A SIMPLE PREPARATION OF 3-CARBAMOYLFURO-[2,3-*b*]QUINOXALIN-2-ONES

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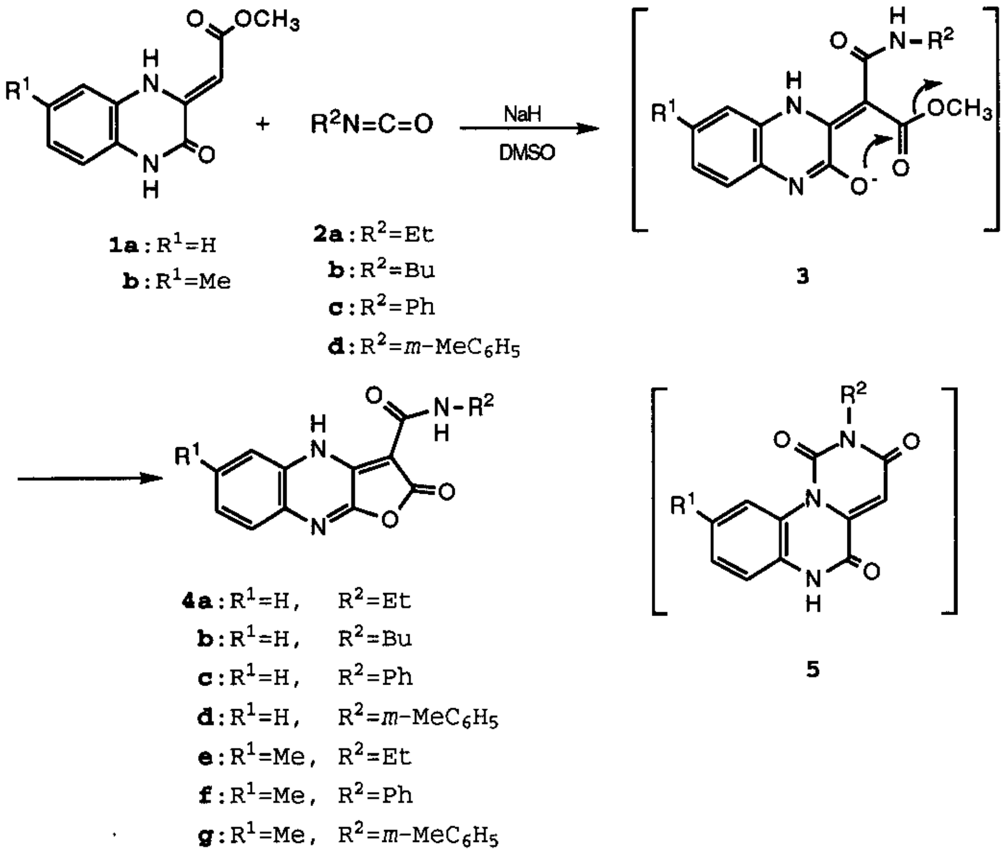
Abstract - A preparation of 3-carbamoylfuroquinoxalin-2-ones (**4a-g**) was easily achieved by treatment of 3-methoxycarbonylmethylene-2-oxoquinoxalines (**1a,b**) and and isocyanates (**2a-d**) with sodium hydride in dimethyl sulfoxide. The structure of **4c** was confirmed by a single crystal X-ray structure determination.

Furoquinoxaline derivatives have been known to possess a variety of biological activities,[1-5] and three methods for their preparations have hitherto been developed: 1) intramolecular cyclizations of 3-acylmethylquinoxaline derivatives under acidic conditions,[6-12] 2) cycloadditions of quinoxalinium iodide with 1,3-dicarbonyl compounds,[13-15] and 3) reactions of furanyldiones with 1,2-diaminobenzene.[16-17] So far carbamoylfuroquinoxalin-2-ones have not been prepared by these three methods.

