A New Method for the Synthesis of Novel 6-Quinoxalinylpyrazolo[5,1-*c*][1,2,4]triazines

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The reaction of the quinoxaline **1** with 4-ethoxycarbonyl-1*H*-pyrazole-5-diazonium chloride **7** at room temperature gave 3-[α-(4-ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **8**. The pmr spectrum of **8** in deuteriodimethylsulfoxide supported the presence of two tautomers **8-I** and **8-II**. Refluxing of **8** in *N,N*-dimethylformamide or acetic acid resulted in cyclization to afford 8-ethoxycarbonyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **9**. Compound **9** was also obtained directly by the reaction of **1** with **7** under reflux in better yield. The reaction of **9** with hydrazine hydrate provided the hydrazinium salt **10**, while the reactions of **9** with triethyl and trimethyl orthoformates in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene produced 8-ethoxycarbonyl-4-ethoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo[5,1-*c*][1,2,4]triazine **11a** and 8-ethoxycarbonyl-4-methoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo[5,1-*c*][1,2,4]triazine **11b**, respectively. The chlorination of **11a** with phosphoryl chloride gave 3-(3-chloroquinoxalin-2-yl)-8-ethoxycarbonyl-4-ethoxylpyrazolo[5,1-*c*]-[1,2,4]triazine **12**, whose reaction with morpholine afforded 8-ethoxycarbonyl-4-ethoxyl-3-[3-(morpholin-4-yl)-quinoxalin-2-yl]pyrazolo[5,1-*c*][1,2,4]triazine **13**.

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In previous papers [1-6], we reported the synthesis of the various 1-arylpyrazolo[3,4-*b*]quinoxalines **4** by the cyclization of the hydrazones **3** obtained from the reactions of the quinoxaline **1** or **2** with chlorobenzene diazonium chlorides **5** (Chart 1). However, the employment of chlorobenzene diazonium chlorides **5** limited the cyclization mode of the hydrazones **3** only to the pyrazolo[3,4-*b*]quinoxaline ring. In order to result in the different type of cyclization, a bifunctional heteroaryl diazonium chloride was considered to be effective. In the present investigation, 4-ethoxycarbonyl-1*H*-pyrazole-5-diazonium chloride **7** generated from the pyrazole **6** [7] was utilized to find a new method for the construction of the pyrazolo[5,1-*c*]-[1,2,4]triazine ring. This paper describes a new synthesis of the novel 3-quinoxalinylpyrazolo[5,1-*c*][1,2,4]triazines **9-13**.

