

A Rare Case of Three Rearrangements During the Cycloaddition-Elimination Reaction of 4-Methyl-5-phenylimino- Δ^2 -1,2,3,4-Thiatriazoline with 2-Pyridyl Isothiocyanate

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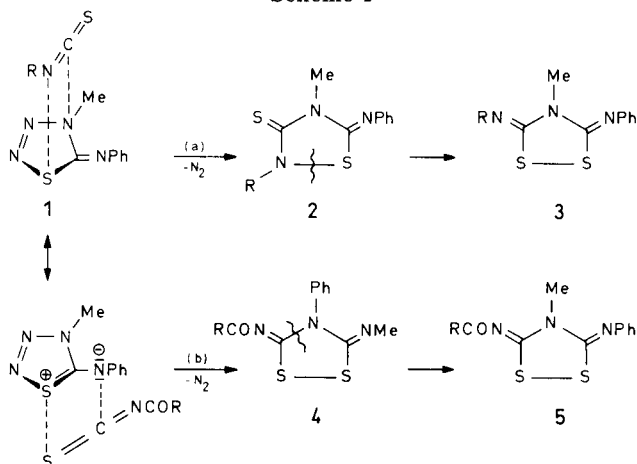
2-Pyridyl isothiocyanate (**7**), with its electrophilic and basic properties, gives a series of ring-transformation reactions with 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**1**) at 60°. Two dithiazolidines, **8** and **10**, are formed as major products at an early stage of the reaction, whereas two thiadiazolidines, **9** and **11**, predominate at the end. The mechanism (Schemes II and III) has been elucidated by following the reaction course under a variety of conditions and by analyzing the products by ^{13}C nmr spectroscopy.

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4-Methyl-5-phenylimino- Δ^2 -1,2,3,4-thiatriazoline (**1**) represents an interesting synthon for the preparation of other heterocycles by way of cycloaddition-elimination reactions with heterocumulenes [1-4]. It is readily prepared by reacting phenyl isothiocyanate with hydrazoic acid, followed by methylation of the resulting 5-anilinothiatriazole with diazomethane [2] or, even better, with trimethyloxonium tetrafluoroborate [4].

In previous studies [2,3], we have shown that **1** reacts with isothiocyanates by one of two different pathways, depending on the nature of the substituents (Scheme I). Thus, benzyl and phenyl isothiocyanate give mainly C=N adducts **2** by path (a), whereas aroyl isothiocyanate and ethoxycarbonyl isothiocyanate follow path (b) (C=S adducts **4**), where **1** reacts as a masked 1,3-dipole. In addition, the primary products **2** and **4** are capable of undergoing further isomerizations to **3** and **5** under the influence of bases and isothiocyanates respectively.

Scheme I



We have now investigated in detail the behavior of **1** towards 2-pyridyl isothiocyanate which has the unique property of having an electrophilic isothiocyanate func-

tion coupled with a basic pyridine group. This results in a series of Dimroth-rearrangements [5], as described below.

Results and Discussion.

The methods used to prepare 2-pyridyl isothiocyanate [6] from 2-aminopyridine yield the dimer **6** as a brick-red crystalline compound which slowly dissociates to the pale-yellow monomer **7** on warming in organic solvent. At 35° in deuterated chloroform solution, an equilibrium at 88% dissociated dimer is reached, but at 55° dissociation is complete. We have determined the rate of dissociation by integration of the *ortho*-pyridyl hydrogen absorptions of the dimer (δ 8.7 and 9.3) and the monomer (δ 8.45) in the 250 MHz nmr spectra as a function of time. The first order rate constants and activation parameters are listed in Table I.

