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### RING-TRANSFORMATION FROM ISOTHIAZOLE TO 1,2,4-THIADIAZOLE - POSSIBLE INTERMEDIACY OF $\pi$ -SULFURANE

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## RING-TRANSFORMATION FROM ISOTHIAZOLE TO 1,2,4-THIADIAZOLE—POSSIBLE INTERMEDIACY OF $\pi$ -SULFURANE

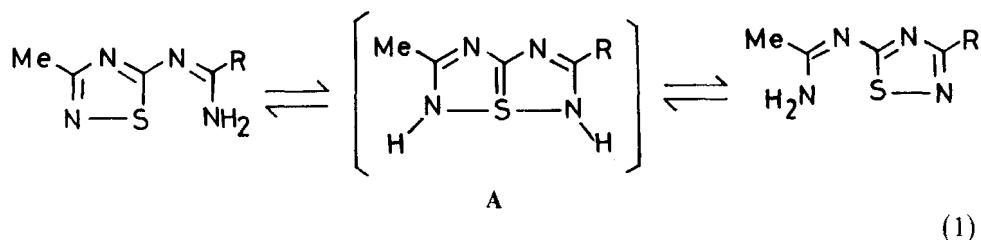
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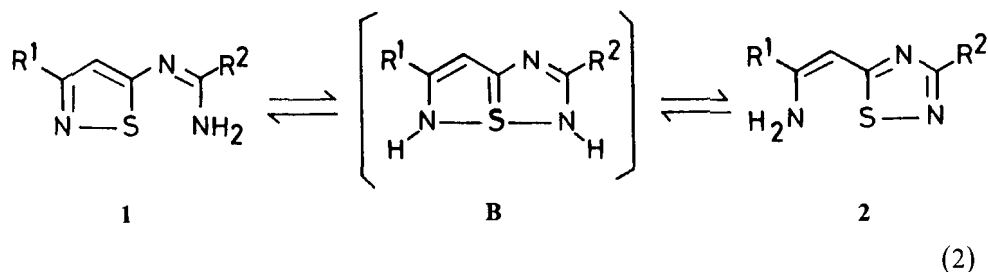
(Received December 19, 1982)

5-Amino-3-methyl- and 5-amino-3-phenylisothiazoles (**3a** and **3b**) afforded 1:1 adducts with aromatic nitriles and imidates. On the basis of their spectral data and the structure of hydrolysis products, the adducts were identified as 3-substituted 5-(2-aminovinyl)-1,2,4-thiadiazole derivatives (**2a-g**), where ring transformation took place from isothiazole to 1,2,4-thiadiazole.

There have been many studies on heterocyclic transformation<sup>1</sup> in which  $\pi$ -hypervalent sulfur plays an important role. In a previous paper,<sup>2</sup> we reported a novel example of ring-transformation equilibrium between thiadiazoles and proposed that the transformation occurred via thiathiophthene analogue sulfurane (**A**) where  $\pi$ -hypervalent sulfur played a crucial role as shown in eq. (1).



This fact prompted a study of the analogous ring-transformation equilibrium between the isothiazole and 1,2,4-thiadiazole system as shown in eq. (2).

