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AN EFFICIENT SYNTHESIS AND MECHANISM OF FORMATION OF 6-ACETYL-1,2-DIHYDRO-2-OXO-3-PYRIDINECARBOXYLIC ACID

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Abstract: Starting with 3,3-dimethoxy-2-butanone (biacetyl monoketal) (**1**), 6-acetyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (**9a**) has been prepared in large quantities by a highly efficient synthetic sequence. The isolation of 2-cyano-5-hydroxy-6-oxo-2,4-heptadienamide (**6**) and the identification of 2-cyano-6,6-dimethoxy-5-oxo-2-heptenamide (**4a**) from the reaction mixture suggests that the final ring closure may involve a dehydration of this sterically hindered enamide.

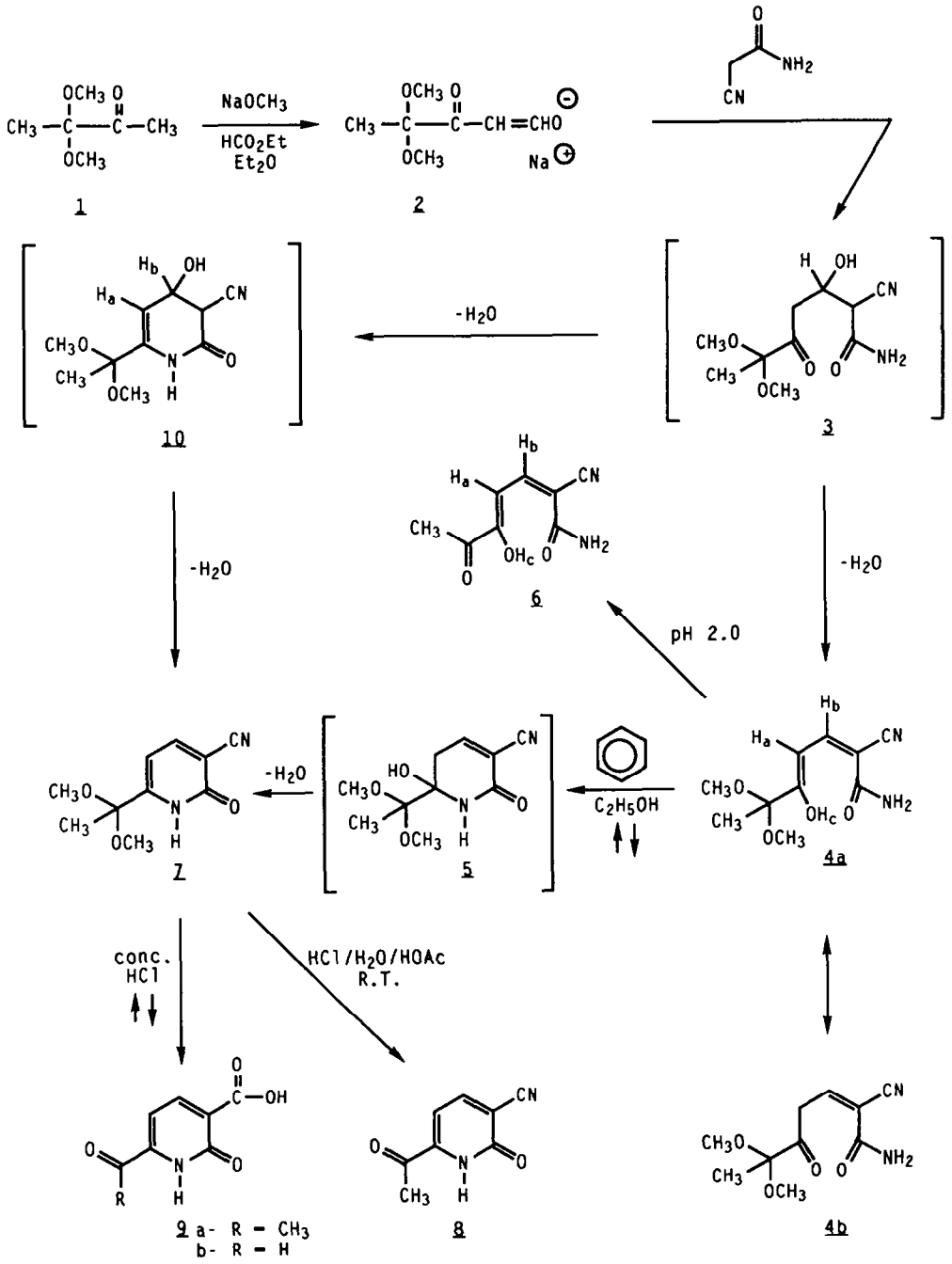
The use of 2-oxo- and 4-oxopyridine-3-carboxylic acids as side chains for β-lactam antibiotics and as starting materials for the preparation of 1,8-naphthyridine antibacterial agents have been greatly expanded. As part of our semisynthetic β-lactam program,[1] it became necessary to prepare large quantities of certain 6-acyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids (e.g., **9a-b**). The carbonyl groups could then be derivatized to produce a new series of side chains for attachment to various penicillin and cephalosporin nuclei.

