Reactivity of the A-CH=N=NR-CX-B System. 1,3,4-Thiadiazoles and Δ^2-Thiadiazolines.

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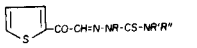
The reactivity of the  system towards ferric chloride has been investigated. The cyclo-oxidation reaction led to the formation of 2-amino-5-thenoyl-1,3,4-thiadiazoles and 4-methyl-5-imino-2-thenoyl-Δ^2-1,3,4-thiadiazolines. Their structures were proven spectroscopically and chemically (nucleophilic attack and formation of the related 2-amino-1,3,4-thiadiazoles and 4-methyl-5-imino-Δ^2-1,3,4-thiadiazolines).

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Some time ago we undertook a systematic study on the reactivity of the A-CH=N-NR-CX-B system towards some cyclizating reagents. Specifically, this research program aims to investigate the influence on the reaction course of: a) the occurence of alkyl and aryl substituents on the semicarbazide and thiosemicarbazide moiety (positions 2, 2-4, 4 and 4-4); b) the type of the substituents A and B; c) the cyclizating reagent employed; and to elucidate the structure and the reactivity of the resulting products (1).

In connection with the above program, we noted recently that treatment with ferric chloride of ethyl glyoxylate 2,4-dimethylthiosemicarbazone (2) and phenylglyoxal 2,4-dimethylthiosemicarbazone (3) resulted in different cyclizations, *e.g.*, 1,2,4-triazole and Δ^2-1,3,4-thiadiazole ring, respectively. The diverse behaviour can be ascribed, at least in these two cases, both to the substituents on 2,4 and to the type of the substituent A.

Therefore, we considered it of interest to investigate the influence of a different substituent A on the reaction course; for this purpose, we tested the action of ferric chloride on a thiosemicarbazone system having several substituents on the positions 2, 2-4, 4 and 4-4 whereas A is a thenoyl group (see Scheme I).

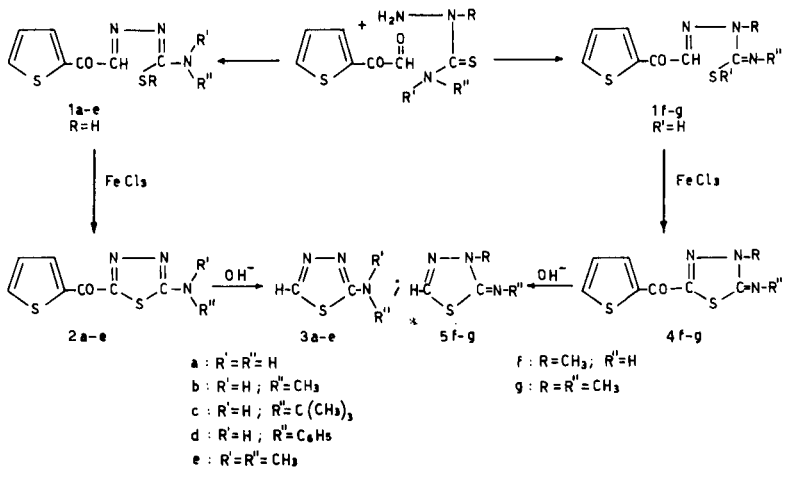
The reaction of thienylglyoxal with the suitable thiosemicarbazides under the usual conditions lead to excellent yield of the related thiosemicarbazones **1a-g**, which have not been previously reported, except one homolog (4). The treatment of these substrates with warm ethanolic ferric chloride solution yields only the 1,3,4-thiadiazoles **2a-e**, the Δ^2-1,3,4-thiadiazolines **4f-g**, respectively. The above products undergo easy nucleophilic attack by ethanolic alkali, expelling the thenoyl group and affording the derivatives **3a-b**, **d-e** and **5f-g**, respectively, already described (3,5) as well as **3c**. This behaviour agrees with the structures suggested for the cyclization products, and is further supported by elemental analyses and spectral data (ir and nmr).

Therefore, the different behaviour of the cyclizating reagent towards the above substrates and the related derivatives of alkyl glyoxylates could also be ascribed to the type of the substituent A in this case. The availability of the thiadiazoles **2a-e** and of the thiadiazolines **4f-g** will allow us to check their behaviour as bidentate nucleophiles. Studies along these lines are currently in progress and will be the subject of future publications.

