Synthesis of Pyridyloxadiazoles 1. Characterization and Thermal Rearrangement of an Unexpected 1,2,4-Oxadiazol-5(4*H*)one

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The synthesis of pyridyloxadiazoles by the reaction of acid chlorides with 5-(2-pyridyl)-tetrazole or 2-pyridineamidoxime was studied. Reaction of 2-pyridineamidoxime with *N,N*-dimethylcarbamyl chloride produced 3-(2-pyridyl)-4-*N,N*-dimethylaminocarbonyl-1,2,4-oxadiazol-5(4*H*)one instead of the expected oxadiazole. The oxadiazolone underwent thermal rearrangement with expulsion of carbon dioxide to yield the desired 3-(2-pyridyl)-5-*N,N*-dimethylamino-1,2,4-oxadiazole.

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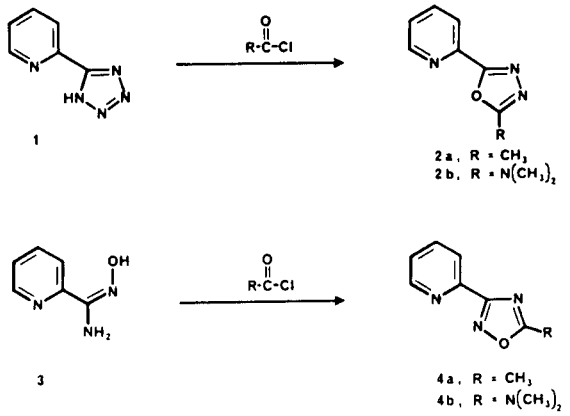
Synthesis of 2-(2-pyridyl)-1,3,4-oxadiazoles (**2**) and 3-(2-pyridyl)-1,2,4-oxadiazoles (**4**) is usually accomplished by reacting 5-(2-pyridyl)tetrazole (**1**) (3) and 2-pyridineamidoxime (**3**) (4), respectively, with the appropriate acid chloride in refluxing pyridine (5-7) (Scheme I). We

Scheme 1



report here the synthesis, characterization and thermal rearrangement of an unexpected 1,2,4-oxadiazol-5-one from the reaction of **3** with *N,N*-dimethylcarbamyl chloride. The conventional oxadiazoles obtained from the reaction of **1** and **3** with acetyl chloride and from the reaction of **1** with *N,N*-dimethylcarbamyl chloride are also described.

Reaction of acetyl chloride with **1** or **3** gave the expected 2-(2-pyridyl)-5-methyl-1,3,4-oxadiazole (**2a**) and 3-(2-pyridyl)-5-methyl-1,2,4-oxadiazole (**4a**), respectively. Likewise, reaction of *N,N*-dimethylcarbamyl chloride with **1** yielded the oxadiazole **2b** as the only isolable product. However, the expected oxadiazole **4b** was not formed when **3** was reacted with *N,N*-dimethylcarbamyl chloride. Instead, a crystalline solid, m.p. 142-143°, with an elemental analysis, ir and mass spectrum which were not consistent with the expected structure was obtained.

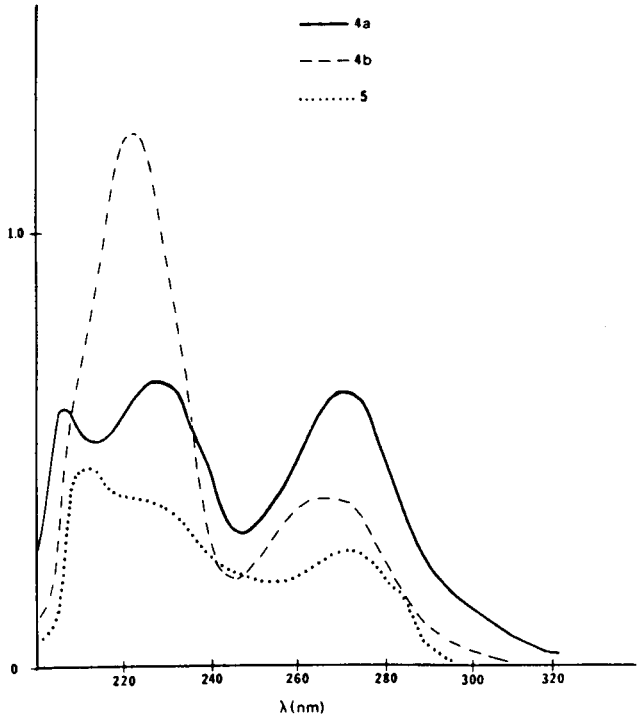


Figure 1. Uv spectra of **4a**, **4b** and **5** (7×10^{-5} *M* in methanol).

