Efficient Synthesis of 1,2,4-Dithiazolidine-3,5-diones (Dithiasuccinoyl-amines) and Observations on Formation of 1,2,4-Thiadiazolidine-3,5-diones by Related Chemistry

Urszula Słomczyńska [1] and George Barany* [2]

Department of Chemistry, University of Minnesota,
Minneapolis, MN 55455

Received July 15, 1983

An efficient synthesis of 1,2,4-dithiazolidine-3,5-diones (**1**) from chlorocarbonylsulfenyl chloride (**3**) plus *O*-dimethylaminoethyl-*N*-alkyl or aryl thiocarbamates (**4**) has been worked out. In this synthesis, 1,2,4-thiadiazolidine-3,5-diones (**5**) have been shown to arise as low-level by-products, and experiments were conducted to elucidate the mechanism of the side reaction. *N,N'*-Dimethyl-1,2,4-thiadiazolidine-3,5-dione (**5a**) was prepared in one step from *N,N'*-dimethylurea plus **3**, or from **4a** plus one equivalent of sulfuryl chloride. A general route to **5** involved reaction of equimolar amounts of isocyanates (**6**), isothiocyanates (**7**) and sulfuryl chloride followed by hydrolysis of intermediate **9**. Heterocycles reported have been characterized by nmr, ir, uv, ms, and hplc.

J. Heterocyclic Chem., **21**, 241 (1984).

Introduction.

The 1,2,4-dithiazolidine-3,5-dione heterocyclic system **1** [3-5] was proposed by one of us [6] as the basis of the novel dithiasuccinoyl (Dts) amino-protecting group for peptide synthesis. Heterocycles **1** have been synthesized (Scheme I) by reaction of *O*-ethyl thiocarbamates (**2**), also referred to as ethoxythiocarbonyl-amines, with chlorocarbonylsulfenyl chloride (**3**). Because this method gives rise [7,8] to low levels of by-products retaining the original *O*-alkyl group of **2**, we have devised and optimized the variation reported in this paper involving dimethylaminoethyl derivatives **4** in place of **2**. The new variation allows removal of most unwanted by-products through an aqueous acid workup. However, we have also observed a stable *N*-alkyl-containing by-product which sometimes contaminates **1**. That by-product has now been identified as the 1,2,4-thiadiazolidine-3,5-dione heterocycle **5** with identical R groups; these are already known *via* other chemistry [5,

SCHEME I

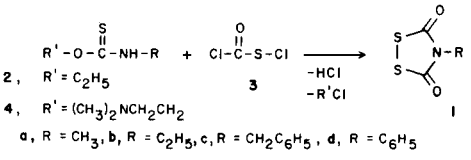


Table I

O-Dimethylaminoethyl-*N*-Alkyl or Aryl Thiocarbamates [a]

Compound No.	Yield, %	Mp °C	Formula (Mol Wt)	Analysis (%) Calcd./Found C	H	N	S	^{1}H-nmr (deuteriochloroform) [b] (δ)
4a	78	62-65° [c]	$C_6H_{14}N_2OS$ (162.25)	44.42 44.57	8.70 8.59	17.27 17.30	19.76 19.81	6.8-6.9 (m, 1 H, NH), 4.53, 4.61 (t, J = 5.6 Hz, 2 H, O-CH_2), 3.07, 2.88 (d, J = 5.0 Hz, 3 H, NH-CH_3), 2.62, 2.69 (t, J = 5.6 Hz, 2 H, N-CH_2), 2.28, 2.31 (s, 6 H, $N(CH_3)_2$), *cis:trans* = 75:25
4b	67	oil [d]	$C_7H_{16}N_2OS$ (176.28)	47.70 47.63	9.15 9.15	15.89 16.06	18.20 18.05	7.0-7.2 (m, 1 H, NH), 4.45, 4.52 (t, J = 5.8 Hz, 2 H, O-CH_2), 3.45, 3.22 (dq, J = 5.5, 7.3 Hz, 2 H, NH-CH_2), 2.55, 2.61 (t, J = 5.8 Hz, 2 H, N-CH_2), 2.20, 2.22 (s, 6 H, $N(CH_3)_2$), 1.12, 1.08 (t, J = 7.3 Hz, 3 H, $NHCH_2CH_3$), *cis:trans* = 76:24
4c	70	58-60°	$C_{12}H_{17}N_2OS$ (238.35)	60.47 60.35	7.61 7.45	11.75 11.89	13.45 13.41	7.1-7.2 (m, 5 H, $C_6H_5CH_2$), 6.9-7.0 (m, 1 H, NH), 4.73, 4.46 (d, J = 5.6 Hz, 2 H, $NHCH_2C_6H_5$), 4.56, 4.62 (t, J = 5.5 Hz, 2 H, O-CH_2), 2.63, 2.65 (t, J = 5.7 Hz, 2 H, N-CH_2), 2.26, 2.27 (s, 6 H, $N(CH_3)_2$), *cis:trans* = 80:20
4d	90	oil	$C_{11}H_{16}N_2OS$ (224.32)	58.92 58.68	7.19 6.92	12.49 12.46	14.29 14.17	8.0-8.4 (m, 1 H, NH), 7.26-7.40 (m, 5 H, C_6H_5), 4.65 (t, J = 5.6 Hz, 2 H, O-CH_2), 2.70 (t, J = 5.6 Hz, 2 H, N-CH_2), 2.29 (s, 6 H, $N(CH_3)_2$)