We had previously reported the synthesis of some of these 6-acyl-2-oxopyridines,[2] but the synthetic routes were not suitable for the preparation of the large amounts required for further biological evaluations. Of particular interest were the 6-acetyl (**9a**) and the 6-formyl (**9b**) compounds from which styryl derivatives could be prepared by either Wittig[3] or Horner-Emmons[4] reactions.

The synthetic sequence (Scheme I) for the preparation of the 6-acetyl compound (**9a**) began with the reaction of biacetyl monoketal (**1**) with ethyl formate in the presence of base to produce the sodium salt of the formyl derivative **2**. When aqueous solutions of **2** and cyanoacetamide were reacted according to several literature procedures,[5] which use slightly different reaction conditions for the preparation of 1,2-dihydro-2-oxopryidines, variable (but always low) yields of the desired product (**7**) were isolated.

However, when the reaction was run at a pH of 9.0 and a temperature of 60°C for 4 h, and the reaction mixture adjusted to nearly neutral pH (6.8), a good yield of a mixture of **7** and a condensed, but ring opened compound (**4a**) was isolated. Examination of the reaction pathway (Scheme I) and the resulting spectra (see experimental) provided for the assignment of the following structures to the products.

Scheme I


NaOCH3
HCO2Et
Et2O
1
2
3
10
6
4a
4b
5
7
8
9 a- R = CH3
b- R = H
-H2O
pH 2.0
C2H5OH
conc. HCl
HCl/H2O/HOAc
R.T.

Compound **4a**, 2-cyano-6,6-dimethoxy-5-oxo-2-heptenamide, is readily formed by the condensation of cyanoacetamide with **2** followed by loss of water from the intermediate **3** and can exist in either the enol form (**4a**) or the keto form (**4b**). This is exemplified in the NMR by the coupling of the diene protons of the enol form. The doublets at 5.62 and 7.86 ppm (J = 13 Hz) are greatly affected by a deuterium exchange experiment due to the keto-enol tautomerization. The proton at 5.62 (H_a) is completely exchanged with deuterium oxide which causes the signal at 7.86 (H_b) to collapse to a singlet, the rest of the spectrum remaining unchanged. The presence of a broad, exchangeable, two proton singlet at 5.90 ppm, indicative of the amide $-NH_2$ as well as a one proton singlet at 10.84 ppm (H_c) supports the assigned structure over the ring closed but still hydrated pyridone structures **5** and **10**. The ring closed product (**7**) could be separated from the mixture by acidifying to pH 2.0, which also hydrolyzed the ketal of the ring opened compound (**4**) to give the α-diketone (**6**). The isolation and complete identification of 2-cyano-5-hydroxy-6-oxo-2,4-heptadienamide (**6**) lends strong support to the previous structural assignment for **4**.

The ring closure of the enamide **4**, under forcing dehydrating conditions, in refluxing ethanol and benzene, provided the 2-oxopyridine nitrile **7** in 72% yield. The failure of the ring closure to take place under the usual aqueous conditions, **4a**→**5**→**7**, is probably due to the bulk of the two methoxyl groups at C-6. Steric factors are probably the reason for a difference mechanistic pathway than the one previously reported.[6] In these cases, a substituted 3-cyano-3,4-dihydro-4-hydroxy-2-oxopyridine (such as **10**) formed by the reaction of cyanoacetamide with the hydroxymethylene ketone (e.g. **2**) is isolated. Elimination of water leads to the final 2-oxopyridine **7**.

