Fluorination of 5'-Deoxy-5'-(methylthio)adenosine with Xenon Difluoride provides an Expedient Synthesis of (Fluoromethylthio)adenosine

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Fluorination of 5'-deoxy-5'-(fluoromethylthio)adenosine derivatives with xenon difluoride at −60 °C in dichloromethane occurs exclusively at the methylthio position to provide a simple and efficient preparation of 5'-deoxy-5'-(fluoromethylthio)adenosine.

5'-Deoxy-5'-(methylthio)adenosine (MTA) is an important product of *S*-adenosylmethionine metabolism formed as a by-product during biosynthesis of the polyamines, spermidine and spermine.[1] Interest in MTA and its analogues has been stimulated since studies have revealed that MTA is a fundamental component of the complex system responsible for cell growth and proliferation.[2,3] Consequently, the inhibitors of the enzymes involved in MTA catabolism, MTA phosphorylase in mammal cells[4] and MTA nucleosidase in many micro-organisms,[5-7] have been examined as potential chemotherapeutic agents.[8-10]

Recently, 5'-deoxy-5'-(fluoromethylthio)adenosine (MFMTA) has been synthesized and evaluated as inhibitor of MTA phosphorylase and its antiproliferative effect tested,[11] but its biological activity has not been fully explored yet. Our interest in MTA nucleosidase[12] led us to examine the effect of MFMTA on the activity of a typical bacterial enzyme and explore a new route to MFMTA since no convenient preparative method is currently available.

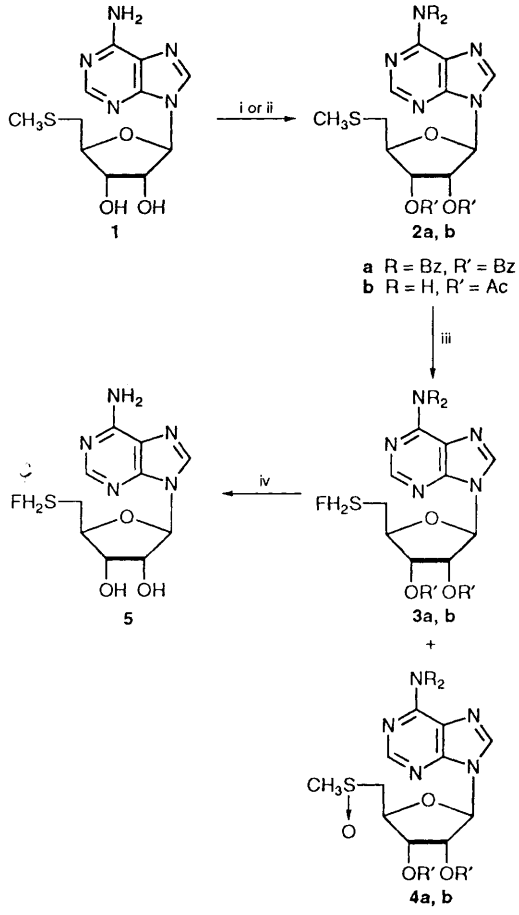
MFMTA has been prepared recently[11,13,14] in low yield (< 10%) using the general procedure of McCarthy.[15] This method gave a regioisomeric mixture, of 5'-deoxy-5'-(fluoromethylthio)adenosine and 5'-fluoro-5'-*S*-(methylthio)adenosine, whose separation is tedious. The finding that XeF_2 is suitable for α-fluorination of a sulfide[16,17] suggested that it might be useful for the preparation of MFMTA.

Herein we report a simple and convenient method for the preparation of MFMTA by means of direct and regioselective fluorination of suitable protected derivatives of MTA. Protecting groups for **2a–b** were chosen to avoid acidic conditions during their removal since α-fluoro thioethers were reported to be unstable under these conditions.[11,18] As Scheme 1 shows, the protected MTAs **2a–b** were subjected to mono-fluorination, exclusively at the methylthio position with xenon difluoride. The only minor side-product formed was 5'-deoxy-5'-methylthioadenosine sulfoxide **4a** or **4b** which could result from hydrolysis of the possible corresponding sulfur(IV) difluoride intermediate, as has been proposed in the mechanism of α-fluorination of alkyl sulfides.[16]

After the optimal reaction conditions had been achieved, the reaction yielded the desired fluorinated nucleosides **3a–b** in isolated yields of 75 and 70% as described below.

Separation of **3a**, **4a** and **3b**, **4b** was performed by flash chromatography on silica gel. Removal of protecting groups was achieved in both cases in nearly quantitative yield to give **5**.

The availability of MFMTA by this procedure will allow the complete evaluation of its biological activity as a potential inhibitor of MTA nucleosidases from various microorganisms. Our preliminary investigations in this field showed that MFMTA inhibits 5'-methylthioadenosine nucleosidase [E.C. 3.2.2.9] from *E. coli* and, furthermore, it serves as substrate for the enzyme.