[a] As evaluated by reversed-phase hplc, acetonitrile-5 m*M* trifluoroacetic acid in water (9:1), 2 ml/minute, detection by uv at 240 nm, all compounds were pure and in particular were free of the *S*-alkyl-*N*-alkyl thiocarbamate isomer. [b] Observed at 300 MHz. As reported by Bauman (ref [18]), two rotational isomers exist on an nmr time scale; shifts of the major (*cis*) isomer are reported first. [c] Lit mp 63-67° (ref [18]). [d] A solid containing approximately half a mole of hydration, and giving satisfactory elemental analysis, was obtained out of the alkaline aqueous phase at that step of the experimental procedure. *In vacuo* drying provided an oil.

Table II

Optimal Conditions for Conversion **3** + **4a** → **1a** [a]

No.	Solvent	Temp (°C)	Yield
1	dichloromethane	40°	77
2	dichloromethane	20°	68
3	dichloromethane	-40°	33
4	chloroform	60°	80
5	chloroform	20°	47
6	chloroform	-40°	23
7	carbon tetrachloride	60°	53
8	benzene	80°	68
9	benzene	40°	56
10	benzene	10°	43
11	acetonitrile	40°	53
12	dioxane	40°	50
13	ether	30°	40
14	ether	0°	41
15	ether	-40°	17 [b]

[a] Over 15 minutes, 2 ml of a 1 *M* solution of **4a** was added to 8 ml of a 0.3 *M* solution of **3** at the indicated temperature. After reaching 25°, reaction mixtures were washed with water, 1 *N* aqueous sodium thiosulfate, 1 *N* aqueous hydrochloric acid, and water, dried over magnesium sulfate, and evaporated, except numbers 10 and 11 which were evaporated first, resuspended in a mixture of dichloromethane and water, and then worked up the same way. [b] Substantial sulfur precipitate.

9-17]. Experiments reported herein quantitate and suggest mechanisms for the side reaction leading to **5**, and also lead to several convenient syntheses of the pure heterocycle **5**.

Results and Discussion.

1. 1,2,4-Dithiazolidine-3,5-diones.

First, the *O*-dimethylaminoethyl-*N*-alkyl or aryl thiocarbamates (**4**) were synthesized, along general lines already suggested [18], by reaction of the alkoxide with the appropriate isothiocyanate (Table I). Taking the *N*-methyl derivative **4a**, a series of experiments was then carried out to optimize the yield of dithiazolidine **1a** (Table II). At a constant temperature, dichloromethane was somewhat the optimal solvent, but results among the other aprotic solvents tested were relatively comparable. Yields of desired **1a** were better at elevated temperatures, presumably because at lower temperature a decomposition to an isocyanate (**6**), gaseous hydrogen chloride and carbonyl sulfide, and solid elemental sulfur competes with heterocycle elaboration [6,8]. Finally, a number of derivatives **1** were synthesized and characterized (Table III). Purities were excellent, and the yields of 75 to 90% were appreciably better than those reported in the literature.

2. 1,2,4-Thiadiazolidine-3,5-diones.

