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Note

Observation of a stable orthoacyl fluoride in the reaction of a reducing sugar with diethylaminosulfur trifluoride

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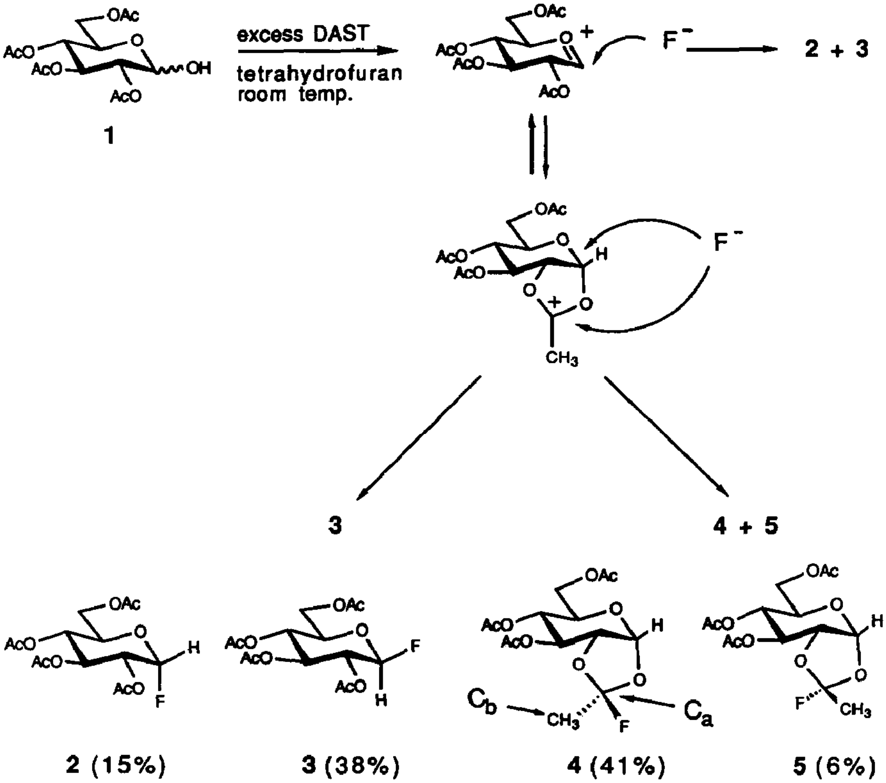
The use of pyranosyl fluorides as glycosylating agents has gained wide popularity, in part due to their enhanched stability over the corresponding bromides or chlorides[1,2]. Many methods are available for their preparation[3–5]. One of the most direct methods is the reaction of reducing sugars with diethylaminosulfur trifluoride (DAST), but the yields of glycosyl fluorides are variable and solvent dependent[1,6,7].



Scheme 1. Possible pathways for the reaction of **1** with DAST.

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We have investigated in detail the conversion of 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**1**) into the α- (**2**) and β-glucosyl fluorides (**3**), respectively, and have found the yields of the products to be solvent dependent. When **1** was treated with DAST in chloroform-*d*, only the α- and β-fluorides **2** and **3** were formed in a ratio of 2:5. When tetrahydrofuran-d_8 was the solvent, the exo- (**4**) and endo-orthoacyl fluorides (**5**) were also formed in a yield of ~50% together with **2** and **3** (Scheme 1). The addition of tetrabutylammonium fluoride prior to the DAST did not change the ratio of orthoacyl fluorides to glycosyl fluorides. Addition of either trifluoromethanesulfonic acid, tetrabutylammonium fluoride, or boron trifluoride etherate after completion of the reaction did not change the ratios of the products.

The orthoacyl fluorides were stable for several days in the reaction medium. Both solvent and reagent could be evaporated under anhydrous conditions and a solution of the residue in chloroform-*d* was stable for at least one week at room temperature (n.m.r. data). Addition of boron trifluoride etherate to this solution caused rapid rearrangement of **4** and **5** into the glycosyl fluorides. As anticipated, addition of methanol to a

TABLE I

Chemical shifts[a] and coupling constants for the anomeric fluorides and orthoacyl fluorides[b]

