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Triethylamine Poly(Hydrogen Fluorides) in the Synthesis of a Fluorinated Nucleoside Glycon

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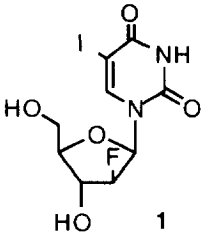
Abstract: The stereospecific synthesis of **6** via a highly selective, noncorrosive fluorination of **4** with $Et_3N{\cdot}3HF$ was discovered. The intermediate fluorosulfonate **5** was isolated, purified and its structure verified.

Selective fluorination at the C-2 (*arabino*) position of a five-membered ring sugar skeleton has attracted much attention in antiviral research.[1] The synthesis of fialuridine (**1**, 2'-deoxy-2'-fluoro-α-D-arabinofuranosyl-5-iodouridine, FIAU) was initiated at Lilly Research Labs in 1992 as an anti-hepatitis B drug candidate.[2] Mitochondrial damage in humans led to suspension of its development.[3] Despite the unfortunate outcome, much progress has been made in the synthesis of fialuridine. Herein, we report the stereospecific introduction of fluorine at the C-2 position.

The original synthesis of fialuridine by Fox and coworkers was based on the use of D-glucose diacetonide as the starting material.[4] The synthesis required 12 steps to prepare the pivotal intermediate, 3-*O*-acetyl-5-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**2**). The fluorination conditions required heating the tosylate ester of D-glucose diacetonide with potassium fluoride in acetamide at 210 °C.



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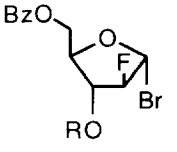
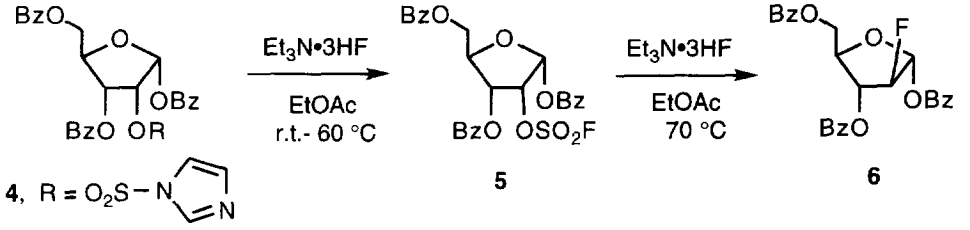


2, R = OAc
3, R = OBz

Another synthesis was developed by chemists at Bristol-Myers.[5] They based their synthesis on a similar intermediate, 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**3**), prepared from D-ribose via an eight step synthesis. Although the overall yield of the Bristol-Myers procedure (ca. 20%) was improved over the Fox procedure (ca. 10%), the fluorination conditions were also corrosive to borosilicate glass and stainless steel reactors, with 1,3,5-tri-*O*-benzoyl-2-imidazolesulfonyl-α-D-ribofuranose (**4**) reacted with potassium hydrogen fluoride and four equivalents of hydrogen fluoride in 2,3-butanediol at 160°C to give 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (**6**). A noncorrosive fluorination method was needed for large scale operations.

We found that the displacement of the imidazolesulfonyl at C-2 by a fluoride ion can be effected by

triethylamine poly(hydrogen fluoride), especially $Et_3N{\bullet}3HF$,[6] in 1,2-dichloroethane (DCE), EtOAc or toluene. The reaction in EtOAc was carried out in a stepwise manner as shown below:



Thus, **4** was converted to the fluorosulfonate derivative **5**[7] with 5-6 equivalents of $Et_3N{\bullet}3HF$ from room temperature to 60 °C. After complete conversion, the temperature was raised to 70 °C to convert **5** to the desired fluorosugar **6**. After recrystallization of **6** in MeOH, the yield of the two-step reaction (shown in Table 1) ranged from 84-88%. The yield reached greater than 90% when 800 kg of **6** was prepared in our manufacturing facilities. The purity of the product (**6**) was greater than 98%.[8]

Table 1. Fluorination of **4**

Solvent	Volume Solvent (L/kg of **4**)	**4** (kg)	**6** (kg)	Yield (%)	Purity (wt %)
DCE	1.87	0.03	0.01875	79.8	98.7
Toluene	2.30	0.03	0.01644	69.9	----[a]
EtOAc	2.00	5.52	3.71	85.8	99.6
EtOAc	2.50	196.5	130.5	84.7	99.5

a) Not determined.