Interest in this heterocyclic system arose because of the discovery of trace nmr signals and one corresponding new hplc peak whenever **1** was prepared even by the improved new procedure starting from **4**. Assignment of structure **5** was originally made in the *N*-methyl series based on the observation of a peak in the high resolution electron impact mass spectrum of crude **1a** at m/e 146.0177 (calcd. for $C_4H_6N_2O_2S$: 146.0149) that was absent from the spectrum of purified **1a**. Confirmation of structure **5a** was by alternative syntheses and co-chromatography. The absolute yield of **5a** was quantitated by hplc and found to be as high as 5% which implies conversion of 10% of the *N*-alkyl groups of starting **2a** or **4a** under conditions where overall conversion to total heterocyclic products was in excess of 85%. In dichloromethane, the purity of **1a** defined as (moles **1a**)/(moles **1a** + **5a**) varied in a regular fashion from 93 to 99% over a 10-fold range of reaction concentration (0.5 *M* to 0.05 *M*), while the yield of **1a** remained constant within experimental error. Also, the purity improved

Table III

1,2,4-Dithiazolidine-3,5-diones [a]

Compound No.	Yield [b] %	Mp °C	Formula (Mol Wt)	Analysis (%) Calcd./Found C	H	N	S	^{1}H-NMR (deuteriochloroform) [c] (δ)
1a	85	33-35° [d]	$C_3H_3NO_2S_2$ (149.18)	24.15 23.93	2.02 2.18	9.39 9.37	42.88 43.00	3.29 (s)
1b	87	oil	$C_4H_5NO_2S_2$ (163.21)	29.43 29.19	3.08 3.10	8.58 8.50	39.28 39.41	3.85 (q, 2 H, J = 7.2 Hz), 1.26 (t, 3 H, J = 7.2 Hz)
1c	75	90-92° [e]	$C_9H_7NO_2S_2$ (225.28)	47.98 47.71	3.13 3.35	6.21 6.03	28.46 28.38	7.1-7.45 (m, 5 H), 4.89 (s, 2 H)
1d	76	164-167° [f]	$C_8H_5NO_2S_2$ (211.25)	45.48 45.59	2.39 2.57	6.63 6.76	30.35 30.34	7.1-7.6 (m, 5 H)

[a] The exact procedure for **1a** is given in the Experimental. Compounds **1b** through **1d** were made in the same fashion but on 20 to 50 mmole scales. All compounds were obtained pure by reversed-phase hplc, methanol-water (6:4), 1 ml/minute, detection by uv at 210 nm. [b] For **1a** and **1b**, as obtained directly, average two separate syntheses. For **1c** and **1d**, yields after recrystallization, respectively from ether-petroleum ether, and from petroleum ether. [c] Observed at 80 MHz. [d] Lit mp 38-39° (ref [4]), lit yield 67%. [e] Lit mp 93-94° (ref [4]), lit yield 35%. [f] Lit mp 168-169° (ref [4]), lit yield 69%.

Table IV

1,2,4-Thiadiazolidine-3,5-diones as By-Products during Synthesis of 1,2,4-Dithiazolidine-3,5-diones in the Presence of Isocyanates [a]

No.	R	R*	Products	HPLC t_R (min)	Proportion (%)
1	C_2H_5	CH_3	**1b**	6.2	99.5
			5b	4.9	0.3
			5f	3.8	0.2
2	CH_3	C_6H_5	**1a**	4.4	97.0
			5a	3.2	1.8
			5g	7.8	1.2
3	C_6H_5	CH_3	**1d**	6.7	97.8
			5d	14.1	0.2
			5h	4.4	2.0
4	C_6H_5	C_2H_5	**1d**	6.7	99.0
			5d	14.1	0.03
			5j	5.9	1.0

[a] Over 5 minutes, 2 ml of a 1 *M* solution of **3** in dichloromethane was added at 40° to 2 ml of a dichloromethane solution that was 1 *M* in **4** (R) and 3 *M* in **6** (R*). After 10 minutes more at 25°, the reaction mixtures were worked up as described in Table II, note a, and then analyzed by reversed-phase hplc, as described in Table III, note a. Absolute yields of total heterocycle were 75 to 90% conversion of **4**.

substantially with decreasing temperature (*e.g.* > 99.8% at -20°), but as already seen (Table II), the temperature parameter also adversely affected the yield of desired **1a** itself. Finally, the extent of **5a** formation under otherwise comparable conditions varied over two orders of magnitude as a function of solvent in the sequence dichloromethane >> chloroform ~ acetonitrile > benzene, dioxane > carbon tetrachloride ~ ether.

