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One-pot synthesis of 3-(*E*)-styrylpyrroles from (*E*)-styrylmethyl ketoximes and acetylene

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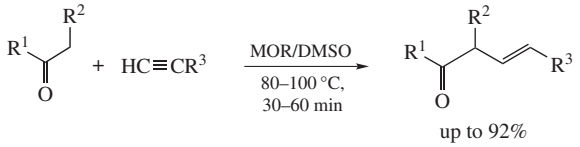
(*E*)-Styrylmethyl ketoximes react with acetylene in KOH/DMSO superbase system (90 °C, 1 h) to afford stereoselectively 3-(*E*)-styrylpyrroles.

β,γ-Unsaturated ketones are the valuable intermediates in fine organic synthesis[1] and key structures in drug design.[2] They are less accessible than their thermodynamically stable α,β-isomers readily accessible by crotonic condensation. Generally, the synthesis of β,γ-enones is multi-stage,[3] often requires exotic starting materials[4] or metal complex catalysts.[5]

Recently, we have found that ketones regio- and stereoselectively add to (het)arylacetylenes at 80–100 °C in the presence of superbase systems MOH/DMSO (M = Na, K, Cs),[6] KOH/Bu^{t}OH/DMSO[7] or Bu^{t}OK/DMSO[8] to afford *E*-configured β,γ-enones in high yields (Scheme 1).



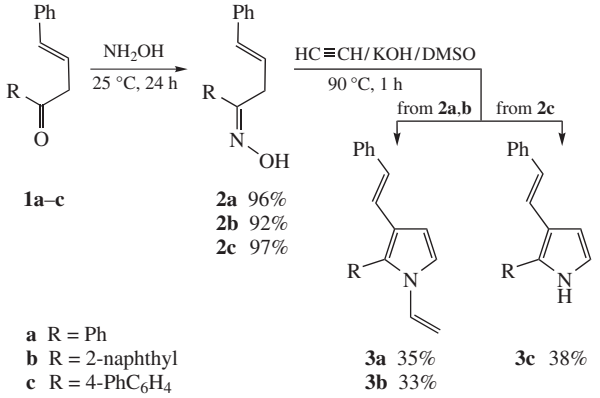
R^1, R^2 = Alk, Ar, cycloalkyl, hetaryl; R^3 = Ar, hetaryl
M = Na, K, Cs; R = H, Bu^t

Scheme 1

The application of this reaction as the first stage in the syntheses of more complex molecules seems to be promising. In this line, over the last few years we have published one-pot syntheses of 2,5-diarylfurans[6] from ketones and 4-nitrophenylacetylene as well as Δ^2-isoxazolines[9] from ketones, arylacetylenes and hydroxyl amine.

In continuation of these studies, here we preliminarily report on the KOH/DMSO superbase system-catalyzed stereoselective synthesis of 3-(*E*)-styrylpyrroles from β,γ-enone oximes and acetylenes through the Trofimov reaction.[10]

We have found that oximes **2a**,**b** (prepared from ketones **1a**,**b** and hydroxylamine hydrochloride in pyridine) on treatment with acetylene in the superbase system KOH/DMSO (molar ratio of oxime **2**:KOH = 1:1, initial acetylene pressure at room temperature, 11–13 atm, 90 °C, 1 h) stereoselectively gave 1-vinyl-3-(*E*)-styrylpyrroles **3a**,**b** (Scheme 2).† Isolated yields of pyrroles **3a**,**b** after column chromatography were 35 and 33%, respectively. The *E*-configuration of the styryl moiety was determined by ^3J values (16.1–16.2 Hz) between olefinic protons.



1a–c

2a 96%
2b 92%
2c 97%

a R = Ph
b R = 2-naphthyl
c R = 4-PhC$_6$H$_4$

3a 35%
3b 33%
3c 38%

Scheme 2

β,γ-Enone oximes **2a–c**. A mixture of enone **1a–c** (3.00 mmol), $NH_2OH{\cdot}HCl$ (0.40 g, 5.75 mmol) and pyridine (15 ml) was stirred at room temperature for 24 h and then poured into water (50 ml). The crystalline precipitate was collected by filtration, washed with water, and dried *in vacuo*. After recrystallization from ethanol pure oximes **2a–c** were obtained, identical in characteristics with the literature.[9] *E*-configuration in the hydroxylamino moiety was confirmed by the published data.[17] *E*-configuration of the olefinic moiety was determined by ^3J values (16.1–16.2 Hz) between protons at the double bond.

