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Reaction of α,β-alkynylketones with β-amino alcohols: pseudoephedrine-assisted cleavage of triple bond *via* formal internal redox process

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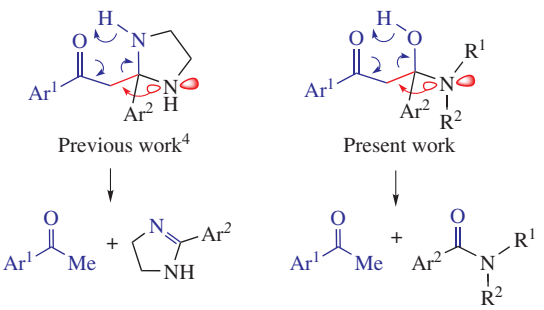
Reaction of 3-aryl-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ones with (+)-pseudoephedrine leads to products of alkyne moiety cleavage, namely, 1-(3,4,5-trimethoxyphenyl)ethanone and *N*-(1-hydroxy-1-phenylprop-2-yl)-*N*-methylbenzamides. In the course of the process one of alkyne carbons undergoes a formal reduction to a Me group, whereas the other one is oxidized to a C(O)NRR′ moiety.

High reactivity and unique electronic features of acetylenic compounds create diverse opportunities for their application in organic synthesis, medicinal chemistry, biotechnology and material science.[1] α-Keto acetylenes due to higher electrophilicity of the triple bond readily undergo addition reactions,[2] in cases of multifunctional reactants the transformations proceeding in more complex fasion.[3] Earlier,[4] we reported that the reaction of 1,3-diarylprop-2-yn-1-ones with 1,2-diaminoethane resulted in the cleavage of the C≡C bond affording acetophenones and 2-substituted imidazolines.

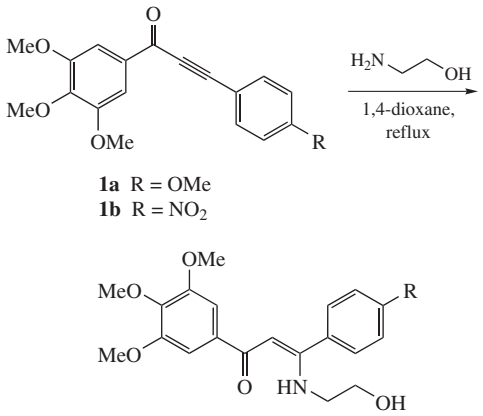
The key features of this cascade were the stereoelectronically favorable[5] 5-*exo-dig* cyclization of the intermediate product followed by retro-Mannich fragmentation, assisted by stereoelectronically optimal interaction of the breaking C–C bond with the lone pair of a nitrogen atom. Furthermore, the fragmentation step is assisted by intermolecular proton transfer to the developing negative charge at the carbonyl oxygen from the properly positioned N–H bond within the six-membered transition state (Scheme 1).

Regarding the stereoelectronic features of this transition state, we envisioned that the key C–C fragmentation can be facilitated on moving to β-amino alcohols whose more acidic O–H moiety is suitable for the proton transfer and more basic *N*,*N*-dialkyl substituent provides the lone pair for stereoelectronic assistance. Herein, we studied reaction between several 1,3-diarylprop-2-yn-1-ones and β-amino alcohols bearing substituents of different nature.



Scheme 1

The reaction of ynones **1a**,**b** with ethanolamine was carried out by refluxing their mixture in dioxane until consumption of the starting ynone (Scheme 2).[†]



1a R = OMe
1b R = NO_2

2a R = OMe (94%)
2b R = NO_2 (85%)

Scheme 2

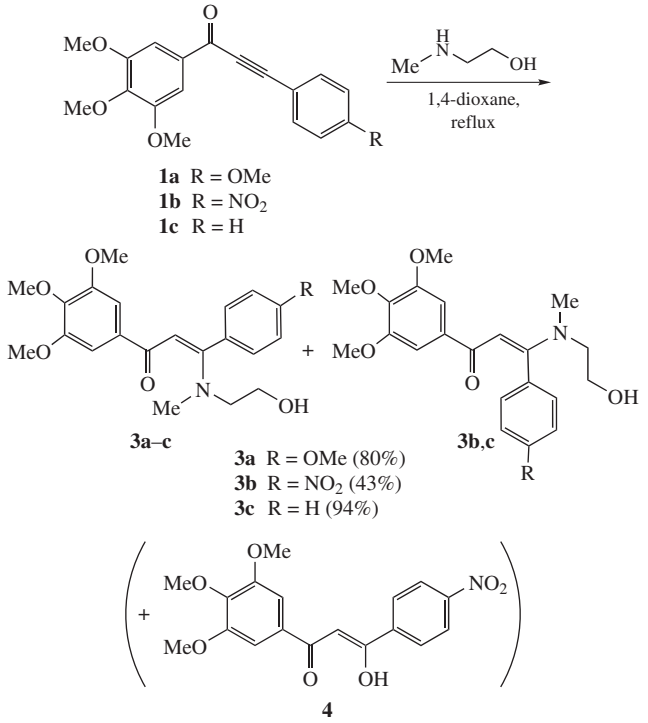
[†] *General procedure*. A mixture of appropriate ynone **1a–c** (1.0 mmol) and ethanolamine (2.0 mmol) or 2-(*N*-methylamino)ethanol (2.0 mmol) in 1,4-dioxane (10 ml) was refluxed for 3–10 h. The volatiles were evaporated *in vacuo*, the residue was recrystallized from benzene or ethanol.

