Synthesis of 2-Amino-5-benzoyl-1,3,4-thiadiazoles and Δ^2-1,3,4-Thiadiazolines from Thiosemicarbazones of Phenylglyoxal

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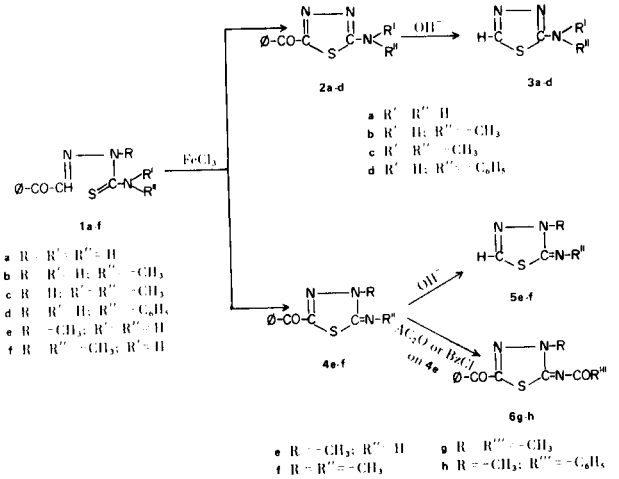
Within the framework of research related to tautomerism and alkylation of 2-amino-5-benzoyl-1,3,4-thiadiazoles, it became necessary to dispose of type 2- and 4-thiadiazole and thiadiazoline derivatives with unequivocally-defined structures. Here we wish to report the synthesis of thiadiazole **2a-d** and thiadiazoline **4e-f** derivatives obtained by oxidative cyclization with ferric chloride of the thiosemicarbazones **1a-f** (1,2). The thiosemicarbazones **1a**, **1d** and **1e** are reported in the literature. The use of the reported methods of preparation led to mixtures (mono-, dithiosemicarbazones and the corresponding triazine) (cases **1**, **3**, **4**, **5**, **6**) and to compounds with different characteristics (case **1**, **4**, **7**). Our method of preparation of **1a-f** involved a reaction of very dilute and cold aqueous solutions of phenylglyoxal hydrate and of the corresponding thiosemicarbazide, with rapid isolation of monothiosemicarbazone as soon as it is formed. In this way the monothiosemicarbazones were obtained pure and in satisfactory yields.



The cyclization with ferric chloride is reported in the literature only for **1a**; the A., (1) working on the reaction with ethanol, claims to have obtained the hydrochloride of the 2-amino-5-benzoyl-1,3,4-thiadiazole at m.p. 194-197°, but he does not report the free base. In our hands, even after repeating the experiment several times, a pitchy, non purifiable mass was obtained. Working in warm water, from **1a** we obtained **2a** directly, with m.p. 200-201°. The hydrochloride melts at 214-216°. All of the other **1b-f** compounds behaved in the same way, leading to **2b-d** and **4e-f**, usually in satisfactory yields. The analytical data, the infrared and nuclear magnetic spectra are consistent with the assigned thiadiazole structures of **2a-d** and the thiadiazoline structures of **4e-f**; these were also confirmed by removal of the benzoyl group by nucleophilic attack with sodium hydroxide in ethanol. A transformation is thus obtained in the thiadiazoles **3a-d** and thiadiazolines **5e-f**, according to a recently studied mechanism (8). Compounds **3a-d** and **5e-f** are identical in every respect with those reported in literature (9,10,11). The proposed structures have been confirmed by nmr spectra.

EXPERIMENTAL

All melting points (Kofler) are uncorrected. Ir spectra (nujol mull) were obtained on a Perkin-Elmer Infracord 137 Spectrophotometer; nmr were obtained on a Jeol C-60 H Spectrometer (TMS as internal reference).

General Procedure of Preparation of Thiosemicarbazones **1a-f**.

To a cooled and stirred solution of the phenylglyoxal hydrate (0.02 mole in 200 ml. of water) was added dropwise and with stirring a cooled solution of thiosemicarbazide (0.02 mole in 150 ml. of water) (for the 4-phenylthiosemicarbazide ethanol-water 1:1 was employed) and the monothiosemicarbazone was filtered rapidly as soon as formed. In the case of preparation of **1a** and of **1e**, leaving the mixture for some hours at room temperature also afforded, respectively, the 5-phenyl-2,3-dihydro-1,2,4-triazine-3-thione and the 2-methyl-5-phenyl-2,3-dihydro-1,2,4-triazine-3-thione (ir superimposable and m.p. undepressed by authentic samples) (3). The triazine could be separated by working up the mixture with potassium carbonate solution 10% (for **1a**) and by fractional crystallization (for **1e**).

