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A peculiar vinylation of 1-substituted imidazoles with α,β-acetylenic γ-hydroxyacid nitriles

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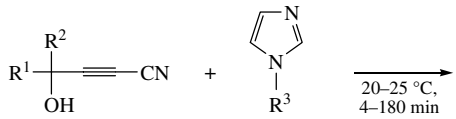
1-Substituted imidazoles react smoothly with α,β-acetylenic γ-hydroxyacid nitriles to give 1-imidazolyl-2-alkenenitriles in 37–56% yields, thus representing an unknown type of the imidazole ring vinylation accompanied by the replacement of the substituent at the nitrogen atom.

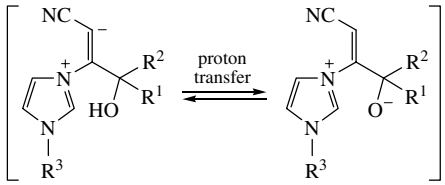
α,β-Acetylenic γ-hydroxyacid nitriles **1a**,**b** are highly potent synthons for building up the 3-cyanomethylene-1,3-oxazolidine moiety at pyridines,[1] tris(pyridyl)ethylphosphineoxide,[2] quinoline and quinoxaline,[3] phenanthridines[4] and natural alkaloids (such as anabazine[5]) to afford new condensed heterocyclic systems, 1,3-oxazolidinodihydroazines. The annelation proceeds through the zwitterionic intermediates resulted from a nucleophilic attack of the pyridine nitrogen atom at the electrophilic triple bond.

One may assume that a similar annelation could take place when cyanoacetylenes **1a**,**b** are allowed to react with an azole possessing a nitrogen atom basic enough to form a zwitterion, *e.g.*, 1-substituted imidazoles **2a**–**c**.

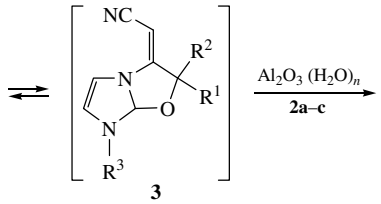
However, in this work, instead of the expected annelation products, 3-cyanomethylene-1,3-oxazolidino-2,3-dihydroimidazoles **3**, 1-alkyl derivatives of imidazole, 1-imidazolyl-2-alkenenitriles **4a**,**b** have been isolated in 37–56% yields (chromatography on Al_2O_3) (Scheme 1).†



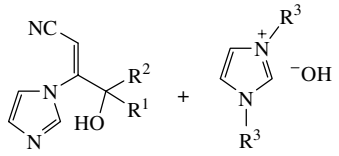
1a $R^1 = R^2 = Me$ **2a** $R^3 = Me$
1b $R^1 + R^2 = (CH_2)_5$ **2b** $R^3 = Et$
2c $R^3 = CH{=}CH_2$



A **B**



3



4a $R^1 = R^2 = Me$
4b $R^1 + R^2 = (CH_2)_5$

5

Scheme 1

However, in this work, instead of the expected annelation products, 3-cyanomethylene-1,3-oxazolidino-2,3-dihydroimidazoles **3**, 1-alkyl derivatives of imidazole, 1-imidazolyl-2-alkenenitriles **4a**,**b** have been isolated in 37–56% yields (chromatography on Al_2O_3) (Scheme 1).†

† The NMR spectra were recorded on a Bruker DPX-400 (400.13 MHz, ^{1}H; 101.61 MHz, ^{13}C) spectrometer with HMDS as an internal standard. The IR spectra of products were measured on a Specord IR-75 instrument in KBr pellets. Preparation procedures for 1-substituted imidazoles **2a**–**c** are described elsewhere;[8,9] cyanoacetylenes **1a**,**b** were prepared by a previously described method.[10,11]

Reaction of **1a** *with* **2a**. A mixture of **1a** (0.44 g, 4 mmol) and **2a** (0.16 g, 2 mmol) was stirred at 20–25 °C for 4 min. Column chromatography (eluent: chloroform–benzene–ethanol, 20:4:1) was used to give 1,4-dioxane **6a** (0.15 g, 34%), mp 220–221 °C (lit.,[7] mp 213 °C) and brown powder (0.26 g). The latter was further chromatographed (ethanol as an eluent) to afford 1-imidazolyl-2-pentenenitrile **4a** (0.15 g, 43%), mp 132–134 °C (lit.,[6] mp 131–132 °C).

