A New Method for the Synthesis of Novel 3-Substituted 4-Amino-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazines and Pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepines

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Novel 3-substituted 4-amino-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazines **7**,**8** were synthesized by the reactions of malononitrile and ethyl cyanoacetate with the pyrazole-5-diazonium salt **3**. Moreover, compounds **7**,**8** were converted into the pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepines **9**, **10**.

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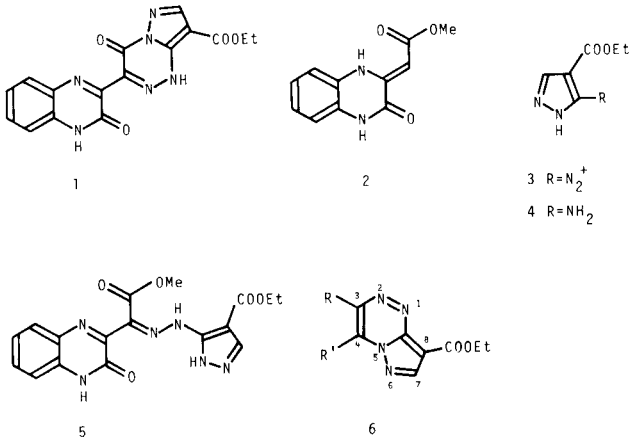
In a previous paper [1], we reported the synthesis of the 3-quinoxalinylpyrazolo[5,1-*c*][1,2,4]triazine **1** from the reaction of the side-chained quinoxaline **2** with the pyrazole-5-diazonium salt **3**, generated from the pyrazole **4**, *via* the pyrazolylhydrazone **5** (Chart). This reaction conveniently brought about a new method for the construction of the pyrazolo[5,1-*c*][1,2,4]triazine ring, but it did not lead to the synthesis of condensed pyrazolo[5,1-*c*][1,2,4]triazines.