Compound **1a**.

This compound (2.3 g., 55%) was recrystallized from ethanol, m.p. 171-172° [lit. (1,4,5), m.p. 156-158° and 216-218°, 201-202°, 170°]; ir: 3289, 3185, 3086 (NH, NH_2) and 1658 cm^{-1} (C=O); nmr (DMSO-d_6): 7.30-8.85 δ (m, 7H, C_6H_5, NH_2), 8.02 δ (s, 1H, CH), 11.90 δ (s, 1H, NH).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.37; N, 20.27.

Found: C, 52.30; H, 4.35; N, 20.27.

Compound **1b**.

This compound (4.12 g., 93%) was recrystallized from ethanol, m.p. 182-184°; ir: 3257-3215 (NH) and 1656 cm^{-1} (C=O); nmr (DMSO-d_6): 2.95 δ (d, 3H, NH-CH_3, J = 4.5 Hz), 8.05 δ (s, 1H, CH), 7.40-8.10 δ (m, 5H aromatic), 8.41 δ (q, 1H, NH-CH_3, J = 4.5 Hz), 11.90 δ (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.49; H, 5.25; N, 18.70.

Compound **1c**.

This compound (4.20 g., 89%) was recrystallized from acetonitrile, m.p. 144-145°; ir: 1623 cm^{-1} (C=O); nmr (DMSO-d_6): 3.30 δ [s, 6H, $N(CH_3)_2$], 8.05 δ (s, 1H, CH), 7.30-8.40 δ (m, 5H aromatic), 11.40 δ (br. s, NH).

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.34; H, 5.56; N, 18.00.

Compound **1d**.

This compound (5.10 g., 90%) was washed with cold ethanol, m.p. 146° [lit. (7) m.p. 135°].

Compound **1e**.

This compound (4.00 g., 90%) was recrystallized from ethanol, m.p. 163-164° [lit. (3) m.p. 162-163°].

Compound **1f**.

This compound (4.52 g., 96%) was recrystallized from benzene-ligroin, m.p. 140-141°; ir: 3322 (NH) and 1645 cm^{-1} (C=O); nmr (DMSO-d_6): 3.05 δ (d, 3H, NH-CH_3, J = 4.5 Hz), 3.84 δ (s, 3H, N-CH_3), 7.88 δ (s, 1H, CH), 7.30-8.30 δ (m, 5H, aromatic), 8.70 δ (q, 1H, NH-CH_3, J = 4.5 Hz).

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.90; H, 5.65; N, 17.75.

General Procedure of Cyclization of Thiosemicarbazones **1a-f**.

To a mixture of starting material (0.01 mole) in water (120 ml.) was added ferric chloride (8.1 g.) in water (25 ml.). The mixture was heated for one hour on a water bath, and after cooling, the precipitate was collected.

Compound **2a**.

This compound (1.8 g.) obtained from **1a** (2.07 g.) was recrystallized from ethanol, m.p. 200-201°; ir: 3356, 3226 (NH_2) and 1639 cm^{-1} (C=O); nmr (acetone-d_6): 7.20-8.40 δ (m, 7H, C_6H_5, NH_2).

Anal. Calcd. for $C_9H_7N_3OS$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.80; H, 3.49; N, 20.44.

The hydrochloride has m.p. 214-216° (methanol-ether) [lit. (1), m.p. 194-197°]; nmr (DMSO-d_6): 7.00-8.40 δ (m, 8H, C_6H_5, NH_3^+).

Anal. Calcd. for $C_9H_7N_3OS.HCl$: C, 44.72; H, 3.34; N, 17.39; Cl, 14.67. Found: C, 45.10; H, 3.25; N, 17.70; Cl, 14.45.

Compound **2b**.

This compound (1.75 g.) obtained from **1b** (2.20 g.) was recrystallized from benzene-ligroin, m.p. 167-168°; ir: 3145 (NH) and 1634 cm^{-1} (C=O); nmr (DMSO-d_6): 3.04 δ (d, 3H, NH-CH_3, J = 3.7 Hz), 7.50-8.50 δ (m, 5H, aromatic), 8.85 δ (br. s, 1H, NH-CH_3, W½ = 13 Hz).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.99; H, 4.04; N, 19.29.

