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Fluorination at C2′, C3′ and C5′ of Nucleosides with 1-Chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(Tetrafluoroborate) Selectfluor™ Reagent

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FLUORINATION AT C2', C3' AND C5' OF NUCLEOSIDES WITH 1-CHLOROMETHYL-4-FLUORO-1,4-DIAZABICYCLO[2.2.2]OCTANE BIS(TETRAFLUOROBORATE) SELECTFLUOR^{TM} REAGENT

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Abstract

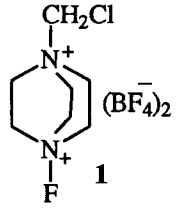
Electrophilic fluorination of thioaryl ethers on the sugar component of nucleosides with commercially available SELECTFLUOR^{TM} reagent provides a new method for the synthesis of C2', C3' and C5' fluoronucleosides.

Introduction

Selective fluorination as a method for modifying the reactivity of biologically active compounds has proven to be a very useful synthetic tool for the medicinal chemist.[1a,b,c] This method has been especially popular in the field of nucleoside chemistry, where the replacement of a hydrogen or hydroxyl by fluorine, has yielded compounds of great therapeutic importance.[2a,b,c] The coupling of fluoro-sugars with heterocyclic nitrogen bases has been frequently utilized for the synthesis of fluorinated nucleosides.[3] Other methods include the nucleophilic displacement of suitable leaving groups by the fluoride anion, and

the reaction of the sugar component of nucleosides with DAST.[3] This latter reagent has also been used to introduce a fluorine atom into the sugar component of nucleosides via the fluoro-Pummerer rearrangement on the phenylsulfoxide substituted derivatives.[4] A similar conversion was effected by the reaction of XeF_2 with C2' and C5' thioarylsubstituted uridine.[5a,b]

Our current interest in the selective fluorination of organic compounds prompted the development of the titled reagent[6]. This compound,**1** (F-TEDA-BF_4) prepared from elemental fluorine and N-chloromethyl -1,4-diazabicyclo[2.2.2] octane tetrafluoroborate is a stable, easy to handle non-hygroscopic solid which is now commercially available[7]. It has proven to be very useful for the site-selective fluorination of a variety of diverse organic compounds.[8a,b,c] This includes the α-fluorination of sulfides via the fluoro-Pummerer rearrangement of an intermediate sulfonium salt[8c]. An application of the latter method for introducing a fluorine atom at C2', C3', and C5' of a variety of nucleosides is described in this report.



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Results and Discussion

The substrate selected for C2' fluorination, 3', 5'-Di-O-acetyl-2'-S-(4-

methoxyphenyl)-2'-thiouridine was obtained by the reaction of 2,2'-cyclouridine with 4 methoxybenzenethiol followed by acetylation of the C3' and C5' hydroxyl groups with acetic anhydride/4-dimethylaminopyridine.[5a] The fluorination of the diacetate (**2**) was carried out at room temperature by reaction with F-TEDA-BF_4 in CH_3CN followed by Et_3N to obtain the product, 3' 5'-Di-O-acetyl-2'-fluoro-2'-S-(4-methoxyphenyl)-2'-thiouridine (**3**) as a mixture of diastereomers (S/R=95/5).[5a]

A similar method was used to introduce a fluorine atom at C3' of thymidine. Acetylation of the C5'-OH of 2',3'-cyclothymidine followed by reaction with 4-methoxybenzenethiol in *N, N*-dimethylacetamide at 120°C according to the procedure of Reese et al[9] afforded 5'-O-acetyl-2'-deoxy-3'-S-(4-methoxyphenyl)-3'-thiothymidine (**4**). The product obtained was the R isomer as determined by NMR NOE correlations. This compound was reacted with F-TEDA-BF_4 in CH_3CN to produce the C3'-fluoroproduct, 5'-O-acetyl-2'-deoxy-3'-fluoro-3'-S-(4-methoxyphenyl)-3'-thiothymidine (**5**) as a mixture of diastereomers (R/S=97/3). The absolute stereochemistry of these diastereomers was assigned using NMR heteronuclear NOE correlations between the C3' fluorine atom and the C4' hydrogen atom.

