A Convenient Synthesis of Novel Spiro[benzoxazole-2',4(1*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] by Ring Transformation of Novel Pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines

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Novel pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5**, **6** and **8** were synthesized, and these compounds were converted into novel spiro[benzoxazole-2',4(1*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] **7** and **9** by ring transformation.

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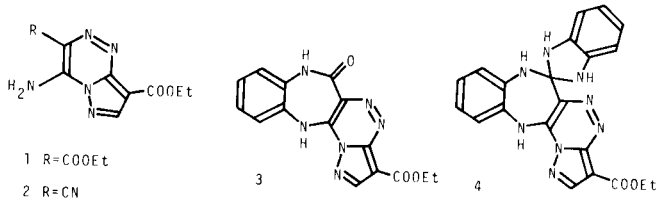
In a previous paper [1], we reported that the reaction of pyrazolo[5,1-*c*][1,2,4]triazines **1** and **2** with *o*-phenylenediamine dihydrochloride gave pyrazolo[1',5':3,4][1,2,4]-triazino[5,6-*b*][1,5]benzodiazepine **3** and spiro[benzimidazole-2',6(5*H*,3'*H*)-pyrazolo[1',5':3,4][1,2,4]triazino-[5,6-*b*][1,5]benzodiazepine] **4**, respectively. In the present investigation, we found that the novel pyrazolo[1',5':3,4]-[1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5**, **6** and **8** synthesized from **1** and **2** were conveniently transformed into novel spiro[benzoxazole-2',4(1*H*,3'*H*)-pyrazolo[5,1-*c*]-[1,2,4]triazines] **7** and **9** (Schemes 1 and 2). This paper describes the synthesis of **5**, **6** and **8** and their ring transformation into **7** and **9**.

