Synthesis of Mesoionic Triazolo[4,3-*a*]quinoxalines

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The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** or 6-chloro-2-(1-methylhydrazino)quinoxaline **5** with phenyl isothiocyanate under reflux in *N,N*-dimethylformamide gave 7-chloro-3-methyl-1,2,4-triazolo[4,3-*a*]quinoxalin-3-ium-1-thioate **4**, which was also obtained by refluxing of 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **2b** or 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline **6** in *N,N*-dimethylformamide.

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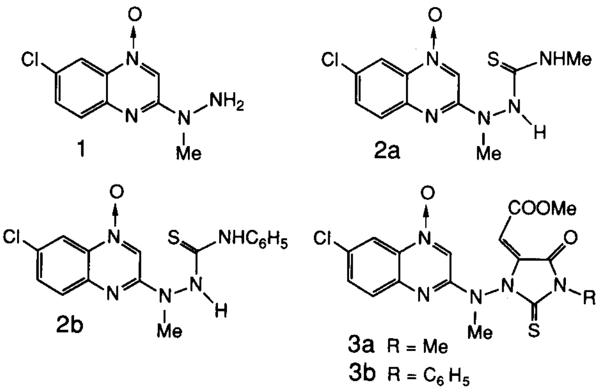
In a previous paper [1], we reported that the reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with methyl isothiocyanate under reflux in dioxane or with phenyl isothiocyanate under reflux in chloroform/ethanol gave 6-chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **2a** or 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline **2b**, respectively, whose reaction with dimethyl acetylenedicarboxylate under reflux in ethanol provided the 6-chloro-2-(*N*-imidazolidinyl)aminoquinoxaline 4-oxides **3a** and **3b**, respectively (Chart 1). In the above synthesis, an attention had to be paid to a preparation of compound **2b**, because this compound was labile at a high temperature to change into a red colored substance. Namely, refluxing of compound **2b** at a high temperature furnished red crystals, and compound **2b** was observed to turn from yellow to red on a melting point measurement. Thus, compound **2b** had to be synthesized under reflux in chloroform/ethanol, although compound **2a** was rather stable when it was refluxed in dioxane. In the present investigation, we studied the above conversion of compound **2b** into the red colored substance. As the result, this red colored substance was found to be the deoxygenated mesoionic compound **4** (Scheme 1). This paper describes the synthesis and structural elucidation of the mesoionic triazolo[4,3-*a*]quinoxaline **4**.

Chart 1



Scheme 1

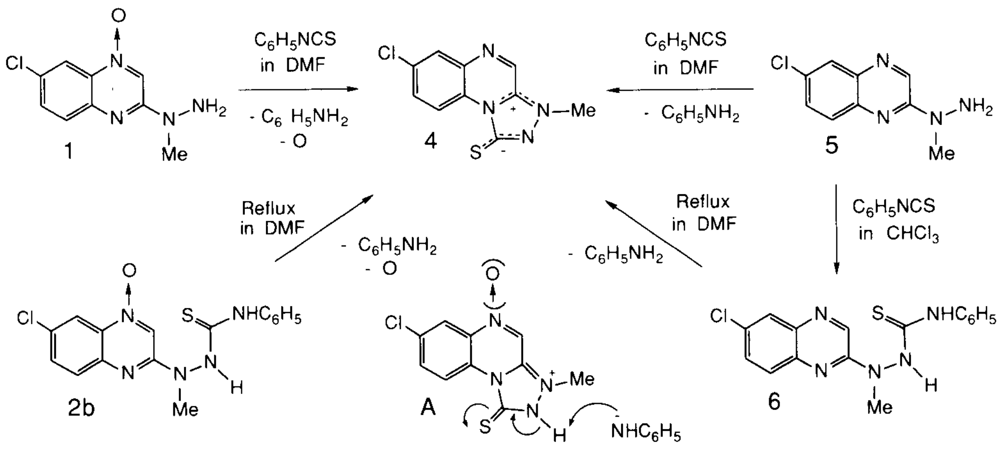


Table 1

Yield of Compound **4** Under Various Reaction Conditions

Method	Starting Material	Molar Ratio of Phenyl Isothiocycnate	Yield of Compound **4** (%)
I	**1**	1.2	55
IIa	**2b**	0 [a]	32
IIb	**2b**	0 [b]	49
IIc	**2b**	1.5	77
III	**5**	1.2	81
IV	**6**	0	80

[a] Reflux in *N,N*-dimethylformamide. [b] Reaction of compound **4** with triphenylphosphine under reflux in *N,N*-dimethylformamide.

