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New selective cyclizations of alk-4-ynals with primary amines and azoles: one-pot synthesis of 2-azolylpyrrolidines and 3-iminocyclopentenes

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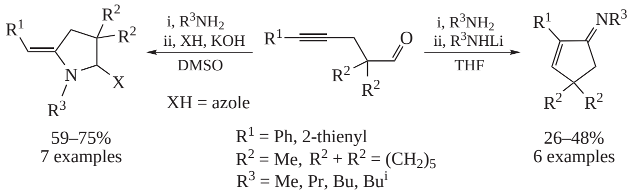
One-pot cyclization of alk-4-ynals with primary aliphatic amines and azoles in DMSO under the action of KOH affords 1-alkyl-2-azolyl-5-arylmethylidenepyrrolidines. Similar processes with lithium monoalkylamides in THF give rise to 3-iminocyclopentenes.



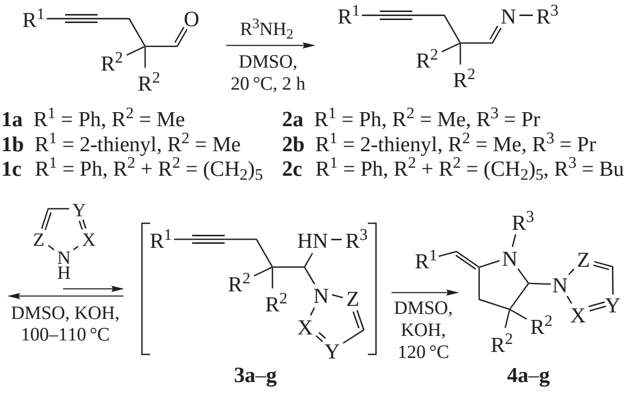
The cyclization of available alkynals with amines was used for the preparation of fused isoquinolines,[1–3] benzimidazoles,[4,5] 1,2-dihydroisoquinolines,[6–11] polycyclic indoles,[12] various pyrroles,[13] and functionalized isobenzofurans.[14]

Earlier we have developed an original cyclization of alk-4-ynals with various diamines, amino alcohols and amino thiols in DMSO in the presence of bases affording octahydropyrrolo[1,2-*a*]pyrimidines,[15,16] hexahydropyrrolo[1,2-*a*]imidazoles,[15,16] the corresponding fused oxazoles, oxazines and thiazoles,[17] tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazines and hexahydropyrrolo[1,2-*a*]quinazolines.[18] The reactions between alk-4-ynals and *o*-diaminoarenes as binucleophilic agents[19,20] in the NH_4Br–base–DMSO system may be regarded as a transition metal-free and stereoselective synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles. Recently, a simple selective one-pot preparation of isoindolo[2,1-*a*]benzimidazoles and benzimidazo[2,1-*a*]isoquinolines from *o*-alkynylbenzaldehydes with *o*-diaminobenzenes was described.[21]

Taking into account these promising results, we proposed that simple primary or secondary amines would react with alk-4-ynals giving new five-membered cyclic aminals with exocyclic double bond as a result of transformations including condensation of the reactants into the corresponding imine, addition of amine at the thus formed C=N bond and subsequent 5-*exo-dig*-hydroamination of the triple bond. Such compounds have high synthetic potential due to the presence of highly reactive aminal and enamine moieties with common nitrogen atom. Moreover, some of their analogues showed interesting biological activities.[22,23]

Addition of slight excess of primary aliphatic amines (*n*-propylamine, *n*-butylamine) to the solutions of aldehydes **1a–c** in dry DMSO, according to NMR spectra of reaction mixtures, leads to the corresponding imines **2a–c** in nearly quantitative yields (Scheme 1). In all cases, these compounds are formed as single stereoisomers, which most likely have sterically favoured *E*-configuration of the C=N double bond. Further addition of equimolar amounts of azoles (pyrazole, imidazole, 3,5-dimethylpyrazole and 2-methylimidazole) and 1.5-fold excess of freshly powdered KOH to the solutions of **2** followed by heating of the mixture at 100–110 °C for 1–6 h results in the full conversion of imines **2** with formation of 2-azolyl-5-arylmethylidenepyrrolidines **4a–g** in 60–75% yields based on starting aldehydes **1a–c** (see Scheme 1).[†] In all cases, compounds **4** are formed stereoselectively with *E*-configuration of the exocyclic double bond. Their identification was performed based on the 2D NOESY proton spectra, showing correlations between *ortho*-protons in arylmethylidene substituent and methylene fragment at the 4-position.

