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2-(2-Ethynyl-1-aziranyl)-3,4-dihydro-2*H*-pyrrole: a one-pot assembly from isopropyl phenyl ketoxime and acetylene during the synthesis of 3*H*-pyrrole

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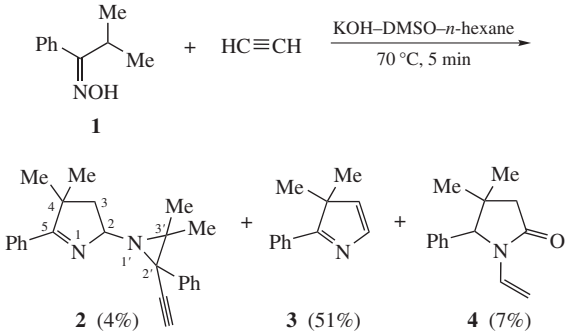
Reaction between isopropyl phenyl ketoxime and acetylene in the KOH–DMSO–*n*-hexane system (70 °C, ~5 min), along with known 3,3-dimethyl-2-phenyl-3*H*-pyrrole (51% yield) and 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone (7% yield), affords also unexpected 2-(2-ethynyl-3,3-dimethyl-2-phenyl-1-aziranyl)-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole (4% yield).

The most straightforward route to 3*H*-pyrroles by reaction between acetylene and ketoximes having just one α-hydrogen atom[1,2] still remains unoptimized. One means to improve moderate yields (~50%) of the target products seems in studying the intermediates and minor products of the reaction, which can shed light on the mechanism and hence provide better control of the process. The following intermediates and minor products have been isolated and identified: *O*-vinyloximes,[3] 2-hydroxypyrrolines,[4] pyrrolines,[5] and 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone,[6] most of them supporting the common mechanism[7] of the reaction course.

Here we report that during the further scrutinized work-up of the reaction mixture obtained from isopropyl phenyl ketoxime **1** and acetylene in the KOH–DMSO–*n*-hexane system (70 °C) we isolated and characterized (X-ray, ^{1}H, ^{13}C, ^{15}N NMR, IR, MS) the absolutely unexpected minor product, 2-(2-ethynyl-3,3-dimethyl-2-phenyl-1-aziranyl)-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole **2** apart from the regular 3,3-dimethyl-2-phenyl-3*H*-pyrrole **3**[1] and the aforementioned 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone **4**[6] (Scheme 1).†



Scheme 1

† The IR spectra were recorded on a Bruker IFS25 spectrophotometer as KBr pellets or thin films. Mass spectra were measured on an Agilent 5975C spectrometer. Sample introduction was carried out through an Agilent 6890N gas chromatograph: the column was an HP-5MS (0.25 mm × 30 m × × 0.25 μm); carrier gas – helium, constant flow. NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C, and 40.5 MHz for ^{15}N) in $CDCl_3$ using HMDSO as internal standard. Basic aluminum oxide was used for column chromatography, and Silufol plates for TLC (eluent, hexane–diethyl ether, 1:1). Visualization was made with iodine vapor.

Although molecule **2** contains two asymmetric carbon atoms, only one diastereomer is formed: the NMR spectra manifest only one set of signals.

The structure of compound **2** unambiguously follows from single-crystal X-ray diffraction analysis (Figure 1)‡ and ^{1}H, ^{13}C

The reaction between isopropyl phenyl ketoxime **1** *and acetylene in the KOH–DMSO*–n-*hexane system*. A 0.3 dm^3 Parr reactor equipped with a magnetic stirrer (250 rpm) was charged with hexane (40 ml) and a potassium oximate solution in DMSO prepared by heating of a mixture of isopropyl phenyl ketoxime **1** (2.04 g, 12.5 mmol) and KOH·0.5H_2O (0.81 g, 12.5 mmol) in DMSO (50 ml) at 110–115 °C for 1 h. The reactor was fed with acetylene and then decompressed to atmospheric pressure to remove air. The reactor was fed again with acetylene (initial pressure was 10 atm) and heated up to 70 °C and then heating was immediately ceased that took overall 20 min (about 5 min at 70 °C). After cooling, the reaction mixture was discharged and the hexane layer was separated. The DMSO solution was poured into ice water (250 ml), neutralized with NH_4Cl, and extracted with diethyl ether (5×50 ml). The organic layers were combined, washed with H_2O (3×50 ml) and dried over $MgSO_4$ overnight. After distilling off the solvents, the residue (2.14 g, brown oil) was chromatographed on the column (1.9×30 cm, CH_2Cl_2 as eluent) to afford the fractions with R_f = 0.45–0.70 and 0.20–0.45.

