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A facile annelation of pyridines with nitriles of α,β-acetylenic γ-hydroxyacids

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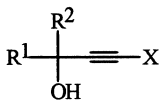
Abstract—Pyridines are readily annelated with nitriles of α,β-acetylenic γ-hydroxyacids under mild conditions (ambient temperature, no catalyst, no solvent) to give new condensed dihydropyridine systems, 4-cyanomethylidene-1,3-oxazolidine[3,2-*a*]-1,2-dihydropyridines in 75–83% yields. © 2002 Elsevier Science Ltd. All rights reserved.

The pyridine structural unit occurs in a large number of biologically important compounds including drugs, alkaloids and pesticides. This is why interest in the chemistry and the synthesis of pyridine derivatives remains stable.

A number of diverse heterocycles with a condensed pyridine moiety have been synthesized via activated acetylenes, mostly esters of acetylene mono- and dicarboxylic acids.[1]

Recently,[2,3] a large new family of functionalized activated acetylenes, esters and nitriles of α,β-acetylenic γ-hydroxyacids **1**, has been introduced to organic synthesis as versatile building blocks for a great diversity of biologically related heterocycles.



1 X = CO_2Me, CN

Astonishingly, among numerous cyclizations with the participation of **1**, no one has referred to the annelation with pyridines. Meanwhile, such reactions may open a straightforward route to rare derivatives of 1,3-oxazolidine condensed dihydropyridines, bearing an acrylic function which can be converted to unusual amino acids and their derivatives. The availability of such amino acids is a key to the design of ligands for biological systems to gain a better understanding of their functions at a molecular level and thereby develop new approaches to the search for therapeutics.

In this paper, we wish to report on the extremely facile and clean annelation of nitriles of α,β-acetylenic γ-hydroxyacids **1** (X = CN) with pyridine and its methyl derivatives, 2-, 3- and 4-picolines.

Pyridine and its 2-, 3- and 4-methyl derivatives smoothly add to acetylenes **1a**,**b** under mild conditions (ambient temperature, 15–60 h, equimolar ratio of reactants, no solvent, no catalyst) to furnish 4-cyanomethylidene-1,3-oxazolidine[3,2-*a*]-1,2-dihydropyridines **4a–e** in 75–83% yield.[4] The reaction proceeds as shown in Scheme 1.

Obviously, in the initial intermediate zwitterion **2**, the proton transfer from hydroxyl to quench the carbanionic center (at the α-position to the nitrile group) takes place to give the thermodynamically more stable oxygen-centered anion, the zwitterion **3**, which undergoes further annelation to the 1,3-oxazolidino[3,2-*a*]-1,2-dihydropyridine **4**.

As expected, the reaction rate depends on the position of the methyl substituent on the pyridine ring. For unsubstituted pyridine or 3- and 4-picolines, the reaction is completed within 15–20 h, whilst in the case of 2-picoline, it takes 60 h.

Keywords: pyridines; nitriles of α,β-acetylenic γ-hydroxyacids; 4-cyanomethylidene-1,3-oxazolidine[3,2-*a*]-1,2-dihydropyridines.

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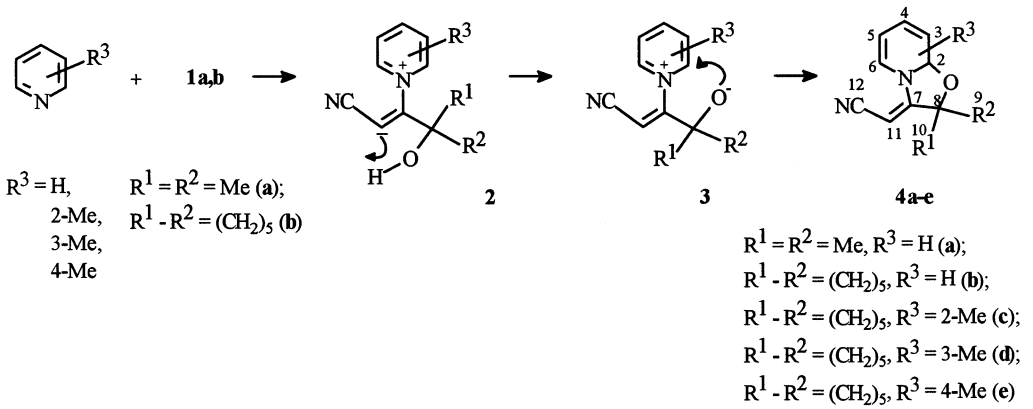

Scheme 1.

