Reaction of Enol Type Acyl Cyanide with *o*-Aminophenol

Yoshihisa Kurasawa*, Noriko Yoshishiba, Tomomi Kureyama and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University,
Shirokane, Minato-ku, Tokyo 108, Japan

Ho Sik Kim

Department of Chemistry, Hyosung Women's University,
Gyongsan 713-900, Korea

Yoshihisa Okamoto

Division of Chemistry, College of Liberal Arts
and Sciences, Kitasato University,
Kitasato, Sagamihara, Kanagawa 228, Japan

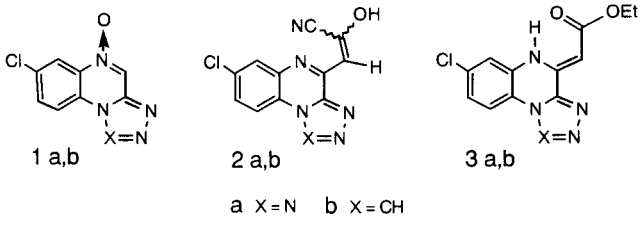
Received February 2, 1993

The reaction of 7-chloro-4-(2-cyano-2-hydroxyvinyl)tetrazolo[1,5-*a*]quinoxaline **2a** with *o*-aminophenol gave 7-chloro-4-(*b*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **4**, while the reaction of compound **2a** with *o*-aminophenol hydrochloride afforded 4-[2-(2-benzoxazolyl)-2-hydroxyvinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **5**, whose acetylation provided 4-[2-acetoxy-2-(2-benzoxazolyl)vinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **6**. The behavior in a deuteriodimethyl sulfoxide or deuteriotrifluoroacetic acid solution is described for compounds **4-6**.

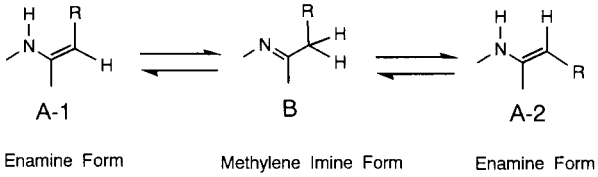
J. Heterocyclic Chem., **30**, 1149 (1993).

In a previous paper [1], we reported that the 1,3-dipolar cycloaddition reaction of 7-chlorotetrazolo[1,5-*a*]quinoxaline 5-oxide **1a** and 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **1b** with 2-chloroacrylonitrile gave the enol type acyl cyanides **2a** and **2b**, respectively, whose alcoholysis provided the ester derivatives **3a** and **3b**, respectively (Chart 1). Moreover, compounds **3a,b** were clarified to exist as the enamine **A** and methylene imine **B** forms in a dimethyl sulfoxide or trifluoroacetic acid medium (Scheme 1) based on the nmr spectral data. In the present investigation, we further studied the reactivity of the enol type acyl cyanide moiety to find that the reaction of compound **2a** with *o*-aminophenol resulted in aminolysis to furnish the amide **4**, while the reaction of compound **2a** with *o*-aminophenol hydrochloride gave the benzoxazole derivative **5**, which was converted into the acetyl derivative **6** (Scheme 2). This paper describes the synthesis of novel compounds **4-6** together with their behaviors in a dimethyl sulfoxide or trifluoroacetic acid solution.

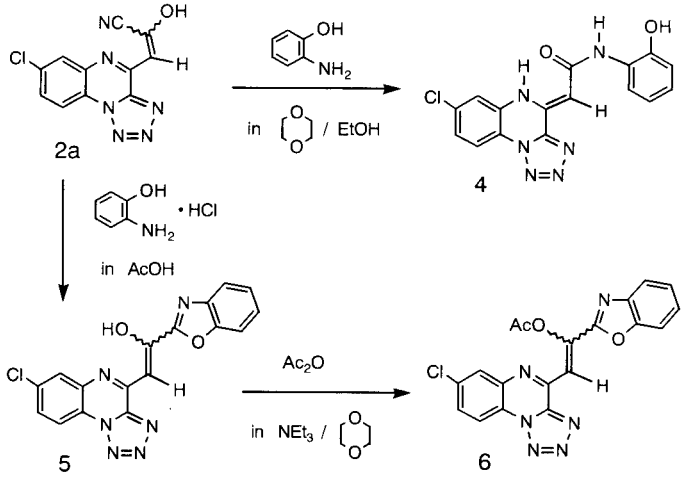
Chart 1



Scheme 1



Scheme 2



The reaction of 7-chloro-4-(2-cyano-2-hydroxyvinyl)tetrazolo[1,5-*a*]quinoxaline **2a** with *o*-aminophenol in dioxane/ethanol effected aminolysis, but not alcoholysis, to provide 7-chloro-4-(*o*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **4**. On the other hand, the reaction of compound **2a** with *o*-aminophenol hydrochloride in acetic acid furnished 4-[2-(2-benzoxazolyl)-2-hydroxyvinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **5**, whose acetylation gave 4-[2-acetoxy-2-(2-benzoxazolyl)-vinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **6**.

