Nucleophilic Substitution on Dialkoxy Disulfides. III.[1] Reaction with Thioureas

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(Received March 26, 1980)

1,3- and 1,1-Disubstituted thioureas reacted with diethoxy disulfide to give carbodiimides and 1,2,4-thiadiazoles respectively. 1,1,3-Trisubstituted thioureas and diethoxy disulfide afforded trialkyl(trialkylamidino)-thioureas.

The alkoxyl group of dialkoxy disulfide (**1**) is readily displaced by various nucleophiles. The reactions of **1** and amines, thiols,[2] thiocarboxylic acids,[3] or *N*-arylhydrazines[1] proceeded readily to give a variety of products. In the case of the reaction of thiobenzamide and diethoxy disulfide (**1a**), hydrogen sulfide was eliminated and benzonitrile was obtained in 80% yield.[2] This interesting dehydrosulfurization by **1** suggested that carbodiimides might be produced by the reaction of **1** and thiourea derivatives.

$$\mathrm{ROSSOR} \xrightarrow[-\mathrm{ROH}]{\mathrm{XH}} \mathrm{ROSSX} \xrightarrow[-\mathrm{ROH}]{\mathrm{YH}} \mathrm{YSSX}$$

(XH, YH; R'_2NH, R'SH, R'C(=O)SH)

$$\mathrm{Ph{-}C(=S){-}NH_2} + \mathrm{EtOSSOEt} \xrightarrow[-\mathrm{EtOH},\ -\mathrm{S}]{} \mathrm{Ph{-}C{\equiv}N}$$

1a

Results and Discussion

When 1,3-disubstituted thioureas (**2**) were treated with **1a** at room temperature or in refluxing CH_2Cl_2 in the presence of molecular sieves (type 4A), carbodiimides (**3**) were obtained in 19—66% yield. The results are shown in Table 1. Molecular sieves (type 4A) were good absorbents of ethanol and promoted the elimination reaction.

$$\mathrm{R^1NH{-}C(=S){-}NHR^2} + \mathrm{EtOSSOEt} \xrightarrow[-\mathrm{EtOH},\ -\mathrm{S}]{} \mathrm{R^1N{=}C{=}NR^2}$$

2 **1a** **3**

The reaction of 1,1,3-trisubstituted thiourea (trimethylthiourea) (**4a**) and **1a** in refluxing toluene gave a light yellow liquid. The IR spectrum of the product showed an absorption at 1645 cm^{-1} assignable to the C=N stretching band, but no N–H absorption. The NMR spectrum exhibited four methyl singlets; the two signals at 3.27 and 2.88 ppm were assigned to $N(CH_3)_2$ protons. The mass spectrum allowed detection of the typical fragment (M^+—SH) of thiourea. On the basis of these data the product was formulated to be trimethyl(trimethylamidino)thiourea (**5a**). Similarly, *N,N*-diethyl-*N'*-methylthiourea (**4b**) and **1a** gave *N,N*-diethyl-*N'*-methyl-*N'*-(*N*^{1},*N*^{1}-diethyl-*N*^{2}-methylamidino)thiourea (**5b**).

$$2\ \mathrm{R^1_2N{-}C(=S){-}NHR^2} + \mathbf{1a} \longrightarrow \mathrm{R^1_2N{-}C(=NR^2){-}C(=S){-}NR^1_2}$$

4 **5**

Table 1. Carbodiimide R^1–N=C=N–R^2 (**3**)

R^1	R^2	Bp/°C (mmHg)	Yield %	Reaction time/h (Refluxing in CH_2Cl_2)
i-Pr	*i*-Pr	44(15)	66	4
Cyclohexyl	Cyclohexyl	110(0.15)	63	7
Ph	Ph	170(13)	62	5
2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	121(0.07)	43	2
Ph	Cyclohexyl	114(0.5)	41	8[a]
Et	Cyclohexyl	54(1)	42	23
2-ClC_6H_4	Cyclohexyl	130(0.5)	19	3[a]
Allyl	Cyclohexyl	72(5)	20	6

a) Standing at room temperature [d].

