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REACTIONS OF GLYCALS WITH XENON FLUORIDE: AN IMPROVED SYNTHESIS OF 2-DEOXY-2-FLUOROSACCHARIDES

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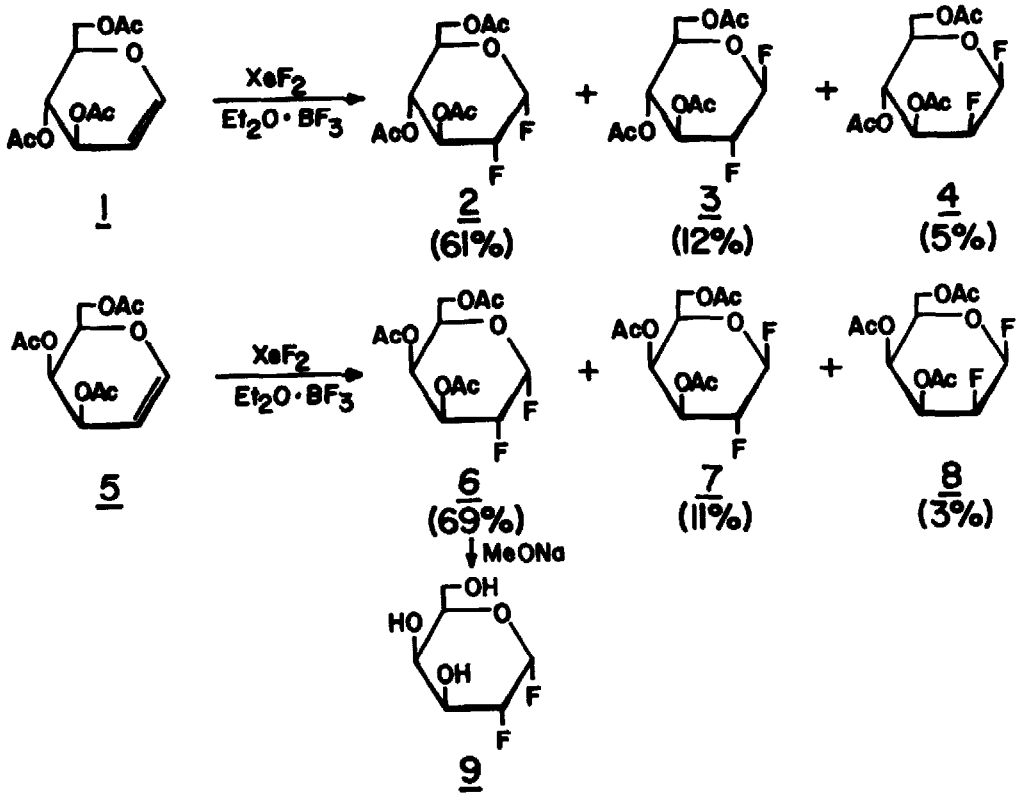
Summary: The 1,2-double bond in acetylated glycals has been fluorinated with XeF_2 in the presence of BF_3 to give 1,2-deoxy-1,2-difluorosaccharides. A mechanism for this reaction has been proposed. This method represents an improvement in the synthesis of 2-deoxy-2-fluorosaccharides.

The synthesis and biological activities of fluorinated carbohydrates has received considerable attention;[1,2] of particular interest are 2-deoxy-2-fluorohexoses, such as 2-deoxy-2-fluoro-D-glucopyranose, both in regards to their biological activities as inhibitors or modifiers of cell surface glycoconjugates[3] as well as for emission tomography, if labeled with ^{18}F.[4]

The synthesis of 2-deoxy-2-fluoro-D-glucose has been achieved by conventional displacement reactions[5], by the electrophilic additions of trifluoromethyl hypofluoride[6] or elemental fluorine[7] to 1 and subsequent hydrolysis. Although these electrophilic addition reactions simplify the synthesis, they involve the handling of toxic and corrosive gases. In addition, CF_3OF has often led to complex mixtures of products [8] and its commercial availability has been restricted.