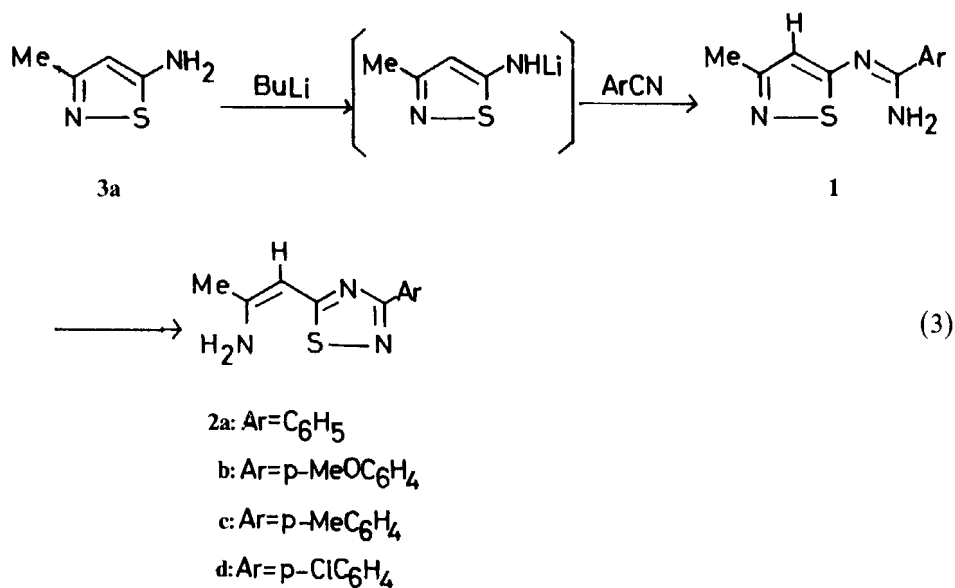


We now report the result of such an investigation which showed that the equilibrium (2) is totally shifted to the 1,2,4-thiadiazole ring (2).<sup>3</sup>

## RESULTS AND DISCUSSION

*Characterization of the Adduct of 5-Amino-3-Methylisothiazole (3a) and 4-Substituted Benzonitriles*

5-Amino-3-methylisothiazole (**3a**) was prepared by the procedure of Adams *et al.*<sup>4</sup> Reaction of the *N*-lithio derivative of **3a** with benzonitrile gave a crystalline product, mp 121.5–122.5°C, in moderate yield. The product was isolated and recrystallized from hexane–benzene, but it gradually decomposed on exposure to silica gel. Elemental analysis indicated formation of the 1:1 adduct (**2a**) of **3a** and benzonitrile. The <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> showed the following signals; a singlet at  $\delta = 2.02$  (3 H: —CH<sub>3</sub>), a singlet at  $\delta = 5.38$  (1 H: =CH—), and a broad singlet at  $\delta = 6.40$ – $6.90$  (2 H: —NH<sub>2</sub>) together with a multiplet for aromatic protons at  $\delta = 7.30$ – $7.60$  (3 H) and  $\delta = 8.00$ – $8.40$  (2 H). By comparison of <sup>1</sup>H NMR spectra of the adduct (**2a**) with **3a**, it is apparent that the heteroaromatic proton ( $\delta = 6.10$ ) at the 4-position of the starting material shifted upwards by 0.72 ppm in the product, and the methyl protons ( $\delta = 2.28$ ) also shifted in the same direction by 0.26 ppm. This high field shift indicates the ring opening of the isothiazole to afford the aminovinyl group. Moreover, the distinct difference of chemical shift among the ortho and meta-para protons of the aromatic ring reveals that the aromatic ring is conjugated with some heterocycle,<sup>5</sup> the thiadiazole in this case. By means of these spectroscopic analyses, the structure of the product was assigned as **2a** instead of **1a**.



To confirm the above assignment, hydrolysis of **2a** in aqueous ethanol in the presence of oxalic acid was tried and gave 5-(2-oxopropyl)-3-phenyl-1,2,4-thiadiazole (**4a**, mp 112–114°C) in 40% yield, thus illustrating the presence of the 2-aminovinyl group in the adduct (**2a**). The <sup>1</sup>H NMR spectrum of **4a** shows the corresponding signals of the methyl and methylene group at  $\delta = 2.40$  (3 H) and  $\delta = 4.40$  (2 H)

TABLE I  
Yields and physical data of 3-substituted 5-(2-aminovinyl)-1,2,4-thiadiazoles (**2a-g**)