Table 2

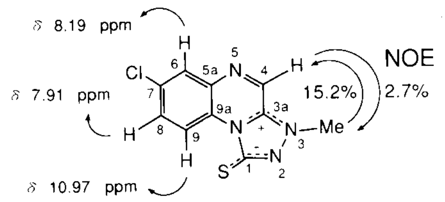
Carbon Chemical Shifts for Compound **4**

Carbon No.	Chemical Shift [a]
1	164.37
3a	126.15
4	139.42
5a	137.52
6	128.41
7	131.95
8	129.45
9	117.83
9a	135.50
Me	36.49

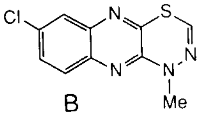
[a] Assigned by the ^{13}C-^{1}H COSY, long range ^{13}C-^{1}H COSY and LSPD spectral data.

The reaction of compound **1** with phenyl isothiocyanate under reflux in *N,N*-dimethylformamide gave 7-chloro-3-methyl-1,2,4-triazolo[4,3-*a*]quinoxalin-3-ium-1-thioate **4** (Method I, 55%), which was also obtained by refluxing of compound **2b** in *N,N*-dimethylformamide (Method IIa, 32%) (Table 1). These reactions would proceed *via* an intermediate **A**. The yield of compound **4** from compound **2b** under reflux in *N,N*-dimethylformamide was improved by addition of triphenylphosphine (Method IIb, 49%) or by addition of phenyl isothiocyanate (Method IIc, 77%). The structural assignment of compound **4** was based on the analytical and spectral data. In the pmr spectral data of compound **4**, the C_9-H proton signal was observed in a much lower magnetic field than that of the C_6-H and C_8-H proton signals presumably due to the anisotropy or steric compression effect by the C-S moiety (Chart 2). Moreover, the NOE was observed between the C_3-methyl and C_4-H proton signals. In the ^{13}C-nmr spectrum of compound **4**, the C_1-S carbon signal was observed at δ 164.37 ppm (Table 2), while the C=S carbon signal of compound **2b** was observed at δ 180.98 ppm. These data left no doubt for the structure of compound **4**, excluding the structure of a species **B** (Chart 2).

Chart 2



4



B

^{1}H-Chemical Shift and NOE Data for Compound 4

In order to ascertain the production of compound **4** concomitant with deoxygenation, its alternate synthesis was carried out as described below. The reaction of 2,6-dichloroquinoxaline [2] with methyl hydrazine gave 6-chloro-2-(1-methylhydrazino)quinoxaline **5**, whose reaction with phenyl isothiocyanate under reflux in *N,N*-dimethylformamide afforded compound **4** (Method III, 81%). On the other hand, the reaction of compound **5** with phenyl isothiocyanate under reflux in chloroform provided 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline **6**, whose subsequent refluxing in *N,N*-dimethylformamide furnished compound **4** (Method IV, 80%).

The yield of compound **4** in Method III is similar to that in Method IV, but the yield of compound **4** in Method I is 1.7-fold as much as that in Method IIa (Table 1). However, the yield of compound **4** was improved by addition of triphenylphosphine (Method IIb) or phenyl isothiocyanate (Method IIc). These results suggest that phenyl isothiocyanate participates the deoxygenation mechanism, and phenyl isothiocyanate is superior to triphenylphosphine as a deoxygenation agent in this case.

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 with VXR-300 spectrometer at 300 MHz. Chemical shifts are given in δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Microanalyses were performed on a Perkin-Elmer 240B instrument.

7-Chloro-3-methyl-1,2,4-triazolo[4,3-*a*]quinoxalin-3-ium-1-thioate **4**.

Method I.

A solution of compound **1** (5 g, 22.3 mmoles) and phenyl isothiocyanate (4.52 g, 33.5 mmoles) in *N,N*-dimethylformamide (80 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave orange needles **4**, which was triturated with hot ethanol and then collected by suction filtration (4.22 g, 55%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded orange-red needles.

Method IIa.

A solution of compound **2b** (5 g) in *N,N*-dimethylformamide (80 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave orange crystals **4**, which were triturated with hot ethanol and then collected by suction filtration (1.52 g, 32%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange-red needles.

Method IIb.

A solution of compound **2b** (5 g, 13.9 mmoles) and triphenylphosphine (5.48 g, 20.9 mmoles) in *N,N*-dimethylformamide (80 ml) was refluxed in an oil bath for 5 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate orange-red needles **4**, which were collected by suction filtration (1.02 g). An addition of *n*-hexane and ethanol to the filtrate precipitate orange-red needles **4**, which were collected by suction filtration (0.69 g), total yield 1.69 g (49%).

Method IIc.

