1,3-DIPOLAR CYCLOADDITION OF ARYL AZIDES WITH 5-ALKOXY-3-PYRROLIN-2-ONES. SYNTHESIS OF 4-ALKOXY-6-ARYL-3,6-DIAZA-BICYCLO[3.1.0]HEXAN-2-ONES

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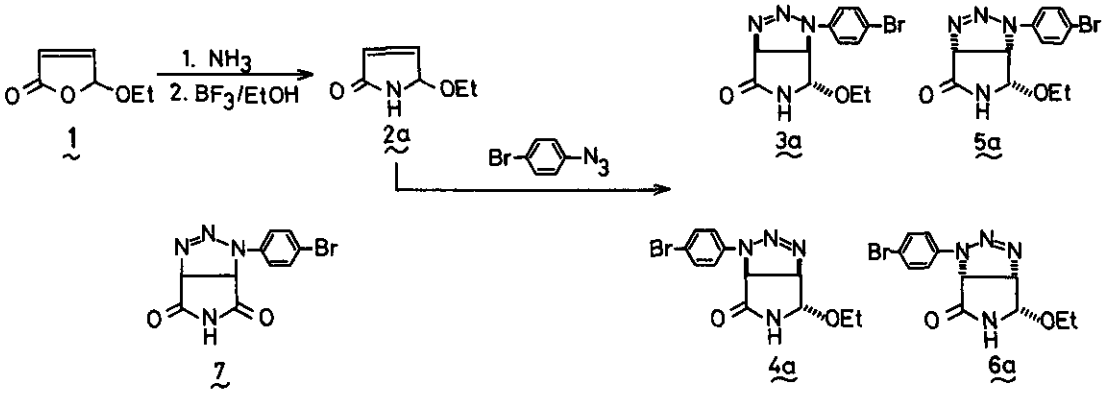
Abstract——1,3-Dipolar cycloaddition of p-bromophenyl azide with 5-ethoxy-3-pyrrolin-2-one (**2a**) gave a regioisomeric mixture of triazolines. While thermal decomposition of the triazolines (**3a**,**4a**) afforded aziridine (**10a**) and enamines (**12**,**13**), **3a** and **4a** underwent photo-decomposition to give the aziridine [*6-(4-bromophenyl)-4-ethoxy-3,6-diazabicyclo[3.1.0]hexan-2-one* (**10a**)] exclusively.

5-Alkoxy- or 5-hydroxy-2-pyrrolidinones, which have been prepared mainly by the reduction of succinimide derivatives with sodium borohydride or by the anodic oxidation of appropriate γ-lactams, are useful intermediates for the synthesis of pyrrolizidine or indolizidine derivatives.[1] In the course of our studies on the chemistry of 5-alkoxy-2-pyrrolidinones, it was shown that 3,3,5-trimethoxy-2-pyrrolidinones were conveniently obtained from α-halo-β-formylacrylic acids [3-halo-5-hydroxy-2(5H)-furanones] which were derived from 5-ethoxy-2(5H)-furanone (**1**) in a short step.[2] This experiment prompted us to investigate the conversion of **1** to new 5-alkoxy-2-pyrrolidinones having nitrogen functions at the 3- and/or 4-position. In this paper, the 1,3-dipolar cycloaddtion of aryl azides with 5-alkoxy-3-pyrrolin-2-ones (**2**), which were derived from ammonolysis of **1**, and subsequent ring contraction of the cycloadducts are described.

It is well known that aryl azides readily react with polarized C-C double bonds to give triazolines with high regioselectivity.[3] However, it is difficult to anticipate the orientation in the cycloaddition to α,β-unsaturated carbonyl

compounds, because of little difference between energys for HOMO(dipole) controlled and LUMO(dipole) controlled transition states.[4] Thus, in the case of the reaction with 5-alkoxy-3-pyrrolin-2-ones, four possible regio- and stereo-isomers should be considered.

