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Direct S_NAr amination of fluorinated imidazo[4,5-*c*]-pyridine nucleosides: efficient syntheses of 3-fluoro-3-deazaadenosine analogs

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Abstract—This paper describes the ready preparation of 3,6-difluoro-3-deazapurine (4,7-difluoroimidazo[4,5-*c*]pyridine). This novel base was glycosylated under mild conditions using three different ribose sugar analogs. 3,6-Difluoro-3-deazapurine ribonucleoside analogs underwent direct S_NAr amination reactions with liquid ammonia to give 3-fluoro-3-deazaadenosine analogs in excellent yield; in contrast, 6-chloro-3-fluoro-3-deazapurine nucleosides were inert under similar reaction conditions.

Fluorinated organic molecules perform a wide range of biological functions.[1] In many cases, the introduction of one or more fluorine atoms into biologically important molecules enhances their activity, liphophilicity, bioavailability, and metabolic stability.[2] Accordingly, an enormous amount of work has been performed to prepare fluorinated nucleoside analogs; several of these analogs have been studied in clinical trials and a few have been approved as drugs, including the pancreatic cancer drug Gemcytabine (Gemzar) and the HIV drug 5F-3TC. It was reported[3] quite recently that 7-fluoro-7-deaza-2′-C-methyladenosine **1**, a nucleoside derivative in which a C–F bond appears at the 7-position of 7-deaza-2′-C-methyladenosine **2a** or 2′-C-methyladenosine **2b**, inhibits the replication of hepatitis C virus (HCV) with higher inhibitory potency (EC_{50} = 0.07 μM) than its parent compounds **2a** (EC_{50} = 0.25 μM) and **2b** (EC_{50} = 0.26 μM). 3-Deazaadenosine **3** analogs[4] display broad-spectrum antiviral and anticancer activities, and 3′-deoxyribonucleosides exhibit interesting antiviral, antifungal, antibacterial, antiparasitic, and anticancer properties.[5] Furthermore, ribonucleosides having 2′-β-C-methyl substituents display anti-HCV properties.[6] These findings prompted us to synthesize a series of 3-fluoro-3-deazaadenosine analogs, **4a**–**c**, that combine the 3-fluoro-3-deazapurine heterocycle with the active compounds' ribosugar moieties. The introduction of a C–F bond at the 3-position of purine could not only isosterically mimic the regular adenine and guanine bases but also the 3-deazaadenine and 3-deazaguanine bases (Fig. 1).

Although syntheses of 3-fluoro-3-deazaadenosine (3F-3-deaza-Ad) have been reported,[7] there are difficulties encountered when applying these procedures to the synthesis of modified-sugar analogs of 3F-3-deaza-Ad and, therefore, an efficient and general methodology is desirable. 6-Chloro-3-deazapurine (4-chloroimidazo[4,5-*c*]pyridine) nucleosides are highly inert toward nucleophiles (e.g., ammonia) in S_NAr reactions, which is the main drawback for their use in the synthesis of 3-deaza-Ad analogs.[8] Thus, an alternative two-step synthesis (displacement of the 6-chloro-substituent with hydrazine under reflux conditions and subsequent cleavage of the N–N bond using Raney Ni) for the amination of 6-chloro-3-deazapurine has been developed.[9,10] This approach has its limitations, however, including poor-to-moderate yields and the generation of side products. Moreover, use of hydrazine under reflux is not a condition tolerated by various sugar or base modifications; indeed, Matsuda and co-workers[7a] reported that nucleoside **5a** decomposed when attempting to perform the displacement reaction using hydrazine under reflux (Scheme 1).[11]

