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Reaction of anabasine with 3-(1-hydroxycyclohexyl)-2-propynenitrile: a new route to functionalised anabasine alkaloids

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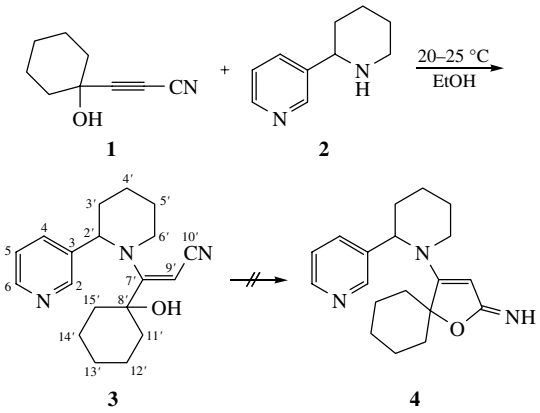
Chemo- and regioselective addition of anabasine to 3-(1-hydroxycyclohexyl)-2-propynenitrile in ethanol results in 52% yield of a monoadduct, (*Z*)-3-(1-hydroxycyclohexyl)-3-[2-(3-pyridinyl)piperidino]-2-propenenitrile: in this case, only the piperidine ring of anabasine takes part in the reaction. In acetonitrile, both piperidine and pyridine rings participate in the process giving a diadduct, (*Z*)-3-{2-[3-[(*Z*)-cyanomethylidene]-2-spirocyclohexyl-8*aH*-[1,3]oxazolo[3,2-*a*]pyridine-8(2*H*)-yl]piperidino}-3-(1-hydroxycyclohexyl)-2-propenenitrile in 68% yield.

Nucleophilic addition of primary and secondary amines (including piperidine) to 4-hydroxyalk-2-ynenitriles results in hydroxyalkenenitriles, which further cyclise to iminodihydrofurans.[1–3] We discovered a facile cyclization of pyridine, α-, β-, γ-picolines and tris[2-(4-pyridyl)ethyl]phosphine oxide with 4-hydroxyalk-2-ynenitriles under mild conditions to form new group of heterocyclic compounds, 1,3-oxazolidinodihydropyridines.[4,5]

Here we describe a reaction between 3-(1-hydroxycyclohexyl)-2-propynenitrile **1** and a natural alkaloid, 2-(3-pyridino)-piperidine (anabasine) **2**, containing pyridine and piperidine moieties and thus capable of reacting with functionalised acetylene **1** by two pathways. The goal of this work was to study the reactivity of the two above nucleophilic centres toward the push-pull acetylenic system and to develop synthetic routes to new semisynthetic alkaloids, anabasine derivatives, possessing useful properties (anabasine salts are widely used as insecticides[6–8]).

Our experiments demonstrated that, when an equimolar ratio of the biomimetic reactants in ethanol is used, acetylene **1** reacts with anabasine **2** under mild conditions (no catalysts, 20–25 °C,



Scheme 1

4 h) to give the N-adduct, 3-(1-hydroxycyclohexyl)-3-[2-(3-pyridinyl)piperidino]-2-propenenitrile **3** in *Z*-configuration in 52% yield. This implies that only a piperidine ring participates in the reaction. Unlike unsubstituted piperidine,[3] adduct **3** does not cyclise to iminodihydrofuran **4** (Scheme 1).†

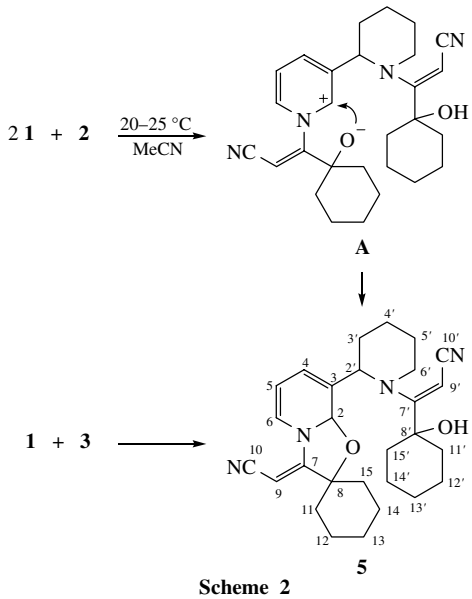
A weak-field shift of $H^{2'}$ and $H^{6'a,b}$ proton signals in the ^1H NMR spectrum (by 1.87 and 0.74 ppm, respectively, relative to the corresponding values in starting anabasine **2**) owing to the anisotropy of the CN group indicates that adduct **3** has *Z*-configuration.

