Mechanism of the Cycloaddition-Elimination Reactions of 4-Methyl-5-phenylimino-Δ^2-1,2,3,4-thiatriazoline with Alkyl and Aryl Isothiocyanates

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The formation of thiadiazolidines **3a-c** and dithiazolidines **4a-c** and **5a-b** from the title reactions has been studied in detail under a variety of conditions. On the basis of kinetic measurements, isomerization studies and cross experiments a mechanism is proposed involving path (b) (Scheme 1) as the first step, followed by a series of isomerizations as shown in Scheme 3.

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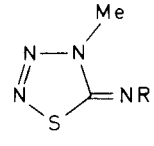
Thiatriazolin-5-imines **1** (R = alkyl, aryl) are interesting synthons for the preparation of other *S,N*-heterocycles since they can extrude a molecule of nitrogen during cycloaddition-elimination reactions with a = b unsaturated systems [1-5]. Three possible pathways are conceivable as shown in Scheme 1. According to path (a) the heterocycle reacts as an electron-deficient system, whereas in paths (b) and (c) it behaves as a masked 1,3-dipole. This dipole, however, is fundamentally different from those studied by Huisgen [6] (*e.g.* sydnones and Münchnones), since it does not contain a central onium atom. Hence, the mechanistic details of the process will be different and are described in this paper. Furthermore, path (b) is favoured over path (c) by the occurrence of a thiapentalene-like intermediate or transition state.

Scheme 1



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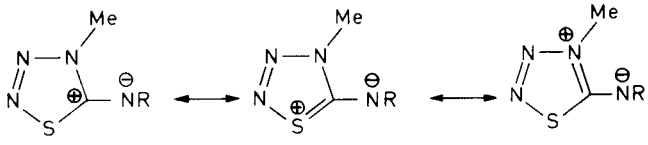
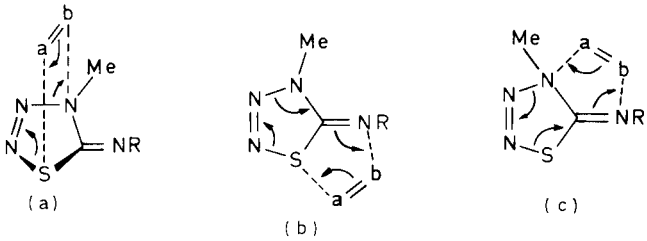




(a) (b) (c)

Our earlier investigations with **1** (R = Ph) showed that benzyl isothiocyanate and phenyl isothiocyanate react at room temperature apparently by path (a), whereas the electrophilic acyl isothiocyanates prefer path (b) [2,3]. Path (c) has been suggested only once to account for a product in low concentration [2]; its existence remains questionable.

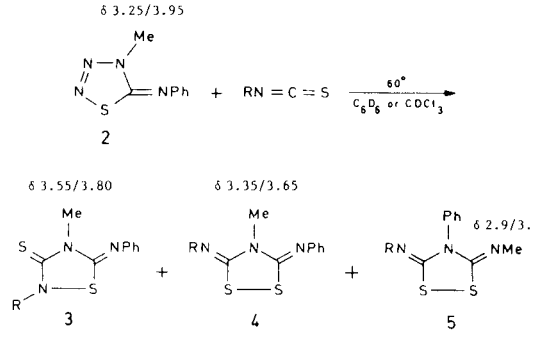
A point of much concern is path (a) which seems not to be favoured by electron-withdrawing R-substituents. Indeed, *N*-sulfonyl substituted thiatriazolinimines **1** (R = SO_2Ar) do not react with isothiocyanates at room temperature by path (a), but at 60° *via* thiaziridinimine intermediates [7]. The reactions follow first order kinetics and are independent of the concentration of the heterocumulene.

