

A Facile Preparation of 4-(1-Acetyl-4(1*H*)-pyridylidene)-2-oxazolin-5-ones

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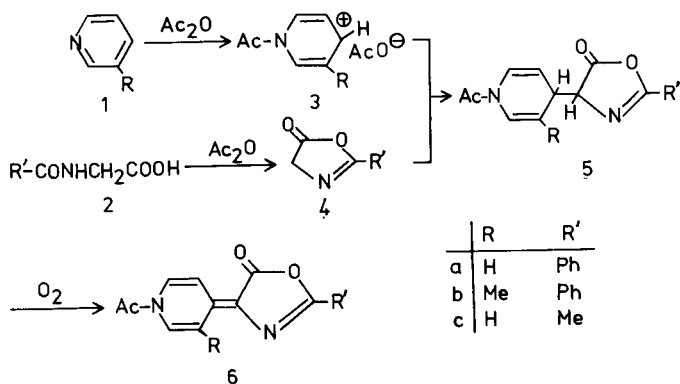
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4-(1-Acetyl-4(1*H*)-pyridylidene)-2-oxazolin-5-ones were prepared by the reaction of acylglycines with pyridine and acetic anhydride under oxygen. Acidic and alkaline hydrolysis of 2-oxazolin-5-ones provided oxazole derivatives, pyridine derivatives, and carboxylic acids.

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In the studies of chromogen in the colorimetric determination (1) of benzoylglycine (**2a**), we have found that the reaction of **2a** with pyridine and acetic anhydride yields a yellow compound, 2-oxazolin-5-one **6a** with a pyridylidene ring (2). The reaction probably proceeds through oxidation of an intermediate **5** formed by the nucleophilic substitution of 2-oxazolin-5-one **4a** for pyridinium cation **3a** as shown in Scheme 1. This mechanism suggests that the presence of an oxidant in the reaction mixture can accelerate the oxidation of the intermediate, and facilitate the formation of 2-oxazolin-5-one derivatives **6**.

Scheme 1



We wish to report a one step preparation of **6** by the condensation of acylglycine with pyridine and acetic anhydride. Oxygen was used as an oxidant, and the results are listed in Table 1. It was found that yields of **6** were higher when oxygen was bubbled into the reaction vessel was just open to the air.

Table 1

2-Oxazolin-5-ones

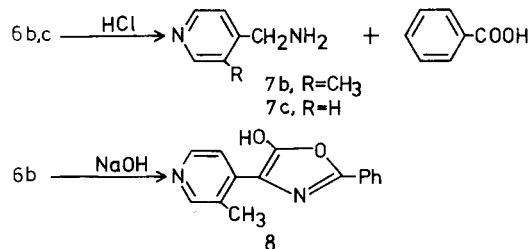
Compound	Reaction temperature	Yield (a) %	
		Method A (b)	Method B (c)
6a	-15°	25	11
6b	-15°	40	4
6c	20°	14	2

(a) Isolated yield based on **2** used. (b) Yield when oxygen was bubbled into the reaction mixture. (c) Yield when the reaction vessel was open to air.

The yield varied with the reaction temperature. At ambient temperature **6c** precipitated from the reaction mixture, but **6a,b** did not and instead a heavy brown solution was produced. The optimum temperature for **6a,b** was -15°. None of the compounds **6** were produced when 2,3-dichloro-5,6-dicyanobenzoquinone or peracids (perbenzoic acid and peracetic acid) were used instead of oxygen as an oxidant for the intermediate **5**.

The assignment of the structure **6** was mainly carried out by nmr and mass spectral analysis. Additional confirmation of the structure of the new compounds **6b,c** was obtained by hydrolysis as shown in Scheme 2. The acidic hydrolysis of **6b** and **6c** yielded 4-aminomethylpyridines **7b** and **7c** in addition to carboxylic acids, respectively. The alkaline hydrolysis of **6b** gave the deacetylated compound **8**. However, isolation of the corresponding **8** from **6c** was not successful.

Scheme 2



Very little has been reported about the preparation of 2-oxazolin-5-ones having a pyridylidene ring at the C₄-position. Steglich and Höfle (3) had previously prepared **6a** in 52-56% overall yield in five steps from glycine and benzoyl chloride. *N*-Alkylpyridylidene derivatives (4) were prepared by the reaction of alkylamine with 4-(4-pyranylidene)-2-oxazolin-5-one, which was derived from 4*H*-pyran and benzoylglycine (32-69% overall yield). Our method possesses advantages over the previous methods in the facile preparation of **6**.

EXPERIMENTAL

Melting points were uncorrected and determined on a Kofler hot-stage microscope. The nmr spectra were recorded on a JEOL FX-100 spectrometer. Internal standards were tetramethylsilane for solvents of tri-

fluoroacetic acid-d₁, and dimethylsulfoxide-d₆, and 3-(trimethylsilyl)propionic acid-d₄ for a solvent of deuterium oxide. The quantitative ¹³C-nmr spectrum was obtained by using gated decoupling without NOE. The ir spectra were determined by using a Nipponbunko A-102 spectrophotometer. Mass spectra were determined on a Shimadzu LKB Type 9000 spectrometer at an ionizing energy of 70 eV. Adsorption spectra were recorded with a Shimadzu UV-180 spectrophotometer. Thin-layer chromatography was run on glass plates (Merck, silica gel GF) by using a developing solvent of benzene:dimethylformamide (5:1 v/v).