Most likely, this reaction proceeds *via* mixed aminals **3a–g** which are in equilibrium with imines **2** and azoles. Taking into



1a R^1 = Ph, R^2 = Me
1b R^1 = 2-thienyl, R^2 = Me
1c R^1 = Ph, $R^2 + R^2 = (CH_2)_5$

2a R^1 = Ph, R^2 = Me, R^3 = Pr
2b R^1 = 2-thienyl, R^2 = Me, R^3 = Pr
2c R^1 = Ph, $R^2 + R^2 = (CH_2)_5$, R^3 = Bu

3a–g

4a–g

a R^1 = Ph, R^2 = Me, R^3 = Pr, X = N, Y = Z = CH (2 h, 70%)
b R^1 = Ph, R^2 = Me, R^3 = Pr, X = N, Y = Z = CMe (2 h, 75%)
c R^1 = Ph, R^2 = Me, R^3 = Pr, X = Z = CH, Y = N (6 h, 59%)
d R^1 = Ph, R^2 = Me, R^3 = Pr, X = CMe, Y = N, Z = CH (6 h, 64%)
e R^1 = 2-thienyl, R^2 = Me, R^3 = Pr, X = N, Y = Z = CH (1 h, 68%)
f R^1 = 2-thienyl, R^2 = Me, R^3 = Pr, X = N, Y = Z = CMe (1 h, 74%)
g R^1 = Ph, $R^2 + R^2 = (CH_2)_5$, R^3 = Bu, X = N, Y = Z = CH (2 h, 73%)

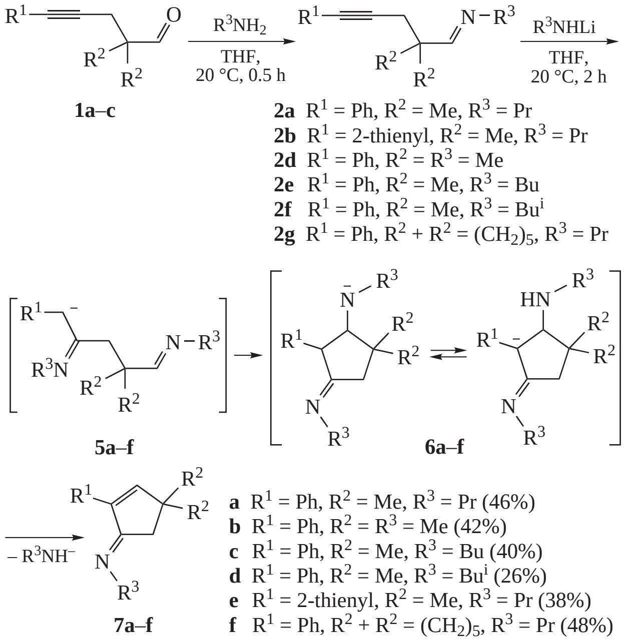
Scheme 1

[†] *Synthesis of 1-alkyl-2-azolyl-5-arylmethylidenepyrrolidines* **4a–g** *(general procedure)*. A solution of alkylamine (1.1 mmol) in anhydrous DMSO (2 ml) was slowly added to a solution of the corresponding ynal **1** (1 mmol) in DMSO (2 ml). The mixture was stirred for 1 h at room temperature, then the corresponding azole (1.1 mmol) and freshly powdered KOH (112 mg, 2 mmol) were added, and the resulting suspension was stirred in argon atmosphere at 100–110 °C for time specified in Scheme 1 (NMR monitoring). Then, DMSO was evaporated *in vacuo* (0.5–1 Torr, 80–100 °C) and the residue was extracted with Et_2O (2 × 10 ml). The combined extracts were dried over anhydrous K_2CO_3, and the solvent was evaporated. The residue was subjected to column chromatography on basic Al_2O_3 (hexane–Et_2O, 20 : 1 → 5 : 1) to give compounds **4a–g** as viscous liquids.

account that these aminals were not detected by NMR during the reaction course, it can be concluded, that this equilibrium is strongly shifted towards starting compounds and their concentration in reaction medium is low.

