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Diversifying the superbase-catalyzed C=N bond ethynylation: triaryl-1-pyrrolines and triaryl-1*H*-pyrroles from *N*-benzyl aldimines and arylacetylenes

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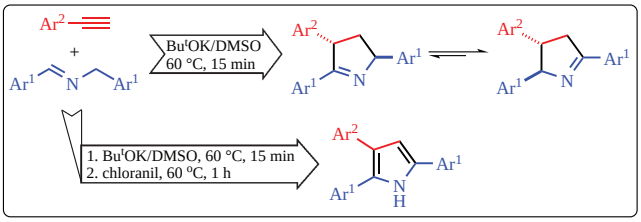
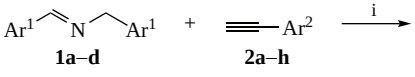
***N*-Benzyl aldimines react with arylacetylenes in the presence of Bu^{t}OK/DMSO superbase system to afford 2,3,5-triaryl-1-pyrrolines as two tautomers with 1,2- and 1,5-location of the double bond, both being the *trans*-diastereomers. This version of the C=N bond ethynylation differs from the previous one with *N*-benzyl ketimines. The oxidation of the pyrroline tautomeric mixtures without their isolation gives 2,3,5-triaryl-1*H*-pyrroles.**



Keywords: acetylenes, imines, superbases, ethynylation, vinylation, pyrroles, pyrrolines.

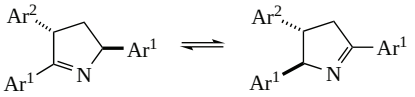
The superbase-catalyzed C=N bond ethynylation (analogue of the Favorsky C=O bond ethynylation)[1] discovered in 2018[2] now received a rapid development owing to its obvious synthetic advantages such as mild transition metal-free conditions, available inexpensive catalytic systems and starting materials, one-pot implementation, energy- and resource-saving, and, particularly, its divergent character. The latter is expressed by metamorphosing into essentially other reactions upon changing the structure of the starting C=N bond compounds. Indeed, apart from the normal preparation of propargylic amines from aryl ketimines and acetylenes,[2] the efficient syntheses of 1-azadienes from aldimines and arylacetylenes,[3] 2-azadienes from *N*-benzyl ketimines and acetylene gas,[4] 1-pyrrolines and 2*H*-pyrroles from *N*-benzyl ketimines and arylacetylenes[5] were elaborated.



1a–d **2a–h**

a Ar^1 = Ph
b Ar^1 = 4-MeC_6H_4
c Ar^1 = 4-$MeOC_6H_4$
d Ar^1 = 4-FC_6H_4

a Ar^2 = Ph
b Ar^2 = 3-MeC_6H_4
c Ar^2 = 4-MeC_6H_4
d Ar^2 = 4-PhC_6H_4
e Ar^2 = 3-$MeOC_6H_4$
f Ar^2 = 3-FC_6H_4
g Ar^2 = 4-FC_6H_4
h Ar^2 = 3-pyridyl



3a–k **3′a–k**

a Ar^1 = Ar^2 = Ph, 45% (18 : 82)[a]
b Ar^1 = 4-MeC_6H_4, Ar^2 = Ph, 51% (20 : 80)[a]
c Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph, 55% (18 : 82)[a]
d Ar^1 = 4-FC_6H_4, Ar^2 = Ph, 21% (11 : 90),[a] [72%][b]
e Ar^1 = Ph, Ar^2 = 3-MeC_6H_4, 45% (18 : 82)[a]
f Ar^1 = Ph, Ar^2 = 4-MeC_6H_4, 48% (17 : 83)[a]
g Ar^1 = Ph, Ar^2 = 4-PhC_6H_4, 41% (17 : 83)[a]
h Ar^1 = Ph, Ar^2 = 3-$MeOC_6H_4$, 21% (17 : 83),[a] [90%][b]
i Ar^1 = Ph, Ar^2 = 3-FC_6H_4, 36% (12 : 88),[a] [98%][b]
j Ar^1 = Ph, Ar^2 = 4-FC_6H_4, 36% (17 : 83),[a] [89%][b]
k Ar^1 = Ph, Ar^2 = 3-pyridyl, 25% (18 : 82),[a] [87%][b]

Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, DMSO, 60 °C, 15 min. [a] **3**/**3′** Molar ratio (according to ^{1}H NMR). [b] Conversion of starting aldimine.

In this communication, we share with the results obtained during further diversification of ethynylation of *N*-benzyl imines. When *N*-benzylaryl aldimines **1** were taken instead of the *N*-benzylaryl ketimines for the reaction with arylacetylenes **2**, the process again proceeded differently, namely, delivering 2,3,5-triaryl-1-pyrrolines as two tautomers with 1,2- and 1,5-location (**3** and **3′**, respectively) of the double bond in average ratio of ~1 : 4 in 20–55% total yields (Scheme 1). At the same time, in the case of the corresponding ketimines, the pyrrolines were isolated in much higher yields (43–91%) with only 1,5-location of the double bond and as two diastereomers.[5] Another distinctive feature of this new version was its diastereoselectivity: both isomeric pyrrolines **3** and **3′** were formed exclusively as *trans*-diastereomers.

