Direct heptafluoropropylation of purines with bis(heptafluorobutyryl) peroxide

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Abstract

Some silylated purines react with bis(perfluorobutyryl) peroxide to provide ring-C_3F_7 derivatives. The introduction of the C_3F_7 group occurs predominantly at C-8: 6-methoxypurine also gave the C-2 isomer in isolable yield. Replacement of the 6-amino group of adenine with dimethylamino or methoxy improved the yields of the C_3F_7 derivatives.

Introduction

In the preceding paper of this series [1], we described the facile synthesis of 5-perfluoroalkylpyrimidines and their nucleosides by reaction of the fully silylated derivatives with bis(perfluoroalkanoyl) peroxides. These perfluoroalkylpyrimidines are of interest because of their potential biological activities, as well as their use as precursors to other fluorine-containing pyrimidines [2]. For the same reasons, we have now explored the use of bis(perfluoroalkanoyl) peroxides for the synthesis of perfluoroalkyl purines. To our knowledge, the only previous work in this direction involves the replacement of a halogen at C-8 of purines and of their nucleosides by the trifluoromethyl group, using trifluoromethyl iodide and copper powder [3]. Since we had already demonstrated that homologous perfluoroalkyl derivatives of pyrimidines are readily obtained by variation in the chain length of the peroxide [1], we have limited our present study to the incorporation of the heptafluoropropyl residue as a prototype of the general method.

Results and discussion

The product of the silylation of adenine with chlorotrimethylsilane was treated with bis(heptafluorobutyryl) peroxide, but only starting material was recovered following hydrolytic deprotection. However, more extensive silylation of adenine with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) proved to be moderately effective and 7.7% of 8-(heptafluoropropyl)adenine (**3a**) was obtained, together with 0.77% of the 2-heptafluoropropyl isomer (**4a**) (Scheme 1, Table 1) [4]. In contrast to the very low solubility of adenine in both water and organic solvents, introduction of the heptafluoropropyl group increases the solubility considerably in organic solvents such as ethyl acetate. The major isomer **3a** could be purified by silica gel chromatography, while the minor isomer (**4a**) was obtained as a mixture with **3a**, and the yield of **4a** was determined by ^{19}F NMR spectroscopy. Because N–Si bonds are more moisture-sensitive than O–Si bonds, we could not detect Me_3Si-purine intermediates by mass spectrometry (MS). Even in cases of silylation by the more stable Bu^tMe_2Si group, no heptafluoropropylated Bu^tMe_2Si-purines were detected. Accordingly, silylated intermediates were hydrolyzed prior to isolation or purification of products. The reaction led to the formation of a considerable amount of yellow amorphous material which was not further investigated because it showed no fluorine peaks in the ^{19}F NMR spectrum.

Structural assignment is based on the observation that the H-8 signal, in the ^1H NMR spectra of adenine and its derivatives, appears at slightly higher field than that of H-2; however, the difference in δ value is insufficient to inspire confidence and our assignments must therefore be considered tentative*. Previously, it

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*Preliminary examination of the ^{13}C NMR spectra failed to provide more conclusive assignments.

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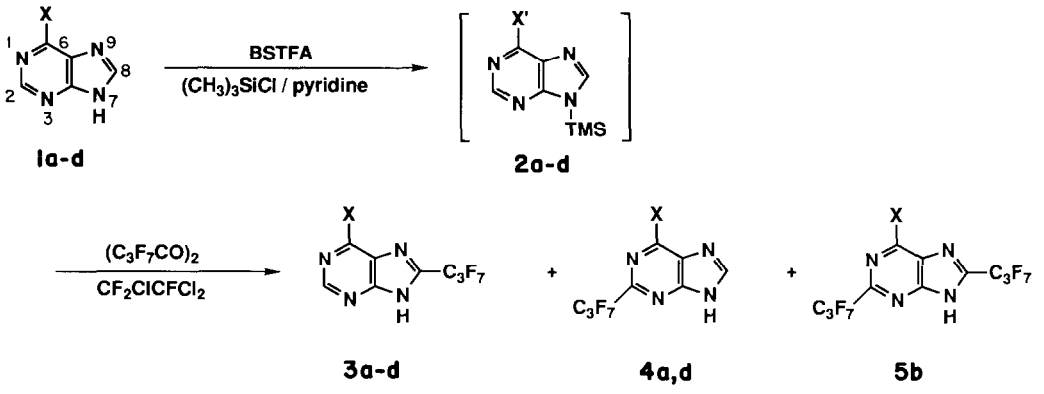


