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Mendeleev Commun., 2007, **17**, 40–42
Mendeleev Communications

Unexpected formation of 4-methyl-1-vinyl-δ-carboline in the reaction of 3-acetylindole oxime with acetylene

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DOI: 10.1016/j.mencom.2007.01.016

3-Acetylindole oxime reacts with acetylene (KOH/DMSO, 120 °C, 1 h, 20–25 atm) to unexpectedly give 4-methyl-1-vinyl-δ-carboline **2** in 40% yield along with minor product 1-vinyl-3-(1′-vinyl-2′-pyrrolyl)indole **3** (6%).

Carbolines (pyridoindoles) are important biologically active compounds.[1] Among them, δ-carbolines (pyrido[3,2-*b*]indoles) remain least addressed, partially due to the lack of expedient methods for their synthesis. The known ones include low or moderate multistep procedures based on inaccessible starting materials to mainly furnish functionalised representatives, whereas simple alkyl δ-carbolines are much less studied, being synthesised from 1-acetylindolin-3-one[2] or functionalised pyridines.[3]

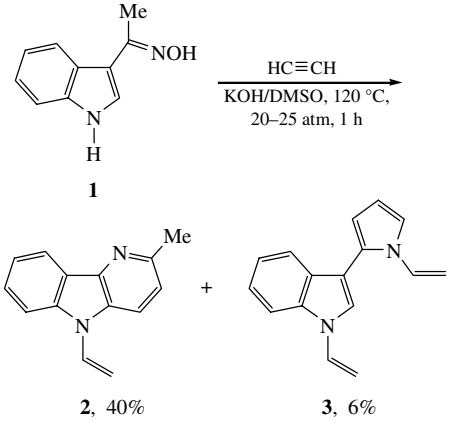
Meanwhile, the δ-carboline structure is found in nature (the alkaloids cryptoquindoline and cryptolepine[4]) and is a key unit of orthochromatic photosensitizers.[5] The antitumor,[6] antimalarial,[7] antimicrobial and antifungal[4] activities of cryptolepine were also reported.

Thus, a search for a more straightforward efficient approach to the δ-carboline construction keeps staying demanding.

To meet the demand, we briefly report here on the reaction of 3-acetylindole oxime **1** with acetylene in the KOH/DMSO system (120 °C, 1 h, acetylene pressure of 20–25 atm), which unexpectedly affords 2-methyl-5-vinylpyrido[3,2-*b*]indole (4-methyl-1-vinyl-δ-carboline) **2** in a yield of up to 40%, along with expected[8] 1-vinyl-3-(1′-vinyl-2′-pyrrolyl)indole **3** (6% yield)† (Scheme 1).

When carried out at atmospheric pressure (120 °C, 5 h), the reaction leads mainly to 3-acetyl-1-vinylindole **4** (26%), the vinylated product of deoximation of starting oxime **1** (earlier observed for other ketoxime under similar conditions[9]) with the carboline **2** and pyrrolylindole **3** being minor products (9% and 17%, respectively) (Scheme 2).

Interestingly, other 3-acylindole oximes, when reacted with acetylene under conditions close to the employed in this work,



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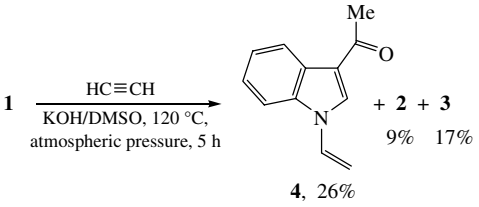
2, 40% **3**, 6%

