Reaction of 2-(5-Aminopyrazol-1-yl)quinoxaline 4-Oxides with Dimethyl Acetylenedicarboxylate

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The reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **6** with ethyl 2-(ethoxymethylene)-2-cyanoacetate or (1-ethoxyethylidene)malononitrile gave 2-(5-amino-4-ethoxycarbonylpyrazol-1-yl)-6-chloroquinoxaline 4-oxide **7a** or 2-(5-amino-4-cyano-3-methylpyrazol-1-yl)-6-chloroquinoxaline 4-oxide **7b**, respectively. The reaction of compound **7a** or **7b** with dimethyl acetylenedicarboxylate resulted in the 1,3-dipolar cycloaddition reaction and then ring transformation to afford 4-(5-amino-4-ethoxycarbonylpyrazol-1-yl)-8-chloro-1,2,3-tris-methoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8a** or 4-(5-amino-4-cyano-3-methylpyrazol-1-yl)-8-chloro-1,2,3-tris-methoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8b**, respectively.

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In previous papers [1,2], we reported that the 1,3-dipolar cycloaddition reaction of the quinoxaline 4-oxides **1** with dimethyl acetylenedicarboxylate gave the isoxazolo[2,3-*a*]quinoxalines **2**, whose reaction with another dimethyl acetylenedicarboxylate resulted in ring transformation to afford the pyrrolo[1,2-*a*]quinoxalines **3** presumably *via* an intermediate **A** (Chart 1) [3]. Moreover, we found that the 1,3-dipolar cycloaddition reaction of the quinoxaline 4-oxide **4** with dimethyl acetylenedicarboxylate provided the pyridazino[3,4-*b*]quinoxaline **5** presumably *via* intermediates **B** and **C** (Chart 2) [3-5]. In the above two reactions, the species **A** and **C** are similar type of intermediates. An intramolecular dehydration was predominant in an intermediate **C** to form a pyridazine ring owing to the presence of the strongly nucleophilic hydrazino group, while an intermediate **A** reacted with another dimethyl acetylenedicarboxylate to construct the pyrrolo[1,2-*a*]-quinoxaline **3**. In relation to the above results, we further examined the reaction of the 2-(5-aminopyrazolyl)quinoxaline 4-oxides **7a,b** (Scheme 1) with dimethyl acetylenedicarboxylate. Namely, this reaction would give an intermediate **D** and then **E**. Since an intermediate **E** has an amino group, an intramolecular dehydration was expected to afford a product **F**. However, an intermediate **E** reacted with another dimethyl acetylenedicarboxylate to provide the 4-pyrazolylpyrrolo[1,2-*a*]quinoxalines **8a,b**. This paper describes the synthesis of novel pyrrolo[1,2-*a*]quinoxalines **8a,b**.

Chart 1

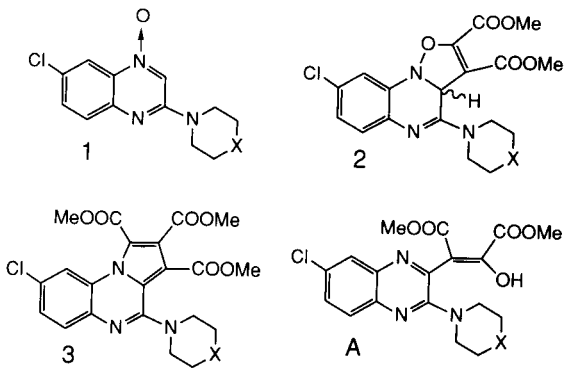
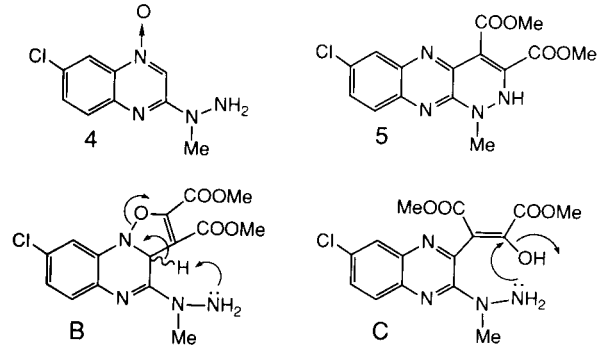
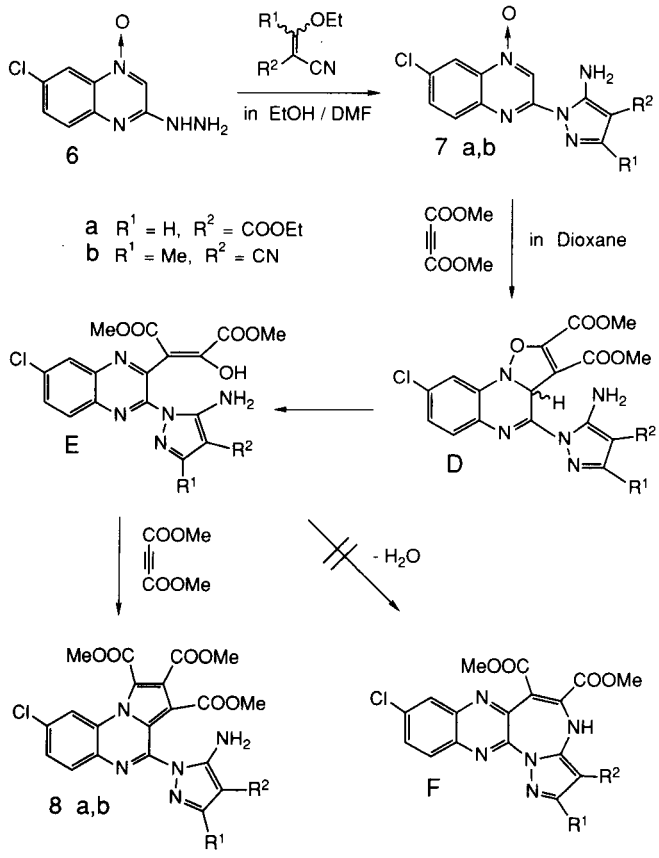