1a-d 2a-d 3a-d 4a,d 5b

BSTFA : $CF_3C[=NSi(CH_3)_3]OSi(CH_3)_3$

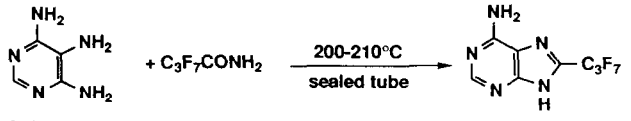
a, X = NH_2, X'= $NHSi(CH_3)_2$; **b**, X = X'= NHAc; **c**, X = X'= $N(CH_3)_2$; **d**, X = X'= OCH_3;

Scheme 1.

TABLE 1. Reaction of protected purines with bis(perfluorobutyryl) peroxide[a]

Compound	Yield of product (%)[b]		
	3	4	5
1a	7.7	0.77[c]	–
1b	8.1	–	trace[d]
1c	17.5	–	–
1d	14.7	5.8	–

[a]For reaction conditions, see Experimental section.
[b]Isolated yield based on purines.
[c]Determined by ^{19}F NMR spectroscopy.
[d]Detected by mass spectrometry.



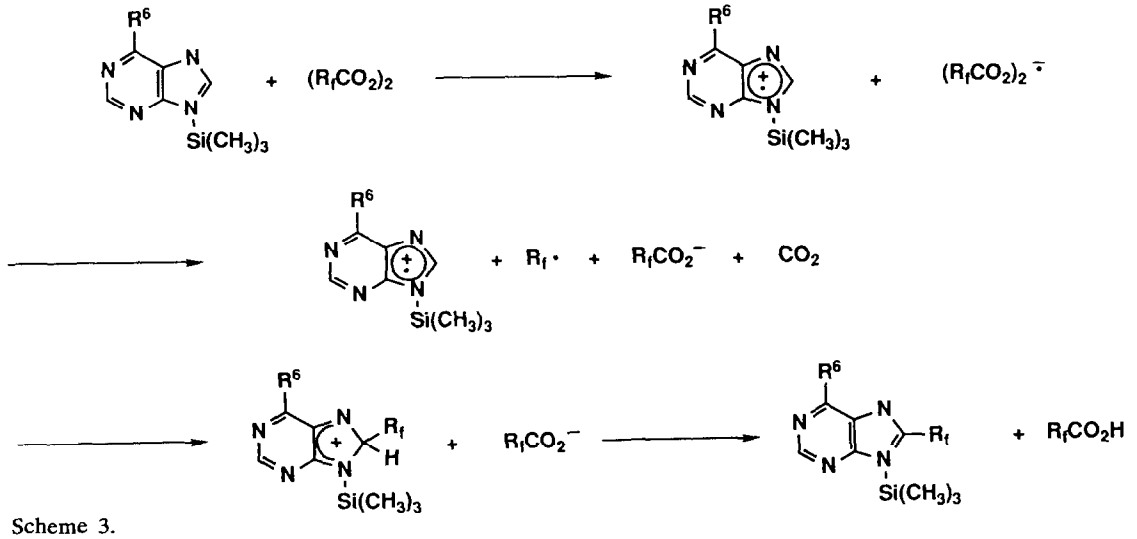
Scheme 2.

was reported that thermal condensation of 4,5,6-triaminopyrimidine with trifluoroacetamide provided only 8-(trifluoromethyl)adenine [5]. In order to confirm the structure of **3a**, we performed an analogous condensation of 4,5,6-triaminopyrimidine sulfate with heptafluorobutyramide (Scheme 2). At 175–180 °C, the condensation failed because the amide sublimed out of the reaction mixture. In a glass ampoule under vacuum at 200–210 °C, the mixture of pyrimidine and amide provided 8-(heptafluoropropyl)adenine in a 7.3% yield; this product coincided with **3a** in all respects.

