Cascade cyclization of quinoline and quinoxaline with nitriles of α,β-acetylenic γ-hydroxy acids

Ludmila V. Andriyankova,* Anastasiya G. Mal'kina, Andrei V. Afonin and Boris A. Trofimov

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax +7 3952 39 6046; e-mail: andr@irioch.irk.ru

10.1070/MC2003v013n04ABEH001789

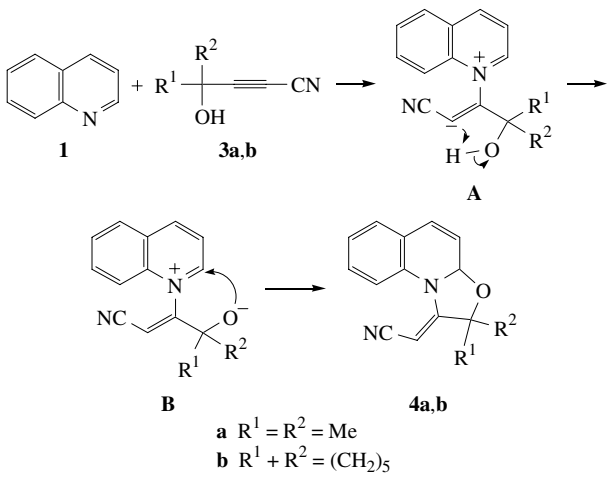
Quinoline and quinoxaline react regiospecifically and stereoselectively with the nitriles of α,β-acetylenic γ-hydroxy acids to form new annelated heterocyclic systems, 1,3-oxazolidinedihydrazines.

The reactions of the nitriles of α,β-acetylenic γ-hydroxy acids with N-centered nucleophiles (ammonia, primary and secondary amines, imidazole and benzimidazole) have been covered in reviews.[1(a),(b)] As a result of this research, general approaches to the synthesis of 4-aminoalkyl(azolyl)-2,5-dihydro-2-iminofuranes and conjugated iminodihydrofuranes were developed. Recently, we found a facile cyclization of pyridine, α-, β-, γ-picolines and tris[2-(4-pyridyl)ethyl]phosphine oxide with the nitriles of α,β-acetylenic γ-hydroxy acids under mild conditions to form a new group of heterocyclic compounds, 1,3-oxazolidinedihydropyridines.[2(a),(b)] No data on the reactions of quinoline and quinoxaline with the above nitriles were published. It was only reported[3(a),(b)] that the reactions of quinoline and quinoxaline methyl derivatives with acetylenedicarboxylates result in the formation of substituted quinolizines and azepines in moderate yields (1–6%).

We studied the reaction of quinoline **1** and quinoxaline **2** with 4-hydroxy-4-methyl-2-pentynenitrile **3a** and 3-(1-hydroxycyclohexyl)-2-propynenitrile **3b** in order to extend the synthetic potentialities of the nitriles of α,β-acetylenic γ-hydroxy acids and to synthesise new functionally substituted 1,3-oxazolidinazines.

Quinoline **1** reacts with nitriles **3a**,**b** under mild conditions (molar ratio **1**:**3** = 1:1, 20–25 °C, without catalyst and solvent) to form the products of annelation, 4-cyanomethylene-5,5-dimethyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydroquinoline **4a** and 4-cyanomethylene-5-spirocyclohexyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydroquinoline **4b** in 92 and 54% yields, respectively (Scheme 1).†

The formation of 1,3-oxazolidinequinolines **4a**,**b** probably involves, like with pyridine,[2(a)] zwitterionic intermediates **A** and **B**.



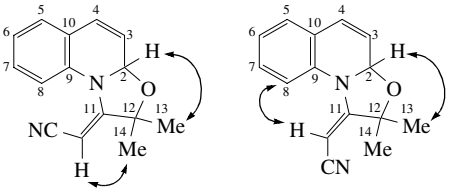
a $R^1 = R^2 = Me$
b $R^1 + R^2 = (CH_2)_5$

Scheme 1

The formation of **4a** was accomplished in 20 h, whereas the formation of **4b** required 80 h; the yield was only 54%. Evidently, the introduction of a bulky cyclohexyl substituent into the acetylene molecule impedes both the formation of intermediates **A** and **B** and their subsequent cyclization to 1,3-oxazolidinequinoline **4b**.