Attempts to involve alkylamines instead of azoles into similar transformations failed. Thus, addition of equimolar amount of *n*-propylamine or morpholine and 1.5-fold excess of freshly powdered KOH to the solution of imine **2a** in DMSO at room temperature did not cause any reaction, probably due to the lower nucleophilicity of alkylamines compared to azolyl anions. Raising temperature to 100 °C resulted in the formation of complex inseparable mixtures.

However, changing the solvent from DMSO to THF with simultaneous use of lithium *N*-alkylamides as nucleophiles brought unexpected results. Mixing equimolar amounts of ynals **1a–c** and primary amine in dry THF followed by addition of 4-fold excess of the corresponding lithium monoalkylamide at room temperature and stirring for 2 h led to iminocyclopentenes **7a–f** in moderate yields (Scheme 2).[‡] This reaction appeared to be sensitive to the steric hindrance of amine used. In case of ynal **1a** and sterically more hindered isobutylamine and lithium isobutylamide, corresponding imine **7d** was formed in only 26% yield. Similar reactions with isopropylamine and *sec*-butylamine gave only complex mixtures and the desired imines were not detected. All imines **7** were formed exclusively as *E*-isomers, which was determined from NOESY spectra showing correlations between protons in the fragment C*H*$_2$–N=C–C*H*$_2$.



Scheme 2

The suggested pathway of this transformation is presented in Scheme 2. At the first step, acetylenic imines **2a**,**b**,**d–g** are formed upon fast condensation of ynals **1** with primary amines. Thereafter, lithium alkylamide adds at the triple bond giving rise to linear anionic intermediates **5**, which are transformed into cyclic anions **6a–f** as a result of 5-*exo-trig*-cyclization with participation of C=N bond. At the final step, retro-Michael reaction occurs with elimination of alkylamide anion affording compounds **7a–f**. Note that this mechanism is in good agreement with previously suggested pathway[24] of cyclization of methyl 7-oxohept-2-ynoate with primary amines.

In summary, original stereoselective syntheses of 1-alkyl-2-azolyl-5-arylmethylidenepyrrolidines and 3-iminocyclopentenes based on previously unknown cyclizations of alk-4-ynals with primary amines and azoles under the action of bases, have been developed.

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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.2018.03.002.