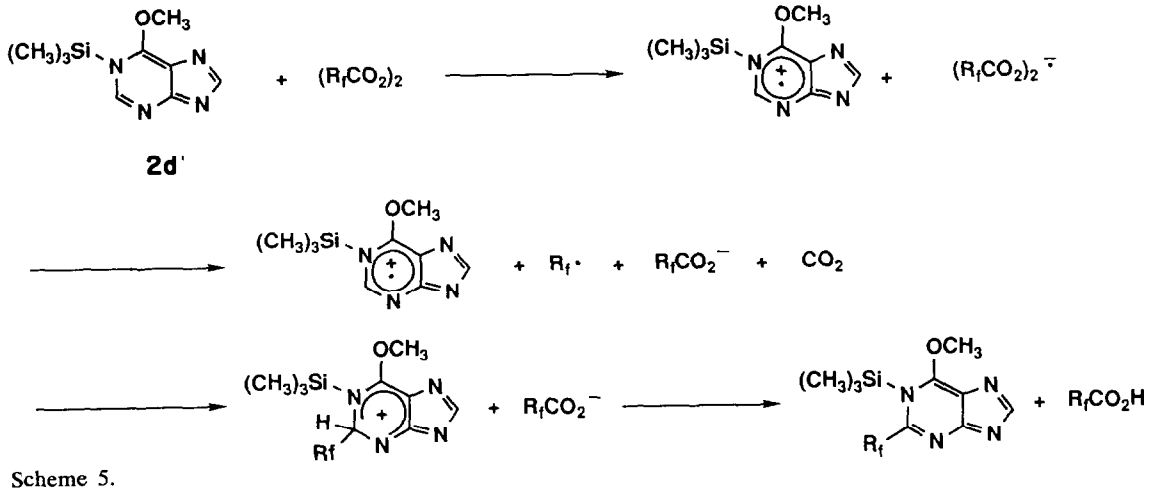
In the case of N^6-acetyladenine (**1b**), perfluoroalkylation occurs at C-8 in 8.1% yield (**3b**); a minor by-product was considered to be the 2,8-bis derivative (**5b**) on the basis of its mass spectrum, but no evidence for the C-2 isomer was found. However, 6-(dimethylamino)purine (**1c**) gave an 18% yield of the C-8 isomer (**3c**) as the only isolable product. In contrast, 6-methoxypurine (**1d**) gave modest yields of both the C-8 isomer (**3d**) and the C-2 isomer (**4d**). The structures of **3d** and **4d** were assigned by comparison of ^1H and ^{19}F chemical shifts with those of **3a** and **4a**. Protection of the amino group of adenine with acetyl had little effect on the product yield, but replacement of the amino group by dimethylamino or methoxy resulted in a doubling of the yield of the 8-heptafluoropropyl derivative. By analogy with other heteroaromatic ring systems [1, 6], perfluoroalkylation of silylated purines is considered to begin with a single electron transfer (SET) mechanism (Scheme 3). Thus, the availability of a dissociable hydrogen on R^6 (**1a**, **1b**) may lead to reduced reactivity in the subsequent coupling step. The reason for a more competitive yield of **4d** is not obvious, although ^1H NMR spectroscopy suggested the presence of isomeric silyl derivatives (**2d**, **2d'**) in the silylation mixture (Scheme 4).

The silylated derivatives of hypoxanthine (**6e**, Scheme 5) gave some fluorinated products, but these compounds showed no ring heptafluoropropyl peaks and could not be separated by silica gel chromatography without decomposition while that of xanthine (**6f**) failed to give any fluorinated product. The product of the silylation of guanine (**6g**) provided 8.4% of the 8-(heptafluoropropyl) derivative (**7g**), together with a more complex product whose structure is under investigation.

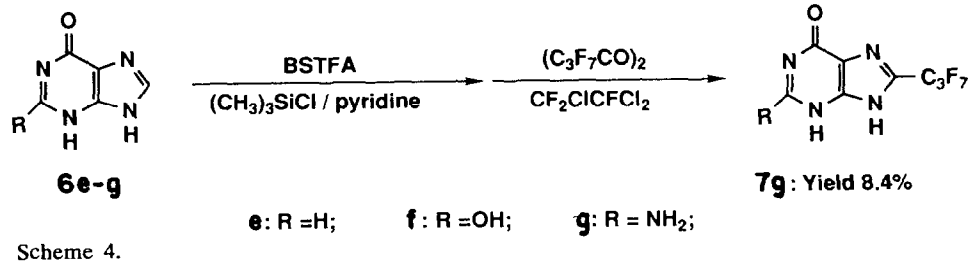
Although quite reasonable yields were obtained in the perfluoroalkylation of persilylated uridines [1], similar efforts in the purine nucleoside series have thus far given only traces of fluorine-containing products according to ^{19}F NMR spectroscopy, but all these products decomposed during silica gel chromatography.



