Cycloaddition-Elimination Reactions of Freund's "Methyl Isothiocyanate Sulfide" with Electrophilic Nitriles

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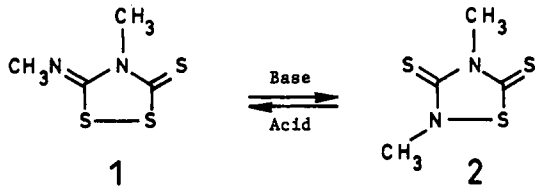
Received October 26, 1990

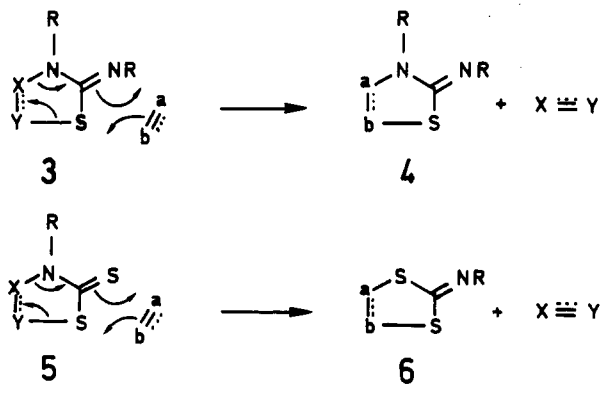
The 1,2,4-dithiazolidine 1 and the 1,2,4-thiadiazolidine 2 are interconvertible in the presence of electrophilic nitriles and furnish 1,2,4-thiadiazoline-5-thiones 7 as final products. A mechanistic rationalization involving consecutive cycloaddition-elimination reactions via hypervalent sulfur intermediates is proposed.

The bromine oxidation of methyldithiocarbamate ion ($MeNHCS_2^-$) leads to the formation of *N,N'*-dimethylthiuram disulfide (MeNHCS—S—S—CSNHMe) and then to 4-methyl-5-(methylimino)-1,2,4-dithiazolidine-3-thione (**1**).[1] This so-called "methyl isothiocyanate sulfide" of formula $(MeNCS)_2S$ was also obtained by Freund[1] from methyl isothiocyanate by successive treatment with bromine and hydrogen sulfide. Compound **1** isomerizes in alkaline media (e.g., alcohol containing a few drops of ammonia) to 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**2**), while the reverse reaction occurs in acid solution.[1,2] The structures **1** and **2** have been confirmed by IR[2] and ^{13}C NMR[3] and in the case of **2** by an X-ray crystal structure analysis.[2]



1 **2**

The heterocycle **1** is of particular interest since it possesses two functions (S—C=N and S—C=S) that are, in principle, capable of reacting as masked 1,3-dipoles in cycloaddition-elimination reactions with electrophilic unsaturated systems (a=b) according to the general equations **3** → **4** and **5** → **6**. Examples of both types of



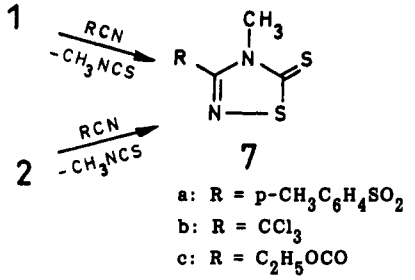
3 **4**

5 **6**

reaction are known,[5,6] but have never been studied competitively. Compound **1** offers this possibility, giving either methyl isothiocyanate or carbon disulfide as the extruded molecule. The isomer **2** can only react via the S—C=S bond with elimination of methyl isothiocyante, unless it first isomerizes to **1** under the influence of the electrophilic reagents. The reactions of **1** and **2** with electrophilic nitriles are described here.

Results

Compound **1** reacted with *p*-toluenesulfonyl cyanide in refluxing toluene to yield the 1,2,4-thiadiazoline **7a** and methyl isothiocyanate as the sole end-products. When the reaction was monitored by ^1H NMR spectroscopy in deuterated toluene, the appearance and disappearance of methyl singlets at δ 2.6 and 3.3, respectively, were observed, corresponding to structure **2**. This was verified by addition of authentic **2** to the NMR sample, thus increasing the intensities of the peaks already present at δ 2.6 and 3.3. A typical reaction profile is given in Figure 1.



