

Synthesis of (Z)-N-[5-(3-Aryl)-[1,2,4]oxadiazolyl]-N-[(methylcarbamoyl)methyl]benzamidoximes¹⁾

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(Z)-N-[5-(3-Aryl)-[1,2,4]oxadiazolyl]-N-[(methylcarbamoyl)methyl]benzamidoximes (**3**) were synthesized through the reaction of 3-methylglycociamidine (**2**) with primary nitroalkanes (**1**) and acetyl chloride. The structural determination of **3** by single crystal X-ray analysis is reported.

Keywords primary nitro alkane; nitrile oxide; glycociamidine; [1,2,4]oxadiazole; 1,3-dipolar cycloaddition; X-ray analysis

As a part of the extensive application of one-pot synthesis of various heterocycles containing an N—O bond by use of nitrile oxides generated *in situ* through the O-acylation of primary nitroalkane (**1**) with acetyl chloride,²⁾ we have reported the synthesis of N,1-bis[5-(3-substituted)-[1,2,4]oxadiazolyl]dimethylamine by the reaction of the nitrile oxides with creatinine.³⁾ This paper deals with a formation of a new type of 5-amino[1,2,4]oxadiazole derivatives by use of another glycociamidine derivative, *i.e.*, 3-methylglycociamidine (**2**), in the above-mentioned reaction. When **2** was allowed to react with excess nitrile oxides (**5a**: R=H, **5b**: R=CH₃) generated by the method reported (ref. 2), N-[5-(3-aryl)-[1,2,4]oxadiazolyl]-N-[(methylcarbamoyl)methyl]benzamidoximes (**3a**: R=H, **3b**: R=CH₃) were obtained in 52 and 51% yields, respectively (Chart 1).

The structure of **3a** was determined by single crystal X-ray analysis. A perspective drawing of the molecular

structure of **3a** is shown in Fig. 1. The molecule consists of both the 3-phenyl-[1,2,4]oxadiazolyl moiety and the glycineamide moiety attached to N(3) of the benzamidoxime, and the oxime OH group is *anti* to the phenyl group of the benzamidoxime moiety, *i.e.*, the molecule is in the Z configuration.

The postulated mechanism of formation of **3** is illustrated in Chart 2. Thus the imidazoline ring of 3-methylglycociamidine (**2**) is cleaved by methoxide anion and the resulting imine intermediate (**4**) reacts with the nitrile oxide (**5**), in an 1,3-dipolar cycloaddition to give the intermediate oxadiazole (**6**). Further electrophilic attack of excess nitrile oxide (**5**) on the NH group of the glycineamide moiety of **6** finally gives the benzamidoxime (**3**).

Further detailed studies are in progress.

Experimental

N-[(Methylcarbamoyl)methyl]-N-[5-(3-phenyl)-[1,2,4]oxadiazolyl]-benzamidoxime (**3a**) 3-Methylglycociamidine hydroiodide⁴⁾ (241 mg,

