Communications

Regioselective Fluorination of Substituted Guanines with Dilute F_2: A Facile Entry to 8-Fluoroguanine Derivatives

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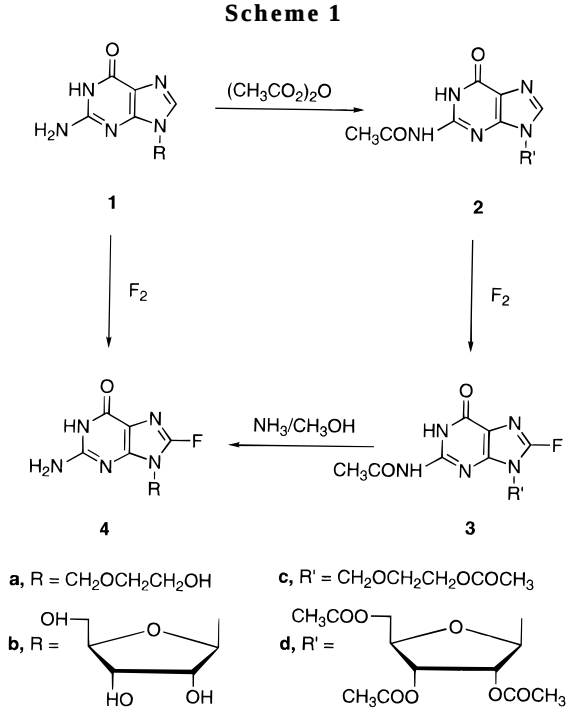
Received April 26, 1996 (Revised Manuscript Received July 8, 1996)

We wish to report the first direct fluorination of guanine derivatives with dilute F_2 for the synthesis of 8-fluoroguanines. When 9-substituted guanines (**1** and **2**) were reacted with elemental fluorine (1% in helium) a clean reaction took place and the 8-fluoro-9-substituted guanines **4** and **3**, respectively, were isolated (Scheme 1). Earlier approaches to 8-fluoropurines have been limited to a few reports, involving nucleophilic displacements,[1,2] Schiemann reactions,[3] halogen exchange reactions,[4,5] and electrochemical oxidations.[6] Driven by the interest generated in their potential antitumor and antiviral activities,[7] however, several other fluoropurines (and their nucleosides) with fluorine substituted at the 2- and 6-position of the purine ring system[5,8] or the sugar moiety[9] have been synthesized. Nevertheless, none of the synthetic methods involved the use of elemental fluorine or similar reagents (e.g., acetyl hypofluorite[10]) that have been successfully used in the synthesis of substituted and unsubstituted 5-fluorouracil and 5-fluorocytosine.[8a,11] Indeed, an attempted fluorination of an oxopurine with phosphoryl fluoride was unsuccessful.[12]

In a typical experiment, F_2[13] (1% in He, 0.6 mmol) was bubbled into a solution of N^2,2′,3′,5′-tetraacetylguanosine

Scheme 1



(**2d**)[14a] or N^2-acetyl-9-[(2-acetoxyethoxy)methyl]guanine (**2c**)[15] (0.4 mmol) in $CHCl_3$ (6 mL) or CH_3CN (15 mL) at room temperature over a period of 1 h. The reaction mixture was concentrated and chromatographed (silica gel). Appropriate fractions were collected and the solvents evaporated to afford the 8-fluoro derivatives **3d** and **3c**, respectively, in 30% yields. Deprotection with methanolic ammonia[14b] afforded the nucleoside analogs **4b** and **4a** in 40% yields. Similarly, the direct fluorination of guanosine (**1b**) and 9-[(2-hydroxyethoxy)methyl]guanine (**1a**, acyclovir, Zovirax)[17] in absolute EtOH and tetraethylammonium hydroxide also proceeded smoothly to yield the corresponding 8-fluoro derivatives **4a** and **4b** in 10 and 7% isolated yields, respectively (52 and 46% based on the recovered starting material). Remarkably, substitution of the C(8) hydrogen with the fluorine atom was the only isolated product. Proton NMR, ^{19}F NMR, and high-resolution mass spectra fully support the structure of the products (**3c**, **3d**, **4a**, **4b**).[18] 8-Fluoro substitution also induced a bathochromic shift of the largest $\pi \rightarrow \pi^*$ transition (e.g., **4a** [$\lambda_{max}(H_2O)$: 242 nm (ϵ 9530), 275 (7100)] vs **1a** [$\lambda_{max}(H_2O)$: 252 nm (ϵ 14 570), 275, sh (9600)].

