Giuseppe Werber, Francesco Buccheri, Nicolò Vivona and Manlio Gentile

Istituto di Chimica Organica, Facoltà di Scienze dell'Università, Via Archirafti 20, Palermo, Italy

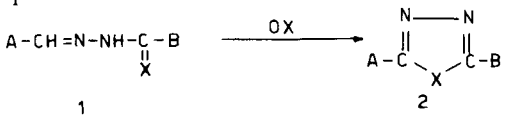
Received September 19, 1977

The behaviour of phenylglyoxal thiosemicarbazones towards aqueous sodium hydroxide have been studied. Examples of addition compounds, 5-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thiones, are reported.

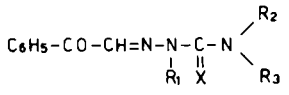
J. Heterocyclic Chem., **14**, 1433 (1977)

In the framework of our research on the reactivity of systems of type **1** towards oxidative cyclization into 1,3,4-oxadiazoles **2** (X = O) (1), or 1,3,4-thiadiazoles **2** (X = S) (2), we reported recently (3) on the synthesis of a series of 2-benzoyl-1,3,4-thiadiazoles (or thiadiazolines) from phenylglyoxalthiosemicarbazones **3** (X = S) by means of ferric chloride.

However, besides the oxidative cyclization, compounds **3** could exhibit a different type of reactivity, *e.g.*, through a nucleophilic attack by an X atom or a terminal nitrogen atom adjacent to a carbonyl group or to a -CH=N- system. Therefore, continuing our research in this field, we became interested in elucidating the behaviour of compounds **3** by changing the nature of X, R_1, R_2, R_3 or the experimental conditions.



1 2



3

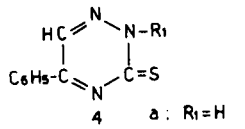
a : $R_1 = R_2 = R_3 = H$
b : $R_1 = CH_3$; $R_2 = R_3 = H$
c : $R_1 = R_2 = H$; $R_3 = CH_3$
d : $R_1 = R_2 = CH_3$; $R_3 = H$
e : $R_1 = H$; $R_2 = R_3 = CH_3$

In this paper we report on the behaviour of compounds **3** (X = S) towards aqueous sodium hydroxide.

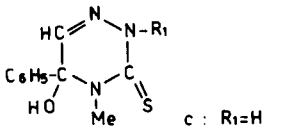
As reported (4), compounds **3a** and **3b** (*i.e.*, $R_2 = R_3 = H$), when treated with aqueous sodium hydroxide, gave the 1,2,4-triazine derivatives **4a** and **4b**.

In contrast with the two derivatives above, compounds **3c** and **3d**, by similar treatment, gave the addition products **5c** and **5d**, derived from nucleophilic attack of the terminal nitrogen atom with the carbonyl group. Structures were assigned on the basis of analytical and spectroscopic data. The ir spectra do not show bands for C=O stretching, and the mass spectra show characteristic patterns for the proposed structures; *e.g.*, for **5c**: 221 (M^+), 204 $(M-OH)^+$, 116 $(M-C_6H_5CO)^+$, 105 $(C_6H_5CO)^+$.

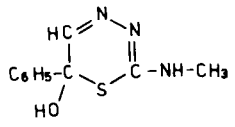
The nmr spectra provides sufficient confirmation for the assigned structures. In the case of **5c**, the following signals are present: a singlet at 2.99 δ [N-CH_3, eliminating the thiadiaza structure **6** (5)], and singlets at 6.76, 7.37, 7.76 (exchangeable with deuterium oxide), and 11.61 δ (exchangeable with deuterium oxide) for CH, aromatic, OH, and NH protons, respectively. Aromatic protons in **5c** and **5d** appear as a singlet as a consequence of the absence of an anisotropic effect on the *ortho* protons of the phenyl ring linked to an sp^3 carbon atom. In the starting compounds, aromatic protons appear as two sets of signals due to the carbonyl effect.



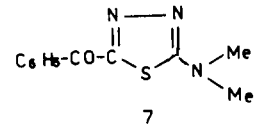
4 a : $R_1 = H$ b : $R_1 = Me$



5 c : $R_1 = H$ d : $R_1 = Me$



6



7

In the case of thiosemicarbazone **3e**, (*i.e.*, $R_2 = R_3 = CH_3$), we were able to isolate only the thiadiazole **7**. Formation of compound **7** could be explained through an oxidative process of a thiadiazoline structure, arising from a nucleophilic attack of the sulfur atom on the CH=N system (6).

Research is in progress to study the reactivity of the addition compound **5**, and the possible tautomeric equilibrium **3** ⇌ **5**.

