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Synthesis of 6-(arylmethylidene)octahydropyrrolo[1,2-*a*]pyrimidines and 5-(arylmethylidene)hexahydropyrrolo[1,2-*a*]imidazoles by the interaction of alk-4-ynals with α,ω-diaminoalkanes in DMSO in the presence of KOH

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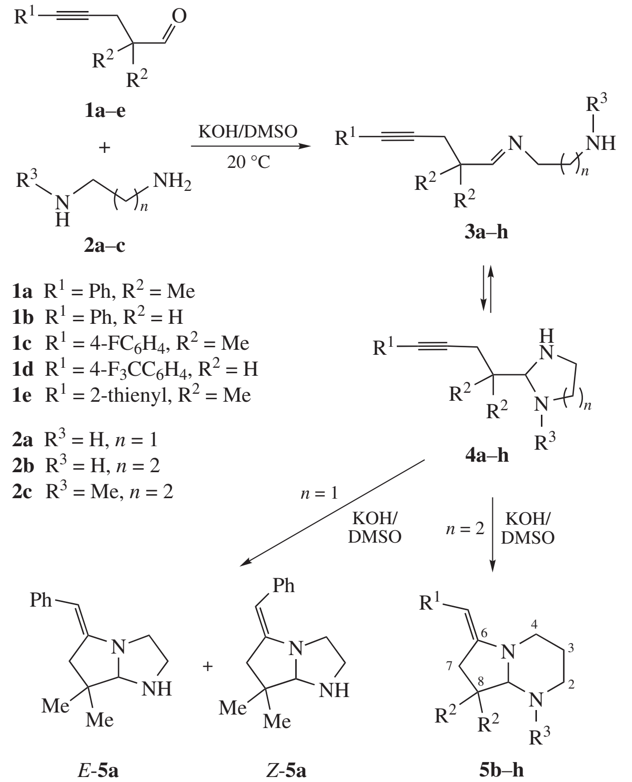
Cyclization of alk-4-ynals with α,ω-diaminoalkanes in DMSO under the action of KOH affords bicyclic *N*,*N*-enaminals – 6-(arylmethylidene)octahydro[1,2-*a*]pyrimidines and 5-(arylmethylidene)hexahydro[1,2-*a*]imidazoles.

The cyclization of available alk-4-ynals, alk-5-ynals and corresponding alkynones with amines leading to various nitrogen-containing heterocyclic compounds has been intensively studied in recent years. Thus, new approaches to the preparation of fused isoquinolines,[1–3] 1,2-dihydroisoquinolines,[4–9] various pyrroles,[10] chiral 2-alkoxy-5-methoxycarbonylmethylidenepyrrolidines[11] and the corresponding piperidines[11] have been described. Nitrogen-containing heterocycles with an endocyclic double bond were obtained in the majority of these reactions. Products with an exocyclic double bond were formed on the interaction of amines with alk-4-ynals and alk-5-ynals that contained activated triple bonds.[11] Note that such cyclizations in the presence of strong bases were not reported.

Previously, we have reported preparation of 5-methylidenehexahydropyrrolo[1,2-*a*]imidazoles and 6-methylideneoctahydropyrrolo[1,2-*a*]pyrimidines by the interaction of 1-alkynyl-1-chlorocyclopropanes with the lithium derivatives of 1,2-diaminoethane and 1,3-diaminopropane.[12,13] Compounds from these series exhibit various biological activities,[14] and they are of considerable synthetic interest[15] due to the presence of highly reactive enamine and aminal fragments with a common nitrogen atom. We found[13] that formation of these compounds occurs through the participation of the intermediate alk-4-ynylideneamines, which are the condensation products of the corresponding alk-4-ynals with diaminoalkanes. In this context, we hypothesized that the addition of acetylenic aldehydes and an appropriate strong base to these latter would perform a simple one-pot synthesis of bicyclic *N*,*N*-enaminals with an exocyclic double bond.