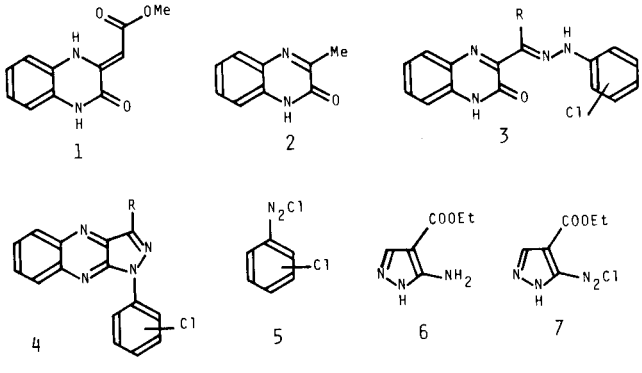
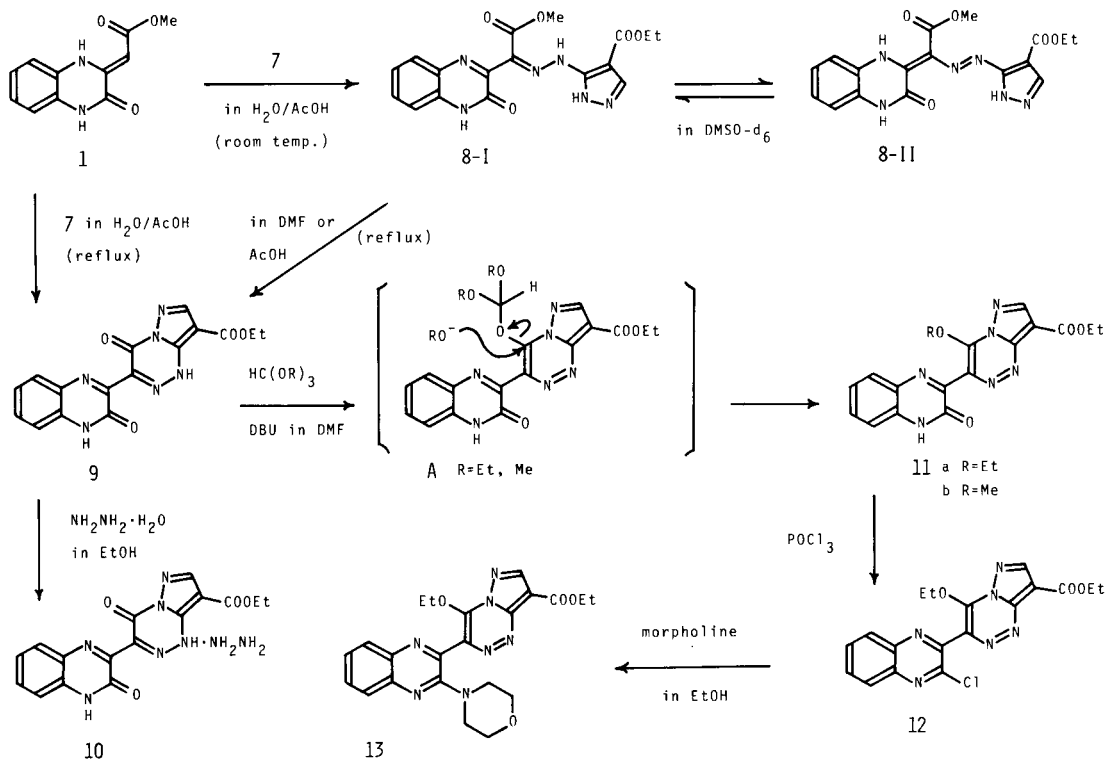


Chart 1

The reaction of the quinoxaline **1** with **7** at room temperature gave 3-[α-(4-ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **8**, whose structural assignment was based on the spectral and analytical data. In particular, its pmr spectrum in deuteriodimethylsulfoxide supported the presence of two tautomers **8-I** and **8-II** [5,8,10], whose molar ratio was indicated to be 22 *versus* 3 (or 3 *versus* 22) from the integral ratios of NH proton signals. Refluxing of **8** in acetic acid or *N,N*-dimethylformamide resulted in cyclization to afford 8-ethoxycarbonyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]-triazine **9**. Compound **9** was also produced directly by the reaction of the quinoxaline **1** with **7** under reflux in better yield. The C_8-ethoxycarbonyl group of **9** seldom reacted with the nucleophilic reagents such as amine and hydrazine, while the reaction of **9** with hydrazine hydrate formed the hydrazinium salt **10**, presumably due to the presence of the acidic N_1-H proton. For the sake of further modification of **9**, the substitution of the N_1-H proton was undertaken at first. The reaction of **9** with triethyl and trimethyl orthoformates in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) provided 8-ethoxycarbonyl-4-ethoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo-[5,1-*c*][1,2,4]triazine **11a** and 8-ethoxycarbonyl-4-methoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo[5,1-*c*][1,2,4]-triazine **11b**, respectively, presumably *via* intermediates **A**. Chlorination of **11a** with phosphoryl chloride gave 3-(3-chloroquinoxalin-2-yl)-8-ethoxycarbonyl-4-ethoxyl-pyrazolo[5,1-*c*][1,2,4]triazine **12**, whose reaction with morpholine afforded 8-ethoxycarbonyl-4-ethoxyl-3-[3-(morpho-



SCHEME

lin-4-yl)quinoxalin-2-yl]pyrazolo[5,1-*c*][1,2,4]triazine **13**.

In the ir spectra, the absorption maxima due to the ester carbonyl group were observed at 1720 cm^{-1} in **9** and at 1700 cm^{-1} in **11**, **12** and **13**, suggesting the difference of the conjugate system in the triazine ring between **9** and **11-13**. Thus, **9** was assumed to be the 1,4-dihydro form, but not the C_4-hydroxyl structure **14** shown in Chart 2.