The reaction of uridine with diphenyl disulfide under the conditions of Nakagawa et al,[10] provided 5'-thiophenyl-5'-thiouridine which on treatment with acetic anhydride/4-dimethylaminopyridine produced 2',3'-diacetoxy-5'-thiophenyl-5'-thiouridine (**6**). Fluorination with F-TEDA-BF_4 in CH_3CN at room temperature resulted in the formation of 2',3'-diacetoxy-5'-fluoro-5'-

thiophenyl-5'-thiouridine (**7**) as a mixture of diastereomers (R/S = 60/40); F^{19} NMR (DMSO d_6) δ-159.2 (dd, $J_{F,C5'H}$ = 56Hz , $J_{F,C4'H}$ = 22Hz, R-isomer), δ-159.6 (dd, $J_{F,C5'H}$ = 55 Hz, $J_{F,C4'H}$ = 25Hz, S-isomer). The absolute stereochemistry of these isomers was assigned by comparing the ^{19}F NMR chemical shifts and F-H coupling constants with those previously reported for 2'-3'-diacetoxy-5'-fluoro-5'-S-(4-methoxyphenyl)-5'-thiouridine.[5b] In addition, NMR heteronuclear NOE correlations between the C5' fluorine atom and the C3' hydrogen atom confirmed the identity of the C5' fluorodiastereomers.

The purine nucleoside, 2'-3'-diacetoxy-5'-thiophenyl-N^1,N^2N^2 - tribenzoylguanosine (**8**) obtained by the reaction of 2',3'-diacetoxyguanosine with diphenyl disulfide followed by benzoylation with BzCl/pyridine was readily fluorinated at room temperature with F-TEDA-BF_4 to produce a mixture of 5'-fluorodiastereomers (**9**), (R/S = 66/34). The characteristic ^{19}F NMR downfield shift and smaller $J_{F\text{-}C4'H}$ observed for the 5'R-fluoropyrimidine isomer (**6**) compared to the 5'S isomer were found to be useful in distinguishing between the 5'-fluoro isomers obtained on fluorination of this purine nucleoside (**8**). Similar ^{19}F NMR spectral characteristics were observed for the diastereomers of 2',3'-diacetoxy-5'-fluoro-5'-thiophenyl-N^1, N^2N^2-tribenzoylguanosine (**9**). ^{19}F NMR (DMSO d_6) δ-154.12 (dd , $J_{F,C5'H}$ = 49 Hz, $J_{F,C4'H}$ = 12 Hz, R-isomer), δ-159.50 (dd, $J_{F,C5'H}$ = 49 Hz, $J_{F,C4'H}$ = 18Hz, S-isomer).

This method for fluorination of nucleoside thioethers with F-TEDA-BF_4 provides several advantages over those previously used.[5a,b] The procedure allows direct fluorination of a sulfide intermediate and thus avoids the oxidation

step and addition of Lewis acids as required when DAST is applied for this transformation. Unlike DAST or XeF_2, the reagent is stable, non-hygroscopic and does not require special handling techniques. In addition, the method employing F-TEDA-BF_4 is facile, rapid and does not produce toxic HF as a by-product.

Experimental Section

The nucleosides were obtained from Sigma Chemical and used as received. The reagents, 4-methoxybenzenethiol, diphenyl sulfide, acetic anhydride, 4-dimethylaminopyridine (DMAP), triethylamine, tributylphosphine were purchased from Aldrich Chemical Company. The solvents, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, and acetonitrile were dried with calcium hydride prior to use. Other solvents, hexane, and ethyl acetate were used without further purification. The reagent, Selectfluor™ was obtained from Air Products and Chemicals[7] Inc.

NMR Spectra were recorded on a Brucker ACP-300FT spectrometer operating at 282.4 MHz (^{19}F), 300.13 MHz (^{1}H, ^{13}C). Chemical shifts were referenced to neat $CFCl_3$ (^{19}F), TMS (^{1}H, ^{13}C). Mass spectra were obtained on a VG 2AB-EQ instrument with FAB ionization (perfluorokerosene as reference).

(a) Preparation of 2', 3', and 5' thioaryl substituted nucleosides.