Triethylamine poly(hydrogen fluoride) was found to be relatively noncorrosive to Hastelloy C reactors. Two corrosion studies (160 and 333 hours with $Et_3N{\bullet}3HF$ in EtOAc at 70 °C) with a Hastelloy C coupon indicated that the corrosion rate was 0.13 and 0.17 mil/year, respectively.

We were able to isolate and characterize pure fluorosulfonate **5**. A sample of **5**, contaminated with a small amount of **6**, was purified by silica gel column chromatography to give the first isolated fluorosulfonate compound. The structure of **5** was confirmed by high resolution MS, ^1H, ^{13}C and ^{19}F NMR spectra.[9] The ^{19}F NMR spectrum of **5** in $CDCl_3$ showed a singlet at δ +32.6 ppm (in reference to $CFCl_3$ at δ 0.0 ppm) corresponding to the fluorine atom on the fluorosulfonate.

The fluorosulfonate group in **5** is unique in that it is not only stable but also very reactive in the subsequent fluoride displacement reaction. Also, unlike the C-2 triflate (**8**),[5b] the fluorosulfonate **5** was stable to temperature and organic base, as **5** did not undergo elimination when treated with triethylamine or decompose in refluxing toluene.

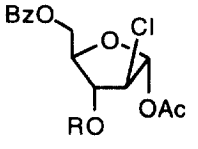
The rate of fluorination was found to depend upon the stoichiometry of the triethylamine poly(hydrogen fluoride) reagent. The rate of the first step (from **4** to **5**) was directly proportional to the weight percent of HF in the fluorinating reagent[5b] whereas the rate dependence of the second step (from **5** to **6**) was inversely

proportional.

We assume that the first step is acid-catalyzed. Taking advantage of this result, we were able to prepare **5** in 93% yield by fluorinating **4** with triethylamine poly(hydrogen fluoride) containing a high HF content (weight percent HF by ion chromatography analysis was 40.2%).[10] However, the displacement of the fluorosulfonate **5** by fluoride ion was influenced by the nucleophilicity of the fluoride ion. A poly(hydrogen fluoride) complex with lower HF content may have been more concentrated with the HF_2^- anionic species than with the $H_2F_3^-$ and $H_3F_4^-$ species.[11] The more nucleophilic HF_2^- anion may be responsible for the high rate of the fluorosulfonate displacement reaction.[12] The more nucleophilic poly(hydrogen fluoride) was prepared by addition of Et_3N to $Et_3N{\cdot}3HF$. The fluorosulfonate **5** was heated with 6 equivalents of $Et_3N{\cdot}3HF$ and 3 equivalents of Et_3N in EtOAc to afford **6** in 3.5 hours.

Fluorination in DCE was inferior to those in EtOAc because of the formation of **7**, a chloro analog of **6**. The chloride source was $Et_3N{\cdot}HCl$, which was produced from β-elimination of HCl from DCE by Et_3N.[13]

The fluorination of **4** to **6** with triethylamine poly(hydrogen fluoride) proceeded with remarkable regio- and stereoselectivity in solvents with such diverse dielectric constants as EtOAc, toluene and DCE. We attribute the high selectivity to an S_N2 nucleophilic substitution of the fluorosulfonate group of **5** via a pentavalent transition state (**9**). However, a nucleophilic displacement via an S_N1 intimate ion pair mechanism has not been ruled out.