1,3-Oxazolidine[3,2-*a*]-1,2-dihydroquinolines **4a**,**b** are crystalline substances soluble in organic solvents. Their structure was proven by IR and ^{1}H, ^{13}C NMR spectroscopy (including a 2D method).‡

1,3-Oxazolidinequinolines **4a**,**b** are represented by only *Z*-isomers. In the 2D (^{1}H, ^{1}H) NOESY spectrum of **4a**, there is a cross peak between the signals of the olefin proton and the protons of one of the methyl groups. Moreover, a correlation between the protons at the 2-position of the quinoline ring and the protons of the second methyl group can be revealed.



In contrast to 1,3-oxazolidinepyridines obtained *via* the reaction of pyridine and acetylenes **3**, which do not change their configuration in storage,[2(b)] 1,3-oxazolidinequinolines **4a**,**b** undergo izomerization on keeping. Thus, in the ^{1}H NMR spectrum of freshly prepared compound **4a**, which was immediately recorded by two-dimensional (NOESY) spectroscopy ($CDCl_3$), there is only one olefin proton signal at 3.97 ppm, which corresponds to the *Z*-isomer of **4a**. Three days later in the spectrum of this solution (heating in an ampoule to 30–40 °C) the second olefin proton signal due to the *E*-isomer of **4a** appeared at 4.77 ppm, and the corresponding doubling of all other signals was observed. The ratio of *E*:*Z*-isomers was 1:3.

† *4-Cyanomethylene-5,5-dimethyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydroquinoline* (*Z*)-**4a**. Acetylene **3a** (0.22 g, 2 mmol) and quinoline **1** (0.26 g, 2 mmol) were stirred at 20–25 °C for 20 h. Then the reaction mixture was separated chromatographically on an Al_2O_3 column (chloroform–benzene–ethanol, 20:4:1 as an eluent), the solvents were removed in a vacuum. We obtained 0.44 g (92%) of 1,3-oxazolidine (*Z*)-**4a** as white crystals.

*4-Cyanomethylene-5-spirocyclohexyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydroquinoline* (*Z*)-**4b**. Analogously, from acetylene **3b** (0.15 g, 1 mmol) and quinoline **1** (0.13 g, 1 mmol), 0.15 g (54%) of light-yellow crystals of 1,3-oxazolidine (*Z*)-**4b** were obtained in 80 h.

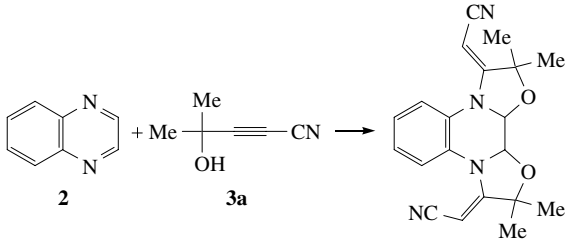
*Di(4-cyclomethylene-5,5-dimethyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydro)-quinoxaline* (*E*,*Z*)-**5a**. Quinoxaline **2** (0.13 g, 1 mmol) and acetylene **3a** (0.11 g, 1 mmol) were stirred at 70–80 °C for 12 h. The reaction mixture was separated on a chromatographic column with Al_2O_3 (chloroform–benzene–ethanol, 20:4:1 as an eluent), the solvents were removed in a vacuum. We obtained 0.10 g (29%) of 1,3-oxazolidinequinoxaline (*E*,*Z*)-**5a** as a white powder.

*Di(4-cyanomethylene-5,5-dimethyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydro)-quinoxalines* (*E*,*E*; *E*,*Z*)-**5a**. Analogously, from quinoxaline **2** (0.13 g, 1 mmol) and acetylene **3a** (0.22 g, 2 mmol), 0.21 g (60%) of a gray powder of a 3:1 mixture of two adducts [(*E*,*E*)-**5a** and (*E*,*Z*)-**5a**] was prepared.

