A Selective Synthesis of 1-Aryl-3-quinoxalinyl-1,2,4-triazole and Furo[2,3-*b*]quinoxaline

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The reaction of the ester **1** with ethyl benzoate-2-diazonium chloride gave the α-arylhydrazonoester **2b**, whose reaction with hydrazine hydrate afforded the α-arylhydrazonoacylhydrazide **3b**. The reaction of **3b** with sodium nitrite in water/acetic acid under heating on a boiling water bath provided the 1-aryl-3-quinoxalinyl-1,2,4-triazole **5b**, presumably *via* the α-arylhydrazonoacylazide **4b**, while the isolation of **4b** and then its refluxing in dioxane/water furnished the furo[2,3-*b*]quinoxaline **6**. The tautomeric behavior of **2b** and **3b** between the hydrazone imine and diazenyl enamine forms was described together with the tautomer ratio determined by the nmr spectral data.

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In previous papers [2,3], we reported that the quinoxaline ring conjugated or condensed azoles **I-III** (Chart 1) showed the antibacterial and/or antifungal activities against *Xanthomonas oryzae, Pythium debaryanum, Pyricularia oryzae* and *Rhizoctonia solani*. In the serial studies to search for new active compounds, we synthesized the 1-aryl-3-quinoxalinyl-1,2,4-triazoles **5a** by the Curtius rearrangement of the α-arylhydrazonoacylazides **4a** obtained *via* the ester **1**, α-arylhydrazonoesters **2a** and α-arylhydrazonoacylhydrazides **3a** (Chart 2) [4,5]. However, the later screening test clarified that the 1-aryl-3-quinoxalinyl-1,2,4-triazoles **5a** showed no growth inhibitory activity against the above bacteria and fungi [6]. In continuation of the above works, we further studied the synthesis of novel 1-aryl-3-quinoxalinyl-1,2,4-triazoles **5b**, **7**, **8** (Scheme 1) and found that the α-arylhydrazonoacylazide **4b** could be converted into the 1-aryl-3-quinoxalinyl-1,2,4-triazole **5b** and furo[2,3-*b*]quinoxaline **6** selectively. This paper describes the selective synthesis of the 1-aryl-3-quinoxalinyl-1,2,4-triazole **5b** and furo[2,3-*b*]quinoxaline **6** from the α-arylhydrazonoacylazide **4b** and the screening data of **2b**, **3b**, **5b**, **6**, **7** and **8** against the foregoing bacteria and fungi.

