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SIMPLE SYNTHESIS OF GLYCOSYL FLUORIDES

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Treatment of 1-unprotected or -O-acetylated sugar derivatives with a hydrogen fluoride—pyridine mixture affords the corresponding 1-fluoro derivatives in high yields.

Glycosyl fluorides are much more stable and easier to handle than other glycosyl halides. In concert with the recent development of new activation methods,[1,2] the fluoro derivatives are becoming important building blocks in carbohydrate synthesis.[3] The reported procedures for the preparation of glycosyl fluorides include the reactions of O-acetylated or -benzylated glycosyl chlorides or bromides and silver fluoride[4] or silver tetrafluoroborate[5] and the treatment of sugars having the anomeric hydroxyl group with 2-fluoropyridinium tosylate[6] or diethyl-1,1,2,3,3,3-hexafluoropropylamine.[7] The utilization of cheap hydrogen fluoride as the fluorinating agent is obviously among the most attractive methods, and indeed the first glycosyl fluoride was made by the action of anhydrous liquid hydrogen fluoride on the fully acetylated carbohydrate in a platinum vessel.[8] This method, however, is not capable of extension to general use, because the severe reaction conditions sometimes cause undesired side-reactions such as removal of protective groups or even structural change.[3] We have found that appropriately protected sugars are converted readily to the 1-fluoro derivatives by exposure to a 50 to 70% hydrogen fluoride—pyridine mixture [pyridinium poly-(hydrogen fluoride)].[9]

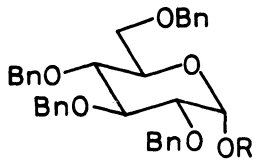
$$\text{G-OR} + C_5H_5NH^+ F(HF)_x^- \longrightarrow \text{G-F}$$

G = glycosyl
R = H or Ac

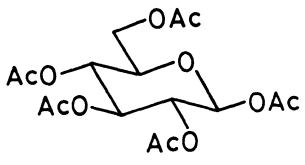
Table 1. Preparation of Glycosyl Fluorides[a)]

Entry	Substrate	HF—pyridine mL/g of substrate	Conditions		Fluoride product	
			Temp/°C	Time/h	% yield[b)]	α:β ratio
1	1	10	0	10	68	97:3[c)]
2	2	4.2	0	6	89	97:3[c)]
3	3	2[d)]	-20	3	84	33:67[e)]
4	3	2	-20	3	86	20:80[e)]
5	3	2[d)]	22	12	72	>95:5[f)]
6	4	4.2	0	6	84	>95:5[f)]
7	5	4.2	0	6	80	>95:5[f)]
8	6	4	0	6	82	>95:5[f)]
9	7	2[d)]	-20	2	92	>95:5[f)]
10	8	4	0	4	68	65:35[e)]
11	9	8	0	6	89	67:33[e)]

a) A toluene solution of the substrate was added to a 50% HF—pyridine mixture in a polyethylene vessel and the mixture was stirred under the stated conditions. b) Isolated yield. c) HPLC analysis. d) A 70% HF—pyridine mixture was used. e) Ratio after isolation by silica-gel chromatography. f) The β isomer was not detectable by ^{1}H-NMR analysis.



1, R = H
2, R = Ac



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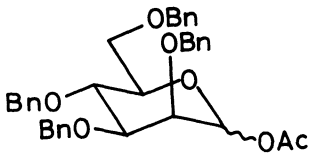

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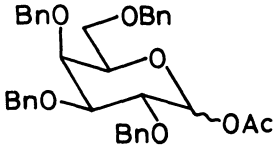

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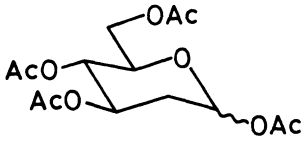

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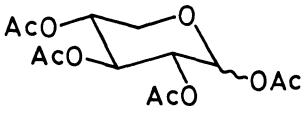

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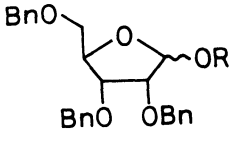

8, R = H
9, R = Ac

Both 1-unprotected[10] and -O-acetylated sugars are usable as starting materials but, in our experience, the latter reacted more smoothly. The present method is advantageous in comparison with the existing procedures in view of its wide applicability, high yield, operational simplicity, and the low cost of the reagent. Table 1 exemplifies the convenient transformations.[11] This provides a convenient way to prepare the thermodynamically favored α-glycopyranosyl fluorides. The reaction of penta-O-acetyl-β-D-glucopyranose, which has a "participating" acetoxy group at 2-position (entry 3 and 4 in Table 1), gave a mixture of the α and β fluorides in which the latter predominated. Under the forcing conditions, the kinetically favored β isomer isomerizes to the more stable α isomer (entry 5).[3]

A typical procedure is illustrated as follows (entry 2 in Table 1). In a 50-mL polyethylene vessel, anhydrous pyridine (4 mL) and a 70% hydrogen fluoride—pyridine (10 mL) were placed. To this mixture cooled at -20 °C was added a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-α-D-glucose (2) (3.0 g) in toluene (2 mL). The reaction was allowed to warm to 0 °C and stirred for 6 h. After confirmation of the completion of the reaction by TLC, the reaction mixture was poured into a mixture of ether (10 mL) and saturated aqueous potassium fluoride (30 mL), and extracted with a 3:1 ether—hexane solution (100 mL × 2). The organic layer was washed with aqueous potassium fluoride (30 mL), saturated sodium hydrogencarbonate (30 mL), and brine (30 mL), and then evaporated. Chromatography of the residue on a silica-gel column (100 g, 1:3 ether—hexane) afforded 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl fluoride (2.5 g, 89% yield), mp 68.0—69.0 °C, $[\alpha]_D^{22}$ +8.3° (c 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 5.55 (H-1, dd, $J_{H-1,H-2}$ = 2.68 Hz, $J_{H-1,F}$ = 53.22 Hz), ^{13}C NMR (CD_3CN) δ 105.2 (C-1, d, $J_{C-1,F}$ = 224.6 Hz), ^{19}F NMR ($CDCl_3$, C_6F_6) δ 149 (dd, $J_{H-1,F}$ = 53.7 Hz, $J_{H-2,F}$ = 25.4 Hz).

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