Chart 2



The reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **6** [3] with ethyl 2-(ethoxymethylene)-2-cyanoacetate or (1-ethoxyethylidene)malononitrile gave 2-(5-amino-4-ethoxycarbonylpyrazol-1-yl)-6-chloroquinoxaline 4-oxide **7a** or 2-(5-amino-4-cyano-3-methylpyrazol-1-yl)-6-chloroquinoxaline 4-oxide **7b**, repectively. The reaction of com-

Scheme 1



pound **7a** or **7b** with dimethyl acetylenedicarboxylate afforded 4-(5-amino-4-ethoxycarbonylpyrazol-1-yl)-8-chloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8a** or 4-(5-amino-4-cyano-3-methylpyrazol-1-yl)-8-chloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8b**, respectively, presumably *via* intermediates **D** and **E**. The nucleophilicity of the amino group in an intermediate **E** was not enough strong to result in an intramolecular dehydration in comparison with that of the hydrazino group in an intermediate **C** (Chart 2), and hence the species **F** was not produced.

The spectral and elemental analytical data supported the structural assignment of novel compounds **7a,b** and **8a,b**.

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 nmr spectra were measured in deuteriodimethyl sulfoxide with 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-Amino-4-ethoxycarbonylpyrazol-1-yl)-6-chloroquinoxaline 4-Oxide **7a**.

A solution of compound **6** (10 g, 47.5 mmoles) and ethyl 2-(ethoxymethylene)-2-cyanoacetate (8.70 g, 71.3 mmoles) in *N,N*-dimethylformamide (100 ml)/ethanol (300 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow prisms **7a**, which were collected by suction filtration and then washed with ethanol to give an analytically pure sample (11.61 g, 73%), mp 225-226°; ir: ν cm^{-1} 3400, 3280, 3080, 2960, 1675, 1605; ms: m/z 333 (M^+), 335 ($M^+ + 2$); pmr: 8.93 (s, 1H, C_3-H), 8.40 (d, J = 2.5 Hz, 1H, C_5-H), 8.29 (d, J = 9.0 Hz, 1H, C_8-H), 8.01 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, C_7-H), 7.90 (s, 1H, pyrazole C_3-H), 7.80 (brs, 2H, NH_2), 4.25 (q, J = 7.0 Hz, 2H, CH_2), 1.30 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{12}ClN_5O_3$: C, 50.38; H, 3.63; Cl, 10.62; N, 20.99. Found: C, 50.31; H, 3.68; Cl, 10.67; N, 20.85.

2-(5-Amino-4-cyano-3-methylpyrazol-1-yl)-6-chloroquinoxaline 4-Oxide **7b**.