Nucleus	**2**	**3**	**4**	**5**
H-1 ($J_{1,2}$, $J_{1,F}$)	5.742 (2.7. 53.0)	5.420 (7.0, 53.0)	5.795 (5.5, –)	5.785 (6.0, –)
H-2 ($J_{2,3}$, $J_{2,F}$)	4.987 (10, 25.0)	5.030 (9.0, 12.0)	4.497 (2.8, –)	4.434 (5.0, 3.0)
H-3 ($J_{3,4}$)	5.415 (10.0)	5.260 (9.0)	5.130 (2–3)	5.435 (8.0)
H-4 ($J_{4,5}$)	~5.13 (10)	5.152 (10.0)	4.13–4.14 (n.d.)	n.d.[c]
H-5 ($J_{5,6}$)	4.176 (4.5)	3.982 (5.0)	4.13–4.14 (n.d.)	n.d.
H-6 ($J_{6,6'}$)	4.360 (12.5)	4.242 (12.2)	4.884 (9.7)	4.317 (12.3)
H-6′ ($J_{5,6'}$)	4.085 (2.1)	4.128 (2.5)	3.850 (m)	4.065 (2.3)
OAc	2.030, 2.002, 1.975, 1.925	2.005, 2.017, 1.970, 1.937	2.052, 2.025, 1.992	1.965, n.d., n.d.
H_b (J_{CH_3F})	–	–	1.767 (12.5)	1.652 (13.0)
C-1 ($J_{C,F}$)	103.60 (228.0)	106.05 (220.5)	96.80	n.d.
C-2 ($J_{C,F}$)	69.95 (24.5)	71.00 (28.5)	72.55	n.d.
C-3 ($J_{C,F}$)	n.d.	71.53 (8.5)[d]	69.20	n.d.
C-4 ($J_{C,F}$)	67.15	67.25	67.75	n.d.
C-5 ($J_{C,F}$)	69.6 (4.5)	71.75 (4.0)[d]	67.00	n.d.
C-6 ($J_{C,F}$)	61.00	61.55	62.75	n.d.
C_a ($J_{C,F}$)[e]	–	–	126.30 (249.0)	n.d.
C_b ($J_{C,F}$)[e]	–	–	20.20 (41.0)	n.d.
^{19}F ($J_{F,2}$)	–150.42 (24.5)	–142.03 (11.8)	–56.86 (–)	–52.64 (3.0)
($J_{F,1}$)	(53.0)	(53.7)	(–)	(5.0)
($J_{F,CH3}$)	–	–	(13.0)	(13.0)

[a] Chemical shifts of the ^1H-n.m.r. resonances are relative to Me_4Si (δ 0), for ^{19}F-n.m.r. to external $CFCl_3$ (δ 0), and for ^{13}C-n.m.r. to $CDCl_3$ (δ 77.05); splittings are reported as if they were first-order coupling constants. [b] ^1H- and ^{19}F-n.m.r. spectra were recorded for solutions in tetrahydrofuran-d_8, and the ^{13}C-n.m.r. spectra for solutions in $CDCl_3$. [c] n.d., Not determined. [d] Could be interchanged. [e] C_a is C-2 of the dioxolane ring; C_b is the carbon atom of the methyl group attached to C-2 of the dioxolane ring.

solution of **2**–**5** in tetrahydrofuran resulted in the quantitative conversion of **4** and **5** into the corresponding methyl orthoesters, but the glycosyl fluorides did not react. Addition of water to the mixture of **2**–**5** in tetrahydrofuran resulted in the production of **1** (34%) and 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (15%), as expected following the well-known reaction pathways of the intermediate acetoxonium ion[8].

To our knowledge, this is the first time an orthoacyl fluoride has been characterised in detail by n.m.r. spectroscopy, as orthoacyl halides reported previously have been