The ketal of **7** could be hydrolyzed leaving the nitrile intact, using a mixture of $HCl/H_2O/HOAc$ to give **8**, in nearly quantitative yield. Complete hydrolysis to the pyridone keto acid **9a** was accomplished by refluxing **7** in concentrated HCl for a brief period (0.5 h).

This methodology is probably suitable for other cases involving steric bulk at the point of ring closure of the amide nitrogen on the carbonyl of the hydroxymethylene ketone.

EXPERIMENTAL SECTION

Melting points were taken on a Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm^{-1} resolution. Proton magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with 11/250 Data System. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 30-45°C and pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry

nitrogen atmosphere. Elemental Analyses were performed on a Perkin-Elmer 240 elemental analyzer.

1-Hydroxy-4,4-dimethoxy-1-penten-3-one, sodium salt, 2

A suspension of 146.1 g (2.7 mol) of sodium hydroxide in 5.5 L of anhydrous ether was cooled to 5°C and treated with a solution of 250.2 g (3.38 mol) of ethyl formate and 353.9 g (2.68 mol) of 3,3-dimethoxy-2-butanone[7] over 1.5 h. When the addition was complete, the reaction was stirred at 5°C for 1 h and then at room temperature for 18 h. The resulting precipitate was removed by filtration, washed with ether and dried in vacuo to give 435 g (89%) of **2**; IR (KBr) 1640, 1490 cm^{-1}; NMR (D_2O) δ 1.45 (s, 3H, CH_3), 3.25 (s, 6H, OCH_3), 5.55 (d, J = 10 Hz, 1H), 9.18 (d, J = 10 Hz, 1H).

6-(1,1-Dimethoxyethyl)-1,2-dihydro-2-oxo-3-pyridinecarbonitrile, 7, Method A.[5]

A solution of 23.1 g (0.18 mol) of **2** in 500 mL of H_2O was cooled to 5°C, adjusted to pH 9.0 with glacial HOAc and treated with 25.2 g (0.3 mol) of cyanoacetamide. The system was purged with N_2 for 15 minutes, heated to 80°C for 2.5 h and then stirred at room temperature for 18 h. The solution was acidified to pH 4.5 with glacial HOAc, and the resulting green-black precipitate was removed by filtration and washed with H_2O. The wet filter cake was recrystallized from EtOH clarifying with Norit to give 10.3 g (31%) of white crystals of **7**; mp 181-183°C; Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.72; H, 5.76; N, 13.31. IR (KBr) 2228 (CN), 1670 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 1.50 (s, 3H, CH_3), 3.13 (s, 6H, OCH_3), 6.50 (d, J = 8 Hz, 1H, C_5H), 8.07 (d, J = 8 Hz, 1H, C_4H), 12.20 (bs, 1H, NH).

2-Cyano-6,6-dimethoxy-5-oxo-2-heptenamide (4a)

A solution of 18.2 g (0.1 mol) of **2** in 400 mL of H_2O was adjusted to pH 9.0 with HOAc and treated with 9.2 g (0.11 mol) of cyanoacetamide. The resulting solution was heated to 60°C for 4 h. The solvent was removed in vacuo at 50°C to give 2.42 g of a 3:1 mixture of **4a** to **7**, plus inorganics (NMR analysis). A 300 mg sample was streaked onto a 20 x 20 cm, silica gel, preparative thick layer chromatography plate. After developing in a pH 8.0 buffer system, the two spots were scraped off and dissolved in ethanol. The compound with R_f 0.83 had spectra identical to **7**. The compound with R_f 0.56, **4a**, had: Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.23; N, 12.39. Found: C, 52.98; H, 6.01; N, 12.45. IR (KBr) 2195 (CN), 1650, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.12 (s, 3H, CH_3), 2.96 (s, 6H, OCH_3), 5.62 (d, J = 13 Hz, 1H, H_a), 5.90 (bs, 2H, NH_2), 7.86 (d, J = 13 Hz, 1H, H_b), 10.84 (br s, 1H, H_C). A D_2O wash exchanged the protons at 10.84, 5.90, and 5.62 with the doublet at 7.86 collapsing to a singlet.

