Cyclization of 1-Aryl-1-nitroso-3-(2-pyridylmethyl)ureas to 2-Aryl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-ones

Shozo KAMIYA,*[,a] Kentaro YAMAGUCHI,[b] Makoto MIYAHARA,[a] and Naoki MIYATA[a]

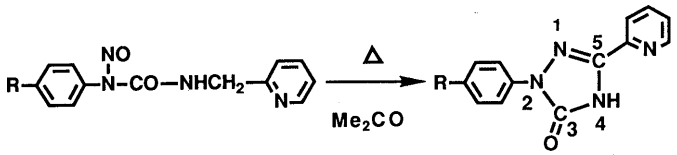
Division of Organic Chemistry, National Institute of Hygienic Sciences,[a] 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan and School of Pharmaceutical Sciences, Showa University,[b] Shinagawa-ku, Tokyo 142, Japan. *Received April 13, 1990*

1-Aryl-1-nitroso-3-(2-pyridylmethyl)ureas cyclize to 2-aryl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-ones on being heated in acetone, chloroform or ether, in 59—86% yields. Their structures were confirmed by X-ray crystallography, and the molecular geometry of the 2,4-dihydro-1,2,4-triazol-3-one ring is discussed in comparison with those of related zwitterionic ring compounds. Similar treatment of the corresponding 4-pyridyl derivative, 1-aryl-1-nitroso-3-(4-pyridylmethyl)urea did not give any cyclized compound, and 1,3-bis(4-pyridylmethyl)urea was obtained in 60% yield. Mechanisms are proposed for the above reactions.

Keywords *N*-nitrosourea; pyridylmethylnitrosourea; 1-aryl-1-nitroso-3-(2-pyridylmethyl)urea; 1-phenyl-1-nitroso-3-(4-pyridylmethyl)urea; thermal decomposition; cyclization; 2,4-dihydro-1,2,4-triazol-3-one; 2-aryl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-one; X-ray crystallography; bond length

One hundred thirty *N*-nitrosoureas have been synthesized in this laboratory aiming at effective antitumor agents, and their antitumor activities were tested in our first screening system, consisting of rat ascites hepatoma AH13 and mouse lymphoid leukemia L1210 cells.[1-6] Formation of active chemical species from these antitumor *N*-nitrosoureas in tumor cells was chemically and biologically elucidated.[1,2,6] During the synthetic studies we found several cyclization reactions which occurred on the nitrosation of ureas.[7] This paper describes a new cyclization of 1-aryl-1-nitroso-3-(2-pyridylmethyl)ureas (Ia, b) to give 2-aryl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-ones (IIa, b).

When a solution of 1-nitroso-1-phenyl-3-(2-pyridylmethyl)urea (Ia) in acetone was refluxed for 30 min, crystals were produced. The infrared (IR) spectrum of the product in Nujol showed a strong absorption at 1725 cm^{-1}, presumably due to a five-membered ureidocarbonyl group. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum in DMSO-d_6 showed the presence of a phenyl nucleus and a 2-pyridyl nucleus, and did not show any signals due to the pyridylmethylene protons of the starting *N*-nitrosourea (Ia). Elementary analysis and mass spectrum (MS) data indicated the molecular formula $C_{13}H_{10}N_4O$.



Ia : R=H
Ib : R=OCH_3

IIa : R=H
IIb : R=OCH_3

Chart 1

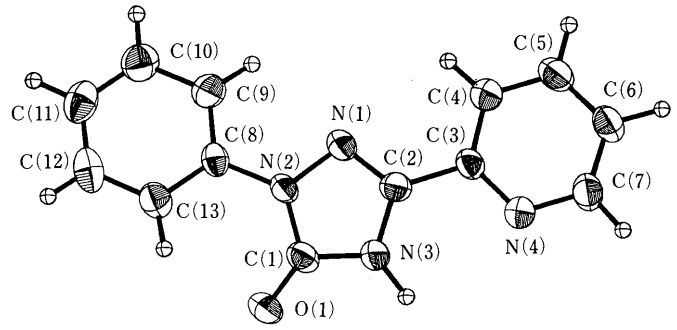
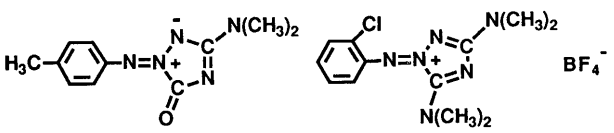