EXPERIMENTAL

All melting points (Kofler) are uncorrected. The spectra were recorded as follows: Ir (nujol mull), Perkin-Elmer Infracord 137

SCHEME I



Spectrophotometer: nmr Jeol C-60 H Spectrometer (TMS as the internal reference).

General Procedure for Preparation of the Thiosemicarbazones **1a-g.**

To a solution of the thiosemicarbazide (0.02 mole in water) (for the 4-*t*-butyl- and for the 4-phenylthiosemicarbazide ethanol-water 1:1 was employed), acidified with acetic acid (0.5 ml.) was added dropwise at room temperature and with stirring, an ethanolic solution of the thienylglyoxal (0.02 mole in 20 ml. of ethanol). The precipitate was collected and washed with water.

Compound **1a.**

This compound (3.95 g., yield 92%), m.p. 188-190° [lit. (4), m.p. 176.5° dec.] was purified by suspension in ethanol at room temperature; ir: 3344, 3205, 3030 (NH, NH_2) and 1616 cm^{-1} (C=O); nmr (DMSO-d_6): 7.30 δ (q, H_4, J = 5.4 and 4.1 Hz), 7.92 δ (s, 1H, CH), 8.15 δ (q, H_5, J = 5.4 and 1.1 Hz), 8.30 δ (q, H_3, J = 4.1 and 1.1 Hz), 7.82 δ (br. s, 1H, NH_2), 9.30 δ (br. s, 1H, NH_2), 12.44 δ (br. s, 1H, NH) (6).

Anal. Calcd. for $C_7H_7N_3OS_2$: C, 39.44; H, 3.31; N, 19.72. Found: C, 39.40; H, 3.15; N, 19.50.

Compound **1b.**

This compound (4.25 g., yield 93%), m.p. 167-169° was purified by suspension in ethanol at room temperature; ir: 3425, 3135 (NH) and 1631 cm^{-1} (C=O); nmr (DMSO-d_6): 3.06 δ (d, 3H, NH-CH_3, J = 4.8 Hz), 7.24 δ (q, H_4, J = 5.2 and 4.1 Hz), 7.86 δ (s, 1H, CH), 8.43 δ (br. s, 1H, NH-CH_3), 12.25 δ (br. s, 1H, NH), 8.00-8.25 δ (m, 2H, H_5 and H_3).

Anal. Calcd. for $C_8H_9N_3OS_2$: C, 42.29; H, 3.99; N, 18.50. Found: C, 42.65; H, 4.05; N, 18.80.

Compound **1c.**

This compound (5.20 g., yield 96%) had m.p. 171-172° (ethanol); ir: 3333, 3115 (NH) and 1634 cm^{-1} (C=O); nmr (deuteriochloroform): 1.67 δ (s, 9H, *t*-butyl), 7.15 δ (q, H_4, J = 5.2 and 4.1 Hz), 7.70 δ (q, H_5, J = 5.2 and 1.1 Hz), 7.69 δ (br. s, 2H, =CH and NH), 8.08 δ (q, H_3, J = 4.1 and 1.1 Hz), 10.70 δ (br. s, 1H, NH).

Anal. Calcd. for $C_{11}H_{15}N_3OS_2$: C, 49.07; H, 5.62; N, 15.61. Found: C, 48.85; H, 5.80; N, 15.60.

Compound **1d.**

This compound (5.40 g., yield 92%) had m.p. 137° *ca.* Elemental analytical data and spectral data (ir, nmr) could not be obtained because of the product was not purifiable.

Compound **1e.**

This compound (3.45 g., yield 71%), m.p. 145-146° was purified by suspension in ethanol at room temperature; ir: 3205 (NH) and 1645 cm^{-1} (C=O); nmr (DMSO-d_6): 3.38 δ [(s, 6H, $N(CH_3)_2$], 7.28 δ (q, H_4, J = 4.9 and 3.7 Hz), 8.12 δ (q, H_5, J = 4.9 and 1.1 Hz), 8.82 δ (q, H_3, J = 3.7 and 1.1 Hz), 8.00 δ (s, 1H, CH), 11.65 δ (br. s, 1H, NH).

Anal. Calcd. for $C_9H_{11}N_3OS_2$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.55; H, 4.55; N, 17.30.

Compound **1f.**

This compound (4.35 g., yield 95%) had m.p. 151-152° (ethanol); ir: 3378, 3300 (NH_2) and 1639 cm^{-1} (C=O); nmr (DMSO-d_6): 3.83 δ (s, 3H, NCH_3), 7.40 δ (q, H_4, J = 5.2 and 3.9 Hz), 7.76 δ (s, 1H, CH), 8.10 δ (br. s, 1H, NH_2), 9.20 δ (br. s, 1H, NH_2), 8.20-8.45 δ (m, 2H, H_3 and H_5) (6).

