Multiple Reactivity of Freund's "Methyl Isothiocyanate Sulfide" in Cycloaddition-Elimination Reactions

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4-Methyl-5-methylimino-1,2,4-dithiazolidine-3-thione (**1**) and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**2**) are interconvertible in acetone at 50°. They react with ketenes and electrophilic acetylenes to give the thiazole derivatives **6** and **7** after elimination of methyl isothiocyanate or carbon disulfide. Electrophilic isothiocyanates and phenylsulfonyl isocyanate transform the C=S function of **1** in an imine function (**8**), and a similar transformation of the thiourea C=S function of **2** is observed on reaction with phenylsulfonyl isocyanate, giving **9**.

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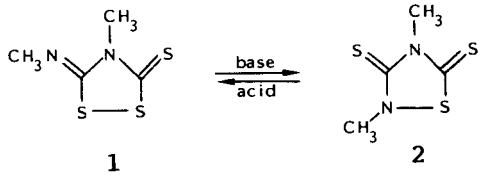
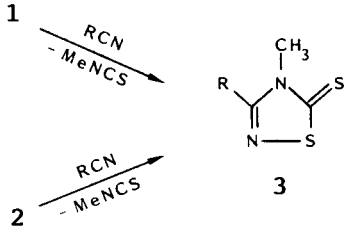
The bromine oxidation of methyl isothiocyanate in the presence of hydrogen sulfide, or the bromine oxidation of methyl dithiocarbamate leads to the formation of 4-methyl-5-methylimino-1,2,4-dithiazolidine-3-thione (**1**), also called Freund's "methyl isothiocyanate sulfide" [1]. This compound isomerizes in alkaline solution to 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**2**), while the reverse reaction occurs in acid media [1,2].



1 **2**

The two isomers **1** and **2** possess functional groups (C=N and C=S), as well as masked 1,3-dipolar groups (S-C=N and S-C=S) which, in principle, are capable of reacting with π-systems [3]. In a recent publication we have established that both **1** and **2** undergo cycloaddition-elimination reactions with electrophilic nitriles to furnish 1,2,4-thiadiazoline-5-thiones **3** as final products [4]. The reactions occur by initial cycloaddition at the peripheral S-C=S atoms of the heterocycles and proceed *via* thiapentalenoids as intermediates. These thiapentalenoids are also responsible for the partial interconversion of **1** and **2** during the course of the reactions.

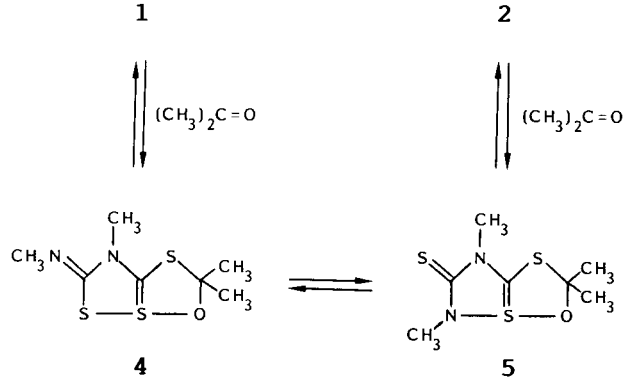


3

In continuation of this research, we have studied the reactions of **1** and **2** with a variety of unsaturated systems, and found that three pathways are operating, involving the C=S, S-C=S and S-C=N functions of the heterocycles. The results are described below and summarized in Schemes 1 and 2.

Although **1** and **2** are thermally stable when heated in toluene or acetonitrile solution, interconversion occurs in hot acetone. The ^{1}H nmr spectrum, recorded after 16 hours in deuterated acetone shows an equilibrium mixture of 15% **1** and 85% **2**, starting either from pure **1** or pure **2**. The isomerization probably proceeds *via* the thiapentalene intermediates **4** and **5** which are interconvertible by a one-bond cleavage (S-S or S-NMe) and recombination process (Scheme 1).