Fig. 1. ORTEP Drawing of 1-Phenyl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-one (IIa)

These spectral and elementary analysis data suggested that the structure of the product is 2-phenyl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-one (IIa).

This type of compound, 2,5-diphenyl-2,4-dihydro-1,2,4-triazol-3-one,[8] has been synthesized by the treatment of benzaldehyde 2-phenylsemicarbazone [$C_6H_5CH=NN(C_6H_5)CONH_2$] with sulfur monochloride, in 32% yield. Since an attempt to synthesize an authentic sample of the above product by a similar method did not succeed, the structure was finally determined by X-ray crystallography. An ORTEP drawing of IIa, confirming the proposed structure, is shown in Fig. 1, and the final atomic coordinates for the nonhydrogen atoms are listed in Table II in the experimental section.

The bond lengths and angles of the 2,4-dihydro-1,2,4-triazol-3-one ring in IIa (listed in Table III in the experimental section) were compared with those found in zwitterionic 1-(4-tolyl)imino-5-dimethylamino-2,4-triazolin-3-one (III) and 1-(2-chrolophenyl)imino-5-di-



III IV

Chart 2

Table I. Yields of 2-Aryl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-ones (IIa, IIb) Obtained by Cyclization of 1-Aryl-1-nitroso-3-(2-pyridylmethyl)ureas (Ia, Ib) in Various Solvents

Solvent	Yield (%)	
	IIa	IIb
Me_2CO	62	86
$CHCl_3$	75	77
Et_2O	59	65

methylamino-1,2,4-triazolium fluoroborate (IV).[8]

In the cases of III and IV, unusually long bond lengths for N–CO of III (1.546 Å) and for N–C of IV (1.483 Å) were reported,[9] whereas that of IIa was 1.372 Å, which is close to a normal value for a usual conjugated N–C bond. This feature, together with the good planarity of the IIa ring, indicates extensive electron delocalization, and the contribution of the zwitterionic form is smaller than in the mesoionic compounds (III, IV).

Similarly, reflux of a solution of 1-nitroso-1-(4-methoxyphenyl)-3-(2-pyridylmethyl)urea (Ib) in acetone for 30 min gave 2-(4-methoxyphenyl)-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-one (IIb).

Yields of IIa and IIb obtained by refluxing solutions of Ia and Ib in acetone, in chloroform and in ether are shown in Table I. It is clear that Ib having a 4-methoxy group in the 1-aryl group gave a better yield than Ia in each solvent, and no significant solvent dependence of the yields was observed.

The mechanism of this type of cyclization is proposed to be as follows.

With the electronic participation of the 2-pyridyl nitrogen, the *N*-nitroso oxygen and the ureido hydrogen, as shown in Chart 3, one of the pyridylmethylene protons adjacent to the strongly electron-withdrawing 2-pyridyl nucleus moves to the *N*-nitroso oxygen, and the cyclized intermediates Va and Vb, thus formed, are then dehydrated to yield 2-aryl-5-(2-pyridyl)-1,2,4-triazol-3-ones (IIa, IIb).

Another cyclization mechanism, involving *N*-nitroso group migration to the pyridylmethylene to yield a *C*-nitroso compound [ArNHCONHCH(NO)2-Py], followed by cyclodehydration, was considered. However, since the products IIa, b were not isolated on nitrosation of the starting urea [ArNHCONHCH$_2$2-Py] under various conditions, the *N*-nitroso group migration mechanism can be ruled out.