*Di(4-cyanoethylene-5-spirocyclohexyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydro)quinoxalines* (*E*,*E*; *Z*,*Z*; *E*,*Z*)-**6b**. Analogously, from quinoxaline **2** (0.13 g, 1 mmol) and acetylene **3b** (0.30 g, 2 mmol), 33 g (77%) of a light-yellow powder of a mixture of three adducts **6b** was obtained at 70–78 °C for 28 h.

When kept in a $CDCl_3$ solution at 20–25 °C, *Z*-isomer **4b** isomerized gradually. Its ^{1}H NMR spectrum measured five days later showed an olefin proton signal related to *E*-isomer **4b** at 4.72 ppm, whereas the olefin proton signal at 3.91 ppm of *Z*-isomer **4b** decreased, and the *E*:*Z* ratio became equal to 2:1. After 15 days, the intensity of the *E*-isomer olefin proton signal at 4.72 ppm increased (*E*:*Z* = 3:1), and after 35 days the *E*:*Z* ratio was 4:1.

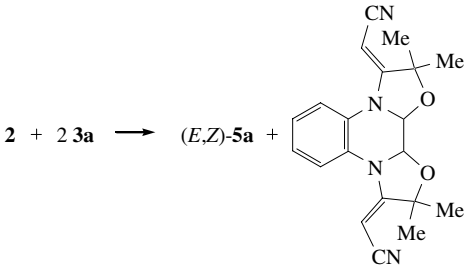
On going from quinoline **1** to quinoxaline **2**, which contains two 'pyridinic' nitrogen atoms, a possible formation of both mono- and dioxazolidines in the reaction with acetylenes **3a**,**b** has been suggested. However, we found that only dioxazolidines were formed independently of the **2**:**3a** molar ratio. Note that the reaction did not occur without solvent (20–25 °C, 130 h) or in acetonitrile (82 °C, 30–50 h), analogously to ref. 3. The heating of equimolar quantities of quinoxaline **2** and acetylene **3a** (without solvent) at 70–80 °C for 12 h leads to di(4-cyanomethylene-5,5-dimethyl-1,3-oxazolidine[3,2-*a*]-1,2-dihydro)quinoxaline (*E*,*Z*)-**5a** in 29% yield (Scheme 2).†



2 **3a** (*E*,*Z*)-**5a**

Scheme 2

With a twofold excess of acetylene **3a** over quinoxaline, under similar conditions, along with *E*,*Z*-diadduct **5a**, *E*,*E*-diadduct **5a** was also formed (total yield of 60%). The (*E*,*E*):(*E*,*Z*)-**5a** ratio was 3:1 (Scheme 3).



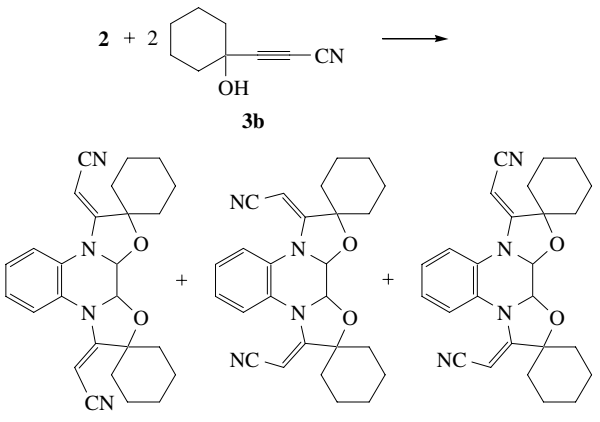
(*E*,*E*)-**5a**

Scheme 3

Evidently, following the formation of the first oxazolidine ring, the basicity of the second nitrogen atom increased due to a change in the conjugation, and the assemblage of the second oxazolidine ring occurred at a considerably higher rate.