Interestingly, under the conditions originally recommended for annelation of pyridines with acetylenedicarboxylate (pyridine:acetylene molar ratio 1:2, dry diethyl ether),[5] no reaction between pyridines and **1a**,**b** occured, both at ambient temperature and in boiling diethyl ether even after 6 days.

In the ^{1}H and ^{13}C NMR spectra, signals of the compounds **4a**–**e** have been unambiguously assigned using 2D HMQC, HMBC and NOESY experiments ($CDCl_3$, spectrometer Bruker DPX 250). Formation of the dihydropyridine ring is accompanied by a considerable high-field shift of the C-4, C-5 and C-6 signals as well as those of the corresponding protons relative to their positions in the pyridine nucleus due to the electron density redistribution. The chemical shift of C-2, like that of C-8, has a value typical of an sp^3 carbon between two heteroatoms. The abnormal high-field shift of the C-11 and H-11 resonances and the low-field resonance of C-7 result from the strong push–pull polarization of the C-7–C-11 double bond owing to the π-donation of the dihydropyridine moiety and the π-electron withdrawing effect of the cyano group. The cross-peaks between the ethenyl and *ortho*-cyclohexyl protons in the NOESY spectrum are evidence that compounds **4b**–**d** are *Z*-isomers.

In the ^{1}H NMR spectra of all 1,3-oxazolidino[3,2-*a*]-1,2-dihydropyridines, only one signal due to the ethenyl proton (in the region of 3.92–4.60 ppm) is present, meaning that the annelation is stereospecific relative to the configuration of the cyanoethenyl moiety. According to the 2D (^{1}H, ^{1}H) NOESY spectra of **4b**,**c**,**d** this configuration is *Z*, the cross-peak from the ethenyl and *ortho*-cyclohexyl protons was observed (*Z*-**4b**,**c**,**d**), whereas the interaction between the ethenyl proton and the pyridine proton at position 6 (characteristic for the configuration *E*-**4b**,**c**,**d**) was not observed, Fig. 1.

In the case of 2-picoline, two regioisomers of **4c** might be formed (Fig. 2).

In fact, only one regioisomer was isolated. Analysis of the ^{13}C NMR spectra indicated that ring-closure occured at position 2 of the pyridine ring, i.e. the regioisomer **4c**-2-Me was the only product (the signal of the C-2 carbon of the pyridine ring is shifted down-field by 9 ppm compared to the same position in **4b** due to the effect of the neighboring methyl group).[4]

Therefore, the stabilization due to the hyperconjugation of the adjacent methyl substituent on the positive charge exceeds its adverse steric effect.

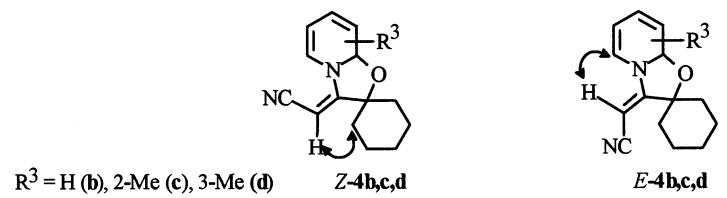

Figure 1.

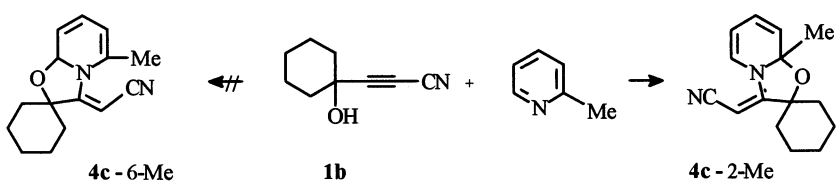

Figure 2.