2-Cyano-5-hydroxy-6-oxo-2,4-heptadienamide (6)

A solution of 18.2 g (0.1 mol) of **2** in 500 mL of H_2O was cooled to 5°C, adjusted to 9.0 with glacial HOAc and treated with 12.6 g (0.15 mol) of cyanoacetamide. The system

was purged with N_2 for 15 min and then heated to 60°C for 5 h. After cooling to 5°C, the reaction was acidified to pH 2.0 with 6.0 M HCl and stirred for 1 h. The resulting yellow precipitate was removed by filtration, washed with H_2O, Et_2O and dried in vacuo to give 11.9 g (57%) of **6**, mp 179-180°C; Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.58; N, 15.55. Found: C, 53.30; H, 4.89; N, 15.93. IR (KBr) 3480 (OH), 3290 (br, NH_2), 3177, 2220 (CN), 1675 (br, C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 2.48 (s, 3H, CH_3), 6.37 (d, J = 12 Hz, 1H, H_a), 7.74 (br s, 2H, NH_2), 8.23 (d, J = 12 Hz, 1H, H_b), 10.67 (br s, 1H, H_c). A D_2O wash exchanged the protons at 10.67, 7.74 and 6.37 with the doublet at 8.23 collapsing to a singlet.

6-(1,1-Dimethoxyethyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (7) - Method B

A solution of 432 g (2.37 mol) of **2** in 5.5 L of water was cooled (5°C), adjusted to pH 9.0 with glacial HOAc and treated with 242.5 g (2.92 mol) of cyanoacetamide. The mixture was heated to 60°C for 4 h, cooled to 5°C and acidified to pH 6.8 with 6.0 M HCl. The solution was evaporated to dryness in vacuo at 50°C. The residue was suspended in a mixture of 4.4 L of EtOH and 4.4 L of benzene and azeotroped under a Dean-Stark trap for 24 h. The solvent was removed in vacuo and the residue was suspended in 6 L of 5°C water and acidified to pH 4.3 with 6.0 M HCl. The resulting precipitate was removed by filtration and the wet filter cake was recrystallized from 5 L of 95% EtOH to give 383.6 g (78%) of **7**, mp 181-182.5°C. The spectra obtained was identical to the material prepared by procedure A.

6-Acetyl-3-cyano-1,2-dihydro-2-oxopyridine (8)

A suspension of 20.8 g (0.1 mol) of **7**, 20 mL of concentrated HCl, 100 mL of H_2O and 250 mL of glacial HOAc was stirred at room temperature for 18 h. The solvent was removed in vacuo, the residue triturated with water and the solid was removed by filtration. After washing with water, it was dried in vacuo to give 15.6 g (96%) of **8**, mp 214-216°C; Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.40; H, 3.86; N, 17.43. IR (KBr) 2240 (CN), 1690 (C=O) cm^{-1}; NMR (DMSO-d_6) δ 2.52 (s, 3H, CH_3), 7.12 (d, J = 8 Hz, 1H, C_5H), 8.28 (d, J = 8 Hz, 1H, C_4H), 10.25 (bs, 1H, NH).

6-Acetyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (9a)

A suspension of 41.6 g (0.2 mol) of **7** in 250 mL of concentrated HCl was heated at reflux for 0.5 h. A solution formed followed by a heavy precipitate. The reaction mixture was stirred at reflux an additional 3 h, cooled to 5°C and the precipitate was removed by filtration. After washing with H_2O (2 x 100 mL), 95% EtOH (100 mL) and Et_2O (3 x 100 mL), the solid was dried at 50°C for 18 h to give 33.9 g (94%) of **9a**, mp 279-280°C; Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 52.86; H, 3.96; N, 7.75. IR (KBr) 3105 (NH), 1745, 1708, 1643 cm^{-1}; NMR (Me_2SO-d_6) δ 2.62 (s, 3H, CH_3), 7.40 (d, J = 8 Hz, 1H, C_5H), 8.48 (d, J = 8 Hz, 1H, C_4H).

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