By the repeated chromatography (1.8×20 cm, hexane–diethyl ether, 9:1) of the first fraction, 2-(2-ethynyl-3,3-dimethyl-2-phenyl-1-aziranyl)-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole **2** (0.09 g, 4%, R_f = 0.62) and 3,3-dimethyl-2-phenyl-3*H*-pyrrole **3** (1.09 g, 51%, R_f = 0.49) were isolated.

From the second fraction, 0.19 g (7%, R_f = 0.42) of 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone **4** was isolated by the repeated column chromatography (1.2×20 cm, hexane–diethyl ether, 3:1).

Physical-chemical characteristics of the isolated compounds corresponded to the literature data: compound **3**,[1] compound **4**.[6]

*2-(2-Ethynyl-3,3-dimethyl-2-phenyl-1-aziranyl)-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole* **2**: colourless crystals, mp 118–120 °C (hexane). IR (KBr, ν/cm^{-1}): 3229, 2962, 2929, 2106, 1628, 1601, 1492, 1449, 1339, 1147, 765, 697. ^{1}H NMR ($CDCl_3$) δ: 1.00 (s, 3H, C$^{3'}$Me), 1.42 (s, 3H, C^{4}Me), 1.50 (s, 3H, C^{4}Me), 1.75 (s, 3H, C$^{3'}$Me), 2.09 (dd, 1H, CH_2, ^3J 7.1 Hz, ^2J 12.5 Hz), 2.31 (dd, 1H, CH_2, ^3J 6.4 Hz, ^2J 12.5 Hz), 2.47 (s, 1H, ≡CH), 4.84 (dd, 1H, CH, ^3J 6.4 Hz, ^3J 7.1 Hz), 7.26 (m, 1H, *p*-H, C$^{2'}$Ph), 7.34 (m, 2H, *m*-H, C$^{2'}$Ph), 7.40 (m, 3H, *p*-H, *m*-H, C^{5}Ph), 7.58 (m, 2H, *o*-H, C$^{2'}$Ph), 7.80 (m, 2H, *o*-H, C^{5}Ph). ^{13}C NMR ($CDCl_3$) δ: 16.6 (C$^{3'}$*Me*), 23.4 (C$^{3'}$*Me*), 26.8 (C^4*Me*), 27.6 (C^4*Me*), 45.8 (C$^{2'}$), 48.7 (C^3), 49.6 (C$^{3'}$), 50.5 (C^4), 73.2 (C≡*C*H), 82.6 (C^2), 82.7 (*C*≡CH), 127.2 (*p*-C, C$^{2'}$Ph), 128.0 (*o*-C, *m*-C, C$^{2'}$Ph), 128.2 (*m*-C, C^{5}Ph), 128.3 (*o*-C, C^{5}Ph), 129.6 (*p*-C, C^{5}Ph), 134.9 (*i*-C, C^{5}Ph), 139.5 (*i*-C, C$^{2'}$Ph), 181.2 (C=N). ^{15}N NMR ($CDCl_3$) δ: –309.2 (N$^{1'}$), –50.0 (N^1). MS (EI), *m*/*z*: 342 [M]$^+$.

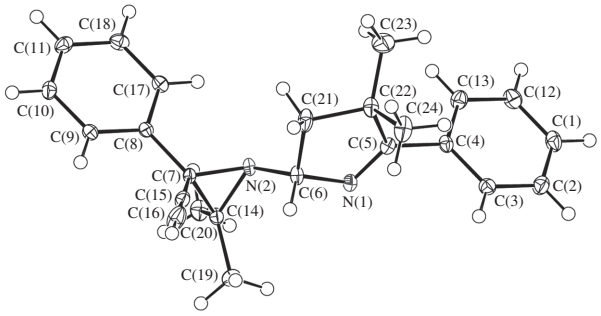
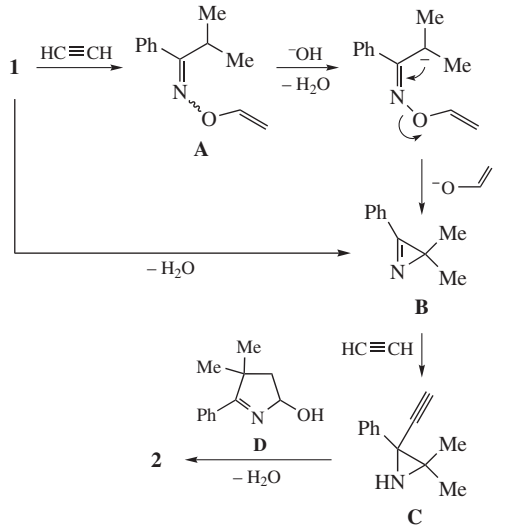