The reaction of quinoxaline **2** and acetylene **3b** (molar ratio of 1:2, 70–80 °C, 28 h) leads to *E*,*E*-, *Z*,*Z*- and *E*,*Z*-dioxazolidines **6b** (total yield of 77%).† The *E*,*E*-, *Z*,*Z*- and *E*,*Z*-isomer **6b** ratio in the mixture is 1:3:2.7 (Scheme 4).‡

The structure of 1,3-oxazolidinequinoxalines **5**, **6** was proven by IR and ^{1}H NMR spectroscopy. Their IR spectra showed intense absorption bands arising from the =CH*CN* group at 2190 cm^{-1}, whereas absorption bands corresponding to the hydroxyl group in the region of 3300–3600 cm^{-1} were absent.‡



(*E*,*E*)-**6b** (*Z*,*Z*)-**6b** (*E*,*Z*)-**6b**

Scheme 4

‡ ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-250 (250 MHz) spectrometer in $CDCl_3$; HMDS was used as an internal standard. IR spectra were recorded on a Specord IR-75 instrument (KBr pellets). Quinoline **1** and quinoxaline **2** were commercial reagents. 4-Hydroxy-4-alkyl-2-alkynenitriles **3a**,**b** were prepared using a published procedure.[4]

4a: Mp 154–155 °C (hexane). ^{1}H NMR ($CDCl_3$) δ, for *Z*-isomer: 1.47 (s, 3H, Me), 1.52 (s, 3H, Me), 3.97 (s, 1H, =CH–CN), 5.95 (dd, C^{3}H, $^3J_{3-4}$ 9.8 Hz), 5.99 (dd, C^{2}H, $^3J_{2-3}$ 1.2 Hz, $^4J_{2-4}$ 1.8 Hz), 6.50 (dd, C^{4}H), 7.12 (dd, C^{5}H, $^3J_{5-6}$ 7.6 Hz, $^4J_{5-7}$ 1.8 Hz), 7.14 (td, C^{7}H, $^3J_{6-7} = {}^3J_{7-8}$ 7.6 Hz), 7.36 (td, C^{6}H, $^4J_{6-8}$ 1.8 Hz), 7.50 (dd, C^{8}H); for *E*-isomer: 1.62 (s, 3H, Me), 1.81 (s, 3H, Me), 4.77 (s, 1H, =CH–CN), 5.96 (dd, C^{3}H, $^3J_{3-4}$ 9.7 Hz), 6.06 (dd, C^{2}H, $^3J_{2-3}$ 1.3 Hz, $^4J_{2-4}$ 1.5 Hz), 6.46 (dd, C^{4}H), 7.12 (dd, C^{5}H, $^3J_{5-6}$ 7.7 Hz, $^4J_{5-7}$ 1.8 Hz), 7.16 (td, C^{7}H, $^3J_{6-7} = {}^3J_{7-8}$ 7.3 Hz), 7.33 (td, C^{6}H, $^4J_{6-8}$ 1.5 Hz), 7.34 (dd, C^{8}H). ^{13}C NMR ($CDCl_3$) δ, for *Z*-isomer: 24.94 (C^{14}), 26.55 (C^{13}), 56.21 (C^{15}), 85.40 (C^{12}), 87.84 (C^2), 117.77 (C^{16}), 123.36 (C^8), 125.83 (C^6), 126.76 (C^4), 127.01 (C^5), 127.25 (C^3), 127.40 (C^{10}), 127.57 (C^7), 132.35 (C^9), 159.39 (C^{11}); for *E*-isomer: 24.26 (C^{14}), 26.54 (C^{13}), 57.61 (C^{15}), 85.06 (C^{12}), 87.56 (C^2), 119.21 (C^{16}), 120.18 (C^8), 125.40 (C^6), 126.17 (C^4), 127.40 (C^{10}), 127.48 (C^5), 128.15 (C^3), 128.48 (C^7), 134.12 (C^9), 163.61 (C^{11}). IR (ν/cm^{-1}): 3060, 3020, 2960, 2920, 2820, 2190, 1640, 1620, 1590, 1490, 1450, 1430, 1380, 1370, 1320, 1290, 1260, 1170, 1140, 1120, 1070, 1010, 960, 910, 850, 830, 800, 770, 750, 730, 690, 650, 560, 540, 520, 500. Found (%): C, 75.39; H, 5.87; N, 11.46. Calc. for $C_{15}H_{14}N_2O$ (%): C, 75.61; H, 5.92; N, 11.76.