As a study on the synthesis of condensed heterocyclic compounds from diamine,[18-19] we examined the reaction of 3-methoxycarbonylmethylene-2-oxoquinoxalines (**1a** and **b**) [20] with various isocyanates (**2a-d**) in NaH/DMSO and found that 3-carbamoylfuro[2,3-*b*]quinoxalin-2-ones (**4a-g**) showing a strong fluorescence were prepared in one step. The reaction was carried out by adding **2** to a DMSO solution of **1** in the presence of sodium hydride. After stirring for 12 h at room temperature, the reaction mixture was treated with water to afford compound (**4**) (Scheme 1).



Scheme 1

The structures of compounds (**4a-g**) were assigned on the basis of spectral data. In the ir spectra the carbamoyl C=O, lactone C=O, and NH absorption bands were observed at 1660-1680 cm^{-1}, and 1730-1756cm^{-1}, and 3200-3354 cm^{-1}, respectively. The ^{13}C-nmr spectrum of compound (**4c**) by the DEPT method showed 7 methine carbon and 8 quaternary carbon signals with no methine carbon situated α to an α,β-unsaturated carbonyl group. This result readily eliminated the structure (**5**).

Moreover, compound (**4c**) was submitted to the X-ray diffraction analysis in order to clarify the tautomeric structure in a solid state. The molecular structure (Figure 1) shows the oxygen of dimethyl sulfoxide forming a hydrogen bond with the hydrogen at N-4 of **4c**. The distances between N4-C4a and N9-C8a are shortened due to aromatization. The bonds between N4-C3a and C3-C3a are obviously conjugated.

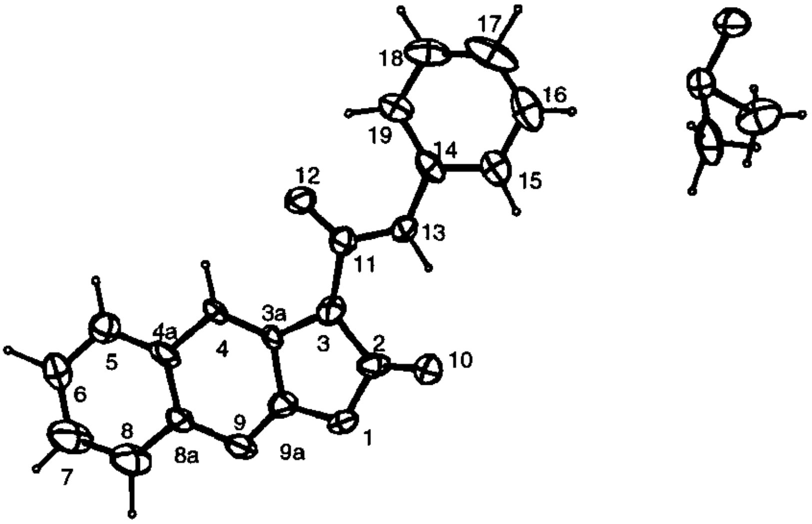


Figure 1 ORTEP Diagram of 3-Phenylcarbamoyl furo-[2,3-*b*]quinoxalin-2-one (**4c**) dimethyl sufoxide

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded as KBr pellets on a JASCO IRA-1 grating infrared spectrometer. ^{1}H-Nmr spectra were determined with either an Hitachi R-600 spectrometer (60 MHz) or a JEOL JMN GX400(400 MHz) using tetramethylsilane as an internal standard. ^{13}C-Nmr spectra were measured with a JEOL JMN GX400(100 MHz) spectrometer. Mass spectra were measured with a JEOL JMX-DX 303HF mass spectrometer.

General Procedure for the Synthesis of 3-Carbamoylfuro[2,3-*b*]-quinoxalin-2-ones (4): To a solution of quinoxaline (**1**)[20] (2.18 g, 10 mmol) in dry DMSO (20 ml) is added 60% sodium hydride (1.2 g, 30 mmol) under an argon atmosphere at room temperature. After stirring for 20 min, isocyanate (**2**) (10 mmol) is added to the solution using a syringe. The reaction mixture is stirred for 12 h. Addition of water to the reaction mixture gave yellow precipitate, which was recrystallized from DMSO.

