Dimroth Rearrangement of 5-Hydrazino-1,2,3-thiadiazoles

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The reversible isomerization of 5-hydrazino-1,2,3-thiadiazoles and 1-amino-5-mercapto-1,2,3-triazoles has been established for an ester function at the 4-position (**4a** ⇌ **5a**). Thus, **4a** was isolated by reacting **3a** with two equivalents of hydrazine, whereas **5a** resulted when an excess of hydrazine was used. Acid treatment of **5a** yielded **4a** again, and its hydrazone **8** was obtained from **5a** and benzaldehyde. Compound **5a** was also converted into the derivatives **6a**, **7**, **9** and **10a-c**. The less reactive 5-chloro-1,2,3-thiadiazoles **3b,c** afforded the bis-heterocycles **6b,c** on heating with hydrazine.

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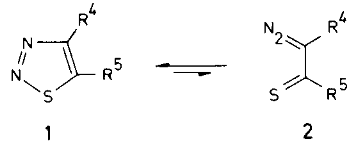
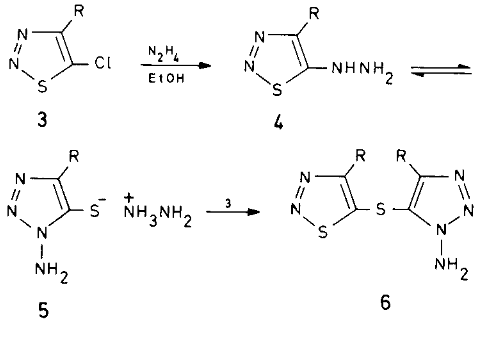
Several rearrangements of 1,2,3-thiadiazoles are already known. These are: (i) the reversible isomerization of 5-amino-1,2,3-thiadiazoles into 5-mercapto-1,2,3-triazoles [1], (ii) the base-induced rearrangement of 1,2,3-thiadiazole-4-thiocarboxamides into 5-mercapto-1,2,3-triazoles [2], (iii) the spontaneous rearrangement of 5-azido-1,2,3-thiadiazoles into 5-diazoalkyl substituted thiatriazoles [3], and (iv) the ring-degenerate rearrangement of 5-diazomethyl-1,2,3-thiadiazoles [4]. They all proceed through electrocyclic ring-opening of **1**, followed by ring-closure of the intermediate α-diazothioketone **2** involving the substituent at the 4- or 5-position.

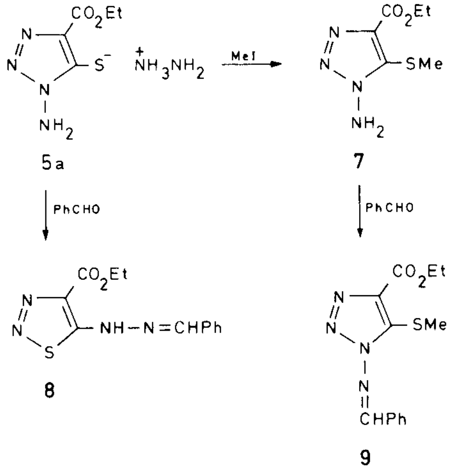


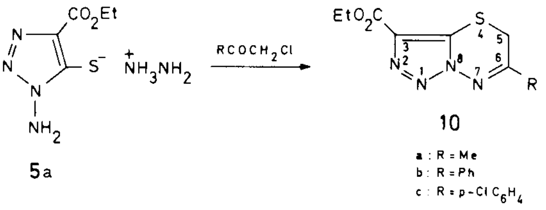
During attempts to synthesize the then unknown 5-hydrazino-1,2,3-thiadiazoles **4** as potential precursors of 5-azido-1,2,3-thiadiazoles, we have observed the title rearrangement. Thus, when **3a** was allowed to react with two equivalents of hydrazine hydrate in ethanol at room temperature, **4a** was obtained, but with an excess of hydrazine hydrate the rearrangement product **5a** was isolated in high yield (97%). The less reactive **3b** and **3c** required refluxing conditions and afforded the bis-heterocycles **6b,c**. These evidently result from rearrangement of **4b,c** and subsequent reaction of **5b,c** with the starting materials **3b,c**. Indeed, compound **5a** was also transformed into **6a** by treatment with **3a** at room temperature.



a: R = CO_2Et ; b : R = H ; c : R = Ph

Acidification of **5a** with hydrochloric acid yielded **4a**, thus indicating the reversibility of the rearrangement. Also, treatment of **5a** with benzaldehyde at room temperature furnished the rearranged derivative **8**. On the contrary, methylation of **5a** and reaction of the resulting **7** with benzaldehyde yielded **9**. Finally, **5a** was condensed with α-chlorocarbonyl compounds to give the fused heterocycles **10a-c**.





