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Chemo-, regio- and stereospecific non-catalytic addition of isonicotinic acid to α,β-acetylenic γ-hydroxy nitriles

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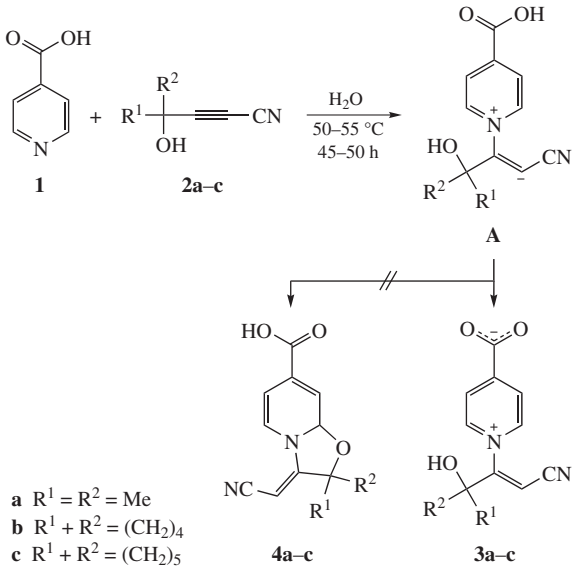
Isonicotinic acid is readily added to α,β-acetylenic γ-hydroxy nitriles through its nitrogen atom under mild non-catalytic conditions in water (50–55 °C, 45–50 h) to afford chemo-, regio- and stereospecifically 1-[(*Z*)-2-cyano-1-(1-hydroxy-1-alkylethyl)ethenyl]-pyridinium-4-carboxylates, densely functionalized derivatives of isonicotinic acid (45–90% yields). The structure and zwitterionic character of the adducts are proved by X-ray analysis.

The pyridine nucleus is incorporated in many important heteroaromatic compounds with a variety of applications. It is presented in many drugs, vitamins, flavourings, insecticides, herbicides, dyes, rubbers and adhesives.[1] Among the pyridine compounds, a special place belongs to isonicotinic acid, the derivatives of which are widely used as anti-tuberculosis drugs (*e.g.*, Isoniazid).[1(*b*),2] Presently, the search for anti-tuberculosis drugs is still urgent; therefore, the functionalization of isonicotinic acid remains a challenge in organic synthesis.[2(*b*)]

In this work, we studied the reaction of isonicotinic acid with available α,β-acetylenic γ-hydroxy nitriles.[3,4] Such nitriles as electron-deficient acetylenes have been recently found to readily annulate with pyridines,[5,6] quinoline, quinoxaline,[7] phenanthridines[8] and natural alkaloids[9] to afford previously inaccessible heterocyclic systems.

One might expect that similar annulation could take place when isonicotinic acid **1** is allowed to react with α,β-acetylenic γ-hydroxy nitriles **2a–c**. However, the reaction takes another pathway: unlike the above examples,[5–9] intermediate zwitterions **A** are transformed chemo-, regio- and stereospecifically to final zwitterionic adducts **3a–c** but are not annulated to oxazolidines **4**.[†]



Obviously, in this case, the carbanionic centre in primary intermediate zwitterions **A** is quenched by protons of the medium, where molecule of water, carboxylic and hydroxyl functions are in exchange interaction. Indeed, when the reaction is carried out in D_2O, no olefinic proton at 6.49–6.57 ppm is detected.

[†] IR spectra were measured on Bruker IFS-25 in KBr pellets. The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on a Bruker DPX-400 spectrometer in D_2O. The reaction was controlled by TLC on neutral Al_2O_3 (chloroform–benzene–ethanol, 20:4:1 as an eluent). Isonicotinic acid is a commercial reagent. α,β-Acetylenic γ-hydroxy nitriles **2a–c** were prepared according to a published method.[6,14]

General procedure for the preparation of compounds **3a–c**. Isonicotinic acid (1.0 mmol) and water (4 ml) were heated to 50–55 °C; then, α,β-acetylenic γ-hydroxy nitrile **2a–c** (2.0 mmol) was added. The mixture was stirred for 45–50 h at 50–55 °C. The water was evaporated. The residue was washed consecutively with diethyl ether and acetone and then dried in a vacuum to give compounds **3a–c**.

1-[(Z)-2-Cyano-1-(1-hydroxy-1-methylethyl)ethenyl]pyridinium-4-carboxylate **3a**: yield 90%, beige solid, mp 206–208 °C (decomp.). ^{1}H NMR (400.13 MHz, D_2O) δ: 8.87 (d, 2H, H_{Py}-2,6), 8.33 (d, 2H, H_{Py}-3,5), 6.49 (s, 1H, =CHCN), 1.36 (s, 6H, Me). ^{13}C NMR (100.62 MHz, D_2O) δ: 167.73 [C(O)O$^-$], 164.19 (NC=), 154.97 [C(4)], 145.20 [C(2), C(6)], 126.95 [C(3), C(5)], 112.17 (CN), 102.09 (=*C*HCN), 71.35 [(HO)*C*Me$_2$], 25.82 (Me). ^{15}N NMR (40.55 MHz, D_2O) δ: –174.15 (N_{Py}), –113.08 (CN). IR (KBr, ν/cm^{-1}): 3400, 3260, 3100, 3010, 2970, 2930, 2920, 2220, 1620, 1610, 1540, 1470, 1440, 1400, 1370, 1350, 1305, 1250, 1200, 1175, 1150, 1130, 1020, 985, 960, 945, 870, 830, 810, 780, 740, 680, 630, 620, 520, 450. Found (%): C, 61.63; H, 5.32; N, 11.89. Calc. for $C_{12}H_{13}N_2O_3$ (%): C, 61.79; H, 5.62; N, 12.01.

