

Multimolecular self-organization of acetylene and arylamines into 1-aryl-3-ethyl-4-vinylpyrroles in the KOBu^t/DMSO system

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A new superbase-driven self-organization of four molecules of acetylene with one molecule of arylamine to 1-aryl-3-ethyl-4-vinylpyrroles in the KOBu^t/DMSO system has been discovered. The process includes four acts of nucleophilic addition to acetylene followed by intramolecular cyclization of intermediate *N,N*-bis(1,3-dienyl)-*N*-arylamine.



Keywords: acetylene, arylamines, pyrroles, superbases, nucleophilic addition, self-assemblies.

Today, a great attention is drawn to environmentally benign chemical transformations, which are implemented as pot-, atom-, and step-economical processes (PASE paradigm).¹ In this line, superbase-driven cascade reactions involving acetylene are especially attractive. They usually include the formation of several C–C and C–heteroatom bonds in a one synthetic operation and often afford potentially useful heterocyclic compounds.² Under these conditions, acetylene behaves as a triggering, driving and organizing molecule toward other reactants. Most of these assemblies are launched by the nucleophilic addition to the triple bond in simple and readily available superbase systems like alkali metal hydroxides or alkoxides/DMSO ($pK_a \sim 30\text{--}32$).³ In such systems, electrophilicity of the acetylene is increased due to complexation with alkali metal cation, and nucleophilicity of the reactants attacking the triple bond also becomes stronger because of their desolvation. Over the last few years, we have found a number of examples of the superbase-promoted self-organization of complex molecules involving several molecules of acetylene. Now there comes an understanding that this phenomenon is fairly general.⁴

Just recently, we have described the self-assembly of 1-aryl-2,5-dimethylpyrroles with participation of three molecules of acetylene and one molecule of arylamine in the KOH/DMSO superbase system (100 °C, 3 h, Scheme 1).⁵ In this paper, we disclose one more astonishing result of superbase-mediated self-organization of four molecules of acetylene and one molecule of arylamines **1a–d** into 1-aryl-3-ethyl-4-vinylpyrroles **2a–d** (Scheme 2).

It turned out, on example of the reaction between aniline **1a** and acetylene (Table 1), that the crucial factor for implementation of the synthesis of these rarely substituted pyrroles is the fine tuning of the superbase system and reaction conditions. The best yield of pyrrole **2a** (20%) was achieved in the KOBu^t/DMSO

system at 80 °C for 1 h with **1a**/KOBu^t molar ratio of 1:1 (entry 6).[†] The LiOH/CsF/DMSO system appeared to be absolutely inactive as a catalyst (entry 13). In the case of KOH/DMSO system, the major product was 2,5-dimethyl-1-phenylpyrrole (entries 11, 12, see Table 1).⁵ Note that other KOBu^t/polar nonhydroxylic solvent systems were inefficient to promote this reaction (entries 8–10).

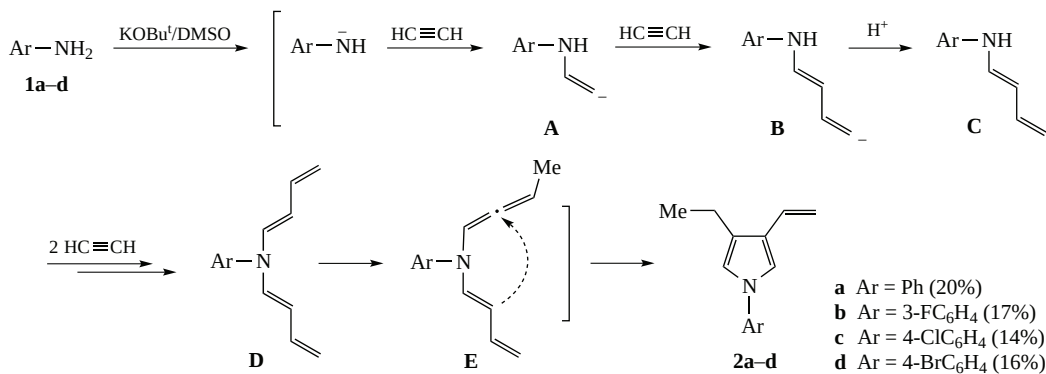
To examine the functional group tolerance of this unexpected assembly of pyrroles, three halo-substituted in the benzene ring arylamines **1b–d** were used in the reaction with acetylene under the above conditions. In this way, the expected pyrroles **2b–d** were obtained in modest yields (see Scheme 2). Halogens as substituents provide additional opportunities for functionalization of the pyrroles obtained. Modest yields of the target products **2**

