A Facile Synthesis of Novel Pyrazolo[5′,1′:3,4]-[1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepines

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The reaction of the 3-substituted 4-aminopyrazolo[5,1-*c*][1,2,4]triazines **1a-d** with thiosemicarbazide hydrochloride in acetic acid gave new pyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepines **3**, **4** and **6**, which were converted into the 5-oxo derivatives **5** and **7** by hydrolysis in hydrochloric acid/acetic acid.

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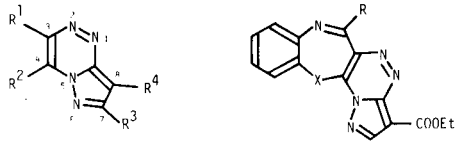
Various pyrazolo[5,1-*c*][1,2,4]triazines **1** (Chart 1) have been synthesized so far by many research groups [2-11], and some of compounds **1** have been reported to possess biological activities such as antifungal [2] and tumor growth inhibitory [3] activities. In addition to the biological activity of compounds **1**, we were interested in further conversion of **1** into 3,4-fused tri- or tetracyclic pyrazolo-[5,1-*c*][1,2,4]triazines. The synthesis of pyrazole, pyrimidine and quinoline ring condensed pyrazolo[5,1-*c*][1,2,4]-triazines has already been reported by some research groups [11-14], and the 1,5-benzodiazepine and 1,5-benzoxazepine ring condensed pyrazolo[5,1-*c*][1,2,4]triazines **2a,b** have recently been synthesized by us [2,15]. In continuation of these works, we further devised a construction of a new ring system and found that the reaction of the 3-substituted 4-aminopyrazolo[5,1-*c*][1,2,4]triazines **1a-d** with thiosemicarbazide hydrochloride provided the 1,3,4-thiadiazepine ring condensed pyrazolo[5,1-*c*][1,2,4]triazines **3,4,6**. We want to report herein a convenient synthesis of novel pyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*][1,3,4]-thiadiazepines **3-7**.

Chart 1

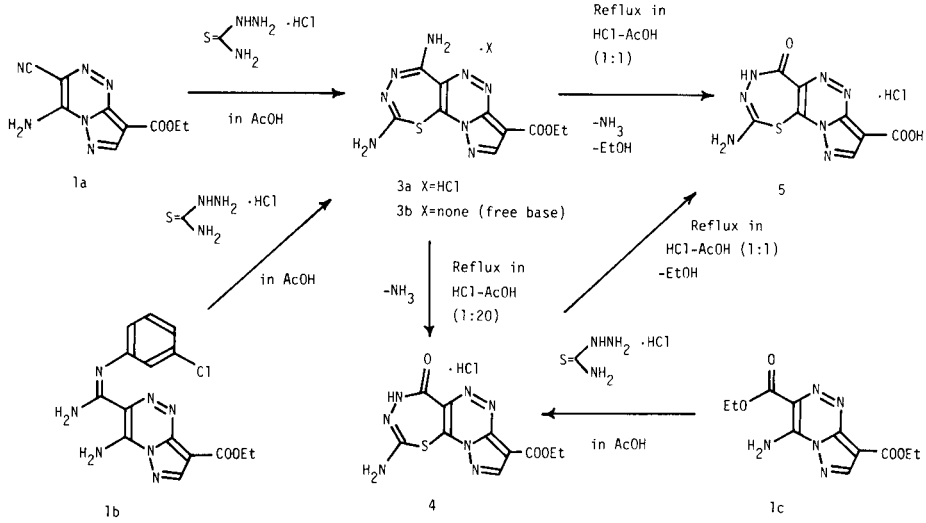


1

2a X=NH
2b X=O

The reaction of **1a** [2] with thiosemicarbazide hydrochloride in acetic acid provided 2,5-diamino-8-ethoxycarbonylpyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine hydrochloride **3a** (83%), which was also obtained by the reaction of **1b** [14] with thiosemicarbazide hydrochloride in acetic acid (76%) (Scheme 1). Treatment of **3a** with 10% sodium hydroxide solution furnished the free base **3b**. Refluxing of **3a** in concentrated hydrochloric acid/acetic acid (1:20) resulted in C_5-deamination to give 2-amino-8-ethoxycarbonyl-5-oxo-4,5-dihydropyrazolo-[5′,1′:3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine hydrochloride **4** (84%). This C_5-deamination was supported by the alternate synthesis of **4** from the reaction of **1c** [2] with