Keywords: Nucleosides; 3-Deazaadenosine; S_NAr reactions, Fluorinated nucleosides.
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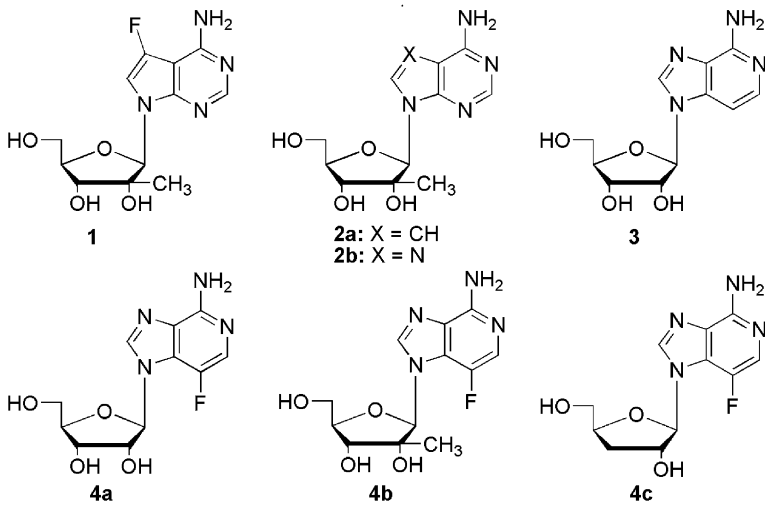
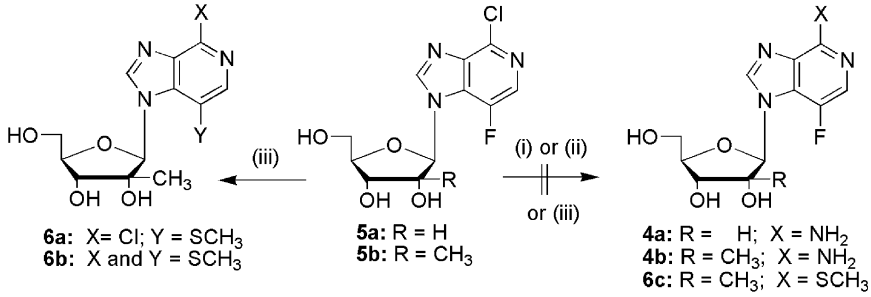


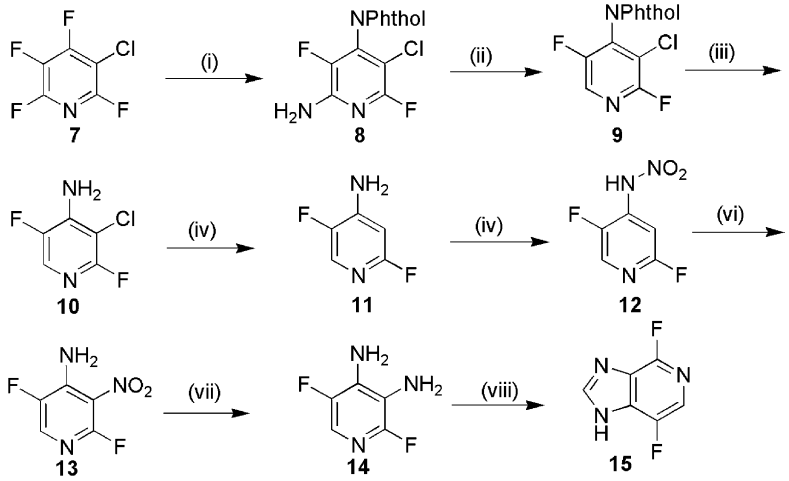
Figure 1. Rationale for the synthesis of target compounds **4a**–**c**.



Scheme 1. Reagents and conditions: (i) (a) hydrazine, reflux; (b) Raney nickel; (ii) liquid NH_3 or MeOH saturated with NH_3 at 0 °C, (iii) NaSMe, DMF.

