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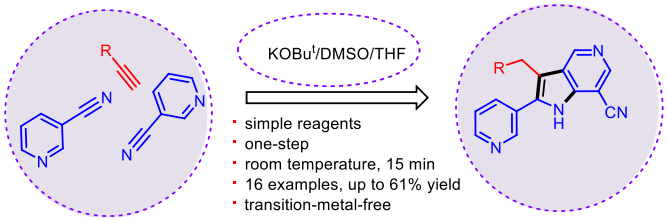
Smart molecules: quick assembly of functionalized 5-azaindoles from acetylenes and nicotinonitrile

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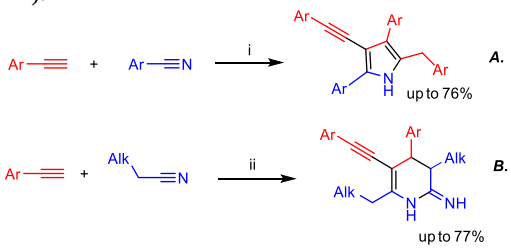
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One molecule of (het)aryl acetylene and two molecules of nicotinonitrile in the KOBu^t/DMSO/THF system undergo fast (15 min), low-temperature (10-22 ºC) self-organization to functionalized 5-azaindoles. Unprecedented features of this process include the nucleophilic addition of the intermediate nitrogen-centered anion to the pyridine core and the double nucleophilic substitution of hydrogen in the heteroaromatic ring in a one synthetic operation.



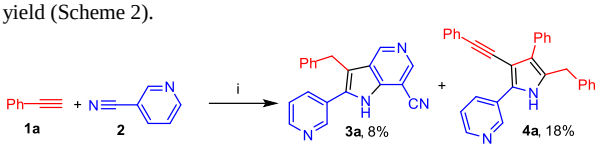
Keywords: acetylenes, nicotinonitrile, azaindoles, superbases, nucleophilic substitution.

The high and flexible reactivity of the carbon-carbon triple bond enables cost-effective, energy-saving, environmentally benign, and one-pot technologies.[1-6] The recently discovered phenomenon of the self-organization of complex molecules triggered and driven by acetylenic carbanions[7,8] is based on the dual nature of the acetylene reactivity (nucleophilic/electrophilic dichotomy), which is enhanced in superbasic media (pK_a ~ 30-35).[9,10] For example, in the KOBu^t/DMSO system, three molecules of (het)aryl acetylene and one molecule of (het)aromatic nitrile are self-organized to tetrasubstituted 1*H*-pyrroles (Scheme 1A).[7] With aliphatic nitriles, the self-organization took a different course affording 2-iminopyridines. This process requires two molecules of nitrile and two molecules of acetylene (Scheme 1B).[8]



Scheme 1 *Reagents and conditions*: i, KOBu^t, DMSO, rt, 15 min; ii, KOBu^t, DMSO, 40 °C, 5 h.

Here we report that, against all the odds, under the conditions shown in Scheme 1A, acetylene **1a** reacted with nicotinonitrile **2** to give 5-azaindole **3a** in 8% yield. The expected pyrrole **4a** being formed in 18% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: i, KOBu^t, DMSO, rt, 15 min.

This serendipitous observation allows us hoping to achieve the one-pot selective synthesis of functionalized 5-azaindoles, provided that the parallel formation of substituted pyrroles would be suppressed. Efforts in this direction are justified by the potential value of such compounds in medicinal chemistry and materials science owing to their specific biological[11-13] and photochemical[14-16] properties. For example, the natural 5-azaindoles, marine sponge Guitarrins A–E, are inhibitors of alkaline phosphatase.[17,18] The 5-azaindole scaffold is a key structural motif found in many pharmaceutically important compounds.[19-28]

Often, 5-azaindoles are synthesized by two strategies based on pyridines or pyrroles.[29-32] For instance, the pyrrole ring is built up on the pyridine core using alkynes with a Pd/Cu catalyst[33-35] or suitably substituted pyridines are subjected to intramolecular cyclization.[36-38] Functionalized pyrroles can also be employed as a platform to construct the pyridine ring onto them.[39-42] Nevertheless, the synthesis of 5-azaindoles still represents a challenge often requiring expensive metal catalysts, laborious pre-functionalization of the starting materials and/or high temperatures.