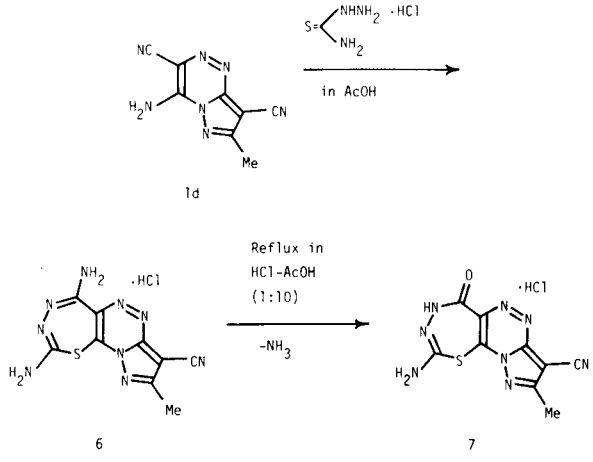
Scheme 1



thiosemicarbazide hydrochloride in acetic acid (34%). Further refluxing of **4** in concentrated hydrochloric acid/acetic acid (1:1) effected C_8-ester hydrolysis, but not C_2-deamination, to afford 2-amino-5-oxo-4,5-dihydropyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine-8-carboxylic acid hydrochloride **5** (46%), which was also obtained from **3a** under a similar reaction condition (46%).

In order to prepare some other analogues of the above compounds **3-5**, compound **1d** [14] (Scheme 2) was used as a starting material. The reaction of **1d** with thiosemicarbazide hydrochloride in acetic acid provided 2,5-diamino-8-cyano-9-methylpyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*]-[1,3,4]thiadiazepine hydrochloride **6** (84%), whose refluxing in concentrated hydrochloric acid/acetic acid (1:10) also resulted in C_5-deamination to furnish 2-amino-8-cyano-9-methyl-5-oxo-4,5-dihydropyrazolo[5′,1′:3,4][1,2,4]-triazino[6,5-*f*][1,3,4]thiadiazepine hydrochloride **7** (74%).

Scheme 2



The structures of the above compounds **3-7** were assigned by the analytical and spectral data. If there were two other cyclization routes **a** and **b** in an intermediate **I** (Chart 2), the pyrazole **II** and triazepine **III** would be produced, respectively. However, the pmr spectrum of the free base **3b** showed the C_2- and C_5-NH_2 proton signals at δ 7.62 and 9.17 ppm, respectively, excluding a possibility of the triazepine **III** as the cyclization product. The pyrazole structure **II** would be also denied, since thiocarbamoyl group connecting with an endocyclic pyrazole nitrogen was easily eliminated under a similar reaction condition to that of the present investigation. Namely, the reaction of the furo[2,3-*b*]quinoxaline **8** with thiosemicarbazide hydrochloride in acetic acid gave the quinoxalinylpyrazolone **9** (66%) [16], presumably *via* an intermediate **IV** (Chart 3). In the ^{13}C-nmr spectra, the C_2 carbon signals of **3-7** and C_5-C=O carbon signals of **3-5** were observed at δ 170-168 and 163-161 ppm, respectively.