A solution of compound **2b** (10 g, 27.8 mmoles) and phenyl isothiocyanate (5.63 g, 41.7 mmoles) in *N,N*-dimethylformamide (80 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave orange-red needles **4**, which were triturated with hot ethanol and then collected by suction filtration (5.35 g, 77%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded orange-red needles.

Method III.

A solution of compound **5** (5 g, 24.0 mmoles) and phenyl isothiocyanate (3.89 g, 28.8 mmoles) in *N,N*-dimethylformamide (80 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate orange-red needles **4**, which were collected by suction filtration and then washed with ethanol to provide an analytically pure sample (4.86 g, 81%).

Method IV.

Compound **4** was obtained in a similar manner to that described in Method III by refluxing of compound **6** (5 g) in *N,N*-dimethylformamide (80 ml) for 2 hours. The yield was 2.80 g (80%).

Compound **4** had mp 314-315°; ir: ν cm^{-1} 1595, 1570, 1545, 1475, 1430; ms: m/z 250 (M$^+$), 252 (M$^+$ + 2); pmr: 10.97 (d, J = 9.0 Hz, 1H, C$_9$-H), 9.52 (s, 1H, C$_4$-H), 8.19 (d, J = 2.5 Hz, 1H, C$_6$-H), 7.91 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, C$_8$-H), 4.17 (s, 3H, NCH$_3$).

Anal. Calcd. for $C_{10}H_7ClN_4S$: C, 47.91; H, 2.82; Cl, 14.14; N, 22.35; S, 12.79. Found: C, 47.96; H, 2.79; Cl, 14.13; N, 22.15; S, 12.89.

6-Chloro-2-(1-methylhydrazino)quinoxaline **5**.

A solution of 2,6-dichloroquinoxaline (30 g, 150.8 mmoles) and methylhydrazine (15.26 g, 331.8 mmoles) in chloroform (500 ml) was refluxed on a boiling water bath for 4 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **5**. The crystals were recrystallized from ethanol/water to provide yellow needles, which were collected by suction filtration (22.33 g). Evaporation of the filtrate *in vacuo* and a similar treatment to the above furnished additional yellow needles **5** (6.63 g), total yield 28.96 g (92%).

Compound **5** had mp 128-129°; ir: ν cm^{-1} 3300, 3170, 1959, 1570, 1545; ms: m/z 208 (M$^+$), 210 (M$^+$ + 2); pmr: 9.20 (s, 1H, C$_3$-H), 7.80 (d, J = 2.0 Hz, 1H, C$_5$-H), 7.55 (d, J = 9.0 Hz, 1H, C$_8$-H), 7.52 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C$_7$-H), 5.00 (s, 2H, NH$_2$), 3.62 (s, 3H, CH$_3$).

Anal. Calcd. for $C_9H_9ClN_4$: C, 51.81; H, 4.35; Cl, 16.99; N, 26.85. Found: C, 52.11; H, 4.12; Cl, 16.81; N, 26.77.

6-Chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline **6**.

A solution of compound **5** (10 g, 48.0 mmoles) and phenyl isothiocyanate (7.78 g, 57.6 mmoles) in chloroform (200 ml) was refluxed on a boiling water bath for 2 hours to precipitate colorless needles **6**, which were collected by suction filtration and then washed with chloroform to furnish an analytically pure sample (9.52 g). Evaporation of the filtrate *in vacuo* afforded colorless needles **6**, which were collected by suction filtration and then washed with chloroform (4.80 g), total yield 14.32 g (87%), mp 204-205° (red coloration); ir: ν cm^{-1} 3250, 3120, 2960, 1600, 1590, 1570, 1550, 1530, 1500; ms: m/z 343 (M$^+$), 345 (M$^+$ + 2), pmr: 10.28 (s, 1H, NH), 10.20 (s, 1H, NH), 8.58 (s, 1H, C$_3$-H), 8.01 (s, 1H, C$_5$-H), 7.80 (d, J = 8.0 Hz, 1H, C$_7$-H), 7.72 (d, J = 8.0 Hz, 1H, C$_8$-H), 7.53 (d, J = 7.5 Hz, 2H, aromatic), 7.35 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H, aromatic), 7.19 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, aromatic), 3.38 (s, 3H, NCH$_3$); ^{13}C-nmr: 180.98 (C=S).

Anal. Calcd. for $C_{16}H_{14}ClN_5S$: C, 55.89; H, 4.10; Cl, 10.31; N, 20.37; S, 9.32. Found: C, 56.10; H, 4.01; Cl, 10.49; N, 20.51; S, 9.37.

REFERENCES AND NOTES

[1] Y. Kurasawa, R. Katoh, A. Takada, H. S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, in press.

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