The structural assignment of novel compounds **4-6** was based on the analytical and spectral data. The ir spectrum of compound **4** showed the amide C=O absorption band at 1655 cm^{-1}, while the ir spectrum of compound **5** exhibited the C=N absorption band at 1625 cm^{-1}, but not C=O absorption band in a region of 1700-1600 cm^{-1}. The acetyl derivative **6** showed the acetyl C=O absorption

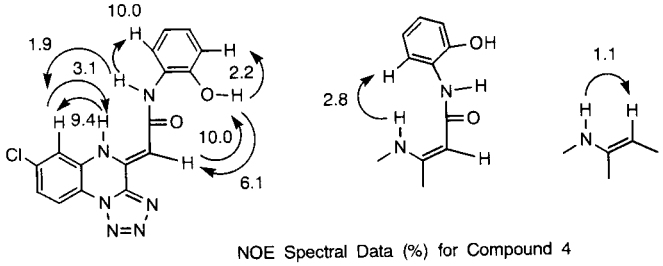
Table 1
NMR Spectra Data (δ) for Compound **4**

Solvent	Tautomer Ratio A	B	Proton Signal Vinyl	Methylene	C_6-H	C_8-H	C_9-H	Carbon Signal Vinyl	Methylene	Others
DMSO-d_6	19	1	6.48	-----	7.93	7.24	8.04 [a]	90.20	-----	166.99 (C=O), 134.53 (C_4)
			-----	4.61	8.34	[c]	8.63 [b]	-----	40.60	145.34 (C_{3a}) (^3J = 5.0, 7.0 Hz)
DMSO-d_6	19	1	-----	-----	7.93	7.24	8.04 [a]			
D_2O			-----	-----	8.38	[c]	8.63 [b]			
TFA-d_1	3	2	-----	-----	[d]	[d]	8.01 [a]			
			-----	-----	8.26	7.86	8.50 [b]			

[a] Signals due to the tautomer **A**. [b] Signals due to the tautomer **B**. [c] Overlapped with other signal. [d] The C_6- and C_8-H proton signals of the tautomer **A** overlapped with the $C_{3'}$-, $C_{4'}$-, $C_{5'}$- and $C_{6'}$-H proton signals.

band at 1775 cm^{-1}. The nmr spectral data of compound **4** exhibited the vinyl and methylene proton signals at δ 6.48 and 4.61 ppm (Table 1) [1,2], respectively, which were due to the tautomers **A** and **B** (Scheme 1), respectively. The vinyl and methylene carbon signals were observed at δ 90.20 and 40.60 ppm, respectively. Furthermore, NOE was observed between the N_5-H and C_6-H proton signals and between the N_5-H and vinyl proton signals (Chart 2) [1]. The above data supported that compound **4** occurred as the three tautomers **A-1**, **B** and **A-2** in a deuteriodimethyl sulfoxide solution (Scheme 3). When the nmr spectra of compound **4** were measured in deuteriodimethyl sulfoxide/deuterium oxide or in deuteriotrifluoroacetic acid, the vinyl and methylene proton signals disappeared as well as the NH and OH proton signals, suggesting the formation of the deuterized species shown in Scheme 4.

