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SYNTHESIS OF FLUORINATED DERIVATIVES OF METHIONINE AND 5'-DEOXY-5'-(METHYLTHIO)-ADENOSINE USING THE MCCARTHY TRANSFORMATION OF SULFOXIDES TO α -FLUORO THIOETHERS

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SUMMARY

Treatment of N-acetylmethionine sulfoxide methyl ester with diethylamino-sulfur trifluoride (DAST) or dimethylaminosulfur trifluoride (meDAST) yielded N-acetyl-S-(monofluoromethyl)homocysteine methyl ester as the sole fluorinated product. In contrast, treatment of 2',3'-di-O-acetyl-5'-(methylthio)adenosine sulfoxide with DAST or meDAST unexpectedly produced three novel fluorinated products.

INTRODUCTION

The recent report by McCarthy *et al.* [1] of a general procedure for transforming sulfoxides to α -fluoro thioethers using DAST, prompted us to



explore the utility of this method for preparing novel fluorinated derivatives of methionine and of 5'-deoxy-5'-(methylthio)adenosine (MTA) [3] with potentially interesting biological properties.

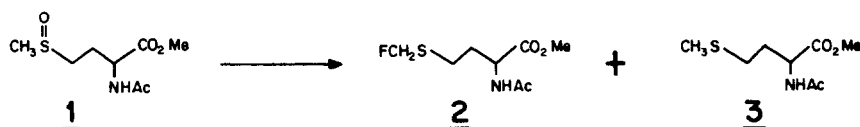
RESULTS AND DISCUSSION

The proposed mechanism of this fluorine insertion reaction [1] includes a possible six-membered transition state to explain the regioselective,

sterically controlled formation of fluoromethyl ethyl sulfide from methyl ethyl sulfoxide. Accordingly, our expectations that treatment of N-acetyl-L-methionine sulfoxide methyl ester 1 with DAST would yield the corresponding S-monofluoromethyl derivative 2 proved correct (TABLE 1); however, by changing reaction conditions, N-acetyl-L-methionine methyl ester 3 was obtained as the predominant product (TABLE 1). Although Houston and Honek [2] have recently reported using DAST for the transformation of 1 to 2, they did not note any variability in product formation.

TABLE 1

Reactions of N-acetyl-L-methionine sulfoxide methyl ester with DAST and meDAST



<u>Sulfoxide</u>	<u>Reagent</u> (equiv)	<u>Temp</u> (°C)	<u>Time</u> (hr)	<u>Products</u> (% yield ^a)
<u>1</u>	DAST(2)	RT	2-18	<u>2</u> (8) + <u>3</u> (78)
<u>1</u>	DAST(2)	reflux	1.5	<u>2</u> (85)
<u>1</u>	meDAST(2)	reflux	1.5	<u>2</u> (85)

^a isolated product or product mixture; RT = room temperature.

The reaction of 2',3'-di-O-acetyl MTA sulfoxide 4 with DAST proved to be highly complex [3], yielding not only the expected monofluorinated product 5, but also the diastereomeric α -fluoro derivatives 6 and the MTA derivative 7 (TABLE 2). The desire to find reaction conditions which would optimize the yield of 5, prompted further studies, presented herein, comparing the reactivities and specificities of DAST versus meDAST under a variety of

reaction conditions [4]. Additional derivatives of MTA sulfoxide were prepared and included for study. A summary of these results is presented in TABLE 2. The nonspecific reactivity of DAST towards 4 was in contrast to its unreactive behavior towards 8 and 12 under a variety of experimental conditions. Steric factors most likely contributed to these differing results. MeDAST proved somewhat more reactive than DAST towards 8 and yielded slightly different product distributions, but was equally unreactive towards 4. MeDAST was as effective as DAST in converting the methionine sulfoxide derivative 1 to 2.

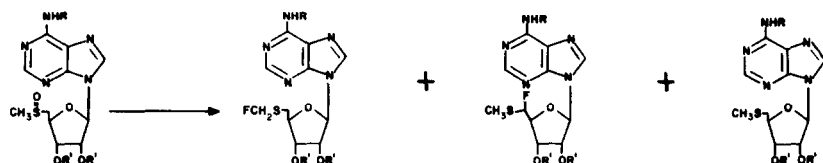
Our further investigations of the McCarthy transformation of sulfoxides to α -fluoro thioethers have provided important information about its general applicability:

1. Product formation can be highly variable, depending upon reaction conditions employed. In this regard, time, temperature and number of DAST or MeDAST equivalents are all critical factors.
2. Product mixtures must be carefully monitored for the presence of reduced, unfluorinated sulfides which can be formed competitively and which tend to coelute with the desired fluorinated products.
3. MeDAST can be used as well as DAST, and in some cases, its greater reactivity may be advantageous.
4. The N-6-amino substituent of adenosine does not need protection during reactions with DAST or MeDAST, and appears to facilitate the McCarthy transformation when left unprotected.
5. The preferential formation of α -fluoromethyl sulfides does not always occur, as originally proposed [1].

The thermal instability of DAST is well known [5] and may, in part, be responsible for the complexities we have observed in its reaction with nucleoside sulfoxides. Morpholinosulfur trifluoride [5], a more stable analog of DAST that has been recently developed, may prove more useful for further applications of the McCarthy transformation of sulfoxides to α -fluoro thioethers.

TABLE 2

Reactions of 5'-deoxy-5'-(methylthio)adenosine sulfoxide derivatives with DAST and meDAST



Cpd.	R	R'	Cpd.	R	R'	Cpd.	R	R'	Cpd.	R	R'
<u>4</u>	H	Ac	<u>5</u>	H	Ac	<u>6</u>	H	Ac	<u>7</u>	H	Ac
<u>8</u>	H	Ip	<u>9</u>	H	Ip	<u>10</u>	H	Ip	<u>11</u>	H	Ip
<u>12</u>	MMTr	Ip									

Ip = 2', 3'- Isopropylidene; MMTr = Monomethoxytrityl

Sulfoxide	Reagent (equiv)	Temp (°C)	Time (hr)	Products (% yield)
<u>4</u>	DAST(10)	55	2.5	<u>5</u> (11) + <u>6</u> (31) ^a
<u>4</u>	meDAST(10)	55	2.5	<u>5</u> (14) + <u>6</u> (40) + <u>7</u> (13) ^a
<u>4</u>	meDAST(5)	55	2.5	<u>5</u> (14) + <u>6</u> (46) + <u>7</u> (23) ^b
<u>4</u>	meDAST(5)	RT	20	SM ^c
<u>8</u>	DAST(3)	reflux	1.5	SM ^c
<u>8</u>	DAST(3) ZnI ₂ (0.03)	reflux	16	SM ^c
<u>8</u>	meDAST(5)	50	3-5	<u>9</u> (37) + <u>10</u> (37) + <u>11</u> (20) ^b
<u>12</u>	DAST(3)	reflux	3	SM ^c
<u>12</u>	meDAST(5)	RT	96	SM ^c
<u>12</u>	meDAST	50	3	SM ^c

^aisolated yields of deacetylated products, purified as described [3].

^bbased on isolated yields of product mixture and subsequent determination of product ratios from ¹H NMR and/or ¹⁹F NMR spectra.

^cthin layer chromatography and ¹H NMR indicated presence of unidentified minor products.

SM = starting material; RT = room temperature.

EXPERIMENTAL

All reactions were run in CHCl_3 under N_2 or argon. All product mixtures were characterized by ^1H NMR and thin layer chromatography. Presence of fluorinated products in ^1H NMR was confirmed by ^{19}F NMR. ^1H and ^{19}F NMR spectra were taken on a 60-MHz Varian EM-390 spectrometer using CDCl_3 as solvent. MTA sulfoxide [6] was converted to its 2',3'-di-O-acetylated derivative 4 [7] and to its 2',3'-di-O-isopropylidene derivative 8 using standard procedures [8]. Compound 8 was further converted to its N-monomethoxytrityl derivative 12 using general methods [9]. Products from the reaction of 4 with DAST or meDAST were deacetylated in $\text{CH}_3\text{OH}/\text{NH}_3$, and the resultant deprotected nucleosides were separated and characterized as described [3].

Fluorine-19 NMR spectroscopy

<u>Compound</u>	<u>Chemical Shift</u> <u>$[\delta(\text{from CFC}_3)]$</u>	<u>Coupling Constant</u> <u>(Hz)</u>
<u>2</u>	- 183 (t)	55.5
<u>5</u>	- 182 (t) [3]	54 [3]
<u>6</u>	- 163.5 (m) [3]	52.5 [3]
<u>9</u>	- 185.3 (t)	53.4
<u>10</u>	- 165.0 (2d) - 164.5 (2d)	55.5 54.2

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REFERENCES

- 1 J.R. McCarthy, N.P. Peet, M.E. LeTourneau and J. Inbasekaran, J. Am. Chem. Soc., 107 (1985) 735.
- 2 M.E. Houston, Jr. and J.F. Honek, J. Chem. Soc., Chem. Commun., (1989) 761.
- 3 J.R. Sufrin, A.J. Spiess, D.L. Kramer, P.R. Libby and C.W. Porter, J. Med. Chem., 32 (1989) 997.
- 4 The use of antimony trichloride as a catalyst in DAST transformation of 4 to 5 and 6 has been reported recently by M.J. Robins and S.F. Wnuk, Tetrahedron Lett., 29 (1988) 5729.
- 5 P.A. Messina, K.C. Mange and W.J. Middleton, J. Fluorine Chem., 42 (1989) 137.
- 6 R. Kuhn and W. Jahn, Chem. Ber., 98 (1965) 1699.
- 7 A. Matsuda, M. Shinozaki, M. Suzuki, K. Watanabe and T. Miyasaka, Synthesis, (1986) 385.
- 8 A. Hampton, J. Am. Chem. Soc., 83 (1961) 3640.
- 9 A. Nyilas and J. Chattopadhyaya, Synthesis, (1986) 196.