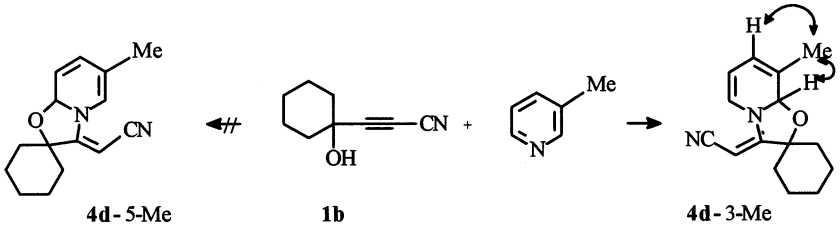

Figure 3.

In an analogous manner two regioisomers of **4d** would be expected to form from 3-picoline (Fig. 3).

In the 2D (^{1}H,^{1}H) NOESY spectrum of product **4d**, the methyl group had cross-peaks with both H-2 and H-4, thus indicating that only the **4d**-3-Me isomer was formed, i.e. the reaction was also regioselective in this case.

Compounds **4b–e** are crystalline, compound **4a** is a brown oil and all were soluble in most organic solvents. Their IR spectra contain intense absorption bands in the region 2180–2190 cm^{-1} due to the nitrile group and no hydroxyl absorbtion in the region of 3300–3360 cm^{-1}.[4] Compounds **4a–e** were characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analyses.[4]