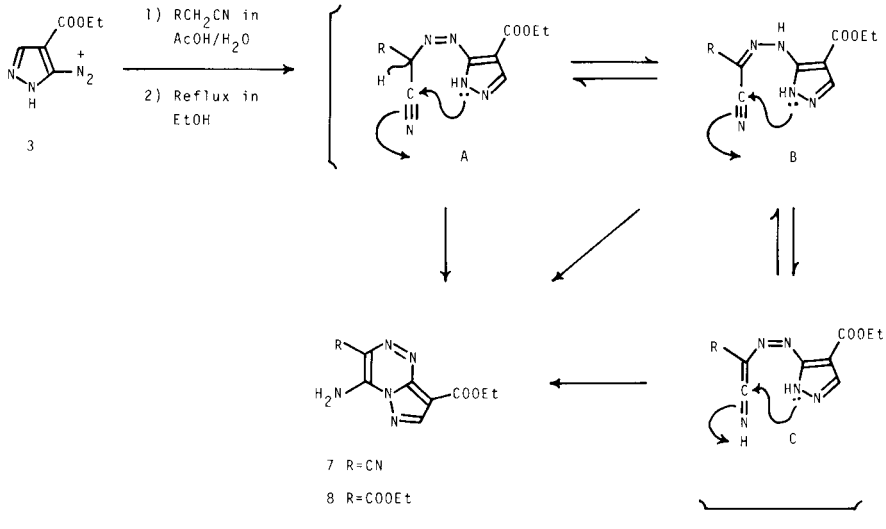
Chart



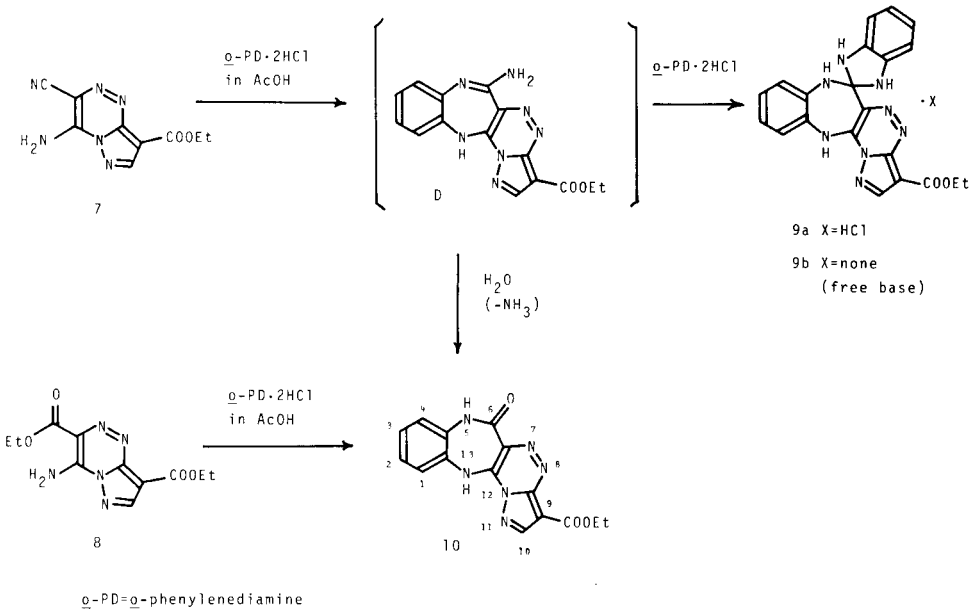
In order to prepare various condensed pyrazolo[5,1-*c*][1,2,4]triazines, it was necessary to produce the 3,4-bifunctional pyrazolo[5,1-*c*][1,2,4]triazine such as **6** shown in the chart. Accordingly, we devised a new method for the synthesis of the novel 3-substituted 4-amino-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazines **7**,**8** (Scheme 1). Furthermore, compounds **7** and **8** were converted into the novel pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepines **9**,**10** (Scheme 2). This paper describes a new synthesis of the novel pyrazolo[5,1-*c*][1,2,4]triazines **7**,**8** and pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*c*][1,5]benzodiazepines **9**,**10**.

The reactions of the pyrazole-5-diazonium salt **3** with malononitrile and ethyl cyanoacetate in acetic acid/water gave possible intermediate **A**, **B** or **C** as colorless crystals, whose refluxing in ethanol resulted in cyclization to afford 4-amino-3-cyano-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazine **7** as ethanol complex and 4-amino-3,8-bisethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazine **8** in 85% and 65% yields, respectively (Scheme 1).

Scheme 1



Scheme 2



The reaction of **7** with a 3-fold molar amount of *o*-phenylenediamine dihydrochloride in acetic acid under reflux for 5 hours provided 9-ethoxycarbonyl-5*H*,13*H*-2',3'-dihydrospiro[benzimidazole-6,2'-pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine] hydrochloride **9a** and 9-ethoxycarbonyl-6-oxo-13*H*-5,6-dihydropyrazolo[1',5':3,4]-[1,2,4]triazino[5,6-*b*][1,5]benzodiazpine **10** in 53% and 28% yields, respectively, presumably *via* an intermediate **D** [2]. Treatment of **9a** with 10% sodium hydroxide solution gave the free base **9b**. The reaction of **8** with a 1.5-fold molar amount of *o*-phenylenediamine dihydrochloride in acetic acid under reflux for 5 hours also afforded **10** in 56% yield (Scheme 2).

The structural assignments for the above new compounds **7-10** were based on their analytical and spectral data.

EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr spectra were measured in deuteriodimethylsulfoxide with an EM 390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

4-Amino-3-cyano-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazine **7** (Ethanol Complex) and 4-Amino-3,8-bisethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazine **8**.

A solution of sodium nitrite (4.45 g, 64.5 mmoles) in water (50 ml) was added dropwise to a solution of the pyrazole **4** (10 g, 64.5 mmoles) in acetic acid (150 ml) with stirring for 10 minutes in an ice-water bath to give a clear solution, to which malononitrile (6.39 g, 96.8 mmoles) or ethyl cyanoacetate (10.94 g, 96.8 mmoles) was added portionwise or dropwise, respectively. Stirring was continued for an additional 20 minutes to precipitate colorless crystals, and the mixture was heated on a boiling water bath for 10 minutes in order to accomplish the diazotization. Then, ethanol (200 ml) was added to the reaction mixture to dissolve the colorless crystals under reflux on a boiling water bath, and refluxing was continued for an additional 30 minutes. The solvents were evaporated *in vacuo* to give colorless crystals, which were dissolved in ethanol (500 ml) under reflux on a boiling water bath.

When malononitrile was used, refluxing was continued for additional 4 hours to precipitate yellow crystals **7** as ethanol complex, which were collected by suction filtration (15.09 g, 85%).

When ethyl cyanoacetate was employed, refluxing was continued for an additional 4 hours to give a clear solution. The hot clear solution was filtered, and the filtrate was allowed to stand at room temperature to precipitate analytically pure colorless needles **8**, which were collected by suction filtration (11.7 g, 65%).

Compound **7** was recrystallized from *N,N*-dimethylformamide/ethanol to afford yellow needles as ethanol complex, mp 270-275° dec; ir: ν cm^{-1} 3490, 2960, 2230, 1660; ms: m/z 232 (M^+); pmr: 9.63 (s, 2H, NH_2), 8.73 (s, 1H, C_7-H), 4.37 (q, J = 7 Hz, 2H, CH_2), 4.27 (s, 1H, OH), 3.44 (q, J = 7 Hz, 2H, CH_2), 1.33 (t, J = 7 Hz, 3H, CH_3), 1.04 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_9H_8N_6O_2 \cdot C_2H_5OH$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.18; H, 4.94; N, 30.32.