3-Ethylcarbamoylfuro[2,3-*b*]quinoxalin-2-one (4a): Compound (**4a**) was obtained as light yellow powder. Yield 1.85 g (72%); mp 280-281°C; ir (KBr) ν 3200 (NH), 1750, 1660 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 1.16 (t, 3H, CH_3, J=7.2 Hz), 3.31 (q, 2H, CH_2, J=7.2 Hz), 7.42-7.78 (m, 4H, arom), 8.03 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ 15.06 (CH_3), 3 3.00 (CH_2), 84.98 ($-\overset{|}{\underset{|}{C}}-$), 118.37, 125.38, 127.90, 128.42 (CH), 129.18, 133.76, 140.05, 154.50 ($-\overset{|}{\underset{|}{C}}-$), 161.57, 166.00(C=O); HRms (EI): m/z (M^+) Calcd for $C_{13}H_{11}N_3O_3$: 257.0764, Found: 257.0800; *Anal.* Calcd for $C_{13}H_{11}N_3O_3$: C, 60.68; H, 4.31; N, 16.34. Found: C, 60.35; H, 4.50; N, 16.15.

3-Butylcarbamoylfuro[2,3-*b*]quinoxalin-2-one (4b): Compound (**4b**) was obtained as light yellow powder. Yield 1.94 g (68%); mp 179-180°C; ir (KBr) ν 3350 (NH), 1750, 1660 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 0.92 (t, 3H, CH_3, J=7.3 Hz), 1.34 (sextet, 2H, CH_2, J=7.3 Hz), 1.53 (qui, 2H, CH_2, J=7.3 Hz), 3.33 (m, 2H, CH_2), 6.99-7.48 (m, 5H, arom), 7.91 (s, 1H, NH), 8.11 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ 19.46 (CH_3), 31.42, 37.58 (CH_2), 85.09 ($-\overset{|}{\underset{|}{C}}-$), 118.03, 125.38, 127.87, 128.45 (CH), 128.75, 133.61, 139.65, 154.49 ($-\overset{|}{\underset{|}{C}}-$), 161.51, 166.03 (C=O); HRms (EI): m/z (M^+) Calcd for $C_{15}H_{15}N_3O_3$: 285.1113, Found: 285.1139; *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.94; H, 5.08; N, 14.47.

3-Phenylcarbamoylfuro[2,3-*b*]quinoxalin-2-one (4c): Compound (**4c**) was obtained as yellow orthorhombic crystals. Yield 1.83 g (60%); mp 280-281°C; ir (KBr) ν 3200 (NH), 1740, 1670 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 7.30-8.03 (m, 5H, arom), 8.13(br, 1H, NH), 9.25 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ 85.43 ($-\overset{|}{\underset{|}{C}}-$), 118.73, 124.44, 126.65, 126.75, 127.93, 127.99, 128.08 (CH), 128.84, 128.93, 129.63, 138,07, 154.37($-\overset{|}{\underset{|}{C}}-$), 160.17, 166.36 (C=O); HR-ms (EI): m/z (M^+) Calcd for $C_{17}H_{11}N_3O_3$: 305.0800, Found: 305.0796. *Anal.* Calcd for $C_{17}H_{11}N_3O_3$ C_2H_6OS:

C, 59.52; H, 4.47; N, 10.96. Found: C, 59.62; H, 4.54; N, 10.85.

3-*m*-Tolylcarbamoylfuro[2,3-*b*]quinoxalin-2-one (4d): Compound (**4d**) was obtained as light yellow powder. Yield 2.07 g (65%); mp 263-264°C; ir (KBr) ν 3310 (NH), 1740, 1670 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.88-8.12 (m, 9H, arom and NH), 9.11 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ 20.71 (CH_3), 85.16 ($-\overset{|}{\underset{|}{C}}-$), 116.22, 118.07, 119.74, 123.93, 127.75, 128.33, 128.45, 137.68 (CH), 125.53, 128.54, 133.73, 137.86, 139.53, 154.04 ($-\overset{|}{\underset{|}{C}}-$), 159.75, 166.06 (C=O); HRms (EI): m/z (M^+) Calcd for $C_{18}H_{13}N_3O_3$: 319.0957, Found: 319.0944. *Anal.* Calcd for $C_{18}H_{13}N_3O_3$ C_2H_6OS: C, 67.71; H, 4.11; N, 13.16. Found: C, 68.11; H, 4.32; N, 12.88.