Chart 2

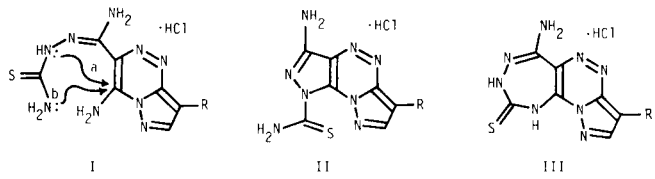
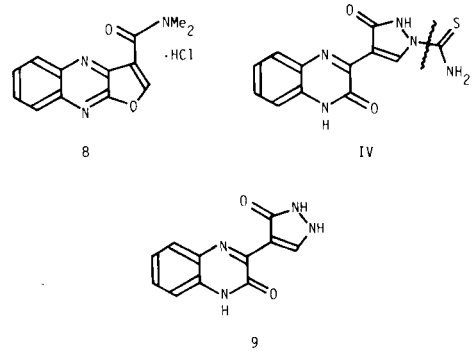


Chart 3



EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr and ^{13}C-nmr spectra were measured in deuteriodimethylsulfoxide with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

2,5-Diamino-8-ethoxycarbonylpyrazolo[5′,1′:3,4][1,2,4]triazino-[6,5-*f*][1,3,4]thiadiazepine Hydrochloride **3a** and Free Base **3b**.

Hydrochloride **3a**.

A suspension of **1a** (8 g, 28.78 mmoles) and thiosemicarbazide hydrochloride (9.97 g, 86.34 mmoles) in acetic acid (400 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles **3a**, which were collected by suction filtration (8.18 g, 83%). Trituration with hot ethanol gave an analytically pure sample, mp above 320°; ir: ν cm^{-1} 3360, 3240, 3020, 2640, 1715, 1630; ms: m/z 306 (M^+).

Anal. Calcd. for $C_{10}H_{11}ClN_6O_2S$: C, 35.04; H, 3.24; Cl, 10.36; N, 32.69; S, 9.35. Found: C, 34.99; H, 3.16; Cl, 10.29; N, 32.77; S, 9.09.

Free Base **3b**.

A slight excess of 10% sodium hydroxide solution was added dropwise to a suspension of the hydrochloride **3a** in ethanol/water with stirring on a boiling water bath, and the crystals were adequately triturated. Then, a small amount of acetic acid was added to the suspension, and yellow free base **3b** was collected by suction filtration. The free base **3b** was washed with hot ethanol/water and then with ethanol to give analytically pure yellow

needles, mp above 320°; ir: ν cm^{-1} 3360, 3270, 1700, 1650, 1605; ms: m/z 306 (M^+); pmr: 9.17 (br, 2H, C_5-NH_2), 8.68 (s, 1H, C_9-H), 7.62 (s, 2H, C_2-NH_2), 4.32 (q, J = 7 Hz, 2H, CH_2), 1.34 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{10}N_8O_2S$: C, 39.21; H, 3.29; N, 36.58; S, 10.47. Found: C, 38.94; H, 3.23; N, 36.41; S, 10.21.

Synthesis of Hydrochloride **3a** from Amidine **1b**.

A suspension of **1b** (1 g, 2.38 mmoles) and thiosemicarbazide hydrochloride (0.76 g, 5.96 mmoles) in acetic acid (30 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles **3a** (0.65 g, 76%).

2-Amino-8-ethoxycarbonyl-5-oxo-4,5-dihydropyrazolo[5′,1′:3,4]-[1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine Hydrochloride **4**.

A suspension of **3a** (5 g) in concentrated hydrochloric acid (10 ml)/acetic acid (200 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles **4**, which were collected by suction filtration (4.23 g, 84%). Trituration with hot ethanol gave an analytically pure sample, mp above 320°; ir: ν cm^{-1} 3240, 1735, 1695, 1610; ms: m/z 307 (M^+); pmr: 9.60 (br, N_4-H, C_2-NH_2, =NH-, H_2O), 8.45 (s, 1H, C_9-H), 4.35 (q, J = 7 Hz, 2H, CH_2), 1.32 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{10}ClN_7O_3S$: C, 34.92; H, 2.93; Cl, 10.31; N, 28.52; S, 9.33. Found: C, 34.75; H, 2.83; Cl, 10.13; N, 28.52; S, 9.09.