Chart 1

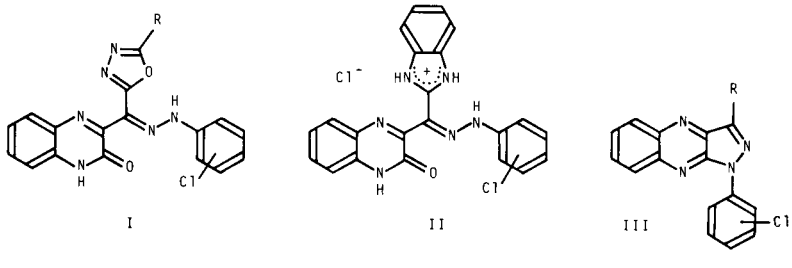
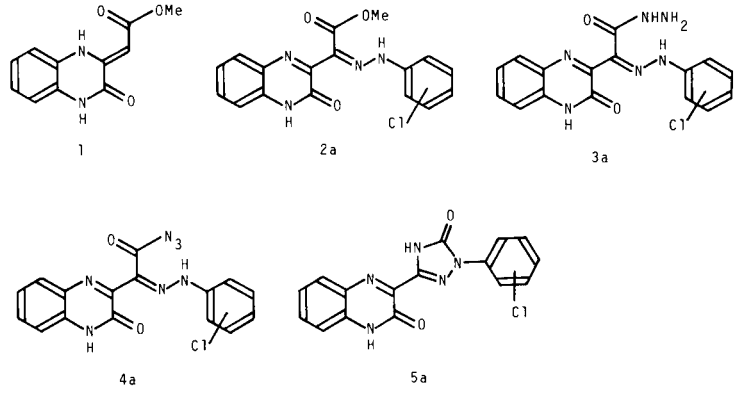
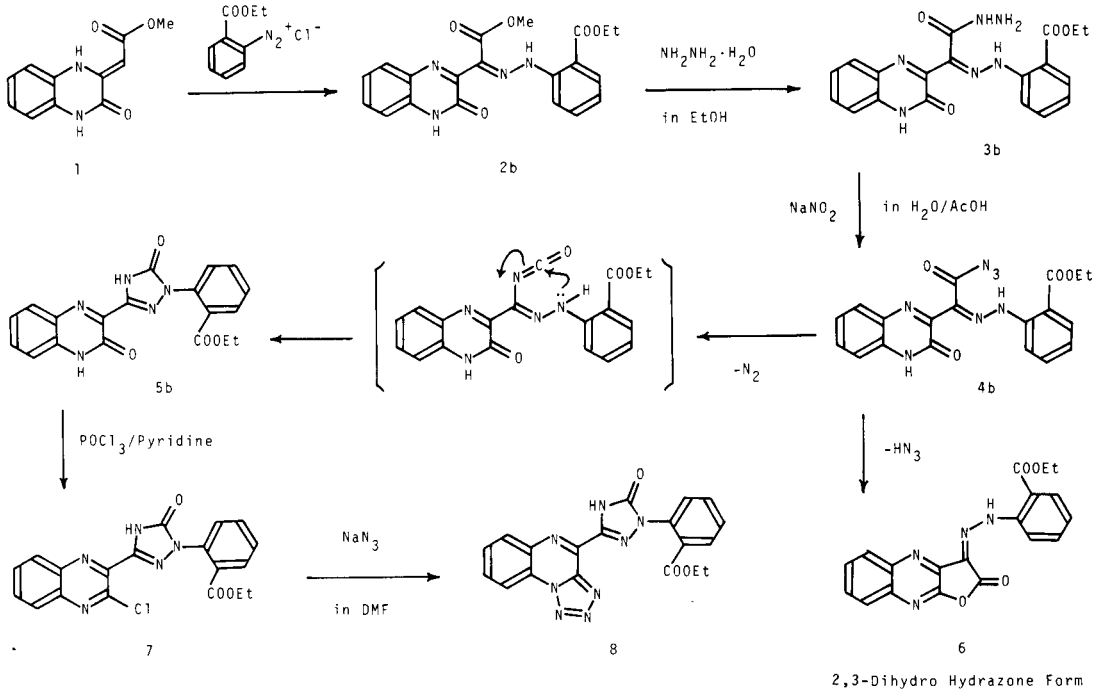


Chart 2

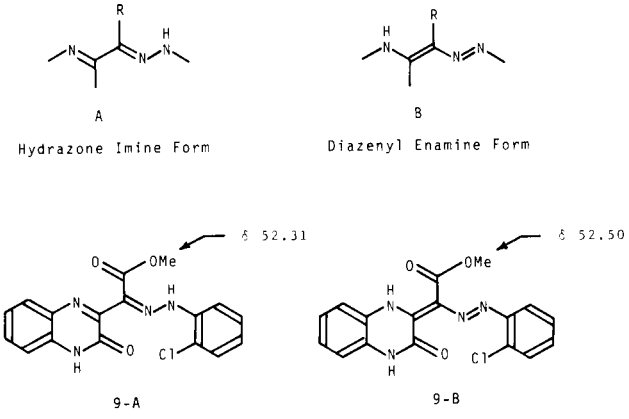


Scheme 1



The reaction of 3-methoxycarbonylmethylene-2-oxo-1,2,-3,4-tetrahydroquinoxaline **1** with ethyl benzoate-2-diazonium chloride gave 3-[α-(*o*-ethoxycarbonylphenylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (**2b**), whose reaction with hydrazine hydrate afforded 3-[α-(*o*-ethoxycarbonylphenylhydrazono)hydrazinocarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (**3b**). The reaction of **3b** with sodium nitrite in water/acetic acid under cooling precipitated 3-[α-(*o*-ethoxycarbonylphenylhydrazono)-azidocarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (**4b**), and subsequent heating of the reaction mixture resulted in the Curtius rearrangement to provide 1-(*o*-ethoxycarbonylphenyl)-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**5b**), while the isolation of **4b** and then its refluxing in dioxane/water furnished 3-(*o*-ethoxycarbonylphenylhydrazono)-2-oxo-2,3-dihydrofuro-[2,3-*b*]quinoxaline (**6**). The reaction of **5b** with phosphoryl chloride gave 1-(*o*-ethoxycarbonylphenyl)-3-(3-chloroquinoxalin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**7**), whose reaction with sodium azide afforded 1-(*o*-ethoxycarbonylphenyl)-3-(tetrazolo[1,5-*a*]quinoxalin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**8**).