In view of these conflicting observations, and to understand better the underlying principles of the cycloaddition-eliminations of **1** (R = Ph) with isothiocyanates, we have now performed a detailed mechanistic study of the title reactions. They were carried out at 60° in order to avoid the thermal decomposition of **1** (R = Ph) which occurs at 90-120° [3].

Results.

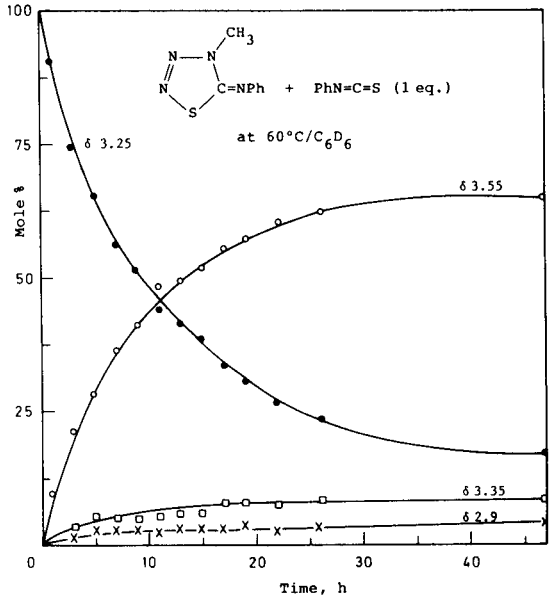
The reaction of **2** with an equimolar amount of phenyl isothiocyanate in deuterated benzene at 60° proceeds by second-order kinetics and yields three products, **3a-5a**, having methyl singlet absorptions at δ 3.55, 3.35 and 2.9 in the ^{1}H nmr spectra (Scheme 2, Figure 1). The thiadiazolidine **3a** is the major product which reaches a concentration of 64% after 47 hours, while **4a** and **5a** are secondary products (9 and 5% respectively).

Scheme 2



a: R = C_6H_5, b: R = p-$NO_2C_6H_4$, c: R = $C_6H_5CH_2$

(δ-values are given in C_6D_6 and $CDCl_3$ respectively)



1. Reaction of **2** (0.5 *M*) with an equimolar amount of phenyl isothiocyanate in deuterated benzene at 60°. Relative concentrations of **2** (●), **3a** (○), **4a** (□) and **5a** (x).

Test experiments have shown that **4a** is thermodynamically the most stable isomer since it remains unaltered when heated with phenyl isothiocyanate in benzene at 60° for 160 hours. Compounds **3a** and **5a**, on the contrary, isomerize under the influence of phenyl isothiocyanate, the former giving **4a** exclusively (Table 1) and the latter yielding **4a** and **3a** in the proportion of *ca* 1.6:1 (Table 2). The two isomerization processes are, however, very slow and their effect on the product distribution of Figure 1 is considered to be small. This has been verified by following the reaction of **2** with five equivalents of phenyl isothiocyanate, giving a reaction profile similar to that of Figure 1 (see Figure 2).

Table 1

Isomerization of **3a** (0.5 *M*) into **4a** under the influence of PhNCS in deuterated benzene at 60°

Equivalents of PhNCS	Reaction time (hours)	% **4a** (δ 3.35)
1	23	8
	29	10
	97	25
	161	35
3	10	9
	27	20
	49	27
	78	41
5	10	14
	27	27
	49	40
	78	57

Table 2

Isomerization of **5a** (0.25 *M*) into **3a** and **4a** under the influence of PhNCS (0.25 *M*) in deuterated benzene at 60°

Reaction time (hours)	% **3a** (δ 3.55)	% **4a** (δ 3.35)	Ratio **4a**/**3a**
28	2.3	3.8	1.6
45	3.8	5.3	1.4
68	6	10	1.6
197	16	28	1.7

