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# FLUORINATION AT C5' OF NUCLEOSIDES. SYNTHESIS OF THE NEW CLASS OF 5'-FLUORO-5'-*S*-ARYL (ALKYL) THIONUCLEOSIDES FROM ADENOSINE.[1]

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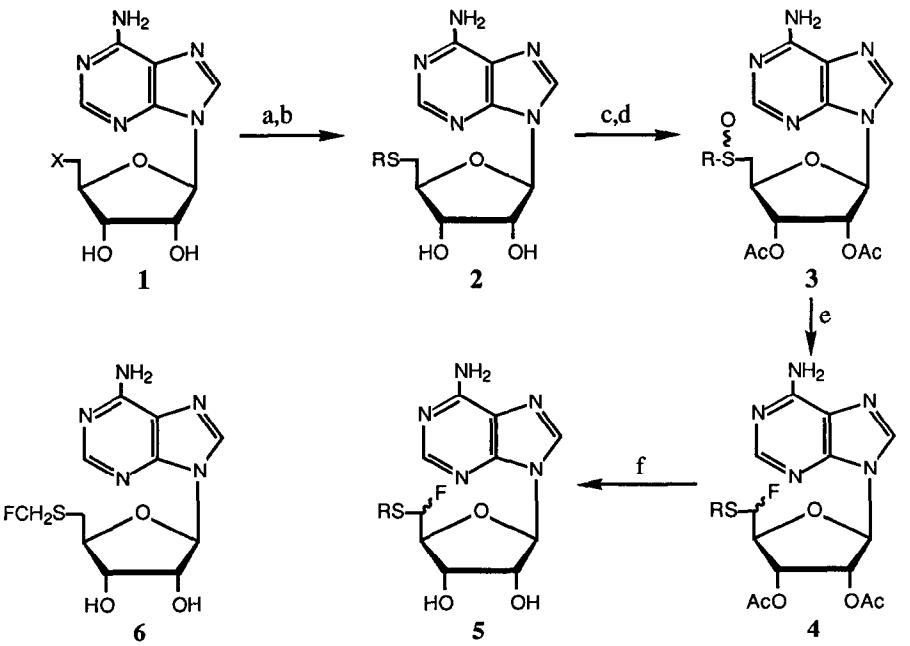
*Summary* : Treatment of protected 5'-*S*-aryl (alkyl) thioadenosine sulfoxides (**3**) with diethylaminosulfur trifluoride (DAST)/antimony trichloride ($SbCl_3$) and deprotection resulted in high-yield syntheses of the new 5'-fluoro-5'-*S*-aryl (alkyl) thioadenosines (**5**).

The biochemically ubiquitous *S*-adenosylmethionine (Ado-Met, SAM) serves as the methyl donor for most enzyme-mediated methylations, producing *S*-adenosylhomocysteine (Ado-Hcy, SAH) as the nucleosidic by-product.[3] Alternatively, enzymatic decarboxylation of Ado-Met gives the corresponding 5'-aminopropyl sulfonium compound that serves as the aminopropyl donor for biosynthesis of the polyamines spermidine and spermine. The nucleosidic by-product of that pathway is 5'-*S*-methylthioadenosine (MTA, **2, R = Me**).[4] Ado-Hcy functions as a feedback inhibitor of crucial methylation enzymes, and MTA exerts feedback inhibition on polyamine biosynthesis.[3,4] Therefore, enzymatic removal (by degradation) of Ado-Hcy and MTA are crucial for the continuing biosynthesis of nucleic acids and other biomolecules required for cell division. It has been found that 5'-*S*-isobutylthioadenosine (SIBA, **2, R = *i*-Bu**) has significant inhibitory activity in some cells,[5] and 5'-*S*-phenylthioadenosine (**2, R = Ph**) has been reported to have antiviral activity.[6] Thus, 5'-fluoro analogues of these metabolically crucial thionucleosides are fascinating new types of putative inhibitory agents. Such 5'-*S*-aryl (alkyl) thio-5'-fluoronucleosides (**5**) are α-fluorothioethers (thioacetal analogues) that might function as alternative substrates to provide mechanism-based (suicide) enzyme inhibitors. We now report the efficient preparation of this previously unknown class of C5' α-fluorothioether derivatives of nucleosides in the adenosine series.

McCarthy *et al.*[7] had reported that treatment of alkyl aryl sulfoxides with DAST

(diethylaminosulfur trifluoride) gave aryl α-fluorothioethers. Catalysis by zinc(II) iodide was noted.[7] We have developed modified procedures that give high yield conversions of adenosine (**1, X = OH**) to 5'-*S*-aryl (alkyl) thioadenosines (**2**) via 5'-chloro-5'-deoxyadenosine (**1, X = Cl**).[8] Acetylation of **2** (**R = Ph**) in the usual manner followed by oxidation with 1 equiv. of 3-chloroperoxybenzoic acid (MCPBA) at -40°C afforded the protected phenyl sulfoxides (**3, R = Ph**) with a 58/42 ratio of diastereomers ($^1$H NMR).