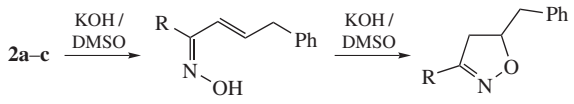
Pyrroles **3a–c**. A mixture of oxime **2** (3.50 mmol), $KOH{\cdot}0.5H_2O$ (0.23 g, 3.50 mmol) and DMSO (50 ml) was placed into a 0.25-l steel rotating autoclave. The autoclave was fed with acetylene to the pressure of 11–13 atm and then decompressed to atmospheric pressure to remove air. The autoclave was fed with acetylene again (initial pressure at ambient temperature was 11–13 atm, which reached a maximum of 23–25 atm on heating to 90 °C and then dropped upon acetylene consumption during the reaction), and heating was maintained for 1 h. The reaction mixture, after cooling to room temperature, was diluted with cold (5–10 °C) water (50 ml), neutralized with NH_4Cl and extracted with diethyl ether (5×20 ml). The organic extracts were washed with water (3×15 ml) and dried (K_2CO_3). After removal of the solvent, the crude residue was subjected to column chromatography (SiO_2, eluent benzene) to give pure pyrroles **3a–c** and isoxazolines **4a–c**.

*2-Phenyl-3-(*E*)-styryl-1-vinylpyrrole* **3a**: yield 0.33 g, 35%; yellow oil. IR (film, ν/cm^{-1}): 3182, 1631, 1597, 1518, 1415, 1247, 1063, 1035, 960, 912, 893, 748, 733, 695. ^{1}H NMR, δ: 7.52–7.50 (m, 2H, H$_m$), 7.38–7.39 (m, 1H, H$_p$), 7.36–7.34 (m, 2H, H$_{o'}$), 7.33–7.31 (m, 2H, H$_o$), 7.26–7.24 (m, 2H, H$_{m'}$), 7.13–7.11 (m, 1H, H$_{p'}$), 7.11 (d, 1H, H^5, ^3J 3.2 Hz), 6.88 (d, 1H, H$_a$, ^3J 16.1 Hz), 6.82 (d, 1H, H$_b$, ^3J 16.1 Hz), 6.72 (dd, 1H, H$_X$, ^3J 15.8 Hz, ^3J 8.9 Hz), 6.63 (d, 1H, H^4, ^3J 3.2 Hz), 5.10 (dd, 1H, H$_A$, ^3J 15.8 Hz, ^2J 1.2 Hz), 4.60 (dd, 1H, H$_B$, ^3J 8.9 Hz, ^2J 1.2 Hz). ^{13}C NMR, δ: 138.4 (C$_{i'}$), 132.5 (C^2), 131.5 (N–*C*H=CH$_2$), 131.3 (C$_o$), 130.8 (C$_i$), 128.6 (C$_{m'}$), 128.5 (C$_m$), 128.0 (C$_p$), 126.6 (C$_{p'}$), 125.9 (C$_{o'}$), 125.8 (C$_b$), 122.1 (C^3), 121.6 (C$_a$), 118.1 (C^5), 107.2 (C^4), 98.2 (N–CH=*C*H$_2$). ^{15}N NMR, δ: –208.0. Found (%): C, 88.39; H, 6.37; N, 5.07. Calc for $C_{20}H_{17}N$ (%): C, 88.52; H, 6.31; N, 5.16.

† ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on a Bruker AVANCE 400 instrument (400.13, 100.61 and 40.56 MHz respectively) equipped with inverse gradient 5 mm probe in $CDCl_3$ with HMDS as internal standard. All 2D NMR spectra were recorded using a standard gradient Bruker pulse programs. IR spectra were obtained on a Bruker Vertex 70 spectrometer.

Noteworthy, oxime **2c** reacted with acetylene under the same conditions to furnish 3-(*E*)-styryl-1*H*-pyrrole **3c** (Scheme 2), the corresponding 1-vinylpyrrole was detected in the reaction mixture in trace amounts only (^{1}H NMR).

In all the cases, the reaction was accompanied by the formation of Δ^2-isoxazolines **4a–c** due to the competitive intramolecular nucleophilic addition of the oxime moiety to the double bond of α,β-unsaturated oximes **5a–c** (Scheme 3).



5a–c

4a R = Ph, 18%
4b R = 2-naphthyl, 15%
4c R = 4-PhC_6H_4, 22%

Scheme 3

The target pyrroles **3a–c** were easily isolated from their mixture with Δ^2-isoxazolines **4a–c** by column chromatography (SiO_2, eluent benzene).