Scheme 1

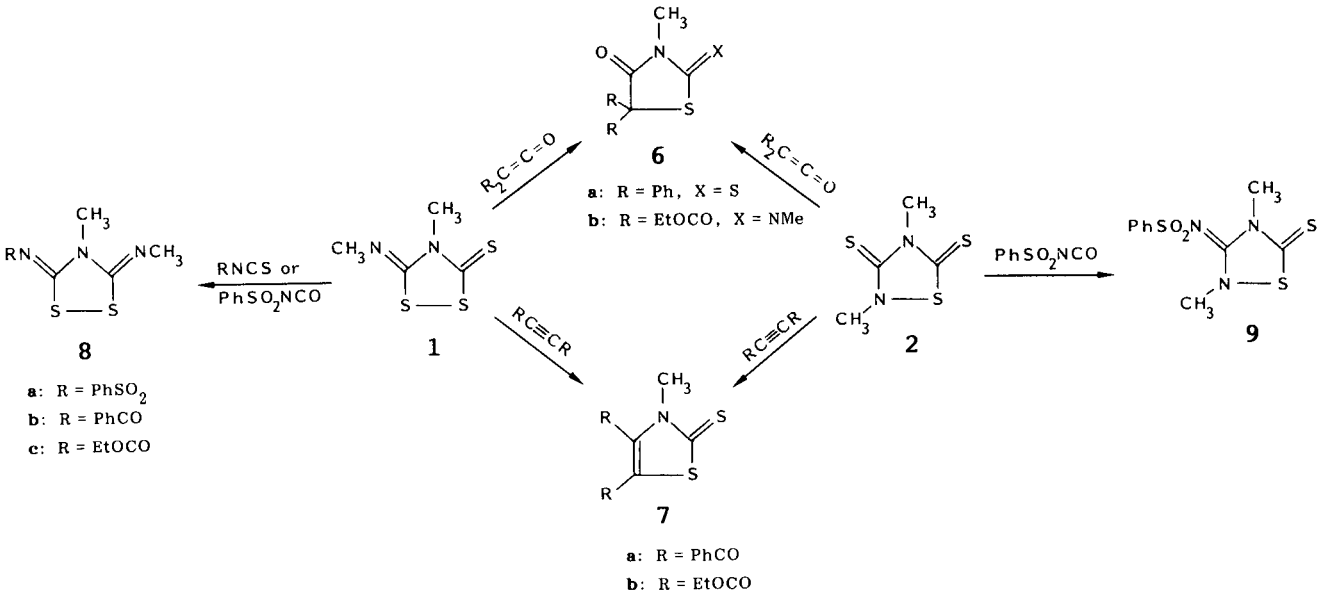


4 **5**

Diphenylketene reacts with **1** or **2** in toluene at room temperature, yielding the rhodanine derivative **6a** as a result of initial attack at the peripheral S-C=S atoms of the heterocycles with elimination of methyl isothiocyanate; the details of the mechanism have been discussed earlier [4]. Compound **1** was observed by ^{1}H nmr during the reaction of **2** with diphenylketene, and its formation is rationalized by a process similar to that with acetone.

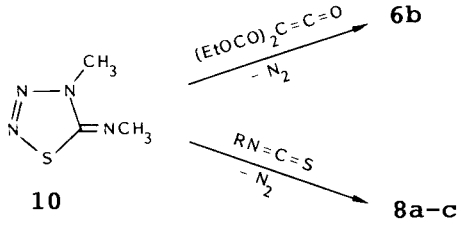
In contrast, bis(ethoxycarbonyl)ketene reacts with **1** at room temperature to give **6b** by cycloaddition at the S-C=N side of the molecule and elimination of carbon disulfide. The same product is obtained from **2**, although at higher temperature (90°). In this case, we assume that **2** is

Scheme 2



first isomerized to **1** under the influence of the ketene, and then converted into **6b**. Compound **6b** was independently prepared by reacting 4-methyl-5-methylimino-1,2,3,4-thiatriazoline **10** with bis(ethoxycarbonyl)ketene according to an established mechanism [5].

Scheme 3



Dibenzoylacetylene reacts with **1** or **2** at 60° in a similar manner to diphenylketene to give the thiazoline **7a** and methyl isothiocyanate. The less reactive diethyl acetylenedicarboxylate does not combine with **2**, but reacts with **1** at 90° to yield **7b**.

Whereas **2** is unreactive towards benzoyl isothiocyanate, ethoxycarbonyl isothiocyanate and phenylsulfonyl isothiocyanate in toluene at 90°, **1** reacts with these reagents under elimination of carbon disulfide. The 1,2,4-dithiazolidines **8a-c**, thus obtained, were independently synthesized from 4-methyl-5-methylimino-1,2,3,4-thiatriazoline **10** and isothiocyanates (Scheme 3). The mechanistic aspects of these ring transformations have been discussed in detail [6].