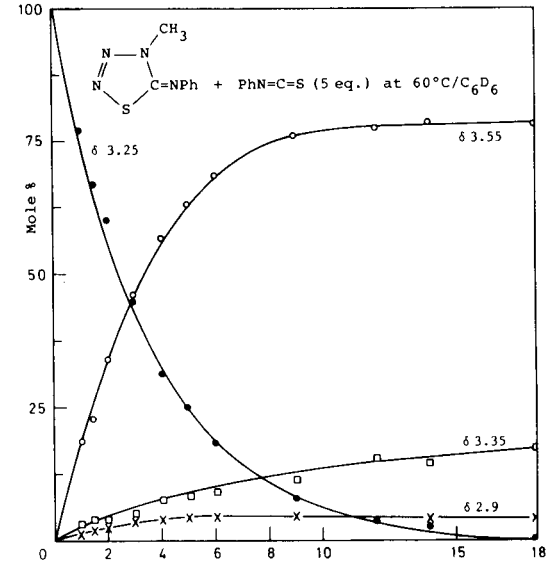


Figure 2. Reaction of **2** (0.5 *M*) with five equivalents of phenyl isothiocyanate in deuterated benzene at 60°. Relative concentrations of **2** (●), **3a** (○), **4a** (□) and **5a** (x).

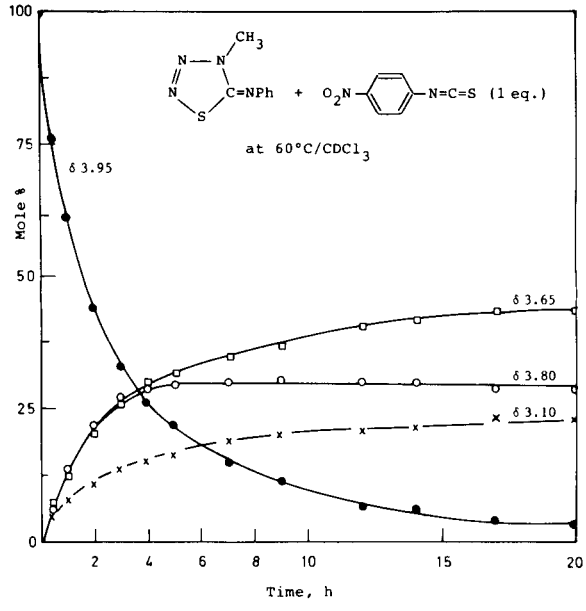


Figure 3. Reaction of **2** (0.5 *M*) with an equimolar amount of *p*-nitrophenyl isothiocyanate in deuteriochloroform at 60°. Relative concentrations of **2** (●), **3b** (○), **4b** (□) and **5b** (x).

p-Nitrophenyl isothiocyanate is more reactive towards **2** than is phenyl isothiocyanate, and the distribution of **3b-5b** depends both on the concentration of isothiocyanate and the polarity of the solvent (Figures 3-5). From Figures 3 and 4 we deduce that **3b** readily isomerizes into **4b** with isothiocyanate, whereas **5b** does so much slower. Independent experiments have shown that this is indeed the case and that single products are obtained (Table 3). Furthermore, the isomerizations of **3b** and **5b** are much faster than those of **3a** and **5a** and therefore, significantly influence the reaction course.

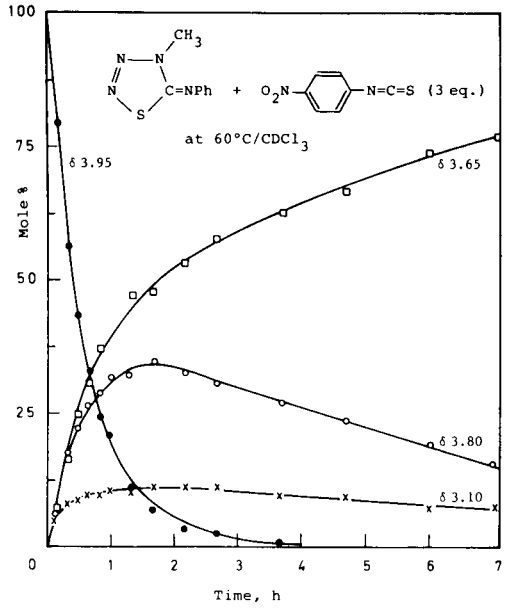


Figure 4. Reaction of **2** (0.5 *M*) with three equivalents of *p*-nitrophenyl isothiocyanate in deuteriochloroform at 60°. Relative concentrations of **2** (●), **3b** (○), **4b** (□) and **5b** (x).