Compound **2c**.

This compound (0.25 g.) obtained from **1c** (2.35 g.) was recrystallized from ethanol-water, m.p. 102°; ir: 1621 cm^{-1} (C=O); nmr (deuteriochloroform): 3.30 δ [s, 6H, $N(CH_3)_2$], 7.40-8.70 δ (m, 5H, aromatic).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.40; H, 4.65; N, 17.75.

Compound **2d**.

This compound (2.0 g.) obtained from **1d** (2.83 g.) was recrystallized from acetic acid, m.p. 281-282°; ir: 3333 (NH) and 1629 cm^{-1} (C=O); nmr (DMSO-d_6): 7.0-8.40 δ (m, 10H, aromatic), 11.00 δ (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.14; H, 4.07; N, 14.86.

Compound **4e**.

This compound (1.65 g.) obtained from **1e** (2.20 g.) was recrystallized from ligroin, m.p. 74-75°; ir: 3247 (NH) and 1634 cm^{-1} (C=O); nmr (deuteriochloroform): 3.72 δ (s, 3H, N-CH_3), 6.95 δ (s, 1H, NH), 7.40-8.40 δ (m, 5H, aromatic).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.85; H, 3.96; N, 18.95.

Compound **6g**.

This compound was recrystallized from ethanol, m.p. 169-170°; ir: 1639, 1623 cm^{-1} (2 C=O); nmr (deuteriochloroform): 2.40 δ (s, 3H, $COCH_3$), 4.10 δ (s, 3H, N-CH_3), 7.40-8.50 δ (m, 5H, aromatic).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.00; H, 4.30; N, 16.04.

Compound **6h**.

This compound was recrystallized from ethanol, m.p. 191°; ir: 1637, 1613 cm^{-1} (2 C=O); nmr (deuteriochloroform): 4.10 δ (s, 3H, N-CH_3); 7.25-8.40 δ (m, 10H, aromatic).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S$: C, 63.15; H, 4.05; N, 13.00. Found: C, 63.02; H, 3.98; N, 12.93.

Compound **4f**.

This compound (1.6 g.) obtained from **1f** (2.35 g.) was recrystallized from ligroin, m.p. 120-121°; ir: 1667 cm^{-1} (C=O); nmr (acetone-d_6): 2.97, 3.57 δ (2s, 6H, 2 x N-CH_3), 7.20-8.20 δ (m, 5H, aromatic).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.84; H, 4.78; N, 17.90.

Compound **4f** was obtained also from **4e** by methylation with dimethyl sulphate-anhydrous potassium carbonate (ir superimposable).

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

A solution of 0.005 mole of compound in 25 ml. of ethanol was heated under reflux for 6 hours with sodium hydroxide (0.5 g. in 1 ml. of water). After removing the solvent, the residue was extracted with acetone, dried and evaporated to dryness, giving hydrolysis products (40-60%) **3a** and **5e** (9), **3b**, **3d** and **5f** (10), and **3c** (11). The structures were confirmed by direct comparison with authentic samples (9,10,11) and by spectroscopic evidence (nmr):

Compound **3a**; nmr (DMSO-d_6: 7.16 δ (s, 2H, NH_2), 8.50 δ (s, 1H, CH).

Compound **3b**; nmr (DMSO-d_6): 2.92 δ (d, 3H, NH-CH_3, J = 4.5 Hz), 7.75 δ (br. s, 1H, NH-CH_3), 8.70 δ (s, 1H, CH).

Compound **3c**; nmr (deuteriochloroform): 3.14 δ [s, 6H, $N(CH_3)_2$], 8.37 δ (s, 1H, CH).

Compound **3d**; nmr (DMSO-d_6): 6.85-7.90 δ (m, 5H, aromatic), 9.00 δ (s, 1H, CH), 10.35 δ (s, 1H, NH).

Compound **5e**; nmr (deuteriochloroform): 3.50 δ (s, 3H, N-CH_3), 5.97 δ (s, 1H, NH), 7.59 δ (s, 1H, CH).

Compound **5f**; nmr (deuteriochloroform): 3.03, 3.56 δ (2s, 6H, 2N-CH_3), 7.82 δ (s, 1H, CH).

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