Then, 1-nitroso-1-phenyl-3-(4-pyridylmethyl)urea (VI) having a 4-pyridylmethyl group in place of the 2-pyridylmethyl group in Ia, b, was heated in acetone. However, the products were 1,3-bis(4-pyridylmethyl)urea (VII) (60% yield), the structure of which was identified by elementary analysis and NMR spectroscopy, and the denitrosated urea, 1-phenyl-3-(4-pyridylmethyl)urea (VIII) (11% yield), together with a considerable amount of an

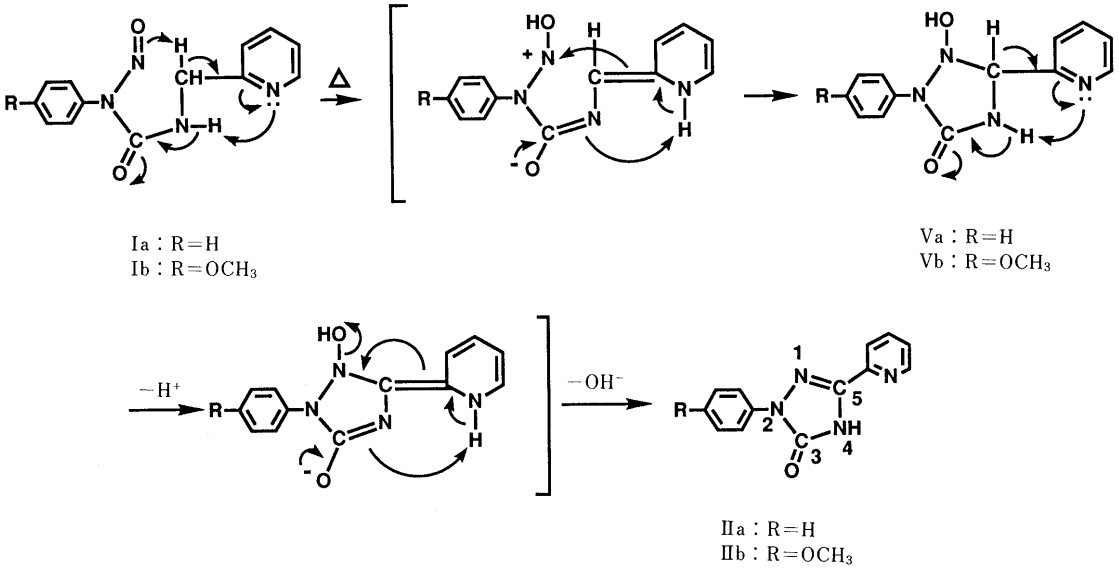


Chart 3

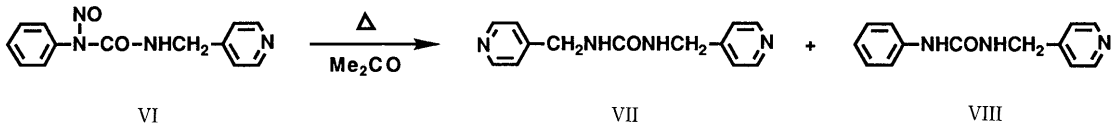


Chart 4

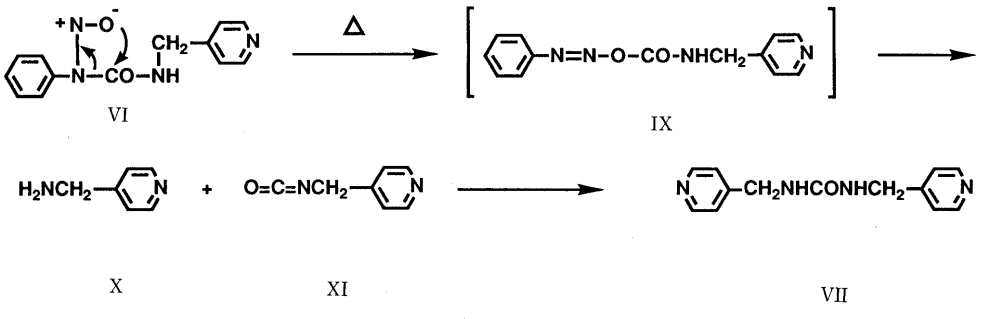


Chart 5

intractable tar, and no cyclized compound was obtained. It is concluded that this type of cyclization is characteristic of the 1-aryl-1-nitroso-3-(2-pyridylmethyl)ureas.

Thermal decomposition reactions of 1,3-disubstituted *N*-nitrosoureas in various organic solvents were studied in our laboratory, and in most of these reactions, the formation of aryldiazo carbamates [ArN=NOCONHAr'(R)] as reaction intermediates has been confirmed.[1,5,7]

It is considered that the 4-pyridyl nitrogen of VI does not interact with the ureido hydrogen as the 2-pyridyl nitrogens of Ia and Ib do. Consequently, as shown in Chart 5, an aryldiazo carbamate IX is proposed as an intermediate to give the product VII. Compound VI rearranges to phenyldiazo *N*-(4-pyridylmethyl)carbamate (IX), which decomposes to yield 4-pyridylmethylamine (X) and 4-pyridylmethylisocyanate (XI), together with phenyldiazo hydroxide. The successive reaction of X and XI gives a bisurea VII.

Product VIII in Chart 4 is the thermally denitrosated urea of VI.