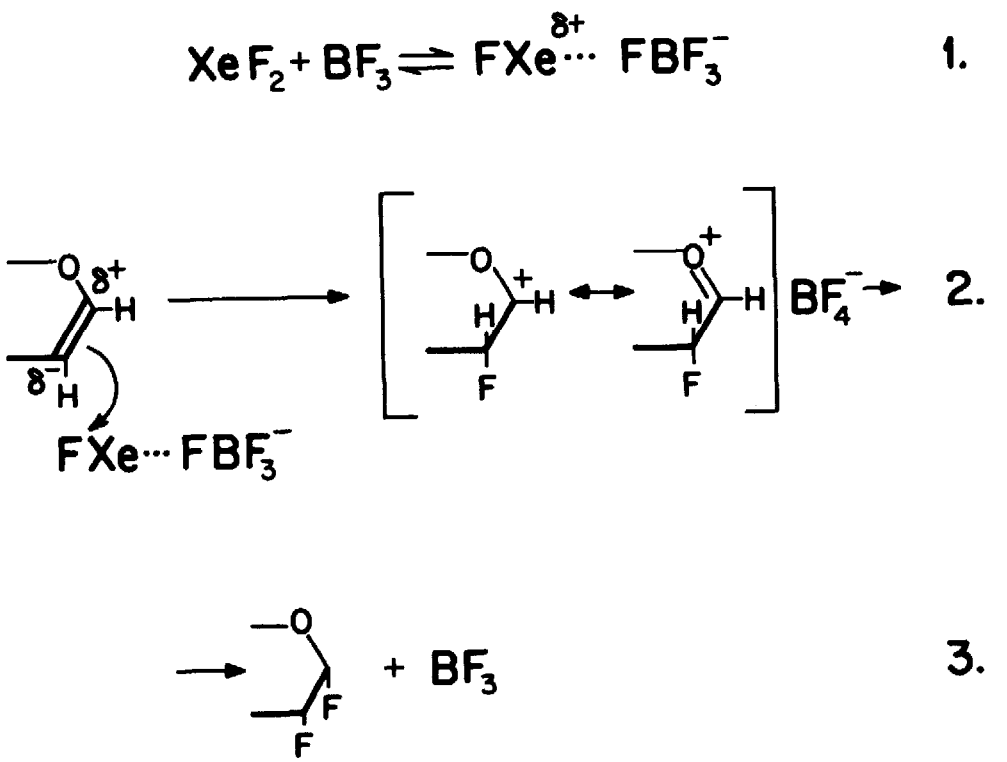
We have adapted xenon difluoride[9], an easily handled and available solid for fluorinations of glycals. This is exemplified by reactions with 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (3,4,6-tri-O-acetyl-D-glucal) 1 and the D-lyxo epimer (tri-O-acetyl-D-galactal) 5 in Scheme 1 (yields are given in parenthesis):

Scheme 1: Fluorinations of Glycals with Xenon Fluoride



In a typical experiment, 1 (1 mmol) was dissolved in Et_2O (5ml) and added while stirring to XeF_2 (1 mmole) at room temperature. A solution of $BF_3.OEt_2$ (0.2 mmole) in dry benzene (5ml) was added dropwise and the stirring was continued for 24 hrs, when no starting material could be detected. Products 2 to 4 have been separated on a silica gel column and their identity confirmed by physical data reported in the literature[10] and by analysis of their ^1H and ^{19}F NMR spectra. The fluorination of 5 under identical conditions gave products that were stereochemically similar to that obtained from 1, indicating that an opposite configuration of the acetoxy group in the 4 position has little effect on the stereochemical course of the reaction. Hydrolysis with acid of either 2 or 3 gave 2-deoxy-2-fluoro-D-glucose and of 6 or 7 2-deoxy-2-fluoro-D-galactose, respectively. The deacetylation of the adducts has also been carried with NaOMe yielding almost quantitatively 2-deoxy-2-fluoro-D-glycopyranosyl fluorides, as shown by the synthesis of 9 from 6 (Scheme 1).

The mechanism of the fluorination reaction can be rationalized by the following reaction sequence:



In the first reaction XeF_2 forms a complex with BF_3; this is followed by the nucleophilic attack of the $\tilde{\pi}$-electron system of the 1,2-double bond upon the fluorine of the complex to afford the 2-fluorinated and resonance stabilized carbocation, initially complexed with fluoroborate ion (reaction 2). In the last step (reaction 3), BF_4^- donates F^- to the anomeric carbon. The initial attack of the complex occurs predominantly from the less hindered side of the double bond resulting in a certain degree of stereoselectivity.

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