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Short communication

Stereocontrolled halofluorination of glycals with silicon tetrafluoride, leading to a facile synthesis of glycosyl fluorides

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Dedicated to Prof. Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

Bromofluorination of glycals was carried out with SiF_4, 1,3-dibromo-5,5-dimethylhydantoin (DBH), and H_2O in 1,4-dioxane in the presence of HMPA to give bromofluoro sugars in good yields with good selectivities. Subsequent debromination with *n*-Bu_3SnH gave 2-deoxy sugars in good yields. Furthermore, hydroxyfluorination of glycal was also successfully conducted using SiF_4-$PhI(OAc)_2$-H_2O to give fluoroglucose in 73% yield.

Keywords: Bromofluorination; Fluorosugar; Glycal; Silicon tetrafluoride

1. Introduction

For the formation of glycoside bonds, glycosyl halides play an important role as a glycosyl donor in terms of stereoselectivity [1,2]. Among the glycosyl halides, the fluoride analogues have recently received considerable attention due to their enhanced stability and the stereoselectivity on the glycoside synthesis [3,4]. There have been several approaches to glycosyl fluorides, involving transformations of glycals [5–7], lactols [3], glycosyl halides [8], glycosyl acetate [9], and phenylthioglycosides [10]. However, there appears to be an important problem on their preparations especially on the stereoselectivity. We have already introduced a convenient method for the preparation of bromofluorides from olefins using SiF_4 and DBH [11–15]. The same reagent system was successfully used for the preparation of glycosyl fluorides from glycals. This paper describes a facile approach to 2-bromo- and 2-deoxyglycosyl fluorides.

2. Experimental

Bromofluorination of glycals was carried out as follows: Under an argon atmosphere, to DBH (1.1 mmol) placed in a flask was added 1,4-dioxane (4 ml), H_2O (1.0 mmol), and HMPA (0–5.0 mmol) successively, and the mixture was stirred at room temperature (for acetate) or at 50°C (for benzoate). A balloon filled with SiF_4 gas was fitted to the flask, and a solution of glycal (1.0 mmol) in 1,4-dioxane (1 ml) was added. After being stirred at room temperature for 1 h, the reaction mixture was quenched by adding an aq. solution of KF. The whole mixture was extracted with AcOEt, and the organic layer was washed successively with 20% aq. $Na_2S_2O_3$ and saturated aq. NaCl. After usual work-up the crude oil was purified by silica gel column chromatography to give the 2-bromoglycosyl fluoride as a mixture of isomers.

Debromination of the bromofluoride: A mixture of the bromofluoride (1 mmol) and *n*-Bu_3SnH (1.5 mmol) in toluene (10 ml) was heated at 50–55°C for 2 h. Usual work-up followed by purification on preparative TLC gave the 2-deoxyglycosyl fluoride.

Hydroxyfluorination of glycal: Under an argon atmosphere, to $PhI(OAc)_2$ (156 mg, 0.3 mmol) placed in a flask was added dichloromethane (8 ml), H_2O (4.5 μl) and HMPA (130 μl, 0.75 mmol), and the mixture was stirred

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Table 1
Bromofluorination of glycal **1**[a]

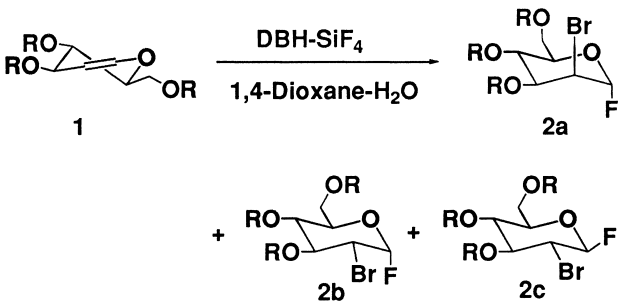
Entry	R	HMPA (eq)	Yield of **2**[b] (%)	2a(α): 2b(α); 2c(β)[c]
1	Bz	None	70	47:27:26
2	Bz	1.0	79	66:14:20
3	Bz	2.0	80	71:10:19
4	Bz	3.0	84	70:22:8
5	Bz	5.0	78	73:19:8
6	Ac	None	82	36:28:36
7	Ac	3.0	85	59:17:24

[a] The reaction was carried out according to the typical experimental procedure.
[b] Isolated yield.
[c] Ratio determined by HPLC and/or ^{19}F NMR.