(*Z*)-**4b**: Mp 162–164 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.60–1.73 [m, 10H, $(CH_2)_5$], 3.91 (s, 1H, =CH–CN), 5.91 (dd, C^{3}H, $^3J_{3-4}$ 9.7 Hz), 5.96 (dd, C^{2}H, $^3J_{2-3}$ 1.1 Hz, $^4J_{2-4}$ 1.4 Hz), 6.35 (dd, C^{4}H), 7.10 (dd, C^{5}H, $^3J_{5-6}$ 7.5 Hz, $^4J_{5-7}$ 1.7 Hz), 7.14 (td, C^{7}H, $^3J_{6-7} = {}^3J_{7-8}$ 7.5 Hz), 7.32 (td, C^{6}H, $^4J_{6-8}$ 1.8 Hz), 7.48 (dd, C^{8}H). ^{13}C NMR ($CDCl_3$) δ: 21.98, 22.13, 25.13, 33.29, 35.58 (C-cyclohexyl), 56.79 (C^{15}), 86.78 (C^{12}), 88.03 (C^2), 117.36 (C^{16}), 123.61 (C^8), 125.76 (C^6), 126.03 (C^4), 126.91 (C^5), 127.43 (C^{10}), 127.69 (C^3), 128.38 (C^7), 132.57 (C^9), 159.19 (C^{11}). IR (ν/cm^{-1}): 3060, 2950, 2930, 2850, 2180, 1620, 1580, 1480, 1460, 1410, 1390, 1350, 1320, 1280, 1260, 1180, 1140, 1120, 1090, 1070, 1000, 960, 940, 910, 880, 850, 840, 830, 760, 750, 700, 670, 640, 560, 520, 500. Found (%): C, 77.45; H, 6.60; N, 9.97. Calc. for $C_{18}H_{18}N_2O$ (%): C, 77.67; H, 6.52; N, 10.06.

(*E*,*Z*)-**5a**: Mp 263–266 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ: 1.52 (s, 3H, Me), 1.53 (s, 3H, 2Me), 1.70 (s, 3H, Me), 1.83 (s, 3H, Me), 4.21 (s, 1H, *Z*- =CHCN), 5.06 (s, 1H, *E*- =CHCN), 4.75 and 4.80 (d, 2H, C^{2,3}H, $^3J_{2-3}$ 6.7 Hz), 7.23–7.57 (m, 4H, C^{5,6,7,8}H arom.). IR (ν/cm^{-1}): 3050, 2980, 2930, 2850, 2190, 1630, 1590, 1500, 1460, 1440, 1420, 1370, 1320, 1310, 1280, 1180, 1140, 1130, 1110, 970, 920, 870, 850, 820, 780, 750, 730, 690, 640, 630, 570, 470, 450. Found (%): C, 68.52; H, 5.31; N 16.05. Calc. for $C_{20}H_{20}N_4O_2$ (%): C, 68.95; H, 5.79; N, 16.08.

5a: Mp 258–265 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ, for *E*,*E*-isomer: 1.69 (s, 3H, Me), 1.82 (s, 3H, Me), 4.74 (s, 2H, C^{2,3}H), 4.99 (s, 2H, 2 =CHCN), 7.23–7.46 (m, 4H, C^{5,6,7,8}H arom.); for *E*,*Z*-isomer: 1.24 (s, 3H, Me), 1.52 (s, 3H, Me), 4.21 (s, 1H, *Z*- =CHCN), 4.76 and 4.80 (d, 2H, C^{2,3}H, $^3J_{2-3}$ 6.7 Hz), 5.05 (s, 1H, *E*- =CHCN), 7.23–7.46 (m, 4H, C^{5,6,7,8}H arom.). IR (ν/cm^{-1}): 3050, 2980, 2930, 2870, 2190, 1630, 1580, 1490, 1450, 1430, 1410, 1360, 1320, 1310, 1290, 1190, 1140, 1130, 1050, 1110, 960, 920, 890, 860, 820, 770, 750, 730, 700, 670, 640, 630, 530, 460. Found (%): C, 68.34; H, 5.42; N, 15.93. Calc. for $C_{20}H_{20}N_4O_2$ (%): C, 68.95; H, 5.79; N, 16.08.