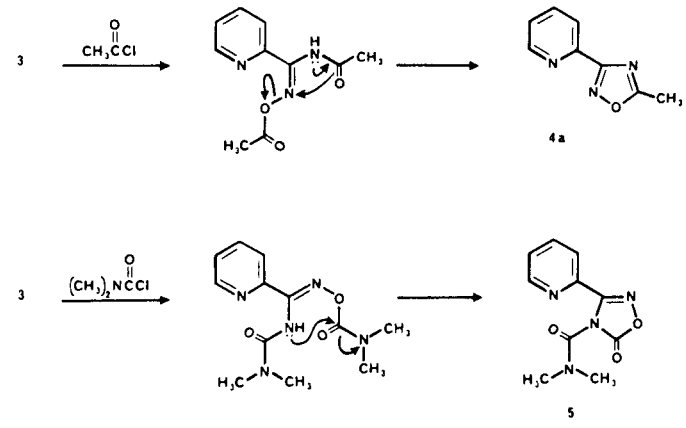
This compound was subsequently identified as 3-(2-pyridyl)-4-*N,N*-dimethylaminocarbonyl-1,2,4-oxadiazol-5-(4*H*)one (**5**) after analysis of the following data.

The nmr spectrum of **5** indicated the presence of only the *N,N*-dimethyl group and the aromatic protons, while the uv spectrum was not well-defined and showed little resemblance to the spectra of the previously described oxadiazoles (Figure 1). An ir band at 1730 cm^{-1} was characteristic of an amide carbonyl while a second band at 1800 cm^{-1} appeared to be due to a carbonyl group with an unusually high absorption. The mass spectrum indicated a molecular ion at m/e 234, 44 amu above the calculated molecular weight for oxadiazole **4b**. High resolution mass spectral analysis revealed that this ion had

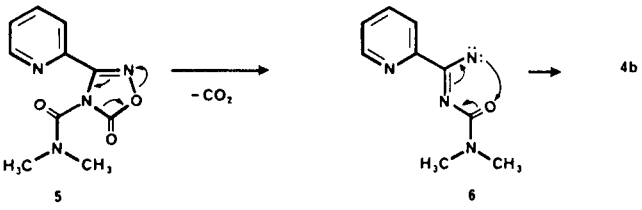
an elemental composition of $C_{10}H_{10}N_4O_3$ (Found: 234.0749, Calcd. 234.0751), indicating that this compound contained the elements of the expected oxadiazole **4b** plus CO_2. A strong peak was also present at m/e 190, the molecular weight of the expected product **4b**, and the doublet at nominal mass 44 indicated both CO_2^+ (Found: 43.9908, Calcd: 43.9898) and $C_2H_6N^+$ (Found: 44.0508, Calcd: 44.0500). Since no metastable ion corresponding to the transition 234 to 190 was seen and structure **4b** did not account for all the ions in the mass spectrum, the compound was subjected to analysis by combined gas chromatography-mass spectrometry (GC-MS) to see if a mixture existed. Only one major GC peak (>95%) which gave a mass spectrum with the molecular ion (m/e 190) as base peak was observed. Surprisingly, this mass spectrum was consistent with structure **4b** since the pyridine ring was intact and the *N*,*N*-dimethylaminocarbonyl moiety (m/e 72) now no longer dominated the mass spectrum as before when it was by far the most abundant fragment. This data suggested the thermal decomposition of the unknown compound in the GC injector port (240°) or on the GC column (160°) by extrusion of CO_2 to the expected oxadiazole **4b**.