When the reaction temperature was raised to 100 °C (0.5–1 h), significant resinification occurred, thus hindering isolation of the target products. At 70–80 °C (0.1–2 h), the content of Δ^2-isoxazolines **4a–c** was higher. Selective one-pot synthesis of Δ^2-isoxazolines directly from ketones, acetylenes and hydroxylamine has been published.[9]

3-(*E*)-Styrylpyrroles synthesized represent heterocyclic analogues of stilbenes, widely abundant in nature (plant antioxidants resveratrol[11] and pterostilbene[12]), which are used in medicine and optoelectronics (for the information recording and storage,[13] nonlinear-optical materials[14]). The known methods for the synthesis of 3-styrylpyrroles (not always stereoselective) are laborious and multi-stage. They are limited by the Wittig reaction of *N*-methyl-3-formylpyrrole with the corresponding phosphorus ylides[15] and reduction of *N*-tosyl protected 3-benzoylpyrrole with subsequent dehydration of the forming secondary alcohol.[16] Despite the moderate yields of 3-(*E*)-styrylpyrroles, their synthesis from β,γ-enone oximes and acetylene may have preparative significance as one-pot stereoselective approach from readily available starting materials (in fact from ketones and acetylenes) under transition-metal-free conditions.

*2-(2-Naphthyl)-3-(*E*)-styryl-1-vinylpyrrole* **3b**: yield 0.37 g, 33%; yellow oil. IR (KBr, ν/cm^{-1}): 3181, 3056, 2604, 1631, 1596, 1521, 1504, 1414, 1336, 1237, 1131, 960, 914, 894, 861, 822, 748, 732, 695. ^{1}H NMR, δ: 7.92–7.57 (m, 7H, $H_{naphthyl}$), 7.36–7.35 (m, 2H, H_o), 7.28–7.26 (m, 2H, H_m), 7.20 (d, 1H, H^5, ^3J 3.3 Hz), 7.17–7.15 (m, 1H, H_p), 6.97 (d, 1H, H_a, ^3J 16.2 Hz), 6.90 (d, 1H, H_b, ^3J 16.2 Hz), 6.81 (dd, 1H, H_X, ^3J 15.6 Hz, ^3J 8.8 Hz), 6.72 (d, 1H, H^4, ^3J 3.3 Hz), 5.18 (dd, 1H, H_A, ^3J 15.6 Hz, ^3J 1.1 Hz), 4.66 (dd, 1H, H_B, ^3J 8.8 Hz, ^3J 1.1 Hz). ^{13}C NMR, δ: 138.3 (C_i), 133.2, 132.8, 131.5, 130.6, 128.8, 128.3, 128.1, 127.8 (10$C_{naphthyl}$), 132.4 (C^2), 131.5 (N–*C*H=CH_2), 128.6 (C_m), 126.6 (C_p), 125.9 (C_o, C_b), 122.4 (C^3), 121.5 (C_a), 118.3 (C^5), 107.2 (C^4), 98.3 (N–CH=*C*H_2). Found (%): C, 89.31; H, 5.71; N, 4.24. Calc. for $C_{24}H_{19}N$ (%): C, 89.68; H, 5.96; N, 4.36.

*2-(Biphenyl-4-yl)-3-(*E*)-styrylpyrrole* **3c**: yield 0.43 g, 38%; white powder, mp 132–134 °C. IR (KBr, ν/cm^{-1}): 3423, 3027, 1632, 1599, 1488, 1444, 1267, 1248, 1098, 1074, 1006, 959, 908, 843, 766, 728, 659. ^{1}H NMR, δ: 8.23 (br. s, 1H, NH), 7.74–7.72 (m, 2H, H_m), 7.70–7.68 (m, 2H, $H_{o'}$), 7.58–7.56 (m, 2H, H_o), 7.52–7.49 (m, 4H, $H_{m'}$, $H_{o''}$), 7.43–7.41 (m, 1H, $H_{p'}$), 7.38–7.35 (m, 2H, $H_{m''}$), 7.32 (d, 1H, H_a, ^3J 16.1 Hz), 7.25–7.23 (m, 1H, $H_{p''}$), 6.98 (d, 1H, H_b, ^3J 16.1 Hz), 6.90–6.88 (m, 1H, H^5), 6.68–6.67 (m, 1H, H^4). ^{13}C NMR, δ: 140.6 ($C_{i'}$), 139.8 (C_p), 138.6 ($C_{i''}$), 131.9 (C_i), 130.9 (C^2), 129.0 ($C_{m'}$), 128.9 ($C_{p'}$), 128.6 ($C_{m''}$), 128.1 (C_o), 127.6 (C_m), 127.1 ($C_{o'}$), 126.9 ($C_{p''}$), 126.0 ($C_{o''}$), 126.2 (C_b), 122.0 (C_a), 120.0 (C^3), 119.2 (C^5), 107.2 (C^4). ^{15}N NMR, δ: –234.5 (1H, NH, ^1J 96.0 Hz). Found (%): C, 89.45; H, 6.14; N, 4.19. Calc. for $C_{24}H_{19}N$ (%): C, 89.68; H, 5.96; N, 4.36.

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