Structure elucidation of the reaction products was essentially based on ^{13}C nmr analysis and on comparison with the model compounds shown in Scheme 1 (Table 1). Thus, as was expected [5], **4a** exhibits a small upfield shift for C-4 ($\Delta\delta$ = 4 ppm) and downfield shift for C-5 ($\Delta\delta$ = 5 ppm) compared with **11**. Compound **8** has similar absorptions for the ring carbon atoms, and, in addition, exhibits a diagnostic hydrazone C=N resonance at δ 147.7 comparable with that of our model compound **14** [6]. The

Table 1

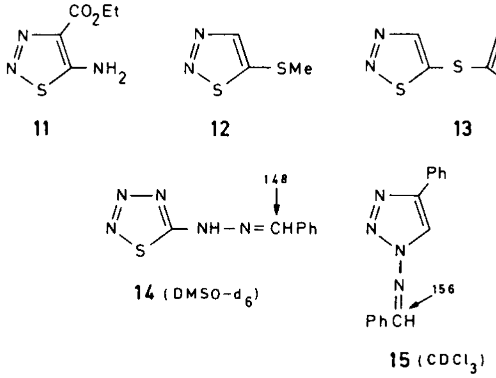
^{13}C NMR Chemical Shifts of the Heterocycles

Compound	Solvent	Thiadiazole		Triazole		Other absorptions
		C-4	C-5	C-4	C-5	
3a	$CDCl_3$	149.3 [a]	152.5 [a]			159.3 (C=O)
3b	$CDCl_3$	146.9	145.7			
3c	$CDCl_3$	157.6	140.3			
4a	DMSO-d_6	128.6	174.7			161.8 (C=O)
5a	DMSO-d_6			133.1	151.6	162.3 (C=O)
6a	$CDCl_3$	147.0	160.7	140.2	129.8	159.2/160.5 (C=O)
6b	DMSO-d_6	149.0	152.0	139.1	127.4	
6c	DMSO-d_6	156.8	146.6	146.9	122.2	
7	$CDCl_3$			138.4	135.3	17.3 (MeS), 160.5 (C=O)
8	$CDCl_3$	131.0	167.3			147.7 (C=N), 163.2 (C=O)
9	$CDCl_3$			138.7	136.2	17.5 (MeS), 157.2 (C=N), 160.6 (C=O)
11	DMSO-d_6	132.2	169.4			162.2 (C=O)
12	$CDCl_3$	143.7	155.9			
13	$CDCl_3$	147.5	148.8	139.7	126.7	

[a] The reversed assignment is possible.

hydrazone C=N signal of **9** is shifted downfield by 10 ppm, similar to that in model compound **15** [7].

Scheme 1



EXPERIMENTAL

Compounds **3a-c** and **11** were prepared according to the literature procedures [8].

4-Ethoxycarbonyl-5-hydrazino-1,2,3-thiadiazole (**4a**).

A solution of **3a** (0.5 g, 2.6 mmoles) and two equivalents of hydrazine hydrate (0.25 g) in 25 ml of ethanol was stirred overnight at room temperature. The precipitate was removed by filtration and the filtrate was evaporated. The residue was extracted with hot hexane to remove impurities and then crystallized from ether to give **4a** in 21% yield (51% before crystallization), mp 126°; ir (potassium bromide): 3340 (s) and 3220 (br, NH_2), 1675 cm^{-1} (s, CO); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 4.75 (s, 2H, NH_2), 8.35 (br, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6); δ 14.3 and 60.1 (C_2H_5), see also Table 1.