Chart 3



In our previous paper [7], the α-arylhydrazonoester **9** was reported to exist as the mixture of the hydrazone imine form **9-A** and diazenyl enamine form **9-B** (Chart 3) in the dimethyl sulfoxide solution in the ratio of 9 *versus* 2. In addition, the methyl carbon signals of **9-A** and **9-B** were found to appear at δ 52.31 and 52.50 ppm, respectively (Table 1). This assignment could be easily accomplished from the carbon signal intensity. Thus, the methyl carbon signal of the hydrazone imine form **9-A** was observed in a higher magnetic field than that of the diazenyl enamine form **9-B**. The α-arylhydrazonoester **2b** in the present investigation also existed as the mixture of the hydrazone imine form **2b-A** and diazenyl enamine form **2b-B** in the dimethyl sulfoxide solution (Scheme 2, Table 1). In the methyl ester group of **2b**, the methyl proton signals were observed at δ 3.67 and 3.78 ppm in the ratio of 1 *versus* 2, respectively. The methyl carbon signals of **2b-A** and **2b-B** were observed at δ 52.00 (low ratio) and 52.33 (high ratio) ppm, respectively. Accordingly, the methyl proton signal of **2b-A** were also found to appear in a higher magnetic field than that of **2b-B**. In the ethyl ester group of **2b**, to the contrary, all the signals of **2b-A** were observed in a lower magnetic field than those of **2b-B**. In the α-arylhydrazonoacylhydrazide **3b**, the tautomer ratio of **3b-A** was

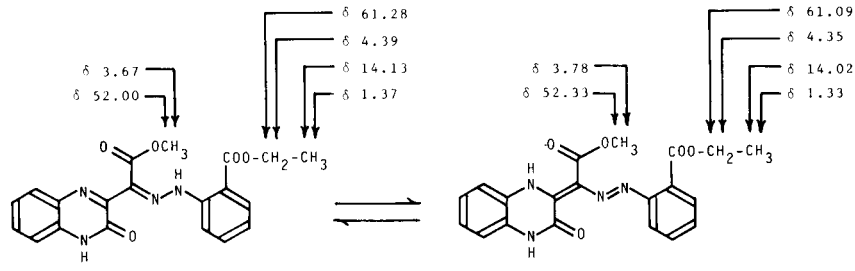
Table 1

^{13}C-NMR Spectral Data for **9**, **2b** and **3b**

Compound	Tautomer	Ratio [a]	Carbon Signal (δ) OMe	CH_2	Me	Proton Signal (δ) OMe	CH_2	Me
9	**A**	9	52.31					
	B	2	52.50					
2b	**A**	1	52.00	61.28	14.13	3.67	4.39	1.37
	B	2	52.33	61.09	14.02	3.78	4.35	1.33
3b	**A**	smaller		61.10	14.27		4.39	1.34
	B	larger		60.94	14.11		4.30	1.31

[a] The ratios of the **A** and **B** forms in **9**, **2b** and **3b** were based on the integral ratio of the NH proton signals, the integral ratio of the OMe proton signals and the carbon signal intensity, respectively.

Scheme 2

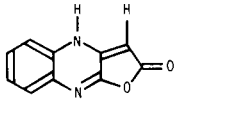


2b-A 2b-B

also smaller than that of **3b-B** (Table 1). In the ethyl ester group of **3b**, all the signals of **3b-A** also appeared in a lower magnetic field than those of **3b-B**.

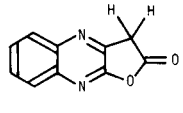
The structural assignment of the furo[2,3-*b*]quinoxaline **6** was based on the analytical and spectral data. The ir spectrum of **6** showed the lactone C=O absorption band at 1795 cm^{-1} as well as the ester C=O absorption band at 1690 cm^{-1}. Moreover, the report on the lactone **10** (Chart 4) by Chapman [8] was helpful for the structural assignment of **6**. Namely, the lactone **10** predominated as the 2,4-dihydro form **10a** [ν (C=O), 1745 cm^{-1}], but not the 2,3-dihydro form **10b**, in solid and solution. Accordingly, our lactone **6** would not exist as the 2,3-dihydro diazenyl form **11b**. Furthermore, the 2,4-dihydro diazenyl form **11a** would be also denied, since the lactone C=O absorption band of **6** at 1795 cm^{-1} was so much higher (by 50 cm^{-1}) than that of **10a** at 1745 cm^{-1}. Therefore, our lactone was assumed to predominate as the 2,3-dihydro hydrazone form **6** at least in a solid state.