Insights into the mechanism of formation of **5** were provided by experiments in which the reaction of **3** plus **4** to provide **1** was carried out in the presence of an alkyl or aryl isocyanate (**6**) carrying an R* group *different* from the *N*-alkyl group of the starting thiocarbamate (Table IV). Note that in addition to **5** with both R groups of **4**, "crossed" **5** with R* and R appearing at the 2 and 4 positions of

SCHEME II

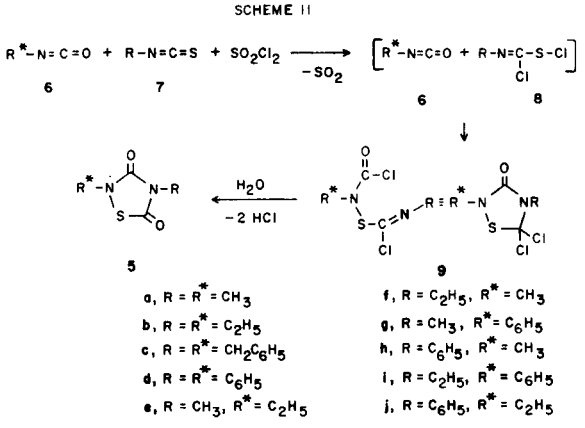


Table V

1,2,4-Thiadiazolidine-3,5-diones [a]

Compound No.	Yield [b] %	Mp °C	Formula (Mol Wt)	Analysis (%) Calcd./Found C	H	N	S)	^{1}H-NMR (deuteriochloroform) [c] (δ)
5a	36	58-60° [d]	$C_4H_6N_2O_2S$	32.86	4.14	19.17	21.93	3.20 (s, 6 H) [e]
			(146.16)	32.87	4.16	19.34	22.04	
5d	46	110-114° [f]	$C_{14}H_{10}N_2O_2S$	62.21	3.73	10.36	11.86	7.30-7.90 (m, 10 H)
			(270.31)	62.17	3.70	10.58	11.78	
5e	63	oil [g]	$C_5H_8N_2O_2S$	37.49	5.03	17.49	20.01	3.70 (q, 2 H, J = 7.1 Hz), 3.19 (s, 3
			(160.19)	37.70	4.90	17.45	19.89	H), 1.27 (t, 3 H, J = 7.1 Hz)
5f	53	oil	$C_5H_8N_2O_2S$	37.49	5.03	17.49	20.01	3.73 (q, 2 H, J = 7.1 Hz), 3.19 (s, 3
			(160.19)	37.43	5.04	17.44	19.91	H), 1.25 (t, 3 H, J = 7.1 Hz)
5g	58	110-111° [h]	$C_9H_8N_2O_2S$	51.91	3.87	13.45	15.40	7.10-7.70 (m, 5 H), 3.29 (s, 3 H)
			(208.24)	51.76	4.09	13.65	15.29	
5h	54	178-180° [i]	$C_9H_8N_2O_2S$	51.91	3.87	13.45	15.40	7.00-7.70 (m, 5 H), 3.27 (s, 3 H)
			(208.24)	51.84	4.00	13.65	15.33	
5i	21	69-70° [j]	$C_{10}H_{10}N_2O_2S$	54.04	4.54	12.60	14.42	7.35-7.57 (m, 5 H), 3.84 (q, 2 H, J =
			(222.26)	53.97	4.46	12.84	14.39	7.2 Hz), 1.33 (t, 3 H, J = 7.2 Hz)
5j	27	84-85°	$C_{10}H_{10}N_2O_2S$	54.04	4.54	12.60	14.42	7.35-7.60 (m, 5 H), 3.84 (q, 2 H, J
			(222.26)	53.83	4.49	12.74	14.53	=7.2 Hz), 1.33 (t, 3 H, J = 7.2 Hz)

[a] General procedure in the Experimental. All compounds were obtained pure by reversed-phase hplc, see Table IV for some retention data. [b] Yields were not optimized. [c] Observed at 80 MHz. [d] Lit mp 65° (ref [5]). [e] Two methyl singlets were resolved when the solvent was carbon tetrachloride, or when pyridine was added to the deuteriochoroform solution. [f] Lit mp 114-115° (ref [10]). [g] Distilled, bulb-to-bulb, oven 110-115° (0.2 mm). [h] Lit mp 106-107° (ref [13]). [i] Lit mp 182-184° (ref [16]). [j] Recrystallized from methanol to constant mp, and pure by elemental analysis and hplc. Reported lit mp 94-95° (ref [10]) is considerably higher.