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4. Typical experimental procedure. Preparation of **4a**.
Pyridine (0.16 g; 2 mmol) was slowly added with stirring to acetylene **1a** (0.22 g; 2 mmol). The reaction mixture was stirred at room temperature for 20 h. The mixture was chromatographed on Al_2O_3 (chloroform–benzene–alcohol, 20:4:1 as eluent). The solvents were removed in vacuum to give 0.30 g (79%) of compound **4a** as a brown oil. IR (neat): 3070, 3050, 2970, 2930, 2860, 2830, 2190, 1640, 1620, 1560, 1450, 1380, 1370, 1310, 1290, 1210, 1160, 1140, 1080, 1050, 990, 930, 850, 790, 760, 710, 650, 630, 540 cm^{-1}. ^{1}H NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 4.60 (s, 1H, =CH), 6.11 (m, 1H, Py*H*-2), 5.66 (d, $^3J_{3-4}$=9.6 Hz, 1H, Py*H*-3), 6.09 (dd, $^3J_{4-5}$=5.5 Hz, 1H, Py*H*-4), 5.56 (dd, $^3J_{5-6}$=7.0 Hz, 1H, Py*H*-5), 7.30 (d, 1H, Py*H*-6). ^{13}C NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 86.25 (C-2), 122.01, 123.17 (C-4), 107.55 (C-5), 123.15 (C-6), 161.03 (C-7), 82.81 (C-8), 23.15 (C-9), 26.09 (C-10), 57.52 (C-11), 118.93 (C-12). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.40; H, 6.20; N, 14.52.
Compound **4b**: Yield 77%, mp 125–126°C. IR (KBr): 3070, 3040, 2930, 2840, 2180, 1640, 1620, 1560, 1450, 1440, 1430, 1350, 1340, 1310, 1280, 1210, 1150, 1130, 1070, 1040, 970, 960, 940, 910, 870, 840, 780, 750, 740, 710, 650, 600, 550, 520, 500, 460 cm^{-1}. ^{1}H NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 1.64 (m, 10H, $5CH_2$), 4.01 (s, 1H, =CH), 5.96 (m, 1H, Py*H*-2), 5.55 (d, $^3J_{3-4}$=9.6 Hz, 1H, Py*H*-3), 5.95 (dd, $^3J_{4-5}$=5.5 Hz, 1H, Py*H*-4), 5.39 (dd, $^3J_{5-6}$=7.0 Hz, 1H, Py*H*-5), 7.39 (d, 1H, Py*H*-6). ^{13}C NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 86.70 (C-2), 118.55 (C-3), 123.34 (C-4), 107.36 (C-5), 122.86 (C-6), 160.96 (C-7), 84.55 (C-8), 21.67, 21.94, 24.80, 31.55, 35.32 (C cyclohexyl), 58.17 (C-11), 118.97 (C-12). Anal. calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.45; H, 6.99; N, 12.06.
Compound **4c**: Yield 83%, mp 113–115°C. IR (KBr): 3040, 3010, 2940, 2850, 2180, 1640, 1610, 1550, 1440, 1410, 1360, 1290, 1260, 1250, 1170, 1130, 1105, 1090, 980, 970, 940, 920, 910, 850, 840, 810, 740, 710, 690, 670, 630, 590, 540, 530, 520, 490, 480, 450, 440 cm^{-1}. ^{1}H NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.69 (m, 10H, $5CH_2$), 3.98 (s, 1H, =CH), 5.70 (d, $^3J_{3-4}$=9.5 Hz, 1H, Py*H*-3), 5.96 (dd, $^3J_{4-5}$=5.6 Hz, 1H, Py*H*-4), 5.65 (dd, $^3J_{5-6}$=7.1 Hz, 1H, Py*H*-5), 7.45 (d, 1H, Py*H*-6). ^{13}C NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 95.38 (C-2), 126.31 (C-3), 119.99 (C-4), 109.30 (C-5), 122.72 (C-6), 162.75 (C-7), 84.68 (C-8), 21.79, 22.02, 24.83, 37.61, 38.58 (C cyclohexyl), 58.96 (C-11), 119.33 (C-12), 26.87 (CH_3). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.22; H, 7.30; N, 11.41.
Compound **4d**: Yield 83%, mp 97–99°C. IR (KBr): 3060, 3040, 2940, 2850, 2180, 1640, 1620, 1570, 1450, 1440, 1360, 1270, 1260, 1210, 1160, 1130, 1080, 1040, 1020, 980, 950, 930, 890, 870, 860, 840, 770, 720, 650, 560, 530, 490 cm^{-1}. ^{1}H NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 1.84 (s, 3H, CH_3), 1.62 (m, 10H, $5CH_2$), 3.92 (s, 1H, =CH), 5.83 (m, 1H, Py*H*-2), 5.69 (d, $^3J_{4-5}$=5.4 Hz, 1H, Py*H*-4), 5.41 (dd, $^3J_{5-6}$=6.9 Hz, 1H, Py*H*-5), 7.34 (d, 1H, Py*H*-6). ^{13}C NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 88.99 (C-2), 128.95 (C-3), 127.61 (C-4), 108.37 (C-5), 121.35 (C-6), 160.95 (C-7), 84.73 (C-8), 21.89, 22.22, 25.13, 31.98, 35.74 (C cyclohexyl), 57.83 (C-11), 118.69 (C-12), 16.99 (CH_3). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.50; H, 7.32; N, 11.38.
Compound **4e**: Yield 75%, mp 105–106°C. IR (KBr): 3050, 2930, 2850, 2190, 1640, 1620, 1510, 1450, 1400, 1320, 1280, 1205, 1140, 1130, 1070, 1040, 950, 910, 850, 840, 740, 720, 650, 620, 590, 520 cm^{-1}. ^{1}H NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 1.80 (s, 3H, CH_3), 1.64 (m, 10H, $5CH_2$), 3.97 (s, 1H, =CH), 5.96 (m, 1H, Py*H*-2), 5.34 (m, 1H, Py*H*-3), 5.29 (d, $^3J_{5-6}$=7.2 Hz, 1H, Py*H*-5), 7.38 (d, 1H, Py*H*-6). ^{13}C

NMR (250.1 and 62.4 MHz, $CDCl_3$): δ 87.22 (C-2), 114.21 (C-3), 132.13 (C-4), 110.88 (C-5), 122.38 (C-6), 160.86 (C-7), 84.46 (C-8), 21.73, 22.02, 24.96, 31.73, 35.54 (C cyclohexyl), 58.21 (C-11), 118.49 (C-12), 20.57 (CH_3). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.37; H, 7.40; N, 11.54.

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