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A Rapid Stereoselective Synthesis of Fluorinated Carbohydrates: Addition of Acetyl Hypofluorite to Vinyl Ether Derivatives of Sugars[1]

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Abstract

Acetyl hypofluorite has been added to six unsaturated carbohydrates which contain the vinyl ether moiety. All reactions were rapid (less than 5 min.) at -78°C and gave, with one exception, high yields of isomerically pure products. The hypofluorite was shown to add exclusively in a cis mode and with a strong preference for a particular "face" of the double bond. As well as the syntheses, NMR data and preferred conformations for the fluorinated products are also discussed.

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The synthesis of fluorinated carbohydrates has been a very active area for many years principally because of the interesting biological properties associated with these compounds[3,4,5]. Recently there has been a renewed interest because of the use of ^{18}F-2-deoxy-2-fluoro-D-glucose, a proven glucose analogue[6], as an imaging agent in studies of regional cerebral glucose metabolism by positron emission tomography (PET)[7].

Previous electrophilic routes to fluorinated carbohydrates such as the addition of trifluoromethyl hypofluorite (CF_3OF)[8], elemental fluorine[9], and xenon difluoride[10] to glycals are less than ideal. Generally product yields are low and the reactions lead to the production of isomeric product mixtures and difluorinated compounds. These approaches have further disadvantages in the context of ^{18}F-radiolabelling in that these reagents, with the exception of F_2, are difficult to produce[11] routinely with ^{18}F.

Prompted by a recent report[12] of a simple preparation of acetyl hypofluorite ($MeCO_2F$) from F_2, we have investigated the reaction of this electrophilic fluorinating agent with a number of unsaturated sugars **1,2,3,4,5,6**. These substrates impart varying degrees of steric hindrance with regard to attack by the incoming acetyl hypofluorite on a particular face of the double bond. In all but one case, **6**, a preferred face can be determined; hence information about the stereoselectivity of acetyl hypofluorite can be obtained. NMR data and preferred conformations for the fluorinated products are also discussed.

Synthesis

There is precedent in the literature for the exclusive cis addition of acetyl hypofluorite to unsaturated systems such as stilbenes[12]. The

addition of acetyl hypofluorite to the sugars 1, 2 and 3 also occurs in a cis mode to give the fluorinated sugars 7, 8 and 9 (scheme 1). This behaviour is not unique in itself since other eletrophilic fluorinating agents, including CF_3OF, are known to add to unsaturated sugars to give exclusively cis products. However, the addition of acetyl hypofluorite to 1, 2 and 3 as well as to the terminal double bonds in 4, 5 and 6, reveals a greater degree of stereo-selectivity since these reactions not only form cis products, but also favour addition to a preferred face of the double bond. Thus reaction of $MeCO_2F$ with 1, 2 and 3 occurs exclusively by cis addition to the less hindered face to give the isomerically pure products 7, 8 and 9 in 78%, 84% and 96% yield respectively in less than 5 minutes; the other isomer in each case was not detected in the reaction product mixture. Essentially all three of these products could be crystallized directly from the reaction mixtures after washing of the organic layer and evaporation. The fluoro-glucose derivative 7 required further purification by either column chromatography or recrystallization to remove impurities with lower Rf values (see experimental). Compounds 7 and 8, as shown from the nmr data (Table I), have the α anomeric configuration. Surprisingly, these compounds have never been fully characterized as they were previously only synthesized as either an α, β mixture, or in pure β-anomeric form, by acetylation of the 'free' 2-fluoro sugars[8,13]. In the context of PET chemistry this method represents a significant improvement in the synthesis of 2-deoxy-2-fluoro-glucose and is currently being used at some PET centres to synthesize ^{18}F-2FDG[14].

Addition of $MeCO_2F$ to the terminal double bonds in 4, 5 and 6, while not quite as stereospecific as the previous examples, is also highly

selective and generally occurs in high yield (scheme 1). Compound **10** was obtained in the lowest yield (53%) in isomerically pure form after column chromatography. About 22% by weight of the crude reaction mixture contains two by-products with lower Rf values. From the nmr spectra (^{1}H and ^{19}F) it appears that neither of these are simple isomeric forms of **10** and may instead be the result of the addition of fluorine to the terminal carbon atom (C_6) of the double bond and addition of the acetate moiety to the asymmetrical tertiary carbon of the benzylidene group, followed by ring opening and formation of a carbonyl function at C_5[15].