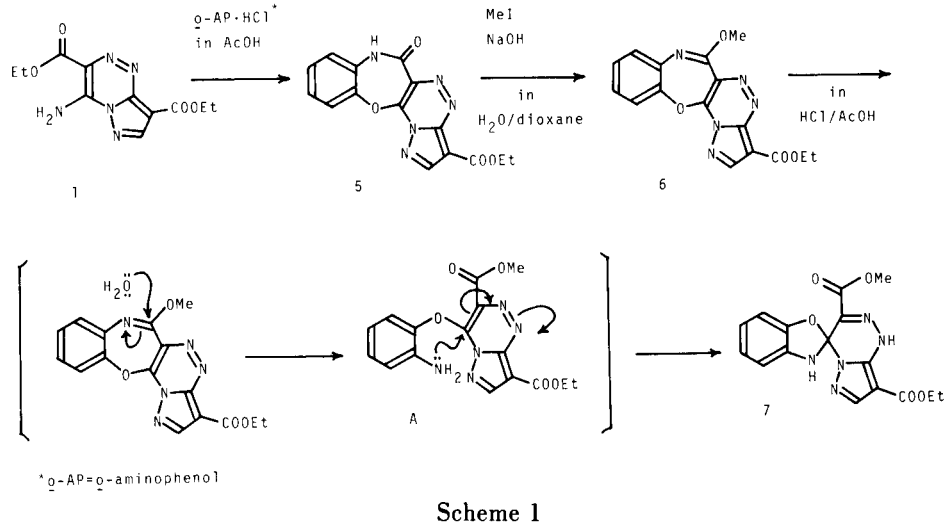


Chart

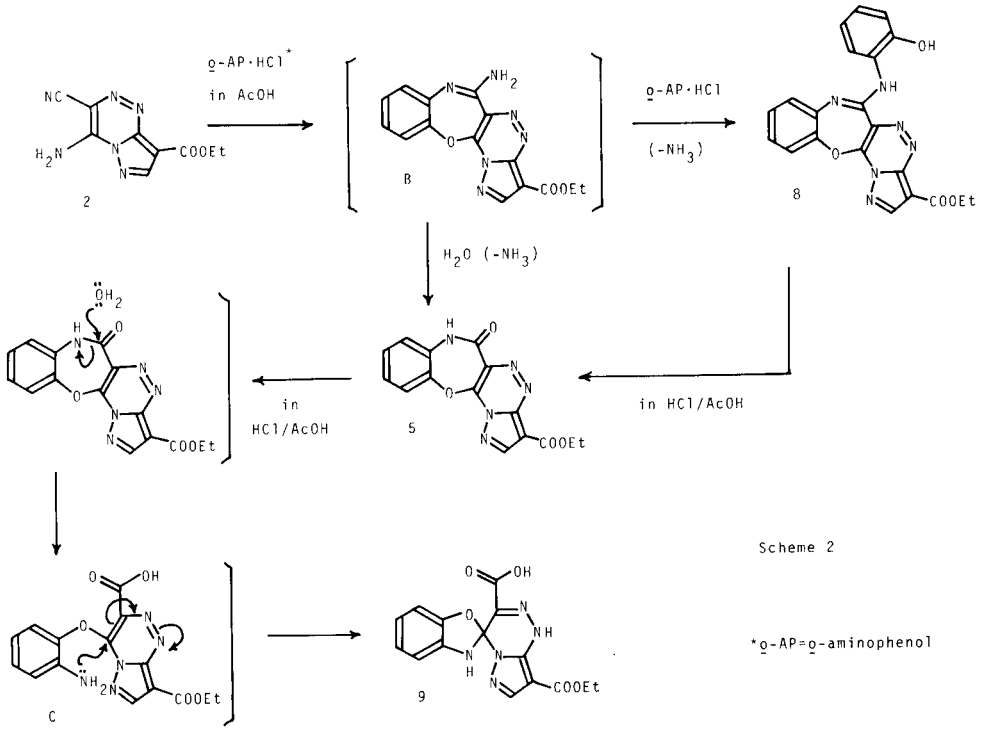
The reaction of **1** with *o*-aminophenol hydrochloride gave 9-ethoxycarbonyl-6-oxo-5,6-dihydropyrazolo[1',5':-3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepine **5** (66%), whose methylation with methyl iodide afforded 9-ethoxycarbonyl-6-methoxylpyrazolo[1',5':3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepine **6** (80%). Refluxing of **6** in hydrochloric acid/acetic acid resulted in ring transformation to produce 8-ethoxycarbonyl-3-methoxycarbonylspiro-[benzoxazole-2',4(1*H*,3'*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7** (93%), presumably *via* an intermediate **A** (Scheme 1).

The reaction of **2** with a 3-fold molar amount of *o*-aminophenol hydrochloride furnished 9-ethoxycarbonyl-6-(*o*-hydroxyphenyl)aminopyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepine **8** (68%) and **5** (22%), presumably *via* an intermediate **B** (Scheme 2). Refluxing of **5** and **8** in hydrochloric acid/acetic acid effected ring transformation to give 8-ethoxycarbonylspiro[benzoxazole-2',4(1*H*,3'*H*)-pyrazolo[5,1-*c*][1,2-4]triazine]-3-carboxylic acid **9** in 86% and 83% yields, respectively, presumably *via* an intermediate **C**.

The structural assignments for the above new compounds **5-9** were based on their analytical and spectral data.



Scheme 1



Scheme 2

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 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.

9-Ethoxycarbonyl-6-oxo-5,6-dihydropyrazolo[1′,5′:3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepine **5**.

A solution of **1** (5 g, 17.90 mmoles) and *o*-aminophenol hydrochloride (7.82 g, 53.80 mmoles) in acetic acid (300 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **5**, which were triturated with hot ethanol/water and then collected by suction filtration (3.82 g, 66%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 306-307°; ir ν cm^{-1} 3160, 1720, 1660, 1600; ms: m/z 325 (M$^+$); pmr: 8.42 (s, 1H, C_{10}-H), 8.00-7.67 (m, 2H, aromatic), 7.63-7.33 (m, 2H, aromatic), 4.35 (q, J = 7 Hz, 2H, CH_2), 3.90-2.60 (br, NH and H_2O), 1.33 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.38; H, 3.41; N, 21.53. Found: C, 55.39; H, 3.26; N, 21.59.

9-Ethoxycarbonyl-6-methoxylpyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]-benzoxazepine **6**.

Methyl iodide (2.62 g, 18.46 mmoles) was added to a suspension of **5** (5 g, 15.38 mmoles) and sodium hydroxide (0.74 g, 18.46 mmoles) in dioxane (200 ml)/water (100 ml), and the suspension was heated on a boiling water bath for 2 hours to give a clear solution. Evaporation of the solvent *in vacuo* afforded yellow crystals **6**, which were collected by suction filtration (4.15 g, 80%). Recrystallization from *N,N*-dimethylformamide/methanol furnished yellow needles, mp 259-260°; ir: ν cm^{-1} 1700, 1550, 1500; ms: m/z 339 (M$^+$); pmr: 8.48 (s, 1H, C_{10}-H), 8.00-7.73 (m, 2H, aromatic), 7.66-7.33 (m, 2H, aromatic), 4.40 (s, 3H, OCH_3), 4.32 (q, J = 7 Hz, 2H, CH_2), 1.33 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{13}N_5O_4$: C, 56.63; H, 3.86; N, 20.64. Found: C, 56.54; H, 3.81; N, 20.67.

