Synthesis of Isoxazolo[2,3-*a*]quinoxalines and Pyrrolo[1,2-*a*]quinoxalines by 1,3-Dipolar Cycloaddition Reaction [1]

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The isoxazolo[2,3-*a*]quinoxalines **11a,b** and pyrrolo[1,2-*a*]quinoxalines **12a,b** were selectively synthesized from the 2-substituted 6-chloroquinoxaline 4-oxides **10a,b**. The pyrrolo[1,2-*a*]quinoxalines **12a,b** were clarified to be produced by the ring transformation of the isoxazolo[2,3-*a*]quinoxalines **11a,b**. The pyrrolo[1,2-*a*]quinoxalines **14a,b** were obtained from both 2,6-dichloroquinoxaline 4-oxide **9** and compounds **12a,b**.

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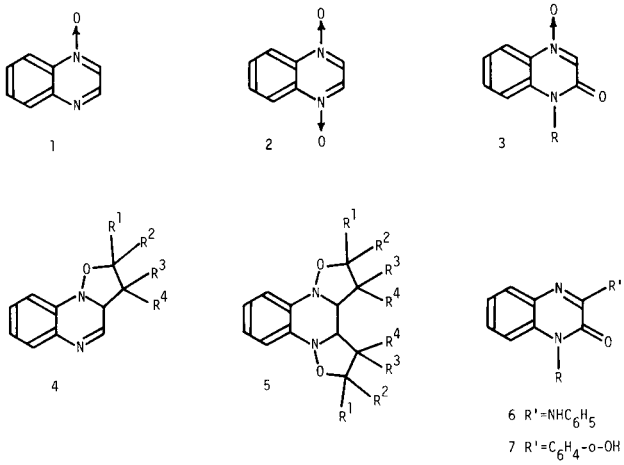
There have been many papers on the synthesis of various heterocyclic compounds utilizing the 1,3-dipolar cycloaddition reaction [3], while there have been a few papers concerning the 1,3-dipolar cycloaddition reaction of quinoxaline *N*-oxides. For example, the reaction of the quinoxaline 1-oxide **1** with dimethyl maleate or *N*-phenylmaleimide gave the isoxazolo[2,3-*a*]quinoxalines **4**, and the reaction of the quinoxaline 1,4-dioxide **2** with dimethyl acetylenedicarboxylate (DMAD) or *N*-phenylmaleimide afforded the diisoxazolo[2,3-*a*:3′,2′-*c*]quinoxalines **5** (Chart 1) [4]. On the other hand, the reaction of the quinoxaline 4-oxide **3** with phenyl isocyanate or benzyne provided the 3-anilinoquinoxaline **6** or 3-(*o*-hydroxy)phenylquinoxaline **7** *via* the decarboxylation or isomerization of intermediary condensed quinoxalines, respectively [5]. However, there have been few papers concerning the synthesis of pyrrolo[1,2-*a*]quinoxalines by the 1,3-dipolar cycloaddition reaction of quinoxaline *N*-oxides or by the ring transformation of isoxazolo[2,3-*a*]quinoxalines [6]. In the present investigation, we found that the 2-substituted 6-chloroquinoxaline 4-oxides **10** were selectively transformed into the isoxazolo[2,3-*a*]quinoxalines **11** and pyrrolo[1,2-*a*]quinoxalines **12** (Scheme 1). Moreover, the pyrrolo[1,2-*a*]quinoxalines **12** were found to be produced by the ring transformation of the isoxazolo[2,3-*a*]quinoxalines **11**. This paper describes the above selective synthesis of **11** and **12** together with a postulated mechanism for the ring transformation of **11** into **12**.