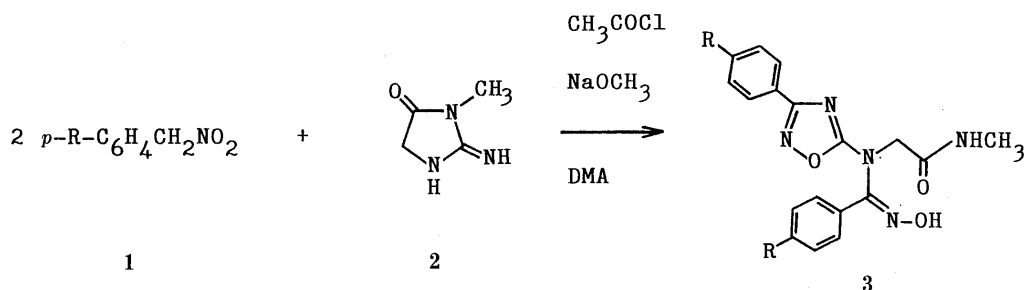


Chart 1

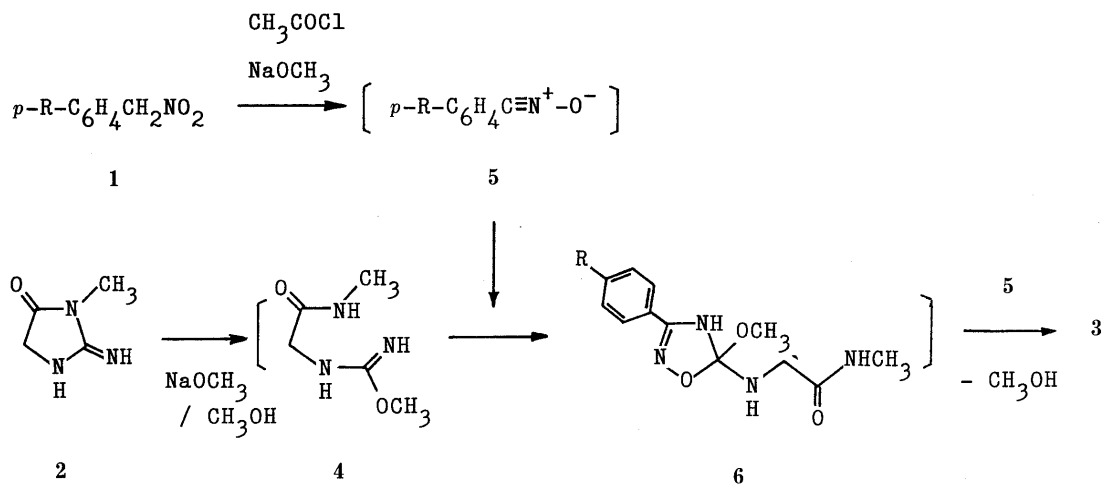
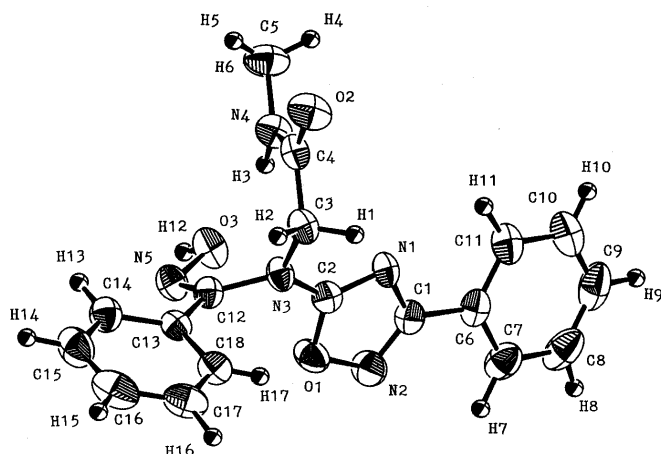


Chart 2

Fig. 1. Molecular Structure of Compound **3a**

1.0 mmol) was added to a solution of phenylnitromethane (**1a**)⁵⁾ (548 mg, 4.0 mmol) and acetyl chloride (0.28 ml, 4.0 mmol) in *N,N*-dimethylacetamide (DMA, 10 ml) with 1*N* sodium methoxide (4 ml) under cooling to 0°C. The mixture was stirred at room temperature overnight. After neutralization with 10% aqueous sodium hydrogen carbonate followed by extraction with ethyl acetate, further purification by column chromatography on silica gel (CHCl₃–EtOAc, 4:1) was carried out. The main product was **3a** (184 mg), colorless prisms, yield 52%. **3a**: mp 150–152°C (from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{−1}: 3360 (NH), 2800–3200 (N–OH), 1658 (C=O). ¹H-NMR (δ in CDCl₃, 300 MHz) δ : 2.87 (3H, d, NCH₃), 4.79 (2H, s, CH₂), 6.00 (1H, br s, NH, exchangeable with deuterium oxide), 7.4–8.2 (10H, m, 2C₆H₅), 12.07 (1H, s, =N–OH, exchangeable with deuterium oxide). ¹³C-NMR (δ in DMSO-*d*₆) δ : 25.7 (NCH₃), 52.0 (CH₂), 126.0 (phenyl *C-ipso*), 126.7 (phenyl *C-ipso*), 126.8 (phenyl *C-meta*), 127.0 (phenyl *C-meta*), 128.7 (phenyl *C-meta* and *C-ortho*), 129.1 (phenyl *C-ortho*), 130.1 (phenyl *C-ortho*), 131.3 (phenyl *C-para*), 131.7 (phenyl *C-para*), 146.2 (C=N–OH), 167.2 (–C=N–), 167.8 (–C=N–), 169.7 (–CO–NH–). MS *m/z*: 351 (M⁺). Anal. Calcd for C₁₈H₁₇N₅O₃: C, 61.55; H, 4.97; N, 19.70. Found: C, 61.53; H, 4.88; N, 19.93.

N-[(Methylcarbamoyl)methyl]-*N*-[5-(3-tolyl)-[1,2,4]oxadiazolyl]-benzamidoxime (**3b**) was prepared in a similar manner. The crude products were separated by column chromatography on silica gel (CHCl₃–EtOAc, 4:1). The main product **3b** was obtained in 51% yield, mp 155°C (dec., from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{−1}: 3330 (NH), 2800–3200 (N–OH), 1650 (C=O). ¹H-NMR (δ in CDCl₃, 300 MHz) δ : 2.36, 2.38 (each 3H, s, *p*-CH₃), 2.77 (3H, d, *J*=4.8 Hz, NHCH₃), 4.38 (2H, s, CH₂), 7.76 (1H, s, NH, exchangeable with deuterium oxide), 7.10–7.90 (8H, m, 2*p*-CH₃C₆H₄), 12.15 (1H, s, NOH, exchangeable with deuterium oxide). ¹³C-NMR (δ in CDCl₃) δ : 21.4 (*p*-CH₃), 21.6 (*p*-CH₃), 26.3 (NHCH₃), 52.8 (CH₂), 123.9 (*p*-tolyl *C-ipso*), 125.9 (*p*-tolyl *C-ipso*), 126.2 (*p*-tolyl *C-meta*), 127.3 (*p*-tolyl *C-meta*), 128.0 (*p*-tolyl *C-meta*, *C-ortho*), 129.4 (*p*-tolyl *C-ortho*), 129.6 (*p*-tolyl *C-ortho*), 129.8 (*p*-tolyl *C-ortho*), 141.5 (*p*-tolyl *C-para*), 141.6 (*p*-tolyl *C-para*), 147.5 (C=NOH), 168.3 (–C=N–), 168.8 (–C=N–), 169.1 (–CONH–). MS *m/z*: 379 (M⁺). Anal. Calcd for C₂₀H₂₁N₅O₃: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.15; H, 5.60; N, 18.33.

