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Multi-channel annulation of acetylene with 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime in the KOH/DMSO superbasic system

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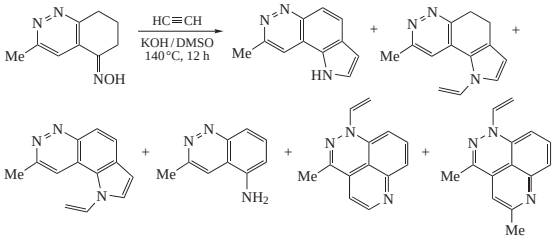
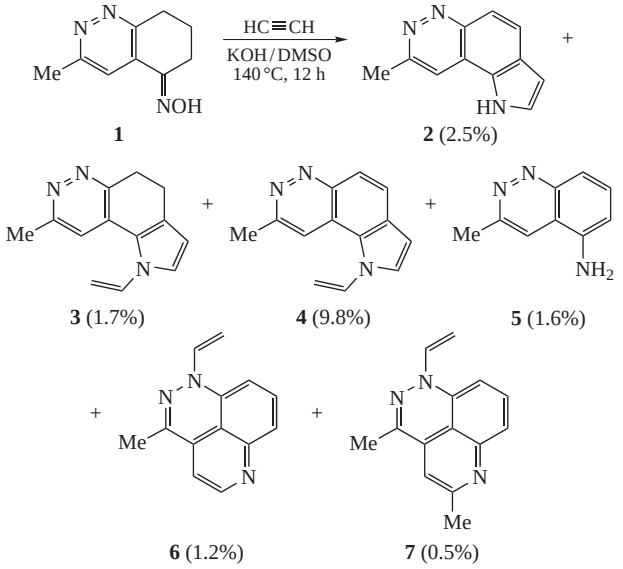
Acetylene in the KOH/DMSO system (1 bar, 140 °C, 12 h) is annulated with 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime in several directions: along with the building up of pyrrole fragment over cyclohexane ring, transformation of the oxime function to the amino one occurs. This amine undergoes other annulations to form tricyclic compounds with pyridine moieties.



Ketoximes are known to readily cyclize with acetylene in superbasic system KOH/DMSO to form pyrroles.[1,2] This synthesis is particularly facile for oximes of various six-membered cyclic ketones.[2–7] Until now no exception from this regularity was observed. Thus, we intended to analogously fuse a pyrrole structure onto the cyclohexanone moiety of 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime **1**.[8] This oxime has been chosen since cinnoline derivatives exhibit numerous pharmaceutically important activities including antitumor, hypotensive, anti-inflammatory, bacteriostatic, analgesic, anti-asthmatic, and sedative properties.[9] However, to our surprise, the experiments show that, instead of the expected smooth and selective pyrrolization, other transformations have taken place. In fact, along with the formation of pyrrole **2** and *N*-vinylpyrroles **3**, **4**, transformation of the oxime function bringing about amine **5** and formation of N-vinylated tricycles with a pyridine ring **6**, **7** were observed (Scheme 1).[†] Insoluble in methanol pyrrole **2** was isolated from the reaction mixture by precipitation. Other ptoducts **3**–**7** were separated by column chromatography, though in small preparative yields, and adequately characterized (^{1}H, ^{13}C and ^{15}N NMR, IR spectroscopy, mass spectrometry and elemental analysis). The exception was



Scheme 1

[†] *Reaction of oxime* **1** *with acetylene in KOH/DMSO system.* Acetylene was passed through the stirred mixture of oxime (as monohydrate) **1** (1.125 g, 5.8 mmol) and KOH (0.410 g, 6.3 mmol) in DMSO (16 ml) at 140 °C for 12 h [until disappearance of the oxime signal at 11.95 (OH) and 2.59 (Me) ppm in the ^{1}H NMR spectra of the reaction mixture aliquot]. After cooling to room temperature, the reaction mixture was diluted with brine (80 ml) and NH_4Cl (0.337 g, 6.3 mmol) was added. The obtained solution was extracted with diethyl ether (8 × 40 ml), the ether extracts were washed with water (4 × 40 ml) and dried over K_2CO_3. The residue after removing diethyl ether (0.344 g, dark red oil) was diluted with methanol (2 ml) and the precipitated crystals were filtered off and dried to afford pyrrole **2** (0.020 g, 1.8%). Next, the aqueous layer was extracted with CH_2Cl_2 (6 × 40 ml), the extracts were washed with water (3×50 ml) and dried over K_2CO_3. The residue after removing the solvent (0.274 g, brown oil) was diluted with methanol (1.5 ml) and the precipitated crystals were filtered off and dried to give the second crop of pyrrole **2** (0.007 g, 0.7%); total yield 2.5%.