Synthesis of Hydrochloride **4** from Ester **1c**.

A suspension of **1c** (1 g, 3.58 mmoles) and thiosemicarbazide hydrochloride (1.24 g, 10.7 mmoles) in acetic acid (50 ml) was refluxed in an oil bath for 30 minutes to give a clear solution, which was refluxed for an additional 30 minutes to precipitate yellow needles **4** (420 mg, 34%).

2-Amino-5-oxo-4,5-dihydropyrazolo[5′,1′:3,4][1,2,4]triazino[6,5-*f*]-[1,3,4]thiadiazepine-8-carboxylic Acid Hydrochloride **5**.

A solution of **4** (2 g) in concentrated hydrochloric acid (60 ml)/-acetic acid (60 ml) was refluxed for 5 hours to precipitate yellow needles **5**, which were collected by suction filtration (840 mg, 46%). Trituration with hot ethanol gave an analytically pure sample, mp above 320°; ir: ν cm^{-1} 3340, 3250, 1700, 1680, 1610; ms: m/z 235 (M^+-CO_2) [M^+ of this compound (m/z 279) could not be observed when measured by DIEI method.]; pmr: 9.40 and 6.50 (br, C_2-NH_2, N_4-H, =NH-, C_8-COOH, H_2O), 8.40 (s, 1H, C_9-H).

Anal. Calcd. for $C_8H_6ClN_7O_3S$: C, 30.43; H, 1.92; Cl, 11.22; N, 31.06; S, 10.16. Found: C, 30.70; H, 2.09; Cl, 11.23; N, 30.93; S, 10.23.

Synthesis of Hydrochloride **5** from Hydrochloride **3a**.

A similar reaction of the hydrochloride **3a** (10 g) in concentrated hydrochloric acid (200 ml)/acetic acid (200 ml) furnished the carboxylic acid hydrochloride **5** (4.24 g, 46%).

2,5-Diamino-8-cyano-9-methylpyrazolo[5′,1′:3,4][1,2,4]triazino-[6,5-*f*][1,3,4]thiadiazepine Hydrochloride **6**.

A suspension of **1d** (10 g, 36.6 mmoles) and thiosemicarbazide hydrochloride (14 g, 109.8 mmoles) in acetic acid (500 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles **6**, which were collected by suction filtration (12.0 g, 84%). Trituration with hot acetic acid and then with hot ethanol afforded an analytically pure sample, mp above 320°; ir: ν cm^{-1} 3380, 3220, 3020, 2620, 2240, 1620; ms: m/z 273 (M^+); pmr: 10.06 (s, 2H, C_5-NH_2), 8.90 (s, 2H, C_2-NH_2), 6.82 (br, =NH-, H_2O), 2.58 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_8ClN_9S$: C, 34.90; H, 2.60; Cl, 11.45; N, 40.70; S, 10.35. Found: C, 35.09; H, 2.68; Cl, 11.31; N, 40.84; S, 10.51.

2-Amino-8-cyano-9-methyl-5-oxo-4,5-dihydropyrazolo[5′,1′:3,4]-[1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine Hydrochloride **7**.

A suspension of **6** (2 g) in concentrated hydrochloric acid (10 ml)/acetic acid (100 ml) was refluxed in an oil bath for 5 hours to precipitate yellow needles **7**, which were collected by suction filtration (1.81 g, 90%). Trituration with hot acetic acid and then with hot ethanol provided an analytically pure sample, mp above 320°; ir: ν cm^{-1} 3320, 3040, 2680, 2220, 1700, 1610; ms: m/z 274 (M^+); pmr: 3.74 (br, NH, NH_2, =NH-, H_2O), 2.61 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_7ClN_8OS$: C, 34.79; H, 2.27; Cl, 11.41; N, 36.06; S, 10.32. Found: C, 34.58; H, 2.42; Cl, 11.27; N, 35.79; S, 10.56.

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