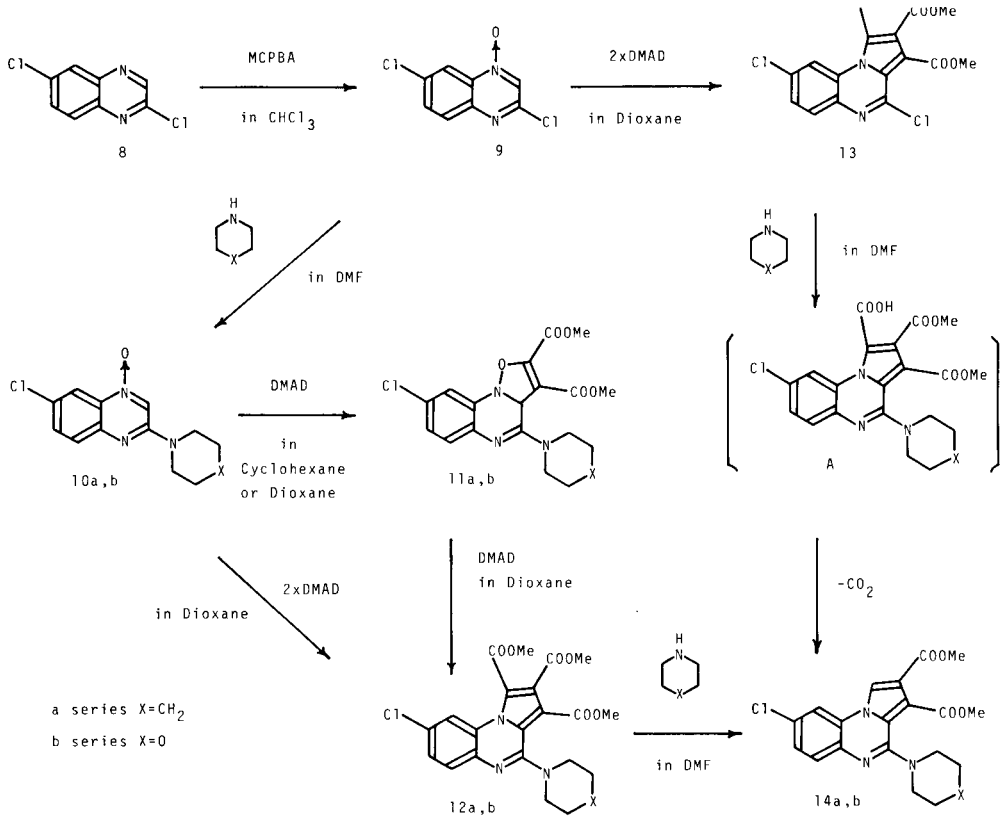
Chart 1



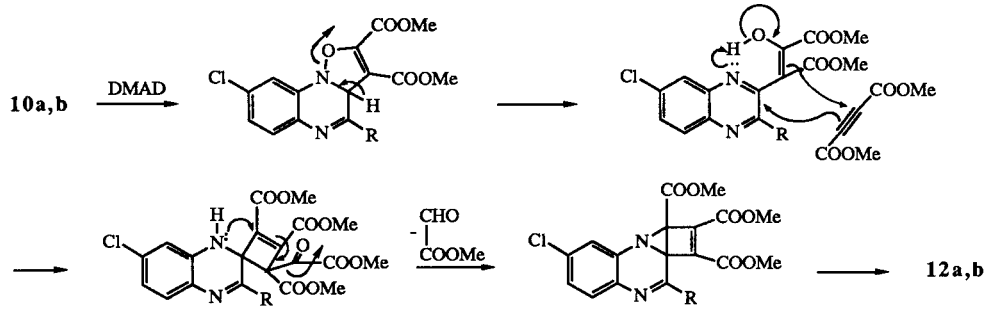
The reaction of 2,6-dichloroquinoxaline **8** [7] with *m*-chloroperbenzoic acid gave 2,6-dichloroquinoxaline 4-oxide **9**, whose reaction with piperidine or morpholine afforded 6-chloro-2-(piperidin-1-yl)quinoxaline 4-oxide **10a** or 6-chloro-2-(morpholin-4-yl)quinoxaline 4-oxide **10b**, respectively. The reaction of **10a** or **10b** with an equimolar amount of DMAD provided 8-chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11a** or 8-chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11b**, respectively. On the other hand, the reaction of **10a** or **10b** with 2-fold molar amount of DMAD furnished 8-chloro-1,2,3-trismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **12a** or 8-chloro-1,2,3-trismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **12b**, respectively. The reaction of **11a** or **11b** with an equimolar amount of DMAD resulted in ring transformation to give **12a** or **12b**, respectively.

The reaction of **8** with 2-fold molar amount of DMAD provided 4,8-dichloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **13**, while an attempt was unsuccessful to isolate 2,6-dichloro-2,3-bismethoxycarbonylisoxazolo[2,3-*a*]quinoxaline from the reaction of **8** with an equimolar amount of DMAD. The reaction of **13** with piperidine or morpholine did not produce **12a,b**, but resulted in hydrolysis and decarboxylation of the C_1-ester group to

Scheme 1



Scheme 2

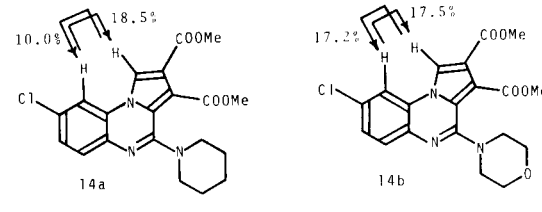


furnish 8-chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)-pyrrolo[1,2-*a*]quinoxaline **14a** or 8-chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **14b**, respectively. Moisture and secondary amine would promote the formation of intermediates **A**. Compounds **14a,b** were also obtained from **12a,b** under a similar reaction condition.