On the other hand, 1,1-disubstituted thioureas (**6**) reacted with **1a** in refluxing carbon tetrachloride to give 3,5-bis(disubstituted amino)-1,2,4-thiadiazoles (**7**) with a small amount of disubstituted cyanamides (**8**). The results are shown in Table 2.

$$\mathrm{R_2N{-}C(=S){-}NH_2} + \mathbf{1a} \longrightarrow \mathbf{7} + \mathrm{R_2N{-}C{\equiv}N}$$

6 **7** **8**

The thiadiazole systems comprise 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-thiadiazoles. However, the structure of the product was identified as 1,2,4-thiadiazole by the ^{13}C-NMR and mass spectra. For example, the off-resonance ^{13}C decoupled spectrum of **7a** was as follows: (1) 12.7 ppm (q), (2) 13.6 (q), (3) 43.2 (t), (4) 45.7 (t), (5) 167.5 (s), (6) 186.6 (s). The four upfield signals correspond to the ethyl carbons, and the two downfield signals correspond to ring carbons. The mass spectrum of the product showed the thiazirene fragment formed by the loss of Et_2NCN from the molecular ion,[4] but no thiirene fragment.[5] All of the evidence supports the

$$\mathbf{7a}^+ \longrightarrow \mathrm{N{\equiv}C^+}$$

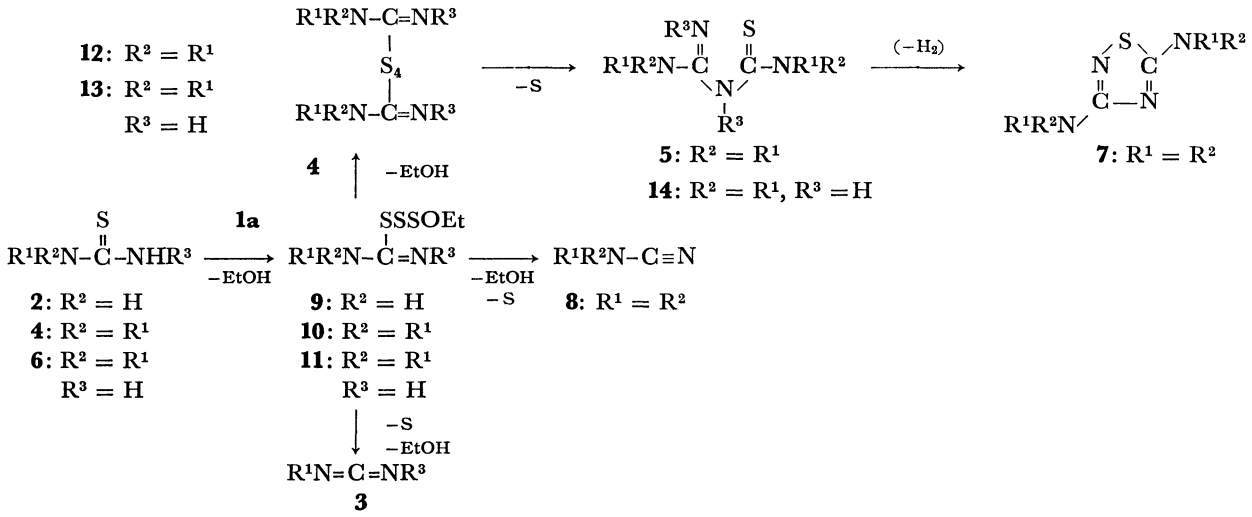
proposed structure.

The formation of these products can be rationalized by assuming the reaction path shown in Scheme 1. First, the ethoxyl group of **1a** was replaced by **2** to give ethoxy amidino trisulfide (**9**). The trisulfide then

Table 2. 1,2,4-Thiadiazole (**7**), and cyanamide (**8**)

	R	Reaction time/h	**7** Bp/°C (mmHg), or Mp/°C	**7** Yield %	**8** Bp/°C (mmHg)	**8** Absorption of $\nu_{C=N}$/cm^{-1}	**8** Yield %
a	Et	7	117(4)	75	65(9)[a]	2210	5
b	Pr	7	145(3)	72	91(11)[b]	2210	3
c	Bu	8	165(5)	48	120(10)[c]	2210	5
d	R_2N=Morpholino	11[d]	102.5—103.5	51	—	2210	0
e	Ph	6	158.0[e]	69	—	2230	0

a) Lit, 68(10).[6] b) Lit, 88—90(10).[7] c) Lit, 147—151(35).[8] d) CH_3CN was used as the solvent. e) Lit, 155 °C.[a]



Scheme 1.

underwent intramolecular substitution by the remaining –NHR group, followed by the elimination of sulfur to give **3**.[2]

The reaction of **4** and **1a** proceeded by successive substitution of **1a** by 2 mol of **4** to give the tetrasulfide (**12**), which then rearranged to yield **5** with elimination of sulfur. In the case of the reaction of **1a** and **2**, intramolecular substitution of **9** would predominate over intermolecular substitution by **2**.