3-Ethylcarbamoy-6-methyllfuro[2,3-*b*]quinoxalin-2-one (4e): Compound (**4e**) was obtained as light yellow powder. Yield 1.62 g (60%); mp 218-220°C; ir (KBr) ν 3354 (NH), 1756, 1660 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 1.20 (t, 3H, CH_3, J=7.2Hz), 2.40 (s, 3H, CH_3), 2.30-3.87 (m, 2H, CH_2), 7.00-7.54 (m, 4H, arom and NH); HRms (EI): m/z (M^+) Calcd for $C_{14}H_{13}N_3O_3$ 271.0953, Found: 271.0957. *Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.58; H, 5.02; N, 15.28.

3-Phenylcarbamoy-6-methyllfuro[2,3-*b*]quinoxalin-2-one (4f): Compound (**4f**) was obtained as light yellow powder. Yield 2.01 g (63%); mp 263-264°C; ir (KBr) ν 3300 (NH), 1730, 1670 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 7.08-8.08 (m, 10H, arom and NH), 9.24 (s, 1H, NH); HRms (EI): m/z (M^+) Calcd for $C_{18}H_{13}N_3O_3$: 319.0949, Found: 319.0957. *Anal.* Calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.58; H, 4.13; N, 13.02.

3-*m*-Tolylcarbamoyl-6-methylfuro[2,3-*b*]quinoxalin-2-one (4g): Compound (**4g**) was obtained as yellow powders. Yield 1.33 g (40%); mp 271-272°C; ir 3310 (NH), 1730, 1660 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.77-8.06 (m, 9H, arom and NH), 9.12 (s, 1H, NH); HRms (EI): m/z(M^+) Calcd for $C_{19}H_{15}N_3O_3$: 333.0949, Found: 333.1113. *Anal.* Calcd for $C_{19}H_{15}N_3O_3$: C, 68.45; H, 4.54; N, 12.61. Found: C, 68.73; H, 4.75; N, 12.29.

Crystal Data for 4c: Single crystals of compound (**4c**) were prepared by allowing to stand the dimethyl sulfoxide solution for about one month. The cell constants were obtained from least squares refinement of the 2θ angle of 20 reflections. The density was measured by flotation in a mixture of light petroleum and chloroform. The crystal data are as follows: $C_{17}H_{11}N_2O_3$ C_2H_6SO, M=383.4, orthorhombic, *a*=22.105(19), *b*=12.107(9), *c*=6.731(6) Å, *V*=1801(3)$Å^3$, space group $Pna2_1$,Z= 4, *Dc*=1.414, *Dm*=1.420 gcm^{-3}.

Data Collection and Processing: Intensity data were collected on a Rigaku AFC-6 automated diffractometer with graphite monochromated Mo-Kα (0.71069Å) radiation using the 2θ /ω scan mode to a limit of 2θ=55°. Two reflections were monitored after every measurement of 100 reflections. Of 1643 independent reflections, 1056 were treated as observed [$Fo>3.0\sigma F$] for **4c**. The intensities were corrected for Lorentz and polarization effects, but no correction was applied for absorption. Observed structure factors were converted into a normalized strucutre factor amplitude value (E) by use of a scale factor and the overall temperature factor was obtained from Wilson's statistics. The structure was solved by direct method using the MULTAN78[21] series of programs. An E map calculated with 339 signed E's.(E>1.1), which gave an absolute figure of merit of 1,292, revealed the positions of the all expected non-hydrogen atoms. Several further cycles of block-diagonal least squares refinement for the non-hydrogen atoms converted to R=0.12. All the hydrogens were located at calculated positions. After adding the hydrogens, keeping their vibrational amplitudes fixed (B(H)=B(C)+1.0), and refining, we obtained a final R value of 0.069.

All calculations were performed on a FACOM M-780 computer in the Computer Center of Kumamoto University with the Universal Crystallographic Computation Program System (UNICS III).[22]

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