1 **2** **7**

a: R = p-$CH_3C_6H_4SO_2$
b: R = CCl_3
c: R = C_2H_5OCO

The reactions of **1** with trichloroacetonitrile and ethyl cyanoformate exhibited a similar behavior, producing **2** as an intermediate and **7b,c** as final products. The following reactivity sequence was noticed: TsCN > CCl_3CN > EtOCOCN.

Compound **2** also reacted with the electrophilic nitriles and furnished **7a-c** in high yields. When the NMR spectra in deuterated toluene were recorded during the reactions, **1** was observed as an intermediate that disappeared as the reaction progressed. Thus, the two heterocycles **1** and **2** are interrelated in these reactions and produce the same products **7a-c**.

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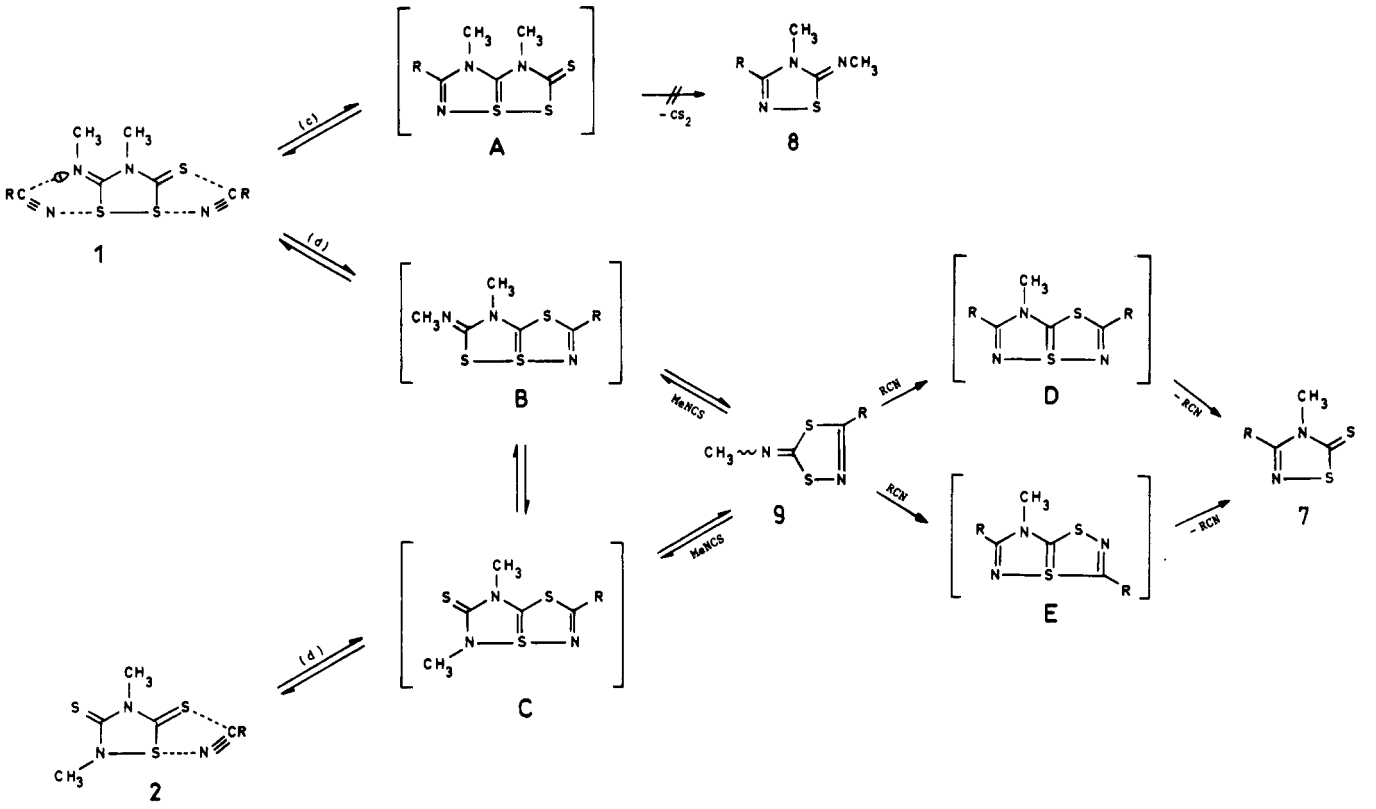
Scheme I