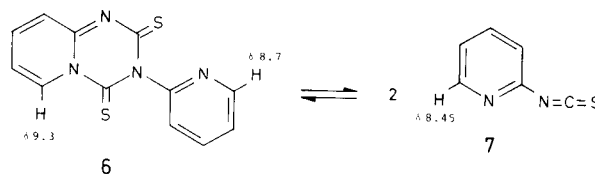


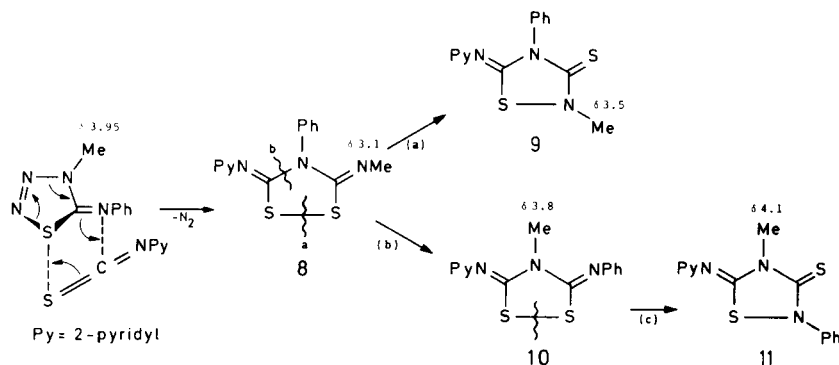
Table I

Kinetics of the Reaction **6** \rightarrow **7** in Deuteriochloroform Solution

T (°C)	35°	45°	50°	55°
$10^5 k_1$ (s $^{-1}$)	5.5	23.1	51.7	89.1
E_a = 28.1 kcal/mol				
ΔS^\ddagger (50°) = +11 e.u.				

Since the dimer **6** decomposes to the monomer with a half life of 13 minutes at 55°, we have used chloroform solutions of **6** preheated at 60° for 30 minutes to ensure complete conversion to **7**. Addition of an equimolar amount of **1** to such a solution at 60° gives rise to four pro-

Scheme II



ducts, **8-11**, (see Scheme II), having methyl singlet absorptions at δ 3.1, 3.5, 3.8 and 4.1 in the ^1H nmr spectrum. In order to obtain more insight into the mechanistic details of the process, the reaction was followed by ^1H nmr spectroscopy and the results are shown in Figure 1.

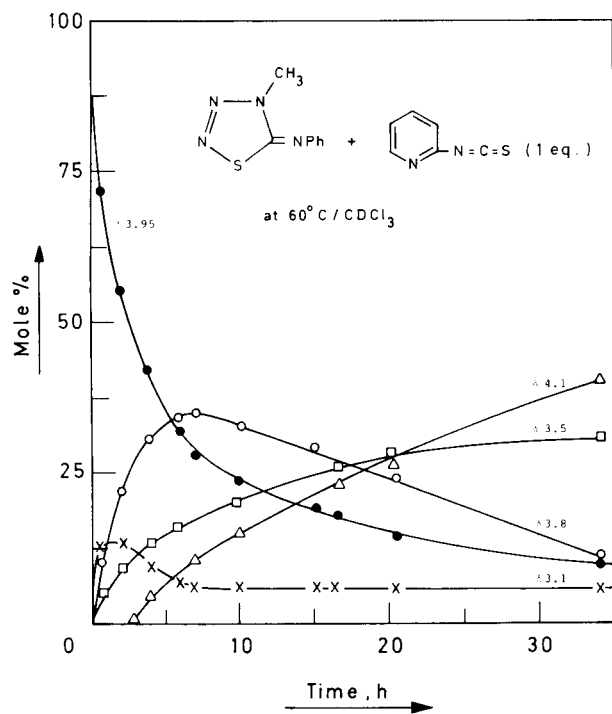


Figure 1. Reaction of **1** (0.5 M) with an equimolar amount of **7** in deuteriochloroform at 60°. Relative concentrations of **1** (●), **8** (x), **9** (□), **10** (○), **11** (△).

As expected, **1** (δ 3.95) disappears according to second-order kinetics. The dithiazolidine **8** (δ 3.1) is formed as the major product at a very early stage of the reaction (12% after 50 minutes), but decreases after 3 hours to a steady value of ca. 7%. The isomeric dithiazolidine **10** (δ 3.8) also increases sharply at the beginning of the reaction and reaches a maximum concentration of 35% after 6-7 hours

where it constitutes the major product. It then decreases as the reaction progresses. The other compounds **9** (δ 3.5) and **11** (δ 4.1) increase continuously during the reaction and are the major end products (30% and 40% respectively after 34 hours). Note also that **11** only appears after an induction period of at least 3 hours when a considerable amount of **10** has already been formed.

When 1.5 equivalents of 2-pyridyl isothiocyanate is used (saturated solution), the same general trends are observed with the notable difference that **10** now reaches a maximum concentration of 55% after 6 hours. The isothiocyanate function thus catalyzes the conversion of **8** to **10**.

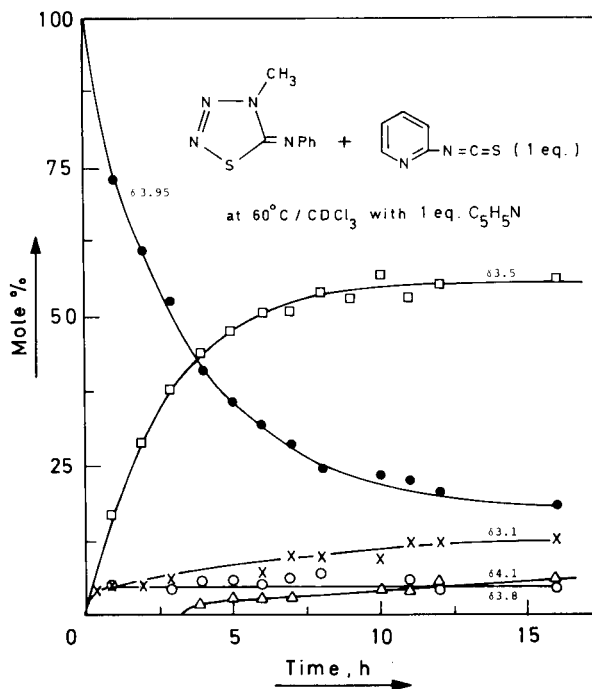


Figure 2. Reaction of **1** (0.5 M) with equimolar amounts of **7** and pyridine in deuteriochloroform at 60°. Relative concentrations of **1** (●), **8** (x), **9** (□), **10** (○) and **11** (△).

The addition of 1 equivalent of pyridine to the reaction mixture has no influence on the rate of decomposition of **1**, but favors the production of **9** (57% after 16 hours) at the expense of **11** (see Figure 2). Since **10** also remains at low concentration throughout the reaction, we conclude that it is the precursor of **11**. When DABCO (20 moles %) is used instead of pyridine, the same behavior is observed.

Further information about the mechanism was obtained when a sample, containing **9** and **10** in a ratio of 1:2, was treated with an equivalent of 2-pyridyl isothiocyanate in chloroform at 60°. The methyl singlet at δ 3.8 of **10** disappeared within 4 hours and was replaced by the singlet at δ 4.1 for **11**, whereas the resonance at δ 3.5 of **9** remained unaltered. The same phenomenon occurred, although at the lower rate, when pyridine (reaction time 7 hours) or DABCO (reaction time 30 hours) was used as catalyst.

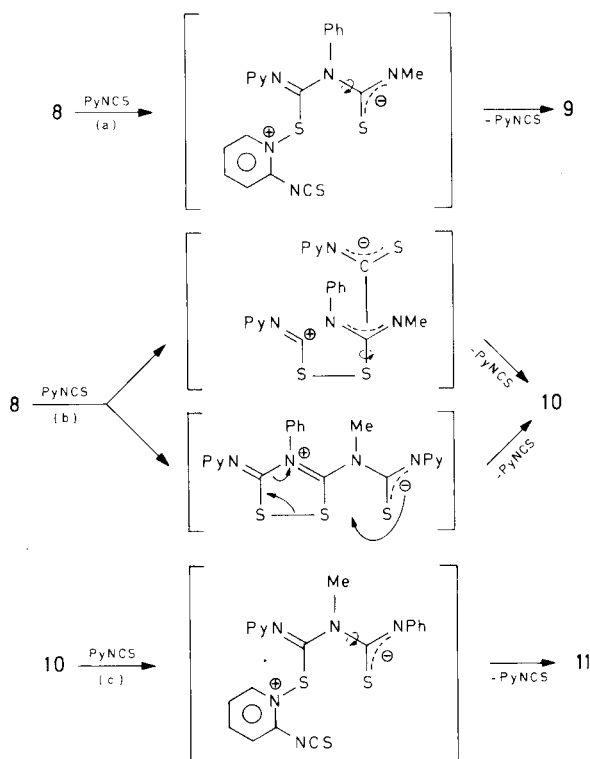
On the basis of these results we interpret the reaction course as follows (see Scheme II). The thiaziazoline **1** reacts as a masked 1,3-dipole with the C=S function of 2-pyridyl isothiocyanate to give, after loss of nitrogen, the dithiazolidine **8**. This rather unstable compound rearranges by two pathways in order to yield the less basic and, hence, thermodynamically more stable isomers **9** and **10**. The isomerizations are promoted by the pyridine nitrogen and isothiocyanate function respectively and may proceed as shown in Scheme III. For path (b) two mechanisms are conceivable, depending on whether the

reacting pyridyl isothiocyanate functions as a catalyst or as a reagent. In the latter case, **8** behaves as a masked 1,3-dipole similar to **1**, and eliminates the first added isothiocyanate. From Figure 1 we deduce that path (b) is faster than path (a). Finally, the isomerization of **10** to **11** is similar to **8** \rightarrow **9** and is catalyzed by the basic centers present in pyridine, 2-pyridyl isothiocyanate or DABCO.