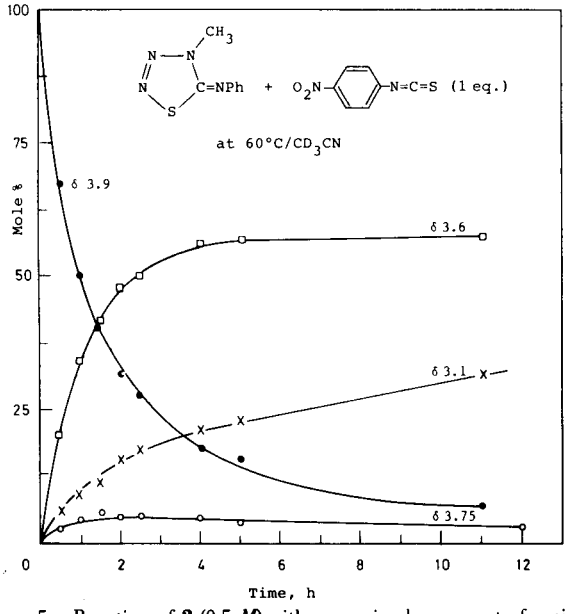


Figure 5. Reaction of **2** (0.5 *M*) with an equimolar amount of *p*-nitrophenyl isothiocyanate in deuterated acetonitrile at 60°. Relative concentrations of **2** (●), **3b** (○), **4b** (□) and **5b** (x).

Table 3

Isomerizations of **3b** and **5b** (0.25 *M*) into **4b** under the influence of *p*-$NO_2C_6H_4NCS$ (0.25 *M*) in deuteriochloroform at 60°

Reaction time (hours)	**3b** ⟶ **4b** %	**5b** ⟶ **4b** %
5	24	8
10	39	15
15	48	22
20	53	28

Finally, we have found that benzyl isothiocyanate reacts with **2** four times slower than does phenyl isothiocyanate (Figure 6), yielding **3c** as the principal product. Compound **4c** only appears after 50 hours and remains at low concentration (below 5%). It evidently results from isomerization of **3c** under the influence of the remaining benzyl isothiocyanate.