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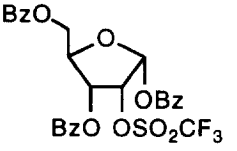

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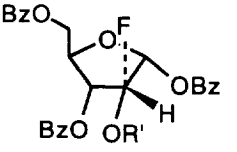

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In conclusion, we have found that $Et_3N{\cdot}3HF$ is a highly efficient fluoride ion source which is noncorrosive to borosilicate glass and Hastelloy C reactors and is suitable for use in large scale fluorination reactions. Spectroscopic data presented confirms that fluorosulfonate **5** is the intermediate in this fluoride ion displacement reaction.

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6. The boiling point of $Et_3N{\cdot}3HF$ is about 78 °C / 1.5 mbar. Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423.
7. H.G. Howell and coworkers speculated that the fluorosulfonate (**5**) was the intermediate involved in their fluorination reaction using aqueous HF and KHF_2 as the fluorinating agents (see reference 5b). The reactions in EtOAc and DCE were homogeneous and were run by the two-step method described. However, the fluorination in toluene was not homogeneous and was run at 70 °C only.
8. The weight percent purity of **6** was determined by HPLC analysis of a CH_3CN solution of the product with various concentrations of standard **6** in CH_3CN. HPLC conditions: Zorbax® RX-C18, 25 cm x 4.6 mm, CH_3CN / H_2O gradient,

1.0 mL / min, λ = 230 nm, injection volume = 20 mL (Courtesy of David K. Robbins of LRL Chemical Process R & D).

9. NMR spectra of **5**: ^{1}H NMR ($CDCl_3$): δ 4.55 (dd, $J_{5,5'}$ = 12 Hz, $J_{4,5}$ = 3 Hz, 1H, H-5); 4.66 (dd, $J_{5,5'}$ = 12 Hz, $J_{4,5}$ = 3 Hz, 1H, H-5'); 4.76 (dt, $J_{4,5} = J_{3,4}$ = 3 Hz, 1H, H-4); 5.46 (dd, $J_{2,3}$ = 6 Hz, $J_{1,2}$ = 4 Hz, 1 H, H-2); 5.74 (dd, $J_{3,4}$ = 3 Hz, $J_{2,3}$ = 6 Hz, 1H, H-3); 6.83 (d, $J_{1,2}$ = 4 Hz, 1H, H-1); 7.28-8.06 (m, aromatic-H). ^{13}C NMR ($CDCl_3$): d 62.5 (C-5); 68.6 (C-3); 78.6 (C-2); 81.6 (C-4); 91.8 (C-1); 127.4-133.1 (aromatic-C); 163.7, 164.5,164.8 (C=O). ^{19}F NMR ($CDCl_3$): d +32.6 (SO_2F). Standards for ^{1}H, ^{13}C and ^{19}F NMR are tetramethylsilane, chloroform and trichlorofluoromethane respectively.
10. Ion chromatography and ion selective electrode (ICE) methods were developed for determining the weight percent of fluoride ion. The weight percent of free HF was determined by NaOH(aq) titration in polypropylene vessels. The average weight percent of F^- from the ion chromatographic assays was 37.8%, which is equal to 3 molar equivalents of F^- in the triethylamine polyhydrogen fluoride. The average weight percent of free HF from the NaOH titration was 25.1%, which is equivalent to 2 molar equivalents of HF in the $Et_3N{\cdot}xHF$. Apparently, NaOH only titrates 2 out of 3 equivalents of the HF in the sample (Courtesy of Thomas K. Lobdell and Donald W. Hodges of LRL Chemical Process R & D).
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12. Giudicelli, M.B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527.
13. The LC-MS data showed two peaks with *m/z*+ ratios of 481 and 483 which correspond to the chlorine isotopes in **7** (Courtesy of Gary G. Cook and Craig A. Kemp of Lilly Research Labs). The β-elimination of HCl from 1,2-dichloroethane was confirmed by preparing **7** by heating the fluorosulfonate **5** in DCE in the presence of Et_3N.

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