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FACILE SYNTHESIS OF 3-OXO-1,2,5-THIADIAZOLES; 7ß-[3-OXO-1,2,5-THIADIAZOL-2-YL] CEPHALOSPORINS

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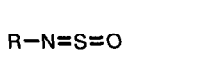
ABSTRACT - A simple procedure is described for the preparation of 3-oxo-1,2,5-thiadiazoles under mild conditions. This procedure has provided hitherto unknown 7ß-[3-oxo-1,2,5-thiadiazol-2-yl] cephalosporins.

N-Sulfinylamines, **1**, have been shown to offer considerable synthetic opportunities.[1,2,3] They have often been prepared by the reaction of thionyl chloride on the corresponding amines.[1,2,3] More recently, Sakai and co-workers have used the action of sulfur dioxide on lithiated amines.[4] Porskamp and Zwanenburg later found that sulfur dioxide and N-trimethylsilyl-lithioamines provided good yields of N-sulfinylamines.[5] In this last procedure, the need for an excess of sulfur dioxide was stressed, this minimizing the formation of sulfurdiimines, **2**.

α-Aminoamides have been converted to 3-hydroxy-1,2,5-thiadiazoles **3** by sulfur monochloride, thionyl chloride or thionyl aniline[6,7,8] while the disubstituted 3-oxo-1,2,5-thiadiazolones **4** have been reported by Rokach and colleagues using sulfur monochloride.[9] These thiadiazole syntheses may involve sulfinylamine intermediates.



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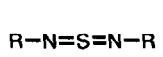

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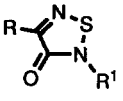

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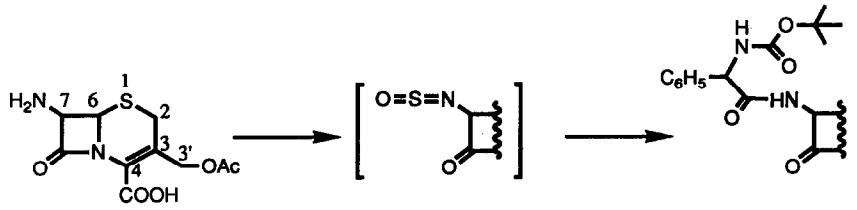
The only application of this type of chemistry to cephalosporins appears to be that recorded in a patent assigned to Kanebo.[10] In that case 7-aminocephalosporins were treated with thionyl chloride and an organic base, such as dimethylaniline. As exemplified by **5**, the sulfinylamines were treated *in situ* with carboxylic acids to give 7ß-acylamido-cephalosporins.



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In the course of studies on cephalosporins with N-S bonds in the 7-side chains, we discovered an extremely facile synthesis of the thiadiazolones of structure **7** using sulfur dioxide generated *in situ*. This was extended to penicillin **8**.

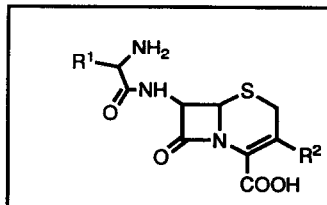
The procedure consisted of preparing a solution of the fully trimethylsilylated cephalosporin **6** in acetonitrile and adding this to a solution of up to 3 mole excess of sulfur dioxide in acetonitrile, this later being prepared *in situ* from thionyl chloride and water. The hydrogen chloride was taken up by pyridine or excess silylating agent. The reaction mixture was generally worked up after 3 hrs. but reaction was often complete after 1 hr. The only complicating factor was contamination of some of the cephalosporin thiadiazolones by their corresponding Δ^2 isomers, which were readily removed by HPLC. The ratio of Δ^2/Δ^3 ranged from essentially zero, with 7a and 7c, to 1:1 in the case of 7b (in which the strongly electronegative Cl increases the acidity of the protons at the 2-position).

The NMR spectra of the ß-lactams were distinguished by the fact that the chemical shifts of the signals of the ß-lactam ring protons appeared 0.3-0.8 ppm downfield from their usual positions. In DMSOd6 the C(7) and C(6) protons of the cephalosporins showed up in the ranges 6.38-6.10 and 5.43-5.28 ppm, respectively, both signals being doublets ($J \approx 5.0$ Hz). The corresponding protons of **8** gave signals at 6.18 and 5.77 ppm.