When the mixture of 5-ethoxy-3-pyrrolin-2-one (**2a**) and p-bromophenyl azide was stored for 48 h at 60°C in a glassware wrapped in aluminum foil to prevent photo-decomposition, the solidified mixture was obtained. The mixture was separated by fractional recrystallization to afford triazolines (**3a** and **4a**) in 43 % and 22 % yield, respectively. Further purification of the remaining mixture by flash chromatography gave trace amount of **5a** and **6a** resulting from an addition proceeded from the same side with the ethoxy group. The structures of **3a**, **4a** and **5a** could readily be determined by comparing the ^{1}H-NMR spectra with that of the maleimide-azide adduct (**7**) as follows. In contrast with the aromatic signals of **3a** and **5a** which showed typical AB patern (7.7-7.2 ppm), the appropriate signal of **4a** appeared at 7.6 ppm as a singlet was similar to that of **7**. This observation clearly indicated that p-bromophenyl group was at the same side with the carbonyl function. The high field shift (0.5 ppm) of methyl protons on the ethoxy group which should be caused by the anisotropic effect of the neighboring aryl group also agreed with the structure of **5a**. The stereochemistry of **6a** was confirmed by photochemical conversion to the same compound (**11a**) as that obtained from **5a**.



Analogously, when the reactions of **2a** with some other aryl azides were performed, the corresponding triazolines were obtained as shown in Table I, where at least two regioisomers were produced in each cases. Treatment of 5-t-butoxy-3-pyrrolin-2-one (**2b**)[7] with p-bromophenyl azide also gave triazolines (**3e** and **4e**) with slight decrease of regioselectivity. On the other hand, in the reaction of

5-ethoxy-2(5H)-furanone (1) with p-methoxyphenyl azide, triazoline (8) and its decomposed product (9) were obtained in 40 % and 11 % yield respectively, but another regioisomer of 8 was not detected. The results presented here suggested that the relatively low regioselectivity in the reaction of 5-alkoxy-3-pyrrolin-2-ones with aryl azides was affected by the FMO interaction between azide (dipole) and 3-pyrrolin-2-one (dipolarophile) rather than by steric hindrance of the 5-alkoxy function.

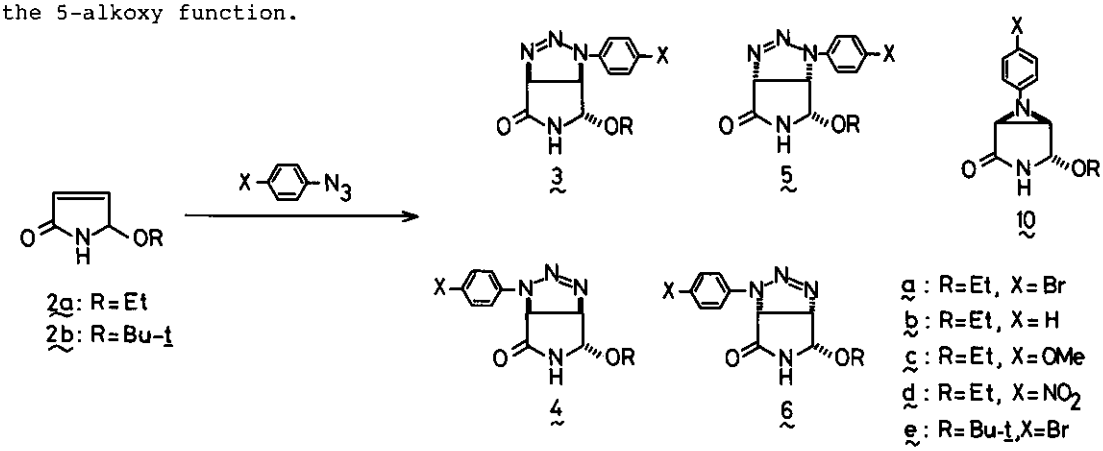
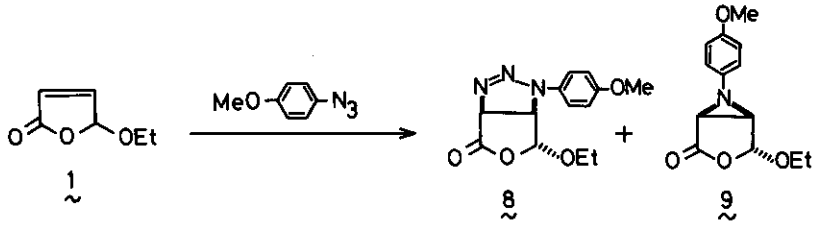
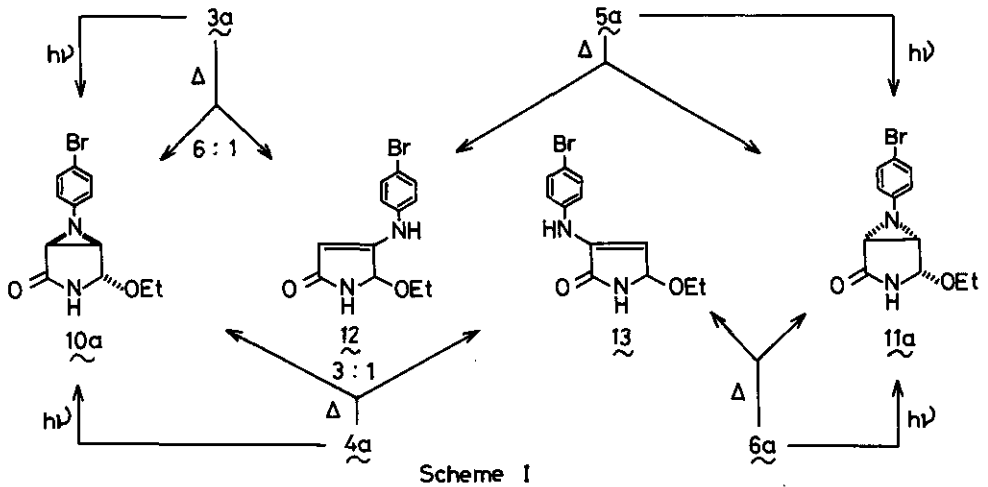