3', 5'-Di-O-acetyl-2'-S-(4-methoxyphenyl)-2'-thiouridine (2) was obtained by a standard literature procedure[5a].

5'-O-acetyl-2'-deoxy-3'-S-(4-methoxyphenyl)-3'-thiothymidine (4). A suspension of 2,3'-anhydrothymidine (1.0 g, 4.46 mmol) in Ac_2O (6.0 mL) was treated with DMAP (30 mg, 0.26 mmol) and stirred at room temperature for 16 h under N_2. Excess Ac_2O was destroyed with MeOH (50 mL) and the solvents were evaporated in vacuo. The residue was dissolved into EtOAc (50 mL), washed with H_2O (25 mL), saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was dissolved into N,N-dimethylacetamide (30 mL) and the solution was treated with tripropylamine (8.5 mL, 44.6 mmol) and 4-methoxybenzenethiol (22.30 mmol). The mixture was heated at 120°C under N_2. After 16 h, the solvents were removed in vacuo. The residue was chromatographed on silica gel (4:1 ethyl acetate/hexane) to afford the product. This product which was the (R) isomer was cleanly separated and characterized. ^1H NMR (DMSO d_6) δ 11.30 (s, 1H), 7.60 (s, 1H), 7.50 (d, 2H), 6.90 (d, 2H), 6.0 (m, 1H), 4.30-3.90 (m, 3H), 3.75 (s, 3H), 2.50-2.35 (m, 1H), 2.30-2.15 (m, 1H), 1.95 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (DMSO d_6) δ 170.25, 164.25, 160, 150.25, 136.25, 135.75, 122.5, 115, 109.75, 84.0, 82.0, 63.75, 55.75, 44.50, 37.50, 20.25, 13.25; high resolution mass spectrum calculated for $C_{19}H_{22}N_2O_6S$, $(M+H)^+ = 407.1277$, found $(M+H)^+ = 407.1239$.

2',3'-di-O-acetyl-5'-S-phenyl-5'-thiouridine (6). Diphenyl sulfide (3.72 g, 5.0 mmol) was added to a solution of uridine (1.2 g, 5.0 mmol) in pyridine (25 mL) under N_2. Tri-n-butylphosphine (3.0 mL, 12.0 mmol) was added and the mixture was concentrated under reduced pressure. The

residue was treated with MeOH (10 mL) diluted with Et_2O (50 mL) and the precipitate obtained was filtered. This precipitate was suspended into Ac_2O (3.0 mL), DMAP (25.0 mg) was added and the mixture was stirred at 90°C for 18 h. The solution was diluted with MeOH (50 mL) and stirred for 1 h at room temperature. The solvents were evaporated in vacuo and the residue was dissolved into EtOAc (50 mL), washed with H_2O (25 mL), saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. Flash chromatography on silica gel (7:3 ethyl acetate/hexane) afforded 1.20 g (87% yield) of product. ^1H NMR ($CDCl_3$) δ 7.35 (d, 2H), 7.25 (t, 1H), 7.18 (t, 2H), 6.0 (d, br, 1H), 5.63 (d, 1H), 5.30 (d, br, 1H), 4.37-4.27 (m, 1H), 3.40 (q, 1H), 3.28 (q, 1H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO d_6) δ 170.25 (2C), 163.75, 150.25, 142.25, 135.75, 129.75 (2C), 129.0 (2C), 126.25, 103.75, 88.25, 80.25, 72.0 (2C), 35.0, 20.25 (2C), high resolution mass spectrum calculated for $C_{19}H_{20}N_2O_7S$, $(M+H)^+ = 421.1069$, found $(M+H)^+ = 421.1080$.

