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Base-Catalyzed [3 + 2] Cycloaddition of *N*-Benzyl Ketimines to Arylacetylenes Followed by Oxidation: A One-Pot Access to Polyarylated 2*H*-Pyrroles via Intermediate Pyrrolines

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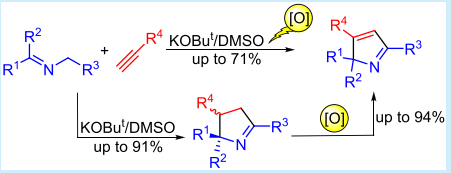
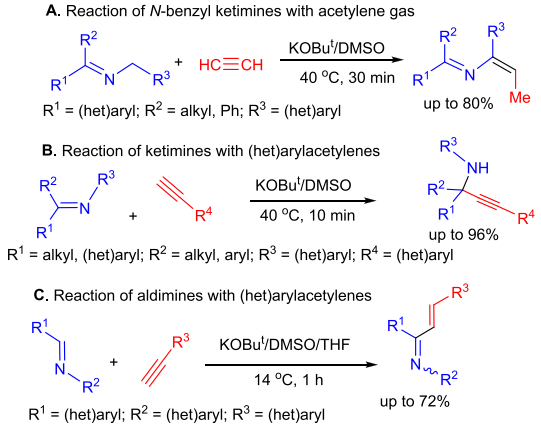
ABSTRACT: *N*-Benzyl ketimines undergo [3 + 2] cycloaddition with arylacetylenes in the KOBu^t/DMSO solution to 2,3,5-triarylpyrrolines, which are oxidized (chloranil, DDQ) in situ to 2,3,5-triaryl-2*H*-pyrroles in 53−71% yields. The intermediate 1-pyrrolines can be isolated in 31−91% yields and separately oxidized to the corresponding 2*H*-pyrroles.



Benzyl ketimines are known to be versatile building blocks for the construction of complex nitrogen-containing heterocycles[1] due to their ability of generating, under the action of strong bases, azaallyl anions, which represent highly active multifaceted intermediates, widely applied in organic synthesis for various carbon−carbon and carbon−heteroatom bond-forming processes.[1]

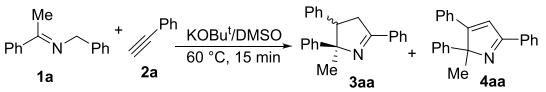
Recently,[2] we have shown that *N*-benzyl ketimines react with acetylene gas in the strong basic KOBu^t/DMSO solution ($pK_a \approx 35$)[3] to stereoselectively afford 1,3-diaryl-2-azapentadienes (Scheme 1A). Earlier,[4] we have reported that ketimines in the same superbasic medium are added to arylacetylenes as C_{sp}-centered carbanions to deliver propargylamines (Scheme 1B). Arylaldimines under similar conditions are formally CH-vinylated with arylacetylenes to 1,2,4-triaryl-1-azabutadienes (Scheme 1C).[5]

Scheme 1. Previous Works



In the light of this knowledge, when conceiving the study of the reaction between *N*-benzyl ketimines and arylacetylenes, which is here reported, we have expected to obtain either the above azadienes or propargylamines. To our surprise, none of these compounds were present in the reaction mixture after the reaction of *N*-benzyl ketimine **1a** with phenylacetylene **2a** in the KOBu^t/DMSO solution. Instead, 2,3,5-triphenylpyrroline **3aa** and small amounts of its oxidized form, 2*H*-pyrrole **4aa**, were detected, meaning that we serendipitously encountered an example of another reaction, which can be defined as [3 + 2] cycloaddition of ketimines to acetylenes (Scheme 2). Importantly, the content of 2*H*-pyrrole **4aa** was noticeably increased upon aeration of the reaction mixture.

Scheme 2. KOBu^t/DMSO-Catalyzed [3 + 2] Cycloaddition of Ketimine 1a to Acetylene 2a



Previously,[6] the [3 + 2] cycloaddition between lithium 1,3-diphenyl-2-azaallyl anions and 1,4-diphenylbutadiyne to form 2,5-dihydro-1*H*-pyrrole was reported by Vo-Quang and Vo-Quang (Scheme 3).