(Z)-3-(2-Hydroxyethylamino)-3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **2a**: yield 365 mg (94%), mp 140–142 °C (benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.40 (dt, 2H, $C^{16}H_2$, *J* 5.4 and 5.6 Hz), 3.72 (t, 2H, $C^{17}H_2$, *J* 5.4 Hz), 3.84 (s, 3H, 7-OMe), 3.86 (s, 3H, 13-OMe), 3.87 (s, 6H, 12,14-OMe), 5.70 (s, 1H, C^2H), 6.95 (m, 2H, C^6H and C^8H), 7.12 (s, 2H, C^{11}H and C^{15}H), 7.36 (m, 2H, C^5H and C^9H), 11.43 (br.t, 1H, NH, *J* 5.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.17 (C^{16}), 54.66 (7-OMe), 55.46 (12,14-OMe), 60.13 (13-OMe), 61.34 (C^{17}), 92.81 (C^2), 103.56 ($C^{11,15}$), 113.25 ($C^{6,8}$), 126.95 (C^4), 128.62 ($C^{5,9}$), 135.03 (C^{10}), 139.71 (C^{13}), 152.14 ($C^{12,14}$), 159.89 (C^7), 166.37 (C^3), 186.68 (C^1). IR (KBr, ν/cm^{-1}): 1606 (C=O), 3437 (OH). HRMS (ESI), *m*/*z*: 387.1671 $[M]^+$ (calc. for $C_{21}H_{25}NO_6$, *m*/*z*: 387.1676).

For characteristics of compounds **2b**, **3a–c** and **4**, see Online Supplementary Materials.

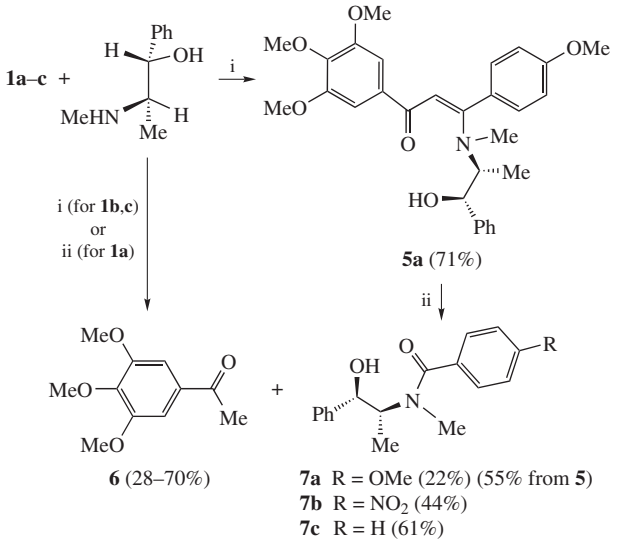
As expected, in the case of ynone **1b** with the acceptor substituent the reaction was faster (3 h), while methoxy derivative **1a** required 10 h for the completion. The *Z*-configuration of the double bond in products **2a**,**b** was proven by ^{1}H-^{1}H 2D NOESY NMR manifesting an intensive cross-peak between olefinic proton and *ortho*-protons of aryl groups. The IR spectra of compounds **2a**,**b** contained stretching vibration ν(C=O) bands at 1605 cm^{-1} (compared to starting ynones with 1646–1664 cm^{-1}) due to hydrogen bond N–H···O=C (*cf.* ref. 6).

2-(*N*-Methylamino)ethanol reacts in the same manner as ethanolamine affording amino enones **3a**–**c** (Scheme 3). Yields of compounds **3a**,**c** were good. Compound **3b** underwent partial hydrolysis during chromatography to give by-product **4** (20%) dropping thus the yield of **3b** to 43% (*cf.* ref. 7). Compared to compounds **2a**,**b**, products **3** do not form intramolecular hydrogen bond. As a result, they are obtained as *E* and *Z* isomers. Configuration of the double bond in each isomer was proved by ^{1}H-^{1}H 2D NOESY NMR spectra which contained an intensive cross-peak between an olefinic proton and *ortho*-protons of both aryl groups for *Z*-isomers and cross-peak between an olefinic proton and NMe with NCH_2 protons for *E*-isomers.