Finally, the reaction of phenylsulfonyl isocyanate with **1** gives **8a** as a result of a (2 + 2)-cycloaddition followed by a (2 + 2)-cyclofragmentation. A similar reaction is observed with **2**, but at the thiourea C=S function, giving **9**.

The structures of the reaction products were unambiguously elucidated by spectral measurements, particularly by ^{13}C nmr analysis (see Experimental).

EXPERIMENTAL

The ir spectra (potassium bromide) were recorded on a Perkin Elmer 1720 FT spectrometer and the nmr spectra (in deuteriochloroform) on a Bruker WM-250 spectrometer at 250 (^1H) and 62.9 MHz (^{13}C).

4-Methyl-5-methylimino-1,2,4-dithiazolidine-3-thione (**1**) and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**2**) were prepared following the literature procedures [1,2]. 4-Methyl-5-methylimino-1,2,3,4-thiatriazoline was synthesized by the method of Toubro and Holm [7].

5,5-Diphenyl-3-methyl-2-thioxothiazolidin-4-one (**6a**).

A solution of **1** (1 g, 5.6 mmoles) and two equivalents of diphenylketene (2.17 g) in dry toluene (50 ml) was stirred at room temperature for 2 hours. After removal of the solvent, the residue was chromatographed on silica gel with dichloromethane as the eluent to give **6a** in 57% yield, mp 112° (ether).

This compound was also obtained by reacting **2** (0.5 g, 2.8 mmoles) with two equivalents of diphenylketene (1.08 g) in dry toluene (50 ml) at room temperature for 3 hours. After removal of the solvent and crystallization of the residue from ether, **6a** was obtained in 51% yield (0.42 g); spectral data, ir: 1735 cm^{-1} (s, C=O); ^1H nmr: δ 3.47 (s, 3H, NCH_3), 7.38 (s, 10H, two Ph); ^{13}C nmr: δ 31.8 (NCH_3, $^1J_{CH}$ = 142 Hz), 70.1 (C-5), 128.2, 128.6, 128.8 and 138.9 (Ph C-atoms), 175.9 (C-4), 198.1 (C-2).

Anal. Calcd. for $C_{16}H_{13}NOS_2$ (mol wt 299): C, 64.19; H, 4.38. Found: C, 64.05; H, 4.45.

5,5-Bis(ethoxycarbonyl)-3-methyl-2-methyliminothiazolidin-4-one (**6b**).

A solution of **1** (1 g, 5.6 mmoles) and two equivalents of bis(ethoxycarbonyl)ketene (2.1 g) in dry toluene (50 ml) was stirred at room temperature for 1 hour. After removal of the solvent, the

residue was chromatographed on silica gel with ethyl acetate/hexane (1:1) as the eluent to give **6b** in 38% yield (0.61 g), mp 43° (hexane/ether).

This compound was also obtained by reacting **2** (1 g, 5.62 mmoles) with two equivalents of bis(ethoxycarbonyl)ketene (2 g) in dry toluene (11 ml) at 90° for 22 hours. After removal of the solvent, the resulting oil was chromatographed on silica gel with *n*-hexane/ethyl acetate (95:5) as the eluent to give **6b** in 28% yield (0.45 g).

This compound was also obtained by reacting **10** (1.21 g, 9.34 mmoles) with bis(ethoxycarbonyl)ketene (2.1 g, 11.2 mmoles) in dry ether (40 ml) at room temperature for 90 minutes. After evaporation of the solvent, the resulting yellow oil was chromatographed on silica gel with ethyl acetate/*n*-hexane (1:1) as the eluent to give **6b** in 23% yield (0.59 g); spectral data; ir: 1768, 1757, 1725 and 1665 cm^{-1} (s); ^1H nmr: δ 1.30 (t, 6H, two CH_3), 3.18 (s, 6H, two NCH_3), 4.33 (q, 4H, two CH_2); ^{13}C nmr: δ 13.7 and 63.8 (C_2H_5), 30.1 (NCH_3), 38.4 (=NCH_3), 60.2 (C-5), 149.4 (C-2), 163.9 and 164.9 (C=O).

Anal. Calcd. for $C_{11}H_{16}N_2O_5S$ (mol wt 288): C, 45.82; H, 5.59. Found: C, 45.73; H, 5.48.

4,5-Dibenzoyl-3-methyl-Δ^4-thiazoline-2-thione (**7a**).