Similarly, **1a** reacted with 2 mol of **6** to give amidinothiourea (**14**). Unlike **5**, however, **14** could cyclize to form **7** with a loss of hydrogen. Presumably **1a** would participate in this step, as in the case of the reaction of **1a** and hydrazine.[1]

The formation of the cyanamide (**8**) as a by-product is considered to be due to the intramolecular substitution of **11**, followed by the loss of sulfur. However, this reaction would not proceed effectively owing to the low nucleophilicity of the imino nitrogen atom in **11**.

Experimental

All melting points and boiling points are uncorrected. Column chromatography was performed on Wako gel C-200 column by eluting with benzene. ^{1}H-NMR spectra were recorded at 100 MHz on a JEOL JNM-FX 100 spectrometer using Me_4Si as the internal standard. The ^{13}C-NMR spectrum was recorded at 25 MHz on a JEOL JNM-FX 100 spectrometer using Me_4Si as the internal standard. Infrared spectra were obtained on a Hitachi model 260-10 infrared spectrometer. Mass spectral data were obtained with a Hitachi Double Focusing Mass spectrometer, RMU-7M.

Diethoxy disulfide (**1a**) was prepared by the method of the literature.[10] Unsymmetrical 1,3-disubstituted thioureas and trialkylthioureas were prepared from isothiocyanates and amines. Molecular sieves (type 4A 1/16 in. pellets) was purchased from Nakarai Chemicals (UCC subdivision). 1,1-Dialkylthioureas were prepared by the methods of the literature.[11] All other reagents were obtained commercially.

*Reactions of **1a** with 1,3-Disubstituted Thiourea.* To a solution of 1,3-disubstituted thiourea (**2**, 0.05 mol) and **1a** (0.05 mol) in 100 ml of CH_2Cl_2, 30 g of molecular sieves was added and the mixture was refluxed for 4—23 h. At the end of the reaction the mixture was cooled and the resulting sulfur and molecular sieves were filtered off. The filtrate was evaporated and the residue was distilled to obtain carbodiimide. The carbodiimides (**3**) were identified by their IR spectra and boiling points.[12–16]

*Reactions of **1a** with Trialkylthiourea.* A solution of 5.9 g (0.05 mol) of trimethylthiourea and 7.7 g (0.05 mol) of **1a** in 150 ml of toluene was refluxed for 20 h. The toluene was evaporated, the precipitated sulfur was filtered off, and the filtrate was distilled to give 2.8 g (55%) of trimethyl (trimethylamidino)thiourea (**5a**): bp 103 °C (0.6 mmHg); Found: C, 40.45; H, 10.20; N, 31.32; S, 18.01%. Calcd for $C_6H_{18}N_4S$: C, 40.43; H, 10.18; N, 31.44; S, 17.95%. IR (neat): $\nu_{C=N}$ 1645 cm^{-1}; NMR ($CDCl_3$) δ, 3.27 (s, 3H), 3.11 (s, 6H), 2.88 (s, 3H), 2.82 (s, 6H); MS *m/e* 202 (M^+, 4), 187 ($M^+ - CH_3$, 15), 169 ($M^+ - SH$, 4), 158 ($M^+ - NMe_2$, 9), 108 (29), 85 (100). *N,N*-Diethyl-*N*-'

methyl-N'-(N^1,N^1-diethyl-N^2-methylamidino)thiourea (**5b**) was obtained similarly: yield 40%; bp 123 °C (0.5 mmHg); Found: C, 51.20; H, 11.21; N, 24.01; S, 13.65%. Calcd for $C_{10}H_{26}N_4S$: C, 51.24; H, 11.18; N, 23.90; S, 13.68%. IR (neat): $\nu_{C=N}$ 1650 cm^{-1}; NMR ($CDCl_3$) δ, 3.48 (q, 4H), 3.15 (s, 3H), 2.86 (s, 3H), 1.16 (t, 6H), 1.07 (t, 6H); MS *m/e* 258 (M^+, 5), 243 ($M^+ - CH_3$, 4), 225 ($M^+ - SH$, 3), 186 ($M^+ - NEt_2$, 15), 146 (4), 113 (100).