These findings show that the cyclization to form the 2,4-dihydro-1,2,4-triazol-3-one ring only occurs in compounds such as 1-aryl-1-nitroso-3-(2-pyridylmethyl)ureas. Studies on the pharmaceutical application of the newly obtained 2,4-dihydro-1,2,4-triazol-3-ones are in progress.

Experimental

All melting points are uncorrected. IR spectra were measured on a JASCO model IR-S spectrophotometer. ^{1}H-NMR spectra were recorded on Varian 360A and JEOL 60 spectrometers with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants (J) are expressed in hertz (Hz). MS were measured on a JEOL LMS-01 SG-2 spectrometer.

2-Phenyl-5-(2-pyridyl)-2,4-dihydro-1,2,4-triazol-3-one (IIa) A solution of 1-nitroso-1-phenyl-3-(2-pyridylmethyl)urea[4] (Ia) (7.68 g, 0.03 mol) in Me_2CO (60 ml) was refluxed on a water bath for 30 min. The reaction mixture became dark red. After cooling, the separated crystals were filtered, washed with Me_2CO, and recrystallized from EtOH to give pink needles, mp 228—229 °C. Yield 4.40 g (62%). IR (Nujol): 1725 cm^{-1}. MS *m/z*: 238 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.47; H, 4.19; N, 23.96.

2-(4-Methoxyphenyl)-5-(2-pyridyl)-2,3-dihydro-1,2,4-triazol-3-one (IIb) 1-(4-Methoxyphenyl)-3-(2-pyridylmethyl)urea: 4-Methoxyphenyl isocyanate (14.9 g, 0.1 mol) was added dropwise into a solution of 2-pyridylmethylamine (10.8 g, 0.1 mol) in ether (100 ml) with stirring under ice cooling. The crystals that separated were filtered, washed with ether, and recrystallized from ethanol to give colorless needles, mp 156 °C. Yield 23.1 g (90%). IR (Nujol): 3240, 1590, 1130, 1100 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.18; H, 5.72; N, 16.55.