Chart 4



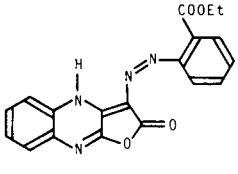
10a

2,4-Dihydro Form



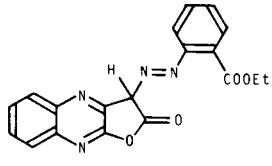
10b

2,3-Dihydro Form



11a

2,4-Dihydro Diazenyl Form



11b

2,3-Dihydro Diazenyl Form

The above compounds **2b-8** showed a weak antifungal activity against *Pythium debaryanum, Rhizoctonia solani* and *Pyricularia oryzae* at a concentration of 100 ppm (Table 2), but they did not exhibit any antibacterial activity against *Xanthomonas oryzae, Erwinia carotovora* and *Pseudomonas lachrmans.*

Table 2

Antifungal Activity of Compounds **2b-8**

Compound	Activity (%) [a] *P.d.*	*R.s.*	*P.o.* [b]
2b	16	15	–
3b	12	58	–
5b	30	20	21
6	30	32	–
7	38	–	17
8	21	–	–

[a] Growth inhibition (%) at 100 ppm. [b] P.d.: *Pythium debaryanum; R.s.: Rhizoctonia solani; P.o.: Pyricularia oryzae.*

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 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.

3-[α-(*o*-Ethoxycarbonylphenylhydrazono)methoxycarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (**2b**).

A solution of sodium nitrite (6.9 g, 0.1 mole) in water (50 ml) was added to a suspension of ethyl *o*-aminobenzoate (16.52 g, 0.1 mole) in 10% hydrochloric acid (30 ml)/acetic acid (70 ml) with stirring in an ice-water bath to give a clear solution, which was added to a suspension of the quinoxaline **1** (10.9 g, 0.05 mole) in acetic acid (100 ml)/water (50 ml) with stirring in an ice-water bath. Stirring was continued for additional 10 minutes. The suspension was heated on a boiling water bath for 40 minutes. After the reaction mixture was cooled to room temperature, the orange crystals precipitated were collected by suction filtration (17.12 g, 87%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles **2b**, mp 245-246°; ir: ν cm^{-1} 3090, 2878, 1735, 1685, 1650, 1595; ms: m/z 394 (M^+); pmr: 14.19 (s, 2/3 H, NH), 12.70 (br, 2/3 H, NH), 11.73 (br, 1/3 H, NH), 11.20 (s, 1/3 H, NH), 8.40-6.60 (m, 8H, aromatic), 4.39 (q, J = 7 Hz, 2/3 H, CH_2), 4.35 (q, J = 7 Hz, 4/3 H, CH_2), 3.78 (s, 2 H, CH_3), 3.67 (s, 1 H, CH_3), 1.37 (t, J = 7 Hz, 1 H, CH_3), 1.33 (t, J = 7 Hz, 2 H, CH_3).

Anal. Calcd. for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 61.06; H, 4.61; N, 14.01.

3-[α-(*o*-Ethoxycarbonylphenylhydrazono)hydrazinocarbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (**3b**).

A suspension of **2b** (10 g, 0.025 mole) and hydrazine hydrate (12.7 g, 0.25 mole) in ethanol (600 ml) was refluxed on a boiling water bath for 4 hours to precipitate yellow crystals, which were collected by suction filtration (8.98 g, 90%). Trituration with ethanol gave analytically pure yellow needles **3b**, mp 264° dec; ir: ν cm^{-1} 3220, 1685, 1655, 1602; ms: m/z 394 (M^+); pmr: 8.27-6.70 (m, 8H, aromatic), 4.39 and 4.30 (q, J = 7 Hz, 2 H, CH_2), 1.34 and 1.31 (t, J = 7 Hz, 3 H, CH_3). NH protons were observed at 14.19 (s), 14.08 (s), 13.48 (s), 13.37 (s), 12.30 (br), 9.90 (br), 9.60 (s), 9.50 (s), 4.47 (br) ppm.

Anal. Calcd. for $C_{19}H_{18}N_6O_4$: C, 57.86; H, 4.60; N, 21.31. Found: C, 57.66; H, 4.60; N, 21.36.

1-(*o*-Ethoxycarbonylphenyl)-3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**5b**).