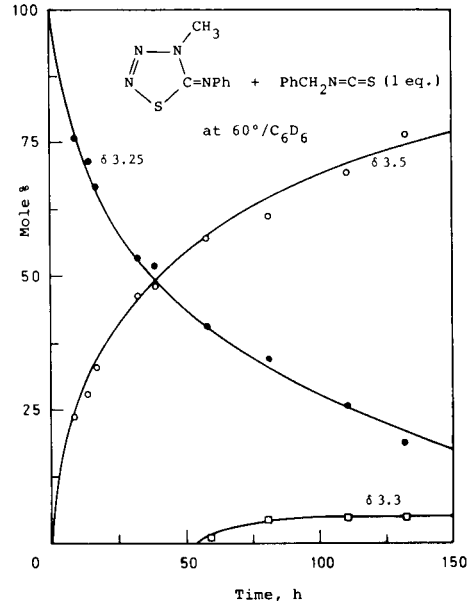
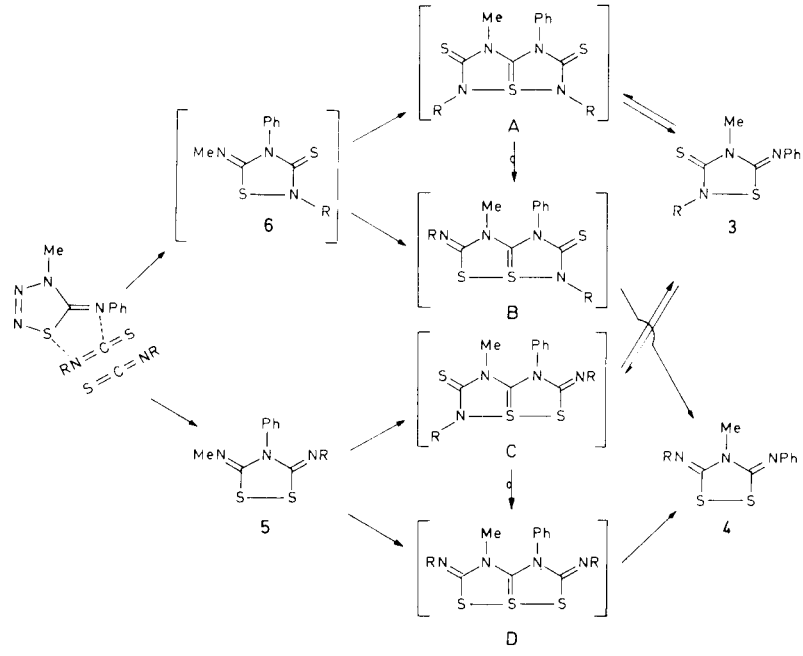


Figure 6. Reaction of **2** (0.5 *M*) with an equimolar amount of benzyl isothiocyanate in deuterated benzene at 60°. Relative concentrations of **2** (●), **3c** (○) and **4c** (□).

Mechanism.

The observed reactivities cannot be explained simply by the operation of two pathways (a) and (b) (Scheme 1) and a changeover from path (a) to path (b) as the electrophilicity of the isothiocyanate increases. Indeed, benzyl isothiocyanate is expected to react best by path (a), but in fact gives the C=N adduct **3c** very sluggishly (75% after 5 days at

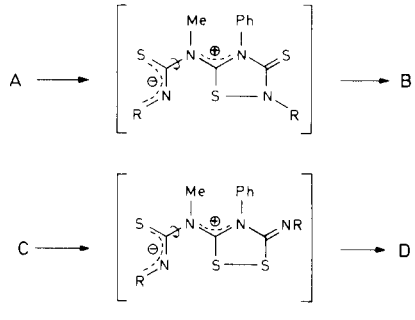
Scheme 3



60°). Furthermore, the rate of formation of **3b** is not decreased compared to that of **3a**, if one takes into account its facile isomerization into **4b**. Our results, on the contrary, point out that the introduction of a *p*-nitro substituent into phenyl isothiocyanate increases the overall reaction rate as well as the individual rates of formation of **3** and **4** (as well as **5**). Hence, path (a) should be abandoned and we are left with path (b) as the only acceptable alternative for explaining the diversity of products.

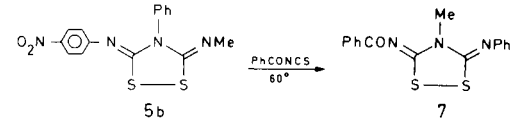
A plausible rationalization is presented in Scheme 3. The heterocycle **2** reacts as a masked 1,3-dipole with both the C=S and C=N bonds of the isothiocyanate to give **5** and **6** respectively. These compounds have a pronounced nucleophilic *N*-alkylimine function and combine with a second molecule of isothiocyanate to give **3** and **4** *via* the thiapentalene-like intermediates **A-D**.