This pyrroline structure differs from pyrroline **3aa** probably because of substantial differences of substrate structures and reaction conditions.

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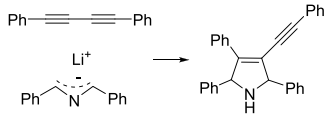
Scheme 3. Cycloaddition of 1,3-Diphenyl-2-azaallyl Anions to 1,4-Diphenylbutadiyne[6]



It is relevant to emphasize that polyarylated 2*H*-pyrroles are of special interest because of their unique structural architecture and applications as precursors in heterocyclic synthesis.[7] Despite the many efforts invested to the development of methodology for the preparation of polyarylated 2*H*-pyrroles, creation of compound libraries of this class remains a challenge.[7,8] In view of steady interest in 2*H*-pyrroles, especially polyarylated ones,[8] we have attempted to optimize the reaction found first in relation to the synthesis of 2*H*-pyrroles. The optimization was implemented using the same substrates pair (**1a** + **2a**). Several selected representative results of these experiments are collected in Table 1.

Table 1. Optimization of 2*H*-Pyrrole 4aa Synthesis from Ketimine 1a and Acetylene 2a (Scheme 2)[a]

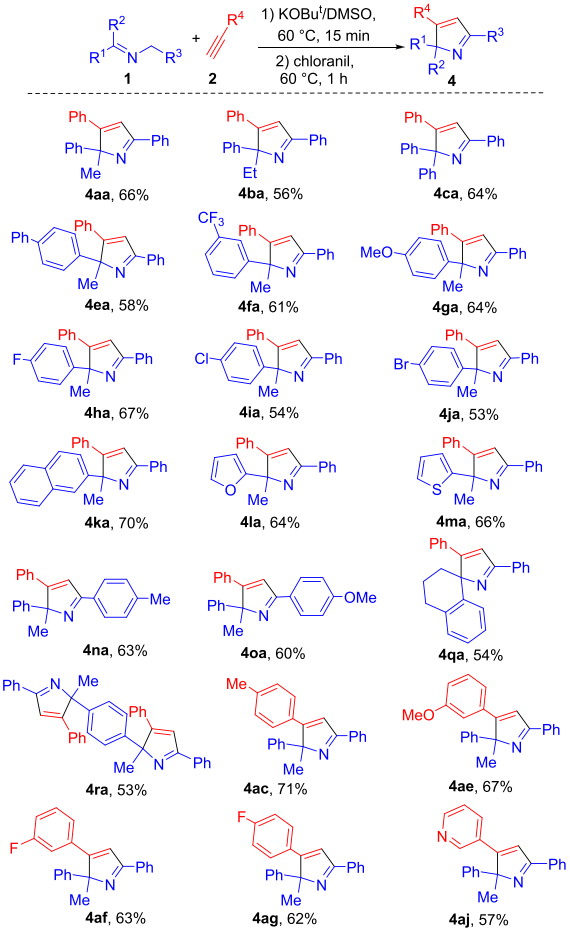
entry	**1a**/KOBu^t molar ratio	oxidant	yield of **3aa** (%)[b]	yield of **4aa** (%)[b]
1	1:1	no	71	traces
2	1:0.2	air[c]	70	traces
3	1:1	air[c]	36	14
4	1:1	air[d]	22	20
5	1:0.2	oxygen[c]	68	traces
6	1:1	oxygen[c]	47	6
7	1:0.2	chloranil[e]	traces	65
8	1:0.2	DDQ[e]	traces	66

[a]Conditions: **1a** (1 mmol), **2a** (1 mmol), KO^{t}Bu, DMSO (3 mL), 60°C, 15 min. [b]Isolated yield after column chromatography (SiO_2, *n*-hexane/ethyl acetate, 20:1). [c]Bubbling of air (oxygen) for 1 h. [d]Bubbling of air for 2 h. [e]1 mmol, 1 h.

