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Base-catalyzed α-vinylation of ketones with acetylenes as a key step in one-pot synthesis of pyrazolines and pyrazoles

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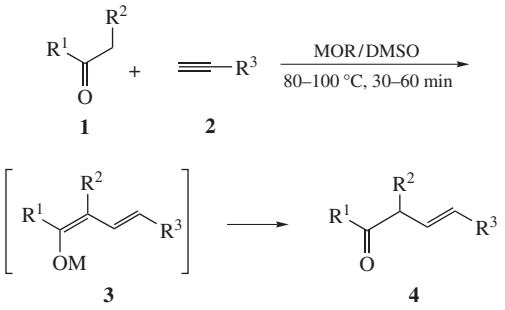
The sequential reaction of ketones with phenylacetylene in the presence of KOH/DMSO system followed by the treatment of the reaction mixture with HCl and monosubstituted hydrazines leads to pyrazolines and pyrazoles in up to 87% total yield.

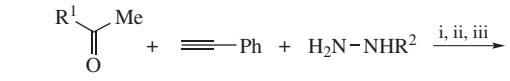
The recently discovered[1] base-catalyzed α-vinylation of ketones **1** with acetylenes **2** proceeds *via* formation of dienolates **3** to afford β,γ-enones **4** in high yields (Scheme 1).



R^1, R^2 = alkyl, cycloalkyl, (het)aryl
R^3 = (het)aryl, CH_2OAlk
M = Na, K, Cs
R = H, Bu^t

Scheme 1

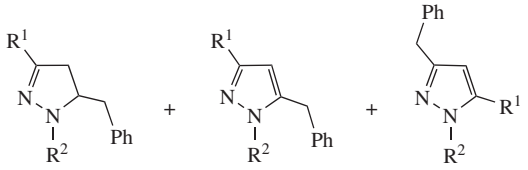
Currently available dienolates **3** and unsaturated ketones **4** find use in a one-pot synthesis of Δ^2-isoxazolines from ketones **1**, acetylenes **2** and hydroxylamine.[2] Also, from oximes of ketones **4** and acetylene, 3-styrylpyrroles have been obtained.[3]



1a R^1 = Ph
1b R^1 = 4-PhC_6H_4
1c R^1 = 2-naphthyl

2

5a R^2 = Et
5b R^2 = Bn



6a–e **7a–e** **8a–e**

a R^1 = Ph, R^2 = Et (**6a** + **7a** + **8a**, 81%)
b R^1 = 4-PhC_6H_4, R^2 = Et (**6b** + **7b** + **8b**, 61%)
c R^1 = 2-naphthyl, R^2 = Et (**6c** + **7c** + **8c**, 65%)
d R^1 = Ph, R^2 = Bn (**6d** + **7d** + **8d**, 87%)
e R^1 = 4-PhC_6H_4, R^2 = Bn (**6e** + **7e** + **8e**, 79%)

Scheme 2 *Reagents and conditions*: i, ketone **1** (5 mmol), phenylacetylene **2** (5 mmol), KOH·0.5H_2O (5 mmol), DMSO (15 ml), 100 °C 1 h; ii, HCl (5 mmol), 25 °C; iii, hydrazine **5** (10 mmol), 100 °C, 1 h.

To further develop this trend, here we disclose a one-pot synthesis of pyrazolines and pyrazoles *via* the three-component reaction between ketones **1a–c**, phenylacetylene **2** and substituted hydrazines **5a**,**b** (Scheme 2). Treatment of ketones **1a–c** with phenylacetylene **2** in the presence of KOH in DMSO, followed by the addition of HCl and monosubstituted hydrazine **5a**,**b**, delivers pyrazolines **6** (major products) and isomeric pyrazoles **7**, **8** (61–87% total yield). Fraction of pyrazoles **7**, **8** is about 15–20%.

Obviously, β,γ-enone **4**, released upon neutralization of potassium dienolate **3**, reacts with monosubstituted hydrazine **5** to give hydrazone **9** which, after preliminary prototropic shift of the double bond towards the hydrazone function, cyclizes to pyrazoline **6** (Scheme 3). A partial aromatization of pyrazoline **6**

† The NMR spectra were measured from solutions in C_6D_6 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) using HDMSO (^{1}H, ^{13}C) and nitromethane (^{15}N) as internal references. The IR spectra were recorded on a Bruker IFS25 spectrophotometer.

