A Rapid, Stereoselective, High Yielding Synthesis of 2-Deoxy-2-fluoro-D-hexopyranoses: Reaction of Glycals with Acetyl Hypofluorite

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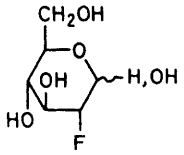
1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranose (**4**) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranose (**5**) have been synthesized in 78% and 84% yields respectively in 5 min by the reaction of acetyl hypofluorite with the corresponding tri-*O*-acetylglycal (**2,3**) at −78 °C.

Fluorinated carbohydrates have continued[1–3] to attract much interest, principally because of the use of [^{18}F]2-deoxy-2-fluoro-D-glucopyranose (**1**) ([^{18}F]2FDG), a proven glucose analogue,[4] as an imaging agent in studies of regional cerebral glucose metabolism by positron emission tomography (P.E.T.).[5] Previous synthetic routes to (**1**) have included the electrophilic addition to tri-*O*-acetyl-D-glucal (**2**) of trifluoromethyl hypofluorite (CF_3OF),[6] of elemental fluorine[7] or of xenon difluoride,[8] and fluoride displacement on an anhydro-sugar.[9] All of these methods have disadvantages, resulting in low product yields, isomeric product mixtures, and/or difluorinated compounds. These approaches have further disadvantages in the context of [^{18}F]-radiolabelling in that all of the above reagents, with the exception of F_2, are difficult to produce with ^{18}F. While the use of [^{18}F]F_2 has become routine in the production of [^{18}F]2FDG[10] only about 10% of the ^{18}F used is incorporated into the desired product.

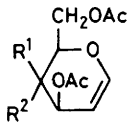
Prompted by the recent report[11] of a simple preparation of acetyl hypofluorite ($MeCO_2F$) from F_2, we have investigated the reaction of this electrophilic fluorinating reagent with (**2**), and also with the D-galacto-analogue (**3**). In each case a high yield of the products (**4**,**5**), corresponding to *cis*-addition of the hypofluorite to the underside of the sugar ring, has been isolated. The free sugar (**1**) was obtained rapidly and in high yield by conventional de-*O*-acetylation using sodium methoxide.

In a typical preparation, acetyl hypofluorite (0.9 mmol) was prepared† by bubbling dilute fluorine gas through a suspension of sodium acetate in Freon-11–acetic acid at −78 °C.[11] The mixture was purged briefly with helium and a solution of (**2**) (0.2 g, 0.73 mmol) in Freon-11 was added. After 5 min the mixture was poured into aqueous sodium thiosulphate, extracted, and dried. Concentration of the organic layer gave a product which was purified by flash-chromatography[12] using

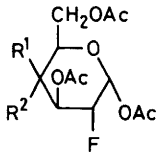
† Experiments conducted on a small scale (60—100 μmol), to determine the combined preparation time of the hypofluorite and of (**4**) for use with ^{18}F ($t_{1/2}$ 110 min), were complete in 30 min.



(1)



(2); R^1 = H, R^2 = OAc
(3); R^1 = OAc, R^2 = H



(4); R^1 = H, R^2 = OAc
(5); R^1 = OAc, R^2 = H

ether–hexane (1.5:1) to give‡ (**4**) in 78% isolated yield; m.p. 78 °C, $[\alpha]_D^{25}$ +146° (c = 1, $CHCl_3$). Alternatively (**4**) could be crystallized directly from the reaction mixture using ether–hexane (1:1), but needed further recrystallization to remove all impurities. De-*O*-acetylation of (**4**), either in purified or crude form, using methanolic sodium methoxide (0.03 M) was complete in 10 min. After flash-chromatography using dry silica gel ($CHCl_3$–MeOH–H_2O, 30:9:1), 2-deoxy-2-fluoro-D-glucose (**1**) was isolated in 62% overall yield, based on tri-*O*-acetyl-D-glucal (**2**), from pure (**4**) or 55% overall yield from crude (**4**); the material was identical in all respects with an authentic sample of (**1**). The latter procedure, in which the crude reaction product was deblocked prior to purification, is of particular significance for the preparation of [^{18}F](**1**) since having only one purification step saves time and will ultimately reduce the complexity of remotely-handled chemical apparatus.

A separate sequence starting from (**3**), produced (**5**) in 84% yield by direct crystallization of the syrupy crude product using ether–hexane (1:1); m.p. 102 °C, $[\alpha]_D^{25}$ +150° (c = 1, $CHCl_3$). De-*O*-acetylation of this compound was not performed.

Given the high isolated yields, the high stereoselectivity of the reaction, and the ease of deblocking, we believe that this approach represents a significant improvement over the previously available methods for the synthesis of 2-deoxy-2-fluoro-D-hexoses. With regard to P.E.T. chemistry all of these advantages, coupled with the fact that acetyl hypofluorite can be prepared rapidly from F_2† and that the subsequent reaction with tri-*O*-acetyl-D-glucal is also very fast, suggests that this may be a preferred route to [^{18}F]2-deoxy-2-fluoro-glucose.

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‡ The structures of the acetylated products (**4**) and (**5**) were confirmed by 400 MHz ^{1}H n.m.r., ^{19}F n.m.r., and by mass spectral data.

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