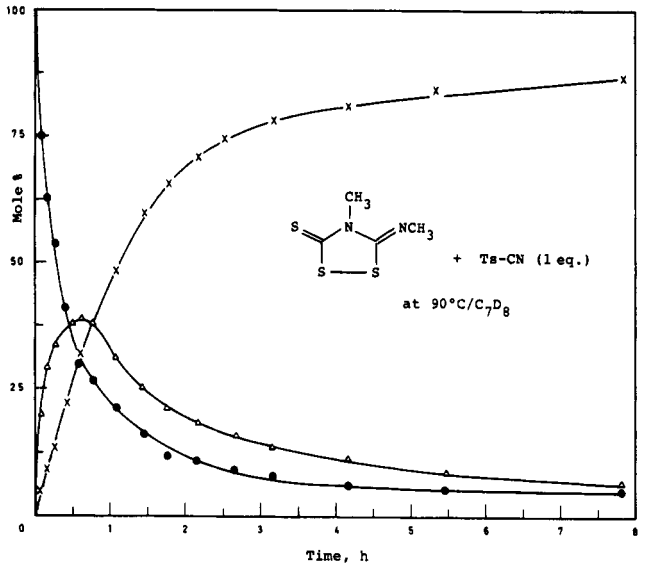
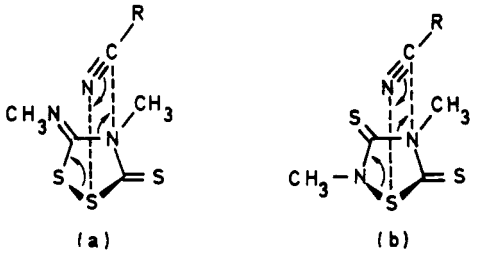


Figure 1. Reaction of 1 (0.5 M) with an equimolar amount of tosyl cyanide in deuterated toluene at 90 °C. Relative concentrations of 1 (●), 2 (△), and 7a (×).

The structures **7a–c** were easily established by analysis of the NMR spectra. For instance, the presence of thioketone functions in the ^{13}C NMR spectra is indicated by low-field absorptions at δ 199–201, whereas the ring C-3 carbons resonate at δ 150–157. Also typical are the *N*-methyl resonances at δ 34 with a characteristic ^1J coupling constant of 144 Hz. In the mass spectra (EI), strong molecular ion peaks are observed in addition to prominent fragment ions at m/z 105, attributable to the radical ion of *N*-methylthiaziridine-3-thione.

Mechanism

There are two possible mechanisms for the formation of **7**. One involves an approach of the nitrile from above the plane of the heterocycle as shown in paths a and b; elimination of methyl isothiocyanate would then produce **7** directly.



Two arguments militate against this mechanism. First, paths a and b should operate with nucleophilic partners rather than with the electrophilic nitriles used in this work. This statement follows from the recognition that electron density in **1** and **2** is delocalized in the two exocyclic π-bonds, leaving the endocyclic atoms positively charged. Secondly, if **1** were to react by path a, the ketone analogue would also be expected to do so. However, 4-benzyl-5-(benzylimino)-1,2,4-dithiazolidin-3-one does not react with *p*-toluenesulfonyl cyanide in refluxing toluene.