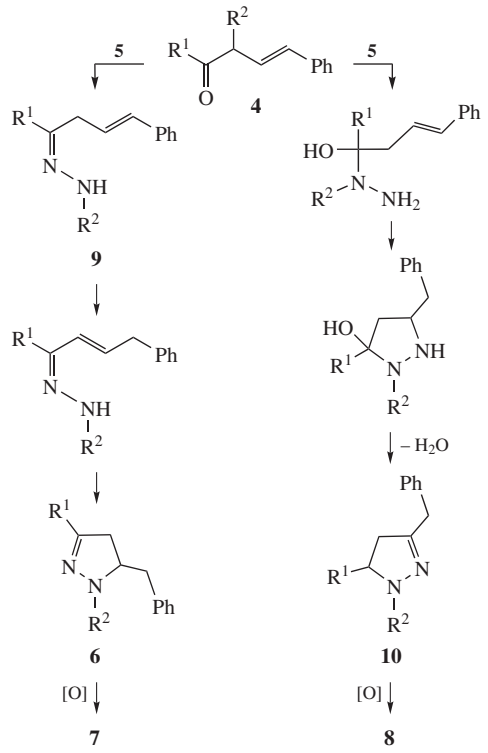
The reaction of ketones **1a–c** *with phenylacetylene* **2** *and hydrazines* **5a**,**b**. A mixture of ketone **1a–c** (5 mmol), phenylacetylene **2** (5 mmol, 0.511 g) and KOH·0.5H_2O (5 mmol, 0.325 g) in DMSO (15 ml) was heated (100 °C) and stirred at 100 °C for 1 h. After cooling (20–25 °C), 0.506 g concentrated hydrochloric acid (5 mmol, 0.182 g) and hydrazine **5a**,**b** (10 mmol) were added and the mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the mixture was diluted with H_2O (15 ml) and extracted with Et_2O (4×10 ml). The organic extract was washed with H_2O (3×5 ml) and dried ($MgSO_4$). After distilling off the solvents, the residue was purified by column chromatography (Al_2O_3, eluent C_6H_6).

*5-Benzyl-1-ethyl-3-phenyl-4,5-dihydro-1*H*-pyrazole* **6a** *with admixture of pyrazoles* **7a** *and* **8a** (**7a**:**8a** ratio is 5:2): yield 1.069 g (81%), yellow oil. IR (film, ν/cm^{-1}): 3061, 3027, 2974, 2934, 2852, 1681, 1603, 1547, 1495, 1454, 1369, 1073, 1029, 959, 762, 737, 699.

For **6a**: ^{1}H NMR, δ: 8.18–7.24 (m, 10H$_{Ar}$), 3.40–3.36 (m, 1H, H^5), 3.20 (dd, 1H, CH_2Ph, ^2J 13.4 Hz, ^3J 4.5 Hz), 3.07 (dd, 1H, CH_2Ph, ^2J 13.4 Hz, ^3J 9.0 Hz), 3.05–2.95 (m, 2H, NCH_2), 2.74 (dd, 1H, H^4, ^2J 16.2 Hz, ^3J 9.3 Hz), 2.50 (dd, 1H, H^4, ^2J 16.2 Hz, ^3J 13.0 Hz), 1.54 (t, 3H, Me, ^3J 7.1 Hz). ^{13}C NMR, δ: 150.4 (C^3), 128.4–125.0 (12C$_{Ar}$), 66.8 (C^5), 47.7 (NCH_2), 39.3 (CH_2Ph), 38.3 (C^4), 12.8 (Me).

For **7a**: ^{1}H NMR, δ: 7.74–7.14 (m, 10H$_{Ar}$), 6.38 (s, 1H, H^4), 3.77 (q, 2H, NCH_2, ^3J 7.2 Hz), 3.69 (s, 2H, CH_2Ph), 1.21 (t, 3H, Me, ^3J 7.2 Hz). ^{13}C NMR, δ: 148.1 (C^3), 141.1 (C^5), 138.4–125.0 (12C$_{Ar}$), 102.9 (C^4), 47.7 (NCH_2), 30.1 (CH_2Ph), 12.4 (Me).

For **8a**: ^{1}H NMR, δ: 7.74–7.14 (m, 10H$_{Ar}$), 6.17 (s, 1H, H^4), 3.97 (q, 2H, NCH_2, ^3J 7.2 Hz), 3.69 (s, 2H, CH_2Ph), 1.45 (t, 3H, Me, ^3J 7.2 Hz). ^{13}C NMR, δ: 152.5 (C^3), 137.0 (C^5), 138.4–125.0 (12C$_{Ar}$), 105.1 (C^4), 48.7 (NCH_2), 37.2 (CH_2Ph), 14.7 (Me).



Scheme 3

(probably due to oxidation by DMSO or air oxygen) occurs to form pyrazole **7**. The formation of isomeric pyrazoles **8** is likely triggered by attack of the NH(R) function of hydrazine **5** to the carbonyl group of ketone **1** with the subsequent closing of the cycle due to addition of the NH_2 group to the styrene fragment (Scheme 3, examples, though scarce, of nucleophilic addition to styrenes are known[4]). Noteworthy, isomeric pyrazolines **10** under the reaction conditions undergo quantitative aromatization.

Nowadays, numerous publications relate to synthesis and application of pyrazoles. Pyrazole structures are incorporated in diverse drugs,[5] and pyrazoles themselves represent medicinally friendly building blocks,[6] therefore, interest in their synthesis is not eroded. When optimized, the proposed approach can open new prospects for the synthesis of a great variety of compounds of the pyrazole series.

Online Supplementary Materials

Supplementary data associated with this article (physico-chemical characteristics of compounds **6b–e**, **7b–e** and **8b–e**) can be found in the online version at doi:10.1016/j.mencom.2015.03.018.

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