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Reaction of (het)aryl cyclohexyl ketoximes with acetylene in the two-phase KOH/DMSO/*n*-hexane system: en route to spirocyclic 3*H*-pyrroles

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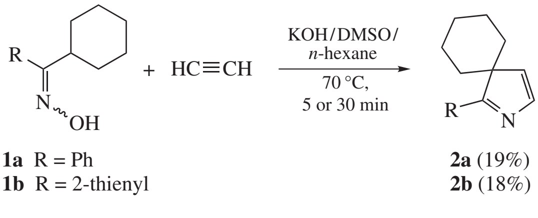
Cyclohexyl phenyl and cyclohexyl (2-thienyl) ketoximes react with acetylene under pressure in the two-phase KOH/DMSO/*n*-hexane system at 70 °C to afford the corresponding spirocyclic 3*H*-pyrroles, 1-(het)aryl-2-azaspiro[4.5]deca-1,3-dienes, in 18–19% yields.

The 3*H*-pyrroles remain scarcely studied non-aromatic pyrrole isomers, which owing to energy excess possess a richer chemistry with regard to addition, cycloaddition and rearrangement reactions as compared with regular aromatic 1*H*-pyrroles.[1,2] Despite their poor accessibility, some of them were shown to exhibit antitumor[3] and antimicrobial activity.[4] Eventually, still poorer understood are spirocyclic 3*H*-pyrroles, azaspiro-1,3-dienes. Meanwhile, they should have additional specific properties due to the spiro ring strain and rigid orientation of bonds in the 3-position of the pyrrole ring. To our knowledge, two first spirocyclic 3*H*-pyrroles were prepared by cyclization of 3-(hydroxyalkyl) pyrroles under the action of trifluoromethanesulfonic anhydride (no spectra and yields were given).[5] Another representative was obtained from exotic 2-cyclohexylidene 1,4-diketone and liquid ammonia *via* dehydration of the intermediate hydroxypyrroline in 16% total yield.[6] Later, a fluorine-containing spirocyclic 3*H*-pyrrole was synthesized by Heck-type 5-*endo*-trig cyclization of 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloxime promoted by vinylic fluorines.[7] Recently, several heavily functionalized heterocyclic structures incorporating spirocyclic 3*H*-pyrrole moieties were synthesized from 4,5-diaroyl-1*H*-pyrrole-2,3-diones[8] or 4-aryl-3-methyl-4-oxobutane-1,1,2,2-tetracarbonitriles.[9]

The reactions of ketoximes, having just one C–H bond adjacent to the oxime function, with acetylene in superbasic[10] systems (the Trofimov reaction)[11] may open a short route to 3*H*-pyrroles. However, until now only two 3*H*-pyrroles, namely, 2-phenyl-3,3-dimethyl-3*H*-pyrrole (53% yield)[12,13] and 2-(2-thienyl)-3,3-dimethyl-3*H*-pyrrole (11% yield)[12] were thus prepared. Apparently, application of (het)aryl cycloalkyl ketoximes to this reaction should afford spirocyclic 3*H*-pyrroles.

This is a preliminary communication about the synthesis of spirocyclic 3*H*-pyrroles from cyclohexyl phenyl and cyclohexyl (2-thienyl) ketoximes (Scheme 1). After the brief optimization of the reaction conditions, we converted oximes **1a**,**b** (acetylene in the two-phase KOH/DMSO/*n*-hexane system under pressure, maximum pressure was 10 atm which was then dropped to about 3 atm, 70 °C, 5 min for oxime **1a** and 30 min for oxime **1b**), into the expected spirocyclic pyrroles **2a** and **2b** (19 and 18% isolated yields calculated by the ketoxime consumed, respectively).[†]



1a R = Ph
1b R = 2-thienyl

2a (19%)
2b (18%)

Scheme 1

Before charging the pressure reactor, oxime **1** and KOH (1 : 1 molar ratio) were preheated in DMSO to give a homogeneous

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[†] The IR spectra were recorded on a Bruker IFS25 spectrophotometer in KBr pellets. 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); carrier gas was helium, constant flow. The NMR spectra were measured on Bruker DPX-400 and AV-400 spectrometers (400.1 for ^{1}H, 100.6 for ^{13}C, and 40.5 MHz for ^{15}N) in $CDCl_3$ using HMDSO (^{1}H, ^{13}C) and $MeNO_2$ (^{15}N) as internal references. Basic aluminum oxide was used for column chromatography, and Silufol plates for TLC (hexane – diethyl ether, 1:1).

