Tetrahedron Letters,Vol.26,No.1,pp 3 - 4,1985
Printed in Great Britain

0040-4039/85 \$3.00 + .00

A NEW METHOD FOR THE SYNTHESIS OF GLYCOSYL FLUORIDES

Wm. Rosenbrook, Jr.,* D.A. Riley and P.A. Lartey
Anti-infective Research Division, Abbott Laboratories, Abbott Park, Illinois 60064, U.S.A.

ABSTRACT: Neat (diethylamino)sulfur trifluoride (DAST) has been found to react with the free anomeric hydroxyl of suitably protected aldoses and ketoses to afford glycosyl fluorides.

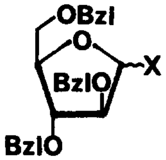
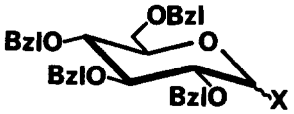
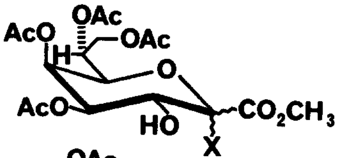
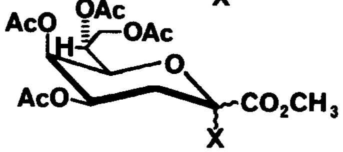
Glycosyl fluorides have recently gained considerable utility as synthetic intermediates in O-glycosylations,[1-3] N-glycosylations[3] and C-glycosylations.[4] In addition to their synthetic utility, these compounds have been studied as substrate analogs for enzymes that effect reactions at the anomeric center of carbohydrates.[5]

The preparation of glycosyl fluorides have involved the reaction of hydrogen fluoride with acylated aldoses,[6] silver fluoride with glycosyl bromides,[7] hydrogen fluoride-pyridine with glycosyl acetates,[2,8] 2-fluoro-1-methyl pyridinium tosylate with aldoses,[1] and diethyl 1,1,2,3,3,3-hexafluoropropyl amine with aldoses.[3] We now wish to report that diethylaminosulfur trifluoride (DAST), historically employed for the direct conversion of primary and secondary hydroxyls of carbohydrates[9] to fluorides (with inversion of configuration), reacts with the free anomeric hydroxyl of suitably protected aldoses and ketoses when used neat, to afford glycosyl fluorides. The reaction appears to proceed in good yield and with inversion of configuration.

In a typical example, 500 mg (1.2 mmol) of well dried 2,3,5-tri-*O*-benzyl-*D*-arabinofuranose (**1**) was treated with 1.9 g (12 mmol; 10 equiv.) of DAST, at 0° and under N_2. The mixture was stirred under N_2 for 16 hrs, gradually warming to room temperature. The mixture was again cooled to 0° and quenched with 2 ml of methanol. After addition of 50 ml of CH_2Cl_2, the mixture was washed with 50 ml of 5% aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford a syrup. The syrup was purified by flash chromatography over silica gel, using hexane: EtOAc (4:1), to afford 390 mg (78%) of 2,3,5-tri-*O*-benzyl-*D*-arabinofuranosyl fluoride (**2**). The structure and anomeric configuration of **2** was based on ^1H and ^{13}C-nmr spectra. The ^{13}C-nmr spectrum showed two doublets in the region of the anomeric carbon at δ 113.5 with $J_{C-1\alpha,F} = 224.6$ Hz and δ 108.3 with $J_{C-1\beta,F} = 228.8$ Hz. The 360-MHz ^1H nmr showed the anomeric protons at δ 5.78 ($J_{H-1\alpha,F} = 63$ Hz) and δ 5.65 ($J_{H-1\beta,F} = 66$ Hz; $J_{H-1\beta,2} = 3.0$ Hz). Integration of these protons revealed the α:β ratio to be 3:1.

Compounds **4**, **6** and **8** (Table 1) were similarly prepared from 2,3,4,6-tetra-*O*-benzyl-$\alpha\beta$-*D*-glucopyranose (**3**), methyl 4,5,7,8-tetra-*O*-acetyl-α-*D*-*glycero*-*D*-*galacto*-2-octulosonate (**5**) and methyl 3-deoxy-4,5,7,8-tetra-*O*-acetyl-α-*D*-*manno*-2-octulosonate (**7**), respectively.

Table 1:

	Starting Material		Product		
	X = OH	a:b	X = F	a:b	% yield
	1	f1:7	2	3:1	78
	3	4:1	4	1:4	91
	5	1:0	6	0:1	60
	7	1:0	8	2:1	73

Structure determination and estimation of anomeric ratios were, similarly, by ^1H and ^{13}C-nmr. As shown in Table 1, reactions with the aldopyranose 3 and ketose 5, proceeded with inversion of configuration. The 3-deoxy ketose, however, afforded a mixture of anomeric glycosyl fluorides (8).

The ready availability of DAST, simplicity of the reaction and high yield of product makes this method complementary to those previously reported.

References

1. T. Mukaiyama, Y. Hashimato, and Shin-/Chiro Shoda, Chem. Lett., 935 (1983).
2. S. Hashimoto, M. Hayashi, and R. Nayori, Tet. Lett., 25, 1379 (1984).
3. K. C. Nicolaou et al., J. Amer. Chem. Soc, 106, 4189 (1984).
4. Y. Araki et al., Carb. Res., 127, C5 (1984).
5. C. Walsh in "Advances in Enzymology," Vol. V, A. Meisler, Ed., John Wiley & Sons, NY, 1983, p. 197.
6. D. H. Brauns, J. Amer. Chem. Soc., 45, 833 (1923).
7. B. Helferich and R. Gootz, Ber. 62, 2505 (1929).
8. M. N. Sharma and R. Eby, Carb. Res., 127, 201 (1984).
9. For a review see: Anna A.E. Penglis in "Advances in Carbohydrate Chemistry and Biochemistry," Vol. 38, Eds. R.S. Tipson and D. Horton, Academic Press, New York, NY, 1981, p. 195.

(Received in USA 23 July 1984)