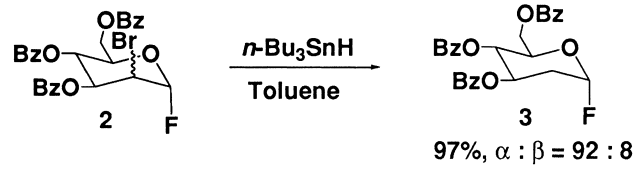
at 0°C. A balloon filled with SiF_4 gas was fitted to the flask, and a solution of glycal-tribenzoate **1** (R=Bz) (111 mg, 0.25 mmol) in dichloromethane (2 ml) was added. After being stirred at room temperature for 2 h, the reaction mixture was quenched by adding an aq. solution of KF. The whole mixture was extracted with AcOEt, and the organic layer was washed with saturated aq. NaCl. After usual work-up the crude oil was purified on silica gel TLC to give the fluoroglucose **11** (88 mg, 73%).

3. Results and discussion

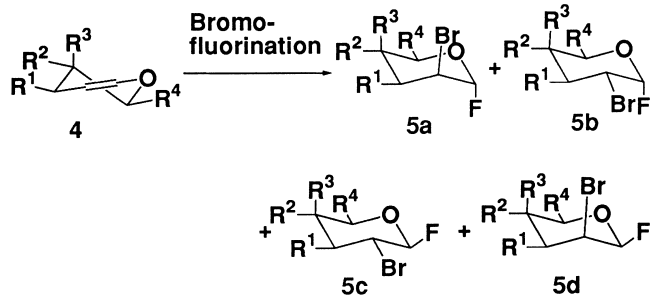
Bromofluorination of the glycals derived from glucose was carried out according to the typical experimental procedure, and the results are shown in Table 1.



Stereoselectivity of the present bromofluorination was highly influenced by the solvent polarity. In the absence of HMPA, formation of the α-fluorides predominated with the ratio of 74:26, and the addition of HMPA improved the selectivity in favour of the α-isomers. The best selectivity was obtained when the bromofluorination was carried out in the presence of 3.0 eq. of HMPA, in which the α- vs. β-isomer ratio was 92:8. The chemoselective reduction of the bromine atom of the bromofluoride **2** derived from the entry 4 in Table 1 was readily carried out with *n*-Bu_3SnH in toluene at 55°C in good yield without affecting the stereochemistry at the C-1 carbon as shown below [16].



Other glycals derived from galactose, rhamnose, fucose, xylose, and arabinose were also subjected to the present bromofluorination, and the results are summarized in Table 2.



As shown in Table 2, the added HMPA effected the predominant formation of α-fluorides in particular in the cases of entries 1–10, where the glycals possess C-6 carbons. In contrast, the glycals derived from xylose and arabinose did not undergo stereoselective bromofluorination even in the presence of HMPA (entries 11–14).