X-Ray Analysis of 3a A colorless prism crystal having approximate dimensions of 0.2×0.3×0.2 mm was mounted on a Rigaku AFC-5R diffractometer and the cell parameters and the intensity data were measured with graphite-monochromated CuK α radiation. The crystal data: (Z)-*N*-(Methylcarbamoyl)methyl-*N*-[5-(3-phenyl)-[1,2,4]oxadiazolyl]benzamidoxime, C₁₈H₁₇N₅O₃, *M_r*=351.36, monoclinic, space group C2/c, *a*=29.8(1), *b*=7.358(4), *c*=17.59(4) Å, β =119.1(2)°, *V*=3375 Å³, *Z*=8, *D*_{cal}=1.383 g cm^{−3}, *D*_{meas}=1.385 g cm^{−3}, μ for CuK α 0.91 cm^{−1}. Of the total of 3292 reflections up to the 2 θ range of 50.1°, 3222 were measured as above the 3 σ (*I*) level and were used for the structure determination. Approximate atomic coordinates were obtained by the direct method using the program MITHRIL⁶⁾ and subsequently they were

TABLE I. The Positional and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviation in Parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
O(1)	0.33185 (8)	0.0166 (3)	−0.0719 (1)	3.92 (9)
O(2)	0.47724 (8)	0.6076 (3)	0.0636 (1)	4.4 (1)
O(3)	0.44059 (8)	−0.0627 (3)	0.0111 (1)	3.8 (1)
N(1)	0.3023 (1)	−0.0281 (3)	−0.0306 (2)	4.1 (1)
N(2)	0.35354 (8)	0.2161 (3)	0.0354 (1)	2.9 (1)
N(3)	0.39140 (8)	0.2335 (3)	−0.0566 (1)	2.8 (1)
N(4)	0.4841 (1)	0.3128 (4)	0.0988 (2)	3.5 (1)
N(5)	0.43292 (9)	−0.0270 (3)	−0.0729 (1)	3.3 (1)
C(1)	0.3168 (1)	0.0949 (4)	0.0303 (2)	3.1 (1)
C(2)	0.3604 (1)	0.1599 (4)	−0.0277 (2)	2.9 (1)
C(3)	0.4092 (1)	0.4198 (4)	−0.0340 (2)	3.2 (1)
C(4)	0.4597 (1)	0.4509 (4)	0.0470 (2)	3.1 (1)
C(5)	0.5324 (1)	0.3344 (6)	0.1787 (2)	4.8 (2)
C(6)	0.2971 (1)	0.0962 (4)	0.0922 (2)	3.3 (1)
C(7)	0.3233 (1)	0.1932 (4)	0.1687 (2)	4.0 (1)
C(8)	0.3066 (2)	0.1857 (6)	0.2298 (2)	5.2 (2)
C(9)	0.2648 (1)	0.0842 (5)	0.2147 (2)	5.1 (2)
C(10)	0.2386 (1)	−0.0108 (6)	0.1388 (2)	5.2 (2)
C(11)	0.2544 (1)	−0.0076 (5)	0.0763 (2)	4.4 (2)
C(12)	0.4099 (1)	0.1243 (4)	−0.1026 (2)	2.8 (1)
C(13)	0.4005 (1)	0.1880 (4)	−0.1884 (2)	2.7 (1)
C(14)	0.4352 (1)	0.1504 (4)	−0.2175 (2)	3.5 (1)
C(15)	0.4247 (1)	0.2060 (5)	−0.2990 (2)	4.6 (2)
C(16)	0.3805 (2)	0.2995 (5)	−0.3517 (2)	5.0 (2)
C(17)	0.3455 (1)	0.3392 (5)	−0.3245 (2)	4.4 (1)
C(18)	0.3564 (1)	0.2833 (4)	−0.2423 (2)	3.6 (1)

TABLE II. Selected Bond Lengths and Torsion Angles

A–X–Y–B	Bond length (1/Å) X–Y	Torsional angle (φ/°) along X–Y
N2–C1–C6–C7	1.466 (5)	−14.4 (4)
N5–C12–C13–C14	1.471 (5)	−33.4 (4)
O1–C2–N3–C3	1.365 (4)	158.4 (2)
N5–C12–N3–C3	1.427 (4)	122.2 (3)

refined by the full-matrix least-squares method. The final *R* value was 0.043 including all seventeen hydrogen atoms. Torsional angles along the bonds connecting each group are listed in Table II.

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