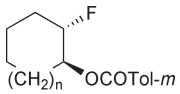
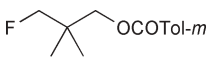
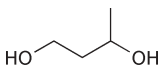
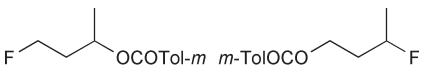
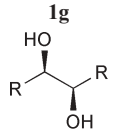
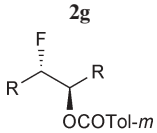
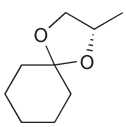
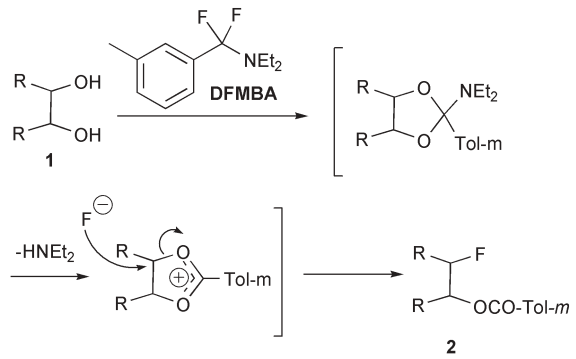
Table 1 The reactions of diols with DFMBA

Diol	Solvent	Conditions	Product	Yield (%)[a]
 **1a:** n = 2 **1b:** n = 3	Heptane	98 °C, 1 h	 **2a:** n = 2 **2b:** n = 3	79
 **1c** n = 1 **1d** n = 7	Diglyme Heptane	100 °C, 1 h MW, 10 min	 **2c** n = 1 **2d** n = 7	75 82
 **1e**	Heptane Heptane	MW, 10 min MW, 2 min	 **2e**	75 88
 **1f**	Diglyme	100 °C, 1 h	 **2f-1** 38 : 62[b] **2f-2**	78
HO–$(CH_2)_{12}$–OH **1g**	Heptane	MW, 10 min	F–$(CH_2)_{12}$–F **2g**	91
 **1i**: R = CH_3 **1j**: R = Ph	Diglyme —	140 °C, 1.5 h 140 °C, 1 h	 **2i** **2j**	74 (≥95) 83 (≥95)
1k R = 	Nonane	MW, 10 min	**2k**	55 (≥95)

[a] Isolated yields are based on the diols used. Diastereoselectivities are given in parentheses. [b] Determined by ^{19}F NMR spectroscopy.



Scheme 1

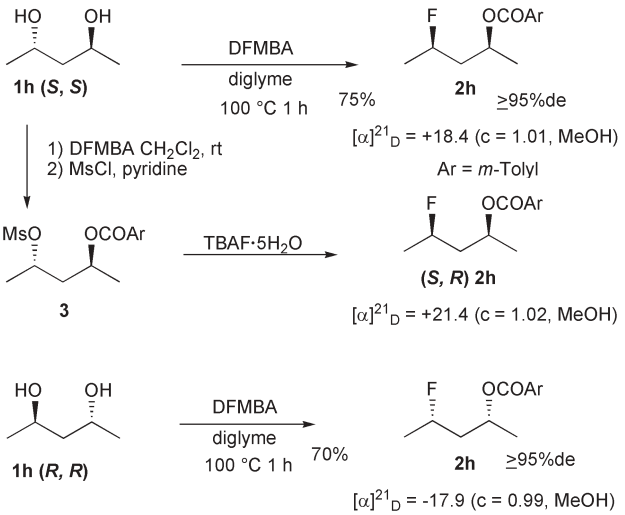
DFMBA and its application to the synthesis of optically-active fluorohydrin derivatives.

When ethylene glycol (**1a**) was subjected to a reaction with 2.4 equiv. of DFMBA in heptane at 98 °C for 1 h, the *meta*-methylbenzoyl ester of 2-fluoroethanol (**2a**) was obtained in 79% yield. Only one hydroxy group of **1a** was fluorinated, the other being esterified by DFMBA. When the reaction was carried out under microwave irradiation (MW), the reaction was complete in 10 min and **2a** was obtained in 73% yield.

Under similar conditions, various 1,2-diols (**1a,c,d**) and 1,3-diols (**1b,e,f**) could be converted to their corresponding fluorohydrin derivatives in good yields, as shown in Table 1. When an unsymmetrical diol (**1f**) was used, a mixture of two regioisomers were obtained non-selectively. On the other hand, the reaction of 1,12-dodecanediol (**1g**), in which the hydroxy groups are well separated from each other by methylene groups, gave a difluorinated product in good yield.

As special care is not required to terminate the reaction at the monofluorination stage, the reaction seems to proceed through a cyclic intermediate, after which the remaining hydroxy group is converted to an ester group, inert to DFMBA (Scheme 1).

When an optically-active (2*S*,4*S*)-2,4-pentandiol (**1h**) was subjected to DFMBA, a monofluorinated product, **2h**, was obtained in 75% yield with high diastereoselectivity. In order to examine the stereochemistry of the reaction, **1h** was converted to the monomesylate **3**. Monofluorination of **3** was carried out with inversion of stereochemistry by using tetrabutylammonium fluoride (TBAF·5H_2O)[7] to give (2*S*,4*R*)-4-fluoro-2-pentanol *meta*-methylbenzoyl ester. As this compound's ^{1}H and ^{19}F NMR spectra, and optical rotation[8] coincided with those of **2h**, fluorination of alcohols by DFMBA was found to also proceed with inversion of stereochemistry. Starting from (2*R*,4*R*)-**1h**, (2*R*,4*S*)-**2h** was obtained selectively (Scheme 2).



Scheme 2

In a similar manner, optically-active fluorohydrin derivatives could be obtained from commercially available, optically-active 2,3-butanediol (**1i**) and 1,2-diphenylethanediol (**1j**) with high diastereoselectivities. In nature, many compounds, such as sugars, have optically-active diol functions. When a manitol derivative, **1k**, was subjected to reaction with DFMBA, a monofluorinated product, **2k**, was obtained with high diastereoselectivity.‡

Notes and references

‡ General procedure for the monofluorination of diols using DFMBA: A mixture of diol (1 mmol), DFMBA (2.2 mmol) and solvent (1 ml) in a Teflon™ PFA vessel was heated using microwaves[6] or an oil bath, at the temperature and time shown in Table 1. After completion of the reaction, the mixture was poured into aqueous $NaHCO_3$ and extracted with ether 3 times. The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica gel, hexane–ether) to give the monofluoride product **2**.

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7 D. Albanese, D. Landini and M. Penso, *J. Org. Chem.*, 1998, **63**, 9587.
8 (2*R*, 4*S*)-**2h**, prepared by reaction with TBAF·5H_2O, was contaminated with about 10% of olefinic by-products, which were difficult to separate. We believe this must be the reason why it had a larger optical rotation value than **2h** itself, prepared from **1h** and DFMBA.