6b: Mp 110–130 °C (Et_2O). ^{1}H NMR, δ, for *E*,*E*-isomer: 4.72 (s, 2H, C^{2,3}H), 4.98 (s, 2H, 2 =CHCN); for *Z*,*Z*-isomer: 4.29 (s, 2H, 2 =CHCN), 4.78 (s, 2H, C^{2,3}H); for *E*,*Z*-isomer: 4.22 (s, 1H, *Z*- =CHCN), 4.71 and 4.77 (d, 2H, C^{2,3}H, $^3J_{2-3}$ 6.7 Hz), 5.02 (s, 1H, *E*- =CHCN). What all the three isomers have are 1.62–1.76 (m, 30H, 6 cyclohexyls), 7.20–7.61 [m, 12H, 3×(4H, C^{5,6,7,8}H) arom.]. IR (ν/cm^{-1}): 3060, 2940, 2930, 2850, 2190, 1630, 1590, 1490, 1460, 1450, 1420, 1360, 1350, 1310, 1270, 1180, 1160, 1140, 1100, 1030, 950, 930, 840, 830, 750, 730, 670, 640, 600. Found (%): C, 72.41; H, 6.27; N, 13.52. Calc. for $C_{26}H_{28}N_4O_2$ (%): C, 72.87; H, 6.59; N, 13.07.

The isomer assignment was based on the data of ^{1}H NMR spectroscopy. The signals of olefin protons in *E*,*Z*-isomers **5a**, **6b** occurred at 4.21 and 4.22 ppm (for *Z*) or 5.06 and 5.02 ppm (for *E*); in *E*,*E*-isomers **5a**, **6b**, at 4.99 and 4.98 ppm; in *Z*,*Z*-isomer **6b** at 4.29 ppm.‡ Attempts to separate isomers **5a** and **6b** by column chromatography and fractional crystallization were unsuccessful.

Thus, a new general approach to the synthesis of earlier unknown annelated heterocyclic systems, 1,3-oxazolidinedihydroazines, was developed. The method involves the reaction of pyridine[2] and quinoline bases with the nitriles of α,β-acetylenic γ-hydroxy acids. The new 1,3-oxazolidinazines are promising reagents for a directed search for biologically active substances since quinoline derivatives are known to be widely used in medicine.

This work was supported by the Russian Foundation for Basic Research (grant no. 02-03-32400a).

References

1 (*a*) B. A. Trofimov, A. G. Mal'kina and Yu. M. Skvortsov, *Zh. Org. Khim.*, 1993, **29**, 1268 (*Russ. J. Org. Chem.*, 1993, **29**, 1053); (*b*) B. A. Trofimov and A. G. Mal'kina, *Heterocycles*, 1999, **51**, 2485.

2 (*a*) B. A. Trofimov, L. V. Andriyankova, S. A. Zhivet'ev, A. G. Mal'kina and V. K. Voronov, *Tetrahedron Lett.*, 2002, **43**, 1093; (*b*) B. A. Trofimov, L. V. Andriyankova, S. I. Shaikhudinova, T. I. Kasanzeva, A. G. Mal'kina and A. V. Afonin, *Synthesis*, 2002, 853.

3 (*a*) O. Diels, K. Alder, T. Kashimoto, W. Friedrichsen, W. Eckardt and H. Klare, *Liebigs Ann. Chem.*, 1932, **496**, 16; (*b*) R. M. Acheson and M. W. Foxton, *J. Chem. Soc.*, 1968, 378.

4 S. R. Landor, B. Demetriou, R. Grzeskowiak and D. Pavey, *J. Organomet. Chem.*, 1975, **93**, 129.

Received: 30th April 2003; Com. 03/2115