A Convenient Synthesis of 1,2,4-Triazolo[4,3,2-*o,p*]-[1,3]diazocino[4,5-*b*]quinoxalines *via* a 1,3-Dipolar Cycloaddition Reaction and a Ring Transformation

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The reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **5** with triethyl orthoformate gave 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **6**. The reaction of compound **6** with phenyl isocyanate afforded 7-chloro-4-phenylamino-1,2,4-triazolo[4,3-*a*]quinoxaline **7**, while the reaction of compound **6** with phenyl isothiocyanate resulted in deoxygenation to provide 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline **8**. However, the reaction of compound **6** with allyl isothiocyanate effected the 1,3-dipolar cycloaddition reaction, but not deoxygenation, to furnish 9-chloro-4,5-dihydroisoxazolo[2,3-*a*][1,2,4]triazolo[3,4-*c*]quinoxalin-5-ylmethylisothiocyanate **9**. Moreover, the reduction of compound **9** with iron/acetic acid resulted in ring transformation to give 11-chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **10**, whose acetylation afforded 5-acetyl-11-chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **11**.

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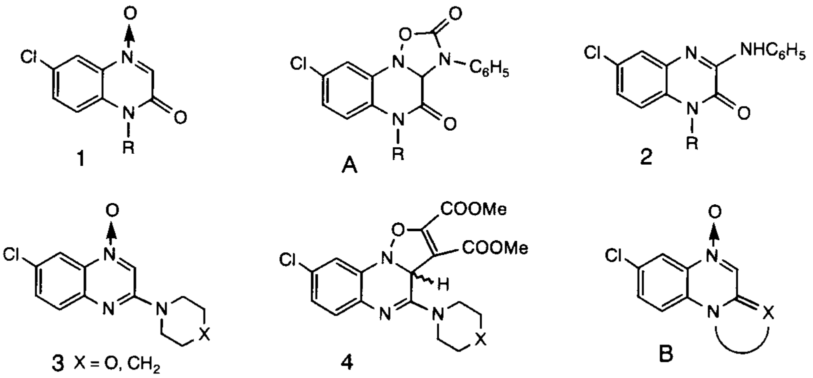
Mason *et al.* [1] reported that the 1,3-dipolar cycloaddition reaction of the 1,2-dihydro-2-oxoquinoxaline 4-oxide **1** with phenyl isocyanate gave the 3-phenylamino-1,2-dihydro-2-oxoquinoxaline **2** *via* an intermediate **A**, and our previous work [2] represented that the 1,3-dipolar cycloaddition reaction of the quinoxaline 4-oxides **3** with dimethyl acetylenedicarboxylate afforded the isoxazolo[2,3-*a*]quinoxalines **4**. However, the quinoxaline 4-oxides **3** did not react with phenyl isocyante or olefins, but recovered the starting material. These results indicate that the lactam type of quinoxaline *N*-oxide **1** is much more active than the aromatic quinoxaline *N*-oxides **3** in the reaction with some dipolarophiles. Accordingly, we have undertaken the synthesis of the starting material such as a species **B** (Chart 1), which is structurally analogous to the 1,2-dihydro-2-oxoquinoxaline 4-oxide **1**, in order to extend the scope of our works on the 1,3-dipolar cycloaddition reaction of quinoxaline *N*-oxides. Thus, 7-chloro-1,2-4-triazolo-[4,3-*a*]quinoxaline 5-oxide **6** (Scheme) was prepared as a starting material from a known compound **5** [3]. As was expected, compound **6** was found to be active as much as the 1,2-dihydro-2-oxoquinoxaline 4-oxide **1** in the reaction