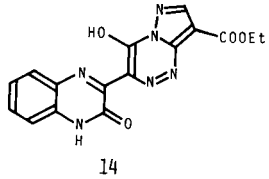


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Chart 2

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.

3-[α-(4-Ethoxycarbonyl-1*H*-pyrazol-5-ylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline **8**.

A solution of sodium nitrite (8.15 g, 118.1 mmoles) in water (100 ml) was added dropwise to a solution of the pyrazole **6** (18.3 g, 118.1 mmoles) in acetic acid (500 ml)/10% hydrochloric acid (100 ml) with stirring in an ice-water bath to give a clear solution, to which the quinoxaline **1** (20.0 g, 91.7 mmoles) was added portionwise. The mixture was stirred for an additional 30 minutes. (The reaction mixture at this stage is also used for the direct synthesis of **9** under reflux.) Then, the mixture was kept at room temperature with stirring for 3 days to afford yellow crystals **8**, which were collected by suction filtration (28.19 g, 64%). The yellow crystals **8** were triturated with hot ethanol, and then collected by suction filtration to provide an analytically pure sample as orange needles, mp 335-336°; ir: ν cm^{-1} 3260, 1730, 1640; ms: m/z 384 (M^+); pmr: 13.87 (s, 3/25 H, NH), 12.80 (s, 3/25 H, NH), 12.73 (s, 3/25 H, NH), 12.35 (s, 22/25 H, NH), 11.14 (s, 22/25 H, NH), 8.33-7.17 (m, aromatic), 7.78 (s, 1H, C_3-H), 7.72 (s, 22/25 H, NH), 7.00-6.33 (m, aromatic), 4.26 (q, J = 7 Hz, 2H, CH_2), 3.73 (s, 3H, CH_3), 1.28 (t, J = 7 Hz, 3H, CH_3). Total four aromatic protons were observed.

Anal. Calcd. for $C_{17}H_{16}N_6O_5$: C, 53.13; H, 4.20; N, 21.87. Found: C, 52.96; H, 4.06; N, 21.63.

8-Ethoxycarbonyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **9**.

The reaction mixture described in the synthesis of **8** was refluxed in an oil bath for 1 hour to precipitate colorless crystals **9**, which were collected by suction filtration (19.96 g, 62%). Recrystallization from *N,N*-dimethylformamide/ethanol gave colorless needles, mp 334-335°; ir: ν cm^{-1} 3180, 1720, 1650; ms: m/z 352 (M^+); pmr: 14.42 (brs, 1H, NH), 12.84 (s, 1H, NH), 8.44 (s, 1H, C_7-H), 8.33-7.23 (m, 4H, aromatic), 4.37 (q, J = 7 Hz, 2H, CH_2), 1.37 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}N_6O_4$: C, 54.45; H, 3.43; N, 23.86. Found: C,

54.22; H, 3.38; N, 23.74.

Synthesis of **9** from **8**.

A solution of **8** (5 g) in acetic acid (150 ml) or *N,N*-dimethylformamide (50 ml) was refluxed in an oil bath for 1 hour. Removal of the solvent *in vacuo* afforded colorless crystals **9**, which were triturated with hot ethanol and then collected by suction filtration [3.65 g (80%) (when refluxed in acetic acid); 3.81 g (83%) (when refluxed in *N,N*-dimethylformamide)].

Hydrazinium Salt **10**.

A suspension of **9** (5 g) and hydrazine hydrate (7 g) in ethanol (500 ml) was refluxed on a boiling water bath for 3 hours to precipitate the hydrazinium salt **10** as yellow needles, which were collected by suction filtration (5.11 g, 94%). Trituration with hot ethanol afforded an analytically pure sample, mp 240-241°; ir: ν cm^{-1} 3280, 1690, 1660; ms: m/z 352 (M^+) (M^+ of the free base due to thermal dissociation in the inlet system of the mass spectrometer).

Anal. Calcd. for $C_{16}H_{16}N_8O_4$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.83; H, 4.21; N, 28.87.

8-Ethoxycarbonyl-4-ethoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo-[5,1-*c*][1,2,4]triazine **11a** and 8-Ethoxycarbonyl-4-methoxyl-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)pyrazolo[5,1-*c*][1,2,4]triazine **11b**.