Scheme 4



This scheme also explains the observed isomerization of **5a** into **3a** and **4a** (*via* **C** and **D**) and of **5b** into **4b** (*via* **D**). The isomerization of **3a,b** into **4a,b** is assumed to proceed either *via* **A** and **B** or *via* **C** and **D**. Indeed, thiapentalenes of this type have weak N-S and S-S bonds [8], allowing for a facile isomerization of **A** into **B** and of **C** into **D** according to Scheme 4. Electron-withdrawing R-substituents (*e.g. p*-nitrophenyl) stablilize the intermediate dipoles and accelerate the isomerization. The final step is the elimination of the first isothiocyanate added, to give the stable products **4a,b**.

Cross-experiments have been carried out successfully with **5**, but not with **3**. Thus, when **5b** was treated with two equivalents of benzoyl isothiocyanate at 60°, **7** was isolated in 56% yield. Compounds **3a** and **3b**, on the contrary, only isomerized into **4a,b** when treated with *p*-tolyl isothiocyanate and benzoyl isothiocyanate respectively. These results are explained by the intermediates A-D which eliminate the isothiocyanate moiety preferably from the right-side of the molecule, giving the thermodynamically most stable heterocycles.



The missing link of Scheme 3 is structure **6** which constitutes the principal intermediate for **3**. Since **3** is less stable than **4**, we can assume that **6** should also be less

stable than **5** and might then be consumed by isothiocyanate at a higher rate. During the experiments in acetonitrile (Figure 5), a small signal appeared at δ 3.0 (maximum concentration 3.7%) which disappeared within 90 minutes. This may correspond to **6b** since the chemical shift is at the expected position.

Finally, a comment on the mechanistic details of path (b) is in order. An important feature of the process is the nucleophilicity of the imine nitrogen since no reaction by path (b) was observed when R is a sulfonyl group [7]. Also, preliminary experiments have shown that the reactivity towards isothiocyanates decreases when electron-withdrawing substitutents (*e.g.* NO_2) are introduced into the phenyl ring of **2**. For a concerted reaction, we believe that the reacting π-electrons of the isothiocyanate (C=N or C=S, represented by a = b in Figure 7) approach the heterocycle in the same molecular plane as the ring atoms. The reaction starts with a nucleophilic attack of the imine lone pair and then proceeds by ring closure at sulfur, elimination of molecular nitrogen, formation of an electron pair at the N-4 nitrogen atom, and, finally, a π-electron flow towards the imine function. The synchronous process is depicted in Figure 7.

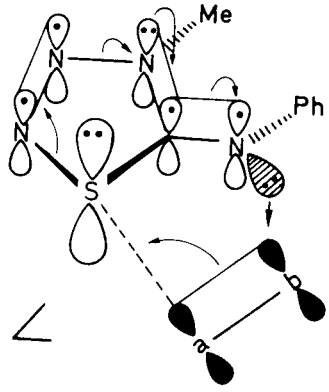
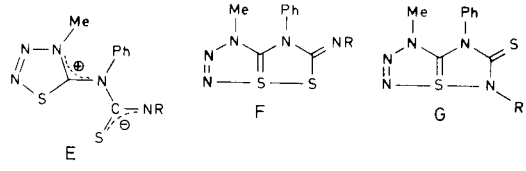


Figure 7. Concerted mechanism for path (b).

If the reaction is not concerted, **E-G** may be considered as possible intermediates. A comparison of Figure 3 and 5 reveals that **2** disappears only 1.5 times faster in acetonitrile than in chloroform, indicating that path (b) is not much affected by the polarity of the solvent. This does not exclude the dipolar intermediate **E** since acetonitrile as solvent may deactivate the isothiocyanate by complexation, thus counteracting the expected rate enhancement during the formation of **E**.



In conclusion, the cycloaddition-elimination reactions of **2** with alkyl and aryl isothiocyanates are best rationalized by path (b), combined with a series of isomerizations *via* thiapentalene-like intermediates as shown in Scheme 3.

Since the structures of the new compounds were assigned on the basis of criteria discussed previously [3,5], we defer the spectral data to the Experimental Section.