The replacement of ethanol by an aprotic solvent (acetonitrile) and the use of a twofold excess of acetylene **1** at room temperature resulted in the reaction of the pyridine moiety of anabasine **2**. The process is accompanied by annelation,[4,5] which results in a diadduct, (*Z*)-3-{2-[3-[(*Z*)-cyanomethylidene]-2-spirocyclohexyl-8*aH*-[1,3]oxazolo[3,2-*a*]pyridine-8(2*H*)-yl]piperidino}-3-(1-hydroxycyclohexyl)-2-propenenitrile **5** (22% yield). Diadduct **5** was also prepared in 68% yield by the reaction of acetylene **1** with monoadduct **3** (Scheme 2).†

The annelation is likely to proceed *via* zwitterionic intermediate **A**.[4] Apparently, the successful attack of the pyridine nucleophilic centre in anabasine **2** on the triple bond of acetylene **1** is possible owing to a strong electron-withdrawing effect of the nitrile group. This assumption is supported by the fact that under these conditions pyridine does not react with 1-ethynylcyclohexanol (an analogue of acetylene **1** containing no nitrile substituent).[4]

The *Z*-configuration of the CN group in the oxazolidine moiety of diadduct **5** follows from the signal position of the olefinic proton at C^9 in the ^1H NMR spectrum (4.01 ppm), which correlates well with known chemical shifts of *Z*-adducts of acetylene **1** and pyridines.[4,5] Olefinic proton signals in the *E*-isomers of 1,3-oxazolidinoazines are usually observed in a weaker field (~5 ppm).[9]

Anabasine derivatives **3**, **5** are crystalline substances soluble in various organic solvents. Their structures were confirmed by ^1H and ^{13}C NMR, IR and UV-VIS spectroscopy.‡ The IR spectra of adducts **3**, **5** show an absorption band at 2190 cm^{-1} corresponding to vibrations of the CN group at the double bond. The ^1H NMR spectra display singlets of olefinic protons (=CH–CN) at 4.01 and 4.83 ppm in oxazolidine and piperidine moieties, respectively. Aliphatic fragments of adducts **3**, **5** in ^{13}C NMR spectra are represented by a large group of signals, apparently, owing to the presence of diastereomers of these compounds.‡



Scheme 2

Thus, anabasine **2** selectively reacts with 3-(1-hydroxycyclohexyl)-2-propynenitrile **1** either at its piperidine ring or simultaneously at piperidine and pyridine rings. With an equimolar ratio of the reactants in ethanol, the attack on the triple bond of acetylene **1** occurs selectively by the most nucleophilic centre, piperidine nitrogen atom, affording monoadduct **3**. The use of a twofold excess of acetylene **1** in acetonitrile allows one to involve the pyridine nitrogen atom in the reaction, as well to obtain diadduct **5**.

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† *3-(1-Hydroxycyclohexyl)-3-[2-(3-pyridinyl)piperidino]-2-propenenitrile* (*Z*)-**3**. A mixture of anabasine **2** (0.16 g, 1 mmol) and acetylene **1** (0.15 g, 1 mmol) in 2 ml of ethanol was stirred for 4 h at 20–25 °C. After the removal of ethanol, the residue was chromatographed on a column with Al_2O_3 (eluent: benzene–chloroform–ethanol, 20:4:1). The solvents were then removed in a vacuum to give 0.16 g (52%) of monoadduct (*Z*)-**3**, as a beige powder.

*3-[2-[3-(Z)-Cyanomethylidene-2-spirocyclohexyl-8*aH*-[1,3]oxazolo-[3,2-*a*]pyridine-8(*2H*)-yl]piperidino]-3-(1-hydroxycyclohexyl)-2-propenenitrile* (*Z*)-**5**.

A. Analogously, from anabasine **2** (0.16 g, 1 mmol) and acetylene **1** (0.30 g, 2 mmol) in 0.3 ml of acetonitrile (20–25 °C, 20 h), a total of 0.10 g (22%) of diadduct (*Z*)-**5** was obtained as red powder.