The alternative mechanism is an approach of the nitrile in the plane of the heterocycle, followed by addition on the S—C=N or the S—C=S side (Scheme I). A reaction at the peripheral S—C=N atoms of **1** (path c) is excluded, since this would yield **8**, which is not observed. Hence, we are left with reaction path d, occurring at the S—C=S side of the starting heterocycles. Thus, both **1** and **2** combine with nitriles to furnish **9** via the thiapentalene-like intermediates B and C. Subsequent reaction of **9** with nitrile yields **7** via D and/or E.

The reversible isomerization of **1** to **2** under the influence of nitrile is assumed to proceed via the intermediates B and C, which are interconvertible through one-bond cleavage (S-S or S-NMe) and recombination. We have checked that the isomerization **1** ⇌ **2** is not simply a

thermal process, since both products were found to be stable at 90 °C in the absence of nitrile.

The missing link in Scheme I is compound **9** which has not been observed in the course of the reactions. We assume that it combines with nitriles much faster than do **1** and **2**, due to a powerful nucleophilic imine function that is devoid of steric hindrance. Indeed, **9** most probably exists in two stereochemical configurations (syn and anti), both capable of reacting with nitriles. Compound **1**, on the contrary, does not react by a similar path (c) because then it would have to adopt a sterically unfavorable *E*-configuration (see Scheme I), which would lead to intermediate A where a strong repulsion exists between the two methyl groups. This steric constraint is absent in intermediates D and E.

Experimental Section

4-Methyl-3-(*p*-toluenesulfonyl)-1,2,4-thiadiazoline-5-thione (7a). This compound was obtained by heating a solution of **1** or **2** (1 g, 5.6 mmol) with 2 equiv of *p*-toluenesulfonyl cyanide (2.03 g) in dry toluene (100 mL) at reflux temperature for 3–4 h. After removal of the solvent under reduced pressure, the residue was crystallized from chloroform to give **7a** in 94 (1.5 g from **1**) and 75% yield (1.2 g from **2**): mp 193 °C; IR (KBr) 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H, CH_3), 4.0 (s, 3 H, NCH_3), 7.5 and 7.95 (two d, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 21.9 (CH_3), 34.4 (NCH_3, $^1J_{CH}$ = 144 Hz), 130.0 and 130.2 (tolyl C_o and C_m), 132.3 (tolyl C_p), 147.5 (tolyl C_i), 157.5 (C-3, $^3J_{CH}$ = 2.5 Hz), 199.2 (C-5, $^3J_{CH}$ = 4 Hz); mass spectrum *m/z* 286 (94, $M^{\bullet+}$), 155 (26, Ts^+), 105 (65, $M^{\bullet+}$ – TsCN), 91 (100, $C_7H_7^+$), 76 (15), 72 (14), 65 (27), 39 (14). Anal. Calcd for $C_{10}H_{10}N_2O_2S_3$ (mol wt 286): C, 41.94; H, 3.52. Found: C, 42.06; H, 3.49.

When the reaction of **2** (0.5 M) with 2 equiv of *p*-toluenesulfonyl cyanide in deuterated toluene at 90 °C was analyzed after 2 h, the ^1H NMR spectrum showed the presence of **1** (12.5%), unreacted **2** (25%), and **7a** (62.5%).

4-Methyl-3-(trichloromethyl)-1,2,4-thiadiazoline-5-thione (7b). This compound was obtained by heating a solution of **1** or **2** (1 g, 5.6 mmol) with 5 equiv of trichloroacetonitrile (4.03 g) in dry toluene (100 mL) at reflux temperature for 7–10 h. The solvent was removed under reduced pressure, and the residue was crystallized from *n*-heptane (50 mL) to give **7b** in 95 (1.33 g from **1**) and 86% yield (1.25 g from **2**): mp 138 °C (ether); IR (KBr) 1525 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, NCH_3); ^{13}C NMR ($CDCl_3$) δ 36.6 (NCH_3, $^1J_{CH}$ = 144 Hz), 87.3 (CCl_3), 154.4 (C-3), 200.9 (C-5); mass spectrum *m/z* 252, 250, and 248 (26, 70, and 67, $M^{\bullet+}$), 215 and 213 (34 and 46, $M^{\bullet+}$ – Cl), 142 and 140 (30 and 47), 105 (100, $M^{\bullet+}$ – CCl_3CN), 76 (24), 73 (24), 72 (40), 64 (58). Anal. Calcd for $C_4H_3Cl_3N_2S_2$ (mol wt 250): C, 19.25; H, 1.21. Found: C, 19.35; H, 1.12.