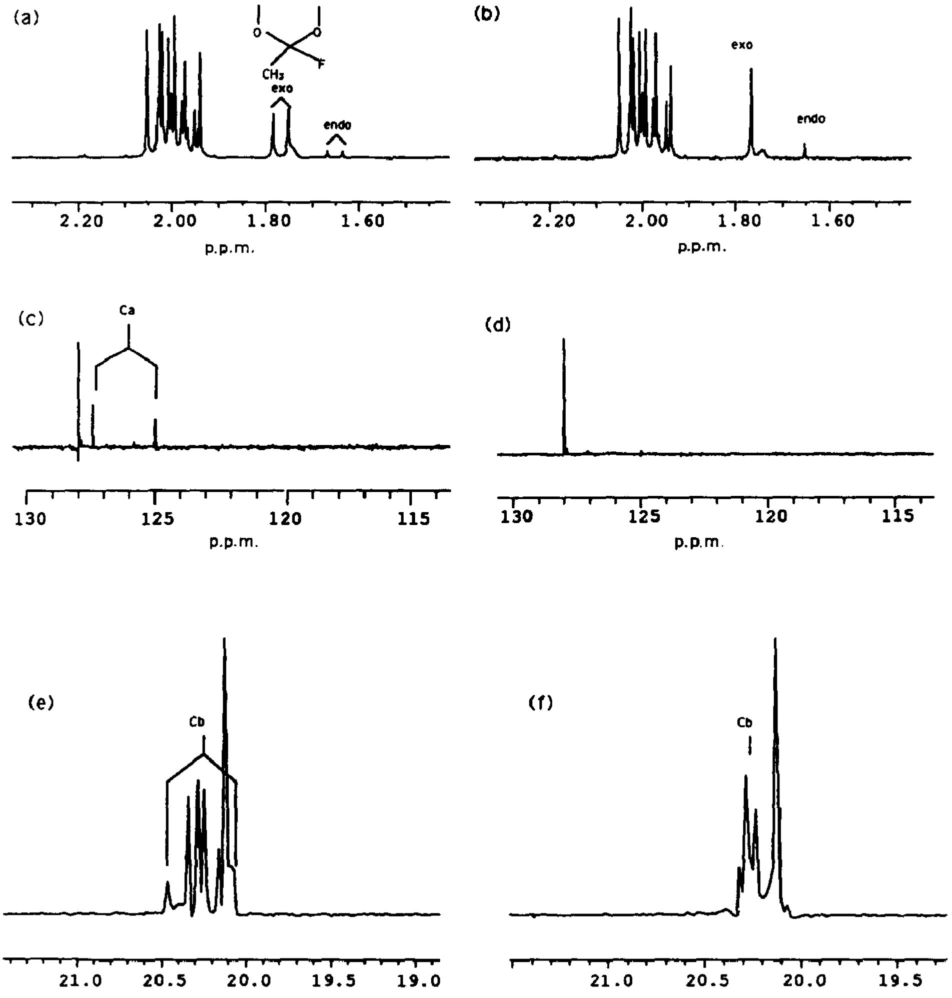

Fig. 1. Partial ^{1}H- and ^{13}C-n.m.r. spectra of the mixture produced by the reaction of **1** with DAST, recorded on a 400-MHz instrument; C$_a$ indicates C-2 of the dioxolane ring and C$_b$ indicates the methyl group attached to C-2 of the dioxolane ring; ^{1}H-n.m.r. spectra, (a) without decoupling, acetate region, and (b) with ^{19}F decoupling at the orthoacyl fluoride, acetate region; ^{13}C-n.m.r. spectra, (c) without ^{19}F decoupling, C$_a$ region, (d) with ^{19}F decoupling at the orthoacyl fluoride, C$_a$ region (decoupling power was not sufficient to coalesce the peaks), (e) without ^{19}F decoupling, C$_b$ region, and (f) with ^{19}F decoupling at the orthoacyl fluoride, C$_b$ region.

too unstable to allow such studies[9,10]. Differences in yield between fluorination reactions performed in tetrahydrofuran and other solvents[1,6] now appear to be due to the formation of orthoacyl fluorides in the former solvent which, on aqueous work-up, regenerate the starting material.

EXPERIMENTAL

Treatment of sugars with DAST. — In a typical experiment, DAST (2–4 equiv.) was added to a solution of the sugar (10–20 mg) in dry tetrahydrofuran (0.3–0.5 mL), and the mixture was shaken. The reaction was complete in a few minutes. DAST was removed by coevaporation with toluene at 25–30° several times and the residue was then dissolved in the desired solvent. The structures of orthoacyl fluorides **4** and **5** were established by ^{1}H-, ^{13}C-, and ^{19}F-n.m.r. spectroscopy (Table I), and the covalency of the C–F bond in these compounds was evident from the ^{19}F-decoupled ^{1}H-n.m.r. spectra (Fig. 1a). The corresponding ^{13}C-n.m.r. signals were also assigned by selective ^{19}F decoupling at the anomeric and orthoacyl fluorine resonances. The n.m.r. data for **2** and **3** accord with those reported by Bock and Pedersen for these compounds[11].

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