Besides adding generality to the procedure, compounds **9a-c** were made as models for UV comparison. Indeed, for example, the UV spectra of **7** and **8** proved to be composites of the absorption of the parent ß-lactams together with that of **9**.

The mechanism of formation of the thiadiazolone ring is presumed to be as shown in Scheme 1, the sulfinylamine being an intermediate. Table 1 gives yields and some identifying spectral details for the thiadiazolones, and Table 2 shows analytical and HRMS data.

We have also found, at least in the case of **7a**, that the thiadiazolone can also be formed by treating silylated **6a** with thionyl chloride, itself, and pyridine. However, this gave a more colored product than when using sulfur dioxide. The yield of pure **7a** was 27% after chromatography, whereas when sulfur dioxide was used the yield was 65% without chromatography. Furthermore, it is quite clear that the sulfur dioxide procedure would offer advantage over the thionyl chloride method when the starting aminoamide contains another function which would react with thionyl chloride



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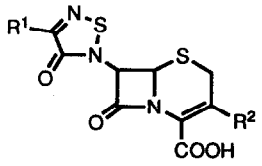

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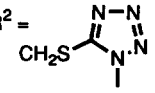
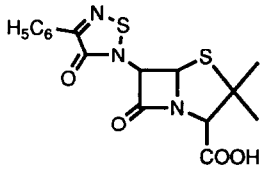
a	$R^1 = C_6H_5$	$R^2 = CH_3$
b	$R^1 = pHOC_6H_4$	$R^2 = Cl$
c	$R^1 = C_6H_5$	$R^2 = CH_2OC(O)CH_3$
d	$R^1 = pHOC_6H_4$	$R^2 =$ 



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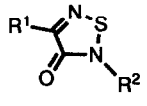

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a	$R^1 = C_6H_5$	$R^2 = H$
b	$R^1 = pHOC_6H_4$	$R^2 = H$
c	$R^1 = C_6H_5$	$R^2 = CH_3$