The selected representative experiments on the reaction optimization (for the model benzyl phenyl aldimine **1a** and phenylacetylene **2a**) are listed in the Table 1. The best result was achieved when the reaction was carried out in the presence of 20 mol% Bu^{t}OK/DMSO superbase system at 60 °C for 15 min, the total yield of pyrrolines **3a** and **3′a** being 45% (both being one *trans*-diastereomer).

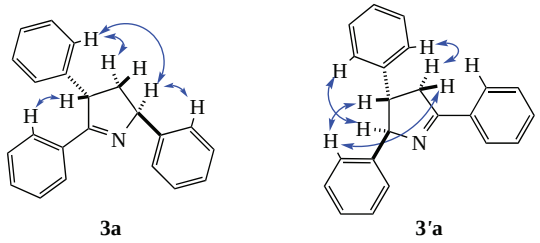
The structure and stereochemistry of pyrrolines **3a** and **3′a** were established by NMR spectroscopy (^{1}H, ^{13}C, ^{15}N) including 2D techniques [NOESY (Figure 1), COSY, HSQC, HMBC].

The optimized conditions thereby determined were extended over other combinations of aryl benzyl aldimines **1b–d** and arylacetylenes **2b–h** and were found to be suitable to prepare a number of diastereomerically pure pyrrolines **3**, though as mixtures of two tautomers, which were not easily separable (see

Table 1 Influence of the reaction conditions on the yield of pyrrolines **3a** and **3′a**.[a]

Entry	Base	T/°C	t/min	Conversion of **1a** (%)[b]	Total yield of **3a** + **3′a** (%)[b]
1	Bu^{t}OLi	60	15	59	7
2	Bu^{t}OLi	60	30	71	10
3	Bu^{t}ONa	60	15	100	40
4	Bu^{t}ONa	60	30	100	34
5	Bu^{t}OK	60	5	100	40
6	Bu^{t}OK	60	15	100	45
7	Bu^{t}OK	60	30	100	35
8	Bu^{t}OK	40	15	99	27
9	Bu^{t}OK	40	30	100	25
10	Bu^{t}OK	80	5	100	31
11	KOH	60	15	87	28
12	KOH	60	30	96	23

[a] Conditions: **1a** (1 mmol), **2a** (1 mmol), Bu^{t}OK (0.2 mmol), DMSO (3 ml).
[b] Isolated yield after column chromatography (SiO_2, hexane / EtOAc, 20 : 1). According to ^{1}H NMR, **3** / **3′** molar ratio was ~1 : 4 for each experiment.

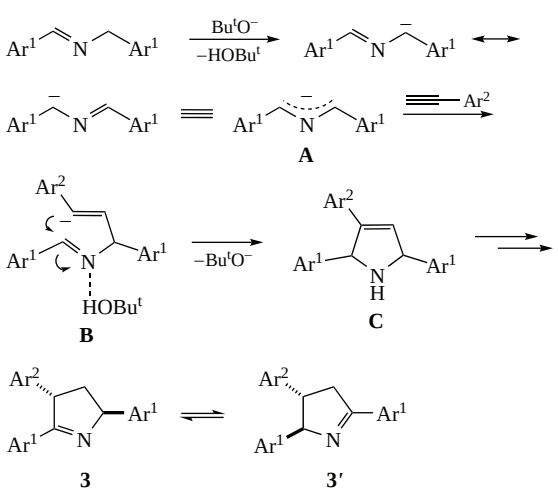


3a **3′a**

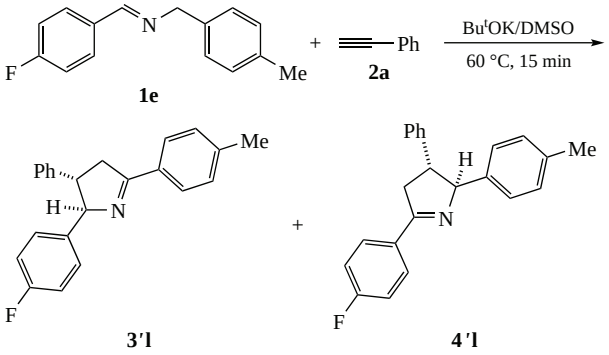
Figure 1 Main NOESY correlations for compounds **3a** and **3′a**.

Scheme 1). The substituent effect on the reactants conversion and the product yields is not clearly expressed obviously due to the complex interactions of mutually related lone electron pairs-, charges-, and proton transfers during the realization of this concerted [3 + 2] cycloaadition reaction.