Scheme 3.



Scheme 5.



Scheme 4.

While the overall yields of (perfluoroalkyl)purines are less impressive than those of pyrimidines, we have demonstrated that such compounds are accessible in sufficient quantity for further transformations and for biological studies.

Experimental

The general methods employed were the same as those described in the preceding paper [1] of this series.

General procedure for the heptafluoropropylation of purines with bis(heptafluorobutyryl) peroxide

To adenine (**1a**) (0.81 g, 5.99 mmol) in a 100 ml flask was added BSTFA (5 ml, 18.8 mmol), pyridine (0.5 ml) and chlorotrimethylsilane (3 drops) in the order given. The reaction mixture was stirred under argon at 100 °C for 1 h, at which time the solution was clear. Unreacted BSTFA, trifluoroacetamide and low-boiling materials were removed at 60 °C and 10–20 mmHg. The residual light yellow oil was dissolved in 30 ml Freon-113 and this solution was added to a 5.1% solution (60.09 g, 7.19 mmol) of bis(heptafluorobutyryl) peroxide in Freon-113. The reaction mixture was stirred at 30 °C for 2 h and was then heated at reflux for 1 h to form an orange suspension. The reaction mixture was evaporated *in vacuo* and the residual yellow orange oil hydrolyzed by addition of water (100 ml) and ethyl acetate (100 ml). The aqueous layer was neutralized with $NaHCO_3$ and extracted with ethyl acetate (4×100 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residual brown amorphous solid was subjected to silica gel chromatography (eluent: ethyl acetate); appropriate fractions were combined, evaporated to dryness and the residual solids were washed with ether and hexane.

8-(Heptafluoropropyl)adenine (**3a**) (nc): eluent, EtOAc; colorless needles (EtOAc); m.p. 290-295 °C (dec.). IR (cm^{-1}): 3480, 3330, 3140 (NH); 1350 (CF_3); 1220 (CF_2). ^1H NMR (acetone-d_6) δ: 7.6 (br s, NH_2); 8.40 (s, H-2) ppm. ^{19}F NMR (acetone-d_6) δ: −3.19 (t, 3F, J=9.9 Hz, γ-CF_3); −34.29 (q, 2F, J=9.9 Hz, α-CF_2); −49.16 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 303 (M^+, 77); 284 (12); 184 (100). Elemental analysis: Calc. for $C_8H_4F_7N_5$: C, 31.70; H, 1.33; N, 23.10%. Found: C, 31.57; H, 1.37; N, 23.50%.

2-(Heptafluoropropyl)adenine (**4a**) (nc): eluent, EtOAc. IR (cm^{-1}): 3490, 3330, 3190 (NH); 1345 (CF_3); 1235 (CF_2). ^1H NMR (acetone-d_6) δ: 7.4 (br s, NH_2); 8.29 (s, H-8) ppm. ^{19}F NMR (acetone-d_6) δ: −3.40 (t, 3F, J=9.9 Hz, γ-CF_3); −36.42 (q, 2F, J=9.9 Hz, α-CF_2); −48.69 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 303 (M^+, 100); 284 (16); 184 (81).

N^6-Acetyl-8-(heptafluoropropyl)adenine (**3b**) (nc): eluent, EtOAc; colorless needles (EtOAc); m.p. 237–238 °C. IR (cm^{-1}): 3290, 2950 (NH); 1720 (C=O); 1340 (CF_3); 1220 (CF_2). ^1H NMR (acetone-d_6) δ: 2.43 (s, CH_3CO); 8.63 (s, H-2); 10.8 (br s, NH) ppm. ^{19}F NMR (acetone-d_6) δ: −3.43 (t, 3F, J=7.4 Hz, γ-CF_3); −36.27 (m, 2F, α-CF_2); −48.72 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 345 (M^+, 41); 303 (92); 284 (14); 184 (100). HRMS *m/z*: Calc. for $C_{10}H_6F_7N_5O$: 345.0460. Found: 345.0462. Elemental analysis: Calc. for $C_{10}H_6F_7N_5O$: C, 34.79; H, 1.75; N, 20.29%. Found: C, 35.11; H, 1.80; N, 20.09%.

N^6-(Acetyl-2,8-bis(heptafluoropropyl)adenine (**5b**) (nc): MS (EI, 70 eV) *m/z*: 513 (M^+, 32); 471 (69); 452 (29); 352 (100).