When the reaction of **1** (0.5 M) with 10 equiv of trichloroacetonitrile in deuterated toluene at 90 °C was analyzed after 2 h, the ^1H NMR spectrum showed the presence of unreacted **1** (18%), **2** (31%), and **7b** (51%). When a similar reaction of **2** was analyzed after 3 h, the ^1H NMR spectrum showed the presence of **1** (11%), unreacted **2** (20%), and **7b** (69%).

3-(Ethoxycarbonyl)-4-methyl-1,2,4-thiadiazoline-5-thione (7c). This compound was obtained by heating **1** or **2** (1 g, 5.6 mmol) with 10 equiv of ethyl cyanoformate (5.54 g) in dry toluene (100 mL) at reflux temperature for 5 days. After removal of the solvent under reduced pressure, the residue was crystallized from *n*-heptane (50 mL) to give **7c** in 63 (0.72 g from **1**) and 84% yield (0.96 g from **2**): mp 56 °C (ether); IR (KBr) 1740 (s), 1525 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, 3 H, *J* = 7 Hz, CH_3), 3.95 (s, 3 H, NCH_3), 4.5 (q, 2 H, *J* = 7 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 13.9 and 63.6 (Et), 35.4 (NCH_3, $^1J_{CH}$ = 144.4 Hz), 150.5 (C-3), 156.2 (CO), 199.4 (C-5); mass spectrum *m/z* 204 (100, $M^{\bullet+}$), 105 (63, $M^{\bullet+}$ – EtOCOCN), 76 (17), 72 (18), 64 (24). Anal. Calcd for $C_6H_8N_2O_2S_2$ (mol wt 204): C, 35.28; H, 3.95. Found: C, 35.28; H, 3.85.

When the reaction of **1** (0.5 M) with 10 equiv of ethyl cyanoformate in deuterated toluene at 90 °C was analyzed after 24 h, the ^1H NMR spectrum showed the presence of unreacted **1** (34%), **2** (24%), and **7c** (42%, determined from the methyl singlet of MeNCS). When a similar reaction of **2** was analyzed after 5 h, the ^1H NMR spectrum showed the presence of **1** (14%), unreacted **2** (38%), and **7c** (48%, determined from the methyl singlet of MeNCS).

Kinetics of the Reaction of 1 with *p*-Toluenesulfonyl Cyanide. An NMR tube containing equimolar amounts of **1** and *p*-toluenesulfonyl cyanide in deuterated toluene (0.5 M) was placed in a thermostat at 90 °C (±0.1 °C). At several time intervals, the NMR tube was cooled to 0 °C and analyzed by ^1H NMR spectroscopy (90 MHz). The concentrations of the products were followed by integration of the *N*-methyl singlets of **1** (δ 3.10), **2** (δ 3.30), and **7a** (δ 3.55) in the spectra. After 85 min, **7a** partly precipitated and its concentration was further estimated by integration of the methyl singlet of methyl isothiocyanate (δ 2.15). Control experiments were carried out by continuous measurements at 90 °C at 250 MHz, giving overlapping results. The reaction profile is shown in Figure 1.

Acknowledgment. We are indebted to Dr. S. Toppet and P. Delbeke for their advice in interpreting the ^{13}C NMR spectra. A.V. thanks the University of Leuven for a post-doctoral fellowship. Financial support from the N.F.W.O. and the Ministerie voor Wetenschapsbeleid is gratefully acknowledged.