Chart 1



Scheme

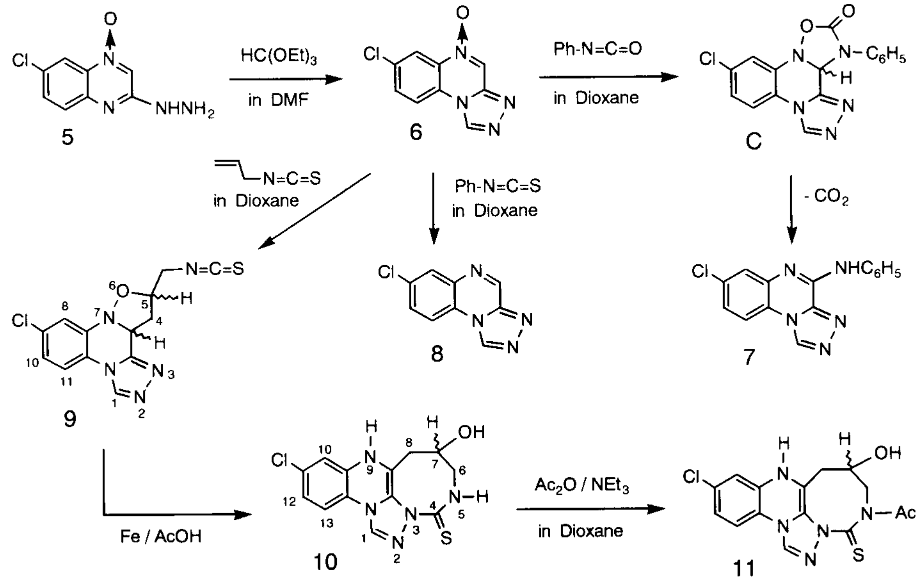
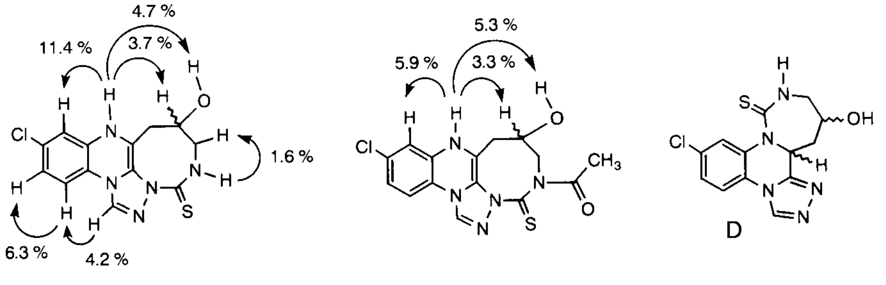


Chart 2



NOE Data for Compound 10

NOE Data for Compound 11

with phenyl isocyanate. Moreover, the reaction of compound **6** with allyl isothiocyanate resulted in the 1,3-dipolar cycloaddition reaction to furnish the isoxazolo[2,3-*a*]-[1,2,4]triazolo[3,4-*c*]quinoxaline **9**, whose reductive ring transformation gave the 1,2,4-triazolo[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **10** having a new ring system. This paper describes the synthesis of novel compounds **7**, **9**, **10** and **11** *via* the 1,3-dipolar cycloaddition reaction and/or ring transformation.

The reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **5** with triethyl orthoformate gave 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **6**. The reaction of compound **6** with phenyl isocyanate effected the 1,3-dipolar cycloaddition reaction and then decarboxylation [1] to afford 7-chloro-4-phenylamino-1,2,4-triazolo[4,3-*a*]quinoxaline **7**, while the reaction of compound **6** with phenyl isothiocyanate resulted in deoxygenation [4] to provide 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline **8** [5]. On the other hand, the reaction of compound **6** with allyl isothiocyanate effected the 1,3-dipolar cycloaddition reaction, but not deoxygenation, to furnish 9-chloro-4,5-dihydroisoxazolo[2,3-*a*][1,2,4]triazolo[3,4-*c*]quinoxalin-5-ylmethylisothiocyanate **9**, whose subsequent reduction with iron/acetic acid resulted in ring transformation to give 11-chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo[4,3,2-*o,p*][1,3]-diazocino[4,5-*b*]quinoxaline **10**. The reaction of compound **10** with acetic anhydride/triethylamine afforded 5-acetyl-11-chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **11**.

The structure of new compounds **6**, **7**, **9**, **10** and **11** was assigned by the analytical and spectral data. Especially, the ir spectrum of compound **9** showed the strong isothiocyanate absorption bands between 2230 and 2040 cm^{-1}, branching at 2230, 2160, 2120 and 2040 cm^{-1}. Furthermore, the NOE spectral data of compounds **10** and **11** excluded the structure of a species **D** (Chart 2). The isothiocyanate carbon signal of compound **9**, thione carbon signals of compounds **10**, **11**, and carbonyl carbon signal of compound **11** were observed at δ 124.12, 187.71, 185.42 and 170.66 ppm, respectively.

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.

7-Chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-Oxide **6**.

A solution of compound **5** (10 g, 47.5 mmoles) and triethyl orthoformate (50 ml) in *N,N*-dimethylformamide (150 ml) was refluxed in an oil bath for 3 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate yellow needles **6**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to afford an analytically pure sample (7.25 g). Evaporation of the filtrate *in vacuo* furnished an additional yellow needles **6**, which were triturated with ethanol and then collected by suction filtration (1.50 g), total yield (8.75 g, 83%).