Compound		Method	Yield (%)	Mp (°C)	<sup>1</sup> H NMR (δ in CDCl <sub>3</sub> ) <sup>a</sup>			IR (nujol) (cm <sup>-1</sup> )
R <sup>1</sup>	R <sup>2</sup>				R <sup>1</sup>	R <sup>2</sup>	-CH=	
<b>2a</b>	Me	A	47	121.5–122.5	2.02 (s, 3 H)	7.30–7.60 (m, 3 H) 8.00–8.40 (m, 2 H)	5.38 (s)	3350 1330
<b>2b</b>	Me	A	33	121.0–122.0	2.00 (s, 3 H)	6.95 (d, 2 H) <sup>b</sup> 3.82 8.18 (d, 2 H) (s, 3 H)	5.38 (s)	3340 1330
<b>2c</b>	Me	A	40	93.0–95.0	2.02 (s, 3 H)	7.25 (d, 2 H) <sup>b</sup> 2.40 8.10 (d, 2 H) (s, 3 H)	5.40 (s)	3350 1330
<b>2d</b>	Me	A	40	132.0–133.0	2.02 (s, 3 H)	7.40 (d, 2 H) <sup>b</sup> 8.20 (d, 2 H)	5.38 (s)	3380 1330
<b>2e</b>	C <sub>6</sub> H <sub>5</sub>	B	69	93.5–95.0	7.30–7.70 (m, 5 H)	2.62 (s, 3 H)	5.78 (s)	3360 1320
<b>2f</b>	C <sub>6</sub> H <sub>5</sub>	B	30	81.5–82.5	7.30–7.80 (m, 5 H)	7.30–7.80 (m, 3 H) 8.20–8.40 (m, 2 H)	5.84 (s)	3400 1330
<b>2g</b>	Me	B	55	96.5–98.0	2.00 (s, 3 H)	2.58 (s, 3 H)	5.30 (s)	3350 1310

<sup>a</sup>The peak of the amino hydrogens appears as a broad singlet between 6.40 and 7.00 for **2a-d**, between 6.60 and 7.30 for **2e-f**, and between 6.20 and 7.20 for **2g**.

<sup>b</sup>Aromatic hydrogens appear as an AB quartet with  $J = 8$  Hz for **2b-d**.

TABLE II  
Physical data of hydrolysis products (4a-e)

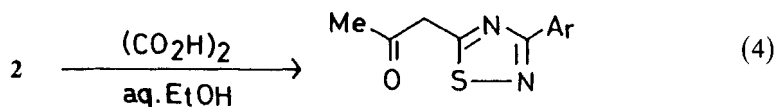
Compound		Yield (%)	Mp (°C)	<sup>1</sup> H NMR (δ in CDCl <sub>3</sub> )			IR (nujol) (cm <sup>-1</sup> )
R <sup>1</sup>	R <sup>2</sup>			R <sup>1</sup>	R <sup>2</sup>	CH <sub>2</sub>	
4a	Me	40	112-114	2.38 (s, 3 H)	7.48 (m, 3 H) 8.28 (m, 2 H)	4.39 (s, 2 H)	1705 1330 1180
4b	Me	25	99-100	2.38 (s, 3 H)	6.97 (d, 2 H) <sup>b</sup> 3.82 8.17 (d, 2 H) (s, 3 H)	4.35 (s, 2 H)	1715 1290 1190
4c	Me	15	58-60	2.38 (s, 3 H)	7.33 (d, 2 H) <sup>b</sup> 2.00 8.17 (d, 2 H) (s, 3 H)	4.32 (s, 2 H)	1710 1320 1185
4d	Me	23	115-116	2.38 (s, 3 H)	7.43 (d, 2 H) <sup>b</sup> 8.23 (d, 2 H)	4.38 (s, 2 H)	1705 1180 1160
4e	C <sub>6</sub> H <sub>5</sub>	50 <sup>a</sup>	113-115	7.30-7.70 (m, 3 H) 7.70-8.25 (m, 2 H)	2.68 (s, 3 H)	4.80-5.20 (bs, 2 H)	1690 <sup>c</sup> 1490 1290

<sup>a</sup> Diluted hydrochloric acid in aqueous methanol was used as the catalyst for hydrolysis; for all others, oxalic acid in aqueous ethanol was used.

<sup>b</sup> Aromatic hydrogens appear as an AB quartet with  $J = 8$  Hz for 4b-d.

<sup>c</sup> The infrared spectrum was measured in carbon tetrachloride solution.

along with the other signals for the aromatic protons, which are almost the same as those of **2a**. By a similar procedure, **2b-d** were converted to **4b-d** in moderate yields. These results are shown in Tables I and II.