Apparently, the reaction mechanism (Scheme 2) involves azaallyl anions **A** generated by the proton abstraction from the starting *N*-benzylaryl aldimines **1**. In the case of the same aryl substitutents in benzyl aldimine moieties, these anions are symmetrical (with charge distribution evenly over two carbons) and, hence, can further react by both anionic sides in equal probability. The rate-determining reaction assumedly is the nucleophilic addition of anions **A** to the triple bond of non-ionized arylacetylenes **2**, the concentration of which should be much higher compared to anions **A** since the acidity of *N*-benzyl



Scheme 2



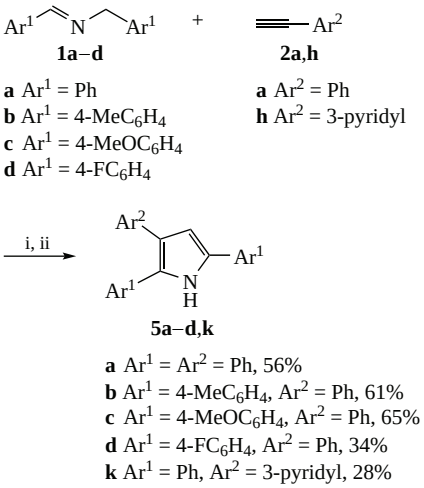
Scheme 3

imines (pK_a ~24)[6] is by 4–5 order greater than that of arylacetylenes (pK_a for phenylacetylene 28.8).[7] The carbanionic species **B**, classic intermediates of the vinylation reaction,[8] attack (upon emerging) in a concerted manner of the electrophilic carbon atom of the aldimine moiety to close the pyrroline cycle accompanied by the electrophilic assistance from external proton (from Bu^{t}OH or arylacetylene). The intermediate pyrrolines **C** rearrange, through a number of proton transfers, to final tautomeric mixtures of pyrrolines **3** and **3′**. The predominance of tautomer **3′** with 1,5-location of the double bond can be explained by the repulsive interaction between *ortho*-protons of the phenyl substituents that should be stronger in minor tautomer **3** (with 1,2-location of the double bond) because of its more rigid planar conformation in the vicinity of position C2. The same steric factor is a plausible cause for the reaction diastereoselectivity. The concerted manner of the cyclization follows from the fact that no open chain products, like 2-azadienes,[4] were detected in the reaction mixture. Such species should necessarily be formed if the intermediates **B** were kinetically independent particles because they should be inevitably intercepted by protons (from Bu^{t}OH or arylacetylene). Thus, we face here a kind of allyl anion-mediated (vicarious) ethynylation of the C=N bond. The formation of the tautomeric mixture **3** and **3′** (~1 : 4) is a thermodynamic result. This follows from the fact that the keeping of pure pyrroline **3′a** (major tautomer) under the reaction conditions leads to the formation of two tautomers in the same ratio.

The substituent effects in aldimines **1** and acetylenes **2**, though not too strong, are in keeping with the above mechanism. Actually, the donor substituents in aldimines (4-MeC_6H_4, 4-MeOC_6H_4) slightly increase the yields of pyrrolines **3b**,**c** (see Scheme 1), while the acceptor substituent (4-FC_6H_4) acts in opposite direction. This supports the rate-determining attack of anions **A** at the triple bond (see Scheme 2). The acceptor substituents in acetylenes **2** (3-MeOC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3-pyridyl) reduce the final product yields. Such, on the first glance, an unexpected result, is likely due to a greater ionization of acetylene moieties because of their higher acidity, hence a lager concentration of acetylide anions, inactive toward the nucleophilic attack.

When the starting *N*-benzyl aryl aldimines have different aryl substituents, the triple bond is attacked predominantly by the most nucleophilic carbanionic site that results in formation of two different pyrrolines, albeit each as pure diastereomer. As an example, for aldimine **1e**, the expected isomers **3′l** and **4′l** were obtained in 35% total yield in 1.2 : 1.0 ratio (^{1}H NMR) with the prevailing of the isomer produced from the attack by the carbanionic site adjacent to the tolyl substituent (Scheme 3).

In some experiments, the reaction mixtures contained small amounts of 2,3,5-triaryl-1*H*-pyrroles implying an easy aromatization (oxidation) of the pyrrolines formed. The oxidation of the pyrroline tautomeric mixtures without their isolation from



1a–d **2a,h**

a Ar^1 = Ph
b Ar^1 = 4-MeC_6H_4
c Ar^1 = 4-$MeOC_6H_4$
d Ar^1 = 4-FC_6H_4

a Ar^2 = Ph
h Ar^2 = 3-pyridyl

5a–d,k

a Ar^1 = Ar^2 = Ph, 56%
b Ar^1 = 4-MeC_6H_4, Ar^2 = Ph, 61%
c Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph, 65%
d Ar^1 = 4-FC_6H_4, Ar^2 = Ph, 34%
k Ar^1 = Ph, Ar^2 = 3-pyridyl, 28%

Scheme 4 *Reagents and conditions*: i, Bu^tOK, DMSO, 60 °C, 15 min; ii, chloranil, 60 °C, 1 h.

the reaction products gave 1*H*-pyrroles **5** in 20–65% yields (Scheme 4). Thus, a novel one-pot synthesis of 2,3,5-triaryl-1*H*-pyrroles from available *N*-benzyl aryl aldimines and arylacetylenes has been found.

In conclusions, the new version of superbase-catalyzed *N*-benzyl aldimine ethynylation opens a short-cut to diastereomerically pure 2,3,5-triaryl-1-pyrrolines and triaryl-1*H*-pyrroles, so far not readily accessible.[9]

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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.2023.01.007.

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