1-[(Z)-2-Cyano-1-(1-hydroxycyclopentyl)ethenyl]pyridinium-4-carboxylate **3b**: yield 74%, beige solid, mp 138–142 °C (decomp.). ^{1}H NMR (400.13 MHz, D_2O) δ: 8.94 (d, 2H, H_{Py}-2,6), 8.37 (d, 2H, H_{Py}-3,5), 6.55 (s, 1H, =CHCN), 1.87–1.75 (m, 8H, CH_2). ^{13}C NMR (100.62 MHz, D_2O) δ: 168.32 [C(O)O$^-$], 163.30 (NC=), 155.19 [C(4)], 145.16 [C(2), C(6)], 127.40 [C(3), C(5)], 112.34 (CN), 101.93 (=*C*HCN), 81.85 [(HO)*C*(CH$_2$)$_4$], 37.46 [cycle C(2), C(5)], 22.01 [cycle C(2), C(6)]. IR (KBr, ν/cm^{-1}): 3512, 3451, 3254, 3118, 3050, 3017, 2785, 2236, 1635, 1624, 1552, 1445, 1370, 1354, 1307, 1291, 1264, 1222, 1206, 1182, 1128, 1110, 1094, 1041, 1023, 873, 852, 786, 746, 706, 684, 644, 618, 567, 521, 501. Found (%): C, 64.58; H, 5.95; N, 10.50. Calc. for $C_{14}H_{15}N_2O_3$ (%): C, 64.85; H, 5.83; N, 10.80.

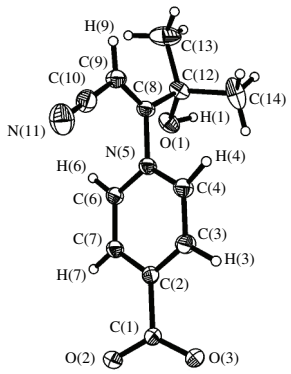


Figure 1 Molecular structure of 1-[(*Z*)-2-cyano-1-(1-hydroxy-1-methylethyl)ethenyl]pyridinium-4-carboxylate **3a**.

For the structure determination we performed the X-ray analysis of a single crystal of product **3a**, which proved to be 1-[(*Z*)-2-cyano-1-(1-hydroxy-1-methylethyl)ethenyl]pyridinium-4-carboxylate (Figure 1).‡

A maximum deviation of the C(7) atom for the pyridine cycle is 0.01 Å. Deviations of C(1) and C(8) atoms out of the pyridine plane are 0.02 and 0.003 Å, respectively. The dihedral angle between the pyridine ring plane and the C(1)O(2)O(3) plane is 18.2°, the dihedral angle formed by the pyridine ring and the C(8)C(9)C(10)N(11) moiety is equal to 96.5°

In the crystal structure of compound **3a**, all the molecules are bound by hydrogen bonds of the O···H–O and O···H–C types [O(2)···H(1) 1.84(3) Å, O(1)···O(2) 2.780(2) Å, O(1)–H(1)···O(2) 175(2)°; O(2)···H(9) 2.18(2) Å, C(9)···O(2) 3.086(2) Å, C(9)–H(9)···O(2) 163(2)°; O(3)···H(4) 2.19(2) Å, C(4)···O(3) 3.146(2) Å, C(4)–H(4)···O(3) 164(2)°] [van der Waals radii are 2.45 (O···H), 3.00 (O···O) and 3.20 Å (C···O)][10] (Figure 2).

For the structure determination of compounds **3a–c**, IR, ^{1}H, ^{13}C, ^{15}N NMR and ^{1}H–^{1}H homonuclear and ^{1}H–^{13}C heteronuclear 2D (COSY, NOESY, HMBC, HSQC) techniques have been employed.

