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Superbase-promoted multi-molecular acetylene/arylamine self-organization to 1-arylpyrroles

Elena Yu. Schmidt,[a,b] Nadezhda V. Semenova,[a] Elena V. Ivanova,[a] Ivan A. Bidusenko[a] and Boris A. Trofimov*[a]

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@irioch.irk.ru*

[b] *Angarsk State Technical University, 665835 Angarsk, Russian Federation*

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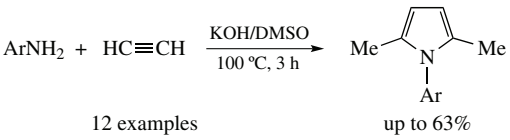
A new superbase-promoted reaction of acetylene involves self-organization of its three molecules with one molecule of arylamine in KOH/DMSO system to afford 1-aryl-2,5-dimethylpyrroles in up to 63% yields. The key step of this reaction cascade is assumed to be the nucleophilic addition of acetylene to the C=N bond of the intermediate aldimine (aza-Favorsky reaction).



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One of the most challenging areas of modern organic chemistry is the search for new synthetic methodologies to design complex molecular structures *via* pot-, atom-, step-economical, resource- and energy-saving procedures using available starting materials and simple, preferably transition-metal-free, catalytic systems.[1] In this context, the application of acetylene is one of the mainstreams.[2] The acetylene renaissance, we now witness, is due not only to its exceptionally high reactivity but also to its large-tonnage supply from oil-, gas- and coal refining.[3] In this regard, cascade multi-molecular assemblies of complex molecules triggered and driven by acetylene are especially attractive. Indeed, in these processes, acetylene plays a crucial role owing to its dual reactivity, alternatively acting as an electrophile and a nucleophile. This is especially clear expressed in superbase media like alkali hydroxide alkoxide)/DMSO (pK_a ~ 30–32),[4] which increase the concentrations of acetylenic anions and enhance the nucleophilicity of the reactants attacking the triple bond. Various combinations of nucleophilic addition to the triple bond and acetylene deprotonation enable the self-assemblies of complex molecular architectures.[5] Among the recent applications of this phenomenon are the base-promoted one-pot assembly of dioxabicyclooctanes,[6] acylcyclopentenols,[7] substituted furans,[8] azabicyclohexanes[9] from several molecules of acetylene and other reactants.

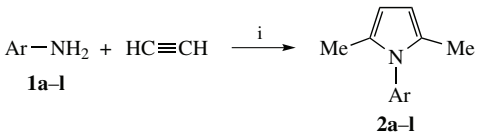
In the present communication, we disclose one more finding of the superbase-assisted self-assembly of three molecules of acetylene and one molecule of aniline or its derivatives to 1-aryl-2,5-dimethylpyrroles.

In order to determine the provisionally optimum conditions for this unexpected reaction, we first tested different superbase systems at various temperatures in the reaction of aniline **1a** with acetylene under pressure (~10 atm, Scheme 1, Table 1). The best yield of 2,5-dimethyl-1-phenylpyrrole **2a** (63%) was achieved in the KOH/DMSO system at 100 °C for 3 h with **1a**/KOH molar ratio = 1 : 1 (entry 6), the conversion of the starting aniline **1a** being 68%. Raising the amount of KOH to 2 equiv. did not noticeably affect the outcome of the reaction (entry 7). When the reaction was carried out at 120 °C, the yield of **2a** was reduced due to rise in polymerization side process (entry 8). Notably,

Table 1 Influence of the reaction conditions on the yield of 2,5-dimethyl-1-phenyl-1*H*-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	1	83	33
2	KOBu^t	1 : 2	DMSO	60	1	85	40
3	KOBu^t	1 : 1	DMSO	80	1	–[d]	–[d]
4[e]	KOBu^t	1 : 1	DMSO	100	6	40	15
5	KOH	1 : 1	DMSO	80	3	31	7
6	KOH	1 : 1	DMSO	100	3	68	63
7	KOH	1 : 2	DMSO	100	3	70	61
8	KOH	1 : 1	DMSO	120	3	90	40[d]
9	KOH	1 : 1	THF	100	3	0	0
10	KOH	1 : 1	NMP	100	3	0	0
11	KOH	1 : 1	DMF	100	3	0	0

[a] **1a** (10 mmol, 0.93 g), solvent (50 ml), closed reactor, acetylene pressure ~10 atm. [b] Unreacted **1a** was isolated. [c] Based on aniline consumed. [d] Polymer formation. [e] Flow process, glass flask (100 ml), pressure ~1 atm, acetylene flow rate ~15 ml min^{-1}.



a Ar = Ph (63%)
b Ar = 2-MeC_6H_4 (12%)
c Ar = 3-MeC_6H_4 (47%)
d Ar = 4-$MeOC_6H_4$ (24%)
e Ar = 3-FC_6H_4 (25%)
f Ar = 4-FC_6H_4 (28%)
g Ar = 2-ClC_6H_4 (12%)
h Ar = 4-ClC_6H_4 (31%)
i Ar = 2-BrC_6H_4 (13%)
j Ar = 4-BrC_6H_4 (21%)
k Ar = 1-naphthyl (40%)
l Ar = 4-pyridyl (10%)

Scheme 1 *Reagents and conditions*: i, KOH, DMSO, 100 °C, 3 h.

when THF, NMP or DMF were used instead of DMSO, the reaction did not proceed at all (entries 9–11), thus proving superiority of DMSO as an activating component of the superbases. Astonishingly, the KOBu^t/DMSO system appeared to be inferior superbase catalyst for the pyrrole assembly, although it was more active in the polymerization (entry 3).