The progress of the conversion of **1** (and **2**) to **4** (and **3**), respectively, was conveniently monitored by ^1H and

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(18) Products **4a** and **4b** were further purified by preparative HPLC (column: Alltech Econosil C-18, 50 × 1 cm, 5 μm, mobile phase: 5% CH_3OH in water, flow rate: 5 mL/min). Products **3c** and **3d** were purified by flash chromatography [silica gel, $CHCl_3$:CH_3OH (95:5) for **3c** and (98:2) for **3d**]. The fluoro analogs **4a**, **4b**, **3c**, and **3d** all gave satisfactory ^1H and ^{19}F NMR and high-resolution mass spectra.

S0022-3263(96)00761-X CCC: $12.00

^{19}F NMR. For example, in the direct fluorination of **1a**, disappearance of the C(8) hydrogen singlet at 7.76 ppm (CD_3OD/TMS) offers easy monitoring of the fluorination reaction, which can be confirmed by appearance of a singlet at −108.2 ppm ($CD_3OD/CFCl_3$) in the ^{19}F NMR, in agreement with previous assignments of fluorine chemical shifts for 8-fluorotheophylline,[2] 8-fluorocaffeine,[2,6] and 2-amino-6,8-difluoro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine.[5] A relatively slow rate of bubbling of dilute fluorine (∼5−10 μmol/min) was found sufficient to assure optimal regiospecificity of fluorination[19] without resorting to the directing effects of group IVA metals (Si, Ge, Sn).[20,21] The transition state of electrophilic fluorination reactions are favored by polar solvents.[22] Further, polar solvents can act as acceptors for the counterion of the electrophile (fluoride ion).[22] The overall result is the lowering of the activation energy of the transition state intermediate below that of the homolytical cleavage of the F−F bond.[22,23] Under these conditions the regiospecific substitution of the C-8 hydrogen of guanine derivatives (**1a**, **1b**, **2c**, **2d**) was well controlled.

It is quite striking to find that electrophilic fluorinations on purines with elemental fluorine are essentially unknown. This is particularly noticeable in light of (a) the successful use of chlorine, iodine, and particularly bromine for selective halogenation of the 8-position of a large variety of purines[12] and (b) the severely limited procedures, as well as their narrow scope, for access to 8-fluoropurines.[1−6] As a result, only very little information is available on the biochemical and pharmacological properties (e.g., antiviral, anticancer activities) of 8-fluoropurine derivatives.[24] To evaluate initially the importance of 8-fluoro substitution on the biological activity of substituted guanines, we determined the ability of the 8-fluoroacycloguanine **4a** to serve as a substrate for Herpes virus simplex-1 thymidine kinase (HSV tk), as reported elsewhere.[25] The fluoro analog **4a** blocked incorporation of [^{3}H]acyclovir (about six times more efficiently than **1a**) into K1735M2 murine melanoma cells expressing the HSV tk gene and selectively killed cells expressing HSV tk, suggesting that **4a** is a functional substrate for the enzyme.[25]

The syntheses of 8-fluoro-9-substituted guanine derivatives reported in this work are examples of a very general and broadly applicable methodology for the synthesis of otherwise inaccessible 8-fluoropurine derivatives. The scope and limitations of the electrophilic fluorination of substituted purines are currently being investigated.

Acknowledgment. This work was supported in part by Department of Energy Grant DE-FC0387-ER60615 and donations for the Jennifer Jones Simon and Ahmansons Foundations.

Supporting Information Available: Typical fluorination procedure and spectral data are provided (2 pages).

JO960761D

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