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An improved synthesis of 5′-fluoro-5′-deoxyadenosines

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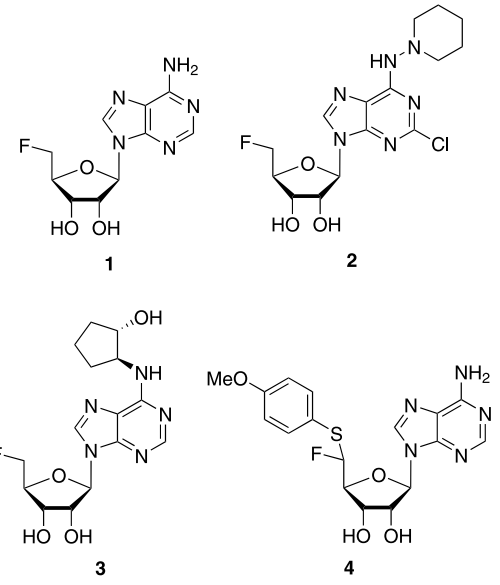
Abstract—Synthesis of 5′-fluoro-5′-deoxyadenosine (5′-FDA) and structurally similar compounds is generally a poor yielding process. This is attributed to the instability of the selected synthetic intermediates. Herein, we report a general synthesis of 5′-fluoro-5′-deoxy-N^6-substituted adenosines including a high yielding access to 5′-FDA.

Adenosine derivatives containing 5′-fluoro-5′-deoxy modifications are increasingly prevalent in current literature. Specifically, 5′-fluoro-5′-deoxyadenosine (5′-FDA, **1**) has been utilized commonly as a tool for studying the Actinomycete bacterium *Streptomyces cattleya*;[1–3] consequently, varying syntheses have appeared. Coupled with other structural features, some 5′-FDA have also been reported to act as adenosine receptor agonists with potential applications in the treatment of cytokine related disorders (e.g., **2**), and as anti-lipolytic agents (e.g., **3**).[4–6] Certain 5′-FDAs also act as inhibitors of the enzyme, *S*-adenosyl-L-homocysteine hydrolase (e.g., **4**).[7]

Three main methods have been employed in the synthesis of 5′-FDA and related compounds: enzymatic cell-free biosynthesis from *S*-adenosyl-L-methionine (SAM),[8,9] Vorbrüggen's conditions (ribosylation reaction),[6,10] which involves coupling of an appropriate fluorinated ribose unit to the adenine ring system, and finally fluorination of the 5′-alcohol.[1,2] Fluorination is generally the preferred method as the starting materials are readily available nucleosides or related derivatives.

Generally, fluorination procedures involve conversion of the 5′-alcohol (of an 2′,3′-isopropylidenated adenosine or derivative) to the corresponding sulfonate leaving group, usually the tosylate or mesylate. This is then followed by substitution using a suitable fluoride nucleophile under S_N2 conditions. These syntheses typically result in poor yields of the desired 5′-fluorinated product. The leaving groups were generally incorporated in good yield (52–83%),[1,2,11] however, once subjected to substitution conditions the yields decreased significantly (35–46%).[1,2] The 5′-sulfonates are regarded as poor precursors for nucleophilic substitution.[11] A number of factors contribute to the decreased efficiency of the synthesis. The instability of the sulfonated intermediates has been demonstrated,[11–13] with intramolecular cyclization of the 5′-carbon and N3-position of the



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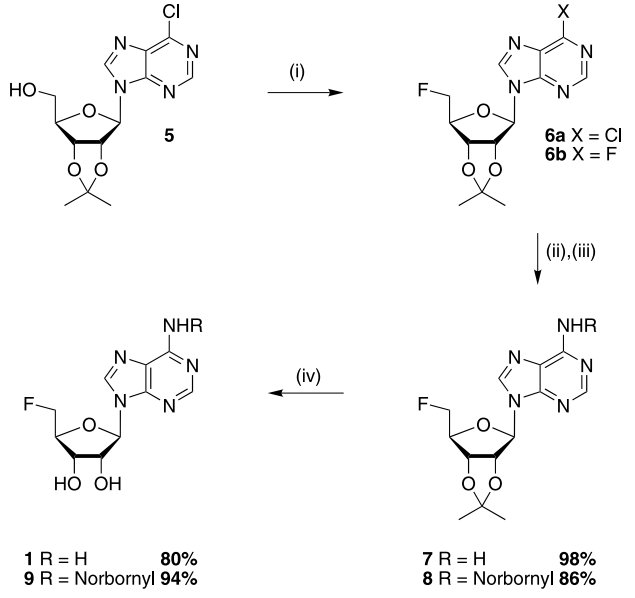
adenine ring the likely pathway. Activation of this process is due to the lone pair on the *exo*-cyclic N^6-nitrogen. The effect of this lone pair can be reduced via functionalization as the N^6-benzoyl; however, this results in the lengthening of syntheses.