Reactions of ***1a*** *with 1,1-Disubstituted Thiourea.* A suspension of 1,1-disubstituted thiourea (**6**, 0.05 mol) and **1a** (0.05 mol) in carbon tetrachloride was refluxed for 6—11 h. At the end of the reaction the mixture was cooled and the resulting sulfur was filtered off. The filtrate was evaporated and the residue was distilled to obtain 3,5-bis(disubstituted amino)thiadiazole (**7**) and disubstituted cyanamide (**8**). In the cases of *N*-thiocarbamoylmorpholine (**6d**) and 1,1-diphenylthiourea (**6e**), the reaction mixture was evaporated and the residue was chromatographed on Wako gel C-200, using benzene as the eluent. The solvent was evaporated and the residue was recrystallized from ethanol, giving **7d** and **7e**. 3,5-Bis(diethylamino)-1,2,4-thiadiazole (**7a**); Found: C, 52.58; H, 8.80; N, 24.32; S, 13.87%. Calcd for $C_{10}H_{20}N_4S$: C, 52.60; H, 8.83; N, 24.53; S, 14.04%. IR (neat): 1570, 1540, 1420 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ, 1.19 (m, 12H), 3.43 (m, 8H). ^{13}C-NMR ($CDCl_3$): δ, 12.7, 13.6, 43.2, 45.7, 165.5, 181.6. MS (70 eV): *m/e* 228 (M^+, 80), 213 (100), 130 (9). Found: *m/e* 228.1390. Calcd for $C_{10}H_{20}N_4S$: 228.1409. 3,5-Bis(dipropylamino)-1,2,4-thiadiazole (**7b**); Found: C, 59.59; H, 10.06; N, 19.34; S, 11.32%. Calcd for $C_{14}H_{28}N_4S$: C, 59.11; H, 9.92; N, 19.70; S, 11.27%. IR (neat): 1565, 1530, 1420 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ, 0.92 (m, 12H), 1.64 (m, 8H), 3.36 (m, 8H). MS (70 eV): *m/e* 284 (M^+, 36), 255 (100). Found: *m/e* 284.2013. Calcd for $C_{14}H_{28}N_4S$: 284.2035. 3,5-Bis(dibutylamino)-1,2,4-thiadiazole (**7c**); Found: C, 63.73; H, 10.79; N, 16.09; S, 9.57%. Calcd for $C_{18}H_{36}N_4S$: C, 63.48; H, 10.65; N, 16.45; S, 9.41%. IR (neat): 1570, 1535, 1420 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ, 0.90 (t, 12H, J=3.5 Hz), 1.30 (m, 8H), 1.58 (m, 8H), 3.36 (m, 8H). MS (70 eV): *m/e* 340 (M^+, 62), 297 (100). Found: *m/e* 340.2690. Calcd for $C_{18}H_{36}N_4S$: 340.2661. 3,5-Dimorpholino-1,2,4-thiadiazole (**7d**); Found: C, 46.27; H, 6.24; N, 21.70; S, 12.56%. Calcd for $C_{10}H_{16}N_4O_2S$: C, 46.86; H, 6.29; N, 21.86; S, 12.51%. IR (KBr): 1560, 1510, 1410, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ, 3.30—3.80 (m). MS (70 eV): *m/e* 256 (M^+, 100), 144 (11). Found: *m/e* 256.0980. Calcd for $C_{10}H_{16}N_4O_2S$: 256.0994. 3,5-Bis(diphenylamino)-1,2,4-thiadiazole (**7e**); Found: C, 74.77; H, 4.81; S, 7.62%. Calcd for $C_{26}H_{20}N_4S$: C, 74.27; H, 4.79; S, 7.62%. IR (KBr): 1590, 1535, 1495, 1450, 1370 cm^{-1}. MS (70 eV): *m/e* 420 (M^+, 100), 226 (8). Found: *m/e* 420.1377. Calcd for $C_{26}H_{20}N_4S$: 420.1409.

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