6-Dimethylamino-8-(heptafluoropropyl)purine (**3c**) (nc): eluent, ether/EtOAc (1:1); colorless needles (EtOAc); m.p. 198–199 °C. IR (cm^{-1}): 1350 (CF_3); 1220 (CF_2). ^1H NMR (acetone-d_6) δ: 3.39 (s, CH_3); 8.37 (s, H-2) ppm. ^{19}F NMR (acetone-d_6) δ: −3.16 (t, 3F, J=8.7 Hz, γ-CF_3); −33.79 (q, 2F, J=7.5 Hz, α-CF_2); −49.10 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 331 (M^+, 99); 316 (64); 312 (16); 302 (100). Elemental analysis: Calc. for $C_{10}H_8F_7N_5$: C, 36.26; H, 2.43; N, 21.15%. Found: C, 36.34; H, 2.43; N, 21.10%.

8-Heptafluoropropyl-6-methoxypurine (**3d**) (nc): eluent, ether; colorless needles (EtOAc); m.p. 163–164 °C. IR (cm^{-1}): 1325 (CF_3); 1220 (CF_2). ^1H NMR (acetone-d_6) δ: 4.19 (s, CH_3O); 8.61 (s, H-2) ppm. ^{19}F NMR (acetone-d_6) δ: −3.16 (t, 3F, J=8.7 Hz, γ-CF_3); −35.03 (q, 2F, J=9.9 Hz, α-CF_2); −49.19 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 318 (M^+, 100); 317 (49); 298 (18); 288 (35); 287 (30); 260 (43). Elemental analysis: Calc. for $C_9H_5F_7N_4O$: C, 33.97; H, 1.58; N, 17.61%. Found: C, 34.04; H, 1.58; N, 17.53%.

2-Heptafluoropropyl-6-methoxypurine (**4d**) (nc): eluent, EtOAc/ether (1:4); colorless plates (EtOAc); m.p. 227–228 °C. IR (cm^{-1}): 1340 (CF_3); 1225 (CF_2). ^1H NMR (acetone-d_6) δ: 8.54 (s, H-2); 4.23 (s, CH_3O) ppm. ^{19}F NMR (acetone-d_6) δ: −3.31 (t, 3F, J=8.7 Hz, γ-CF_3); −36.24 (q, 2F, J=9.9 Hz, α-CF_2); −48.78 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 318 (M^+, 100); 317 (46); 298 (23); 288 (33); 287 (26). Elemental analysis: Calc. for $C_9H_5F_7N_4O$: C, 33.97; H, 1.58; N, 17.61%. Found: C, 34.08; H, 1.57; N, 17.54%.

8-(Heptafluoropropyl)guanine (**7g**) (nc): eluent, 5% MeOH/95% EtOAc; colorless needles (MeOH); m.p. 229–234 °C (dec.). IR (cm^{-1}): 3330, 3160 (NH); 1700 (C=O); 1345 (CF_3); 1240 (CF_2). ^{19}F NMR (methanol-d_4) δ: −3.72 (t, 3F, J=8.7 Hz, γ-CF_3); −35.68 (q, 2F, J=9.9 Hz, α-CF_2); −49.83 (s, 2F, β-CF_2) ppm. MS (EI, 70 eV) *m/z*: 319 (M^+, 100); 300 (18); 269 (18); 200 (100). HRMS *m/z*: Calc. for $C_8H_4F_7N_5O$: 319.0303. Found: 319.0344.

General method for the thermal condensation of poly(amino)pyrimidines and heptafluoropropylbutyramide

A mixture of 4,5,6-triaminopyrimidine sulfate (1.116 g, 5.00 mmol) and heptafluorobutyramide (6.39 g, 0.030 mol) was placed in a glass ampoule. The ampoule was sealed under vacuum and maintained at 200–210 °C for 5 h. The contents of the ampoule were dissolved in ethyl acetate with some material remaining in suspension. Silica gel chromatography (eluent: ethyl acetate) of the total reaction product afforded **3a** (0.11 g, 7.3%) and 4.70 g of heptafluorobutyramide was recovered.

Condensation of 6-hydroxy-2,4,5-triaminopyrimidine sulfate and 6-hydroxy-4,5-diaminopyrimidine sulfate with heptafluoropropylbutyramide was also attempted in the same way, but no fluoroalkylated purines were obtained.

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