The thermally rearranged oxadiazole was prepared on a laboratory scale in order to have sufficient material for conclusive identification. When the unknown material was gradually heated in a sealed tube to 215°, a mixture of starting material and the desired oxadiazole resulted. Prolonged heating, however, failed to increase the yield of the rearranged product and higher temperatures resulted in complete decomposition. The physical data for this new compound were consistent with the structure of the originally expected oxadiazole **4b**; elemental analysis, uv (Figure 1) and nmr all supported an oxadiazole structure and the ir spectrum showed the absence of both previously observed carbonyl bands. As expected, the mass spectrum of **4b** obtained from the sealed tube

Scheme 2



Scheme 3



reaction matched that obtained from the GC-MS analysis of the starting material. Thus the unidentified compound was thermally unstable (above 120°) and decomposed to **4b** by loss of carbon dioxide.

The above information plus a consideration of the probable reaction mechanism for the synthesis of oxadiazoles under conditions employing excess acid chloride (Scheme II) leads to **5** as the structure for the unknown compound. This structure agrees with the elemental analysis and with all available spectral data. In the case of the ir spectrum, the band at 1730 cm^{-1} is due to the side chain amide carbonyl and the band at 1800 cm^{-1}

Table 1.

Physical Properties of Some Pyridyloxadiazoles

Compound	Yield (%)	Chromatographic System (SiO_2)	Rf (a)	Crystn Solvent	M.p. °C	Elemental Analyses Calculated (%) C	H	N	Found (%) C	H	N
2a	46	Benzene-Acetone (1:1)	0.36	Ether	97-99	59.61	4.37	26.07	59.56	4.25	25.90
2b	36	Benzene-Acetone (1:1)	0.25	Ether	110-111	56.83	5.30	29.46	56.75	5.34	29.34
4a	70	Benzene-Acetone (2:1)	0.38	Benzene	88.5-89.5 (b)						
4b	27	Ethyl Ac-Chloroform (2:1)	0.31	Petroleum ether	95-96	56.83	5.30	29.46	56.72	5.25	29.37
5	23	Ethyl Ac-Chloroform (2:1)	0.41	Ether	142-143	51.27	4.30	23.92	51.19	4.36	23.81

(a) Determined by tlc in same system as column chromatography. (b) Lit. m.p. 87-88.5° (6).

can be assigned to an unconjugated cyclic carbonyl group (8). The proposed mechanism shows how the elements of carbon dioxide are incorporated into the molecule. Upon heating, CO_2 should be extruded in a fairly facile manner in order to rearrange to the initially expected oxadiazole **4b** (Scheme III). The observed thermal transformation can be rationalized in terms of a transient nitrene intermediate **6** which subsequently rearranges to the final product. Nitrenes have been postulated as reactive intermediates in other thermal transformations such as thermolysis of substituted 2*H*-azirines (9).

EXPERIMENTAL

All chemical reagents were purchased from E. Merck or Aldrich Chemical Co. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 727 spectrometer using Nujol mulls. Nmr spectra were recorded on a Varian EM-360 instrument and chemical shifts are given in ppm from tetramethylsilane. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer using 1 cm path cells. Both low and high resolution electron impact mass spectra were obtained on a DuPont 21-492B gas chromatograph-mass spectrometer system consisting of a Varian 2740 gas chromatograph coupled to the mass spectrometer *via* a single stage glass jet separator. Mass spectra were normally acquired from samples of the pure compound by direct probe insertion into the ion source. Analysis of **5** by GC-MS was accomplished with a 1.83 m X 2 mm i.d. glass column packed with 3% SE-30 on 100/120 mesh Gas Chrom Q and operated isothermally at 160°. Standard mass spectrometer operating conditions were: transfer line and jet separator, 240°; ion source, 240°; electron energy, 75 eV; ionizing current 250 μamp.; and scan speed, 4 or 10 seconds per decade. High resolution mass spectra were obtained under computer control (VG 2040 data system) at a dynamic resolution of approximately 4000, and accurate masses and probable elemental compositions were calculated using the commercially supplied data system software.

2-(2-Pyridyl)-5-methyl-1,3,4-oxadiazole (**2a**).