The reaction of ketoximes **1a**,**b** *with acetylene in KOH/DMSO/*n*-hexane*. A 0.3-l pressure reactor equipped with a magnetic stirrer (250 rpm) was charged with hexane (40 ml) and a potassium oximate solution in DMSO was prepared by heating a mixture of ketoxime **1** (12.5 mmol) and $KOH\cdot0.5H_2O$ (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, 10 atm) and heated up to 70 °C. In the case of **1a**, heating was immediately ceased that took overall 20 min (~5 min at 70 °C); in the case of **1b** the reaction mixture was heated at 70 °C for 30 min. After cooling to room temperature the 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 Et_2O (5×50 ml). The combined organic layers were washed with H_2O (3×50 ml) and dried over $MgSO_4$ overnight. After distilling off the solvents, the residue was chromatographed on the column (1.9×30 cm, CH_2Cl_2 as eluent) to afford the corresponding 3*H*-pyrroles **2a**,**b**.

1-Phenyl-2-azaspiro[4.5]deca-1,3-diene **2a**: yield 0.42 g, 19% (taking into account 84% oxime conversion); viscous yellow oil, $R_f = 0.54$. IR (ν/cm^{-1}): 3071, 2932, 2857, 1564, 1493, 1450, 1336, 1144, 1047, 915, 846, 770, 752, 695. ^{1}H NMR, δ: 1.38, 1.45, 1.60, 1.92, 1.94, 2.14 (m, 10 H, CH_2), 6.82 (d, 1H, H^4, ^3J 3.6 Hz), 7.16 (d, 1H, H^3, ^3J 3.6 Hz), 7.44 (m, 3H, *m*-H, *p*-H), 8.03 (m, 2H, *o*-H). ^{13}C NMR, δ: 25.1 (C^7, C^9), 25.9 (C^8), 32.1 (C^6, C^{10}), 61.9 (C^5), 127.9 (*o*-C, Ph), 128.5 (*m*-C, Ph), 129.9 (*p*-C, Ph), 133.7 (*i*-C, Ph), 134.4 (C^4), 141.4 (C^3), 183.6 (C^1). ^{15}N NMR, δ: –62.7. MS (EI), *m*/*z*: 211 [M]$^+$.

1-(2-Thienyl)-2-azaspiro[4.5]deca-1,3-diene **2b**: yield 0.38 g, 18% (taking into account 78% oxime conversion); viscous yellow oil, $R_f = 0.47$ or light yellow crystals, mp 59–60 °C (hexane). IR (ν/cm^{-1}): 3071, 2932, 2855, 1563, 1486, 1449, 1431, 1334, 1139, 1057, 1036, 948, 846, 749, 707. ^{1}H NMR, δ: 1.42, 1.51, 1.60, 1.92, 1.94, 2.05 (m, 10H, CH_2), 6.75 (d, 1H, H^4, ^3J 3.6 Hz), 7.11 (d, 1H, H^3, ^3J 3.6 Hz), 7.13 (dd, 1H, H^4-thienyl, ^3J 3.8 Hz, ^3J 5.2 Hz), 7.43 (dd, 1H, H^5-thienyl, ^3J 5.2 Hz, ^4J 1.0 Hz), 7.62 (dd, 1H, H^3-thienyl, ^3J 3.8 Hz, ^4J 1.0 Hz). ^{13}C NMR, δ: 24.9 (C^7, C^9), 26.0 (C^8), 33.3 (C^6, C^{10}), 61.5 (C^5), 127.6 (C^3, thienyl), 127.9 (C^4, thienyl), 128.6 (C^5, thienyl), 133.5 (C^4), 138.6 (C^2, thienyl), 141.9 (C^3), 179.0 (C^1). ^{15}N NMR, δ: –74.2.

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solution of potassium oximate. After cooling, this solution was transferred to the reactor, *n*-hexane was then added to form the two-phase system. The hexane layer is crucial for the successful synthesis since it extracts the reactive intermediates and products from the reaction phase thus preventing their undesirable transformation.

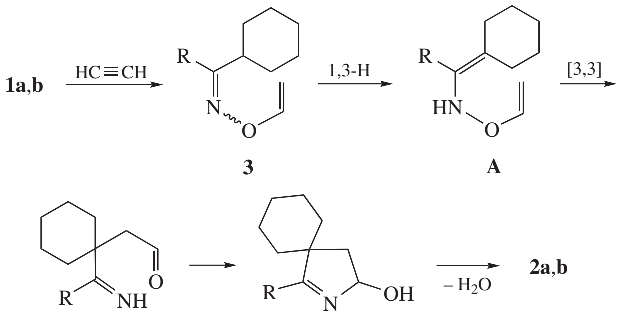
The signals in the ^{1}H and ^{13}C NMR spectra were assigned using 2D NMR technique (COSY, NOESY, HSQC and HMBC). The signals of the cyclohexane methylene protons (1.38–1.42 and 2.05–2.14 ppm) show NOE with the signals of *o*-H protons of the phenyl substituent in the 1-position and with the signals of pyrrole ring protons in the 4-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 be unambiguously assigned in the ^{13}C NMR spectra. The values of chemical shifts of nitrogen atoms in the ^{15}N NMR spectra were obtained from 2D heteronuclear spectra ^{1}H-^{15}N HMBC.