2',3'-Di-O-acetyl-5'-thiophenyl-N^1,N^2,N^2-tribenzoylguanosine (8). A suspension of 2',3'-di-O-acetylguanosine (1.0 g, 2.72 mmol) in pyridine (14.0 mL) was treated with diphenyl sulfide (1.78 g, 8.16 mmol) and tri-n-butylphosphine (1.6 mL, 6.53 mmol) under N_2. The mixture was stirred for 48 h and the solvents were evaporated in vacuo. The residue was dissolved into Et_2O (50 mL) and the insoluble material was filtered. This solid was dissolved into pyridine (16 mL) and benzoyl chloride (0.95 mL, 8.16 mmol) was added. The mixture was stirred for 16 h at room temperature and the solvents were evaporated in vacuo. The residue was dissolved into EtOAc

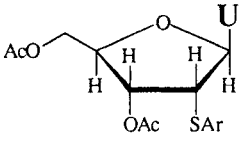
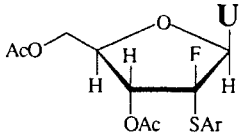
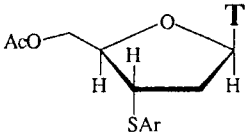
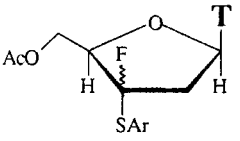
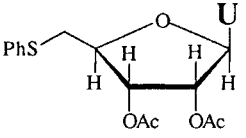
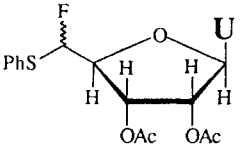
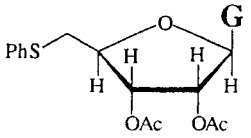
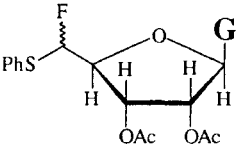
(50 mL), washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated in vacuo. Flash chromatography on silica gel in ethyl acetate/hexane (6/4), afforded 945 mg (45% yield) of the product. ^1H NMR ($CDCl_3$) δ 8.20 (d, 2H), 8.08 (s, 1H), 7.85 (d, 4H), 760-7.10 (m, 14H), 5.98 (d, 1H), 5.70 (t, 1H), 5.48 (dd, 1H), 4.45-4.30 (m, 1H), 3.35-3.25 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H); high resolution mass spectrum calculated for $C_{41}H_{33}N_5O_9S$ $(M+H)^+ = 772.1998$, found $(M+H)^+ = 772.2077$.

(b) **Fluorination of 2', 3' and 5' thioaryl substituted nucleosides.**

A solution of the thioaryl substituted nucleoside (0.5 mmol) in CH_3CN (5.0 mL) under N_2 was treated with F-TEDA-BF_4 (177 mg, 0.5 mmol) and stirred at room temperature for 15 min. Triethylamine (68 µL, 0.5 mmol) was then added and stirring continued for an additional 10 min. The solution was then poured into EtOAc (50 mL), washed with H_2O (2x25 mL), saturated $NaHCO_3$ (25 mL), dried (Na_2CO_3), filtered and evaporated in vacuo. Flash chromatography on silica gel (EtOAc/hexane, 7:3) afforded the pure products. **3',5'-di-O-acetyl-2'-fluoro-2'-S-(4-methoxyphenyl)-2'-thiouridine (3)**[5a], 121 mg (52%). **5'-O-acetyl-3'-fluoro-3'-S-(4-methoxyphenyl)-3'-thiothymidine (5)**, 95 mg (45%). ^1H NMR (DMSO d_6) R-isomer, δ 7.60 (s, 1H), 7.55 (d, 2H), 7.05 (d, 2H), 6.10 (dd, 1H), 4.60-4.25 (m, 3H), 3.80 (s, 3H), 2.75-2.55 (m, 1H), 2.40-2.25 (m, 1H), 2.10 (s, 3H), 1.80 (s, 3H); ^{19}F NMR (DMSO d_6) δ-110 (s, br); ^{13}C NMR (DMSO d_6) δ 170.25, 164.25, 161.75, 150.5, 137.75, 136.0,

