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Improved synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA) using triethylamine trihydrofluoride

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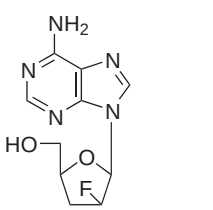
Abstract—An improved synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) via a fluorination of 3′-*O*-benzoyl-5′-*O*-tritylriboside (**4a**) using noncorrosive triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) is described. The method is suitable for large-scale synthesis. In particular, the synthesis of the pivotal intermediate **4a** was much improved in avoidance of the use of toxic tin reagent. Radical deoxygenation with several silanes was also studied. The total yield of FddA from 6-chloropurine riboside (**2**) in this study was greater than that we reported previously.

9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA, lodenosine) is a potent anti-HIV agent,[1] which has significant advantages over non-fluorinated dideoxynucleoside analogs such as dideoxyinosine (ddI, didanosine). One of its most promising advantages is that **1** has been shown to be effective against otherwise resistant HIV strains.[2] Compound **1** is currently being tested in clinical trials for the treatment of AIDS.[1d,3]

FddA has been synthesized by several different methods.[1d,4] A problem in each of these methods is how to introduce a fluorine at C2′-β of the sugar moiety. Most attempts to fluorinate the C2′-β position of nucleoside derivatives lead to a migration or elimination product[5] and give a poor yield,[6] or sometimes even none of the desired fluorinated compound.[1a] Recently, we reported the fluorination of 3′-*O*-benzoyl-5′-*O*-tritylriboside (**4a**) with diethylaminosulfur trifluoride (DAST).[7] The introduction of an electron-withdrawing 6-chloro group to the purine moiety was essential for improving the yield of fluorination, probably because the 6-chloro group decreases the nucleophilicity of purine base and prevents a purine base migration during the fluorination. Although the reaction yield was excellent and neither migration nor elimination occurred, it would be preferable to avoid the use of corrosive DAST in large-scale industrial production.



1 FddA

Chou et al. reported[8a] the large-scale synthesis of C-2 (*arabino*) fluorinated sugar derivatives with noncorrosive triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$).[8b,c] Since the condensation of fluorinated sugar with a nucleic base still presents the problem of the undesired α-anomer formation,[1d,9] we became interested in using $Et_3N{\cdot}3HF$ for fluorination of nucleoside **4a**.[10]

In our previous report,[7] one of the major problems for obtaining the pivotal intermediate **4a** from 6-chloropurine riboside (**2**)[11] was the use of highly toxic dibutyltin oxide during the formation of 3′-*O*-benzoate. Decrease of the reaction yield due to acyl migration between the 2′- and 3′-*O*-benzoyl groups followed by subsequent dibenzoylation[12] was another important

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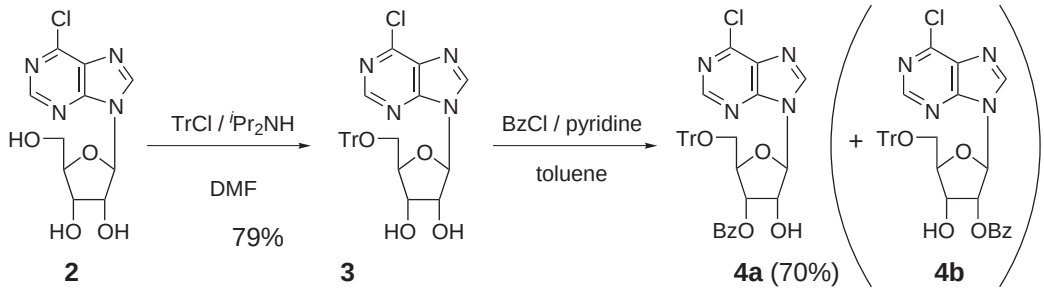


Scheme 1.

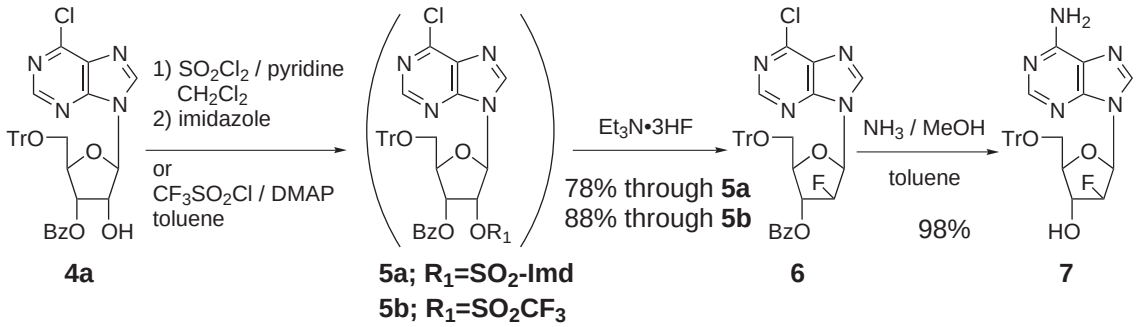
problem. In order to improve the process, the selective tritylation at the 5′-hydroxyl group was performed prior to benzoylation. When we used pyridine as a base for the benzoylation (Scheme 1), undesired dibenzoylation was remarkably suppressed and **4a** was obtained in a moderate yield without using the toxic tin reagent.