As part of our current research, we required an efficient route toward N^6-substituted 5′-FDA derivatives. Given the influence of the N^6 nitrogen, it was envisaged that an electron withdrawing group in the 6-position would negate the formation of any intramolecular cyclized product. Employing a chlorine moiety as the electron withdrawing group in this instance had the advantage of being a common starting point for N^6-substitution products.

Our synthesis begins with the 2′,3′-isopropylidene-6-chloropurine riboside (**5**, Scheme 1) which is easily prepared from 6-chloropurine riboside or purchased directly.[14] The free alcohol was converted to the primary fluoride by refluxing in THF with tosyl fluoride (TsF) and tetrabutylammonium fluoride (TBAF) using the method of Schimizu.[15,16] It was considered that the generation of the cyclized by-product could be further minimized by generating the tosylate in the presence of excess fluoride. This reaction proceeded in very good yield (87%), based on the conversion to the primary fluoride. Substitution at the 6-position of **5** was also observed, however, the resultant aryl fluoride (**6b**) was also reactive toward substitution. Therefore, **6a** and **6b** were obtained as a mixture and carried through forthcoming reactions.

The mixture of **6a** and **6b** was then aminated smoothly by heating in a *t*-BuOH solution saturated with NH_3. The sterically hindered solvent (*t*-BuOH) was chosen to minimize any possible formation of 6-alkoxy products. The desired 2′,3′-isopropylidenated 5′-FDA (**7**) was formed in excellent yield, 98%. Deprotection to give **9** is then achieved in good yield (80%) using 90% trifluoroacetic acid (TFA) as per Cadicamo.[2] From commercially available starting material, 5′-FDA was synthesized in 68% over 3 steps.



Scheme 1. Reagents and conditions: (i) TsF, TBAF, THF, 66 °C; (ii) NH_3, *t*-BuOH, sealed tube, 85 °C; (iii) (±)-*endo*-norborn-2-yl amine·HCl, $N(i\text{-Pr})_2Et$, *t*-BuOH, 83 °C; (iv) TFA (90%), rt.

The desired N^6-substituted product was then conveniently produced from **6a/b** using the (±)-*endo*-norborn-2-yl amine hydrochloride salt in refluxing *t*-BuOH in the presence of Hünigs base ($N(i\text{-Pr})_2Et$) to give **8** in 86% yield. Deprotection was efficiently achieved using 90% TFA, generating 5′-fluoro-5′-deoxy-N^6-(*endo*-norborn-2-yl)adenosine (**9**) in excellent yield, 94%. Over the 3 steps the N^6-substituted 5′-FDA was produced in an overall yield of 70%.

This work represents an efficient entrance to N^6-substituted 5′-FDAs, including a high yielding synthesis of 5′-FDA. Overall yield was 68% over 3 steps from commercially available starting material, **5**, compared with 24% over the same number of steps.[1] Employing readily available starting materials, the formation of the primary fluoride is achieved in a single step. The potential for the formation of a cyclized by-product is deleted via an electron withdrawing group in the 6-position. This approach also provides divergent access to N^6-substituted analogs.

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16. To a stirred solution containing 0.272 g (0.833 mmol) of **5** in 7.5 mL of dry THF was added 0.290 g (1.667 mmol, 2.0 equiv) of TsF, followed by 2.5 mL (2.500 mmol, 3.0 equiv.) of 1 M TBAF in THF and heated at reflux. After 18.5 h the reaction mixture was filtered over a pad of SiO_2 and washed with EtOAc. Concentration of this solution and subsequent column chromatography (hexane/EtOAc, 1:1) gave 0.235 g (0.726 mmol, 87.2% conversion to primary fluoride) of **6a**:**6b** as a yellow oil in a 2.2:1 ratio. A sealed tube was charged with 0.188 g (0.582 mmol) of **6a**:**6b** (1.76:1) and dissolved in 6 mL of *t*-BuOH. NH_3 gas was then bubbled through the solution for 5 min, after which time the tube was sealed and heated at 90 °C for 24 h. The reaction mixture was reduced in vacuo then taken up in $CHCl_3$ (40 mL) and washed using H_2O (30 mL) which was extracted with a further 40 mL of $CHCl_3$. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 0.177 g (0.572 mmol, 98.3%) of **7** as an off white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, H-2/8, 1H), 7.96 (s, H-8/2, 1H), 6.21 (d, J = 2.1 Hz, H-1′, 1H), 5.75 (br s, NH_2, 2H), 5.37 (dm, J = 6.2 Hz, H-2′, 1H), 5.10 (dd, J = 6.2 and 3.0 Hz, H-3′, 1H), 4.76–4.48 (m, H-4′, H-5a′, H-5b′, 3H), 1.65 (s, CH_3, 3H), 1.41 (s, CH_3, 3H).