EXPERIMENTAL

Melting points were determined using a Kofler hot plate and are uncorrected. Ir spectra (nujol mull) were determined on a Perkin-Elmer Infracord 137 instrument. Nmr spectra (60 MHz) were obtained using a Jeol C-60 H spectrometer with TMS as the internal standard. Mass spectra were determined on the Jeol JMS-01S-Z instrument.

Phenylglyoxal thiosemicarbazones **3a-e** were prepared by a standard procedure (3).

Formation of 1,2,4-Triazine-3-thione Derivatives **4a** and **4b** from Thiosemicarbazones **3a** and **3b**.

Thiosemicarbazones **3a** or **3b** (1 g.), treated with 2*N* sodium hydroxide (10 ml.), was kept at room temperature for 24 hours. Dilution with water (and acidification with 10% hydrochloric acid in the case of **3a**) gave the triazine derivatives **4a** and **4b** respectively, in almost quantitative yield. Compound **4a** melted at 197-198° (ethanol) [lit. (4), m.p. 197-198°]; ir: 3077 cm^{-1} nmr (DMSO-d_6): 7.5-8.5 δ (m, 5H, Ar-H), 9.10 δ (s, 1H, CH), 14.9 δ (br. s., 1H, NH).

Compound **4b** melted at 195-196° (ethanol) [lit. (4) m.p. 194°]; nmr (DMSO-d_6): 3.78 δ (s, 3H, N-CH_3), 7.4-8.4 δ (m, 5H, Ar-H), 9.12 δ (s, 1H, CH).

Formation of 4-Methyl-5-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione (**5c**).

Thiosemicarbazone **3c** (2 g.), treated with 2*N* sodium hydroxide (15 ml.), was kept at room temperature for 15 minutes. Dilution with water (20 ml.) and acidification with 10% hydrochloric acid, gave **5c** (1.8 g.), m.p. 189-190° (ethanol); ir: 3268, 3067 cm^{-1}; nmr (DMSO-d_6): 2.99 δ (s, 3H, N-CH_3), 6.76 δ (s, 1H, CH), 7.36 δ (s, 5H, Ar-H), 7.76 δ (s, 1H, OH), 11.61 δ (s, 1H, NH); ms: 221 $(M)^+$, 204 $(M-OH)^+$, 116 $(M-C_6H_5CO)^+$, 105 $(C_6H_5CO)^+$.

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.33; H, 5.22; N, 19.07.

Formation of 2,4-Dimethyl-5-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione (**5d**).

A suspension of thiosemicarbazone **3d** (2 g.) in aqueous 5% sodium hydroxide (40 ml.) was refluxed for 5 minutes. Acidification with 10% hydrochloric acid gave crude material (0.85 g.), which was worked up with 10% aqueous sodium hydrogen carbonate to remove benzoic acid, yielding **5d** (0.4 g.), m.p. 133-135° (ligroin); ir: 3125 cm^{-1}; nmr (deuteriochloroform): 3.24, 3.90 δ (2s, 6H, 2 x N-CH_3), 5.10 δ (br. s., 1H, OH), 6.80 δ (s, 1H, CH), 7.44 δ (s, 5H, Ar-H); ms: 235 $(M)^+$, 218 $(M-OH)^+$, 161, 130, 119, 105.

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.98; H, 5.45; N, 18.09.

Formation of 2-Dimethylamino-5-benzoyl-1,3,4-thiadiazole (**7**).

Thiosemicarbazone **3e** (2 g.), treated with 2*N* sodium hydroxide (15 ml.) was kept at room temperature for 15 minutes. Dilution with water (20 ml.) and filtration gave a crude material which was worked with water and filtered again. The insoluble fraction (0.2 g.) was identified as starting material. From the aqueous solution slowly separated the 2-dimethylamino-5-benzoyl-1,3,4-thiadiazole (**7**) (0.4 g.), m.p. 102° (aqueous ethanol), identified by comparison with an authentic sample (3).

REFERENCES AND NOTES

(1) G. Werber, F. Buccheri and M. L. Marino, *Ann. Chim.* (Rome), **62**, 11 (1972) and references cited therein.

(2) G. Werber, F. Buccheri, M. Gentile and L. Librici, *J. Heterocyclic Chem.*, in press and references cited therein.

(3) G. Werber, F. Buccheri and M. L. Marino, *ibid.*, **12**, 581 (1975); G. Werber, F. Buccheri and N. Vivona, *ibid.*, **12**, 841 (1975) and references cited therein.

(4) M. Tisler, *Croat. Chem. Acta*, **32**, 123 (1960); J. Daunis, R. Jacquier and P. Viallefont, *Bull. Soc. Chim. France*, 3675 (1969) and references cited therein.

(5) For structure **6**, it should be evident the NH-CH_3 coupling as generally observed in DMSO-d_6 solvent.

(6) K. H. Mayer and D. Lauerer, *Ann. Chem.*, **731**, 142 (1970).