4a: Ar = C<sub>6</sub>H<sub>5</sub>

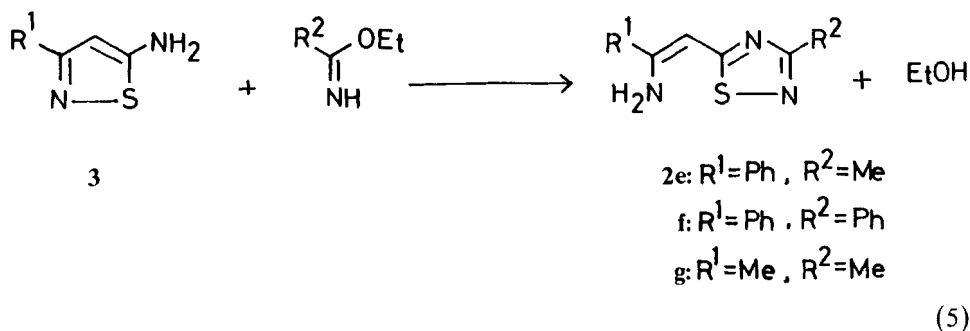
b: Ar = p-MeOC<sub>6</sub>H<sub>4</sub>

c: Ar = p-MeC<sub>6</sub>H<sub>4</sub>

d: Ar = p-Cl C<sub>6</sub>H<sub>4</sub>

*Reaction of 5-Aminoisothiazole Derivatives (3a and 3b) with Imidates*

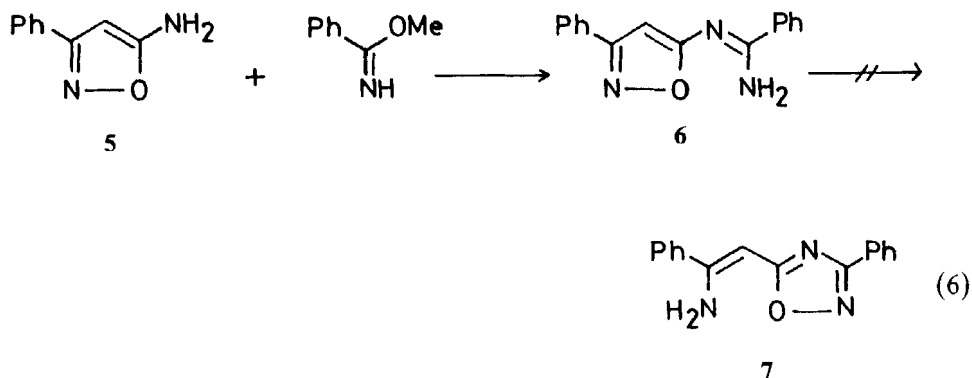
5-Amino-3-phenylisothiazole (**3b**) was obtained in fair yield by suitable modification of the procedure originally developed by Goerdeler *et al.*<sup>6</sup> Although attempts to prepare an adduct of **3b** with nitriles using the N-lithio derivative of **3b** were not successful, **3b** when treated with excess acetimidate without solvent at about 80°C gave the crystalline product, mp 94–95°C, in a 69% yield. Structural assignment as **2e** was made as before. The remarkable upfield shift of the heterocyclic proton of **3b** from  $\delta$  6.70 to 5.78 is a direct consequence of formation of the 2-aminovinyl group owing to the N—S bond-fission in the isothiazole ring. The aromatic ring protons appear as a multiplet mounted on a broad singlet at  $\delta$  7.30–7.70 and the methyl protons lie at  $\delta$  2.62 which is considerably lower than in **2a** ( $\delta$  2.02). Additional supportive evidence for the assignment to **2e** comes from its hydrolysis which gave 3-methyl-5-(2-oxo-2-phenylethyl)-1,2,4-thiadiazole.



Analogously, 5-(2-amino-2-phenylvinyl)-3-phenylthiadiazole (**2f**) and 5-(2-amino-2-methylvinyl)-3-methylthiadiazole (**2g**) were obtained in moderate yields. Their physical data are summarized in Tables I and II.