Table VI

Electron Ionization Mass Spectra of Selected Pure Crossed 1,2,4-Thiadiazolidine-3,5-diones [a]

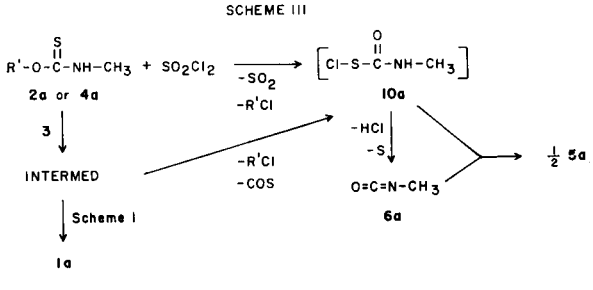
Ion	5e		5f		5g		5h	
	m/e	Rel Int	m/e	Rel Int	m/e	Rel Int	m/e	Rel Int
$M^{+\cdot}$	160	26%	160	71%	208	64%	208	66%
$M^{+\cdot}$ - RNCO	103	35%	89	98%	151	4%	89	91%
$M^{+\cdot}$ - R*NCO	89	--	103	31%	89	1%	151	69%
$R^*NS^{+\cdot}$	75	42%	61	100%	123	100%	61	54%
$RNS^{+\cdot}$	61	--	75	10%	61	2%	123	35%
$RNCO^{+\cdot}$	57	54%	71	21%	57	23%	119	100%
$(RNCO - H)^+$	56	100%	70	18%	56	6%	118	--
R^*NCO^+	71	49%	57	26%	119	47%	57	34%
$(R^*NCO - H)^+$	70	--	56	55%	118	--	56	18%
$S_2^{+\cdot}$	64	9%	64	19%	64	24%	64	36%
Other	60 [b]	14%	60 [b]	12%	91 [c]	40%	91 [c]	49%
			58	18%	77 [d]	20%	77 [d]	11%

[a] Observed at 70 eV, source temperature 200°, solid probe insertion at 25°. All ions at m/e ≥ 56, with relative intensity ≥ 10%, have been identified and tabulated. [b] $COS^{+\cdot}$. [c] $C_6H_5N^{+\cdot}$. [d] $C_6H_5^+$.

the heterocycle respectively (exactly as drawn in text structural diagram) formed as well. Authentic pure crossed **5** were synthesized (Scheme II) by a convenient and specific new method which builds upon several already mentioned primarily in the patent literature [10, 12, 14-17]. Thus, *in situ* chlorination with sulfuryl chloride of an isothiocyanate (**7**) in the presence of an isocyanate (**6**) provided *via* an unstable *S*-chloroisothiocarbamoyl chloride (**8**) the adduct **9** which was collected without purification and hydrolyzed (Table V). In selected cases (*e.g.*, **5g** vs. **5h**), isomeric compounds were resolvable by hplc. Because the nmr spectra of isomers were essentially superimposable, a study of the details of the electron impact mass spectral fragmentation patterns (Table VI) was required to facilitate the distinction.

One of us has recently found [19] that alkoxythiocarbonyl derivatives of secondary amines (compare to **2**) rapidly add sulfuryl chloride and lose alkyl chloride to provide carbamoylsulfenyl chlorides (compare to **10**) which have a limited stability and ultimately lose elemental sulfur to give *N*-carbamoyl chlorides. Application of the same chemistry to primary thiocarbamates (main pathway of Scheme III) was expected to give both **10** and soon thereafter isocyanates **6**. Since **10** is formally the hydrolysis product of **8** (Scheme II), it was hoped that 1,2,4-thiadiazolidine-3,5-diones **5** might be formed directly in these reaction mixtures. In fact, **4a** plus one equivalent sulfuryl chloride gave **5a** as the sole isolable product in a 40% overall yield, pure by nmr and hplc. Formation of **5** as a by-product in the synthesis of **1** can also be rationalized (Scheme III) by supposing that **10** and **6** arise from decomposition of the initial adduct from **3** plus **4**.