Figure 1 X-ray structure of 2-(2-ethynyl-3,3-dimethyl-2-phenyl-1-aziranyl)-4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole. Thermal ellipsoids set at 50% probability.

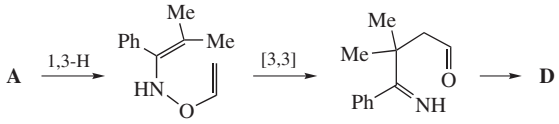
and ^{15}N NMR spectra. The signals in the ^{1}H and ^{13}C NMR spectra have been assigned using 2D NMR technique (COSY, NOESY, HSQC and HMBC). So, the resonance lines at 1.42 and 1.50 ppm are attributed to the methyl groups in the 4-position of the pyrroline cycle according to correlations (2D NOESY) with 3-CH_2 and *o*-H protons of the phenyl cycle in the 5-position. The signals of the methyl groups in the 3′-position (1.00 and 1.75 ppm) show NOE only with *o*-H protons of the phenyl substituent in the 2′-position. In the 2D ^{1}H-^{13}C HMBC spectrum, long-range spin–spin interactions are observed that allows the resonance lines of quaternary carbon atoms to assign unambiguously in the ^{13}C NMR spectra. The values of chemical shifts of nitrogen atoms in the ^{15}N NMR spectrum, obtained from 2D heteronuclear spectra ^{1}H-^{15}N HMBC, confirm the presence of two different nitrogen atoms (sp^3-N$^{1'}$ and sp^2-N^1) in compound **2**.

The assembly of aziranylpyrroline **2** likely involves Hoch–Campbell-like[8] dehydration of the starting oxime **1** or elimination of vinyl alcohol from the intermediate *O*-vinylketoxime **A**[9] to afford azirine **B** which undergoes the Favorsky-type ethynylation involving C=N bond to give ethynylaziridine **C** (Scheme 2). The latter couples with hydroxypyrroline **D**, an isolable intermediate of the pyrrole synthesis from ketoximes and acetylene,[4] to eliminate the molecule of water finalizing the assembly of compound **2**.



Scheme 2

The replacement of the hydroxyl group in hydroxypyrroline **D** by the aziranyl moiety closely relates to the Mannich type processes. Hydroxypyrroline **D** is the product of subsequent *O*-vinylketoxime **A** rearrangements (1,3-prototropic and 3,3-sigmatropic shifts) followed by cyclization of the formed imino aldehyde (Scheme 3).[4]



Scheme 3

The diastereoselectivity of the reaction implies the stereoselective ethynylation of the intermediate azirine **B** which should be of *trans*-mode judging from the mutual disposition of the substituents in the aziridine ring.

Despite the low (though non-optimized) yield of the acetylenic aziranylpyrroline, its simple one-pot preparation from inexpensive widespread basic chemicals deserves attention from both pharmaceutical and synthetic points of view. Pharmaceutically, the rare combination of pharmacophoric fragments in one molecule may result in novel useful properties. Synthetically, the alternative approach to such complex multi-functional molecules should inevitably be multi-step and laborious and consequently far from good total yields. We intend to further develop this conceptually new synthesis.

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‡ *Crystal data for* **2**. Single crystals of **2** were grown from acetonitrile. The determination of the unit cell and the data collection was performed on a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer with MoKα radiation (λ = 0.71073 Å) at 100(2) K using the ω–2θ scan technique. The final cell constants of a = 6.8105(5), b = 24.082(2) and c = 11.8292(10) Å, β = 94.450(3)°, V = 1934.3(3) Å^3, are based upon the refinement of the *XYZ*-centroids of 9914 reflections above 20σ(I) with 4.834° < 2θ < 59.69°. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1/n$, with Z = 4 for the formula unit, $C_{24}H_{26}N_2$. The dihedral angle between the averaged planes of the benzene and pyrrole rings is 104.0°.

CCDC 992245 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.