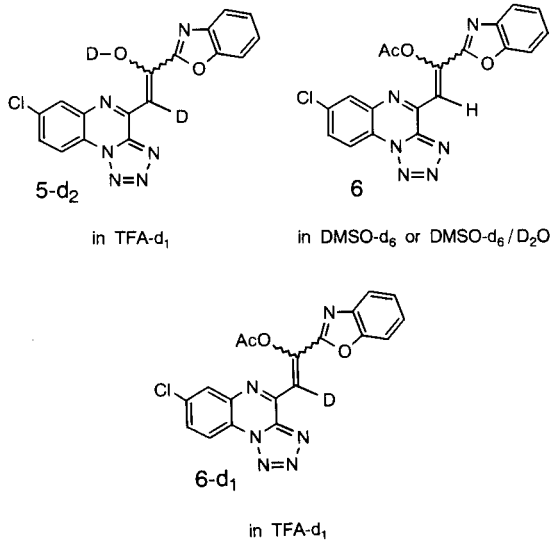
Chart 2



NOE Spectral Data (%) for Compound 4

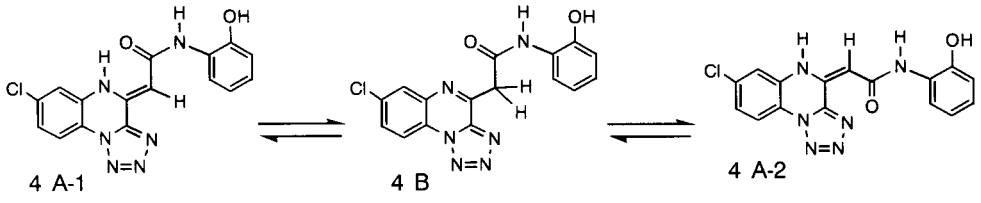
The nmr spectra of compound **5** were measured in deuteriotrifluoroacetic acid because of insolubility in other ordinary solvents (Table 2), and compound **5** was confirmed as the deuterized species **5-d₂** shown in Chart 3. The vinyl proton of compound **5** would be deuterized through the keto-enol tautomerism. The nmr spectra of compound **6** could be measured in deuteriodimethyl sulfoxide, and the vinyl proton signal was observed at δ 8.23 ppm. However, the vinyl proton signal of compound **6** disappeared when measured in deuteriotrifluoroacetic acid. Since there is no keto-enol tautomerism in compound **6**, the D-H exchange mechanism is assumed as shown in Scheme 5.

Chart 3



The C_6-H and C_9-H proton signals of compound **6** in deuteriodimethyl sulfoxide were observed in a similar magnetic field to those of the species **4B**, which has a tetrazolo[1,5-*a*]quinoxaline ring system (Tables 1 and 2).

Scheme 3



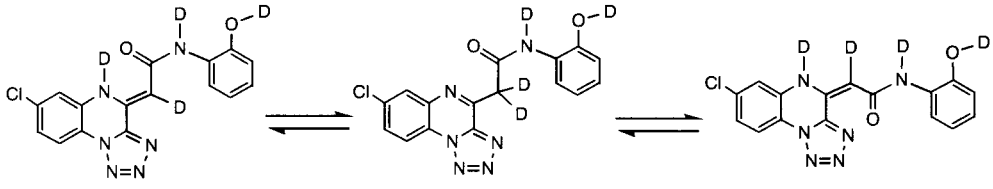
Tautomeric Equilibria of Compound 4 in DMSO-d_6

Table 2
NMR Spectral Data (δ) fro Compounds **5** and **6**

Compound	Solvent	Proton Signal				Carbon Signal			
		Vinyl	C_6-H	C_8-H	C_9-H	Vinyl $C_{1'}$	Vinyl $C_{2'}$	Acetyl C=O	Acetyl Me
5	TFA-d_1	-----	7.73	7.44	8.16	-----	166.88	-----	-----
6	TFA-d_1	-----	7.64	7.34	8.07	-----	167.12	180.90	18.61
	DMSO-d_6	8.23	8.41	8.08	8.64	114.79	168.04	[a]	20.87

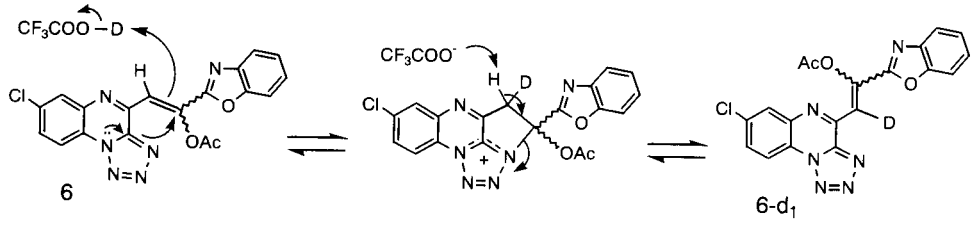
[a] Unobservable.

Scheme 4



Tautomeric Equilibria of Compound 4 in DMSO-d_6 / D_2O or in TFA-d_1

Scheme 5



D-H Exchange Mechanism of Compound 6 in TFA-d_1

On the other hand, the C_6-H and C_9-H proton signals of the tetrazolo[1,5-*a*]quinoxalines **6** and **4B** in deuteriodimethyl sulfoxide were observed in a lower magnetic field than those of the 4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **4A**.

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 a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in a 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-4-(*o*-hydroxyphenylcarbamoylmethylene)-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **4**.