The structural similarity between isothiazole and isoxazole prompted us to investigate the possible occurrence of intramolecular rearrangement from isoxazole to 1,2,4-oxadiazole. Treatment of 5-amino-3-phenylisoxazole (**5**) with methyl benzimi-

date produced only the simple adduct, i.e., isoxazole derivative (6). The aromatic protons of the adduct show characteristic multiplets



with chemical shifts of  $\delta$  7.7–8.0 (2 H),  $\delta$  8.0–8.3 (2 H), and  $\delta$  7.2–7.7 (6 H), which indicate the presence of two sets of ortho protons and indistinguishable meta protons. As discussed above, the aromatic protons of the phenyl of the aminovinyl group in 7 should appear as a multiplet mounted on a broad singlet, and 7 should give characteristic multiplets of  $\delta$  8.0–8.3 (2 H) and 7.2–7.7 (8 H). No vinyl proton of a 2-aminovinyl group is observed in the neighborhood of  $\delta$  5 to 6 in the  $^1\text{H}$  NMR spectrum. Moreover, no  $^{13}\text{C}$  peak is observed which can be attributed to the C-1 of a 2-aminovinyl group in 7. These results suggest that the N—O bond fission in the isoxazole ring did not occur during the reaction of (6). In conclusion, the fact that 5-(2-aminovinyl)-1,2,4-thiadiazole derivatives (2) were the only products in the reactions of (3) and (5) implies that the equilibrium with (2) shifted to the right owing to greater stability of the 1,2,4-thiadiazole compared to isothiazole. The crucial role of the  $\pi$ -hypervalent sulfur atom in these reactions is supported by the contrasting fact that the isoxazole ring (6) remained intact in a similar reaction of (6).

## EXPERIMENTAL

Infrared spectra were recorded on a Hitachi 215 spectrometer.  $^1\text{H}$  NMR spectra were measured with a Varian T-60 instrument and  $^{13}\text{C}$  spectra with a Hitachi R-42 FT spectrometer. Mass spectra were determined with a Hitachi RMU-6L spectrometer.

**Preparation of 5-aminoisothiazole derivatives.** 5-Amino-3-methylisothiazole (3a) was prepared according to the literature<sup>4</sup>; bp 95–100°C/0.35 mm (lit.<sup>4</sup> bp 100–105°C/0.3 mm); IR:  $\nu_{\text{max}}^{\text{neat}}$  3300 and 1615  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\delta$ ,  $\text{CDCl}_3$ ): 2.28 (s, 3 H), 4.30–5.30 (bs, 2 H), and 6.10 (s, 1 H).

**5-Amino-3-phenylisothiazole (3b).** Dry hydrogen sulfide was passed into a solution of  $\beta$ -aminocinnamionitrile (29.35 g, 0.203 mol) in benzene (150 ml) in the presence of sodium hydroxide (0.3 g) for 30 h at 80°C. The solvent was removed under reduced pressure and the solid residue was washed with ether to give 7.0 g (19%) of  $\beta$ -aminothiocinnamoamide. To a mixture of the above thioamide (11.0 g, 0.06 mol) and 16.2 g (0.12 mol) of potassium carbonate in 540 ml of ethanol was added 19 ml of 30% aqueous hydrogen peroxide at room temperature. The mixture was stirred at room temperature for 30 min and diluted with water. The product was extracted with ether several times and the combined ethereal solution

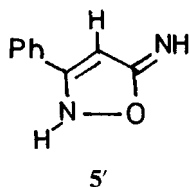
was washed with water before drying. Evaporation of the solvent yielded 6.7 g (63%) of **3b**. The crude isothiazole (**3b**) was treated with dry hydrogen chloride in ether for 3 h. The precipitated hydrochloride was collected, washed with ether, and dried for 20 h at room temperature. The hydrochloride (5.2 g) was added to aqueous sodium hydroxide solution (1.5 g in 50 ml of H<sub>2</sub>O) and the resulting isothiazole was extracted into ether. Removal of the solvent gave 2.30 g (50%) of pure **5**, mp 161–162°C (lit.<sup>6</sup> mp 163°C). <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 4.0–5.0 (brs, 2 H), 6.70 (s, 1 H), 7.30–7.60 (m, 3 H), and 7.70–8.00 (m, 2 H).