Treatment of **3** (**R = Ph**) with DAST/$ZnI_2$/$CH_2Cl_2$ gave the protected diastereomers of 5'-fluoro-5'-*S*-phenylthioadenosine (**4, R = Ph**) as minor products plus deoxygenated starting material. Reduction of sulfoxides to sulfides by sodium iodide and boron trifluoride etherate has been noted.[9] Therefore, other Lewis acid catalysts were examined to circumvent this iodide-based deoxygenative side reaction. It was found that DAST/$SbCl_3$ provided rapid reactions with minimal color and by-product formation in most cases.




(a) (i) $SOCl_2$/Pyridine/MeCN. (ii) $NH_3$/MeOH/$H_2O$ (91%). (b) RSH/NaH/DMF (92%). (c) $Ac_2O$/Pyridine (98%). (d) MCPBA/$CH_2Cl_2$/-40°C (98%). (e) DAST/$SbCl_3$/$CH_2Cl_2$/Ambient/10 h (68%). (f) $NH_3$/MeOH (88%). (Yields in parentheses refer to R = Ph.)

Treatment of (**3, R = Ph**) with 2 equiv. of DAST and 0.1 equiv. of $SbCl_3$ in $CH_2Cl_2$ under $N_2$ for 10 h at ambient temperature gave 68% of the fluoro diastereomers (**4, R = Ph**) after work-up and column chromatography (silica gel). The ratio (39/61) was essentially constant for several reactions as determined by integration of the $^{19}F$ NMR peaks (d of d) centered at δ -155.62 ($^2J$ = 53 Hz, $^3J$ = 10.3 Hz) and -159.61 ($^2J$ = 53 Hz, $^3J$ = 18.4 Hz) (upfield from $CCl_3F$ in $Me_2SO$) for the minor and major diastereomers, respectively. Interestingly, treatment of one diastereomer of sulfoxide **3** (**R = Ph**) under identical conditions resulted in formation of the same isomeric mixture of **4** (**R = Ph**). Therefore, the stereochemistry of this deoxygenative fluorination process is not dependent on the sulfur configuration of the precursor sulfoxide.

As noted by McCarthy and co-workers,[7] introduction of a 4-methoxy substituent on the phenyl ring resulted in improvements to the rate and yield of the fluorination process. Treatment of 2',3'-di-*O*-acetyl-5'-*S*-(4-methoxyphenyl)thioadenosine sulfoxides (**3, R = 4-MeOPh**) with DAST/$SbCl_3$ afforded **4** (**R = 4-MeOPh**) (37/63) in 74% yield after purification. Deprotection ($NH_3$/MeOH) and fractional crystallization (MeOH) gave resolution of the two diastereomers of 5'-fluoro-5'-*S*-(4-methoxyphenyl)adenosine (**5, R = 4-MeOPh**). Catalysis by $ZnI_2$ also gave good fluorination yields (~69%) with **3** (**R = 4-MeOPh**), although the reaction was less clean and proceeded more slowly.

The modified McCarthy method also was successful for fluorination of other 5'-aryl (alkyl) thionucleosides. Thus, treatment of 2',3'-di-*O*-acetyl-5'-*S*-methylthioadenosine sulfoxides (**3, R = Me**) with DAST/$SbCl_3$ gave a regioisomeric mixture of protected 5'-*S*-(fluoromethyl)thio and 5'-fluoro-5'-*S*-methylthio (**4, R = Me,** two diastereomers) compounds in 58% combined yield after purification. The $^{19}F$ NMR triplet for the fluoromethylthio isomer at δ -184.63 ($J$ = 52 Hz, 0.37 F) and two doublets of doublets for **4** (**R = Me**) at -165.08 ($^2J$ = 54 Hz, $^3J$ = 17 Hz, 0.42 F) and -163.62 ($^2J$ = 54 Hz, $^3J$ = 12 Hz, 0.21 F) are diagnostic for the regio and stereochemical composition. Deprotection with methanolic ammonia, and preparative TLC (MeOH/$CHCl_3$) of the resulting mixture gave pure 5'-*S*-(fluoromethyl)thioadenosine (**6**). The 5'-fluoro-5'-*S*-methylthioadenosine diastereomers (**5, R = Me**) are rather unstable and decompose readily on silica gel. Replacement of fluorine by methoxy was suggested by loss of $^{19}F$ signals and appearance of $^1H$ singlets ($OCH_3$) in the NMR spectra.

Treatment of 2',3'-di-*O*-acetyl-5'-*S*-(4-methoxyphenyl)thiouridine sulfoxides with DAST/$SbCl_3$ gave the expected 5'-fluoro diastereomers (50/50) in 85% purified yield. Fractional crystallization has provided clean separation of these diastereomers. Full details of these studies including relative stereochemical assignments at each stage by NMR analysis with absolute configurations defined by X-ray crystallography will be reported. Parallel transformations with selectively labelled 5'(*R* and *S*)-deuterioadenosine precursors are in progress to evaluate further stereochemical features of these processes.

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