B. Analogously, from monoadduct **3** (0.10 g, 0.32 mmol) and acetylene **1** (0.05 g, 0.32 mmol) in 0.2 ml of acetonitrile (20–25 °C, 20 h), 0.10 g (68%) of diadduct (*Z*)-**5** was obtained as red powder.

‡ ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (400 MHz) spectrometer in $CDCl_3$ with HMDS as an internal standard. UV-VIS spectra were measured on a Lambda 35 instrument (EtOH). IR spectra were measured on a Specord IR-75 instrument in KBr pellets. Procedures for isolation of anabasine **2** are described elsewhere;[10,11] 3-(1-hydroxycyclohexyl)-2-propynenitrile was also prepared by a previously described method.[12,13]

3: mp 57–59 °C (hexane). ^1H NMR ($CDCl_3$) δ: 1.17–1.97 (m, 17H, OH, $H^{3'-5',11'-15'}$), 3.25, 3.40 (m, 2H, $H^{6'a,b}$), 4.83 (s, 1H, $H^{9'}$, =CH–CN), 5.26 (t, 1H, $H^{2'}$), 7.23 (q, 1H, H^5), 7.72 (d, 1H, H^4), 8.39 (dd, 1H, H^6), 8.59 (d, 1H, H^2). ^{13}C NMR ($CDCl_3$) δ: 21.52, 21.75, 24.92, 25.99, 37.59, 39.24, 51.29, 58.61, 73.47 ($C^{2'-6',9',11'-15'}$), 79.73 ($C^{8'}$), 118.33 ($C^{10'}$, CN), 123.04 (C^5), 134.96 (C^4), 137.33 (C^3), 147.71 (C^6), 148.30 (C^2), 175.25 ($C^{7'}$). IR (ν/cm^{-1}): 3050, 3000, 2930, 2860, 2190, 1650, 1590, 1550, 1480, 1450, 1420, 1380, 1350, 1270, 1250, 1210, 1160, 1130, 1120, 1070, 1030, 990, 910, 850, 820, 760, 730, 710, 680, 660, 640, 630, 570, 530, 500. Found (%): C, 73.65; H, 8.32; N, 13.84. Calc. for $C_{19}H_{25}N_3O$ (%): C, 73.28; H, 8.09; N, 13.49.

5: mp 199–202 °C (hexane). ^1H NMR ($CDCl_3$) δ: 1.17–2.15 (m, 27H, OH, $H^{3'-5',11-15,11'-15'}$), 3.22, 3.50 (m, 2H, $H^{6'a,b}$), 4.01 (s, 1H, H^9, =CH–CN in an oxazolidine moiety), 4.83 (s, 1H, $H^{9'}$, =CH–CN in a piperidine moiety), 5.48 (t, 1H, $H^{2'}$), 5.73 (q, 1H, H^5), 5.84 (d, 1H, H^4), 5.96 (d, 1H, H^2), 7.34 (dd, 1H, H^6). ^{13}C NMR ($CDCl_3$) δ: 18.67, 21.50, 21.90, 22.23, 24.24, 24.38, 24.88, 25.50, 26.67, 31.46, 33.63, 34.05, 35.42 ($C^{3'-6',11'-15',11-15}$), 55.76 (C^9), 58.31 ($C^{9'}$), 76.97, 77.02 ($C^{2'}$), 79.73 ($C^{8'}$), 82.27 (C^8), 87.29 (C^2), 107.30 (C^5), 118.97 ($C^{10'}$, CN), 121.59 (C^{10}, CN), 127.91 ($C^{4,6}$), 128.10 (C^3), 159.90 (C^7), 171.38 ($C^{7'}$). IR (ν/cm^{-1}): 3080, 3030, 2930, 2860, 2190, 1650, 1620, 1590, 1450, 1400, 1370, 1300, 1280, 1250, 1220, 1180, 1140, 1120, 1090, 1050, 1030, 990, 970, 940, 930, 910, 850, 800, 750, 720, 680, 660, 640, 620, 570, 520, 500. UV-VIS [EtOH, λ/nm (lg *E*)]: 210 (4.03), 281 (4.31), 353 (3.87), 440 (3.35). Found (%): C, 73.55; H, 8.09; N, 12.54. Calc. for $C_{28}H_{36}N_4O_2$ (%): C, 73.01; H, 7.88; N, 12.16.

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