Thus, compound **2** was mono-tritylated with 2 equiv. of trityl chloride (TrCl) in the presence of diisopropylamine ($^{i}Pr_2NH$) in *N*,*N*-dimethylformamide (DMF) at 40°C. Small amounts of the 2′,5′- and 3′,5′-di-*O*-tritylated compounds were also formed. The resulting solution was subjected to conventional work-up and the tritylated compound (**3**) was extracted by toluene. Without further purification, compound **3** was benzoylated with an excess amount of benzoyl chloride (BzCl) in the presence of pyridine at 0°C. After conventional work-up and purification by silica gel chromatography, the mixture of **4a** and **4b** was subjected to crystallization to afford pure **4a** as white crystals in 70% yield. Compound **4b** remained in the mother liquor, and was recycled, after the acyl migration from **4b** to **4a**, by treating with triethylamine (Et_3N).

Compound **4a** was fluorinated with $Et_3N{\cdot}3HF$ in two steps, as shown in Scheme 2. Prior to the reaction with $Et_3N{\cdot}3HF$, the 2′-hydroxyl group of **4a** was converted to imidazolesulfonate (**5a**) or trifluoromethanesulfonate (**5b**). We tried to fluorinate the compound having other leaving group, but without success. It was revealed that the 6-chloro group was effective again in preventing a purine base migration and improving the yield of fluorination.

Compound **5a** was reacted with $Et_3N{\cdot}3HF$ in several solvents at 50°C or 70°C (Table 1). High-performance liquid chromatography (HPLC) analysis showed that the yield of fluorinated compound **6** varied from 54 to 78% including imidazolesulfonation.[13] The best result was obtained when toluene was used as the solvent. It has been reported[14] that the addition of 0.5 equiv. of Et_3N to $Et_3N{\cdot}3HF$ enhances the nucleophilicity of the reagent. We also studied the addition of Et_3N (run 2), but the yield of product decreased.

The trifluoromethanesulfonate (**5b**), which was quantitatively obtained from **4a**, was also reacted with 6

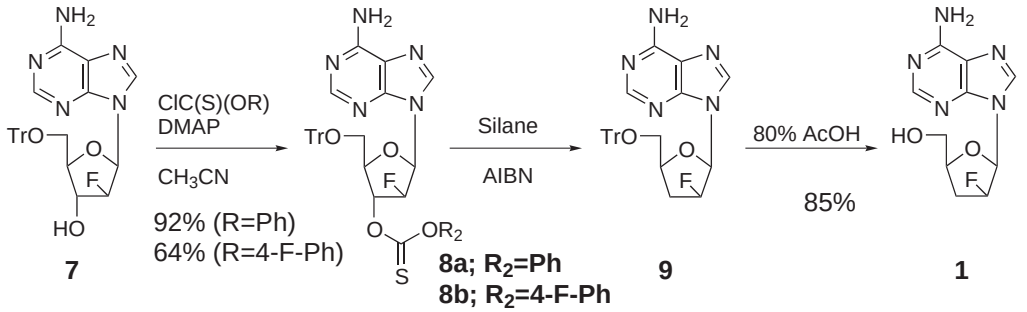


Scheme 2.

Table 1. Fluorination of imidazolesulfonate (**5a**)

Run	Solvent	$Et_3N{\cdot}3HF$ (equiv.)	Et_3N (equiv.)	Temp. (°C)	Time (h)	Yield (%)[a]
1	AcOEt	6.0	–	70	24	67
2	AcOEt	6.0	3.0	70	24	54
3	Toluene	6.0	–	70	24	78
4	CH_3CN	6.0	–	70	24	62
5	CH_2Cl_2	6.0	–	50	24	60

[a] The yield includes imidazolesulfonation of **4a**.



Scheme 3.

Table 2. Deoxygenation of **8a** and **8b** with silanes

Run	R_2	Silane	Solvent	Yield (%)
1	Ph	$[(Me)_3Si]_3SiH$	Toluene	78
2	Ph	Ph_2SiH_2	Dioxane	81
3	Ph	Ph_2SiH_2	Toluene	74
4	Ph	Ph_2MeSiH	Dioxane	69
5	4-F-Ph	Et_3SiH	Dioxane	55
6	4-F-Ph	Et_3SiH	Acetone	56

equiv. of $Et_3N{\cdot}3HF$ and 3 equiv. of Et_3N in ethyl acetate (AcOEt) at reflux temperature overnight.[15] HPLC analysis indicated that the yield of fluorinated compound **6** was 88%. After conventional work-up, a toluene solution of **6** was added to ammonia in methanol and kept in a sealed tube at 100°C for 18 hours. HPLC analysis revealed that the 3′-*O*-deprotected and 6-aminated compound **7** was formed in 98% yield. After purification by silica gel chromatography, pure **7** was obtained as white crystals.