A solution of sodium nitrite (8.6 g, 0.125 mole) in water (100 ml) was added to a suspension of **3b** (10 g, 0.025 mole) in acetic acid (500 ml)/concentrated hydrochloric acid (10 ml)/water (50 ml) with stirring in an ice-water bath to precipitate the α-arylhydrazonoacylazide **4b**. Without isolation of **4b**, the reaction mixture was heated on a boiling water bath with stirring until it gave a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals, which were triturated with ethanol. The yellow crystals were collected by suction filtration and washed with water (7.95 g, 84%). Recrystallization from *N,N*-dimethylformamide/water provided yellow needles **5b**, mp 156-157°; ir ν cm^{-1} 1710, 1695, 1675, 1600; ms: m/z 377 (M^+); pmr: 12.82 (s, 1 H, NH), 12.31 (s, 1 H, NH), 7.84-7.31 (m, 8 H, aromatic), 4.19 (q, J = 7 Hz, 2 H, CH_2), 1.18 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd. for $C_{19}H_{15}N_5O_4$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.27; H, 3.97; N, 18.33.

3-(*o*-Ethoxycarbonylphenylhydrazono)-2-oxo-2,3-dihydrofuro-[2,3-*b*]quinoxaline (**6**).

A solution of sodium nitrite (8.6 g, 0.125 mole) in water (100 ml) was added to a suspension of **3b** (10g, 0.025 mole) in acetic acid (500 ml)/concentrated hydrochloric acid (10 ml)/water (50 ml) with stirring in an ice-water bath to precipitate yellow crystals **4b**. After stirring for 3 hours, the yellow crystals **4b** were collected by suction filtration and washed with water and then ethanol (9.8 g, 97%); ir: ν cm^{-1} 2130, 1738, 1688, 1650, 1600; ms: m/z 405 (M^+). This sample was used for the preparation of the furo[2,3-*b*]quinoxaline **6**, after drying without heating.

A solution of **4b** (1 g, 2.5 mmoles) in dioxane (50 ml)/water (5 ml) was refluxed in an oil bath for 1 hour. Evaporation of the solvent *in vacuo* afforded yellow crystals, which were collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles **6** (0.25 g, 28%), mp 256-257°; ir: ν cm^{-1} 1795, 1690, 1625; ms: m/z 362 (M^+); pmr: 8.27-7.72 (m, 8 H, aromatic), 4.54 (q, J = 7 Hz, 2 H, CH_2), 1.43 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd. for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.87; N, 15.47. Found: C, 62.71; H, 3.82; N, 15.38.

1-(*o*-Ethoxycarbonylphenyl)-3-(3-chloroquinoxalin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**7**).

A solution of **5b** (10 g) in phosphoryl chloride (100 ml)/pyridine (10 ml) was refluxed in an oil bath for 2 hours. The solution was evaporated *in vacuo* to give orange crystals, to which ethanol was added. The mixture was poured onto crushed ice to precipitate yellow crystals, which were collected by suction filtration (9.77 g, 92%). Recrystallization from ethanol/*n*-hexane gave bright yellow crystals **7**, mp 234-235°; ir: ν cm^{-1} 3060, 1710, 1665, 1600; ms: m/z 395 (M^+), 397 ($M^+ + 2$); pmr: 12.88 (s, 1H, NH), 8.21-7.52 (m, 8 H, aromatic), 4.20 (q, J = 7 Hz, 2 H, CH_2), 1.17 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd. for $C_{19}H_{14}ClN_5O_3$: C, 57.65; H, 3.53; Cl, 8.98; N, 17.70. Found: C, 57.46; H, 3.53; Cl, 8.74; N, 17.50.

1-(*o*-Ethoxycarbonylphenyl)-3-(tetrazolo[1,5-*a*]quinoxalin-2-yl)-4,5-dihydro-1*H*-triazol-5-one (**8**).

A solution of **7** (2.5 g, 6.3 mmoles) and sodium azide (0.62 g, 9.5 mmoles) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 3 hours. The solvent was evaporated *in vacuo* to furnish light brown crystals, which were collected by suction filtration and washed with water. Recrystallization from *N,N*-dimethylformamide/*n*-hexane provided light brown needles **8** (1.37 g, 54%); mp 247-248°; ir: ν cm^{-1} 1725, 1715, 1590; ms: m/z 402 (M^+); pmr: 13.19 (s, 1 H, NH), 8.12-7.56 (m, 8 H, aromatic), 4.20 (q, J = 7 Hz, 2 H, CH_2), 1.18 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd. for $C_{19}H_{14}N_8O_3$: C, 56.72; H, 3.48; N, 27.86. Found: C, 56.50; H, 3.69; N, 28.24.

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