118.50, 115.75, 110.25, 84.0, 83.75 (d), 82.50, 63.0, 55.75, 51.50, 20.50, 13.25; high resolution mass spectrum calculated for $C_{19}H_{21}FN_2O_6S$, $(M+H)^+ = 425.1183$, found $(M+H)^+ = 425.1150$. **2',3'-Di-O-acetyl-5'-fluoro-5'-thiophenyl-5'-thiouridine (7)**, 92 mg (42%). ^1H NMR ($CDCl_3$), R-isomer: δ 9.65 (s, 0.6H), 7.6-7.1 (m, 3.0H), 6.25 (d, 0.6H), 6.0 (dd, 0.6H), 5.80 (d, 0.6H), 5.55 (dd, 0.6H), 5.30 (m, 0.6H), 4.45 (dt, 0.6H), 2.05, 2.15 (two (s), 1.8H each). S-isomer: δ 9.60 (s, 0.40H), 7.6-7.1 (m, 2.0H), 6.30 (d, 0.40H), 6.05 (dd, 0.40H), 5.85 (d, 0.40H), 5.45 (dd, 0.40H), 5.30 (m, 0.40H), 4.50 (dt, 0.40H), 2.05, 2.15 (two (s), each 1.2H); ^{19}F NMR ($CDCl_3$), R-isomer: δ-159.2 (dd, 0.6F), S-isomer: δ-159.6 (dd, 0.40F); ^{13}C NMR (DMSO d_6), R-isomer: δ 170.05 (2C), 164.05, 150.75, 142.25, 133.0, 132.05 (2C), 131.0 (2C), 129.0, 103.75, 102.05, 88.25, 81.25 (d), 72.05, 70.05, 20.25 (2C); S-isomer: δ 170.25 (2C), 164.0, 150.70, 142.05, 133.05, 132.00 (2C), 131.05 (2C), 129.05, 103.70, 99.5, 88.5, 83.00 (d), 72.25, 70.00, 20.25 (2C); high resolution mass spectrum calculated for $C_{19}H_{19}FN_2O_7S$, $(M+H)^+ = 439.0975$, found $(M+H)^+ = 439.1019$. **2',3'-Di-O-acetyl-5'-fluoro-5'-thiophenyl-N^1,N^2,N^2-tribenzoylguanosine (9)**, 182 mg (46%). ^1H NMR (DMSO d_6), R-isomer: δ 8.85 (S, 0.66H), 8.15 (d, 1.3H), 8.0-7.4 (m, 12.5H), 6.35-6.25 (m, 0.66H), 5.85-5.70 (m, 0.66H), 5.55-5.65 (m, 0.66H), 4.60-4.50 (m, 0.66H), 2.15 (s, 1.98H), 2.10 (s, 1.98H); S-isomer: 8.80 (0.34H), 8.12 (d, 0.70H), 8.0-7.4 (m, 6.5H), 6.30-6.20 (m, 0.34H), 5.80-5.70 (m, 0.34H), 5.65-5.50 (m, 0.34H), 4.50-4.40 (m, 0.34H), 2.03 (s, 1.02H), 2.00 (s, 1.02H); ^{19}F NMR (DMSO d_6) δ-154.12 (dd, 0.66F), R-isomer. δ-159.50 (dd, 0.34F), S-isomer; ^{13}C NMR (DMSO d_6) δ 82.50 (d), S-isomer, 81.45 (d), R-isomer, high resolution mass

TABLE: FLUORINATION AT C2', C3', AND C5' OF NUCLEOSIDES WITH F-TEDA-BF_4

SUBSTRATE	PRODUCT (YIELD)	^{19}F NMR
 **2**	 (52) **3**	-131 (s, br) S-isomer -141 (s,br) R-isomer
 **4**	 (45) **5**	- 110.0 (s, br) R-isomer -130.0 (m) S-isomer
 **6**	 (42) **7**	-159.2 (dd, J = 56, 22Hz) R-isomer -159.6 (dd, J = 55, 25 Hz S-isomer
 **8**	 (46) **9**	-154.12 (dd, J = 49, 12 Hz) R-isomer -159.50 (dd, J = 49, 18 Hz) S-isomer

Ar = 4-methoxyphenyl, **U** = Uracil, **T** = Thymine, **G** =N^1, N^2, N^2- Tribenzoylguanine

spectrum calculated for $C_{41}H_{32}FN_5O_9S$, $(M+H)^+$ =790.1983, found $(M+H)^+$ = 790.1978.

Conclusions

The previously reported facile fluorination of sulfides bearing α-hydrogen atoms, with F-TEDA-BF_4, has been found to be a useful method for introducing a fluorine atom into the sugar component of nucleosides. The method was successfully used to fluorinate a variety of nucleosides at the C2', C3' and C5' positions.

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