Likewise, our initial attempts to synthesize 3F-3-deaza-2′-C-Me-Ad **4b** based on performing S_NAr reactions with **5b** were also unsuccessful, but we did gather some useful clues about what would be necessary to design a successful synthetic scheme for the target compounds **4a**–**c**: (i) The starting material was completely recovered when compound **5b** was reacted directly with ammonia nucleophiles, that is, NH_4OH, saturated methanolic NH_3 (MeOH saturated with NH_3 at 0 °C), and liquid NH_3. (ii) In an attempt to realize the classical two-step amination, we heated nucleoside **5b** under reflux with anhydrous hydrazine, but observed only decomposition of the starting material.[7a] (iii) To proceed with Seela's methodology,[10b] we attempted the synthesis of 3-fluoro-6-*S*-methyl-3-deazapurine-2′-C-methylriboside **6c**.[12] When we reacted nucleoside **5b** with sodium thiomethoxide in DMF at room temperature, the products we isolated were, surprisingly, **6a** (52%) and **6b** (17%); their formation reveals that the S_NAr reaction of the 3-fluoro substituent is more facile than that of the 6-chloro substituent.[13] It is well established in the literature[14] that a halogen substitutent adjacent to the N-1 position (the 6-position of purine or 3-deazapurine) is most reactive toward nucleophiles, but it is also well known that fluoride is the best leaving group among the halogens in most S_NAr reactions.[15] In addition, the electron-withdrawing 6-chloro substituent in **5b** may enhance the reactivity of the 3-fluoro substituent by reducing the electron density around the six-membered ring.[16] As a result, the 3-fluoro substituent is easily displaced. By exploiting these observations, facile S_NAr reactivity at the 6-position can be tuned by introducing fluorine substituents at both the 3- and 6-positions. On the basis of these concepts, we investigated the direct S_NAr aminations of 4,7-difluoro-imidazo[4,5-*c*]pyridine nucleosides with NH_3 nucleophiles and, consequently, in this paper we present the efficient and general syntheses of 3F-3-deaza-Ad analogs using direct S_NAr amination.

We synthesized (Scheme 2) 3,6-difluoro-3-deazapurine **15** from commercially available 3-chloro-2,4,5,6-tetrafluoropyridine **7**. The synthesis of *N*-(2-amino-5-chloro-3,6-difluoropyridine-4-yl)phthalimide **8** was realized in three steps from **7** by following a reported procedure.[17] Diazotization of compound **8** using *tert*-butylnitrite in THF produced the deaminated product **9**. Treatment of compound **9** with 28% aqueous ammonium hydroxide at room temperature, followed by catalytic dehalogenation under H_2 (50 psi) using 10% Pd on activated carbon, afforded 4-amino-2,5-difluoro-pyridine **11** (55% overall yield from compound **7**). Gratifyingly, the synthesis of compound **11** from compound **7** required only a single purification by column chromatography after the last step, because all of the synthetic steps proceeded with clean conversions and excellent yields. Compound **11** was nitrated using potassium



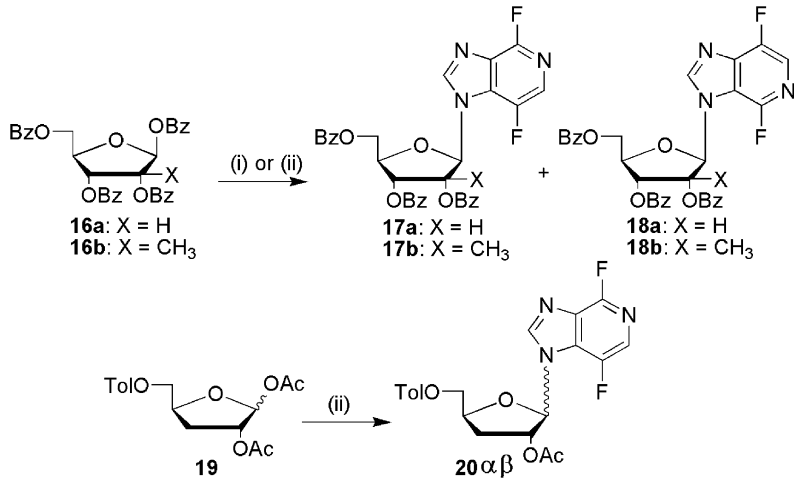
Scheme 2. Reagents and conditions: NPhthol = Phthalimido; (i) See Ref. 17 or Supplementary data; (ii) *tert*-butylnitrite, THF, 60 °C, 1 h; (iii) 28% aqueous NH_4OH, rt, 1.5 h; (iv) 10% Pd/C, 50 psi [H] Et_3N, 24 h; (v) concd H_2SO_4, KNO_3 4 °C to rt, 1.5 h; (vi) concd H_2SO_4, rt, 24 h; (vii) Raney nickel, anhydrous EtOH, 36 psi [H]; (viii) diethoxymethyl acetate, 100 °C, 2 h.