A postulated reaction mechanism for the ring transformation of **11a,b** into **12a,b** is shown in Scheme 2. The formation of **13** from **9** would also follow this mechanism.

The structural assignment for the above compounds **9-14** was based on the analytical and spectral data. The composition of the isoxazolo[2,3-*a*]quinoxalines **11a,b** was checked by the high resolution mass spectral data, since **11a,b** were rather unstable for heating and decomposed in part while recrystallization. The structure of **14a,b** was further confirmed by the NOE measurement between C_1-H

Chart 2



NOE Data for Compounds 14a,b.

and C_9-H (Chart 2). Namely, the radiation at the C_1-H or C_9-H proton signal showed 10-18.5% NOE to the C_9-H or C_1-H proton signal, respectively.

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 nmr spectra were measured in deuteriodimethyl sulfoxide 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.

2,6-Dichloroquinoxaline 4-Oxide **9**.

A solution of **8** (20 g, 0.10 mole) and *m*-chloroperbenzoic acid (27.2 g, 1.1 equivalents) in chloroform (500 ml) was refluxed on a boiling water bath for 10 hours. Removal of the solvent *in vacuo* gave crystals, which were triturated with saturated sodium bicarbonate solution to exclude *m*-chlorobenzoic acid and residual *m*-chloroperbenzoic acid. The crystals were collected by suction filtration and recrystallized from *N,N*-dimethylformamide/-ethanol provided pale yellow needles **9** (15.5 g, 72%); mp 176-178°; ir: ν cm^{-1} 3060, 1595, 1228; ms: m/z 215 (M^+), 217 ($M^+ + 2$); pmr: 8.94 (s, 1H, C_3-H), 8.35 (d, J = 2.5 Hz, 1H, C_5-H), 8.07 (d, J = 9.0 Hz, 1H, C_8-H), 7.83 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H).

Anal. Calcd. for $C_8H_4Cl_2N_2O$: C, 44.68; H, 1.87; Cl, 32.98; N, 13.03. Found: C, 44.80; H, 1.89; Cl, 32.95; N, 12.84.

6-Chloro-2-(piperidin-1-yl)quinoxaline 4-Oxide **10a** and 6-Chloro-2-(morpholin-4-yl)quinoxaline 4-Oxide **10b**.

A solution of **9** (10 g, 46.5 mmoles) and piperidine (5.94 g, 69.75 mmoles) or morpholine (6.08 g, 69.75 mmoles) in *N,N*-dimethylformamide (300 ml) was refluxed in an oil bath for 3 hours. Removal of the solvent *in vacuo* gave yellow crystals **10a** or **10b**, which were collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles **10a** (7.24 g, 59%) or **10b** (8.53 g, 69%).

Compound **10a** had mp 165-166°; ir: ν cm^{-1} 3070, 2910, 1572, 1215; ms: m/z 263 (M^+), 265 ($M^+ + 2$); pmr: 8.59 (s, 1H, C_3-H), 8.14 (d, J = 2.0 Hz, 1H, C_5-H), 7.66-7.55 (m, 2H, C_7-H and C_8-H), 3.68 (t, J = 4.5 Hz, 4H, CH_2-N-CH_2), 1.69-1.51 (m, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; Cl, 13.44; N, 15.93. Found: C, 59.30; H, 5.48; Cl, 13.23; N, 15.65.

Compound **10b** had mp 152-153°; ir: ν cm^{-1} 3070, 2940, 1570, 1220; ms: m/z 265 (M^+), 267 ($M^+ + 2$); pmr: 8.64 (s, 1H, C_3-H), 8.17 (d, J = 2.0 Hz, 1H, C_5-H), 7.71-7.58 (m, 2H, C_7-H and C_8-H), 3.75-3.62 (m, 8H, morpholine CH_2).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; Cl, 13.34; N, 15.82. Found: C, 54.24; H, 4.52; Cl, 13.49; N, 15.65.

8-Chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)-3a*H*-isoxazolo-[2,3-*a*]quinoxaline **11a**.