SCHEME III



EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 297 machine, uv spectra were measured with a Cary 14 PM recording spectrophotometer, and nmr spectra were observed with a Varian HFT 80/CFT 20 or Nicolet NT-300 spectrometer. High pressure liquid chromatography was carried out on a Beckman-Altex Model 334 system consisting of a 421 CRT controller, two 112 pumps, a 165 variable wavelength detector, and an Ultrasphere-ODS column (4.6 mm × 25 cm) together with a Hewlett-Packard 3390A reporting integrator. Mass spectra were obtained on a Kratos/AEI MS-30, and elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

Materials.

Solvents and chemicals were reagent grade and used without further purification. The principal supplier was Aldrich; benzyl isothiocyanate (**7c**) was from Fluka. Petroleum ether refers to solvent with bp 30-60°. *O*-Ethyl-*N*-methylthiocarbamate (**2a**) [20,21], *S*-ethyl-*N*-methylthiocarbamate [18,22], and chlorocarbonylsulfenyl chloride [23,24] were made by known procedures, and had satisfactory physical, spectral, analytical and chromatographic characteristics.

N-Methyl-1,2,4-dithiazolidine-3,5-dione (**1a**).

Method A. (Best).

A solution of **4a** (24.3 g, 0.15 mole) in chloroform (60 ml) was added dropwise over 1 hour to chlorocarbonylsulfenyl chloride (**3**) (15 ml, 0.18 mole) [25] in chloroform (90 ml) at a rate which maintained the reaction temperature at 58-60° by the gentle reflux of solvent provided by the spontaneous exotherm. After 30 minutes, the reaction mixture was cooled, washed with water (2 × 30 ml), 1 *N* aqueous sodium thiosulfate (2 × 30 ml) [26], 1 *N* aqueous hydrochloric acid (2 × 25 ml) and water (2 × 30 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to provide 19.0 g (85%) of the title

product as the hplc-pure oil. Formation of crystals was facilitated by trituration with petroleum ether (50 ml), and recrystallization from heptane provided 15 g of pale yellow plates; ir (dichloromethane): 3035 (w), 1730 (s), 1664 (vs), 1415 (m), 1330 (s), 1315 (s), 1030 (m), 965 (m) cm^{-1}; ^{13}C-nmr: δ 168.2 (s, C=O), 31.6 (s, N-CH_3); uv (absolute ethanol): λ max 256 nm (ε 3,200) and λ max 235 nm (ε 3,400); ms: m/e 149 (M^+, 50%), 121 ($M^+ - CO$, 28%), 64 (S_2^+, 100%), 60 (5%), 57 (8%), 56 (13%); high resolution ms: m/e 148.9598 (calcd. for $C_3H_3NO_2S_2$: 148.9605), 120.9659 (calcd. for $C_2H_3NOS_2$: 120.9656); further properties in Table III.

Method B.

Following Zumach *et al.* [4], **3** (26.4 g, 0.2 mole) was dropped into a solution of *O*-ethyl-*N*-methylthiocarbamate (**2a**) (23.8 g, 0.2 mole) in dry dioxane (100 ml) that was externally cooled with an ice bath, at a rate to maintain the reaction temperature between 20-28°. Subsequently, triethylamine (28 ml, 0.2 mole) was dropped in; the reaction mixture was stirred an additional 10 minutes at 25° and filtered to remove triethylammonium hydrochloride. The product (21 g) after rotary evaporation was further purified by vacuum distillation, bp 66° (0.1 mm) (lit bp 80° (0.2 mm), ref [4]) to provide a pale yellow oil (6.8 g, 23%) that was a mixture of **1a** (83%), **5a** (12%) and *S*-ethyl-*N*-methylthiocarbamate (5%; see note [7]) as shown by nmr, uv, and gc analysis.

General Procedure for *O*-Dimethylaminoethyl-*N*-Alkyl or Aryl Thiocarbamates (**4**).