nitrate in concentrated H_2SO_4 to give the nitrated amino compound **12** in 73% yield, which on further reaction with concentrated H_2SO_4 produced 4-amino-2,5-difluoro-3-nitropyridine **13** in 87% yield. Catalytic reduction of **13** under H_2 (36 psi) using Raney Ni produced the diamino compound **14** in 95% yield, which we reacted with diethoxymethyl acetate[18] to give the ring-closed product, 3,6-difluloro-3-deazapurine **15** in 78% yield.

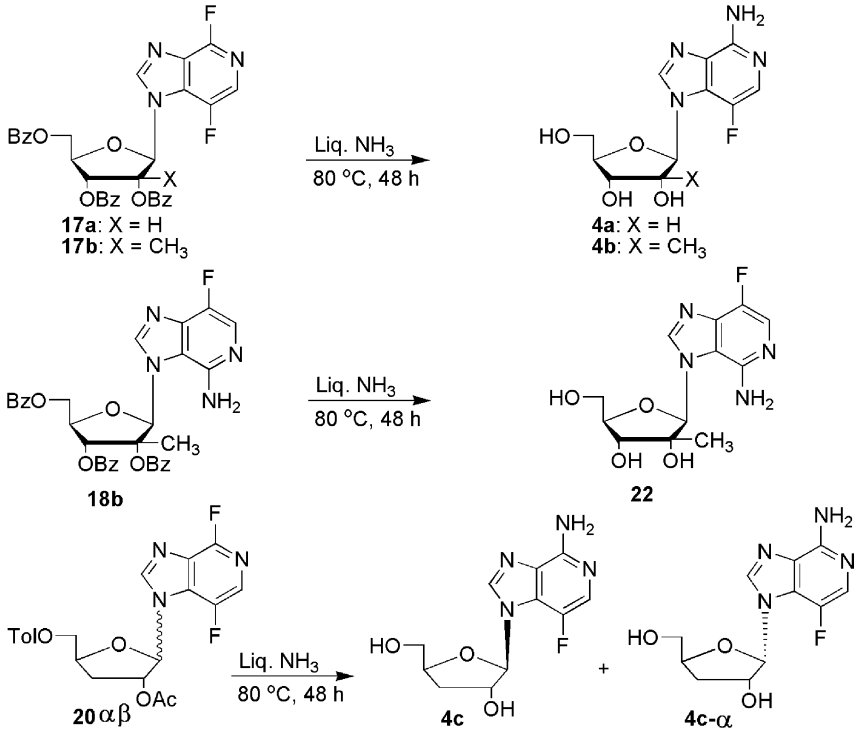
Next we investigated the coupling reactions between base **15** and three different ribosugar analogs: 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose **16a**, 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose **16b**,[19] and 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-3-deoxy-β-D-ribofuranose **19**.[20] The Vorbrüggen-type glycosylation reaction[21] between the silylated base **15** and sugar **16a** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) proceeded smoothly to give **17a** in 70% yield. In contrast, glycosylation reactions between **15** and the 2-*C*-methylribose **16b** failed under both the Vorbrüggen and $SnCl_4$-mediated coupling conditions. The successful coupling of 6-chloropurine and the 2-*C*-methyl sugar **16b** has been reported in the literature[22] when a combination of two coupling reagents, for example, TMSOTf and 1,8-diazabicyclo[4,5,0]undec-7-ene (DBU), was used. Using this procedure, we reacted base **15** with 2-*C*-methylribose **16b** in dichloroethane in the presence of TMSOTf and DBU. After the usual work-up, we isolated the corresponding glycosylated products **17b** and **18b** as a mixture of positional isomers (9-N/7-N = 5:1) in a combined yield of 84%. For comparison, we also realized the coupling reaction between base **15** and ribose sugar **16a** under similar conditions to give a mixture of the corresponding glycosylated products **17a** and **18a** in a 6:1 ratio (82% combined yield). The positional isomers **17** and **18** were readily separated by flash column chromatography (SiO_2; 3% EtOAc in CH_2Cl_2). The major product, the slower-moving one by thin-layer chromatography (TLC), was **17a**, which is also the product obtained under the Vorbrüggen reaction conditions.