Scheme 3

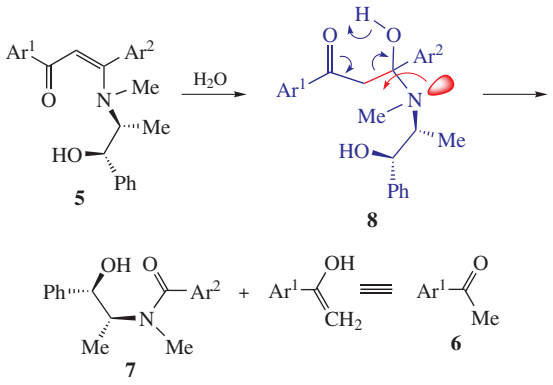
The reaction of α-keto acetylenes **1a**,**b** with sterically hindered (+)-pseudoephedrine turned to be substrate dependent (Scheme 4).‡ Less reactive methoxy-containing ynone **1a** after 50 h of processing gave the 'normal' product **5a** in 70% yield. Other more active ynones reacted quicker (12 h for **1b** and 27 h for **1c**) and were transformed into 'abnormal' acetophenone **6** with benzamides **7b**,**c** (see Scheme 4). However, 'abnormal' products **6**



Scheme 4 *Reagents and conditions*: i, 1,4-dioxane, reflux; ii, CuCl, pyridine, 1,4-dioxane, reflux.

and **7a** were obtained from substrate **1a** as well in the yields 28% and 22%, respectively, when the reaction was performed in the presence of CuCl in pyridine–dioxane mixture. Moreover, when adduct **5a** was contacted to CuCl in boiling pyridine–dioxane mixture, products **6** and **7a** were formed in 31 and 55% yields, respectively.

Formally, products **6** and **7** arise from the cleavage of triple bond in starting ynones **1**. The mechanistic reasons for such a reactivity should be investigated in future. We would preliminary hypothesize that the reaction is promoted by adventitious water present in the solvent (Scheme 5). We have tested this effect by adding excess of water (1 ml of H_2O per 1 mmol of ynone **1c**), which really shortened the reaction time to 6 h.



Scheme 5

The Michael amino enone intermediate **5** is less electrophilic than the starting alkyne due to effect of amino group. The pseudoephedrine secondary hindered OH group is poorly nucleophilic and does not participate in 5-*exo*-*trig* cyclization. As a consequence, the two reactions diverge at this point and the present cascade continues *via* an intermolecular nucleophilic attack that

‡ *General procedure*. A mixture of appropriate ynone (**1a**–**c**) (1.0 mmol) and (+)-pseudoephedrine (2.0 mmol) in 1,4-dioxane (7 ml) was refluxed for 12–50 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane–toluene 1:1, toluene, toluene–ethyl acetate 1:1, ethyl acetate) to give **5a**, **6** and **7a**–**c**.

*(*E*)-3-{N-[(1S,2S)-1-Hydroxy-1-phenylprop-2-yl]-*N*-methylamino}-3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* **5a**. Yield 350 mg (71%), mp 183–185 °C (benzene). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (d, 3H, Me, *J* 6.7 Hz), 3.10 (s, 3H, NMe), 3.82 (m, 1H, CH), 3.85 (s, 3H, OMe), 3.87 (s, 9H, 3OMe), 4.5 (m, 1H, CH), 5.82 (s, 1H, CH), 6.09 (br. s, 1H, OH), 6.93 (d, 2H, CH_{Ar}, *J* 8.9 Hz), 7.09–7.12 (m, 2H, CH_{Ar}), 7.19–7.21 (m, 4H, CH_{Ar}), 7.34 (s, 1H, CH_{Ar}), 7.48–7.49 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.55, 35.10, 54.98, 55.75, 60.45, 73.77, 98.61, 105.09, 113.58, 126.70, 126.97, 127.17, 127.77, 127.87, 128.03, 130.62, 135.29, 137.30, 140.65, 161.33, 169.17, 185.00. IR (KBr, ν/cm^{-1}): 3253 (OH chelated), 1602 (C=O chelated). HRMS, *m/z*: 473.2190 [M – H_2O]$^+$ (calc. for $C_{29}H_{31}NO_5$, *m/z*: 473.2197).

For characteristics of compounds **6** and **7a**–**c**, see Online Supplementary Materials.

leads to the formation of amides (instead of imidazolines) with release of an aryl methyl ketone. The absence of hemiaminal **8** in mixtures suggest that its fragmentation proceeds faster than its formation *via* addition of water to amino enone **5**. The relatively slow rate of this step explains why compound **5a** was isolated whereas **5b** and **5c** were not observed. In the case of **5a**, the donor group at the aromatic ring (R = OMe) would deactivate its double bond.

In summary, we have described a pseudoephedrine-assisted cleavage of all three C–C bonds in a polarized alkyne moiety of 1,3-diarylprop-2-yn-1-ones, leading to the corresponding aryl methyl ketone and *N*-(1-hydroxy-1-phenylprop-2-yl)-4-R-*N*-methylbenzamides. In the overall process, one of the alkyne carbons undergoes formal reduction with the formation of three C–H bonds, whereas the other carbon undergoes formal oxidation *via* the formation of one C–N bond and carbonyl (C=O) moiety.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.021.

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