2-Oxazolin-5-ones (6a,b,c).

Compound **2** (10 g) in a solution of **1** (50 ml) and acetic anhydride (50 ml) was stirred for 1 hour with oxygen bubbling through at the temperature listed in Table 1. The resulting reddish-yellow precipitate was collected on a filter and washed with acetone. The product was recrystallized from pyridine in the yield given in Table 1.

4-(1-Acetyl-4(1H)-pyridylidene)-2-phenyl-2-oxazolin-5-one (6a).

The product melted at 222-225° dec (lit (3) mp 227°). Spectral data (¹H- and ¹³C-nmr, ms) were identical with those obtained from an authentic sample synthesized by a known route (3).

4-(1-Acetyl-4(1H)-pyridylidene)-3-methyl-2-phenyl-2-oxazolin-5-one (6b).

The product melted at 224-225° dec; ¹H-nmr (trifluoroacetic acid-d₁): (5) δ 2.88 (s, 3H), 2.91 (s, 3H), 7.63-8.69 (m, 8H); ir (Nujol): 1720, 1630, 1520 cm⁻¹; λ max (acetic anhydride:pyridine = 1:2 v/v): 496 (ε 39100), 465 (ε 50600), 439 nm (ε 37200); ms: 294 (M⁺, 22), 252 (46), 120 (10), 119 (100), 105 (46), 77 (30), 43 (20); Rf value 0.49.

Anal. Calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found: C, 68.92; H, 4.62; N, 9.28.

4-(1-Acetyl-4(1H)-pyridylidene)-2-methyl-2-oxazolin-5-one (6c).

The product melted at 239-242° dec; ¹H-nmr (trifluoroacetic acid-d₁): δ 2.80 (s, 3H), 2.88 (s, 3H), 7.8 (broad, 2H), 8.7 (d, 2H, J = 7.8 Hz); ¹³C-nmr (trifluoroacetic acid-d₁): δ 14.3 (q), 21.2 (q), 99.6 (s), 115.6 (d), 138.2 (d), 141.6 (s), 148.0 (s), 163.5 (s), 170.6 (s); ms: 218 (M⁺, 32), 176 (73), 106 (48), 105 (100), 79 (15), 43 (50); ir (Nujol): 1720, 1640, 1620, 1560 cm⁻¹; λ max (acetic anhydride: pyridine = 1:2 v/v): 456 (ε 23100), 429 (ε 34100), 405 cm⁻¹ (ε 28100); Rf value 0.21.

Anal. Calcd. for C₁₁H₁₀N₂O₃: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.17; H, 4.48; N, 12.84.

5-Hydroxy-4-(3-methyl-4-pyridyl)-2-phenyloxazole (8).

Compound **6b** (0.5 g) was stirred for 20 minutes with a solution (20 ml) of 1N sodium hydroxide and ethanol (1:1 v/v) at room temperature and the resulting solution was acidified with acetic acid. The precipitate was recrystallized from 50% aqueous ethanol to give the monohydrate of **8** in a yield of 90%, mp 209-216° dec; ¹H-nmr (dimethylsulfoxide-d₆): δ 2.65

(s, 3H), 7.33-8.35 (m, 8H), 12.5 (broad, s, 1H, exchanged with deuterium oxide); quantitative ¹³C-nmr (dimethylsulfoxide-d₆): δ 20.6 (q, 1C, methyl), 107.5 (s, 1C), 112.5 (d, 1C), 123.4 (s, 1C), 124.6 (d, 2C), 128.3 (d, 1C), 128.7 (d, 2C), 128.7 (s, 1C), 134.1 (d, 1C), 136.4 (d, 1C), 146.0 (s, 1C), 147.4 (s, 1C), 166.6 (s, 1C). All of six quaternary and eight tertiary carbon atoms in **8** are observed as a singlet and doublet, respectively. This supports the structure.

Anal. Calcd. for C₁₅H₁₄N₂O₃: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.45; H, 5.30; N, 10.39.

Hydrolysis of 2-Oxazolin-5-ones (6b,c) with Hydrochloric Acid.

A suspension of **6b** (1 g) in 6N hydrochloric acid (15 ml) was refluxed for 3 hours. After standing overnight in a refrigerator, a white solid precipitated. The compound was identified as benzoic acid and gave no depression in mixture melting point determination with a commercial standard sample, mp 122°, yield, 73%. An infrared spectrum of the compound was identical to that of the reported literature (6).

The above filtrate was evaporated *in vacuo* and the residue dissolved in a minimal amount of water. The addition of acetone to the solution gave dihydrochloride of **7b** in a yield of 94%, mp 224° dec; ¹H-nmr (deuterium oxide solution neutralized with sodium carbonate): δ 2.40 (s, 3H), 4.32 (s, 2H), 7.45 (d, 1H), 8.46 (s, 1H), 8.57 (s, 1H).

Anal. Calcd. for C₇H₁₂Cl₂N₂: C, 43.10; H, 6.20; N, 14.36. Found: C, 42.92; H, 6.20; N, 14.31.

The same treatment of **6c** afforded dihydrochloride of **7c** in almost quantitative yield, mp 253-255° (lit (7) 255°); ¹H-nmr (deuterium oxide solution neutralized with sodium carbonate): δ 4.40 (s, 2H), 7.68 (d, 2H), 8.68 (d, 2H).

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