Anal. Calcd. for $C_8H_9N_3OS_2$: C, 42.29; H, 3.99; N, 18.50. Found: C, 42.05; H, 3.75; N, 18.72.

Compound **1g.**

This compound (4.40 g., yield 91%) had m.p. 129-130° (ethanol); ir: 3448 (NH) and 1634 cm^{-1} (C=O); nmr (deuteriochloroform): 3.25 δ (d, 3H, NH-CH_3, J = 4.6 Hz), 3.82 δ (s, 3H, NCH_3), 7.15 δ (q, H_4, J = 5.2 and 3.2 Hz), 7.35 δ (s, 1H, CH), 7.73 δ (q, H_5, J = 5.2 and 1.1 Hz), 8.01 δ (q, H_3, J = 3.2 and 1.1 Hz), 8.30 δ (br. s, 1H, NH).

Anal. Calcd. for $C_9H_{11}N_3OS_2$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.70; H, 4.45; N, 17.35.

General Procedure for Cyclization of Thiosemicarbazones **1a-g.**

To a mixture of the thiosemicarbazone (0.01 mole) in ethanol (30 ml.) was added an ethanolic solution 2*M* of ferric chloride hexahydrate (10 ml.). The mixture was heated for a few minutes and after 24 hours was filtered and diluted with water. The solid was collected and purified. Following the procedure above, the following compounds were obtained:

Compound **1a** (2.13 g.) gave 2-amino-5-thenoyl-1,3,4-thiadiazole (**2a**) (1.80 g., yield 85%), m.p. 248-249° (acetic acid); ir: 3390, 3226 (NH_2) and 1618 cm^{-1} (C=O); nmr (DMSO-d_6): 7.27 δ (q, H_4, J = 5.2 and 4.5 Hz), 8.13 δ (q, H_5, J = 5.2 and 1.5 Hz), 8.26 δ (s, 2H, NH_2), 8.48 δ (q, H_3, J = 4.5 and 1.5 Hz).

Anal. Calcd. for $C_7H_5N_3OS_2$: C, 39.82; H, 2.39; N, 19.90. Found: C, 39.80; H, 2.50; N, 19.75.

Compound **1b** (2.27 g.) gave 2-methylamino-5-thenoyl-1,3,4-thiadiazole (**2b**) (2.02 g., yield 89%), m.p. 190-191° (methanol); ir: 3165 (NH) and 1600 cm^{-1} (C=O); nmr (DMSO-d_6): 3.01 δ (br. s, 3H, $NHCH_3$), 7.28 δ (q, H_4, J = 5.2 and 4.1 Hz), 8.15 δ (q, H_5, J = 5.2 and 1.2 Hz), 8.47 δ (q, H_3, J = 4.1 and 1.2 Hz), 8.78 δ (br. s, 1H, $NHCH_3$).

Anal. Calcd. for $C_8H_7N_3OS_2$: C, 42.67; H, 3.13; N, 18.66. Found: C, 42.70; H, 2.95; N, 19.00.

Compound **1c** (2.69 g.) gave 2-*t*-butylamino-5-thenoyl-1,3,4-thiadiazole (**2c**) (2.50 g., yield 93%), m.p. 202-203° (ethanol); ir: 3125 (NH) and 1613 cm^{-1} (C=O); nmr (DMSO-d_6): 1.50 δ [(s, 9H, $NHC(CH_3)_3$], 7.33 δ (q, H_4, J = 5.2 and 4.1 Hz), 8.18 δ (q, H_5, J = 5.2 and 1.0 Hz), 8.50 δ (q, H_3, J = 4.1 and 1.0 Hz), 8.64 δ (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3OS_2$: C, 49.43; H, 4.90; N, 15.73. Found: C, 49.35; H, 5.15; N, 15.65.

Compound **1d** (2.89 g.) gave 2-phenylamino-5-thenoyl-1,3,4-thiadiazole (**2d**) (2.70 g., yield 94%), m.p. 294-295° (acetic acid); ir: 1600 cm^{-1} (C=O); nmr (DMSO-d_6): 7.10-7.90 δ (m, 5H aromatic and H_4), 8.30 δ (q, H_5, J = 5.3 and 1.2 Hz), 8.68 δ (q, H_3, J = 4.9 and 1.2 Hz), 11.45 δ (br. s, 1H, NH).