EXPERIMENTAL

4-Methyl-5-phenylimino-1,2,3-thiatriazoline (**2**) was prepared by the procedure of Toubro and Holm [4]. For the preparation of **3c**, see ref [2].

Reaction of **2** with Phenyl Isothiocyanate.

A solution of **2** (3 g, 15.6 mmoles) and phenyl isothiocyanate (6.32 g, 46.8 mmoles) was heated in 32 ml of chloroform at 60° for 14 hours. The reaction mixture was subjected to column chromatography on silica gel using first *n*-hexane to elute the excess of phenyl isothiocyanate, and then chloroform to give **3a** and **5a**.

4-Methyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**3a**).

This compound was obtained in 45% yield (2.1 g), mp 86° (ether/*n*-hexane) (lit [2] 86-88°); ^{13}C nmr (deuteriochloroform) δ 35.4 (CH_3, $^1J_{CH}$ = 142.5 Hz), 120.3, 125.2, 127.9, 129.1, 129.4, 129.8, 137.7 and 149.3 (Ph C-atoms), 153.6 (C-5), 177.2 (C=S).

5-Methylimino-4-phenyl-3-phenylimino-1,2,4-dithiazolidine (**5a**).

This compound was obtained in 2.4% yield (0.11 g), mp 189° (ether/*n*-hexane); ir (potassium bromide): 1655 (m), 1630 cm^{-1} (s, br); ^1H nmr (deuteriochoroform): δ 3.1 (s, 3H, CH_3), 6.9-7.6 (m, 10 aromatic H); ^{13}C nmr (deuteriochloroform): δ 39.3 (CH_3, $^1J_{CH}$ = 135 Hz), 121.2, 124.7, 128.8, 129.6, 139.0 and 149.0 (Ph C-atoms), 153.8 (C-3), 152.7 (C-5).

Anal. Calcd. for $C_{15}H_{13}N_3S_2$ (mol wt 299): C, 60.17; H, 4.37. Found: C, 60.05; H, 4.39.

3,5-Bis(phenylimino)-4-methyl-1,2,4-dithiazolidine (**4a**).

This compound was obtained by heating **3a** (0.5 g, 1.67 mmoles) with DABCO (37 mg, 0.33 mmoles) in 3 ml of acetone at 60° for one day, followed by crystallization of the reaction mixture from chloroform/*n*-hexane; yield 60% (300 mg), mp 134° (lit [2] 134-135°); ^{13}C nmr (deuteriochloroform): δ 35.4 (CH_3) 121.6, 125.2, 129.9 and 149.1 (Ph C-atoms), 154.3 (C-3 and C-5).

Compound **4a** was also obtained by heating **3a** (1 g, 3.3 mmoles) with *p*-tolyl isothiocyanate (2.49 g, 16.5 mmoles) in 7 ml of chloroform at 60° for five days. The product was isolated in 43% yield (433 mg) after column chromatography on silica gel with *n*-hexane/ether (varying ratios) as the eluent.

Reaction of **2** with *p*-Nitrophenyl Isothiocyanate.

A solution of **2** (1.5 g, 7.8 mmoles) and *p*-nitrophenyl isothiocyanate (1.40 g, 7.8 mmoles) was heated in 15 ml of chloroform at 60° for 21 hours. The products were separated by column chromatography on silica gel using first *n*-hexane/ether and then dichloromethane as the eluents.

4-Methyl-2-(*p*-nitrophenyl)-5-phenylimino-1,2,4-thiadiazolidine-3-thione (**3b**).

This compound was obtained in 16% yield (0.42 g), mp 154°; ir (potassium bromide): 1635 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, CH_3), 7.0-7.4 (three m, 5H, Ph), 7.75 and 8.25 (two d, 4H, p-$NO_2C_6H_4$); ^{13}C nmr (deuteriochloroform): δ 35.6 (CH_3, $^1J_{CH}$ = 142.5 Hz), 120.2, 124.6, 125.7, 128.3, 130.0, 143.3, 146.8 and 149.1 (aromatic C-atoms); 152.4 (C-5), 177.0 (C=S).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S_2$ (mol wt 344): C, 52.33; H, 3.49. Found: C, 52.29; H, 3.51.