SCHEME 1

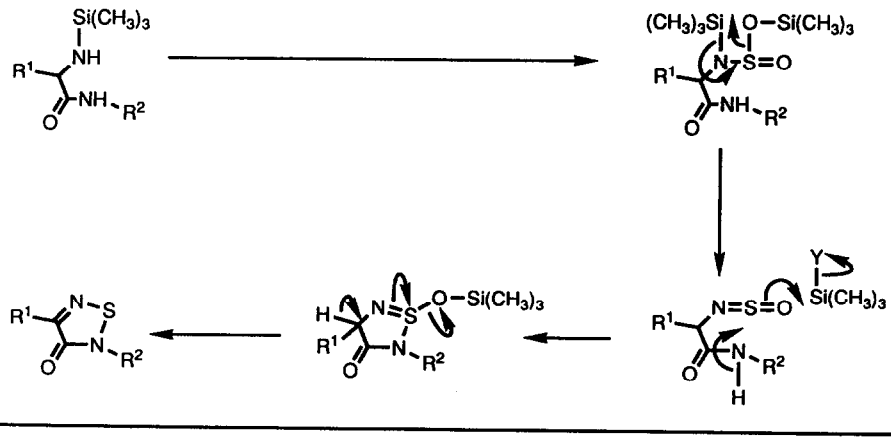

TABLE 1. Yields and Spectral Data for the Synthesized Thiadiazolones

Compound	Yield(%)	UV (MeOH)	NMR (DMSOd6)	
			Aromatic H	β -Lactam H
7a	65	236(12,500)337(14,400)	8.24(2H,m)7.46(3H,m)	6.22(1H,d,J=4.5Hz)5.34(1H,d,J=4.5Hz)
7b	25	236(14,000)344(15,000)	8.12(2H,d) 6.81(2H,d)	6.32(1H,d,J=4.6Hz)5.48(1H,d,J=4.6Hz)
7c	31	230(10,400)335(13,200)	8.28(2H,m)7.49(3H,m)	6.37(1H,d,J=4.9Hz)5.43(1H,d,J=4.9Hz)
7d	17	236(19,600)346(15,700)	8.17(2H,d) 6.86(2H,d)	6.19(1H,d,J=4.5Hz)5.28(1H,d,J=4.5Hz)
8	57	230(9,600) 337(16,800)	8.27(2H,m)7.48(3H,m)	6.18(1H,d,J=4.3Hz)5.77(1H,d,J=4.3Hz)
9a	35	222(8,500)307(13,900)	8.10(2H,m)7.45(3H,m)	
9b	38	227(8,300)317(15,500)	7.96(2H,d) 6.84(2H,d)	
9c	58	234(9,300)332(19,300)	8.47(2H,m)7.60(3H,m)	

TABLE 2. Elemental Analytical Data and High Resolution Mass Spectrometric Data.*

	Formula		C	H	N	S		Formula		C	H	N	S
7a	$C_{16}H_{13}N_3O_4S_2$	T	49.99	3.67	10.93	16.68	**8**	$C_{16}H_{15}N_3O_4S_2$	T	50.92	4.01	11.13	16.99
	0.5 H_2O	F	50.05	3.75	10.73	16.49			F	50.72	3.99	10.93	16.72
7b	$C_{15}H_{10}ClN_3O_5S_2$	T	43.75	2.45	10.20	15.57	**9a**	$C_8H_6N_2OS$	T	53.92	3.39	15.72	17.99
		F	43.70	2.61	9.94	15.24			F	54.04	3.50	15.88	18.05
7c	$C_{18}H_{15}N_3O_6S_2$	T	49.88	3.49	9.69	14.79	**9b**	$C_8H_6N_2O_2S$	T	47.28	3.47	13.79	15.78
		F	49.66	3.70	9.44	14.80		0.5 H_2O	F	47.63	3.57	13.77	15.88
7d	$C_{18}H_{15}N_7O_5S_3$	T	42.38	3.52	16.66	16.35	**9c**	$C_9H_8N_2OS$	T	56.23	4.19	14.57	16.68
	1.38 CH_3COOH#	F	42.15	3.38	17.05	15.95			F	56.17	4.25	14.39	16.57

Trifluoroacetyl **6d**: $C_{20}H_{18}N_7O_6S_2F_3$; Fluorine, T 9.94, F 9.83 % .

FAB-HRMS $C_{18}H_{14}N_3O_6SF_3$ (M^+ - N-methyltetrazolethiol, $C_2H_4N_4S$), T 457.0555, F 457.0548 D.

7d: FAB-HRMS $C_{18}H_{15}N_7O_5S_3Na$ ($M + Na^+$) T 528.0194, F 528.0202 D.

* T= Theory F= Found # CH_3COOH remains from HPLC

An intriguing difference between sulfur dioxide and thionyl chloride was found to occur with the silylated trifluoracetic acid salt of **6e**. Sulfur dioxide (prepared *in situ*) and pyridine gave the thiadiazolone **7e**; whereas thionyl chloride, with or without pyridine, afforded the trifluoracetamide of **6e**. Acylation via the formation of an acid chloride from a silylated carboxylic acid has been reported previously;[11] and silylated trifluoracetic acid may be expected to be one of the acids reacting most readily in this manner. However, reaction of trimethyl silyl trifluoracetic acid with the intermediate sulfinylamine, in a manner somewhat analogous to the procedure of the Kanebo group,[10] cannot be definitively ruled out as the means of amide formation.

Porskamp and Zwanenburg[5] stated that a large excess of sulfur dioxide was necessary for sulfinylamine formation. The fact that a large excess of sulfur dioxide was not necessary in our case probably resulted from the rapid intramolecular trapping of the sulfinylamine function by the amide group, this obviating sulfurdimine formation. This being the case, the trifluoroacetamide formation mentioned above would probably have occurred via the acid chloride.

EXPERIMENTAL

The UV spectra were obtained using Cary 18 or Cary 219/Apple 2 units, NMR spectra were recorded on a JEOL FX90FT instrument, and HRMS were obtained using a Varian-MAT 731 or VG ZAB-2SE machine.