8-Ethoxycarbonyl-3-methoxycarbonylspiro[benzoxazole-2′,4(1*H*,3′*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7**.

A solution of **6** (5 g) in concentrated hydrochloric acid (10 ml)/acetic acid (190 ml) was refluxed in an oil bath for 4 hours to precipitate yellow needles **7**, which were collected by suction filtration (4.91 g, 93%). Recrystallization from *N,N*-dimethylformamdie/ethanol gave yellow needles, mp 310-311°; ir: ν cm^{-1} 1690, 1590, 1540, 1500; ms: m/z 357 (M$^+$); pmr: 11.00 (s, 1H, NH), 10.23 (s, 1H, NH), 8.57 (s, 1H, C_7-H), 8.70-8.00 (m, 1H, aromatic), 7.15-6.75 (m, 3H, aromatic), 4.43 (s, 3H, CH_3), 4.37 (q, J = 7 Hz, 2H, CH_2), 1.35 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{15}N_5O_5$: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.53; H, 4.22; N, 19.57.

9-Ethoxycarbonyl-6-(*o*-hydroxyphenyl)animopyrazolo[1′,5′:3,4][1,2,4]-triazino[5,6-*b*][1,5]benzoxazepine **8** and Compound **5**.

A solution of **2** (5 g, 18.0 mmoles) and *o*-aminopenol hydrochloride (9.32 g, 54.0 mmoles) in acetic acid (300 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals, which were triturated with water and then collected by suction filtration. Recrystallization of the yellow crystals from ethanol gave yellow needles **8**, which were collected by suction filtration (5.10 g, 68%). Evaporation of the filtrate *in vacuo* afforded yellow crystals **5**, which were collected by suction filtration (1.28 g, 22%).

Compound **8** was recrystallized once more from ethanol to give an analytically pure sample as half hydrate, mp 276-277°; ir: ν cm^{-1} 1700, 1590, 1510; ms: m/z 416 (M$^+$); pmr: 14.08 (s, 1H, OH or NH), 13.38 (brs, 1H, NH or OH), 8.27 (s, 1H, C_{10}-H), 8.10-7.73 (m, 4H, aromatic), 7.73-7.27 (m, 4H, aromatic), 4.44 (q, J = 7 Hz, 2H, CH_2), 1.36 (t, J = 7 Hz, 3H,

CH_3).

Anal. Calcd. for $C_{21}H_{16}N_6O_4 \cdot ½ H_2O$: C, 59.29; H, 4.03; N, 19.76. Found: C, 59.02; H, 4.21; N, 19.64.

8-Ethoxycarbonylspiro[benzoxazole-2′,4(1*H*,3′*H*)-pyrazolo[5,1-*c*]-[1,2,4]triazine]-3-carboxylic Acid **9**.

A solution of **5** (2 g) or **8** (2 g) in concentrated hydrochloric acid (5 ml)/acetic acid (80 ml) was refluxed in an oil bath for 3 hours to precipitate yellow crystals **9**, which were collected by suction filtration after cooling to room temperature [1.81 g (86%) from **5**; 1.37 g (83%) from **8**]. Recrystallization from *N*,*N*-dimethylformamide/ethanol gave yellow needles, mp 326-327°; ir: ν cm^{-1} 1680, 1650, 1585, 1540, 1510; ms: m/z 343 (M^+); pmr: 10.97 (s, 1H, NH), 10.20 (s, 1H, NH), 8.48 (s, 1H, C_7-H), 8.60-8.30 (m, 1H, aromatic), 7.10-6.67 (m, 3H, aromatic), 4.38 (q, J = 7 Hz, 2H, CH_2), 1.34 (t, J = 7 Hz, 3H, CH_3). The C_3-carboxylic proton signal was unobservable presumably due to broadening.

Anal. Calcd. for $C_{15}H_{13}N_5O_5$: C, 52.48; H, 3.82; N, 20.40. Found: C, 52.42; H, 3.94; N, 20.41.

REFERENCES AND NOTES

[1] Y. Kurasawa, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, in press.