Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2014, **24**, 100–101
Mendeleev Communications

Synthesis of 3,3-dimethyl-2-phenyl-3*H*-pyrrole from isopropyl phenyl ketoxime and acetylene: a side formation of 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone as clue to the reaction mechanism

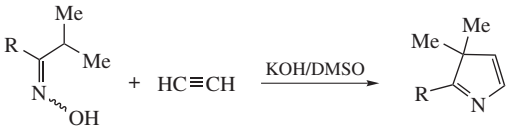
Dmitrii A. Shabalin, Tatyana E. Glotova, Elena Yu. Schmidt, Igor A. Ushakov, Al'bina I. Mikhaleva and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@irioch.irk.ru

DOI: 10.1016/j.mencom.2014.03.012

Isopropyl phenyl ketoxime reacts with acetylene in the KOH/DMSO suspension (atmospheric pressure, 90 °C, 4 h) to afford 3,3-dimethyl-2-phenyl-3*H*-pyrrole (30%) and 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone (5%) that is likely originated from 4,4-dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrol-2-ol as the key reaction intermediate.

3*H*-Pyrroles represent difficult-to-access and hence poorly studied class of non-aromatic pyrroles. They possess potentially rich chemistry as fundamentally prone to diverse rearrangements, addition and cycloaddition reactions.[1,2] Some 3*H*-pyrroles exhibit antimicrobial and antitumor activities.[3] Despite their obvious theoretical and practical appeal, until now no general synthesis of these compounds was elaborated. Just several sporadic reactions leading to functionalized 3*H*-pyrroles were reported.[4] This is likely due to thermodynamic instability of 3*H*-pyrroles,[1] and therefore their high tendency to rearrangements and addition reactions. The reaction of phenyl(2-thienyl) isopropyl ketoximes **1a**,**b** with acetylene in superbasic systems of the KOH/DMSO type, leading to 3,3-dimethyl-2-(het)aryl-3*H*-pyrroles **2a**,**b** in 53 and 11% yields, respectively (Scheme 1), previously briefly described only on two examples[5,6] has a certain potential to be developed into a general methodology.

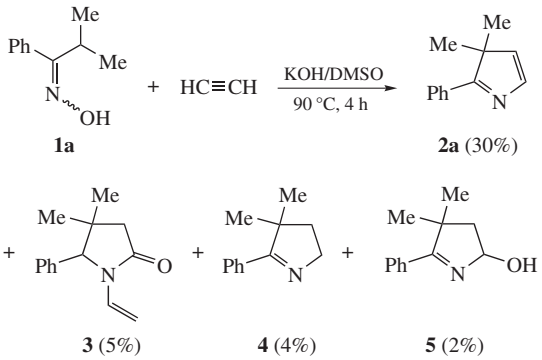


1a,**b** **a** R = Ph; **b** R = 2-thienyl **2a**,**b**

Scheme 1

A better understanding of the reaction mechanism is the shortest way to its optimization. In this connection, side products often serve as reliable indicators of the reaction stages and help to deduce its key intermediates.

Here we report on isolation of a new side product of the superbase-catalyzed reaction between isopropyl phenyl ketoxime **1a** and acetylene, namely 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone **3** along with pyrroline **4** and hydroxypyrroline **5** (Scheme 2).†



1a **2a** (30%) **3** (5%) **4** (4%) **5** (2%)

Scheme 2

In this case, the yield of the major product, 3*H*-pyrrole **2a**, was 30%, and those of side products **3**, **4** and **5** being 5, 4 and

† The IR spectra were recorded on a Bruker IFS25 spectrophotometer as KBr pellets or thin films. Mass spectra were recorded 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); helium as a carrier gas, constant flow. NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1, 100.6 and 40.5 MHz for ^{1}H, ^{13}C and ^{15}N, respectively) in $CDCl_3$ or DMSO-d_6. Aluminum oxide was used for column chromatography, and Silufol plates for TLC. Visualization was performed with iodine vapour.