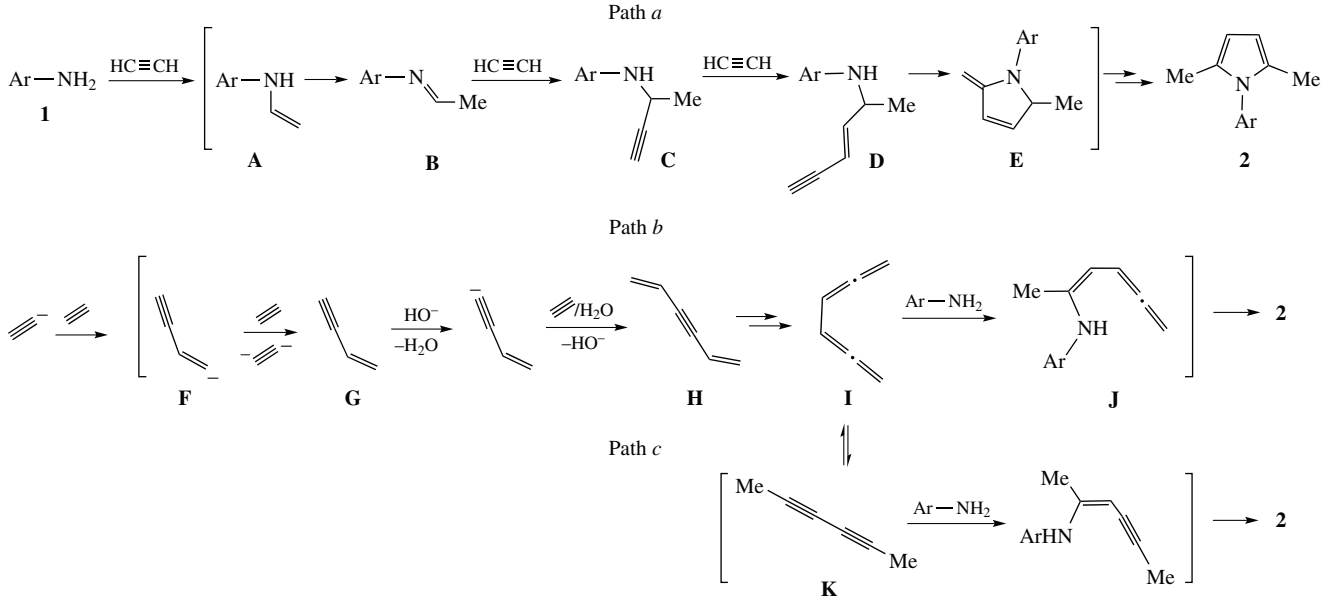
Next, we investigated the reaction of acetylene with a variety of arylamines under the optimal conditions. As follows from Scheme 1, a wide range of diversely substituted anilines, 1-aminonaphthalene **1k** and 4-aminopyridine **1l** were found to be suitable partners to afford the corresponding 1-aryl-2,5-dimethylpyrroles **2a–l** in moderate isolated yields.†

As to the influence of arylamine structure on the yield of pyrroles **2**, the electronic effect of the substituents in the benzene ring could be neglected because no regularity in the behavior of arylamines with donor (**1c**,**d**) and acceptor (**1e–f**,**h**,**j**,**l**) substituents was observed. A lower reactivity of *ortho*-substituted anilines **1b**,**g**,**i** is obviously originated from the steric shielding of the nitrogen atom.

Apparently, the reaction (Scheme 2, path *a*) may be triggered by the nucleophilic addition of arylamine **1** to acetylene. *N*-Vinylamine **A** thus formed undergoes a prototropic rearrangement to aldimine **B**, which further nucleophilically adds the second acetylene molecule to the C=N bond (aza-Favorsky ethynylation).[10] The third acetylene molecule (in its carbanionic form) attacks the triple bond of propargylic amine **C** and the following intramolecular vinylation in the intermediate **D** gives dihydropyrrole **E**, which is finally aromatized to the final product **2**.

This mechanism (see Scheme 2, path *a*) is supported by the results of our previous one-pot synthesis of intermediates **C**, 3-arylamino-1-butynes, from acetylene and anilines catalyzed by the PhNHK/dioxane superbase system (160 °C, 2 h, 25–30% yields), wherein the sequence **A** → **B** → **C** was postulated.[11] At the same time, in the current study none of the intermediates was detected in the reaction mixtures.