Reaction of $MeCO_2F$ with **5** gives **11** in 83% yield, mixed with a by-product after purification by column chromatography; ^{1}H nmr of this column-purified material reveals the ratio of the mixture to be (93:7). Although the by-product was not positively identified, the nmr spectrum and the similar chromatographic behaviour strongly suggest that this is the other cis-isomer; if this is so, then the above ratio gives the relative ease of addition of $MeCO_2F$ to the two faces of the double bond. Fortunately a second column purification gave a sample of **11** in analytically pure form. Similarly, $MeCO_2F$ reacts with **6** to give, after chromatography, 71% of a crystalline mixture (87:13) of **12** and a by-product. The major compound **12** was further purified by recrystallization. Again, although the by-product was not positively identified it appears from the nmr spectrum that this is the other cis-isomer.

Due to the variable production yields of $MeCO_2F$ and the difficulties in its quantification, it was thought to be prudent to use approximately a 2 fold excess of the hypofluorite. However, separate experiments have shown that when a known 1:1 ratio of **1** to the hypofluorite is used the product yield is unaffected and the amount of impurities are also the same. From

this it seems reasonable to conclude that excess $MeCO_2F$ does not cause the overfluorination problems that normally result when excess F_2 is used as the fluorinating agent.

NMR Spectroscopy and proof of structure

2-Deoxy-2-fluoro-derivatives. Examination of the ^{19}F chemical shift values for compounds 7 to 9 (Table I) immediately shows that all are secondary fluorine containing derivatives[16]. Furthermore, the values of $J_{F2,H2}$ in these three cases are only compatible with a ^2J geminal coupling constant[16]. Noteworthy, the analysis of the $^3J_{H,H}$, $^3J_{F,H}$ and long range $J_{F,H}$ coupling constants (Table I) permits unambiguous assignments of both the configurations at the C_1 and C_2 centres, together with conformational assignments depicted in chart 1. Thus, the $^3J_{F2,H3}$ values are in good agreement with the expected one for vicinal, gauche-related, coupled nuclei in pyranose derivatives[5], as are the $^3J_{H2,H3}$ values with the expected coupling constant for vicinal trans-diaxially related, coupled protons. In addition, the zero value of the $^3J_{F2,H1}$ coupling constant for compounds 7 to 9 can be attributed to the high electronegativity of substituents at C_1 and C_2, together with the antiplanar orientation between C_2-F_2 and C_1-O_5 bonds[8,17]. Finally, it is interesting to note that the $^4J_{F2,H4}$ long range coupling for compounds 8 and 9 occurs via "W-coplanar" coupling routes; similarly, the $^5J_{F2,H5a}$ coupling constant observed in the pmr spectrum of 9 can be rationalized by the existence of two different coupling routes, each of them implying two groups of three coplanar bonds.

Fluorinated primary centre derivatives. Again examination of the ^{19}F chemical shift values, together with the $^{2}J_{F,Ha}$ and $^{2}J_{F,Hb}$ geminal coupling constant values, for compounds **10** to **12** (Table I), clearly shows that all are primary fluorine containing derivatives[16]. Configurational assignment on a quaternary centre is probably one of the last problems that NMR spectroscopy cannot easily solve in structural analysis of small molecules. For this reason, configurational assignment on C_5 for compounds **10** and **11** is proposed on the basis of the following chemical evidence. Both the vinyl ether starting derivatives (**4** and **5**) are well-known to undergo hydrogenation reactions to give two products, one of which is strongly favoured[18], because the 3, 4-cis-fused bycyclic systems presented by these substrates define endo and exo faces with respect to the double bond. Obviously, in such hydrogenations starting from **4** and **5**, the exo face is preferred. Furthermore, our recent study on hydroboration-halogenation reactions[19] starting from the same substrates, shows unequivocally that in both cases, the same exo face of these vinyl ether derivatives is preferred in these additions.