The reaction was carried out as follows: the reactants (**1a** + **2a**) were stirred in KOBu^t/DMSO solution at 60°C for 15 min. The reaction mixture turned reddish-purple right after the reactants contacted, indicating the generation of azaallyl anions.[1b] The color was gradually fading to brown during the reaction. Next, oxidation on air (oxygen, chloranil, DDQ) was employed, and the reaction mixture was stirred at the same temperature for 1−2 h more. The oxidation with air allowed 2*H*-pyrrole **4aa** to be synthesized in a yield of not higher than 20% (1 equiv of KOBu^t, 2 h, entry 4). With pure oxygen passing through the reaction mixture with 0.2 equiv of the base, the yield of pyrroline **3aa** was 68%, and 2*H*-pyrrole was formed in traces (entry 5), while with 1 equiv of KOBu^t, the yield of **3aa** dropped to 47%, and the yield of **4aa** was found to be 6% (entry 6). The application of chloranil or DDQ (entries 7, 8) as oxidants resulted in almost quantitative oxidation of pyrroline **3aa** to 2*H*-pyrrole **4aa** for 1 h (65 and 66% yield, respectively), which is in agreement with the literature data concerning oxidation of pyrrolines[9] and pyrrolidines[10] to 2*H*-pyrroles. Under the conditions studied, the possible oxidation of dimsyl anion was not observed.

Next, to assess the scope of the reaction, we have transferred the best conditions found for the synthesis of 2*H*-pyrrole **4aa** to other pairs of benzyl ketimines and arylacetylenes with different combinations of the substituents. As follows from Scheme 4, a number of 2*H*-pyrroles **4** with diverse aryl substituents were obtained in 53−71% yield. The reaction

Scheme 4. Synthesis of 2*H*-Pyrroles[a]



[a]Conditions: **1** (1 mmol), **2** (1 mmol), KOBu^t (0.2 mmol), DMSO (3 mL), chloranil (1 mmol). Isolated yields after column chromatography (SiO_2, *n*-hexane/ethyl acetate, 10:1) are given.

tolerates a considerable structural diversity of *N*-benzyl ketimines covering substituted aromatic, heteroaromatic, and condensed aromatic moieties. Among functionalities in the benzene ring are Ph, CF_3, F, Cl, Br, and OMe substituents. Ketimine **1c**, a derivative of benzophenone, when reacted with phenylacetylene **2a**, gave 2,2,3,5-tetraphenyl-2*H*-pyrrole **4ca**, thereby evidencing suitability of the reaction also for the synthesis of tetraaryl-substituted 2*H*-pyrroles. 1,4-Bispyrrolyl benzene **4ra** was synthesized in 53% yield from diketimine **1r** (adduct of 1,4-diacetyl benzene and benzylamine). The reaction proceeded well with several aryl- and hetarylacetylenes with the donor and acceptor substituents in the benzene ring, the yields of the corresponding 2*H*-pyrroles **4ac**−**aj** being 57−71%.

As it is clear, the synthesized 2*H*-pyrroles **4** are formed by oxidation of the intermediate pyrrolines, the products of superbase-catalyzed [3 + 2] cycloaddition of benzyl ketimines to arylacetylenes. These intermediates, apart from their mechanistic importance, arouse self-standing interest as a valuable class of pyrrole compounds, promising targets for synthetic and biochemistry. Indeed, the 1-pyrroline core is widespread in natural products[11] and living organisms,[12]

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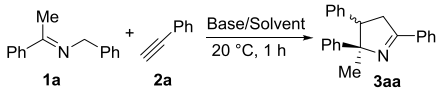
mainly in the form of hemes,[12a] chlorophylls,[12] and alkaloids.[13] 1-Pyrrolines could be used as templates of new drugs,[14] as building blocks for construction of light-driven switches[15] and boranil fluorophores,[16] and as rewarding valuable synthons toward biologically active compounds.[17] Therefore, the next move of our investigation was focused on the formation of these intermediates.