An alternative mechanism (see Scheme 2, path *b*) might be direct nucleophilic addition of arylamine **1** to the linear trimer of acetylene, divinylacetylene **H**. This addition is likely preceded by the Favorsky acetylene–allene isomerization of trimer **H** to allenic intermediate **I** which is attacked by the deprotonated aniline at the C(2) position as usual for allenes. The intramolecular cyclization of intermediate **J** affords pyrrole **2**. Another acetylenic trimer, dimethyldiacetylene **K**, can also be involved into the cyclization with arylamines (path *c*). The synthesis of pyrroles from diacetylenes and primary amines in the presence of copper catalysts is well known.[12]



Scheme 2

† *The reaction of arylamines* **1** *with acetylene in the KOH/DMSO system (typical procedure)*. A mixture of arylamine **1** (10 mmol), KOH·0.5H_2O (10 mmol, 0.65 g) in DMSO (50 ml) was placed into a 0.25 dm^3 stirred reactor. The reactor was fed with acetylene under pressure (initial pressure at ambient temperature was ~10 atm) and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again and heated (100 °C) for 3 h. After cooling to room temperature, the mixture was diluted with water (100 ml) and extracted with Et_2O (7×25 ml). The combined organic extracts were washed with H_2O (3×20 ml) and dried (K_2CO_3). Diethyl ether was evaporated *in vacuo*. Column chromatography (SiO_2, eluent *n*-hexane) gave pure pyrroles **2**.

2,5-Dimethyl-1-phenyl-1*H*-pyrrole **2a** was prepared from **1a** (10 mmol, 0.93 g), yellow oil, yield 0.73 g (63%, based on aniline **1a** consumed). Unreacted aniline **1a** (0.30 g, 68% conversion) was recovered upon column chromatography. ^{1}H NMR, δ: 7.49–7.45 (m, 2H, H^m), 7.42–7.38 (m, 1H, H^p), 7.25–7.22 (m, 2H, H^o), 5.92, (s, 2H, H^3, H^4), 2.05 (s, 6H, Me). Lit.,[13] δ: 7.47–7.44 (m, 2H), 7.40–7.38 (m, 1H), 7.21 (dd, 2H, *J* 8.2, 1.3 Hz), 5.90 (s, 2H), 2.03 (s, 6H). ^{13}C NMR, δ: 139.0 (C^i), 129.0 (C^o), 128.7 (C^p), 128.2 (C^m), 127.5 (C^2, C^5), 105.6 (C^3, C^4), 12.9 (Me). Lit.,[13] δ: 138.9, 128.9, 128.8, 128.2, 127.6, 105.6, 12.9. IR (film, ν/cm^{-1}): 3022, 2963, 2925, 2867, 1666, 1597, 1499, 1450, 1404, 1323, 1166, 1035, 761, 700. Found (%): C, 84.19; H, 7.60; N, 8.21. Calc. for $C_{12}H_{13}N$ (%): C, 84.17; H, 7.65; N, 8.18.

For characteristics of compounds **2b–l**, see Online Supplementary Materials.

In this new superbase-triggered cascade reaction, acetylene again demonstrates its capacity to behave stepwise as both an electrophile and a nucleophile.[5] To distinguish between these mechanisms will be a task of our future investigations.

The formation of trimers **H** and **K** is a result of anionic oligomerization of acetylene, which is initiated by the addition of acetylenic carbanion to another molecule of acetylene generating vinylacetylenic carbanion **F** (vinylation of acetylene, see Scheme 2), which further propagates the oligoene chain. The chain growth can be interrupted by the proton transfer from a molecule of acetylene to the carbanionic center (chain transfer to monomer), and consequently, dimers, trimers and higher oligomers are to be formed. This is supported by the identification (GC-MS) of vinylacetylene **G** in the volatile products of the reaction as well as by the formation of large amount of dark brown solid paramagnetic (g = 2.0043, ΔH = 9.6 G, $N = 3.7 \times 10^{18}$ spin g^{-1}) polymer, which was not investigated so far. The above facile oligomerization of acetylene competes with the self-organization of pyrroles, thereby reducing their yields.

Despite the modest yields of pyrroles, their one-pot synthesis from available starting materials under transition metal-free conditions may be considered as a useful contribution to the heterocyclic chemistry. However, a major aim of this presentation is to acknowledge the generality of superbase-promoted multi-molecular self-organization phenomenon with the participation of acetylene that allows a short-cut to the molecular complexity to be achieved.[5]

In conclusion, the entropy-resistant self-organization of chaotically moving small molecules (acetylene and amines) around the omnipresent ions (K^+, HO^-, H^+) to pyrroles has been described. This is a one more proof for the generality of the phenomenon that opens a straightforward access to the molecular complexity and diversity in the nature-like manner.

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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.2020.01.036.

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