Considering now the results obtained in the synthesis of 2-deoxy-2-fluoro-sugars **7** to **9**, it is clear that the cis-addition of acetyl hypofluorite has showed an unusually high degree of selectivity in approach to the less-hindered face of the glycal derivatives **1** to **3**. The very high susceptibility of acetyl hypofluorite to steric hindrance, together with previous results on the stereochemistry of other cis-addition reactions (hydrogenation or hydroboration) on the double bond of **4** and **5**, both provide strong evidence for supporting the configurational assignment at C_5 for compounds **10** and **11**, as resulting from attack

by acetyl hypofluorite to the exo face of each of the vinyl ether starting derivatives 4 and 5.

Because examination of a Dreiding model of 6 did not indicate a preferred direction for attack of the double bond, and because no previous study of cis-addition on this substrate has ever been reported, we have not assigned the configuration at C_4 for 12.

Analysis of the $^3J_{H,H}$ nmr coupling constants for compounds 10 to 12 permits the assignment of the preferred conformations depicted on Chart 1. It is of interest to note that the conformations for compounds 10 and 11 allow an equatorial orientation of the $-CH_2F$ substituent on C_5 and an axial one for the -OAc substituent on the same atom. In this regard, the twist-boat form (assigned on the basis of the zero value of $J_{2,3}$) for the pyranose ring of 11 allows a maximum distance between both the substituents $-O_1$ on C_1 and -OAc on C_5.

Experimental Section

Melting points were determined either on a hot-stage or capillary-oil bath instrument and are uncorrected. The specific rotation $[\alpha]_D$ values were obtained with a Perkin-Elmer 241 MC polarimeter. ^1H nmr was performed on a homebuilt 270 MHz pulse Fourier Transform nmr instrument. All Chemical shifts are reported in parts per million downfield from Me_4Si. ^{19}F nmr spectra were recorded on a Varian XL-100 spectrometer and chemical shifts were relative to Freon-11 ($CFCl_3$).

Triacetyl-glucal 1 was purchased from Aldrich Chemical Co., Saint Louis MO.. Triacetyl-galactal 2 was purchased from Terochem Laboratories Ltd., Edmonton, Canada and was distilled before use.

Di-acetyl-arabinal 3 was purchased from Raylo Chemicals Ltd., Edmonton, Canada and was distilled before use. Compound 5 was obtained following the published procedure[20] from the 6-deoxy-6-iodo-galactopyranose derivative, and purified by crystallization and sublimation. In the same way, 4[21] and 6[22] were obtained in good yields by the action of AgF in pyridine on the 6-deoxy-6-iodo-glucofuranose and 5-deoxy-5-iodo-xylofuranose derivatives, respectively.

General Procedure for Preparation of Acetyl Hypofluorite and Fluoro Sugars (7), (8), (9), (10), (11), (12). Acetyl Hypofluorite (1.4-2 mmole) was prepared as previously reported by Rozen et al.[12]. Sodium acetate (6.8g, 83 mmole) was added to a stirred solution of Freon-11 ($CFCl_3$) (180 ml) and glacial acetic acid (20 ml) and the mixture cooled to -78°C under an atmosphere of nitrogen gas. After cooling, F_2 (1% in He) was bubbled through the suspension at about 50 ml/min. After 2 hours the F_2 flow was stopped and the mixture purged with inert gas for 2 min. to remove any unreacted F_2. The unsaturated sugar substrate (0.75 mmole) was then added as a solution in either $CHCl_3$ or $CFCl_3$ (5 ml). After 5 min. the mixture was treated with aqueous KI and titrated with $Na_2S_2O_3$ to determine the excess of acetyl hypofluorite. After titration the organic layer was washed successively with saturated Na_2CO_3 and twice with H_2O. The organic layer was then dried over $MgSO_4$, filtered and evaporated to dryness.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranose (7). After evaporation of the solvent, the organic residue was purified by flash chromatography using ether/hexane (1.5:1) to give (7) in 78% isolated yield; m.p. 78°-79°C; $[\alpha]_D^{24}$+146° (c = 1, $CHCl_3$); m/e: 350 (<<1) (M^+), 291(4), 230 (3), 188 (6), 160 (2), 145 (8), 115 (4), 103 (10), 73 (2),