4a: ^{13}C NMR ($CDCl_3$) δ: 27.66 (2Me), 72.18 (Me_2COH), 95.69 (=*C*HCN), 114.21 (CN), 119.91 (C^5), 129.53 (C^4), 136.65 (C^2), 162.30 (*C*=CHCN). IR and ^{1}H NMR spectra are given in ref. 6.

6a: ^{13}C NMR [$(CD_3)_2CO$] δ: 27.24 (4Me), 80.19 (2=*C*HCN), 115.20 (2CN), 171.95 [2Me_2C(O)C=CH], 206.15 (2*C*=CHCN). IR and ^{1}H NMR spectra are given in ref. 7.

Analogously, **6a** (0.09 g, 20%) and **4a** (0.15 g, 43%) were prepared from **1a** (0.44 g, 4 mmol) and **2b** (0.19 g, 2 mmol) (20–25 °C, 4 min). The column was washed with methanol; then, the latter was removed to give a residue containing compound **5** (R^3 = Et). ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 6H, 2Me), 3.99 (q, 2H, CH_2), 4.59 (q, 2H, CH_2, $^+$N), 6.93 (m, 1H, H^5), 7.05 (m, 1H, H^4), 7.49 (m, 1H, H^2).

Analogously, **6a** (0.05 g, 12%) and **4a** (0.20 g, 56%) were prepared from **1a** (0.44 g, 4 mmol) and **2c** (0.19 g, 2 mmol) (20–25 °C, 3 h).

Analogously, **6b** (0.10 g, 16%), mp 257–259 °C (lit.,[7] mp 244–245 °C) and **4b** (0.17 g, 40%), mp 184–186 °C (lit.,[6] mp 187–189 °C) were prepared from **1b** (0.60 g, 4 mmol) and **2a** (0.16 g, 2 mmol) (20–25 °C, 1 h).

4b: ^{13}C NMR ($CDCl_3$) δ: 21.38–35.01 (cyclohexyl), 73.69 (COH), 96.51 (=*C*HCN), 118.20 (CN), 120.08 (C^5), 129.94 (C^4), 137.12 (C^2), 162.70 (*C*=CHCN). IR and ^{1}H NMR spectra are given in ref. 6.

6b: ^{13}C NMR ([$^2H_6$]DMSO) δ: 20.38–34.98 (2cyclohexyl), 79.14 (2=*C*HCN), 115.60 (2CN), 145.56 [2(cyclohexyl)*C*(O)C=CH], 172.08 (2*C*=CHCN). IR and ^{1}H NMR spectra are given in ref. 7.

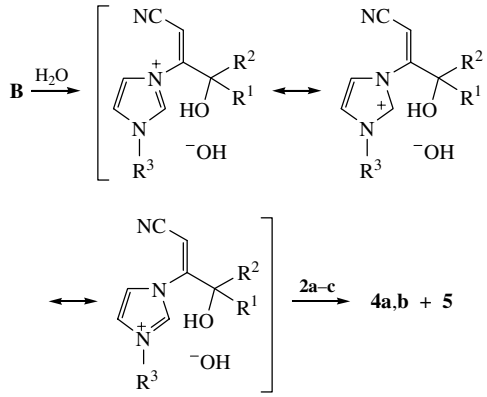
Analogously, **6b** (0.15 g, 24%) and **4b** (0.16 g, 37%) were prepared from **1b** (0.60 g, 4 mmol) and **2b** (0.19 g, 2 mmol) (20–25 °C, 1 h).

Analogously, **6b** (0.03 g, 6%) and **4b** (0.20 g, 45%) were prepared from **1b** (0.60 g, 4 mmol) and **2c** (0.19 g, 2 mmol) (20–25 °C, 3 h).