*General procedure for the preparation of 3-substituted 5-(2-amino-vinyl)-1,2,4-thiadiazole derivatives (2a–g).* Method A. To a stirred solution of **3** (1.00 g, 8.77 mmol) in dry tetrahydrofuran (53 ml) was added 1.6 M *n*-butyllithium in hexane (6.74 ml, 9.65 mmol) under nitrogen at –78°C. After the mixture being stirred for 30 min, benzonitrile (1.08 g, 10.52 mmol) in the same solvent (9 ml) was added to the solution with a syringe at the same temperature. After the reaction mixture was stirred at room temperature for 12 h, it was poured into 90 ml of water and the product was extracted three times with 70 ml portions of ether. The combined organic layers were washed with water prior to drying over magnesium sulfate. Evaporation of the solvent followed by recrystallization (hexane–benzene) gave 0.90 g (47%) of **2a** as pale yellow crystals, mp 121.5–122.5°C: for spectral data, see Table I.

Method B. A 0.95 g (5.4 mmol) sample of **3b** was added to 2.4 g (27 mmol) of ethyl acetimidate and the mixture was heated at 80°C for 5 h. After evaporation of the excess imidate under reduced pressure, the crystalline product was recrystallized from hexane–benzene to give 0.60 g (50%) of **2e**, mp 93.5–95°C: for spectral data, see Table I.

*Hydrolysis of 5-(2-aminovinyl)-1,2,4-thiadiazole derivatives (2).* General procedure. A 200 mg (0.85 mmol) sample of **2a** was stirred at room temperature for 20 h in 50% aqueous ethanol (6 ml) containing 50 mg of oxalic acid. After the usual workup, 180 mg of yellowish solid was obtained. Thin layer chromatographic separation (on SiO<sub>2</sub>; 80% hexane–20% ether) gave 80 mg (40%) of **4a** mp 112–114°C: for spectral data, see Table II.

5-Amino-3-phenylisoxazole (**5**) (mp 109–113°C, lit.<sup>7</sup> 110–112°C) was prepared by the procedure developed by Obrégia. <sup>1</sup>H NMR (δ CDCl<sub>3</sub>) 4.20–5.00 (brs, 2 H), 5.50 (s, 1 H), 7.30–7.60 (m, 3 H), and 7.60–7.90 (m, 2 H). IR:  $\nu_{\max}^{\text{nujol}}$  3460, 1630, and 950 cm<sup>–1</sup>. These data suggest that the structure of **5** is shown as **5'**.



5-(1-Aminobenzylideneimino)-3-phenylisoxazole (**6**). A mixture of **5** (400 mg, 2.5 mmol) and methyl benzimidate (3.40 g, 25.2 mmol) was heated at 110–120°C for 75 h. After evaporation of excess benzimidate under reduced pressure, the residue was washed with benzene and recrystallized from chloroform to give 290 mg (44%) of **6**, mp 207–208°C; <sup>1</sup>H NMR (δ DMSO-d<sub>6</sub>) 6.8–7.30 (brs, 2 H), 7.20–7.70 (m, 7 H), 7.70–8.00 (m, 2 H), and 8.00–8.30 (m, 2 H); IR:  $\nu_{\max}^{\text{nujol}}$  3400, 1650, 1580, and 960 cm<sup>–1</sup>; m/e 263 (M<sup>+</sup>, 100%), 246 (48), 115 (48), and 103 (43); <sup>13</sup>C NMR (ppm from TMS, DMSO-d<sub>6</sub>) 164.65\* (1), 144.54\* (1), 134.44\* (1), 131.44\* (1), 129.67 (1), 129.36 (2), 128.59 (3), 127.98 (1), 127.67 (2), 126.89\* (1), and 125.58 (2). Numerical values with a \* show chemical shifts of quaternary carbons and those in parentheses show the number(s) of carbons. No carbon is observed that can be attributed to a C-1 of the 2-aminovinyl group in **7**. These data indicate that the structure of **6** is as shown in the text.

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