For continuation of the study, we stayed with the same reference pair (**1a** + **2a**), which was further employed for optimization of the initial reaction step. A combination of alkali metal hydroxides or alkoxides with different solvents was tried. The selected results (Table 2) showed that the best systems

Table 2. Effect of Base/Solvent Combination on the Yields of Pyrroline 3aa Formed from Ketimine 1a and Acetylene 2a[a]



entry	base	solvent	conversion of **1a** (%)[b]	yield of **3aa** (%)[c]
1	NaOH	DMSO	73	traces
2	KOH	DMSO	97	48
3	LiOBu^t	DMSO	96	42
4	NaOBu^t	DMSO	100	74
5	KOBu^t	DMSO	100	71
6	NaOBu^t	DMF	97	34
7	NaOBu^t	NMP	15	traces
8	NaOBu^t	THF	28	traces
9	LDA	THF	2	none

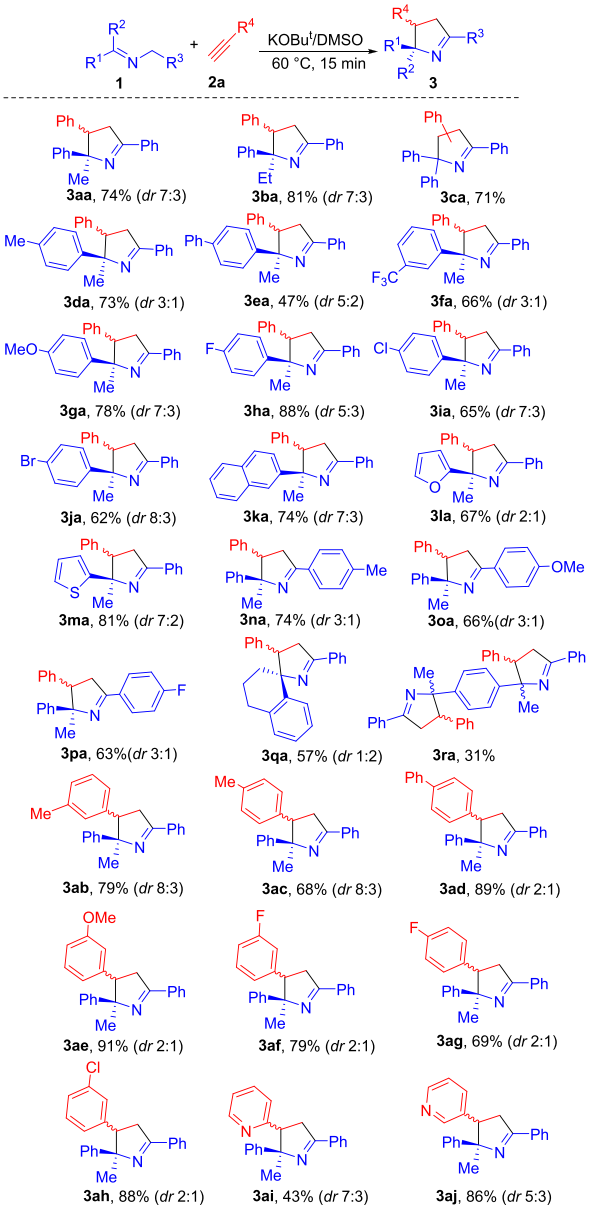
[a]Conditions: **1a** (1 mmol), **2a** (1 mmol), base (1 mmol), solvent (3 mL), 20 °C, 1 h. [b]According to ^{1}H NMR data of the crude product (*n*-dodecane was used as an internal standard). [c]Isolated yield after column chromatography (SiO_2, *n*-hexane/ethyl acetate, 20:1). LDA = Lithium diisopropylamide.

proved to be superbase pairs NaOBu^t/DMSO and KOBu^t/DMSO securing 74 and 71% yields of the target pyrroline **3aa** at 20 °C for 1 h (**1a**/MOBu^t molar ratio = 1:1, entries 4, 5), whereas other base/solvent combinations were less active or inactive at all. Analysis of the ^{1}H NMR spectra of pyrroline **3aa** indicated the formation of two diastereomers.