A solution of compound **6** (10 g, 47.5 mmoles) and (1-ethoxyethylidene)malononitrile (7.75 g, 57.0 mmoles) in *N,N*-dimethylformamide (300 ml)/ethanol (100 ml) was refluxed on a boiling water bath for 2 hours to give a clear solution. Evaporation of the solvent *in vacuo* afforded yellow crystals **7b**, which were triturated with ethanol and then collected by suction filtration (10.53 g, 74%). Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 320-322°; ir: ν cm^{-1} 3370, 3260, 3130, 3070, 2200, 1610, 1565, 1510; ms: m/z 300 (M^+), 302 ($M^+ + 2$); pmr: 8.87 (s, 1H, C_3-H), 8.40 (d, J = 8.5 Hz, 1H, C_8-H), 8.39 (d, J = 2.5 Hz, 1H, C_5-H), 8.35 (brs, 2H, NH_2), 8.00 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, C_7-H), 2.24 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_9ClN_6O$: C, 51.93; H, 3.02; Cl, 11.79; N, 27.95. Found: C, 51.82; H, 3.02; Cl, 11.91; N, 27.75.

4-(5-Amino-4-ethoxycarbonylpyrazol-1-yl)-8-chloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8a**.

A solution of compound **7a** (5 g, 15.0 mmoles) and dimethyl acetylenedicarboxylate (4.68 g, 33.0 mmoles, 2.2-fold) in dioxane (200 ml) was refluxed in an oil bath for 1 hour to give a clear solution. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol to provide yellow needles **8a** (1.69 g, 21%).

Compound **8a** (390 mg, 25%) was also obtained in a similar manner to the above by the reaction of compound **7a** (1 g, 3.37 mmoles) with dimethyl acetylenedicarboxylate (719 mg, 5.06 mmoles, 1.5-fold molar) in dioxane (50 ml).

Compound **8a** had mp 236-237°; ir: ν cm^{-1} 3430, 3300, 3110, 2950, 1740, 1720, 1670, 1640, 1600; ms: m/z 529 (M^+), 531 ($M^+ + 2$); pmr: 8.09 (d, J = 8.5 Hz, 1H, C_6-H), 7.99 (d, J = 2.0 Hz, 1H, C_9-H), 7.79 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_7-H), 7.76 (s, 1H, pyrazole C_3-H), 7.10 (brs, 2H, NH_2), 4.25 (q, J = 7.0 Hz, 2H, CH_2), 4.05 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 1.30 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{23}H_{20}ClN_5O_8$: C, 52.13; H, 3.80; Cl, 6.69; N, 13.22. Found: C, 51.77; H, 4.15; Cl, 6.92; N, 13.37.

4-(5-Amino-4-cyano-3-methylpyrazol-1-yl)-8-chloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **8b**.

A solution of compound **7b** (5 g, 16.6 mmoles) and dimethyl acetylenedicarboxylate (5.18 g, 36.5 mmoles, 2.2-fold molar) in dioxane (200 ml) was refluxed in an oil bath for 2 hours to give a clear solution. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol/water to provide colorless needles **8b** (1.69 g, 20%).

Compound **8b** (0.46 g, 28%) was also obtained in a similar manner to the above by the reaction of compound **7b** (1 g, 3.33 mmoles) with dimethyl acetylenedicarboxylate (568 mg, 4.00 mmoles, 1.2-fold molar) in dioxane (50 ml).

Compound **8b** had mp 200-201°; ir: ν cm $^{-1}$ 3410, 3300, 2950, 2210, 1720, 1660, 1610; ms: m/z 496 (M^+), 498 ($M^+ + 2$); pmr: 8.11 (d, J = 8.5 Hz, 1H, C_6-H), 7.99 (d, J = 2.0 Hz, 1H, C_9-H), 7.76 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_7-H), 7.60 (brs, 2H, NH_2), 4.04 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 2.16 (s, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{17}ClN_6O_6$: C, 53.18; H, 3.45; Cl, 7.13; N, 16.91. Found: C, 53.22; H, 3.34; Cl, 7.26; N, 16.81.

REFERENCES AND NOTES

[1] H. S. Kim, Y. Kurasawa and A. Takada, *J. Heterocyclic Chem.*, **26**, 871 (1989).

[2] H. S. Kim, Y. Kurasawa, C. Yoshii, M. Masuyama, A. Takada and Y. Okamoto, *J. Heterocyclic Chem.*, **27**, 1115 (1990).

[3] An aziridine intermediate is not shown here.

[4] H. S. Kim, Y. Kurasawa and A. Takada, *J. Heterocyclic Chem.*, **26**, 1511 (1989).

[5] H. S. Kim, Y. Kurasawa, C. Yoshii, M. Masuyama, A. Takada and Y. Okamoto, *J. Heterocyclic Chem.*, **27**, 1111 (1990).