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1-[(5E)-5-Benzylidene-3,3-dimethyl-1-propylpyrrolidin-2-yl]-1H-pyrazole **4a** was prepared from ynal **1a**, *n*-propylamine and pyrazole in 70% yield. ^{1}H NMR, δ: 0.60 (s, 3H, Me), 0.83 (t, 3H, Me, *J* 7.4 Hz), 1.10 (s, 3H, Me), 1.25–1.64 (m, 2H, NCH$_2$C*H*$_2$Me), 2.55 (d, 1H, =CC*H*H, *J* 14.8 Hz), 2.77 (ddd, 1H, NC*H*HCH$_2$Me, ^2J 14.1 Hz, ^3J 8.7 Hz, ^3J 5.9 Hz), 2.96 (br. d, 1H, =CCH*H*, *J* 14.8 Hz), 3.13 (ddd, 1H, NC*H*HCH$_2$Me, ^2J 14.1 Hz, ^3J 8.6 Hz, ^3J 6.4 Hz), 5.25 (br. s, 1H, PhC*H*=), 5.27 (s, 1H, NCHN), 6.28 (dd, 1H, C^{4}H, pyrazole, *J* 2.2 Hz, *J* 1.7 Hz), 6.88–6.99 (m, 1H, Ph), 7.08–7.26 (m, 4H, Ph), 7.50 (d, 1H, C^{3}H, pyrazole, *J* 1.7 Hz), 7.72 (d, 1H, C^{5}H, pyrazole, *J* 2.2 Hz). ^{13}C NMR, δ: 11.5 (NCH$_2$CH$_2$*Me*), 19.4 (NCH$_2$*C*H$_2$Me), 21.4 (Me), 27.7 (Me), 40.6 (*C*Me$_2$), 42.5, 45.6 (N*C*H$_2$CH$_2$Me, =C*C*H$_2$–), 85.6 (NCHN), 92.1 (Ph*C*H=), 105.1 (C^4, pyrazole), 122.5 (C^4, Ph), 126.1, 128.1 (C^2, C^3, C^5, C^6, Ph), 129.1 (C^5, pyrazole), 139.1 (C^3, pyrazole), 139.9 (C^1, Ph), 147.9 (PhCH=*C*). Found (%): C, 77.03; H, 8.62; N, 14.03. Calc. for $C_{19}H_{25}N_3$ (%): C, 77.25; H, 8.53; N, 14.22.

For characteristics of compounds **4b–g**, see Online Supplementary Materials.

[‡] *Synthesis of iminocyclopentenes* **7a–f** *(general procedure).* A solution of alkylamine (1.1 mmol) in anhydrous THF (2 ml) was slowly added to a solution of the corresponding ynal **1** (1 mmol) in anhydrous THF (2 ml). The mixture was stirred for 2 h at room temperature, then solution of the corresponding lithium alkylamide (4 mmol) in THF (prepared in separate flask from equimolar amounts of alkylamine and *n*-butyllithium) was added. The resulting mixture was stirred in argon atmosphere at room temperature for 2 h, then water (10 ml) and Et$_2$O (20 ml) were added, and the organic layer was separated. The aqueous layer was additionally extracted with Et$_2$O (2 × 10 ml). The combined organic layers were dried over anhydrous K$_2$CO$_3$, and the solvent was evaporated. The residue was subjected to vacuum microdistillation (in case of compounds **7a–e**) or column chromatography on basic Al$_2$O$_3$ (in case of compound **7f**).

[(1E)-4,4-Dimethyl-2-phenylcyclopent-2-en-1-ylidene]propylamine **7a** was prepared from aldehyde **1a** and *n*-propylamine and isolated in 46% yield by vacuum microdistillation (1 Torr, 100–120 °C). ^{1}H NMR, δ: 1.04 (t, 3H, NCH$_2$CH$_2$*Me*, *J* 7.3 Hz), 1.25 (s, 6H, 2Me), 1.67–1.88 (m, 2H, NCH$_2$C*H*$_2$Me), 2.50 (t, 2H, CH$_2$C=N, ^4J 1.2 Hz), 3.36 (tt, 2H, NC*H*$_2$CH$_2$Me, ^3J 7.1 Hz, ^4J 1.2 Hz), 6.79 (s, 1H, =CH), 7.27–7.44 (m, 3H, C^{3}H, C^{4}H, C^{5}H, Ph), 7.72–7.81 (m, 2H, C^{2}H, C^{6}H, Ph). ^{13}C NMR, δ: 12.3 (NCH$_2$CH$_2$*Me*), 24.1 (NCH$_2$*C*H$_2$Me), 29.0 (2Me), 40.5 (*C*Me$_2$), 43.7 (*C*H$_2$C=N), 55.8 (N*C*H$_2$CH$_2$Me), 127.6, 128.0, 128.3 (Ph), 134.0 (C^1, Ph), 141.1 (*C*=CH), 155.5 (C=*C*H), 174.3 (C=N). HRMS, *m/z*: 228.1745 [M + H]$^+$ (calc. for $C_{16}H_{21}N$, *m/z*: 228.1747).

For characteristics of compounds **7b–f**, see Online Supplementary Materials.

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