This supposition was completely confirmed. We found that *N*,*N*-enaminals **5a–h**[†] were formed in 42–78% yields upon the sequential addition of aldehydes **1a–e** and powdered KOH to the solutions of diaminoalkanes **2a–c** in DMSO (molar ratio amine : aldehyde : KOH of 5 : 1 : 5) (Scheme 1). The best yields were achieved in the cases of 2,2-substituted non-enolizable aldehydes **1a**,**c**,**e**.



1a–e

2a–c

3a–h

4a–h

1a R^1 = Ph, R^2 = Me
1b R^1 = Ph, R^2 = H
1c R^1 = 4-FC$_6$H$_4$, R^2 = Me
1d R^1 = 4-F$_3$CC$_6$H$_4$, R^2 = H
1e R^1 = 2-thienyl, R^2 = Me

2a R^3 = H, *n* = 1
2b R^3 = H, *n* = 2
2c R^3 = Me, *n* = 2

E-**5a** *Z*-**5a** **5b–h**

3, 4, 5	R^1	R^2	R^3	*n*	Yield of **5** (%)
a	Ph	Me	H	1	75
b	Ph	Me	H	2	77
c	Ph	Me	Me	2	78
d	Ph	H	H	2	42
e	Ph	H	Me	2	51
f	4-FC$_6$H$_4$	Me	Me	2	60
g	4-F$_3$CC$_6$H$_4$	H	Me	2	45
h	2-thienyl	Me	Me	2	58

Scheme 1

It is interesting to note high stereoselectivity of this reaction in the case of 1,3-diaminopropane **2b** and *N*-methyl-1,3-diaminopropane **2c**, which leads to corresponding octahydropyrrolo[1,2-*a*]pyrimidines **5b–h** as individual *E*-isomers. Their identification was performed based on the 2D NOESY proton spectra having correlations between the methine protons at the double bond and the protons of the methylidene fragment at 7-position. On the contrary, in the case of 1,2-diaminoethane **2a** the reaction

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[†] GLC analysis was performed on a Hewlett-Packard 5890 Series II instrument with an HP-1 capillary column (30 m × 0.153 mm) and a Hewlett-Packard 3396A automated integrator. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200p spectrometer using the solutions of test compounds in CDCl$_3$ and TMS as an internal standard. The mass spectra were measured on a Finningan DSQ II GC-MS instrument.

Starting aldehydes **1a**,**c**,**e** were prepared by the interaction of isobutyraldehyde with the corresponding 3-aryl-1-chloroprop-2-ynes under phase-transfer catalysis conditions.[16] Pd(PPh$_3$)$_2$Cl$_2$-catalyzed cross-coupling of aryl iodides with pent-4-yn-1-ol followed by pyridinium chlorochromate oxidation was used to prepare α-unsubstituted aldehydes **1b**,**d**.

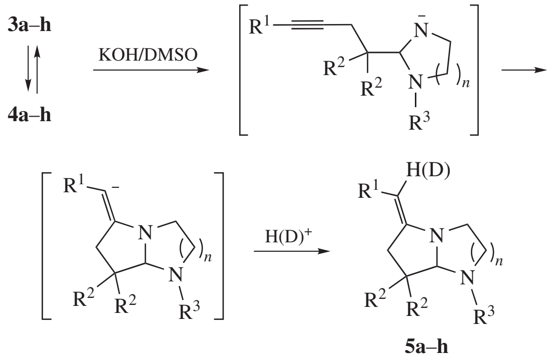
proceeds less selectively, and corresponding product **5a** is formed as a mixture of *E*- and *Z*-isomers in a ratio of 5 : 1.

The structure of the diamine used had a considerable effect on the rate of this reaction. Thus, in the case of 1,2-diaminoethane and 1,3-diaminopropane, the reaction with all aldehydes **1** was complete in 2 h, whereas analogous processes with *N*-methyl-1,3-diaminopropane occurred more slowly and required 10–15 h.

Studying of these reactions in DMSO-d_6 with periodical checking of the reaction mixture by NMR spectroscopy showed that an equilibrium mixture of linear imine **3a** and cyclic aminal **4a** in a ratio that strongly depends on temperature (1 : 5.5 at 23 °C and 1 : 2.3 at 50 °C) was quantitatively formed on the addition of aldehyde **1a** to a fivefold molar amount of 1,2-diaminoethane at room temperature in a short time (10–20 min).