Thiadiazolone Synthesis Using Sulfur Dioxide Generated *In Situ*

The following is the general procedure, the figures quoted being those per mmole of starting aminoamide. The products described were obtained over a range of reaction scales, from 1 mmole to 15 mmole.

General Procedure (for 1 mmole of Aminoamide)

A solution of thionyl chloride (2 mmole) and pyridine (4.5 mmole) in CH_3CN (10 ml) was stirred in an acetone-ice bath while water (2.05 mmole) was added. Fifteen minutes later the cooling bath was removed and N-methyltrimethylsilyltrifluoroacetamide (MSTFA) (4 mmole) was added. This MSTFA was found to prevent the occasional precipitation of cephalosporin when the silylated cephalosporin solution was added. It is presumed that the MSTFA serves to react with the hydrogen chloride of the formed pyridinium hydrochloride, thus preventing stripping of the silyl functions from the silylated cephalosporin. Following another 15 min. stirring, a solution of the starting aminoamide (1 mmole) and MSTFA) (4 mmole) in dry CH_3CN (6 ml) was added. The mixture was then stirred for 3 hrs. prior to work-up.

MSTFA can be purchased from the Aldrich Chemical Co. or, in Kg quantities, from Pierce Chemical Co., Post Office Box 117, Rockford, Illinois 61105, USA

Work-up Procedures

7a through **7d**: The reaction mixture was concentrated to about one-half volume by rotary evaporation, poured into ice water (50-80 ml), the pH adjusted to 1.8 and filtered. When necessary, the product was purified by HPLC on NOVA-PAK reverse-phase C_{18} silica columns (from Waters). The mobile phase was in the range $H_2O/CH_3CN/CH_3COOH$ 70:28:2 to 63:35:2. Compounds **7a** and **7c** did not require chromatography.

8: As with **7a** through **7d** except that the product was extracted into ethyl acetate, rather than filtering. After drying ($MgSO_4$) and rotary evaporation to a dry foam, the foam was placed under house vacuum

overnight to remove traces of ethyl acetate. The foam was then broken up, stirred under water and the mixture filtered to give pure **8**.

9a through **9c**: As with **7a** through **7d**, however, following the filtration and drying **9c** was pure, while **9a** and **9b** were cleaned by a simple chromatography on silica gel using ethyl acetate as the eluent.

Synthesis of Thiadiazolone **7a** Using Thionyl Chloride

A solution of cephalexin monohydrate (530 mg, 1.45 mmole) and MSTFA (2.35 g, 11.8 mmole) in acetonitrile (7 ml) was added to a stirred solution of thionyl chloride (33 mg, 2.8 mmole) in acetonitrile (11 ml). The resulting mixture was stirred for a further 2 1/4 hrs., concentrated to about half-volume by rotary evaporation and dripped into rapidly stirred ice water (40 ml). The pH was adjusted from 2.8 to 2.0 and the supernatant was decanted off a small quantity of gummy solid. Ice-water (10 ml) was added to the decanted solution, with stirring, then the mixture was sonicated and filtered to give crude **7a** (285 mg). Chromatography of this material on a Harrison Research Chromatotron, Model 7924, using ethyl acetate through ethyl acetate methanol 1:1 for elution, gave pure **7a** (149 mg), in 27% yield.

Trifluoracetamide of **6e** from the Trifluoroacetate Salt of **6d**

Bistrimethylsilyltrifluoracetamide (2.06 g, 2.2 ml, 8 mmole) was added to the trifluoracetic acid salt of **6d** (1.18 g, 2 mmole) stirred in acetonitrile (12 ml). The resulting solution was added to a solution of thionyl chloride (476 mg, 4 mmole) in acetonitrile (18 ml). After stirring for 4 hrs., the mixture was dripped into rapidly stirred ice water. The crude product was collected by filtration, water washed, then air dried to give a cream-colored solid (835 mg). Purification by HPLC on a column using acetonitrile:water (25:2) as the eluent gave pure amide (163 mg).

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