Compound **6** had mp 298-299°; ir: ν cm^{-1} 3100, 3060, 2990, 1615, 1600, 1525, 1500; ms: m/z 220 (M^+), 222 (M^+ +2); pmr: 10.00 (s, 1H, C_1-H), 9.30 (s, 1H, C_4-H), 8.54 (d, J = 9.0 Hz, 1H, C_9-H), 8.43 (d, J = 2.0 Hz, 1H, C_6-H), 8.07 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H, C_8-H).

Anal. Calcd. for $C_9H_5ClN_4O$: C, 49.00; H, 2.28; Cl, 16.07; N, 25.40. Found: C, 49.28; H, 2.33; Cl, 16.33; N, 25.30.

7-Chloro-4-phenylamino-1,2,4-triazolo[4,3-*a*]quinoxaline **7**.

A solution of compound **6** (2 g, 9.07 mmoles) and phenyl isocyanate (1.62 g, 13.6 mmoles) in dioxane (100 ml) was refluxed in an oil bath for 1 hour to give a clear solution. The solvent was evaporated *in vacuo* to afford colorless crystals, whose recrystallization from dioxane/water provided colorless needles **7** as the half hydrate (1.16 g, 43%), mp 268-269°; ir: ν cm^{-1} 3380, 3090, 1600, 1580, 1560, 1525, 1500; ms: m/z 295 (M^+), 297 (M^+ +2); pmr: 10.36 (s, 1H, NH), 10.00 (s, 1H, C_1-H), 8.21 (d, J = 8.5 Hz, 1H, C_9-H), 8.17 (d, J = 7.5 Hz, 2H, C_4-anilino o-H), 7.70 (d, J = 2.5 Hz, 1H, C_6-H), 7.44 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, C_8-H), 7.37 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H, C_4-anilino m-H), 7.10 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, C_4-anilino p-H).

Anal. Calcd. for $C_{15}H_{10}ClN_5 \cdot 1/2H_2O$: C, 59.12; H, 3.64; Cl, 11.63; N, 22.98. Found: C, 59.35; H, 3.45; Cl, 11.76; N, 23.19.

7-Chloro-1,3,4-triazolo[4,3-*a*]quinoxaline **8**.

A solution of compound **6** (1 g, 4.55 mmoles) and phenyl isothiocyanate (737 mg, 5.46 mmoles) in dioxane (50 ml) was refluxed in an oil bath for 1 hour to give a clear solution. Evaporation of the solvent *in vacuo* afforded yellow needles **8**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (620 mg, 67%). The ir spectrum of this sample was identical with that of an authentic sample [5].

9-Chloro-4,5-dihydroisoxazolo[2,3-*a*][1,2,4]triazolo[3,4-*c*]quinoxalin-5-ylmethylisothiocyanate **9**.

A solution of compound **6** (5 g, 22.7 mmoles) and allyl isothiocyanate (2.69 g, 27.2 mmoles) in dioxane (250 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, whose crystallization from dioxane/*n*-hexane provided yellow needles **9** (4.56 g, 63%), mp 180-181°; ir: ν cm^{-1} 2230, 2160, 2120, 2040, 1600, 1530, 1500; ms: m/z 319 (M^+), 321 (M^+ +2); pmr: 9.44 (s, 1H, C_1-H), 7.87 (d, J = 8.5 Hz, 1H, C_{11}-H), 7.39 (d, J = 2.0 Hz, 1H, C_8-H), 7.30 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_{10}-H), 5.10 (dd, J = 9.5 Hz, J = 9.5 Hz, 1H, C_{3b}-H), 4.52 (m, 1H, C_5-H), 4.09 (dd, J = 15 Hz, J = 4.5 Hz, 1H, methylene H), 4.03 (dd, J = 15 Hz, J = 4.5 Hz, 1H, methylene H), 2.53 (ddd, J = 12.0 Hz, J = 9.5 Hz, J = 4.5 Hz, 1H, C_4-H), 2.44 (ddd, J = 12.0 Hz, J = 9.5 Hz, J = 4.5 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{13}H_{10}ClN_5OS$: C, 48.83; H, 3.15; Cl, 11.09; N, 21.90; S, 10.03. Found: C, 48.96; H, 3.37; Cl, 11.00; N, 21.83; S, 9.87.

11-Chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo-[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **10**.

Stepwise Synthesis from Compound **9**.