[†] The reaction of arylamines **1a–d** with acetylene in the KOBu^t/DMSO system (typical procedure). A mixture of arylamine **1a–d** (10 mmol) and KOBu^t (10 mmol, 1.12 g) in DMSO (50 ml) was placed into a 0.25 dm³ steel Parr reactor equipped with mechanical stirrer and manometer. The reactor was fed with acetylene under pressure from commercially available acetylene cylinder (initial pressure at ambient temperature was ~12 atm) and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again and heated (80 °C) for 1 h. The mixture after cooling to room temperature was diluted with H₂O (100 ml) and extracted with Et₂O (7 × 25 ml). The combined organic extracts were washed with H₂O (3 × 20 ml) and dried over K₂CO₃. Diethyl ether was evaporated, and the crude product **2a–d** was eluted with *n*-hexane from the SiO₂-packed column.

3-Ethyl-1-phenyl-4-vinyl-1H-pyrrole 2a. Compound **2a** was prepared from aniline **1a** (10 mmol, 0.93 g), yellow oil, yield 0.31 g (20%, based on **1a** consumed). Unreacted aniline **1a** (0.19 g, 80% conversion) was also recovered upon column chromatography. ¹H NMR, δ: 7.41–7.36 (m, 4H, H^a, H^m), 7.24–7.20 (m, 1H, H^p), 7.17 (d, 1H, H⁵, ⁴J 2.2 Hz), 6.85 (m, 1H, H²), 6.66 (dd, 1H, CH=CH₂, ³J 17.7 Hz, ³J 11.3 Hz), 5.45 (dd, 1H, CH=CH₂, ³J 17.7 Hz, ²J 1.6 Hz), 5.05 (dd, 1H, CH=CH₂, ³J 11.3 Hz, ²J 1.6 Hz), 2.63 (q, 2H, CH₂, ³J 7.4 Hz), 11.27 (t, 3H, Me, ³J 7.4 Hz). ¹³C NMR, δ: 140.0 (Cⁱ), 129.4 (C^m), 129.2 (C^p), 129.1 (HC=CH₂), 129.9 (C³), 123.3 (C⁴), 119.8 (C^o), 116.9 (C⁵), 116.7 (C²), 110.4 (HC=CH₂), 19.1 (CH₂), 14.3 (Me). IR (film, ν/cm^{−1}): 2964, 2927, 2873, 1599, 1520, 1512, 1371, 1225, 1061, 889, 757, 694. HRMS (ESI), *m/z*: 198.1288 [M + H]⁺ (calc. for C₁₄H₁₆N, *m/z*: 198.1277).



Scheme 1



Scheme 2

Table 1 Effects of the reaction conditions on the yield of pyrrole **2a** from aniline **1a** and acetylene.^a