44 (3), 43(100), 32(3), 28(14); Anal. Calcd. for $C_{14}H_{19}FO_9$: C 48.02, H 5.43; found: C 47.99, H 5.68.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranose (8). After evaporation of the solvent the syrup was crystallized with ether-hexane (1:1) to give (8) in 84% yield. An analytical sample was obtained by recrystallization from ethanol; mp 126-127°C; $[\alpha]_D^{24}$ + 150 (c=1, $CHCl_3$); m/e: 291(5), 230(2), 188(7), 160(3), 145(6), 130(3), 117(3), 115(3), 103(8), 73(2), 44(2), 43(100), 32(6), 28(26); Anal. Calcd. for $C_{14}H_{19}FO_9$: C 48.02, H 5.43; found: C 47.99, H 5.54.

1,3,4-Tri-O-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranose (9). After evaporation of the solvent, the organic layer yielded 200 mg (96%) of (9) as a single, pure crystalline compound. An analytical sample was obtained after recrystallization from methanol; mp 129-131°C; $[\alpha]_D^{24}$ - 186.5 (c=1, $CHCl_3$); m/e: 219(6), 176(12), 131(15), 117(6), 103(6), 99(7), 88(7), 44(4), 43(100), 32(3), 28(10); Anal. Calcd. for $C_{11}H_{15}FO_7$: C 47.49, H 5.43; found: C 47.68, H 5.35.

5[S] -5-O-Acetyl-3,5-O-benzylidene-6-deoxy-6-fluoro-1,2-O-isopropylidene-α-D-xylo-hexo-1,4-furanos-5-ulose (10). After evaporation of the solvent, the organic layer yielded a crude mixture which showed two major spots (t.l.c.). Column chromatography on silica with hexane/ether (2:1) as eluant, permitted the isolation of 145 mg of (10) (53%) in the first fraction and 40 mg of an unresolved mixture of two by-products in the second fraction. (10) was obtained in crystalline form after evaporation of the first fraction. Recrystallization from methanol did not give better micro-analysis results; mp 102-104°C; $[\alpha]_D^{24}$ + 46.39 (c=0.8, $CHCl_3$); m/e: 308(22), 145(16), 113(53), 107(22), 105(78), 100(12),

77(10), 61(15), 59(22), 43(100), 28(16); Anal. Calcd. for $C_{18}H_{21}FO_7$: C 58.69, H 5.75; found: C 58.30, H 5.69.

5[R] -5-O-Acetyl-6-deoxy-6-fluoro-1,2,3,4-di-O-isopropylidene-β-L-arabino-hexo-1,5-pyranos-5-ulose (11). After evaporation of the solvent, the organic layer yielded the crude product which was purified by column chromatography on silica, with hexane/ether (3:1) as the eluant; 200 mg (83%) of a syrupy mixture (93:7) of (11) plus a minor by-product was obtained. An analytical pure sample of (11) was obtained after an additional purification by LCC on silica, using hexane/ether (6:1) as the eluant; syrup; $[\alpha]_D^{24}$ -47.9 (c=1.5, $CHCl_3$); m/e: 305(12)(M^+-Me), 203(13), 145(12), 117(8), 113(14), 103(37), 100(32), 97(8), 85(13), 61(9), 59(24), 43(100), 41(8), 31(8), 20(12); Anal. Calcd. for $C_{14}H_{21}FO_7$: C 52.50, H 6.61; found: C 52.47, H 6.70.

4-O-Acetyl-5-deoxy-5-fluoro-1,2-O-isopropylidene-3-O-tosyl-β-L-threo-pento-1,4-furanos-4-ulose (12). After evaporation of the solvent, the organic layer yielded a crude product which was purified by liquid column chromatography on silica with hexane/ether (2:1) as the eluant; 215 mg (71%) of a crystalline mixture (87:13) of (12) and a minor by-product was obtained. An analytical pure sample of (12) was obtained by recrystallization from methanol; mp 84-85°C; $[\alpha]_D^{24}$ -83.2 (c=0.6, $CHCl_3$); m/e: 389(18)(M^+-Me), 347(8), 287(7), 213(7), 175(17), 155(59), 90(34), 87(7), 71(7), 65(7), 59(18), 43(100), 32(10), 28(29); Anal. Calcd. for $C_{17}H_{21}FO_8S$: C 50.49, H 5.23; found: C 50.35, H 5.14.

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