Therefore, the chance to develop the preparatively acceptable synthesis of above rarely functionalized 5-azaindoles such as **3a** in a one-pot manner from simple and available starting materials inspired us to conduct a comprehensive study of the aforementioned self-organization (Scheme 2). Thus, the aim of this work was to find the conditions for the selective formation of 5-azaindoles.

As seen from Table 1, shifting the reaction towards the selective formation of 5-azaindole **3a** required the use of 2 equiv. of nitrile **2** was needed to be used (instead of 1 equiv., Scheme 2A).[7] Besides, the special order of the reactant feeding was employed: to nitrile **2** in DMSO, a solution of acetylene **1a** in KOBu^t/DMSO was added dropwise (entry 5). The excess of acetylene **1a** expectedly led to the selective formation of pyrrole **4a** (entries 6 and 7).

Table 1 Tuning the selectivity of the reaction of acetylene **1a** with nicotinonitrile **2** (Scheme 2).[a]

Entry	**1a**:**2**:KOBu^t Molar ratio	t (min)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	1:1:0.5	15	8	18
2	1:2:0.5	30	14	12
3	1:2:1	30	21	11

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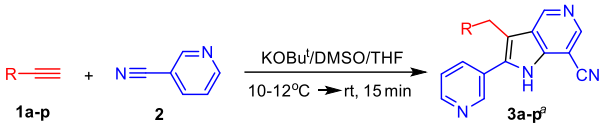
4	1:2:1	60	26	14
5[c]	1:2:1	60	36	nd
6	3:1:0.5	15	nd	28
7	3:1:1	15	nd	39 (34)[d]

[a] *Reagents and conditions*: A solution of **2** in DMSO (2 mL) was added dropwise to a solution of **1a**, KOBu^t in DMSO (4 mL) at 20-22 °C. [b] According to ^{1}H NMR data of the crude product (durene was used as an internal standard). [c] A solution of **1a**, KOBu^t in DMSO (3 mL) was added dropwise to a solution of **2** in DMSO (3 mL) at 20-22 °C. [d] Isolated yield of after column chromatography (SiO_2, *n*-hexane–diethyl ether with gradient from 2:1 to 0:1). nd=not detected.

Next, we looked for the reaction parameters that would secure a higher yield of 5-azaindole **3a** (see Table S1 in the SM). After careful optimization, it was found, to reach a 61% isolated yield of **3a**, the reaction conditions should be as follows (Table S1, entry 15): a mixture of acetylene **1a** with DMSO/THF/KOBu^t prepared at 10-12 °C for 1-2 min was fed dropwise to a solution of nitrile **2** in DMSO/THF at 10-12 °C for 1-2 min. Then the reaction mixture was stirred at room temperature for 15 min. It is noteworthy that this provisionally optimal procedure was elaborated for acetylene **1a** only. Note, the yield of **3a** was proved to be highly sensitive to insignificant changes of the reaction parameters and experimental details. Therefore, a special search for an optimal set of parameters to achieve the highest yield of the target product is required for every other acetylene **1**. The efficiency of such an approach is illustrated by Table 2, when the yield of 5-azaindole **3a** was improved from 36% to 68%.