Anal. Calcd. for $C_{13}H_9N_3OS_2$: C, 54.36; H, 3.16; N, 14.63. Found: C, 54.50; H, 3.25; N, 14.70.

Compound **1e** (2.41 g.) gave 2-dimethylamino-5-thenoyl-1,3,4-thiadiazole (**2e**) (1.70 g., yield 71%), m.p. 148-150° (benzene-ligroin); ir: 1613 cm^{-1} (C=O); nmr (deuteriochloroform): 3.31 δ [(s, 6H, $N(CH_3)_2$], 7.19 δ (q, H_4, J = 4.9 and 3.7 Hz), 7.78 δ (q, H_5, J = 4.9 and 1.1 Hz), 8.69 δ (q, H_3, J = 3.7 and 1.1 Hz).

Anal. Calcd. for $C_9H_9N_3OS_2$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.20; H, 3.90; N, 17.60.

Compound **1f** (2.27 g.) gave 4-methyl-5-imino-2-thenoyl-Δ^2-1,3,4-thiadiazoline (**2f**) (1.70 g., yield 75%), m.p. 143° (methanol); ir: 3300 (NH) and 1600 cm^{-1} (C=O); nmr (DMSO-d_6): 3.66 δ (s, 3H, NCH_3), 7.30 δ (q, H_4, J = 4.9 and 4.1 Hz), 8.18 δ (q, H_5, J = 4.9 and 1.1 Hz), 8.37 δ (q, H_3, J = 4.1 and 1.1 Hz), 8.92 δ (br. s, 1H, NH).

Anal. Calcd. for $C_8H_7N_3OS_2$: C, 42.67; H, 3.13; N, 18.66. Found: C, 42.85; H, 3.25; N, 18.80.

Compound **1g** (2.41 g.) gave 4-methyl-5-methylimino-2-thenoyl-Δ^2-1,3,4-thiadiazoline (**2g**) (1.62 g., yield 67%), m.p. 140° (benzene-ligroin); ir: 1639 cm^{-1} (C=O); nmr (deuteriochloroform):

3.10 δ (s, 3H, NCH_3), 3.72 δ (s, 3H, NCH_3), 7.15 δ (q, H_4, J = 5.2 and 4.1 Hz), 7.72 δ (q, H_5, J = 5.2 and 1.1 Hz), 8.36 δ (q, H_3, J = 4.1 and 1.1 Hz).

Anal. Calcd. for $C_9H_9N_3OS_2$: C, 45.19; H, 3.79; N, 17.57. Found: C, 44.95; H, 3.90; N, 17.40.

Hydrolysis of **2a-e** and **4f-g**.

A solution (or suspension) of compound (0.005 mole in 50 ml. of ethanol) was heated under reflux for six hours with sodium hydroxide (0.5 g. in 1 ml. of water). After removing of solvent the residue was filtered (or extracted with chloroform) giving hydrolysis products (50-60%) **3a-b,d-e** and **5f-g** (3). The structures were confirmed by direct comparison with authentic samples and by spectroscopic evidence (nmr).

Compound **2c** (1.33 g.) gave 2-*t*-butylamino-1,3,4-thiadiazole (**3c**) (0.55 g., yield 70%), m.p. 127° (water); ir: 3257 cm^{-1} (NH); nmr (DMSO-d_6): 1.40 δ [s, 9H, $C(CH_3)_3$], 7.61 δ (br. s, 1H, NH), 8.82 δ (s, 1H, CH).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 45.85; H, 7.05; N, 26.74. Found: C, 45.80; H, 6.90; N, 26.75.

REFERENCES AND NOTES

(1) G. Werber, F. Buccheri, N. Vivona and Manlio Gentile, *Chim. Ind.*, **58**, 382 (1976); G. Werber, F. Buccheri and M. L. Marino, *Ann. Chim.* (Rome), **62**, 11 (1972) and references cited therein.

(2) Unpublished results.

(3) G. Werber, F. Buccheri and M. L. Marino, *J. Heterocyclic Chem.*, **12**, 581 (1975).

(4) S. Rossi, *Gazz. Chim. Ital.*, **83**, 135 (1953).

(5) G. Werber, F. Buccheri and N. Vivona, *J. Heterocyclic Chem.*, **12**, 841 (1975).

(6) The spectral data of the compounds **1a** and **1f** are consistent with the following structures, respectively: