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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

JANICE R. SUFRIN, ARTHUR J. SPIESS AND VITAUTS ALKS

Grace Cancer Drug Center, Roswell Park Cancer Institute,
Buffalo, NY 14263 (U.S.A.)

SUMMARY

Treatment of N-acetylmethionine sulfoxide methyl ester with diethylaminosulfur 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,

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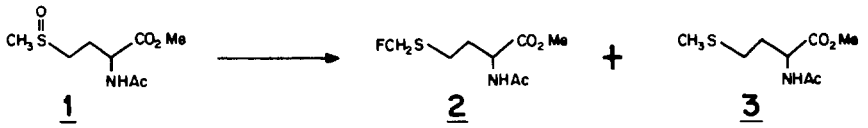
sterically controlled formation of fluoromethyl ethyl sulfide from methyl ethyl sulfoxide. Accordingly, our expectations that treatment of N-acetyl-L-methionine sulfoxide methyl ester 1 with DAST would yield the corresponding S-monofluoromethyl derivative 2 proved correct (TABLE 1); however, by changing 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



Sulfoxide	Reagent (equiv)	Temp (^{o}C)	Time (hr)	Products (% yield[a])
1	DAST(2)	RT	2-18	2(8) + 3(78)
1	DAST(2)	reflux	1.5	2(85)
1	meDAST(2)	reflux	1.5	2(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.

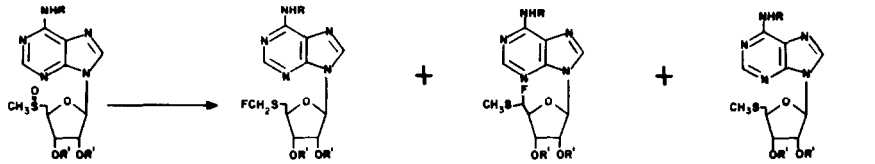
4. The N-6-amino substituent of adenosine does not need protection during reactions with DAST or meDAST, and appears to facilitate the McCarthy transformation when left unprotected.

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'
4	H	Ac	5	H	Ac	6	H	Ac	7	H	Ac
8	H	Ip	9	H	Ip	10	H	Ip	11	H	Ip
12	MMTr	Ip									

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

Sulfoxide	Reagent (equiv)	Temp (^{o}C)	Time (hr)	Products (% yield)
4	DAST(10)	55	2.5	5(11) + 6(31)[a]
4	meDAST(10)	55	2.5	5(14) + 6(40) + 7(13)[a]
4	meDAST(5)	55	2.5	5(14) + 6(46) + 7(23)[b]
4	meDAST(5)	RT	20	SM[c]
8	DAST(3)	reflux	1.5	SM[c]
8	DAST(3) ZnI_2(0.03)	reflux	16	SM[c]
8	meDAST(5)	50	3-5	9(37) + 10(37) + 11(20)[b]
12	DAST(3)	reflux	3	SM[c]
12	meDAST(5)	RT	96	SM[c]
12	meDAST	50	3	SM[c]

[a]isolated yields of deacetylated products, purified as described [3].

[b]based on isolated yields of product mixture and subsequent determination of product ratios from ^{1}H NMR and/or ^{19}F NMR spectra.

[c]thin layer chromatography and ^{1}H 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 CH_3OH/NH_3, and the resultant deprotected nucleosides were separated and characterized as described [3].

Fluorine-19 NMR spectroscopy

Compound	Chemical Shift [δ(from $CFCl_3$)]	Coupling Constant (Hz)
2	- 183 (t)	55.5
5	- 182 (t) [3]	54 [3]
6	- 163.5 (m) [3]	52.5 [3]
9	- 185.3 (t)	53.4
10	- 165.0 (2d) - 164.5 (2d)	55.5 54.2

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