Scheme 1



4, 26%

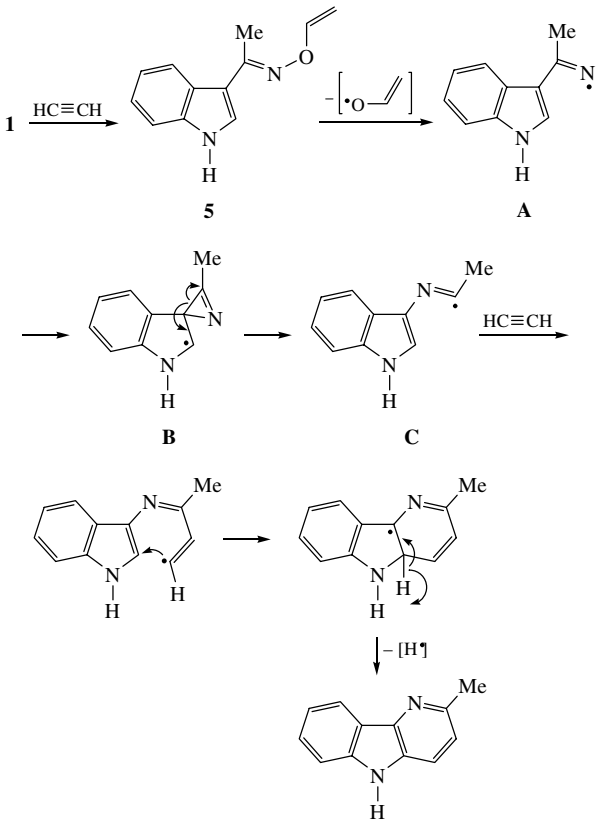
Scheme 2

did not give any carbolines, but only the expected *O*-vinyloximes and 3-pyrrolylindoles.[10]

A probable mechanism of carboline **2** formation may include the homolysis of the N–O bond in *O*-vinyloxime **5** to give N-centered radical **A**, which attacks the adjacent pyrrole ring to form azirine radical **B**, further rearranging to C-centered radical

† A. *Reaction of 3-acetylindole oxime* **1** *with acetylene under pressure.* Oxime **1** (1.00 g, 5.7 mmol) and KOH·0.5H_2O (0.46 g, 7.1 mmol) were dissolved in DMSO (50 ml) with heating (80–90 °C). The solution of potassium oximate thus obtained was placed in a 0.25-litre rotating steel autoclave, and acetylene was fed from a cylinder at room temperature (initial pressure of 14 atm). The autoclave was heated (120 °C) for 1 h (in 30–40 min, the acetylene pressure reached a maximum of 20–25 atm, then began to drop rapidly due to the reaction of acetylene with ketoxime). The reaction mixture, after cooling, was diluted with a three-fold volume excess of water and extracted with diethyl ether (8×20 ml). The organic extracts were washed with cold water (3×20 ml) to remove DMSO; then, the mixture was dried over K_2CO_3 overnight. After the removal of Et_2O, the residue was subjected to column chromatography (Al_2O_3, eluent: *n*-hexane–diethyl ether with the gradient of 1:0 to 0:1) to afford 0.48 g (40% yield) of 2-methyl-5-vinylpyrido[3,2-*b*]indole (4-methyl-1-vinyl-δ-carboline) **2** and 0.08 g (6% yield) of 1-vinyl-3-(1′-vinyl-2′-pyrrolyl)-indole **3**.

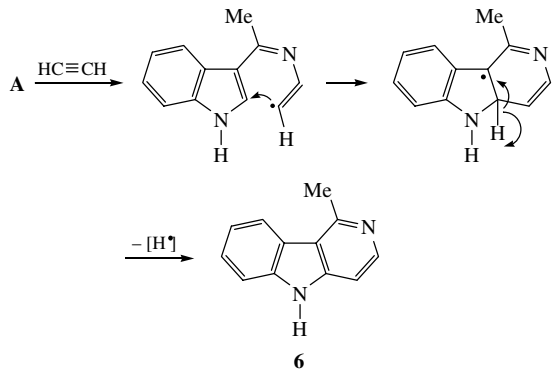
B. *Reaction of 3-acetylindole oxime* **1** *with acetylene under atmospheric pressure.* Oxime **1** (1.00 g, 5.7 mmol), KOH·0.5H_2O (0.46 g, 7.1 mmol) were dissolved in DMSO (50 ml) with heating (80–90 °C). The homogeneous potassium oximate solution in DMSO thus prepared was placed in a three-neck flask equipped with a mechanical stirrer, a reflux condenser and a tube for acetylene feeding. Pure dry acetylene was fed into the reaction mixture with vigorous stirring at 120 °C for 5 h. The reaction mixture, after cooling, was diluted with a three-fold volume excess of water and extracted with diethyl ether (8×20 ml). The organic extracts were washed with cold water (3×20 ml) and then dried over K_2CO_3 overnight. After the removal of Et_2O, the residue was subjected to column chromatography (Al_2O_3, eluent: *n*-hexane–diethyl ether with the gradient of 1:0 to 0:1) to afford 0.28 g (26% yield) of 3-acetyl-1-vinylindole **4**, 0.11 g (9% yield) of 2-methyl-5-vinylpyrido[3,2-*b*]indole **2** and 0.23 g (17% yield) of 1-vinyl-3-(1′-vinyl-2′-pyrrolyl)indole **3**.