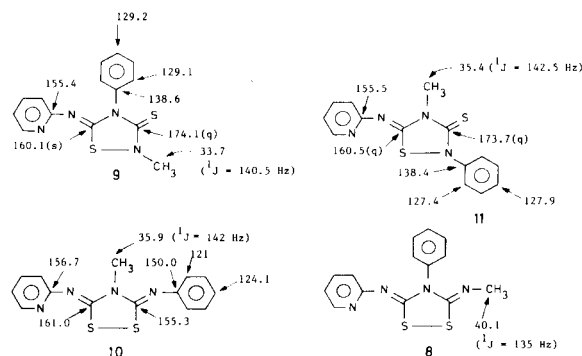
Characterization of the Reaction Products.

The two final products **9** and **11** were isolated in pure form by a combination of fractional crystallization and chromatography. They possess thiourea and isothioureatype carbon atoms which absorb at δ 174 and 160 respectively in the ^{13}C nmr spectra [2] (see Scheme IV). In both cases the phenyl substituent is located at the ring nitrogen atom as evidenced by the position of the C_1 (δ 138), C_o and C_p resonances (δ 127-129). These differ from the values expected for a phenyl attached to an exocyclic imine function, where C_1 (δ 149) is shifted downfield and C_o (δ 121) and C_p (δ 125) are shifted upfield [3]. The pyridyl group, on the contrary, is fixed to an imine nitrogen since it shows a C_2 resonance at δ 155 which would have shifted upfield (δ 151) in the other situation [7]. In addition, the strong ir absorptions at 1565 cm^{-1} point to an electro-negatively substituted imine function. The methyl substituents are attached to electron-deficient nitrogen atoms of the heterocycles since they exhibit a $^1\text{J}_{\text{CH}}$ coupling constant of 140-142 Hz. For a methylimino group, a value of 136 Hz would be expected [3].

Scheme III



Scheme IV



On the basis of these criteria and the fact that **9** and **11** manifest a positive Feigl test for the C=S function [8], we conclude that they have similar structures. The only difference is found in the coupled nmr spectra for the C=N resonance at δ 160; a singlet for **9** and a quartet for **11**. The C=S resonates as a quartet in both molecules. This led us to locate the methyl and phenyl substituents on the ring. The assignment further corroborates the mass spectra, where **9** exhibits significant fragment ions at m/z 227 (54%) and 195 (33%) attributable to $\text{M}^+ - \text{MeNCS}$ and PyNCNPh^+ respectively, whereas **11** gives a fragment ion at m/z 165 (51%) for $\text{M}^+ - \text{PhNCS}$.

The dithiazolidine **10** could not be isolated in the pure state since it isomerizes readily to **11**; for instance by attempted purification on preparative tlc. However, a sample containing **9** and **10** in a 1:2 ratio was obtained under appropriate conditions and analyzed by ^{13}C nmr spectroscopy. The results are shown in Scheme IV. On the basis of the arguments discussed above it is evident that the molecule has two imine functions and exocyclic phenyl and pyridyl substituents.

In order to characterize **8**, a solution of **1** and a half equivalent of 2-pyridyl isothiocyanate was analyzed at the early stage of the reaction (3 hours) when only **8** and **10** had been formed as products (both 14%). The ^{13}C nmr spectrum then shows a methyl resonance at δ 40 for **8** with a $^1J_{\text{CH}}$ coupling constant of 135 Hz. These data, together with the position of the methyl resonance in the ^1H nmr spectrum (δ 3.1) suggest structure **8** [3].

EXPERIMENTAL

4-Methyl-5-phenylimino-1,2,3,4-thiaziazoline (**1**) and 2-pyridyl isothiocyanate dimer **6** were prepared following the procedures of the literature [2,6].

2-Methyl-4-phenyl-5-(2-pyridyl)imino-1,2,4-thiadiazolidin-3-thione (**9**).