Further on using NaOBu^t/DMSO and KOBu^t/DMSO as the best superbase pairs, we have carefully examined the effects of their concentration, reaction temperature, and time on the process efficiency (see the SI for details, Tables S1, S2). Arbitrarily optimized conditions of the synthesis can be accepted: equimolar ratio of imine **1a** and acetylene **2a**, 3 mL of DMSO, 0.2 mmol of KOBu^t per 1 mmol of **1a**, 60 °C, 15 min. These conditions ensure ~100% conversion of the starting imine **1a** and 75% yield of pyrroline **3aa**. In fact, the reaction is highly selective: no products except for the target pyrroline **3aa** are detectable in the reaction mixture (^{1}H NMR).

With the provisionally optimum conditions established, we have investigated the substrate scope for the synthesis of pyrrolines **3** via [3 + 2] cycloaddition of imines **1** to acetylenes **2**. As follows from Scheme 5, the synthesis was successfully extended over a number of ketimines derived from aryl alkyl ketones (including condensed aromatic and heteroaromatic ones) and benzylamines to produce pyrrolines **3aa**−**ra** in good yields. The process tolerated also diketimine **1r** (derived from 1,4-diacetyl benzene and benzylamine), with bispyrrolenyl

Scheme 5. Synthesis of 1-Pyrrolines[a]



[a]Conditions: **1** (2 mmol), **2** (2 mmol), KOBu^t (0.4 mmol), DMSO (6 mL). Isolated yields after column chromatography [SiO_2, *n*-hexane/ethyl acetate = 10:1 (for **3aa**−**3ah**); *n*-hexane/ethyl acetate = 1:1 (for **3ai**, **3aj**)] are given.

benzene **3ra** being obtained in 31% isolated yield. Ketimine **1c** reacted with phenylacetylene **2a** to form two regioisomers in a 7:1 ratio. The minor 4-Ph-regioisomer is likely formed via the addition of the more hindered site of the 2-azaallyl anion to phenylacetylene.[1]

The experiments have demonstrated that the reaction is applicable to a series of aryl- and hetarylacetylenes **2a**−**j**, the yields of the corresponding pyrrolines **3ab**−**aj** reaching 91% (Scheme 4). The reaction of *N*-benzyl ketimine **1a** with internal acetylene (diphenylacetylene) did not take place under the standard conditions.

The diastereomeric ratio of the products **3** ranged from 3:1 to 2:1 with the predominance of the (2*R**,3*R**)-isomer. In all cases, the diastereomers were separated by column chromatography and fully characterized.

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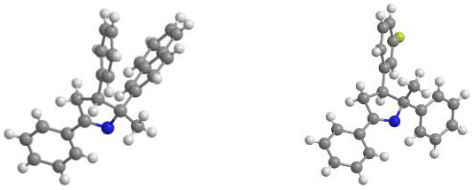
The structure and stereochemistry of pyrrolines **3** were established by NMR spectroscopy (^{1}H, ^{13}C, ^{15}N) including 2D techniques (NOESY, COSY, HSQC, HMBC) and were also confirmed by single-crystal X-ray analysis of (2*R**,3*R**)-**3ka** and (2*R**,3*S**)-**3af** (Figure 1).

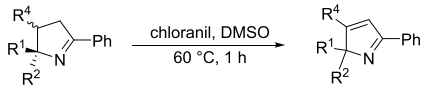


(2*R**,3*R**)-**3ka** (2*R**,3*S**)-**3af**

Figure 1. X-ray structures (from ethyl ether; CCDC 2070913, 2070914).

Expectedly, pure pyrrolines, e.g., **3aa**−**aj**, are readily oxidized to afford the 2*H*-pyrroles **4aa**−**aj** in high yields (Scheme 6), which implies the effective conversion of all synthesized pyrrolines to the corresponding 2*H*-pyrroles.