Anal. Calcd. for $C_5H_8N_4O_2S$ (mol wt 188): C, 31.91; H, 4.28. Found: C, 32.10; H, 4.21.

This compound was also obtained when an aqueous solution of **5a** (1 g in 30 ml) was treated with 1 ml of hydrochloric acid (20%) at room temperature. After 12 days, **4a** crystallized out in 66% yield.

1-Amino-4-ethoxycarbonyl-1,2,3-triazole-5-thiol (Hydrazinium Salt **5a**).

A solution of **3a** (1.8 g, 9.4 mmoles) and an excess of hydrazine hydrate (1.8 g, 36 mmoles) in 75 ml of ethanol was stirred at room temperature for one day. The precipitate was filtered off (yield 97%) and crystallized from ethanol to give **5a** as pale yellow needles, mp 166°; ir (potassium bromide): 3370 and 3300 (NH_2), 3200-2500 (br), 1695 cm^{-1} (s, CO); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.25 (t, 3H, CH_3), 4.18 (q, 2H, CH_2), 6.05 (s, 2H, NH_2), 7.05 (br, $N_2H_5^+$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.5 and 58.3 (C_2H_5), see also Table 1.

Anal. Calcd. for $C_5H_{12}N_6O_2S$ (mol wt 220): C, 27.27; H, 5.49; N, 38.16; O, 14.53. Found: C, 27.42; H, 5.35; N, 38.09; O, 14.75.

5-(1-Amino-4-ethoxycarbonyl-1,2,3-triazol-5-yl)mercapto-4-ethoxycarbonyl-1,2,3-thiadiazole (**6a**).

Compound **3a** (0.44 g, 2.3 mmoles) was added to a warm suspension of **5a** (0.5 g, 2.3 mmoles) in 100 ml of ethanol and the mixture was stirred overnight at room temperature. After addition of water, the solution was extracted with chloroform, the organic layer dried and evaporated to give **6a** in 88% yield, mp 107° (ether); ir (potassium bromide): 3330 with shoulder at 3270 (NH_2), 1730 and 1710 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 1.3 and 1.5 (two t, 2 x 3H, two CH_3), 4.40 and 4.55 (two q, 2 x 2H, two CH_2), 6.25 (s, 2H, NH_2); ^{13}C nmr (deuteriochloroform): δ 14.0 and 14.2 (CH_3), 62.1 and 62.8 (CH_2), see also Table 1.

Anal. Calcd. for $C_{10}H_{12}N_6O_4S_2$ (mol wt 344): C, 34.88; H, 3.51. C, 34.91; H, 3.47.

5-(1-Amino-1,2,3-triazol-5-yl)mercapto-1,2,3-thiadiazole (**6b**).

A solution of **3b** (2.4 g, 20 mmoles) and hydrazine hydrate (3.85 g, 77 mmoles) in 60 ml of ethanol was refluxed for 2 days. After removal of the solvent, the residue was dissolved in chloroform, washed with water and the organic layer dried over calcium chloride. The solvent was evaporated to give **6b** in 13% yield, mp 130° (chloroform); ir (potassium bromide): 3280 and 3170 (NH_2), 1640 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.15 (s, 2H, NH_2), 8.15 (s, 1H, thiadiazole H), 8.85 (s, 1H, triazole H); ^{13}C nmr (dimethyl sulfoxide-d_6): see Table 1.

Anal. Calcd. for $C_4H_4N_6S_2$ (mol wt 200): C, 23.99; H, 2.01; N, 41.97. Found: C, 24.02; H, 1.94; N, 41.83.

5-(1-Amino-4-phenyl-1,2,3-triazol-5-yl)mercapto-4-phenyl-1,2,3-thiadiazole (**6c**).

A solution of **3c** (7.6 g, 40 mmoles) and hydrazine hydrate (7.7 g, 144 mmoles) in 115 ml of methanol was refluxed for 2 days. Crystallization from methanol furnished **6c** in 49% yield, mp 170°; ir (potassium bromide): 3350, 3260, 3160 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.35 (br, 2H, NH_2), 7.4-7.5 (m, 3 aromatic H), 7.5-7.7 (m, 3 aromatic H), 7.85-7.95 (m, 4 aromatic H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 126.5, 128.4, 128.9, 129.10, 129.15, 129.55, 129.6, 129.7 (Ph carbon atoms), see also Table 1.