To a solution of 2 g. (13.5 mmoles) of **1** (1) in 40 ml. of dry pyridine was added 4 ml. of acetyl chloride at room temperature, and the resulting mixture refluxed for 2 hours. When the reaction was over, the mixture was diluted with water and cold 25% sodium hydroxide was added until the *p*H was basic. The pyridine was removed as an azeotrope and the resulting residue taken up in chloroform. Following purification of the crude reaction mixture by column chromatography under the conditions indicated in Table 1, **2a** was obtained as yellow crystals; uv (methanol): 242 nm (ε, 14000), 267 nm (ε, 14000); ir: 1580, 1570, 1560 cm^{-1}; nmr (deuteriochloroform): δ 2.8 (s, 3), 7.50 (m, 1), 7.95 (m, 1), 8.30 (d, 1), 8.80 (d, 1); ms: m/e (relative intensity) 161 (M^+, 100), 133 (12), 119 (20), 106 (15), 105 (12), 104 (19), 91 (55), 79 (26), 78 (97), 64 (20), 43 (66).

2-(2-Pyridyl)-5-*N*,*N*-dimethylamino-1,3,4-oxadiazole (**2b**).

In the same manner as for **2a**, 1 g. (6.8 mmoles) of **1** in 20 ml. of dry pyridine was reacted with 2.92 g. (27 mmoles) of *N*,*N*-dimethylcarbamyl chloride. The final chloroform extract was column chromatographed under the conditions described in Table 1 to afford **2b** which was recrystallized from ether to give white crystals; uv (methanol): 210 nm (ε, 6100), 306 nm (ε, 13000); ir: 1620, 1590 cm^{-1}; nmr (deuteriochloroform): δ 3.20 (s, 6), 7.40 (m, 1), 7.90 (m, 1), 8.20 (d, 1), 8.80 (d, 1); ms: m/e (relative intensity) 190 (M^+, 100), 161 (4), 146 (3), 119 (4), 106 (36), 78 (78), 72 (58), 51 (10).

3-(2-Pyridyl)-5-methyl-1,2,4-oxadiazole (**4a**) (**4**).

To a solution of 2.8 g. (20.4 mmoles) of **3** in 10 ml. of dry pyridine was added 2.17 ml. (38 mmoles) of acetyl chloride. When the exothermic reaction subsided, the mixture was refluxed for 2 hours. Water was added when the reaction was complete and pyridine removed as an azeotrope. The aqueous residue was extracted with chloroform several times, and a solid was obtained after removal of the solvent *in vacuo*. The crude product was purified under the conditions indicated in Table 1 to yield **4a** as white crystals; uv (Figure 1); ir: 1590, 1570 cm^{-1}; the nmr, uv, and mass spectrum corresponded to those previously reported for **4a** (6).

3-(2-Pyridyl)-4-*N*,*N*-dimethylaminocarbonyl-1,2,4-oxadiazol-5(4*H*)-one (**5**).

To a solution of 3.0 g. (21.9 mmoles) of **3** in 14 ml. of dry pyridine maintained at room temperature, 7.04 g. (65.7 mmoles) of *N*,*N*-dimethylcarbambyl chloride was added. The reaction mixture was refluxed for two hours, cooled and the pyridine removed as an azeotrope with water. The residue was extracted into chloroform and then purified under the conditions described in Table 1 to afford pure **5** as white crystals; uv (Figure 1); ir: 1800, 1730, 1590, 1580 cm^{-1}; nmr (deuteriochloroform): δ 3.20 (s, 6), 7.45 (m, 1), 8.00 (m, 2), 8.70 (d, 1); ms: m/e (relative intensity) 234 (M^+, 3), 190 (14), 147 (5), 146 (3), 105 (16), 104 (9), 78 (18), 72 (100).

3-(2-Pyridyl)-5-*N*,*N*-dimethylamino-1,2,4-oxadiazole (**4b**).

In a sealed tube 2.0 g. (8.5 mmoles) of **5** was gradually heated in an oil bath to 215°. After this temperature was reached the tube was cooled, broken open and its contents assayed by tlc. Two spots with Rf values of 0.31 and 0.41 were observed; the spot with the larger Rf corresponded to unrearranged starting material. After column chromatography under the conditions described in Table 1, **4b** was isolated. Recrystallization from benzene afforded pure **4b** as white crystals; uv (Figure 1); ir: 1670, 1650 cm^{-1}; nmr (deuteriochloroform): δ 3.25 (s, 6), 7.35 (m, 1), 7.80 (m, 1), 8.10 (d, 1), 8.80 (d, 1); ms: m/e (relative intensity) 190 (M^+, 100), 146 (21), 121 (5), 120 (6), 119 (4), 105 (58), 104 (17), 78 (16), 72 (15).

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