1-(4-Methoxyphenyl)-1-nitroso-3-(2-pyridylmethyl)urea (Ib): A solution of $NaNO_2$ (0.83 g, 0.012 mol) in water (5 ml) was added dropwise into a solution of 1-(4-methoxyphenyl)-3-(2-pyridylmethyl)urea (2.57 g, 0.01 mol) in 10% HCl (15 ml) with stirring under ice cooling. Stirring was continued for a further 10 min. The reaction mixture was neutralized with sodium bicarbonate under ice cooling. The crystals that separated were filtered, and recrystallized from Et_2O to give yellow needles, mp 107 °C (dec.). Yield 2.03 g (71%). IR (Nujol): 3150, 1715, 1130, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.62 (3H, s), 4.68 (2H, d, J=4).

2-(4-Methoxyphenyl)-5-(2-pyridyl)-2,3-dihydro-1,2,4-triazol-3-one (IIb): A solution of Ib (2.86 g, 0.01 mol) in Me_2CO (60 ml) was refluxed on a water bath for 30 min, then the solvent was evaporated off under reduced pressure, and the residue was recrystallized from EtOH to give pale brownish needles, mp 208—209 °C. Yield 2.30 g (86%). IR (Nujol): 1720, 1135, 1105 cm^{-1}. MS *m/z*: 268 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.48; H, 4.50; N, 20.71.

Refluxing of solutions of Ia and Ib in $CHCl_3$ and in Et_2O was similarly carried out, and the yields of crystalline products are summarized in Table I.

Decomposition of 1-Nitroso-1-phenyl-3-(4-pyridylmethyl)urea (VI) in Me_2CO A solution of 1-nitroso-1-phenyl-3-(4-pyridylmethyl)urea[4,5] (VI) (1.27 g, 0.005 mol) in Me_2CO (40 ml) was refluxed for 1 h. The reaction mixture was concentrated under reduced pressure, the crystals that separated were filtered, and recrystallized from hot water to give pale orange needles, mp 182—183 °C. 1,3-Bis(4-pyridylmethyl)urea (VII). Yield 0.36 g (60%). *Anal.* Calcd for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.13. Found: C, 64.11; H, 5.73; N, 22.83. From the filtrate separated from VII, 1-phenyl-3-(4-pyridylmethyl)urea (VIII), mp 138—140 °C, was isolated. Yield 0.12 g (11%).

X-Ray Crystallography of the Product The observed cell parameters for a crystal of IIa (0.45 × 0.15 × 0.05 mm) recrystallized from EtOH were as follows: molecular formula $C_{13}H_{10}N_4O$, molecular weight 238.25, space group $C2/c$ (monoclinic), $Z=8$, $a=34.577(4)$, $b=3.855(1)$, $c=20.313(2)$ Å, $\beta=125.64(1)°$, $V=2200.6(6)$ Å^3, $D_c=1.438$ g·cm^{-3}. Data were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu$K_{\alpha 1}$ radiation by the $\theta-2\theta$ scan method. The scan speed was 16 degrees/min. The data were corrected for Lorentz and polarization factors, but no absorption correction was applied. A total of 1654 reflections were measured within the 2θ angle of 120°. The crystal structure was determined by the direct method and refined by the full-matrix least-squares method. The final R value was 0.062 for 1093 reflections above $3\sigma(F)$ including anisotropic thermal factors for nonhydrogen atoms and isotropic ones for hydrogen atoms. The final atomic coordinates for hydrogen atoms are listed in Table II, and bond lengths and angles in the triazolone ring listed in Table III.