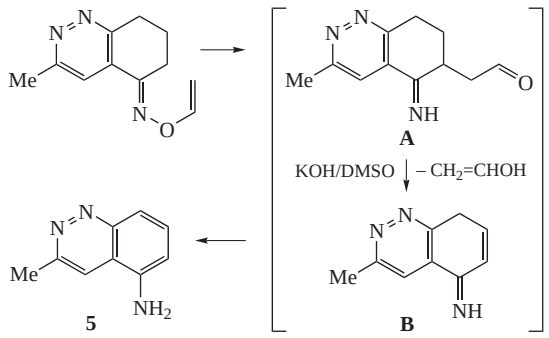
Compounds **3**–**7** were isolated by column chromatography [Al_2O_3, eluent *n*-hexane, *n*-hexane–CH_2Cl_2 (5 : 1, 3 : 1, 1 : 1) and CH_2Cl_2] of the mixture obtained after separating pyrrole **2**. Pyrrole **3** was isolated as a 1 : 1 mixture with pyrrole **4** (^{1}H NMR).

*8-Methyl-1*H*-pyrrolo[2,3-*f*]cinnoline* **2**. Yield 0.027 g (2.5%), mp > 284 °C (MeOH). ^{1}H NMR (DMSO-d_6) δ: 2.86 (s, 3H, Me), 6.72 (m, 1H, H^3), 7.67 (m, 1H, H^2), 7.88 (m, 1H, H^4), 8.00 (m, 1H, H^5), 8.31 (m, 1H, H^9), 12.57 (br.s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 21.9 (Me), 103.9 (C^3), 114.6 (C^9), 116.6 (C^{3a}), 119.9 (C^2), 125.2 (C^5), 125.8 (C^{9b}), 126.4 (C^{9a}), 126.8 (C^4), 147.1 (C^{5a}), 152.8 (C^8). IR (KBr, ν/cm^{-1}): 3438, 3142, 3074, 2979, 2888, 2807, 1612, 1568, 1492, 1446, 1395, 1373, 1191, 1147, 1112, 1035, 920, 883, 812, 799, 744, 701. Found (%): C, 72.37; H, 4.67; N, 22.75. Calc. for $C_{11}H_9N_3$ (%): C, 72.11; H, 4.95; N, 22.94.

For characteristics of compounds **3**–**7**, see Online Supplementary Materials.

pyrrole **3**, which was isolated as a 1 : 1 mixture with close-structured compound **4**.

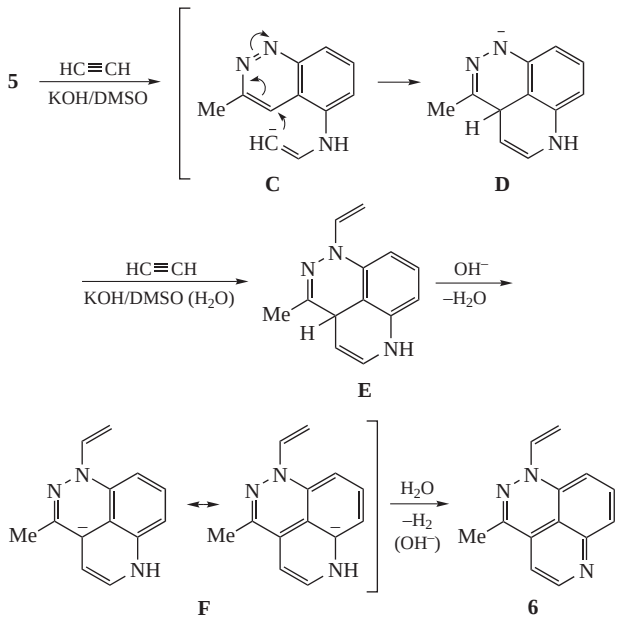
While the cascade transformations of ketoximes to pyrroles under the action of acetylene in the presence of KOH/DMSO system are well understood,[2] the reaction sequences leading to other products (see Scheme 1) need to be rationalized. One of the intermediates of the pyrrole synthesis from ketoximes and acetylene is imino aldehyde,[2] compound **A** (Scheme 2), the result of a 3,3-sigmatropic rearrangement of the preceding intermediate *O*-vinyloxime. Superbase-catalyzed elimination of vinyl alcohol from imino aldehyde **A** should give imine **B**, which, *via* the prototropic shifts, may deliver amine **5** (see Scheme 2).



Scheme 2

The nucleophilic addition of amine **5** to acetylene involves the intermediate anion **C**, which may intramolecularly attack the adjacent heterocycle with the negative charge transfer to form nitrogen-centered anion **D** (Scheme 3). Then the latter is vinylated with the second molecule of acetylene to produce the intermediate **E**. The proton abstraction from this species leads to anion **F**. It further releases hydride ion facilitated by electrophilic assistance from the water molecule to furnish product **6**. Product **7** is likely to result from methylation of pyridine **6** by DMSO whose methylating ability,[10,11] particularly in the superbasic media,[11] is well-documented.

All the above multi-channel annulations extend synthetic potential of the reaction of ketoximes and acetylene in superbasic media allowing one to assemble novel fused heterocyclic systems.



Scheme 3

Notably, a set of different separable pharmaceutically prospective compounds can be prepared from the available starting materials using just one-pot procedure and simple reaction conditions. Apparently, the yield of each compound can be improved provided the optimization will be aimed at the synthesis of this particular product.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.07.007.

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