Anal. Calcd. for $C_{16}H_{12}N_6S_2$ (mol wt 352): C, 54.52; H, 3.43; N, 23.84; S, 18.20. Found: C, 54.52; H, 3.55; N, 23.94; S, 18.09.

1-Amino-4-ethoxycarbonyl-5-methylmercapto-1,2,3-triazole (**7**).

A suspension of **5a** (0.50 g, 2.4 mmoles) in 30 ml of methylene chloride containing 10 ml of methyl iodide was stirred at room temperature of 1 day. The precipitate was filtered off and the filtrate was evaporated. The resulting oil was triturated with petroleum ether (80 ml) to give a white powder in 40% yield, mp 61° (ether); ir (potassium bromide): 3320 and 3190 (NH_2), 1720 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_3), 2.60 (s, 3H, CH_3S), 4.45 (q, 2H, CH_2), 6.05 (br s, 2H, NH_2); ^{13}C nmr (deuteriochloroform): δ 17.1 and 61.3 (Et), see also Table 1.

Anal. Calcd. for $C_6H_{10}N_4O_2S$ (mol wt 202): C, 35.64; H, 4.98. Found: C, 35.80; H, 4.97.

5-Benzylidenehydrazine-4-ethoxycarbonyl-1,2,3-thiadiazole (**8**).

Benzaldehyde (0.28 g, 2.6 mmoles) was added to an aqueous solution of **5a** (0.5 g, 2.3 mmoles) and the mixture was stirred for 15 minutes. The precipitate was filtered off, washed with ether and crystallized from ethanol, yield 32%, mp 211°; ir (potassium bromide): 3180, 1690 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 1.49 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 7.4 and 7.7 (two m, 5 aromatic H), 8.0 (s, 1H, N=CH), 10.5 (br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.3 and 61.7 (Et), 127.3, 128.9, 130.9 and 132.6 (Ph), see also Table 1.

Anal. Calcd. for $C_{12}H_{12}N_4SO_2$ (mol wt 276): C, 52.16; H, 4.38. Found: C, 51.99; H, 4.32.

This compound was also obtained in 61% yield when equimolar amounts of **4a** and benzaldehyde were reacted in ethanol for 30 minutes.

1-Benzylideneamino-4-ethoxycarbonyl-5-methylmercapto-1,2,3-triazole (**9**).

To a solution of **7** (0.35 g, 1.7 mmoles) in 30 ml of ethanol was added benzaldehyde (0.18 g, 1.7 mmoles) and a trace of sulfuric acid, and the solution was stirred for 5 hours. After removal of the solvent, the residue was crystallized from ether to give **9** in 85% yield, mp 95°; ir (potassium bromide): 1710 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 1.42 (t, 3H, CH_3), 2.72 (s, 3H, CH_3S), 4.45 (q, 2H, CH_2), 7.7 and 8.1 (two m, 5 aromatic H), 9.6 (s, 1H, N=CH); ^{13}C nmr (deuteriochloroform): δ 14.3 and 61.5 (Et), 129.3, 129.4, 131.9 and 133.1 (Ph), see also Table 1.

Anal. Calcd. for $C_{13}H_{14}N_4O_2S$ (mol wt 290): C, 53.78; H, 4.86. Found: C, 53.60; H, 4.90.

3-Ethoxycarbonyl-6-methyl-5*H*-1,2,3-triazolo[5,1-*b*] [1,3,4]thiadiazine (**10a**).

Chloroacetone (0.213 g, 2.3 mmoles) was added to a warm suspension of **5a** (0.5 g, 2.3 mmoles) in 15 ml of methanol and the mixture was heated for 10 minutes. After cooling, the white crystals were filtered off in 62% yield, mp 151°; ir (potassium bromide): 1715 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.5 (s, 2H, ring CH_2), 4.4 (q, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 14.3 and 61.5 (Et), 24.0 (C-5), 24.1 (CH_3), 126.6 (C-3a), 133.5 (C-3), 156.7 (C-6), 160.4 (CO).