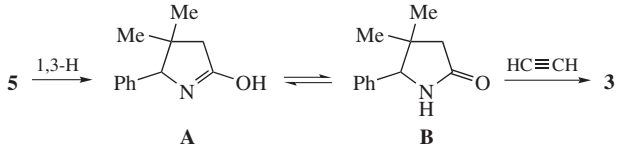
The reaction of isopropyl phenyl ketoxime **1a** *with acetylene in the KOH/DMSO system*. Acetylene was bubbled (40–45 ml min^{-1}) through a solution of oxime **1a** (4.075 g, 25 mmol) and $KOH \cdot 0.5 H_2O$ (1.625 g, 25 mmol) in DMSO (50 ml) at 90 °C for 4 h. The mixture was cooled, poured into ice water (300 ml), and extracted with diethyl ether (5×100 ml). The extract was washed with water (2×50 ml) and dried over $MgSO_4$. After distilling off the solvent, the residue (3.53 g) was chromatographed on the column (1.9×50 cm, basic Al_2O_3, hexane–diethyl ether with gradient from 1:0 to 0:1) to afford recovered oxime **1a** (0.33 g, 9%), 3*H*-pyrrole **2a**, pyrrolidinone **3**, pyrroline **4** and hydroxypyrroline **5**.

*3,3-Dimethyl-2-phenyl-3*H*-pyrrole* **2a**: yield 1.06 g, 30%; yellow oil, R_f = 0.49 (hexane–diethyl ether, 1:1). Physical-chemical characteristics were identical to the literature data.[5] ^{13}C NMR ($CDCl_3$) δ: 22.4 (2 Me), 55.6 (C^3), 127.7, 128.5, 129.9, 133.1 (Ph), 138.7 (C^4), 140.0 (C^5), 183.4 (C^2). ^{15}N NMR ($CDCl_3$) δ: –66.4. MS (EI), *m*/*z*: 171 $[M]^+$.

4,4-Dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone **3**: yield 0.16 g, 5%; viscous yellow oil [R_f = 0.42 (hexane–diethyl ether, 1:1)] or light yellow crystals, mp 74–76 °C (hexane). IR (KBr, ν/cm^{-1}): 2870–2965 (CH), 1697 (C=O), 1633 (C=C, NCH=CH_2). ^{1}H NMR ($CDCl_3$) δ: 0.69 (s, 3 H, Me), 1.30 (s, 3 H, Me), 2.24 (d, 1H, CH_2, ^2J 17.0 Hz), 2.53 (d, 1H, CH_2, ^2J 17.0 Hz), 4.10 (d, 1H, H_β, ^3J 16.2 Hz), 4.32 (d, 1H, H_α, ^3J 9.2 Hz), 4.44 (s, 1H, H^5), 7.08 (m, 2 H, H_o), 7.13 (dd, 1H, H_x, ^3J 9.2 Hz, ^3J 16.2 Hz), 7.30–7.38 (m, 3 H, H_m, H_p). ^{13}C NMR ($CDCl_3$) δ: 24.7 (Me), 30.5 (Me), 37.5 (C^4), 44.7 (C^3), 71.1 (C^5), 96.4 (C_β), 126.4, 127.9, 128.4 (Ph), 128.7 (C_α), 137.4 (C_i), 173.2 (C=O). ^{15}N NMR ($CDCl_3$) δ: –230.2. Found (%): C, 78.36; H, 7.82; N, 6.43. Calc. for $C_{14}H_{17}NO$ (%): C, 78.10; H, 7.96; N, 6.51. MS (EI), *m*/*z*: 215 $[M]^+$.

2%, respectively. Previously, pyrroline **4**[7] and hydroxypyrroline **5**[8] were identified among the products of this reaction.

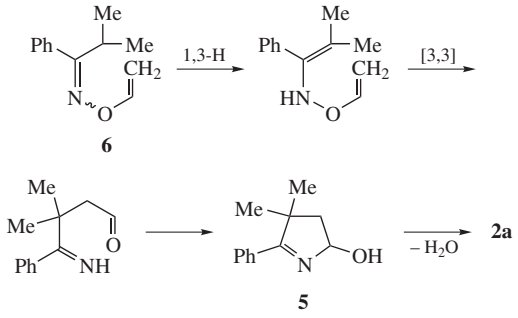
Apparently, pyrrolidinone **3** is resulted from the rearrangement of hydroxypyrroline **5**, which involves 1,3-prototropic shift to give isomeric hydroxypyrroline **A**, the tautomeric form of pyrrolidinone **B**. Its further vinylation with acetylene yields 1-vinylpyrrolidinone **3** (Scheme 3).



A **B**

Scheme 3

The formation of 3*H*-pyrrole **2a** from ketoxime **1a** and acetylene was assumed[6] to involve the tandem transformation of *O*-vinyl oxime **6** including dehydration of hydroxypyrroline **5** as the final step (Scheme 4).



Scheme 4

*4,4-Dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrole* **4**: yield 0.14 g, 4%; yellow oil, $R_f = 0.24$ (hexane–diethyl ether, 1:1). Physical-chemical characteristics were identical to the literature data.[7] ^{13}C NMR ($CDCl_3$) δ: 26.0 (2 Me), 42.0 (C^3), 49.5 (C^4), 56.6 (C^2), 127.8, 128.1, 129.3, (Ph), 134.9 (C_i), 180.1 (C^5). MS (EI), *m*/*z*: 173 $[M]^+$.