Table I 1,3-Dipolar Cycloaddition of Aryl Azides with 5-Alkoxy-3-pyrrolin-2-ones (2a,b)

Dipolarophile	R	X	Yield (%) 3	4	5	6	10	ratio (3/4)
2a	Et	Br	43	22	3	~1	3	2.0
2a	Et	H	38	19	4	-	-	2.0
2a	Et	OMe	50	18	~1	-	2	2.8
2a	Et	NO_2	39	12	-	-	-	3.3
2b	Bu-t	Br	33	19	-	-	-	1.7



We next attempted ring conversion of the triazolines into aziridine derivatives by photolysis and thermolysis. Irradiation of the solution of triazolines (3a,4a) with high pressure Hg lamp led to the stereospecific formation of the



Scheme I

corresponding aziridine (10a) in almost quantitative yield. In the same manner, the stereoisomer (5a) underwent photochemical ring contraction to afford 11a having the aziridine ring with cis relative configuration to the ethoxy group. On the other hand, thermal decomposition provided a different result from the photochemical reaction. On refluxing the solution of triazolines (3a) in DMF, a mixture of aziridine (10a) and enamine (12) was produced in an approximate ratio of 6:1. Thermolysis of 4a also gave a mixture of 10a and 13 in the ratio of 3:1. Scheme I summarized the photochemical and thermal reaction pathways of these triazolines (3a-6a).[5] Similarly, when irradiations of other series of the triazolines in DMSO-d_6 were carried out with monitoring the completion of reactions by ^{1}H-NMR measurement, rapid and exclusive formations of the corresponding aziridines were observed except for 3d and 4d. In the case of 3d and 4d having p-nitrophenyl function on the triazoline ring, prolonged reaction time was required for disappearing the starting materials. The structures of these aziridines were also confirmed by their IR, ^{1}H-NMR and mass spectra, respectively.

In conclusion, these results described here provide a convenient method for the synthesis of 4-alkoxy-6-aryl-3,6-diazabicyclo[3.1.0]hexan-2-ones (10a-e) which are expected to be a synthon for the synthesis of more complexed pyrrolidine derivatives having some kinds of bioactivities. Since 5-alkoxy-2-pyrrolidinones react with nucleophiles sucn as amines, amides and carbamates at the 5-position as we have previously reported,[6] extention of our investigation to the reaction of the compounds shown above with nucleophiles is in progress.

EXPERIMENTAL

Melting points are uncorrected. IR and mass spectra were recorded on Hitachi EPI-G2 and Hitachi RMU-7L spectrometer, respectively. ^{1}H-NMR spectra were obtained with Varian T-60 (60 MHz) and Varian EM-390 (90 MHz) spectrometer. Flash chromatography was performed on Kiesel gel 60 (230-400 mesh) or Wakogel C-300 (200-300 mesh).