Scheme 3

C. The latter adds to acetylene, thus assembling the δ-carboline core (Scheme 3).

Initial radical **A**, which is apparently less stable than its isomer **C**, may also be intercepted by acetylene to afford γ-carboline **6** (Scheme 4).



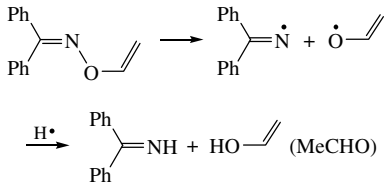
Scheme 4

Seemingly, this process does take place in insignificant scale, since in the ^{1}H NMR spectra‡ of some samples of δ-carboline **2**, doubling signals of small intensity, which can be assigned to a minor admixture of γ-carboline **6**, are discernible.

The homolytic cleavage of the N–O bond is supported by the known data[11] that the thermolysis of *O*-vinyl benzophenone oxime gives benzophenone imine and acetaldehyde, thus indicating a channel of the decomposition (Scheme 5).

We have observed that acetaldehyde is also formed also in the thermolysis of other *O*-vinyl oximes. In the NMR (^{1}H, ^{13}C) spectra of the decomposition products, a nuclear chemical polarization effect was detected, which points to the radical nature of the intermediates.

Vinyl derivative **2** thus synthesised, is actually an N-protected δ-carboline, since the N-vinyl group can be easily converted to the corresponding NH moiety.[12] This circumstance considerably



Scheme 5

extends its synthetic potential for the design of δ-carboline systems. The opportunity to explore the rich reactivity of the vinyl group, including its capacity as a polymerisable moiety, is also attracting.[8(*a*),(*b*),13]

In conclusion, the unexpected formation of 4-methyl-1-vinyl-δ-carboline, a new promising building block for δ-carboline systems, from available 3-acetylindole oxime and acetylene in the KOH–DMSO system, has been described.

This work was supported by the Federal Agency on Science and Innovations (contract no. 02.445.11.7296), the Russian Science Support Foundation and the Siberian Branch of the Russian Academy of Sciences (project no. 8.20).

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‡ NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13 MHz for ^{1}H; 101.61 MHz for ^{13}C) with HMDS as an internal standard. The ^{15}N chemical shifts (40.53 MHz) were referenced to $MeNO_2$ used as an external standard. The assignments of ^{1}H and ^{13}C NMR spectra were performed by COSY, NOESY, HSQC and HMBC experiments. The values of δ_N were measured trough 2D ^{1}H–^{15}N HMBC experiment. IR spectra were obtained on a Bruker IFS 25 instrument.

2-Methyl-5-vinylpyrido[3,2-b]indole **2**: light yellow liquid, n_D^{25} 1.6555. IR (thin film, ν/cm^{-1}): 3060, 2960, 2920, 1645, 1620, 1585, 1490, 1450, 1420, 1380, 1355, 1345, 1305, 1285. ^{1}H NMR (CCl_4) δ: 2.67 (s, 3H, Me), 5.01 (dd, 1H, H^A, *J* 9.2 and 0.8 Hz), 5.39 (dd, 1H, H^B, *J* 16.8 and 0.8 Hz), 7.07 (d, 1H, H^3, *J* 8.4 Hz), 7.20 (dd, 1H, H^X, *J* 16.8 and 9.2 Hz), 7.30 (m, 1H, H^8), 7.42 (m, 1H, H^7), 7.50 (d, 1H, H^6, *J* 8.4 Hz), 7.70 (d, 1H, H^4, *J* 8.4 Hz), 7.26 (d, 1H, H^9, *J* 7.6 Hz). ^{13}C NMR (CCl_4) δ: 23.96 (Me), 100.4 (C$^\beta$), 109.7 (C^6), 117.1 (C^4), 119.4 (C^3), 120.9 (C^8), 121.3 (C^9), 123.4 (C^{9a}), 127.4 (C^7), 129.1 (C$^\alpha$), 130.4 (C^{4a}), 140.0 (C^{5a}), 142.6 (C^{9b}), 151.1 (C^2). ^{15}N NMR (CCl_4) δ: –80.6 (N^1), –251.5 (N^5). MS, *m*/*z*: 208 (M$^+$). Found (%): C, 80.93; H, 5.92; N, 13.29. Calc. for $C_{14}H_{12}N_2$ (%): C, 80.74; H, 5.81; N, 13.45.