The IR spectra of compounds **3a–c** show absorption bands in the regions of 1620–1630 and 1540–1553 cm^{-1}, assignable to C=C, C=N and COO$^-$ groups. The bands at 2220–2236 and 3400–3538 cm^{-1} are assigned to the C≡N and OH groups, respectively. The absence of absorption bands at 1740–1650 cm^{-1} confirms the ionic character of the carboxy group in compounds **3a–c**.[11]

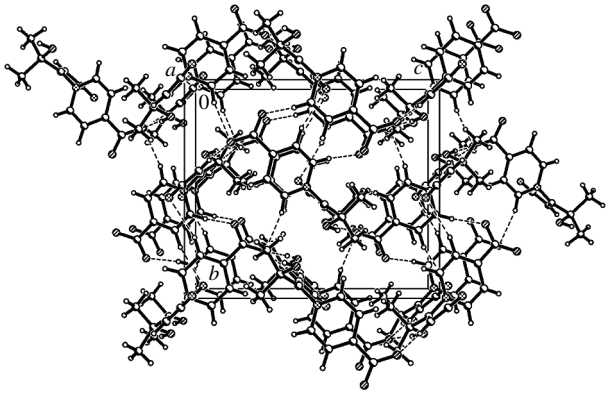


Figure 2 Crystal structure of 1-[(*Z*)-2-cyano-1-(1-hydroxy-1-methylethyl)-ethenyl]pyridinium-4-carboxylate **3a**.

In the ^{1}H NMR spectra of **3a–c** the pyridine protons appear as two doublets at δ 8.88–8.93 (N=CH) and 8.33–8.38 ppm (C=CH) and a signal of olefin proton at 6.49–6.57 ppm that is indicative of the formation of only one isomer. *Z*-Configuration of the isomers followed from the fact that, in the 2D NOESY spectrum of the compound **3a**, the cross-peak between signals of the olefin proton and methyl group protons is observed. The spectrum also contains cross-peaks between the 2-H proton and the protons of a methyl group as well as between the 2-H and 3-H protons of the pyridine ring (Figure 3). In the ^{15}N NMR spectra of compound **3a**, the N nucleus of the pyridine ring occurs at –174.15 ppm, while the N nucleus of CN group, at –113.08 ppm. The ^{13}C NMR spectra correspond to the structure of compounds **3a–c**.

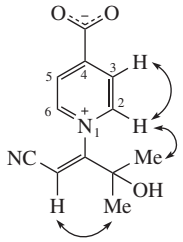


Figure 3 Cross-peaks in the 2D (^{1}H, ^{1}H) NOESY spectrum of the 1-[(*Z*)-2-cyano-1-(1-hydroxy-1-methylethyl)ethenyl]pyridinium-4-carboxylate **3a**.

In conclusion, the stereospecific addition of isonicotinic acid to α,β-acetylenic γ-hydroxy nitriles proceeding under conditions close to biomimetic (water, no catalyst, 50–55 °C) gives rise to a family of densely functionalized pyridines, potent building blocks for drug design, particularly anti-tuberculosis agents.

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1-[(Z)-2-Cyano-1-(1-hydroxycyclohexyl)ethenyl]pyridinium-4-carboxylate **3c**: yield 45%, beige solid, mp 159–162 °C (decomp.). ^{1}H NMR (400.13 MHz, D_2O) δ: 8.76 (d, 2H, H_{Py}-2,6), 8.21 (d, 2H, H_{Py}-3,5), 6.50 (s, 1H, =CHCN), 1.62–1.51 (m, 10H, CH_2). ^{13}C NMR (100.62 MHz, D_2O) δ: 169.13 [C(O)O$^-$], 164.90 (NC=), 153.06 [C(4)], 145.09 [C(2), C(6)], 126.79 [C(3), C(5)], 112.32 (CN), 102.07 (=*C*HCN), 72.74 [(HO)*C*$(CH_2)_5$], 33.33 [cycle C(2), C(6)], 23.84 [cycle C(4)], 20.41 [cycle C(3), C(5)]. IR (KBr, ν/cm^{-1}): 3538, 3123, 3104, 3055, 3018, 2957, 2936, 2883, 2859, 2235, 1964, 1875, 1631, 1554, 1443, 1346, 1298, 1280, 1261, 1232, 1206, 1187, 1161, 1145, 1104, 1082, 985, 904, 868, 858, 843, 746, 643, 617, 409. Found (%): C, 65.74; H, 6.01; N, 10.15. Calc. for $C_{15}H_{17}N_2O_3$ (%): C, 65.92; H, 6.27; N, 10.25.

‡ *Crystallographic data for* **3a**: $C_{12}H_{12}N_2O_3$, M = 232.24, rhombic, space group $P2_12_12_1$, a = 7.450(1), b = 11.686(2) and c = 13.618(3) Å, V = 1185.6(4) Å^3, Z = 4, d_{calc} = 1.30 g cm^{-3}, μ(CuKα) = 0.791 mm^{-1}, F(000) = 488. X-ray diffraction studies were carried out on an Enraf Nonius CAD-4 diffractometer at room temperature (ω-scan mode, CuKα radiation, graphite monochromator). The number of measured reflections, 3277; the number of independent reflections, 2201; the number of refined parameters, 203. R-factor 0.036 for 2114 reflections with $F_0 > 4\sigma(F_0)$. The crystal structure was solved by direct methods followed with Fourier synthesis using SHELXS-97.[12] The structure was refined using a full-matrix least-square anisotropic approximation for all non-hydrogen atoms with SHELXL-97.[13] Coordinates of hydrogen atoms were defined experimentally and refined isotropically.

CCDC 686261 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

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