Upon the interaction of aldehyde **1a** with *N*-methyl-1,3-diaminopropane **2c** only linear product **3c** was detected in the reaction mixture, whereas the exclusive formation of cyclic aminal **4e** was observed in an analogous reaction with α-unsubstituted aldehyde **1b**. It is most likely that this difference was due to the steric effect of two methyl groups, which prevents the cyclization of imine **3c** into corresponding aminal **4c** and strongly shifts the equilibrium toward imine **3c**. In all cases, the reaction mixtures were analyzed by comparing their NMR spectra with the spectra of corresponding adducts **3** and **4**, which were independently prepared by the reactions of aldehydes **1a**,**b** with diamines **2a**,**c** in CH_2Cl_2 in the presence of Na_2SO_4.

Stirring the products of the reaction of aldehydes **1a**,**d** and diamines **2a**,**c** with freshly powdered KOH resulted in the disappearance of signals of compounds **3** and **4** and the appearance of the signals of corresponding aminals **5**. In this case, in all experiments performed in DMSO-d_6, the integral intensity of the signal, corresponding to the methine proton at a double bond in the NMR spectra of products **5** was much lower than the calculated value, which suggests a considerable degree of deuteration at this position. Since we showed in special experiment that the stirring of compound **5c** with KOH in DMSO-d_6 at room temperature did not lead to deuterium exchange, it can be concluded that the final step of the studied reaction – the intramolecular addition of the amino group to the triple bond – has a considerably ionic character and occurs in accordance with Scheme 2.



Scheme 2

The proposed new methodology for synthesis of bicyclic *N*,*N*-enaminals **5** has several advantages in comparison with previously described[12,13] approach. First of all, the scope of the present reaction is much wider, allowing obtaining products (**5d**,**e**,**g**) without substituents in α-position to the carbon atom of NCHN-fragment, as well as N-substituted enaminals **5c**,**e–h** as single entity. Moreover, this reaction does not demand using organometallic reagents and absolute conditions, providing better yields of target products.

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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.2013.05.006.

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Synthesis of bicyclic aminals **5a–h** *from acetylene aldehydes* **1a–e** *and diamines* **2a–c** *(general procedure).* A solution of 1 mmol of aldehyde **1** in 3 ml of DMSO was slowly added with stirring to a solution of diamine **2** (5 mmol) in 3 ml of anhydrous DMSO. The resulting mixture was stirred for 30 min at room temperature; thereafter, 280 mg (5 mmol) of freshly powdered KOH was added, and the resulting suspension was stirred for 2–10 h until the completion of reaction (GLC or NMR monitoring). Then, 30 ml of water and 30 ml of CH_2Cl_2 were added, and the organic layer was separated. The aqueous layer was additionally extracted with dichloromethane (3×10 ml). The combined organic layers were washed four times with water and dried with anhydrous K_2CO_3, and the solvent was evaporated. The residue was subjected to recrystallization or column chromatography to give a target product, which was one of the corresponding aminals **5a–h** with >95% purity according to NMR data and elemental analysis.

*5-Benzilydene-7,7-dimethylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole* **5a** was prepared from aldehyde **1a** and 1,2-diaminoethane **2a** as a mixture of *E*- and *Z*-isomers (a ratio of 5 : 1) and isolated in 75% yield by chromatography on neutral Al_2O_3 [hexane–diethyl ether (5 : 1) as eluent].

*(*E*)-6-Benzilydene-8,8-dimethyloctahydropyrrolo[1,2-*a*]pyrimidine* **5b** was prepared from aldehyde **1a** and 1,3-diaminopropane **2b** and isolated in 77% yield by recrystallization from hexane.

*(*E*)-6-Benzilydene-1,8,8-trimethyloctahydropyrrolo[1,2-*a*]pyrimidine* **5c** was prepared from aldehyde **1a** and *N*-methyl-1,3-diaminopropane **2c** and isolated in 78% yield by recrystallization from hexane.

Spectroscopic data for compounds **5a–c** are consistent with published data.[13]

For characteristics of compounds **5d–h**, see Online Supplementary Materials.