In contrast, the coupling reaction between 3′-deoxy sugar analog **19** and base **15** afforded the anomeric mixture **20αβ** (1:2) in 70% yield; we also observed the anomeric mixture of the N-7 positional isomer (ca. 7%) by ^1H NMR spectroscopic analysis of the crude reaction mixture. We isolated the major product (**20αβ**) as a pure mixture (**α/β** = 1:2) by flash column chromatography (SiO_2; 3% EtOAc in CH_2Cl_2) (Scheme 3).

To realize our synthetic goal, we first investigated the direct S_NAr amination of compound **17a**, which we reacted with liquid NH_3 at 80 °C in a steel bomb.[23] After 48 h, we observed complete conversion of **17a** and the only product isolated was indeed 3F-3-deaza-adenosine **4a** (81% yield). Neither a prolonged reaction time (96 h) nor a higher temperature (110 °C) resulted in the formation of the diamino compound. We confirmed the structure of **4a** by comparing its ^1H and ^{13}C NMR and UV spectra with those of a compound synthesized by Matsuda et al.[7a] This comparison revealed that the slower-moving (by TLC), major glycosylation product was the N-9 positional isomer. To generalize this direct amination reaction, we subjected compounds **17b** and **18b** independently to similar reactions with liquid NH_3 to give **4b** (88%) and **22** (72%), respectively. The assignment of the positional isomers **4b** and **22** is based on the UV absorption spectra of these derivatives:[24] the N-9 positional isomer **4b** displayed its λ_{max} at 269 nm while the undesired (N-7) isomer **22** exhibited λ_{max} at 295 nm. In addition, the value of λ_{max} of **4b** is consistent with that obtained for compound **4a**. In their ^1H NMR spectra, the 8-H protons of the N-9 isomers are always located downfield (ca. 0.1 ppm) relative to the 8-H protons of the N-7 isomers. These data are consistent with those reported for other 3-deazapurine nucleosides.[24] We reacted the pure mixture **20αβ** with liquid NH_3 in a similar fashion to give a mixture of **4c** and **4c-α** in 85% yield after separation by reverse-phase HPLC. We confirmed the glycosylation site and the anomeric configurations of **4c** and **4c-α** by using UV and ^1H NMR spectral data, which are



Scheme 3. Reagents and conditions: (i) (a) compound **15**, HMDS, cat. ammonium sulfate, reflux 3 h; (b) dichloroethane, TMSOTf, rt, 12 h; (ii) compound **15**, DBU, TMSOTf, dichloroethane, 0 °C to rt, 24 h.



Scheme 4.

comparable to those reported for 3′-deoxy-3-deaza-Ad (Scheme 4).[25]

In summary, we have executed an efficient synthesis of a novel base, 3,6-difluoro-3-deazapurine. This base was glycosylated under mild conditions using three different ribose sugar analogs. Our studies on the direct S_NAr amination reactions of fluorinated imidazo[4,5-*c*]pyridine nucleosides have yielded an efficient and generalized methodology for the synthesis of such biologically important molecules as 3-fluoro-3-deazaadenosine analogs. A study of the biological properties of these nucleosides will be published in due course.

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Supplementary data

The supplementary data available online with the paper in ScienceDirect. Supplementary data contains experimental procedures and characterization data of all the compounds. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.03.190.

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