A suspension of **10a** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (1.2 g, 8.36 mmoles) in cyclohexane (200 ml) was refluxed on a boiling water bath for 1 hour to precipitate red needles **11a**, which were collected by suction filtration and then triturated with ethanol (drying: below 80° *in vacuo*) (3.02 g, 98%), mp 224-225°; ir: ν cm^{-1} 3050, 2920, 1730, 1655, 1595; ms: m/z 405 (M^+), 407 ($M^+ + 2$); pmr: 9.35 (s, 1H), 7.90 (s, 2H), 7.70 (s, 1H) (C_{3a}-H, C_6-H, C_7-H and C_9-H), 3.85 (s, 4H, CH_2-N-CH_2), 3.79 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 1.65 (s, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{19}H_{20}ClN_3O_5$: 405.109 (M^+), 407.106 ($M^+ + 2$). Found: 405.110 (M^+), 407.105 ($M^+ + 2$).

8-Chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11b**.

A suspension of **10b** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (1.19 g, 8.36 mmoles) in dioxane (60 ml) was refluxed in an oil bath for 1 hour to precipitate red needles **11b**, which were collected by suction filtration and then triturated with ethanol (drying: below 50° *in vacuo*) (2.97 g, 96%), mp 238-239°; ir: ν cm^{-1} 3050, 2940, 1730, 1658, 1595; ms: m/z 407 (M^+), 409 ($M^+ + 2$); pmr: 9.35 (s, 1H), 7.92 (s, 2H), 7.73 (s, 1H) (C_{3a}-H, C_6-H, C_7-H and C_9-H), 3.85 (s, 4H, CH_2-N-CH_2), 3.78 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.52 (s, 4H, CH_2-O-CH_2).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_6$: 407.088 (M^+), 409.085 ($M^+ + 2$). Found: 407.085 (M^+), 409.082 ($M^+ + 2$).

8-Chloro-1,2,3-trismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo-[1,2-*a*]quinoxaline **12a** and 8-Chloro-1,2,3-trismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **12b**.

A solution of **10a** (2 g, 7.6 mmoles) or **10b** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (2.35 g, 16.7 mmoles) in dioxane (60 ml) was refluxed in an oil bath for 6 hours. Removal of the solvent *in vacuo* afforded crystals, which were triturated with ethanol/hexane and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/water provided colorless needles **12a** (1.06 g, 30%) or **12b** (0.94 g, 27%).

Compound **12a** had mp 152-153°; ir: ν cm^{-1} 3120, 2940, 1730, 1710, 1598; ms: m/z 459 (M^+), 461 ($M^+ + 2$); pmr: 7.69 (d, J = 2.0 Hz, 1H, C_9-H), 7.68 (d, J = 9.0 Hz, 1H, C_6-H), 7.53 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C_7-H), 4.02 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.28 (s, 4H, CH_2-N-CH_2), 1.58 (s, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{22}H_{22}ClN_3O_6$: C, 57.46; H, 4.82; Cl, 7.71; N, 9.14. Found: C, 57.53; H, 4.85; Cl, 8.01; N, 9.25.

Compound **12b** had mp 164-166°; ir: ν cm^{-1} 3110, 2950, 1725, 1710, 1598; ms: m/z 461 (M^+), 463 ($M^+ + 2$); pmr: 7.72 (d, J = 9.0 Hz, 1H, C_6-H), 7.71 (d, J = 2.5 Hz, 1H, C_9-H), 7.57 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, C_7-H), 4.04 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.70 (t, J = 4.5 Hz, 4H, CH_2-O-CH_2), 3.29 (t, J = 4.5 Hz, 4H, CH_2-N-CH_2).

Anal. Calcd. for $C_{21}H_{20}ClN_3O_7$: C, 54.61; H, 4.37; Cl, 7.68; N, 9.10. Found: C, 54.56; H, 4.39; Cl, 7.68; N, 9.22.

Ring Transformation of **11a,b** into **12,b**.

A solution of **11a** or **11b** (2 g) and dimethyl acetylenedicarboxylate (0.77 g, 1.1-fold) in dioxane (60 ml) was refluxed in an oil bath for 7 hours. Removal of the solvent *in vacuo* afforded crystals, which were triturated with ethanol and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/water gave colorless needles **12a** (0.45 g, 20%) or **12b** (0.75 g, 33%).

4,8-Dichloro-1,2,3-trismethoxycarbonylpyrrolo[1,2-*a*]quinoxaline **13**.