A mixture of compound **9** (5 g, 15.6 mmoles) and iron powder (10 g) in acetic acid (200 ml) was refluxed in an oil bath for 2 hours. The solution was filtered, and the filtrate was evaporated *in vacuo* to give an oily residue, which was dissolved in ethanol (250 ml). Sodium bicarbonate (10 g) was added to the solution, and the mixture was refluxed on a boiling water bath for 1 hour to precipitate colorless crystals **10**. A mixture of colorless crystals **10** and residual sodium bicarbonate was collected by suction filtration and then washed with 10% aqueous acetic acid solution until the generation of carbon dioxide ceased, affording colorless crystals **10** (2.27 g). The filtrate of the above ethanol solution was evaporated *in vacuo* to provide colorless crystals **10**, which were triturated with hot ethanol and then collected by suction filtration (0.96 g), total yield 3.23 g (64%). Recrystallization from ethanol/water gave colorless needles.

One-pot Synthesis from Compound **6**.

A solution of compound **6** (5 g, 22.7 mmoles) and allyl isothiocyanate (3.37 g, 34.1 mmoles) in dioxane (250 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 dissolved in acetic acid (200 ml). Iron powder (10 g) was added to the solution, and the mixture was refluxed in an oil bath for 2 hours. The solution was filtered, and the filtrate was evaporated *in vacuo* to provide an oily residue, which was dissolved in ethanol (250 ml). Sodium bicarbonate (10 g) was added to the solution, and the mixture was refluxed on a boiling water bath for 1 hour. The solution was filtered, and the filtrate was evaporated *in vacuo* to furnish colorless crystals **10**, which were triturated with ethanol and then collected by suction filtration (2.94 g, 40%).

Compound **10** had mp 271-272°; ir: ν cm^{-1} 3260, 3100, 3040, 1610, 1540, 1520, 1500; ms: m/z 321 (M^+), 323 (M^+ +2); pmr: 9.97 (s, 1H, N_5-H), 9.29 (s, 1H, C_1-H), 7.68 (d, J = 8.5 Hz, 1H, C_{13}-H), 7.08 (s, 1H, N_9-H), 6.97 (d, J = 2.0 Hz, 1H, C_{10}-H), 6.83 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_{12}-H), 5.18 (m, 1H, C_7-H), 4.96 (d, J = 6.0 Hz, 1H, C_7-OH), 3.82 (dd, J = 10.0 Hz, J = 8.5 Hz, 1H, C_8-H), 3.39 (dd, J = 10.0 Hz, J = 8.5 Hz, 1H, C_8-H), 2.29 (ddd, J = 14.3 Hz, J = 8.5 Hz, J = 4.1 Hz, 1H, C_6-H), 2.14 (ddd, J = 14.3 Hz, J = 8.5 Hz, J = 4.1 Hz, 1H, C_6-H).

Anal. Calcd. for $C_{13}H_{12}ClN_5OS$: C, 48.52; H, 3.76; Cl, 11.02; N, 21.77; S, 9.96. Found: C, 48.42; H, 3.56; Cl, 11.21; N, 21.63; S, 9.88.

5-Acetyl-11-chloro-7-hydroxy-4-thioxo-4,5,6,7,8,9-hexahydro-1,2,4-triazolo[4,3,2-*o,p*][1,3]diazocino[4,5-*b*]quinoxaline **11**.

A solution of compound **10** (1 g, 3.11 mmoles), acetic anhydride (5 ml) and triethylamine (0.5 ml) in dry dioxane (45 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave colorless crystals, whose recrystallization from ethanol afforded colorless needles **11** (380 mg, 33%) as the half hydrate, mp 227-228°; ir: ν cm^{-1} 3260, 3100, 3050, 1705, 1610; ms: m/z 363 (M$^+$), 365 (M$^+$ +2); pmr: 9.29 (s, 1H, C_1-H), 7.69 (d, J = 8.5 Hz, 1H, C_{13}-H), 7.10 (br, 1H, N_9-H), 6.97 (d, J = 2.0 Hz, 1H, C_{10}-H), 6.84 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_{12}-H), 5.13 (m, 1H, C_7-H), 5.01 (br, 1H, C_7-OH), 4.30 (dd, J = 11.0 Hz, J = 8.5 Hz, 1H, C_8-H), 3.86 (dd, J = 11.0 Hz, J = 8.0 Hz, 1H, C_8-H), 2.68 (s, 3H, N_5-$COCH_3$), 2.38 (ddd, J = 14.5 Hz, J = 9.0 Hz, J = 4.5 Hz, 1H, C_6-H), 2.24 (ddd, J = 14.5 Hz, J = 8.5 Hz, J = 4.5 Hz, 1H, C_6-H).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_2S\cdot 1/2H_2O$: C, 48.32; H, 4.06; Cl, 9.51; N, 18.78; S, 8.60. Found: C, 48.75; H, 3.75; Cl, 9.46; N, 18.81; S, 8.45.

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