Deoxygenation of the 3′-hydroxyl group in **7** was achieved by the Barton–McCombie method with silane[16] to avoid the use of toxic tin hydride (Scheme 3). Recently, the same radical reduction of β-fluorinated substrates using dilauroyl peroxide has been reported.[4a] Compound **7** was converted with chlorothionoformate to 3′-*O*-thiocarbonyl derivatives **8a** and **8b** in good yield. The products were then subjected to deoxygenation with various silanes in the presence of 2,2′-azobisisobutyronitrile (AIBN). The results are shown in Table 2. Diphenylsilane gave the best results among various silanes. Finally, separation and purification of **9**, followed by acidic hydrolysis of the 5′-*O*-trityl group, gave FddA (**1**) in good yield. Its spectroscopic properties were identical in all respects to the published data.[1]

In conclusion, FddA (**1**) was synthesized in good yield by fluorination with a noncorrosive fluorinating reagent, $Et_3N{\cdot}3HF$, starting from a readily available nucleoside. The method proceeds without using toxic tin reagent for selective benzoylation and deoxygenation. Accordingly, the method is suitable for large-scale synthesis and is environmentally benign. The total yield of FddA (**1**) from 6-chloropurine riboside (**2**) in this study (30.2%) was greater than that we reported previously (13.5%).

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13. A representative experimental procedure is as follows: **4a** (2.0 g, 3.1 mmol) was dissolved in dichloromethane (15.5 ml) and cooled to −35°C. To this solution was added pyridine (0.45 ml, 5.57 mmol) and sulfuryl chloride (0.30 ml, 3.72 mmol), and the mixture was stirred for 30 minutes. Imidazole (0.96 g, 13.9 mmol) was then added, and the resulting mixture was allowed to return to room temperature and stirred overnight. Water (10 ml) was then added for phase separation. The aqueous layer was washed with 10 ml of dichloromethane. The organic layers were combined, dried with sodium sulfate, filtered, and distilled. The residue was purified by silica gel chromatography to obtain the desired compound (oily). The yield was 2.28 g (FW: 763.22, 2.99 mmol, 96%). This imidazolesulfonate (377 mg, 0.494 mmol) was dissolved in toluene (2.4 ml), triethylamine trihydrofluoride (0.49 ml, 3.00 mmol) was added, and the mixture was stirred overnight at 70°C. After cooling, ethyl acetate and an aqueous saturated solution of sodium hydrogencarbonate were added for phase separation. The organic layer was washed with ethyl acetate. The aqueous layers were combined, dried with sodium sulfate, filtered, and then distilled. The residue was dissolved in acetonitrile and analyzed by liquid chromatography, which revealed that **6** was obtained in 81% yield. The analytical sample was purified by silica gel chromatography. Analytical data for compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (1H, s, H-2), 8.36 (1H, d, $J=3.0$ Hz, H-8), 8.07 (2H, d, $J=7.2$ Hz, C_6H_5CO), 7.66 (1H, t, $J=7.3$ Hz, C_6H_5CO), 7.23–7.54 (ca. 17H, m, C_6H_5CO, trityl), 6.66 (1H, dd, $J=21.7$, 2.8 Hz, H-1′), 5.69 (1H, dd, $J=16.9$, 3.2 Hz, H-3′), 5.28 (1H, dd, $J=50.0$, 2.8 Hz, H-2′), 4.41 (1H, m, H-4′), 3.63 (1H, dd, $J=10.3$, 5.9 Hz, H-5′a), 3.54 (1H, dd, $J=10.3$, 4.2 Hz, H-5′b); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 164.9, 152.2, 151.5, 149.8, 146.1 (d, $J=5.1$ Hz), 143.6, 134.2, 129.8, 129.0, 128.9, 128.4, 128.1, 127.3, 93.4 (d, $J=193.2$ Hz), 86.6, 82.7 (d, $J=16.9$ Hz), 79.6, 76.5 (d, $J=27.3$ Hz), 63.4; IR (KBr): ν 3061, 1732, 1592, 1567, 1492, 1450, 1265, 1218, 1092 cm^{-1}; HRMS (FAB+) calcd for $C_{36}H_{29}ClFN_4O_4$ $(M+H)^+$: 635.1861; found: 635.1846. Anal. calcd for $C_{36}H_{29}ClFN_4O_4$: C, 68.08; H, 4.44; Cl, 5.58; F, 2.99; N, 8.82. Found: C, 68.11; H, 4.54; Cl, 5.82; F, 2.65; N, 8.69.
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