N,N-Dimethylaminoethanol (105 ml, 1.04 moles) was added dropwise to a stirred suspension of sodium hydride (50% w/w in mineral oil, 50 g, 1 mole) in xylene (1.5 *l*) at 25°. Hydrogen gas evolved with a spontaneous exotherm, and the produced sodium alkoxide went almost entirely into solution. The appropriate alkyl or aryl isothiocyanate (0.83 mole) was then added over 15 minutes, again with a slight spontaneous exotherm. After additional stirring for 2 hours at room temperature, the reaction mixture was chilled in an ice-bath (< 15°) and then carefully neutralized with concentrated hydrochloric acid (90 ml, 1.1 moles). The mixture was then diluted with water (650 ml) and further concentrated hydrochloric acid (135 ml, 1.6 moles) was added. The aqueous phase was separated, chilled in ice, and then made alkaline with concentrated aqueous sodium hydroxide (90 ml, 1.7 moles). The precipitated or oily product was extracted into chloroform (3 × 400 ml) and the combined chloroform phases were dried over magnesium sulfate. The crude oily product after rotary evaporation was triturated with petroleum ether (400 ml) to provide crystals in two out of four cases. The scale given was followed for **4a** and **4b**, with **4c** and **4d** prepared on a 10 to 20-fold smaller scale. Further information and spectral data in Table I.

N,N'-Dimethyl-1,2,4-Thiadiazolidine-3,5-dione (**5a**).

Method A.

Following a scanty literature description [5,14], chlorocarbonylsulfenyl chloride (**3**) (20 ml, 0.24 mole) and *N,N'*-dimethylurea (19.0 g, 0.24 mole) in benzene (300 ml) were refluxed for 20 hours during all of which time hydrogen chloride gas was being evolved. Solvent was then removed by rotary evaporation to provide an oil (35.5 g) which contained substantial levels of components other than starting urea or desired **5a**. A distillation fraction at bp 76-81° (0.5 mm) was triturated with petroleum ether, and formed crystals, yield, 7.6 g (21%), mp 56-58°; pure by hplc; ir (deuteriochloroform): 2950 (w), 1755 (w, sh), 1735 (s), 1680 (vs), 1440 (s), 1380 (s), 1300 (w), 1040 (m), 1025 (m) cm^{-1}; uv (absolute ethanol): λ max 237 nm (ε 4,100); ms: m/e 146 (M^+, 100%), 89 ($M^+ - CH_3NCO$, 71%), 61 (CH_3NS^+, 24%), 60 (7%), 58 (21%), 57 (9%); high resolution ms: m/e 146.0132 (calcd. for $C_4H_6N_2O_2S$: 146.0149), 88.9920 (calcd. for C_2H_3NOS: 88.9935).

Method B.

Sulfuryl chloride (0.8 ml, 10 mmoles) was added dropwise with stirring to a solution of **4a** (1.6 g, 10 mmoles) in chloroform (10 ml) that was chilled in ice, at a rate to maintain the reaction at 15-20° by the spontaneous exotherm. After additional 1 hour stirring at room temperature, the reaction mixture was washed with water and 1 *N* aqueous hydrochloric acid. The organic phase was then dried over magnesium sulfate, filtered, and concentrated to provide directly the title product (0.29 g, 40%) as the nmr- and hplc-pure oil. Considerable elemental sulfur was formed during this procedure. When applied in the phenyl series with **4d** as the starting material, **5d** was not formed but rather *N,N*-diphenylurea was obtained (crude yield 41%, 10% after washing with methanol) with identity proved by hplc retention time, ms, mp and mixed mp with authentic urea.

Method C. (Best).

Table V, line 1.

General Procedure for Crossed 1,2,4-Thiadiazolidine-3,5-diones (**5**).

Sulfuryl chloride (0.8 ml, 10 mmoles) was added dropwise with stirring at 5-10° to a solution of alkyl or aryl isocyanate (**6**) and alkyl or aryl isothiocyanate (**7**) (10 mmoles each) in ether (5 ml). The mixture was then stirred for 16 hours at 25°, by which time a yellowish-white precipitate had formed. This crude precipitate, corresponding to **9** in Scheme II, was collected on a Buchner funnel, washed with dry ether, suction-dried, and added directly to water (300 ml) at 25°. Upon completion of the addition, the mixture was brought to boil for 10 minutes, and then cooled to 0°. The fully aliphatic heterocycles **5** which ensued were extracted into ether. After washing, and drying over magnesium sulfate, solvent was removed and crystals were usually obtained by trituration with petroleum ether. Those heterocyclic products with at least one *N*-aryl group precipitated directly from water, were collected by filtration, dried *in vacuo* over phosphorus pentoxide, and further purified by washing with petroleum ether. Results in Table V.

Acknowledgements.