A solution of **9** (10 g), DBU (1 ml) and triethyl (or trimethyl) orthoformate in *N,N*-dimethylformamide was refluxed in an oil bath for 2 hours. Removal of the solvent *in vacuo* afforded crystals **11a** (or **11b**), which were triturated with hot ethanol and then collected by suction filtration. Additional crystals **11a** (or **11b**) were recovered from the filtrate. Total yields were 8.14 g (75%) in **11a** and 7.74 g (74%) in **11b**. Recrystallization from *N,N*-dimethylformamide/ethanol provided colorless needles (**11a**) and yellow needles (**11b**).

Compound **11a** had mp 328-329°; ir: ν cm^{-1} 1700, 1650; ms: m/z 380 (M^+); pmr: 12.87 (s, 1H, NH), 8.52 (s, 1H, C_7-H), 8.00-7.20 (m, 4H, aromatic), 4.94 (q, J = 7 Hz, 2H, CH_2), 4.33 (q, J = 7 Hz, 2H, CH_2), 1.44 (t, J = 7 Hz, 3H, CH_3), 1.37 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found: C, 56.78; H, 4.29; N, 21.85.

Compound **11b** had mp 333-334°; ir: ν cm^{-1} 1700, 1650; ms: m/z 366 (M^+); pmr: 12.83 (s, 1H, NH), 8.47 (s, 1H, C_7-H), 8.00-7.23 (m, 4H, aromatic), 4.37 (s, 3H, CH_3), 4.30 (q, J = 7 Hz, 2H, CH_2), 1.33 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{14}N_6O_4$: C, 55.74; H, 3.85; N, 22.94. Found: C, 55.57; H, 3.76; N, 22.93.

3-(3-Chloroquinoxalin-2-yl)-8-ethoxycarbonyl-4-ethoxylpyrazolo[5,1-*c*]-[1,2,4]triazine **12**.

A solution of **11a** (10 g) in phosphoryl chloride (50 ml)/*N,N*-dimethylformamide (50 ml)/dioxane (100 ml) was heated on a boiling water bath for 2 hours. The solution was cooled to room temperature and then poured onto crushed ice to precipitate colorless crystals **12**, which were collected by suction filtration (8.87 g, 85%). Recrystallization from ethanol gave colorless needles, mp 179-180°; ir: ν cm^{-1} 1700, 1560, 1525; ms: m/z 398 (M^+), 400 ($M^+ + 2$); pmr: 8.58 (s, 1H, C_7-H), 8.40-7.97 (m, 4H, aromatic), 4.92 (q, J = 7 Hz, 2H, CH_2), 4.34 (q, J = 7 Hz, 2H, CH_2), 1.47 (t, J = 7 Hz, 3H, CH_3), 1.37 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{15}ClN_6O_3$: C, 54.20; H, 3.79; Cl, 9.09; N, 21.55. Found: C, 54.18; H, 3.75; Cl, 9.03; N, 21.42.

8-Ethoxycarbonyl-4-ethoxyl-3-[3-(morpholin-4-yl)quinoxalin-2-yl]pyrazolo-[5,1-*c*][1,2,4]triazine **13**.

A solution of **12** (3 g, 7.53 mmoles) and morpholine (3.28 g, 37.65 mmoles) in ethanol (150 ml) was refluxed on a boiling water bath for 6 hours. Removal of the solvent *in vacuo* gave yellow crystals **13**, which were collected by suction filtration (3.3 g, 97%). Recrystallization from ethanol/*n*-hexane afforded yellow needles, mp 168-169°; ir: ν cm^{-1} 2970, 2840, 1695, 1560; ms: m/z 449 (M^+); pmr: 8.51 (s, 1H, C_7-H), 8.33-7.33 (m, 4H, aromatic), 4.88 (q, J = 7 Hz, 2H, CH_2), 4.33 (q, J = 7 Hz, 2H, CH_2), 3.58 (m, 2H, CH_2), 3.39 (m, 2H, CH_2), 1.43 (t, J = 7 Hz, 3H, CH_3), 1.34 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{23}N_7O_4$: C, 58.79; H, 5.16; N, 21.81. Found: C, 58.72; H, 4.93; N, 21.75.

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