Compound **8** had mp 201-202°; ir: ν cm^{-1} 3340, 3260, 3200, 2970, 1685, 1630; ms: m/z 279 (M^+); pmr: 9.14 (brs, 2H, NH_2), 8.73 (s, 1H, C_7-H), 4.44 (q, J = 7 Hz, 2H, CH_2), 4.36 (q, J = 7 Hz, 2H, CH_2), 1.42 (t, J = 7 Hz, 3H, CH_3), 1.34 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.18; H, 4.58; N, 25.11.

9-Ethoxycarbonyl-5*H*,13*H*-2',3'-dihydrospiro[benzimidazole-6,2'-pyrazolo[1',5':3,4]][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine] Hydrochloride **9a** and 9-Ethoxycarbonyl-6-oxo-13*H*-5,6-dihydropyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine **10**.

A suspension of **7** (5 g, 17.99 mmoles) and *o*-phenylenediamine dihydrochloride (9.77 g, 53.97 mmoles) in acetic acid (300 ml) was refluxed in

an oil bath for 1 hour to give a clear solution, and the yellow needles **9a** precipitated. Refluxing was carried out for an additional 4 hours. The yellow needles **9a** were collected by suction filtration, triturated with hot ethanol (500 ml) and then collected by suction filtration to obtain analytically pure yellow needles **9a** (4.28 g, 53%), mp 308-309°; ir: ν cm^{-1} 3160, 2620, 1720, 1610; ms: m/z 414 (M^+); pmr: 9.00-6.33 (br, NH and H_2O), 8.07-7.67 (m, 4H, aromatic), 7.92 (s, 1H, C_{10}-H), 7.60-7.27 (m, 4H, aromatic), 4.48 (q, J = 7 Hz, 2H, CH_2), 1.40 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{18}N_8O_2 \cdot HCl$: C, 55.94; H, 4.25; Cl, 7.86; N, 24.85. Found: C, 55.83; H, 4.13; Cl, 8.15; N, 24.75.

After the yellow needles **9a** were collected by suction filtration, the filtrate (acetic acid solution) was evaporated *in vacuo* to give yellow crystals **10**, which were triturated with hot water and then collected by suction filtration (1.83 g, 28%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles **10** as half hydrate, mp above 330°; ir: ν cm^{-1} 1640, 1615; ms: m/z 324 (M^+); pmr 8.70 (s, 1H, C_{10}-H), 7.83-7.57 (m, 2H, aromatic), 7.45-7.10 (m, 2H, aromatic), 6.67-4.67 (br, NH and H_2O), 4.35 (q, J = 7 Hz, 2H, CH_2), 1.37 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_6O_3 \cdot 1/2\ H_2O$: C, 54.05; H, 3.93; N, 25.21. Found: C, 54.35; H, 3.72; N, 25.19.

Free Base **9b**.

A slight excess of 10% sodium hydroxide solution was added dropwise to a suspension of **9a** in ethanol with stirring on a boiling water bath to dissolve **9a**. Then, the solution was filtered, and acetic acid (0.5 ml) was added to precipitate yellow needles **9b**, mp 339-340°; ir: ν cm^{-1} 1700, 1600, 1560, 1540; ms: m/z 414 (M^+); pmr: 8.00-7.63 (m, 4H, aromatic), 7.85 (s, 1H, C_{10}-H), 7.53-7.13 (m, 4H, aromatic), 6.50-3.33 (br, NH and H_2O), 4.48 (q, J = 7 Hz, 2H, CH_2), 1.40 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{16}N_8O_2$: C, 60.86; H, 4.38; N, 27.04. Found: C, 60.65; H, 4.35; N, 26.87.

Synthesis of **10** from **8**.

A suspension of **8** (3 g, 10.75 mmoles) and *o*-phenylenediamine dihydrochloride (2.92 g, 16.13 mmoles) in acetic acid was refluxed in an oil bath for 5 hours to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals **10**, which were triturated with hot ethanol/water and then collected by suction filtration (2.18 g, 56%).

REFERENCES AND NOTES

[1] Y. Kurasawa, A. Satoh, S. Ninomiya, H. Arai, K. Arai, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, in press.

[2] The reaction of **7** with an equimolar amount of *o*-phenylenediamine dihydrochloride in acetic acid under reflux for 2 hours also gave the hydrochloride **9a** in a poor yield.