Noteworthy are mild (biomimetic) reaction conditions (20–25 °C, 4–180 min, no catalyst and no solvent). Apparently, zwitterions **A** are actually formed, further transforming (through the proton transfer) to zwitterions **B**, their neutral isomers, while expected 3-cyanomethylene-1,3-oxazolidino-2,3-dihydroimidazoles **3** are unstable due to the ring strain.

The formation of 1-vinylimidazoles **4a**,**b**† can be rationalized as the hydrolytic conversion of intermediates **3** or their zwitterionic forms **B** under the action of water present in Al_2O_3 $(H_2O)_n$ upon the chromatographic procedure (Scheme 1).

The loss of the R^3 substituent is likely to occur as *trans*-quaternization with the participation of free starting imidazole molecules **2a–c** to afford product **5**† (Scheme 2).

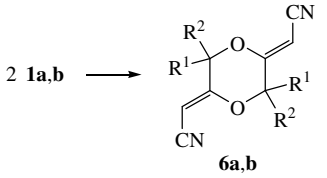


Scheme 2

The driving force of such a *trans*-quaternization should be a higher basicity of starting imidazoles **2a–c** [pK_{aBH^+} = 15.41 (**2a**), 15.00 (**2b**), 13.24 (**2c**), potentiometric titration].

The spectra (IR, ^{1}H NMR) and properties of the vinyl derivatives **4** correspond to those synthesized by the direct nucleophilic addition of unsubstituted imidazole to cyanoacetylenes **1**.[6]

By-products (yield up to 34%) of the reaction are 3,6-di-(cyanomethylene)-1,4-dioxanes **6a**,**b**,† the dimers of starting cyanoacetylenes **1a**,**b**, described elsewhere (Scheme 3),[7] which are formed here under catalytic action of imidazoles **2a–c**, as confirmed by an additional experiment. Thus, cyanoacetylene **1a** in the presence of 20% 1-ethylimidazole **2b** (25 min) affords 1,4-dioxane **6a** in a yield of 41%.‡



Scheme 3

Due to this parallel reaction, to reach better yields of vinyl derivatives **4a**,**b**, a twofold excess of cyanoacetylenes **1a**,**b** was employed.

1-Vinylimidazoles **4a**,**b** and 1,4-dioxanes **6a**,**b** are crystals soluble in organic solvents. Their structures were confirmed by IR, ^{1}H, ^{13}C NMR and 2D NOESY techniques. Spatial localization of cyano groups in 1-vinylimidazoles **4a**,**b** and 1,4-dioxanes **6a**,**b** was determined using 2D spectroscopy. For example, the 2D (^{1}H, ^{1}H) NOESY spectra of 1-vinylimidazoles **4a**,**b** show cross-peaks between signals of olefin protons and protons of methyl groups (compound **4a**) and *ortho*-protons of a cyclohexyl

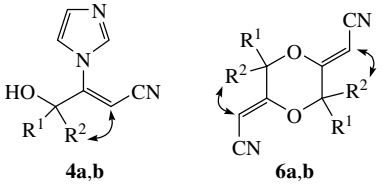


Figure 1 Cross-peaks in the 2D (^{1}H, ^{1}H) NOESY spectra of the 1-vinylimidazoles **4a**,**b** and 1,4-dioxanes **6a**,**b**.

moiety (compound **4b**) that is indicative of *Z*-configuration of 1-vinylimidazoles **4a**,**b**. Similar cross-peaks are observed in the 2D (^{1}H, ^{1}H) NOESY spectra of 1,4-dioxanes **6a**,**b** that points to *Z*-configuration of the cyano groups with respect to the 1,4-dioxane ring (Figure 1).

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‡ *2,2,5,5-Tetramethyl-3,6-dicyanomethylene-1,4-dioxane* **6a**. A mixture of **1a** (0.22 g, 2 mmol) and **2b** (0.04 g, 0.4 mmol, 20%) was stirred at 20–25 °C for 25 min. Column chromatography (eluent: chloroform–benzene–ethanol, 20:4:1) was used to give **6a** (0.09 g, 41%).

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