Compound **1** (1.92 g, 10 mmoles) was added to a preheated solution (30 minutes at 60°) of **7** (1.36 g, 5 mmoles) in 40 ml of chloroform. After a reflux period of 2 days, the solvent was evaporated and the residue crystallized from ether to give **9** in 13% yield, mp 235° (chloroform); ir (potassium bromide): 1565 cm^{-1} (s, C=N); ^1H nmr (deuteriochloroform): δ 3.5 (s, 3H, CH_3), 7.0, 7.3, 7.7 and 8.4 (four m, 4 x 1 H, pyridine), 7.45 and 7.55 (two m, 5H, Ph); ^{13}C nmr (deuteriochloroform): see Scheme IV; ms: m/z (%) 300 (100, M^+), 299 (97), 227 (54, $\text{M}^+ - \text{MeNCS}$), 195 (33 PyNCNPh^+), 169 (37), 132 (25), 78 (64, Py^+), 51 (21, C_4H_5^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{S}_2$ (mol wt 300): C, 55.98; H, 4.03. Found: C, 55.92; H, 3.98.

4-Methyl-2-phenyl-5-(2-pyridyl)imino-1,2,4-thiadiazolidin-3-thione (**11**).

Compound **1** (0.96 g, 5 mmoles) was added to a preheated solution of **7** (0.68 g, 2.5 mmoles) in 20 ml of chloroform. After a reflux period of 34 hours, the solvent was evaporated and the brown oily residue was treated with ether to give a precipitate (0.58 g) of **9** and **11**. After column chromatography on silica gel with chloroform as the eluent, an analytical sample (30 mg) of **11** was isolated, mp 225° ; (ir potassium bromide): 1565 cm^{-1} (s, C=N); ^1H nmr (deuteriochloroform): δ 4.1 (s, 3H, CH_3), 7.05, 7.5, 7.85 and 8.35 (four m of pyridine), 7.5 (Ph); ^{13}C nmr (deuteriochloroform): see Scheme IV; ms: m/z (%) 300 (100, M^+), 235 (15), 165 (51, $\text{M}^+ - \text{PhNCS}$), 132 (39), 78 (74, $\text{C}_5\text{H}_4\text{N}^+$), 51 (20, C_4H_5^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{S}_2$ (mol wt 300): C, 55.98; H, 4.03. Found: C, 56.06; H, 4.01.

4-Methyl-3-phenylimino-5-(2-pyridyl)imino-1,2,4-dithiazolidine (**10**).

Compound **1** (0.96 g, 5 mmoles) was added to a preheated solution of **7** (1.02 g, 3.75 mmoles) in 20 ml of chloroform. After heating at 60° for 6 hours, the solution was cooled and the solvent was evaporated. The residue was treated with ethanol-ether to give on cooling a precipitate

(0.25 g) which was characterized as a mixture of **9** and **10** in a 1:2 ratio. From the filtrate, a second crop (0.3 g) was obtained composed of **9**, **10** and **11** in a 2:4:1 ratio. The ^{13}C nmr data of **10** (deuteriochloroform) are summarized in Scheme IV.

3-Methylimino-4-phenyl-5-(2-pyridyl)imino-1,2,4-dithiazolidine (**8**).

A deuterated chloroform solution of **1** (0.5 M) and **7** (0.25 M) was heated at 60° for 3 hours, and then analyzed by ^1H and ^{13}C nmr spectroscopy. Products **8** and **10** were formed in almost equal amounts (14%) and their spectral data are summarized in Scheme IV.

Kinetics.

A. Dissociation of **6**.

Solutions of **6** in deuterated chloroform (0.13 M) were heated at the appropriate temperatures ($\pm 0.1^\circ$) for decomposition. At several time intervals, the solutions were analyzed on a 250 MHz nmr spectrometer by integration of the *ortho*-pyridine hydrogen signals of the dimer (δ 8.7 and 9.3) and the monomer (δ 8.45). Rate constants were deduced from the semilog plots of the concentrations (%) using the data of the first 50% conversion at 35° and 75% at the other temperatures; thus neglecting the reverse reaction. The correlation coefficients were then better than 0.9994. The activation parameters were calculated by using the Eyring equation. The results are summarized in Table 1.

B. Reaction of **1** with **7**.

The nmr tubes, containing deuterated chloroform solutions (0.5 M) of **1** and **7** (obtained by preheating the dimer **6**) were placed in a thermostat at 60° ($\pm 0.1^\circ$). At several time intervals, the nmr tubes were cooled to 0° and analyzed by ^1H nmr spectroscopy. The concentrations of the products were followed by integration of the methyl singlets at δ 3.95 (**1**), 3.1 (**8**), 3.5 (**9**), 3.8 (**10**) and 4.1 (**11**) and the results are plotted in Figure 1. In the case of Figure 2, one equivalent of pyridine was added to the reaction mixture.

Acknowledgement.

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