Entry	Base	1a /base molar ratio	Solvent	Temperature/°C	Time/h	Conversion of 1a (%) ^b	Isolated yield of 2a (%) ^c
1	KOBu ^t	1:1	DMSO	60	0.5	40	11
2	KOBu ^t	1:1	DMSO	60	1	56	11
3	KOBu ^t	2:1	DMSO	60	1	58	9
4	KOBu ^t	1:1	DMSO	60	2	67	5
5	KOBu ^t	1:1	DMSO	80	0.5	70	10
6	KOBu^t	1:1	DMSO	80	1	80	20
7	KOBu ^t	1:1	DMSO	100	1	92	9
8	KOBu ^t	1:1	THF	80	1	0	0
9	KOBu ^t	1:1	NMP	80	1	0	0
10	KOBu ^t	1:1	DMF	80	1	0	0
11	KOH	1:1	DMSO	80	1	80	0 ^d
12	KOH	2:1	DMSO	100	1	85	<5 ^d
13	CsF/LiOH	1:1	DMSO	100	1	0	0

^a Reagents and conditions: **1a** (10 mmol, 0.93 g), solvent (50 ml), closed stirred reactor, acetylene pressure ~ 12 atm. ^b Unreacted **1a** was isolated. ^c Based on aniline consumed. ^d 2,5-Dimethyl-1-phenylpyrrole was formed.

can be due to the competing oligomerization processes, *e.g.* formation of open-chain and macrocyclic oligomers of the isolated pyrrole, which is retained on the chromatography column. Note that the major side process is the formation of 1-aryl-2,5-dimethylpyrroles,⁵ which also reduces the yield of pyrroles **2**.

The self-organization of 1-aryl-3-ethyl-4-vinylpyrroles **2** (see Scheme 2) likely commences with nucleophilic attack of deprotonated arylamines at the triple bond of acetylene to deliver vinyl carbanion **A**, which is further added to the second molecule of acetylene, and carbanionic intermediate **B** thus formed would be protonated giving arylamino diene **C**. Likewise, the remaining NH function of diene **C** is converted to 1,3-diene moiety via two nucleophilic addition acts involving two molecules of acetylene, thereby producing *N,N*-bis(1,3-dienyl)-*N*-arylamine **D**. Further on, in the intermediate **D**, 1,3-dienic substituent undergoes the prototropic rearrangement to the allenic one followed by the pyrrole ring closure in the intermediate **E** by the nucleophilic addition of the C²–H bond (after its deprotonation) of the unchanged 1,3-dienyl substituent to C^{2'} allenic atom to finalize the organization of four molecules of acetylene around one molecule of arylamine. In the meantime, a coordinative role of K⁺ cation in connecting of these five molecules should not be excluded. Thus, the reaction sequence includes the formation of three C–C and two C–N bonds in a one synthetic operation.

As mentioned above, we have observed the formation of 1-aryl-2,5-dimethylpyrroles when acetylene reacted with arylamines in the KOH/DMSO system.⁵ The assembly of pyrroles **2** in the presence of KOBu^t/DMSO superbase is obviously due to difference in the physical-chemical nature of the catalytic systems. In fact, while the KOH/DMSO system represents a

suspension because KOH is just poorly soluble in DMSO, KOBu^t/DMSO is a homogeneous solution. Consequently, concentration of the catalyzing basic species and their activity is much higher in this case than in the former one. Besides, two-phase catalysis should expectedly be different from homogeneous one.

3-Alkyl-4-vinylpyrrole nucleus (similar to synthesized here) is a mandatory part of chlorophylls and hemes. In addition, 3,4-disubstituted pyrroles with free positions 2 and 5 represent important building blocks for the synthesis of porphyrins,⁶ tetraporphyrins and a number of bioactive compounds.⁷ However, only few syntheses of 3,4-disubstituted pyrroles were as yet described, which are multistep,⁷ require expensive reagents⁸ or/and transition metals catalysts⁹ or provide limited scope and poor yields.¹⁰

Although yields of the pyrroles are modest, taking into account the uniqueness of these molecular transformations, simple transition metal-free catalytic system, pot-atom-step economical procedure, the presented synthesis may be considered as a remarkable contribution to the acetylene and pyrrole chemistry. Evidently, there still remains a lot to do for better understanding and further elaboration of this disorder-to-order chemical phenomenon.⁴

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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.2020.05.018.

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