Anal. Calcd. for $C_8H_{10}N_4O_2S$ (mol wt 226): C, 42.47; H, 4.45. Found: C, 42.20; H, 4.36.

3-Ethoxycarbonyl-6-phenyl-5*H*-1,2,3-triazolo[5,1-*b*] [1,3,4]thiadiazine (**10b**).

This compound was similarly prepared from **5a** and phenacyl chloride, yield 71%, mp 183° (ethanol); ir (potassium bromide): 1730 cm^{-1} (s, CO); ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_3), 3.95 (s, 2H, ring-CH_2), 4.40 (q, 2H, CH_2), 7.5 and 8.0 (two m, 5 aromatic H); ^{13}C nmr (deuteriochloroform): δ 14.3 and 61.5 (Et), 21.5 (C-5), 127.2 (C-3a), 127.6, 129.1, 132.6 and 132.8 (Ph), 133.4 (C-3), 153.2 (C-6), 160.2 (CO).

Anal. Calcd. for $C_{13}H_{12}N_4SO_2$ (mol wt 288): C, 54.16; H, 4.19. Found: C, 54.25; H, 4.24.

6-(*p*-Chlorophenyl)-3-ethoxycarbonyl-5*H*-1,2,3-triazolo[5,1-*b*]-[1,3,4]thiadiazine (**10c**).

This compound was similarly prepared from **5a** and 2,4'-dichloroacetophenone, yield 70%, mp 216° (ethanol); ir (potassium bromide): 1730 and 1700 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_3), 3.95 (s, 2H, ring CH_2), 4.45 (q, 2H, CH_2), 7.5 and 8.0 (two d, 4 aromatic H); ^{13}C nmr (deuteriochloroform): δ 14.3 and 61.7 (Et), 21.4 (C-5), 127.1 (C-3a), 128.9, 129.5, 131.3 and 139.2 (p-ClC_6H_4), 133.5 (C-3), 151.9 (C-6), 160.2 (CO).

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2S$ (mol wt 322): C, 48.38; H, 3.43. Found: C, 48.32; H, 3.45.

5-Methylmercapto-1,2,3-thiadiazole (**12**).

A solution containing sodium sulfide decahydrate (24 g, 0.1 mole), sulfur (3.2 g) and **3b** (6.02 g, 50 mmoles) in 60 ml of 2-propanol was heated for two hours. The upper layer was separated and cooled to room temperature, giving sodium 1,2,3-thiadiazole-5-thiolate in 82% yield. This compound (1 g, 7 mmoles) was allowed to react with methyl iodide (1.42 g, 10 mmoles) in 10 ml of methanol at room temperature for 30 minutes. The solvent was removed and the residual oil was crystallized from petroleum ether to give **12** as crystals which melt at room temperature, yield 30%; ^{1}H nmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3S), 8.4 (s, 1H, thiadiazole CH); ^{13}C nmr (deuteriochloroform): δ 19.5 (CH_3S), see also Table 1.

Anal. Calcd. for $C_3H_4N_2S_2$ (mol wt 132): C, 27.26; H, 3.05. Found: C, 27.51; H, 3.01.

5-(1-Phenyl-1,2,3-triazol-5-yl)mercapto-1,2,3-thiadiazole (**13**).

Aniline (2.33 g, 25 mmoles) was added to a solution of sodium hydride (0.52 g, 16.6 mmoles) in 30 ml of dry tetrahydrofuran and this was stirred at room temperature for 30 minutes. Then, **3b** (1 g, 8.3 mmoles) was added and the solution was refluxed overnight. After removal of the solvent and addition of water, the mixture was extracted with ether. From the ether extracts an oil was obtained which was chromatographed on silica gel with dichloromethane as the eluent to give **13** in 46% yield, mp 92° (ether); ^{1}H nmr (deuteriochloroform): δ 7.55 (s, 5 aromatic H), 8.10 and 8.30 (two s, 2 heterocyclic H); ^{13}C nmr (deuteriochloroform): δ 125.5, 129.5, 130.5 and 135.0 (Ph), see also Table 1.

Anal. Calcd. for $C_{10}H_7N_5S_2$ (mol wt 261): C, 45.96; H, 2.70. Found: C, 46.16; H, 2.62.

Acknowledgement.

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