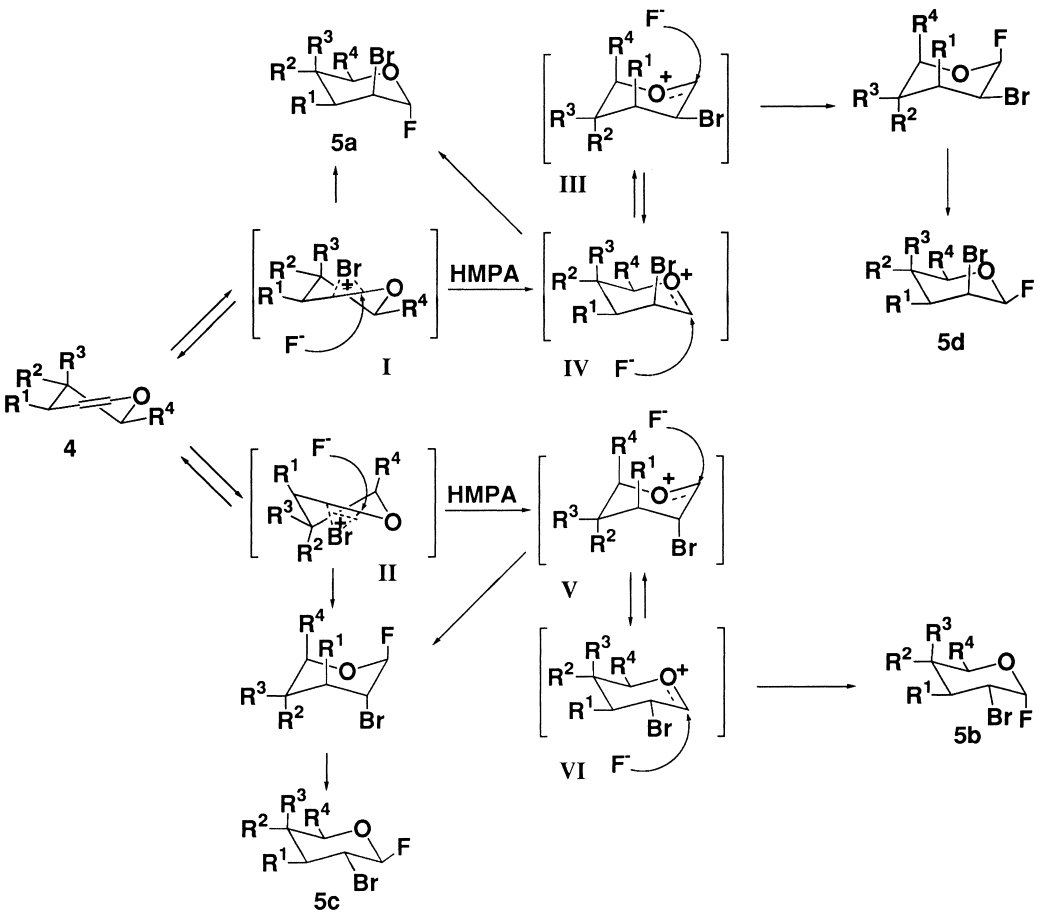
The high α-stereoselectivity of addition of the fluoride anion in the present bromofluorination may be explained as follows: The activation of the olefinic bond with Br^+ species is effected from the pseudo-axial position to form epibromonium species which is attacked by the fluoride anion from the axial position due to the stereoelectronic reason to give *trans*-bromofluorides **5a** and **5c** as depicted in the transition states **I** and **II**. When HMPA is added, the intermediary oxonium ions are more stabilized, and hence the initial oxonium species **IV** and **V** may isomerize to **III** and **VI**, respectively. If there is R^4 group, the intermediate **V** isomerizes to the energetically more stable conformer **VI** to give *cis*-bromofluoride **5b** as an adduct (entries 2, 4, 6, 8, and 10). In the cases with the glycals where R^4 is H, the energetic differences among four species **III**, **IV**, **V**, and **VI**

Table 2
Bromofluorination of glycal **4**[a]