4-Methyl-3-(*p*-nitrophenyl)imino-5-phenylimino-1,2,4-dithiazolidine (**4b**).

This compound was obtained in 26% yield (0.70 g), mp 115°; ir (potassium bromide): 1620 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.65 (s, 3H, CH_3), 6.9-7.4 (four m, 7 aromatic H), 8.2 (d, 2 aromatic H); ^{13}C nmr (deuteriochloroform): δ 35.4 (CH_3, $^1J_{CH}$ = 142.8 Hz), 121.0, 121.9, 125.2, 125.4, 129.6, 144.6, 148.3 and 154.4 (aromatic C-atoms), 153.2 and 154.8 (C-3 and/or C-5).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S_2$ (mol wt 344): C, 52.33; H, 3.49. Found: C, 52.40; H, 3.52.

Compound **4b** was also obtained when **3b** (0.15 g, 0.44 mmole) was heated with benzoyl isothiocyanate (71 mg, 0.44 mmole) in 2 ml of chloroform at 60° for one day. It was isolated in 55% yield (82 mg) by preparative thin layer chromatography (silica gel) using *n*-hexane/ether/dichloromethane as the eluate.

5-Methylimino-3-(*p*-nitrophenyl)imino-4-phenyl-1,2,4-dithiazolidine (**5b**).

This compound was obtained in 15% yield (0.41 g), mp 176°; ir (potassium bromide): 1660 (m), 1625 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.15 (s, 3H, CH_3), 7.0 and 8.2 (two m, 4H, p-$NO_2C_6H_4$), 7.25-7.6 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 39.4 (CH_3, $^1J_{CH}$ = 135 Hz), 121.9, 125.2, 128.7, 129.2, 129.7, 138.5, 144.5 and 154.6 (aromatic C-atoms), 151.7 (C-5), 154.6 (C-3).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S_2$ (mol wt 344): C, 52.33; H, 3.49. Found: C, 52.42; H, 3.46.

3-Benzoylimino-4-methyl-5-phenylimino-1,2,4-dithiazolidine (**7**).

A solution of **5b** (0.12 g, 0.35 mmole) and benzoyl isothiocyanate (114 mg, 0.70 mmole) was heated in 1.5 ml of chloroform at 60° for 17 hours. Compound **7** was isolated in 56% yield (64 mg) by thin layer chromatography (silica gel) using dichloromethane/carbon tetrachloride (1:1) as the eluate, mp 145°. The nmr spectra were compared with those of an authentical sample, prepared by heating **2** with an excess of benzoyl isothiocyanate [3]; ^1H nmr (deuteriochloroform): δ 3.9 (s, 3H, CH_3), 6.95-7.6 (m, 8 aromatic H), 8.3 (d, 2 aromatic H); ^{13}C nmr (deuteriochloroform): δ 36.8 (CH_3, $^1J_{CH}$ = 143 Hz), 120.6, 124.9, 128.4, 129.6, 129.8, 133.1, 134.0 and 149.2 (aromatic C-atoms), 154.8 (C-5), 172.8 (C-3), 177.4 (CO).

Kinetics.

The nmr tubes containing **2** (0.5 *M*) and isothiocyanate in the appropriate deuterated solvents were placed in a thermostat at 60° (±0.1°). At several time intervals the nmr tubes were cooled to 0° and analyzed by ^1H nmr spectroscopy (90 MHz). The concentrations of the products were followed by integration of the methyl singlets in the spectra (estimated error <5%) and the results are plotted in Figures 1-6. The same technique was used for studying the isomerizations recorded in Tables 1-3.

Acknowledgement.

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