Cycloaddition of p-Bromophenyl Azide with **2a**

The solution of p-bromophenyl azide (1.66 g) and **2a**[6] (1.00 g) in ether was carefully concentrated, and the resulting oily mixture was stored at 60°C for 48 h in a glassware wrapped with aluminum foil. The solidified mixture including crystals was obtained. The mixture was separated by fractional recrystallization (from acetone) to afford **3a** (1.09 g, 43%) and **4a** (556 mg, 22%) as crystalline solids. The remaining mother liquid was separated by flash chromatography (SiO_2: $CHCl_3$-MeOH) to give **5a** (77 mg, 3%) and **6a** (16 mg, 0.6%) as crystalline solids. **3a**: mp 175-176°C. IR (KBr) cm^{-1}: 3200-3050(NH), 1715(C=O). ^{1}H-NMR (DMSO-d_6) δ: 9.25 (1H,bs,NH), 7.60(2H,d,J=9Hz,Ar-H), 7.20(2H,d,J=9Hz,Ar-H), 5.60(1H,d,J=10Hz,C_3-H), 4.85(1H,s,C_5-H), 4.55(1H,d,J=10Hz,C_4-H), 3.60(2H,m,$OC\underline{H}_2CH_3$), 1.20(3H,t,J=7Hz, $OCH_2C\underline{H}_3$). **4a**: ^{1}H-NMR (DMSO-d_6) δ: 9.3(1H,bs,NH), 7.50(4H,s,Ar-H), 5.20(1H,d, J=11Hz,C_4-H), 5.15(1H,s, C_5-H), 5.05(1H,d,J=11Hz,C_3-H), 3.65(2H,q,J=7Hz,$OC\underline{H}_2CH_3$), 1.20(3H,t,J=7Hz,$OCH_2C\underline{H}_3$). **5a**: ^{1}H-NMR (DMSO-d_6) δ: 9.15(1H,bs,NH), 7.55(2H,d, J=9Hz,Ar-H), 7.30(2H,d,J=9Hz,Ar-H), 5.35-4.85(3H,m,CH), 3.35(2H,m,$OC\underline{H}_2CH_3$), 0.75 (3H,t,J=7Hz,$OCH_2C\underline{H}_3$).

Photo-decomposition of **3a**

The DMSO-d_6 solution (0.4 ml) of **3a** (22 mg) in a NMR spinning tube was irradiated for 15 min with high pressure Hg lamp (100 W) through Pyrex filter. After the completion of the reaction was approved with ^{1}H-NMR spectrum, the solution of the product was evaporated under reduced pressure (5 mmHg) and the residue was purified by flash chromatography (SiO_2: benzene) to give **10a** (19 mg, 95%) as a crystalline solid: mp 168°C. IR (KBr) cm^{-1}: 3200-3050(NH), 1715(C=O). MS m/z: 296 and 298(M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.35(2H,d,J=9Hz,Ar-H), 6.90(2H,d,J=9Hz,Ar-H), 6.65(1H,br,NH), 4.95(1H,m,C_5-H), 3.65(2H,m,$OC\underline{H}_2CH_3$), 3.35(1H,dd,J=2Hz,4Hz,C_3-H), 3.20(1H,m,C_4-H), 1.25(3H,t,J=7Hz,$OCH_2C\underline{H}_3$).

Thermal Decomposition of **4a**

The solution of **4a** (500 mg) in DMF (10 ml) was refluxed for 30 min and then evaporated in reduced pressure (10 mmHg). The residual mixture was separated by flash chromatography (SiO_2: hexane-acetone) to give **10a** (215 mg, 47%) and **13** (72 mg, 16%) as crystalline solids. **13**: mp 156°C(decomp.). IR (KBr) cm^{-1}: 3350 (NH), 3195(NH), 1730(C=O). MS m/z: 296 and 298(M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.1(1H, br,NH), 7.40(2H,d,J=9Hz,Ar-H), 7.05(1H,br,NH), 7.00(2H,d,J=9Hz,Ar-H), 5.75(1H,dd, J=2Hz,0.5Hz, C_4 or C_5-H), 5.50(1H,dd,J=2Hz,0.5Hz, C_4 or C_5-H), 3.60(2H,q,J=7Hz, OCH_2CH_3), 1.20(3H,t,J=7Hz,OCH_2CH_3).

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5. Because only a small amount of triazolines (**5a** and **6a**) having cis configuration was obtained in the cycloaddition reaction, the reaction pathways of **5a** and **6a** were confirmed by ^{1}H-NMR and TLC analysis.
6. Y. Kosugi, F. Hamaguchi, T. Nagasaka, N. Ozawa and S. Ohki, Heterocycles, 1980, **14**, 1245.
7. 5-Alkoxy-3-pyrrolin-2-ones (2) were prepared from furfural via 5-ethoxy-2(5H)-furanone (1) by using Fariña's procedure adapted from: F. Fariña, M. V. Martín and M. C. Paredes, Synthesis, 1973, 167.

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