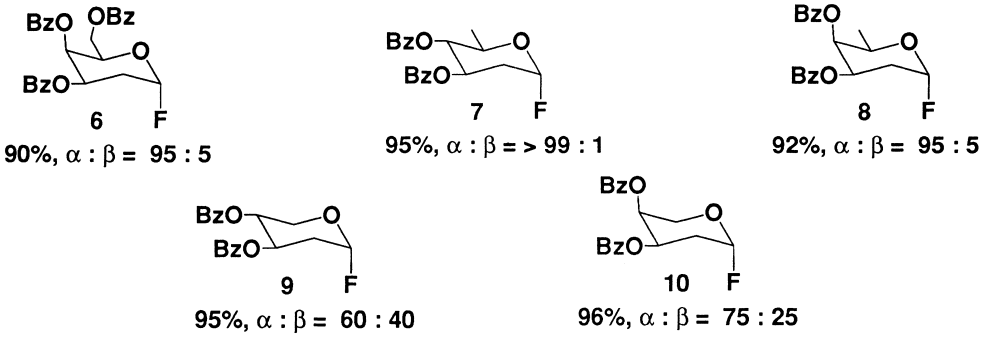
Entry	R^1	R^2	R^3	R^4	HMPA (eq)	5 (%)[b]	5a(α): 5b(α); 5c(β); 5d(β)[2c]
1	AcO	H	AcO	$AcOCH_2$	None	79	27:31:42:0
2	AcO	H	AcO	$AcOCH_2$	3.0	69	43:57:0:0
3	BzO	H	BzO	$BzOCH_2$	None	88	41:20:39:0
4	BzO	H	BzO	$BzOCH_2$	3.0	90	54:41:5:0
5	AcO	AcO	H	CH_3	None	64	36:20:44:0
6	AcO	AcO	H	CH_3	3.0	69	65:35:0:0
7	BzO	BzO	H	CH_3	None	83	43:24:33:0
8	BzO	BzO	H	CH_3	3.0	90	56:44:0:0
9	BzO	H	BzO	CH_3	None	76	24:45:31:0
10	BzO	H	BzO	CH_3	3.0	73	42:53:5:0
11	BzO	BzO	H	H	None	75	47:5:37:11
12	BzO	BzO	H	H	3.0	83	32:30:25:13
13	BzO	H	BzO	H	None	75	20:24:54:2
14	BzO	H	BzO	H	3.0	75	23:52:12:13

[a] The reaction was carried out according to the typical experimental procedure.
[b] Isolated yield.
[c] Ratio determined by HPLC and/or ^{19}F NMR.

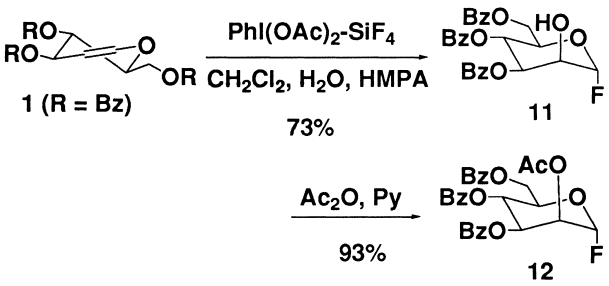
are not large, resulting in the formation of four possible adducts **5a**–**5d** (entries 11–14).



The debromination was carried out as described above using *n*-Bu_3SnH to give 2-deoxy sugars **6** (using the products from entry 4 in Table 2), **7** (from entry 8), **8** (from entry 10), **9** (from entry 12), and **10** (from entry 14) in good yields, in which the stereochemical integrities at the C-1 carbons of the starting bromofluoro sugars were not affected in every case.



For the preparation of fluoroglucose hydroxyfluorination of glycal-tribenzoate **1** (R=Bz) using $PhI(OAc)_2$-SiF_4 proved to be an efficient method, giving the α-fluoride **11** in good yield in a stereospecific manner [17,18]. Subsequent acetylation with acetyl chloride–pyridine gave **12** as a single isomer.



4. Conclusions

The bromofluorination studied here provides a rapid access to this important class of compounds in a stereoselective manner. Since a variety of glycals are readily available, this method offers a convenient procedure for the synthesis of 2-deoxyfluorosugars. Moreover, the hydroxyfluorination using $PhI(OAc)_2$-SiF_4 provides fluoroglucose in a stereospecific manner.

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