A solution of **1** (1 g, 5.6 mmoles) and three equivalents of dibenzoylacetylene (3.9 g) in dry chloroform (12 ml) was heated at 60° for 2 hours. After removal of the solvent, the residual oil was crystallized from hot diethyl ether (100 ml) to give **7a** in 41% yield (790 mg), mp 127°.

This compound was also obtained by reacting **2** (1 g, 5.6 mmoles) with three equivalents of dibenzoylacetylene (3.93 g) in dry chloroform (12 ml) at 60° for 3 hours. The excess of dibenzoylacetylene was removed by crystallization from chloroform/*n*-hexane and the filtrate was chromatographed on silica gel with *n*-hexane/ethyl acetate (80:20) as the eluent to give **7a** in 18% yield (348 mg); spectral data, ir: 1678 and 1642 cm^{-1} (s); ^1H nmr: δ 3.61 (s, 3H, NCH_3), 7.3-7.8 (m, 10H, two Ph); ^{13}C nmr: δ 35.6 (NCH_3, $^1J_{CH}$ = 143.5 Hz), 123.2 (C-5), 128.5, 128.7, 129.1, 129.2, 133.5, 135.0, 135.3 and 136.9 (Ph C-atoms), 145.7 (C-4), 184.0 and 186.8 (C=O), 189.2 (C=S, $^3J_{CH}$ = 4.5 Hz).

Anal. Calcd. for $C_{18}H_{13}NO_2S_2$ (mol wt 339): C, 63.69; H, 3.86. Found: C, 63.61; H, 3.97.

4,5-Bis(ethoxycarbonyl)-3-methyl-Δ^4-thiazoline-2-thione (**7b**).

A solution of **1** (1 g, 5.6 mmoles) and five equivalents of diethyl acetylenedicarboxylate (4.76 g) in dry toluene (15 ml) was heated at 90° for 17 hours. The solvent was distilled off under reduced pressure, and the resulting oil was chromatographed on silica gel with a light petroleum/diethyl ether elution gradient to give **7b** in 47% yield (0.72 g), mp 60°; ir: 1736 and 1702 cm^{-1} (s); ^1H nmr: δ 1.32 and 1.43 (two t, 6H, two CH_3), 3.64 (s, 3H, NCH_3, $^1J_{CH}$ = 142.5 Hz), 4.30 and 4.48 (two q, 4H, two CH_2); ^{13}C nmr: δ 13.8, 14.0, 62.3 and 63.7 (two C_2H_5), 35.4 (NCH_3), 115.1 (C-5), 140.5 (C-4), 158.2 and 159.5 (C=O), 188.9 (C=S).

Anal. Calcd. for $C_{10}H_{13}NO_4S_2$ (mol wt 275): C, 43.62; H, 4.76. Found: C, 43.83; H, 4.67.

4-Methyl-3-methylimino-5-phenylsulfonylimino-1,2,4-dithiazolidine (**8a**).

A solution of **1** (1 g, 5.6 mmoles) and five equivalents of phenylsulfonyl isothiocyanate (5.6 g) in dry toluene (50 ml) was refluxed for 3 hours. After removal of the solvent, the resulting oil was flash-chromatographed on silica gel with ether as the eluent to give **8a** in 73% yield (1.23 g), mp 143° (ether).

This compound was also obtained by heating **1** (1 g, 5.6 mmoles) with five equivalents of phenylsulfonyl isocyanate (5.12 g) in dry toluene (50 ml) for 4 days. After removal of the solvent, the resulting oil was chromatographed on silica gel with dichloromethane as the eluent to give **8a** in 72% yield (1.22 g).

This compound was also obtained by adding dropwise phenylsulfonyl isothiocyanate (2.4 g, 12 mmoles) to an ice-cooled solution of **10** (1.4 g, 10.9 mmoles) in dry chloroform (15 ml). After stirring the mixture at room temperature for 15 minutes, dry ether was added and the saturated solution cooled to give **8a** in 40% yield (1.3 g); spectral data, ir: 1645 and 1520 cm^{-1} (s); ^1H nmr: δ 3.2 (s, 3H, =NCH_3), 3.45 (s, 3H, ring CH_3), 7.5-7.65 and 8.0-8.1 (two m, 5H, Ph); ^{13}C nmr: δ 36.3 (ring CH_3, $^1J_{CH}$ = 143 Hz), 39.7 (=NCH_3, $^1J_{CH}$ = 136 Hz) 126.7, 128.9, 132.9 and 140.8 (Ph C-atoms), 151.0 (C-3), 166.1 (C-5).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S_3$ (mol wt 301): C, 39.85; H, 3.68. Found: C, 40.08; H, 3.76.