A solution of compound **2a** (5 g, 18.3 mmoles) and *o*-aminophenol (3 g, 27.5 mmoles) in dioxane (150 ml)/ethanol (100 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow needles **4**, which were collected by suction filtration (3.32 g). Evaporation of the solvent *in vacuo* afforded yellow crystals **4**, which were triturated with ethanol and then collected by suction filtration (0.53 g), total yield, 3.85 g (59%). Recrystallization from *N,N*-dimethylformamide/dioxane/*n*-hexane provided yellow needles, mp 277-278°; ir: ν cm^{-1} 3420, 3100, 1655, 1625, 1595; ms: m/z 354 (M^+), 356 (M^++2); pmr (deuteriodimethyl sulfoxide): 11.83 (s, NH), 9.87 (s, 1H, CONH), 9.66 (s, 1H, $C_{2'}$-OH), 8.63 (d, J = 8.5 Hz, C_9-H), 8.38 (d, J = 2.0 Hz, C_6-H), 8.04 (d, J = 8.5 Hz, C_9-H), 7.93 (d, J = 2.0 Hz, C_6-H), 7.85 (dd, J = 1.5 Hz, J = 8.5 Hz, 1H, $C_{3'}$-H), 7.24 (dd, J = 2.0 Hz, J = 8.5 Hz, C_8-H), 6.96 (ddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.5 Hz, 1H, $C_{4'}$-H), 6.89 (dd, J = 1.5 Hz, J = 8.0 Hz, 1H, $C_{6'}$-H), 6.80 (ddd, J = 8.0 Hz, J = 8.0 Hz, J = 1.5 Hz, 1H, $C_{5'}$-H).

Anal. Calcd. for $C_{16}H_{11}ClN_6O_2 \cdot \frac{1}{2}H_2O$: C, 52.83; H, 3.32; Cl, 9.75; N, 23.10. Found: C, 53.10; H, 3.14; Cl, 9.86; N, 23.19.

4-[2-(2-Benzoxazolyl)-2-hydroxyvinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **5**.

A suspension of compound **2a** (5 g, 18.3 mmoles) and *o*-aminophenol hydrochloride (4 g, 27.5 mmoles) in acetic acid (200 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was cooled to room temperature to precipitate yellow needles **5**, which were collected by suction filtration (5.83 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals **5**, which were collected by suction filtration (0.75 g), total yield, 4.33 g (65%). Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 290-291°; ir: ν cm^{-1} 3090, 3030, 1625, 1585; ms: m/z 364 (M^+), 366 (M^++2); pmr (deuteriotrifluoro-

acetic acid): 8.16 (d, J = 9.0 Hz, 1H, C_9-H), 7.73 (d, J = 1.5 Hz, 1H, C_6-H), 7.72 (d, J = 8.5 Hz, 1H, $C_{4'}$-H), 7.69 (d, J = 8.5 Hz, 1H, $C_{7'}$-H), 7.62 (dd, J = 8.5 Hz, J = 7.0 Hz, 1H, $C_{5'}$-H), 7.54 (dd, J = 8.5 Hz, J = 7.0 Hz, 1H, $C_{6'}$-H), 7.44 (dd, J = 9.0 Hz, J = 1.5 Hz, 1H, C_8-H).

Anal. Calcd. for $C_{17}H_9ClN_6O_2$: C, 55.98; H, 2.49; Cl, 9.72; N, 23.04. Found: C, 55.79; H, 2.37; Cl, 9.55; N, 23.10.

4-[2-Acetoxy-2-(2-benzoxazolyl)vinyl]-7-chlorotetrazolo[1,5-*a*]quinoxaline **6**.

A solution of compound **5** (2 g, 5.49 mmoles), acetic anhydride (50 ml) and triethylamine (2 ml) in dioxane (50 ml) was refluxed in an oil bath for 2 hours. The solution was allowed to stand overnight to precipitate yellow prismic needles **6**, which were collected by suction filtration (0.76 g). Evaporation of the filtrate *in vacuo* gave yellow needles **6**, which were triturated with dioxane/ethanol and then collected by suction filtration (0.53 g), total yield, 1.29 g (58%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 257-258°; ir: ν cm^{-1} 3060, 1775, 1640, 1600; ms: m/z 406 (M^+), 408 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.64 (d, J = 8.5 Hz, 1H, C_9-H), 8.41 (d, J = 2.0 Hz, 1H, C_6-H), 8.23 (s, 1H, vinylic H), 8.08 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_8-H), 7.94 (ddd, J = 7.5 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H, $C_{4'}$-H), 7.93 (ddd, J = 7.5 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H, $C_{7'}$-H), 7.60 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.5 Hz, 1H, $C_{5'}$-H), 7.52 (ddd, J = 8.0 Hz, J = 7.5 Hz, J = 1.5 Hz, 1H, $C_{6'}$-H), 2.63 (s, 3H, acetyl CH_3).

Anal. Calcd. $C_{19}H_{11}ClN_6O_3$: C, 56.10; H, 2.73; Cl, 8.71; N, 20.66. Found: C, 55.91; H, 2.79; Cl, 8.47; N, 20.94.

REFERENCES AND NOTES

[1] Y. Kurasawa, T. Kureyama, N. Yoshishiba, T. Okano, A. Takada, H. S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, **30**, 781 (1993).

[2] Y. Kurasawa and A. Takada, *Heterocycles*, **24**, 2321 (1986), and references cited therein.