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THE SYNTHESIS OF GLYCOSYL FLUORIDES USING PYRIDINIUM POLY (HYDROGEN FLUORIDE)

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Partially protected monosaccharides, having the anomeric hydroxyl group underivatized, react with poly(hydrogen fluoride) to yield the corresponding glycosyl fluorides.

The utility of glycosyl fluorides in enzymology¹⁾ and for glycoside synthesis²⁻⁴⁾ has stimulated interest in their preparation³⁻⁶⁾ and chemistry.^{2,5)} The original synthesis⁷⁾ of glycosyl fluorides employed the reaction of peracetylated aldoses with hydrogen fluoride, a reagent now known^{5,8)} to afford 1-deoxy-1-fluoro compounds from a range of carbohydrate derivatives. As well, glycosyl fluorides have been obtained by treatment of an acylated glycosyl chloride or bromide with silver fluoride⁹⁾ or silver tetrafluoroborate.¹⁰⁾

The replacement of the anomeric hydroxyl group by a chlorine or bromine atom has been effected¹¹⁾ readily by reactions involving the intermediacy of oxophosphonium ions. However, the fluorination procedure¹²⁾ for the conversion of alcohols into fluorides by the use of difluorotriphenylphosphorane has been less successful. We now report a synthetic procedure in which the substitution of a free, anomeric hydroxyl group by fluorine can be accomplished without prior activation of the substrate. Specifically, we have found that pyridinium poly(hydrogen fluoride), a reagent introduced by Olah <u>et al.</u>,¹³⁾ efficiently replaces the anomeric hydroxyl group of partially protected monosaccharides by fluorine, to afford the corresponding glycosyl fluorides as the major products. Examples which illustrate the scope of this reaction are given in Table 1. The utilization of Olah's reagent for the fluorination of carbohydrates at sites other than the anomeric carbon failed in a series of experiments with methyl hexopyranosides

Substrate	Product	Yield/%	{a} _D (CHCl ₃)/°	Melting point/°C
BzOCH2 BzO BzO 1	BzOCH2 BzO BzO 8	78.8 [°]	+80.7	
BnocH ₂ Bno OH	Bn0CH2 0 Bn0CF	74 (α)	+21.9	
2	9 Bhoch	58.0 (total)		
	OBn 10	26 (β)	- 9.0	7778
Me2C OCH OCH	Me ₂ C ^{OCH₂} OCH 11	31.4	-12.9	
Ac0 Ac0 Ac0 Ac0 Ac0 Ac0 Ac0 Ac0 Ac0 Ac0	Aco OAc	53	+90.0	102—105
Bno OBn OH 5	Bno Bno 13	82 ^d	+ 9.7	64—64.5
	ACO HZOAC ACO 14	69	+21.4	67—68
Aco CH20Ac QAC O QAC 	Aco CH20Ac 0Ac 15	62	+103.0	

Table 1. Synthesis of Glycosyl Fluorides^{a,b)}

a) Abbreviations: Bz, benzoyl; Bn, benzyl; Ac, acetyl.

b) The assigned structures are supported by ¹H-NMR and ¹⁹F-NMR spectra and,

in the case of new compounds, also by elemental analysis.

c)1 H-NMR data indicated that the ratio of $\alpha-$ and $\beta-isomers$ was ${\color{black}{\sim}}1:1.$

^{d)} A trace of the β -isomer was indicated by the ^lH-NMR spectrum.

or their partially protected derivatives (see Ref. 14).

In a typical procedure pyridinium poly(hydrogen fluoride) (4.2 mL; Aldrich Chemical Co.) was added to a solution of 2,3,5-tri-<u>O</u>-benzoyl-<u>D</u>-ribofuranose (1; 0.834 g) in anhydrous dichloromethane¹⁵⁾ (3.0 mL) and the solution was shaken at room temperature for 10 h¹⁶⁾ in an atmosphere of dry argon. The reaction solution was poured into ice-cold water and immediately extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was purified by column chromatography {silica gel; toluene—ethyl acetate, 20:1 (v/v)} to afford 2,3,5-tri-<u>O</u>-benzoyl- $\alpha\beta$ -<u>D</u>-ribofuranosyl fluoride (8; 0.660 g, 78.8%)¹⁷⁾ as a syrup.

The action of pyridinium poly(hydrogen fluoride) on compounds 3-7 resembles that of anhydrous hydrogen fluoride on peracetylated <u>D</u>-glucopyranose,^{5,7)} and of silver tetrafluoroborate in diethyl ether (when prolonged) on peracetylated α -<u>D</u>glucopyranosyl chloride¹⁰⁾ in that it gives rise to the thermodynamically stable isomer. Moreover, with compounds 4, 6, and 7, Olah's reagent contrasts with both 2,4,6-trimethylpyridinium fluoride¹⁸⁾ and silver fluoride⁹⁾ in affording the α -glycosyl fluoride from a partially acetylated aldose regardless of whether the participating group at C-2 is <u>cis</u>- or <u>trans</u>-related to the fluorine atom.

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- 15) Anhydrous acetone was found to be equally effective in most reactions. The reaction of compound 2 with Olah's reagent required the use of anhydrous acetone or anhydrous dichloromethane—collidine $\{1:1 (v/v)\}$; in the case of compound 4 the addition of collidine was disadvantageous, whereas in the case of compound 5 best results were obtained using anhydrous acetone— collidine $\{1:1 (v/v)\}$ as the solvent. Compounds 6 and 7 were treated using pyridinium poly(hydrogen fluoride) as the only solvent.
- 16) The progress of the reaction was monitored by TLC. Reaction times are unoptimized and varied from 2 h for compound 5 to more than 12 h for 6 and 7.
- 17) Yields are unoptimized and are based on the quantity of product isolated.
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