A solution of **9** (5 g, 23.26 mmoles) and dimethyl acetylenedicarboxylate (7.26 g, 51.17 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 4 hours. Evaporation of the solvent *in vacuo* gave colorless crystals, which were triturated with ethanol/hexane

and then collected by suction filtration (2.1 g, 22%). Recrystallization from ethanol/hexane provided colorless needles, mp 200-202°; ir: ν cm^{-1} 2950, 1730, 1680, 1610; ms: m/z 410 (M^+), 412 ($M^+ + 2$); pmr: 7.96 (d, J = 8.5 Hz, 1H, C_6-H), 7.74 (d, J = 8.5 Hz, J = 2.0 Hz, 1H, C_7-H), 7.70 (d, J = 2.0 Hz, 1H, C_9-H), 4.09 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 3.87 (s, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_6$: C, 49.66; H, 2.94; Cl, 17.24; N, 6.81. Found: C, 49.88; H, 2.92; Cl, 17.08; N, 6.88.

8-Chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]-quinoxaline **14a** and 8-Chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **14b**.

A solution of **13** (1 g, 2.43 mmoles) and piperidine (620 mg, 7.29 mmoles) or morpholine (634 mg, 7.29 mmoles) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* gave an oily substance, which was dissolved in hot ethanol. Cooling of the solution to room temperature precipitated colorless needles **14a** or **14b**, which were collected by suction filtration, yield, **14a** (340 mg, 35%), **14b** (460 mg, 47%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded colorless needles **14a** and colorless prisms **14b**.

Compound **14a** had mp 214-215°; ir: ν cm^{-1} 1735, 1690; ms: m/z 401 (M^+), 403 ($M^+ + 2$); pmr: 9.02 (s, 1H, C_1-H), 8.57 (d, J = 2.1 Hz, 1H, C_9-H), 7.66 (d, J = 8.5 Hz, 1H, C_6-H), 7.45 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, C_7-H), 3.88 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.24 (s, 4H, CH_2-N-CH_2), 1.59 (s, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; Cl, 8.82; N, 10.46. Found: C, 59.57; H, 5.05; Cl, 8.77; N, 10.45.

Compound **14b** had mp 225-226°; ir: ν cm^{-1} 1730, 1710; ms: m/z 403 (M^+), 405 ($M^+ + 2$); pmr: 9.08 (s, 1H, C_1-H), 8.62 (d, J = 2.3 Hz, 1H, C_9-H), 7.66 (d, J = 8.5 Hz, 1H, C_6-H), 7.49 (dd, J = 8.5 Hz, J = 2.3 Hz, 1H, C_7-H), 3.88 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.70 (t, J = 4.0 Hz, 4H, CH_2-O-CH_2), 3.26 (t, J = 4.0 Hz, 4H, CH_2-N-CH_2).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49: Cl, 8.78; N, 10.41. Found: C, 56.46; H, 4.53; Cl, 8.85; N, 10.39.

Synthesis of **14a,b** from **12a,b**.

A suspension of **12a** (500 mg, 1.08 mmole) and piperidine (277 mg, 3.26 mmoles) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* gave an oily substance, which was dissolved in hot ethanol/water. Cooling of the solution to room temperature precipitated colorless needles **14a**, which were collected by suction filtration (370 mg, 79%).

The reaction of **12b** (500 mg, 1.08 mmole) and morpholine (284 mg, 3.25 mmoles) in *N,N*-dimethylformamide (30 ml) under a similar condition to the above provided **14b** as colorless prisms (400 mg, 92%).

REFERENCES AND NOTES

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

[2] Present address: Department of Chemistry, Teacher's College, Hyosung Women's University, Gyongsan 713-900, Korea.

[3] A. Padwa, 1,3-Dipolar Cycloaddition Chemistry, Vols **I**, **II**, E. C. Taylor and A. Weissberger, eds, John Wiley and Sons, New York, Chichester, Brisbane, Toronto, Singapore, 1984; D. P. Curran, Advances in Cycloaddition, Vol **I**, D. P. Curran, ed, JAI Press Inc., Connecticut, London, 1988, and references cited therein.

[4] M. Ungreanu, I. Druta and I. Zugravescu, *An. Stiint. Univ.* "Al. I. Cuza" Iasi, Sect. 1c, **20**, 29 (1974); *Chem. Abstr.*, **82**, 125351q (1975).

[5] J. C. Mason and G. Tennant, *J. Chem. Soc., Chem. Commun.*, 218 (1972).

[6] G. W. H. Cheeseman and R. F. Cookson, The Chemistry of Heterocyclic Compounds. Condensed Pyrazines, A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, New York, Chichester, Brisbane, Toronto, 1977, pp 598-622, and references cited therein.

[7] K. Makino, G. Sakata, K. Morimoto and Y. Ochiai, *Heterocycles*, **23**, 2025 (1985).