We thank Steven J. Eastep for expert and enthusiastic technical assistance, and National Institutes of Health (GM 28934 and AM 01099), Research Corporation (Leo H. Baekeland Grant), and Chicago Community Trust (Searle Scholars Program) for generous financial support.

REFERENCES AND NOTES

[1] On leave of absence from the Institute of Organic Chemistry, Technical University, Lódź, Poland.

[2] Searle Scholar, 1982; National Institute of Health Research Career Development Award, 1982-1987.

[3] G. Zumach, W. Weiss and E. Kühle, Belgian Patent 682,820 (June 20, 1966); *Chem. Abstr.*, **68**, 105203a (1968).

[4] G. Zumach, W. Weiss and E. Kühle, British Patent 1,136,737 (June 21, 1966); Belgian Patent 682,991 (June 23, 1966); *Chem. Abstr.*, **70**, 7795 p (1969).

[5] Review: G. Zumach and E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).

[6] G. Barany and R. B. Merrifield, *J. Am. Chem. Soc.*, **99**, 7363 (1977).

[7] G. Barany, unpublished observations. Starting compounds **2** are prone to rearrange to the thermodynamically more stable *S*-alkyl thiocarbamate isomers under a variety of conditions including prolonged standing. This rearrangement may also occur up to 5%, although often less, under the precise reaction conditions described for synthesis of **1** from **2** plus **3** that are given in ref. 4.

[8] G. Barany and U. Slomczyńska, unpublished observations. *O*-Alkyl carbamates and related structures have been identified which appear to arise from **2,3**, and trace amounts of water contaminating the nominally anhydrous reaction conditions.

[9] Review: F. Kurzer, *Adv. Heterocyclic Chem.*, **32**, 285 (1982).

[10] G. Ottmann and H. Hooks, *Angew. Chem., Int. Ed. Engl.*, **5**, 672 (1966).

[11] P. Fischer and W. Weiss, German Patent 1,670,917 (September 4, 1967); cited in ref [5].

[12] G. F. Ottmann and H. Hooks, U.S. Patent 3,374,240 (June 29, 1965); *Chem. Abstr.*, **69**, 52146w (1968).

[13] G. Zumach, L. Eue, W. Weiss, E. Kühle and H. Hack, British Patent 1,115,350 (May 23, 1966); *Chem. Abstr.*, **69**, 96732p (1968).

[14] H. Holtschmidt, G. Zumach, F. Doring and E. Kühle, Belgian Patent 712,734 (March 25, 1968); cited in ref [5].

[15] W. Rohr, A. Fischer and A. Zschocke, U. S. Patent 3,711,492 (December 8, 1970); *Chem. Abstr.*, **78**, 84420h (1973).

[16] W. Rohr and A. Fischer, German Patent 2,109,755 (March 2, 1971); *Chem. Abstr.*, **7**, 164674p (1972).

[17] J. Kreuzer, U. S. Patent 3,900,485 (August 19, 1975); *Chem. Abstr.*, **84**, 44069t (1976).

[18] R. A. Bauman, *J. Org. Chem.*, **32**, 4129 (1967).

[19] G. Barany, unpublished observations.

[20] J. F. Harris, Jr., *J. Am. Chem. Soc.*, **82**, 155 (1960).

[21] G. Barany, B. W. Fulpius and T. P. King, *J. Org. Chem.*, **43**, 2930 (1978).

[22] By Schotten-Baumann acylation of methylamine with (ethylthio)-carbonyl chloride, in analogy to synthesis of *N*-methyl urethane described by W. W. Hartman and M. R. Brethren, *Organic Syntheses*, Coll. Vol. 2, John Wiley, New York, 1943, p 278.

[23] W. Weiss, German Patent 1,224,720 (Nov. 11, 1964); *Chem. Abstr.*, **65**, 12112h (1966).

[24] G. Barany, A. L. Schroll, A. W. Mott and D. A. Halsrud, *J. Org. Chem.*, **48**, in press (1983).

[25] One equivalent of **3** is sufficient for all of **4** to be converted to products. The protocol reported here with **3** always in excess was designed to minimize the problem described in note 7.

[26] The thiosulfate wash destroys excess **3** according to $Cl(C=O)SCl + 2\ S_2O_3^{2-} \rightarrow COS + 2\ Cl^- + S_4O_6^{2-}$.