5-Benzoylimino-4-methyl-3-methylimino-1,2,4-dithiazolidine (**8b**).

A solution of **1** (1 g, 5.6 mmoles) and five equivalents of benzoyl isothiocyanate (5.7 g) in dry toluene (50 ml) was refluxed for 1 week. The solvent was replaced by ether (200 ml) and cooled to give **8b** in 77% yield (1.15 g), mp 139° (toluene).

This compound was also obtained by reacting **10** (1 g, 7.7 mmoles) with three equivalents of benzoyl isothiocyanate (3.76 g) in chloroform (10 ml) at room temperature for 1 day. After addition of ether, **8b** precipitated in 64% yield (1.30 g); spectral data, ir: 1625 and 1600 cm^{-1} (s); ^1H nmr: δ 3.2 (s, 3H, =NCH_3), 3.8 (s, 3H, ring CH_3), 7.4-7.6 and 7.28 (m, and d, 5H, Ph); ^{13}C nmr: δ 36.4 (ring CH_3), $^1J_{CH}$ = 143 Hz), 40.2 (=NCH_3, $^1J_{CH}$ = 136 Hz), 128.4, 129.9, 133.0 and 134.2 (Ph C-atoms), 153.9 (C-3), 172.9 (C-5), 177.5 (C=O).

Anal. Calcd. for $C_{11}H_{11}N_3S_2O$ (mol wt 265): C, 49.81; H, 4.15. Found: C, 49.92; H, 4.16.

5-Ethoxycarbonylimino-4-methyl-3-methylimino-1,2,4-dithiazolidine (**8c**).

A solution of **1** (1 g, 5.6 mmoles) and five equivalents of ethoxycarbonyl isothiocyanate (3.7 g) in dry toluene (50 ml) was refluxed for 14 hours. The solvent was replaced by ether (200 ml) and cooled to give **8c** in 80% yield (1.05 g), mp 124°.

This compound was also obtained by reacting **10** (1 g, 7.7 mmoles) with two equivalents of ethoxycarbonyl isothiocyanate (2 g) in chloroform (10 ml) for 1 day. The solvent was replaced by ether (100 ml) and cooled to give **8c** in 72% yield (1.30 g); spectral data; ir: 1635 and 1533 cm^{-1} (s); ^1H nmr: δ 1.35 (t, 3H, CH_3), 3.15 (s, 3H, =NCH_3), 3.6 (s, 3H, ring CH_3), 4.3 (q, 2H, CH_2); ^{13}C nmr: δ 14.2 and 62.8 (C_2H_5), 36.1 (ring CH_3, $^1J_{CH}$ = 143.5 Hz), 39.7 (=NCH_3, $^1J_{CH}$ = 136 Hz), 153.0 (C-3), 163.9 (C=O), 172.6 (C-5).

Anal. Calcd. for $C_7H_{11}N_3O_2S_2$ (mol wt 233): C, 36.04; H, 4.75. Found: C, 36.00; H, 4.64.

2,4-Dimethyl-3-phenylsulfonylimino-1,2,4-thiadiazolidine-5-thione (**9**).

A solution of **2** (1 g, 5.6 mmoles) and five equivalents of phenylsulfonyl isocyanate (5.1 g) in dry toluene (50 ml) was heated at 90° for 63 hours. After removal of the solvent, the residue was crystallized from chloroform/*n*-hexane and further purified by column chromatography on silica gel with *n*-hexane/ethyl acetate

(80:20) as the eluent; yield 29% (488 mg), mp 205°; ir: 1603 cm^{-1} (s); ^1H nmr: δ 3.39 and 3.81 (two s, 6H, two CH_3), 7.5-8.0 (two m, 5H, Ph); ^{13}C nmr: δ 33.4 and 38.5 (two CH_3, $^1J_{CH}$ = 144 Hz), 126.0, 128.7, 132.1 and 143.3 (Ph C-atoms), 151.2 (C-3), 187.5 (C-5).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S_3$ (mol wt 301): C, 39.85; H, 3.69. Found: C, 39.73; H, 3.61.

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