TABLE II. Fractional Atomic Coordinates and Isotropic Thermal Parameters

	X	Y	Z	B_{eq}
C(1)	0.4111 (1)	0.2068 (10)	0.5686 (2)	3.90 (15)
C(2)	0.4082 (1)	0.3243 (9)	0.6729 (2)	3.39 (15)
C(3)	0.4224 (1)	0.4477 (8)	0.7520 (2)	3.29 (14)
C(4)	0.3898 (1)	0.4610 (10)	0.7704 (2)	4.04 (16)
C(5)	0.4040 (1)	0.5838 (11)	0.8451 (2)	4.71 (18)
C(6)	0.4502 (1)	0.6903 (11)	0.8989 (2)	4.42 (17)
C(7)	0.4807 (1)	0.6683 (11)	0.8760 (2)	4.43 (17)
C(8)	0.3271 (1)	−0.0182 (8)	0.4809 (2)	3.22 (14)
C(9)	0.2843 (1)	−0.0064 (11)	0.4715 (2)	4.09 (16)
C(10)	0.2437 (1)	−0.1347 (12)	0.4002 (2)	4.73 (18)
C(11)	0.2462 (1)	−0.2701 (11)	0.3403 (2)	4.70 (19)
C(12)	0.2889 (1)	−0.2777 (10)	0.3507 (2)	4.98 (21)
C(13)	0.3301 (1)	−0.1526 (10)	0.4210 (2)	4.29 (17)
N(1)	0.3665 (1)	0.1937 (7)	0.6187 (1)	3.70 (12)
N(2)	0.3684 (1)	0.1151 (8)	0.5539 (1)	3.39 (12)
N(3)	0.4367 (1)	0.3354 (7)	0.6467 (1)	3.66 (12)
N(4)	0.4675 (1)	0.5510 (7)	0.8038 (1)	4.04 (13)
O(1)	0.4240 (1)	0.1801 (6)	0.5243 (1)	5.24 (11)

$B_{eq}=1/3\sum_i\sum_j B_{ij}a_i^*a_j^*a_ia_j$.

TABLE III. Bond Lengths (Å) and Angles (°) in 2,4-Dihydro-1,2,4-triazol-3-one (IIa)

Bond length (Å)		Bond angle (°)	
C(2)–N(1)	1.302 (4)	C(2)–N(1)–N(2)	104.2 (4)
N(1)–N(2)	1.388 (6)	N(1)–N(2)–C(1)	112.1 (9)
N(2)–C(1)	1.372 (7)	N(2)–C(1)–N(3)	103.4 (4)
C(1)–N(3)	1.382 (5)	C(1)–N(3)–C(2)	108.0 (3)
N(3)–C(2)	1.368 (8)	N(3)–C(2)–N(1)	112.1 (4)

Acknowledgement The authors are grateful to Prof. Y. Masaki, Gifu Pharmaceutical University for valuable suggestions concerning the cyclization mechanism.

References

1) S. Kamiya, *Bulletin of National Institute of Hygienic Sciences*, **104**, 1 (1986).
2) Mi. Miyahara, Dissertation, Tohoku University, 1986.
3) Mi. Miyahara, S. Kamiya, A. Maekawa, and S. Odashima, *Gann*, **70**, 731 (1979).

4) S. Kamiya and S. Sueyoshi, *Chem. Pharm. Bull.*, **31**, 1738 (1983).
5) S. Kamiya, M. Miyahara, and Mi. Miyahara, *Chem. Pharm. Bull.*, **34**, 385 (1986).
6) S. Kamiya, Mi. Miyahara, and M. Miyahara, 13th Symposium in Progress in Organic Reactions and Syntheses—Applications in the Life Sciences—Symposium Papers, Tokushima, Nov. 1986, p. 87.
7) M. Miyahara and S. Kamiya, Abstracts of Papers, 17th Congress of Heterocyclic Chemistry, Sapporo, Aug. 1985, p. 24; M. Miyahara and S. Kamiya, *Chem. Pharm. Bull.*, **30**, 3466 (1986).
8) R. Milcent and Thu-Huong Nguyen, *J. Heterocycl. Chem.*, **23**, 881 (1986).
9) A. E. Baydar, G. V. Boyd, P. F. Lindley, and A. R. Walton, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 415; P. F. Lindley, A. R. Walton, A. E. Baydar, and G. V. Boyd, *Acta Cryst.*, **C41**, 1669 (1985).