Scheme 1 *Reagents and conditions:* i, BzCl, pyridine (16 h, room temp., 85%); ii, Ac_2O, DMAP and NEt_3, CH_3CN (1 h, room temp., 78%); iii, XeF_2 (1.3 equiv.), CH_2Cl_2 (−60 °C, 6 h); iv, Na_2CO_3 (2 equiv.), MeOH (15 h, room temp.)

Experimental

General Procedure for Fluorination with XeF_2.—Compound **2a** or **2b** (1 mmol) in CH_2Cl_2 (1 cm^3) was injected under argon into a stirred solution of XeF_2 (1.3 mmol) in CH_2Cl_2 (4 cm^3) at −60 °C. The mixture was stirred at −60 °C for 6 h after which hexamethyldisilazane (1.3 mmol) in CH_2Cl_2 (1 cm^3) was added to it to quench the HF formed. Volatile material was removed under reduced pressure to leave a residue which was analysed by NMR. This showed the absence of starting material and the presence of the fluorinated derivatives **3a** or **3b**, formed with < 5% of their corresponding sulfoxides **4a** or **4b** (identified by their known NMR spectrum).[13,14] Purification of **3a** or **3b** was

achieved by flash chromatography on silica gel using ethyl acetate–hexane as eluting solvent (1:1, v/v) for **3a** and (4:1, v/v) for **3b**.

Deprotection of the hydroxy and amino groups in **3a** and **3b** was achieved by treatment with Na_2CO_3 (2 mol equiv.) in MeOH for 15 h at room temperature. The methanolic solution was passed through a short column of Dowex resin (AG3, X4-OH^-) extensively washed with MeOH. The methanolic resulting solution was neutralised with (AG 50 WX8-H^+) and evaporated to afford pure **5** in 95% yield.

N^6,N^6-*Dibenzoyl*-2′,3′-O-*dibenzoyl*-5′-*deoxy*-5′-*fluoromethylthioadenosine* **3a**. M.p. 132 °C; δ_H(250 MHz, $CDCl_3$, *J*/Hz) 3.3 (m, 2 H, 5′- and 5″-H), 4.7 (m, 1 H, 4′-H, $J_{4',5'} = J_{4',5''}$ 4.5), 5.5 (d, 2 H, CH_2F, $J_{H,F}$ 51), 6 (t, 1 H, 3′-H, $J_{3',4'}$ 5), 6.3 (t, 1 H, 2′-H, $J_{2',3'}$ 5.2), 6.4 (d, 1 H, 1′-H, $J_{1',2'}$ 5), 7 and 7.7 (m, 20 H, PhCO) and 8.7 and 8.3 (2 s, 2 H, 2- and 8-H); δ_F(250 MHz, $CDCl_3$), *J*/Hz) −183 (t, 1 F, $J_{H,F}$ 51); *m*/*z* (DCI/NH_3) 732 $(M, H)^+$; $[\alpha]_D^{20}$ 86.6 (*c* 0.86 in $CHCl_3$).

2′,3′-O-*Diacetyl*-5′-*deoxy*-5′-*fluoromethylthioadenosine* **3b**. M.p. 163 °C; δ_H(250 MHz, $CDCl_3$, *J*/Hz) 2 and 2.1 (2 s, 6 H, CH_3CO), 3.2 (m, 2 H, 5′- and 5″-H), 4.4 (m, 1 H, 4′-H, $J_{4',5'} = J_{4',3'}$ 5.7), 5.5 (d, 2 H, CH_2F, $J_{H,F}$ 52), 5.6 (dd, 1 H, 3′-H, $J_{2',3'}$ 4.5), 5.9 (s large, 2 H, NH_2), 6.01 (dd, 1 H, 2′-H), 6.13 (d, 1 H, 1′-H, $J_{1',2'}$ 5.7) and 7.9 and 8.35 (2 s, 2 H, 2- and 8-H); δ_F(250 MHz, $CDCl_3$, *J*/Hz) −183 (t, 1 F, $J_{H,F}$ 52); $[\alpha]_D^{20}$ −75.6 (*c* 1.54 in $CHCl_3$).

5′-*Deoxy*-5′-*fluoromethylthioadenosine* **5**. M.p. 196 °C (decomp.); δ_H(250 MHz, $CDCl_3$–CD_3OD) 3.07 (m, 2 H, 5′- and 5″-H, $J_{5',5''}$ 14, $J_{4',5'} = J_{4',5''}$ 4.6, $J_{5',F} = J_{5'',F}$ 2), 4.2 (m, 2 H, 3′- and 4′-H), 4.6 (t, 1 H, 2′-H, $J_{2',3'}$ 4.5), 5.5 (m, 2 H, CH_2F, $J_{H,F}$ 52), 5.9 (d, 1 H, 1′-H, $J_{1',2'}$ 4.5) and 8.05 and 8.1 (2 s, 2 H, 2- and 8-H); δ_F(250 MHz, $CDCl_3$–CD_3OD) −183 (t, 1 F, $J_{H,F}$ 52); *m*/*z* (DCI/NH_3) 316 $(M, H)^+$.

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Paper 3/06958C
Received 22*nd November* 1993
Accepted 23*rd November* 1993