1-Vinyl-3-(1′-vinyl-2′-pyrrolyl)indole **3**: light yellow liquid, n_D^{25} 1.5165. IR (thin film, ν/cm^{-1}): 3100, 3040, 2905, 2850, 1615, 1580, 1480, 1450, 1410, 1380, 1350, 1305, 1280, 1200, 1180, 1050, 1000, 950, 910, 850, 720, 700, 550. ^{1}H NMR ($CDCl_3$) δ: 4.62 (dd, 1H, H$^{A'}$, *J* 9.0 and 0.9 Hz), 4.81 (dd, 1H, H^A, *J* 10.2 and 1.3 Hz), 5.16 (dd, 1H, H$^{B'}$, *J* 15.9 and 0.8 Hz), 5.21 (dd, 1H, H^B, *J* 15.9 and 0.8 Hz), 6.32 (m, 1H, H$^{3'}$), 6.34 (m, 1H, H$^{4'}$), 6.93 (dd, 1H, H$^{X'}$, *J* 15.9 and 9.0 Hz), 7.16 (m, 1H, H$^{5'}$), 7.18 (m, 1H, H^5), 7.22 (dd, 1H, H^X, *J* 15.9 and 10.2 Hz), 7.28 (m, 1H, H^6), 7.38 (s, 1H, H^2), 7.47 (d, 1H, H^7, *J* 7.8 Hz), 7.59 (d, 1H, H^4, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 97.2 (C$^{\beta'}$), 97.9 (C$^\beta$), 109.7 (C^7), 110.4 (C$^{4'}$), 110.6 (C$^{3'}$), 110.7 (C^3), 117.5 (C$^{5'}$), 120.8 (C^4), 121.4 (C^5), 122.7 (C^2), 123.4 (C^6), 126.7 (C$^{2'}$), 128.7 (C^{3a}), 129.4 (C$^\alpha$), 132.0 (C$^{\alpha'}$), 135.7 (C^{7a}). ^{15}N NMR ($CDCl_3$) δ: –208.5 (N$^{1'}$), –229.7 (N^1). Found (%): C, 82.16; H, 5.99; N, 11.77. Calc. for $C_{16}H_{14}N_2$ (%): C, 82.02; H, 6.02; N, 11.96.

3-Acetyl-1-vinylindole **4**: white crystals, mp 74–76 °C. IR (KBr, ν/cm^{-1}): 3114, 1613, 1530, 1482, 1464, 1380, 1322, 1224, 1176, 955, 737, 647, 559, 549. ^{1}H NMR ($CDCl_3$) δ: 2.56 (s, 3H, Me), 5.02 (dd, 1H, H^A, *J* 8.8 and 1.5 Hz), 5.42 (dd, 1H, H^B, *J* 15.7 and 1.5 Hz), 7.21 (dd, 1H, H^X, *J* 15.7 and 8.8 Hz), 7.30 (m, 1H, H^5), 7.33 (m, 1H, H^6), 7.46 (m, 1H, H^7), 8.00 (m, 1H, H^2), 8.36 (m, 1H, H^4). ^{13}C NMR ($CDCl_3$) δ: 27.9 (Me), 101.4 (C$^\beta$), 109.8 (C^7), 119.3 (C^3), 123.0 (C^4), 123.5 (C^5), 124.3 (C^6), 126.6 (C^{3a}), 129.4 (C$^\alpha$), 130.0 (C^2), 136.3 (C^{7a}), 193.4 (C=O). ^{15}N NMR ($CDCl_3$) δ: –225.2. Found (%): C, 77.79; H, 6.07; N, 7.74. Calc. for $C_{12}H_{11}NO$ (%): C, 77.81; H, 5.99; N, 7.56.

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Received: 17th October 2006; Com. 06/2795