According to ^{1}H NMR analysis of the crude material, real yields of the spirocyclic 3*H*-pyrroles are 42–56%, but much of them is lost during chromatography due to their high reactivity.

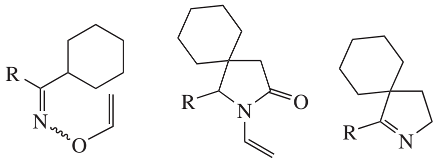
Like in the pyrrole synthesis from ketoximes and acetylene,[11] the formation of spirocyclic 3*H*-pyrroles **2a**,**b** expectedly involves generation of the intermediate *O*-vinyl ketoxime **3** which then undergoes 1,3-prototropic shift to deliver the second intermediate **A**. This intermediate rearranges in 3,3-sigmatropic manner to imino aldehyde **B** cyclizing to hydroxypyrroline **C**. Dehydration of the latter yields the target products (Scheme 2).

The scrutinized inspection of the reaction mixtures allows the following remaining intermediates and minor side products to be detected (^{1}H NMR): *O*-vinyl oximes **3a**,**b**, *N*-vinylpyrrolidinones **4a**,**b** and pyrrolines **5a**,**b**.[‡]

Trace amounts of 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone, close analogue of *N*-vinylpyrrolidinones **4a**,**b**, have been recently found among the products of the reaction between isopropyl phenyl ketoxime and acetylene.[13] Analogues of pyrrolines **5a**,**b** were identified as side products of the reaction between isopropyl (het)aryl ketoximes and acetylene.[14]



Scheme 2



a R = Ph	**3a** (8%)	**4a** (6%)	**5a** (3%)
b R = 2-thienyl	**3b** (1%)	**4b** (10%)	**5b** (<1%)

In conclusion, we have demonstrated that the reaction of (het)aryl cycloalkyl ketoximes with acetylene in the two-phase system KOH/DMSO/*n*-hexane has a potential to be the shortest route to so far inaccessible spirocyclic 3*H*-pyrroles. Further optimization of the reaction to extend its scope and to increase the product yields is now underway.

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[‡] Since area of signals in the ^{1}H NMR spectra of reaction mixtures, concerning (het)aryl and cyclohexyl moieties, is sufficiently rich, the amount of intermediates **3a**,**b** and minor side-products **4a**,**b** and **5a**,**b** was estimated by the integration of characteristic signals described below.

Cyclohexyl(phenyl)methanone O*-vinyloxime* **3a**. ^{1}H NMR, δ: 4.15 (dd, 1H, H$^{\alpha}$, ^{2}J 1.6 Hz, ^{3}J 6.7 Hz), 4.64 (dd, 1H, H$^{\beta}$, ^{2}J 1.6 Hz, ^{3}J 13.8 Hz), 7.00 (dd, 1H, H^{x}, ^{3}J 6.7 Hz, ^{3}J 13.8 Hz).

Cyclohexyl(2-thienyl)methanone O*-vinyloxime* **3b**. ^{1}H NMR, δ: 4.22 (dd, 1H, H$^{\alpha}$, ^{2}J 1.3 Hz, ^{3}J 6.6 Hz), 4.76 (dd, 1H, H$^{\beta}$, ^{2}J 1.3 Hz, ^{3}J 14.2 Hz), 7.00 (dd, 1H, H^{x}, ^{3}J 6.6 Hz, ^{3}J 14.2 Hz).

1-Phenyl-2-vinyl-2-azaspiro[4.5]decan-3-one **4a**. ^{1}H NMR, δ: 2.42 (d, 1H, CH$_2$, ^{2}J 17.1 Hz), 2.54 (d, 1H, CH$_2$, ^{2}J 17.1 Hz), 4.10 (d, 1H, H$^{\beta}$, ^{3}J 16.2 Hz), 4.30 (d, 1H, H$^{\alpha}$, ^{3}J 9.3 Hz), 4.44 (s, 1H, H^{1}).

1-(2-Thienyl)-2-vinyl-2-azaspiro[4.5]decan-3-one **4b**. ^{1}H NMR, δ: 2.50 (d, 1H, CH$_2$, ^{2}J 17.1 Hz), 2.56 (d, 1H, CH$_2$, ^{2}J 17.1 Hz), 4.31 (d, 1H, H$^{\beta}$, ^{3}J 16.2 Hz), 4.39 (d, 1H, H$^{\alpha}$, ^{3}J 9.2 Hz), 4.76 (s, 1H, H^{1}).

1-Phenyl-2-azaspiro[4.5]dec-1-ene **5a**. ^{1}H NMR, δ: 2.02 (t, 2H, H^{4}), 3.91 (t, 2H, H^{3}).

1-(2-Thienyl)-2-azaspiro[4.5]dec-1-ene **5b**. ^{1}H NMR, δ: 3.91 (t, 2H, H^{3}).