Scheme 6. Oxidation of Pyrrolines 3 to 2*H*-Pyrroles 4

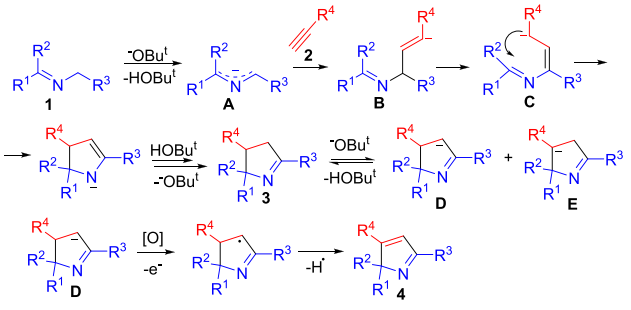


3aa: R^1=R^4=Ph, R^2=Me
3ca: R^1=R^2=R^4=Ph
3ma: R^1=2-Thienyl, R^2=Me, R^4=Ph
3af: R^1=Ph, R^2=Me, R^4=3-FC_6H_4
3aj: R^1=Ph, R^2=Me, R^4=3-Pyridyl

4aa: R^1=R^4=Ph, R^2=Me (87%)
4ca: R^1=R^2=R^3=R^4=Ph (83%)
4ma: R^1=2-Thienyl, R^2=Me, R^4=Ph (91%)
4af: R^1=Ph, R^2=Me, R^4=3-FC_6H_4 (94%)
4aj: R^1=Ph, R^2=Me, R^4=3-Pyridyl (88%)

Thus, a general mechanistic picture for the synthesis of 2*H*-pyrroles **4** via pyrrolines **3** by superbase-catalyzed [3 + 2] cycloaddition of *N*-benzyl ketimines **1** to arylacetylenes **2** can be represented as follows. The reaction includes the addition of deprotonated *N*-benzyl ketimines (azaallyl anions **A**) to the triple bond followed by isomerization of carbanions **B** into the conjugated carbanions **C** and their cyclization to pyrrolines **3**. The latter, after addition of an oxidant (chloranil, DDQ), are transformed to the corresponding 2*H*-pyrroles **4** likely via carbanion **D** (Scheme 7).

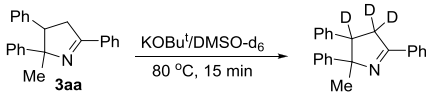
Scheme 7. Tentative Mechanism



If, according to ref 5, the reaction starts with the addition of acetylide anions to the C=N bond, then another regioisomeric pyrroline (with R^4 in the position 4) would be formed.

The formation of intermediate carbanions **D** and **E** is supported by exchange of protons in the positions 3 and 4 of pyrroline **3aa** for deuterium (Scheme 8) in DMSO-d_6 with 1 equiv of KOBu^t. The incorporation of deuterium (^{1}H NMR) in the positions 3 and 4 of pyrroline **3aa** was quantitative.

Scheme 8. Deuterium Exchange in Pyrroline 3aa



The concerted [3 + 2] cycloaddition seems to be also probable, though in such case less sterically hindered 4-Ph regioisomers might be formed, but experimentally, the latter were not observed.

To check electron-transfer/radical pathways as a possible channel in the reaction mechanism, the reaction of ketimine **1n** with phenylacetylene **2a** in the presence of TEMPO (20 mol %), a typical radical scavenger, was carried out under the standard conditions. As a result, pyrroline **3na** was isolated in 69% yield (without TEMPO, the yield was 74%, Scheme 4), i.e., the process proceeds efficiently in both cases. Thus, the free radical mechanism does not contribute to the overall process. This also agrees with the absence of dimers of azaallyl anions, which might be expected if the single-electron transfer process takes place.[18]

In summary, we have developed a superbase-catalyzed [3 + 2] cycloaddition reaction between *N*-benzyl ketimines and arylacetylenes followed by the intermediate oxidation to afford eagerly sought polyarylated 2*H*-pyrroles and their precursors, the corresponding 1-pyrrolines, which are of importance for heterocyclic synthesis, pharmaceutics, and materials science. This methodology has several attractive features: a facile procedure, available starting materials, simple catalytic systems, mild reaction conditions, and a wide structural variety of the products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01009.

Experimental procedures, compound characterizations, NMR spectra, and crystallographic data (PDF)

Accession Codes

CCDC 2070913−2070914 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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