*4,4-Dimethyl-5-phenyl-3,4-dihydro-2*H*-pyrrol-2-ol* **5**: yield 0.06 g, 2%; colourless crystals, $R_f = 0.08$ (hexane–diethyl ether, 1:1). Mp, IR and ^{1}H NMR spectra were identical to the literature data.[8] ^{13}C NMR ($CDCl_3$) δ: 26.9 (Me), 27.4 (Me), 49.4 (C^3), 50.1 (C^4), 91.4 (C^2), 128.2, 128.4, 130.2, 133.5 (Ph), 180.8 (C^5). ^{15}N NMR ($CDCl_3$) δ: –60.7. MS (EI), *m*/*z*: 189 $[M]^+$.

Thus, isolation of pyrrolidinone **3** from the reaction products additionally supports the formation of hydroxypyrroline **5** as the key intermediate of 3*H*-pyrroles synthesis.

References

1 M. P. Sammes and A. R. Katritzky, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1982, vol. 32, p. 243.

2 (*a*) M. P. Sammes, in *Pyrroles, Part 1*, J. Wiley & Sons, New York, 1990, p. 549; (*b*) B. A. Trofimov, S. G. Shevchenko, S. E. Korostova, A. I. Mikhaleva, M. V. Sigalov and L. B. Krivdin, *Chem. Heterocycl. Compd.*, 1989, **25**, 1314 (*Khim. Geterotsikl. Soedin.*, 1989, 1566); (*c*) S. Perrin, K. Monnier and B. Laude, *J. Chem. Res. (S)*, 1997, 104; (*d*) K. D. Welch, P. L. Smith, A. P. Keller, W. H. Myers, M. Sabat and W. D. Harman, *Organometallics*, 2006, **25**, 5067; (*e*) A. A. Shimkin, V. Z. Shirinian, D. M. Nikalin, M. M. Krayushkin, T. S. Pivina, N. A. Troitsky, L. G. Vorontsova and Z. A. Starikova, *Eur. J. Org. Chem*., 2006, 2087.

3 (*a*) G. Cirrincione, A. M. Almerico, G. Dattolo, E. Aiello, S. Grimaudo, P. Diana and F. Misuraca, *Farmaco*, 1992, **47**, 1555; (*b*) G. Cirrincione, A. M. Almerico, S. Grimaudo, P. Diana, F. Mingoia, P. Barraja and F. Misuraca, *Farmaco*, 1996, **51**, 49; (*c*) V. Padmavathi, T. Radha Lakshmi, K. Mahesh and A. Padmaja, *Chem. Pharm. Bull*., 2009, **57**, 1200.

4 (*a*) P. Merot, C. Gadreau and A. Foucaud, *Tetrahedron*, 1981, **37**, 2595; (*b*) G. Schmitt, B. Nasser, N. Dinh, B. Laude and M. Roche, *Can. J. Chem*., 1990, **68**, 863; (*c*) M. Depature, J. Grimaldi and J. Hatem, *Eur. J. Org. Chem*., 2001, 941; (*d*) X. Xu and Y. Zhang, *Synth. Commun*., 2002, **32**, 2643; (*e*) J. Ichikawa, K. Sakoda, J. Mihara and N. Ito, *J. Fluorine Chem*., 2006, **127**, 489.

5 B. A. Trofimov, S. G. Shevchenko, S. E. Korostova, A. I. Mikhaleva and V. V. Shcherbakov, *Chem. Heterocycl. Compd*., 1985, **21**, 1299 (*Khim. Geterotsikl. Soedin*., 1985, 1573).

6 S. E. Korostova, S. G. Shevchenko and M. V. Sigalov, *Chem. Heterocycl. Compd*., 1991, **27**, 1101 (*Khim. Geterotsikl. Soedin*., 1991, 1371).

7 S. E. Korostova, S. G. Shevchenko and V. V. Shcherbakov, *Zh. Org. Khim*., 1993, **29**, 1639 (in Russian).

8 B. A. Trofimov, S. E. Korostova, A. I. Mikhaleva, L. N. Sobenina, V. V. Shcherbakov and M. V. Sigalov, *Chem. Heterocycl. Compd*., 1983, **19**, 231 (*Khim. Geterotsikl. Soedin*., 1983, 276).

Received: 24th September 2013; Com. 13/4210