To evaluate the substrate scope of the self-organization process, a set of acetylenes **1** was tested employing the above provisionally optimal conditions and procedure (Scheme 3). As seen, aryl- and hetaryl acetylenes **1** satisfactorily tolerated the above reaction parameters to warrant the isolated yield of the expected 5-azaindoles **3** in the range of 8–61%. This broad yield range for 5-azaindoles **3** confirms their high sensitivity to the structure of the starting acetylenes **1**. The substituents at the triple bond should influence both the concentration of acetylenic carbanions and their nucleophilicity and, hence, the structural effect on the reaction output is difficult to predict. Moreover, the reactants in the reaction mixture can undergo various transformations involving acetylenic carbanions (dimerization, diverse types of oligomerization and polymerization), the nitrile function (addition of a *tert*-butoxide ion[43] and oligomerization), alone along with various cross-coupling and conjugated side-reactions of the intermediates. The halo substituted aryl acetylenes **1f-k**, under superbasic conditions, can react with the acetylenic carbanions, *tert*-butoxide ions and diverse intermediate anions via nucleophilic substitution mode.

Expectedly, the modest yields of 5-azaindoles **3a-p** are primarily the result of the anionic oligomerization processes of both the starting compounds and the intermediates. In support of this inference, the polymeric product (21% relative to the mass of the reactants) was isolated from the reaction with acetylene **1a**. According to the polymeric composition (**1a**:**2** = 2:1), per two molecules of acetylene **1a** are involved in co-oligomerization with one molecule of nitrile **2**, while **3a**, on the contrary, was assembled from one molecule of **1a** and two molecules of **2**.



3a R = Ph; 61% (57%)[b]
3b R = 3-MeC$_6$H$_4$; 29%
3c R = 4-F$_3$CC$_6$H$_4$; 3%[c]
3d R = 3-MeOC$_6$H$_4$; 41%
3e R = 4-MeOC$_6$H$_4$; 8%[d] (5%)[a]
3f R = 3-FC$_6$H$_4$; 21%
3g R = 4-FC$_6$H$_4$; 26%
3h R = 3-ClC$_6$H$_4$; 37%
3i R = 4-ClC$_6$H$_4$; 24%
3j R = 3-BrC$_6$H$_4$; 37%
3k R = 4-BrC$_6$H$_4$; 3%[c]
3l R = 4-PhC$_6$H$_4$; 26%
3m R = 1-naphthyl; 21%
3n R = 3-thienyl; 21%[d] (10%)[a]
3o R = 2-pyridin; 14%
3p R = 3-pyridin; 15%

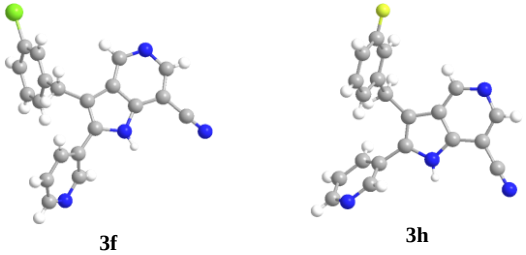
Scheme 3 Substrate scope. [a]*Reagents and conditions*: **1** (1.3 mmol), **2** (2.0 mmol), KOBu^t (2.0 mmol), DMSO (6.0 mL), THF (0.6 mL), 10-12→22 °C, 15 min. Isolated yields are given. [b]Gram scale synthesis [**1** (13 mmol), **2** (20 mmol), KOBu^t (20 mmol)]. [c]According to ^{1}H NMR data of the crude product (durene was used as an internal standard). [d]KOBu^t (1.5 mmol), 60 min.

In the synthesis of 5-azaindole **3f** (21% yield) from 1-ethynyl-3-fluorobenzene **1f**, acetylenic dimer [(*E*)-but-1-en-3-yne-1,4-diyldibenzene] was isolated. At the same time, 1-ethynyl-4-(trifluoromethyl)benzene **1c** and 1-bromo-4-ethynylbenzene **1k** under the standard conditions generated the expected products **3c** and **3k** just in trace amounts (3% according to ^{1}H NMR data of the crude product). To obtain 5-azaindoles **3e** and **3n** in 8% and 21% yields, 1.5 equiv. of KOBu^t was required and the process took 60 min, while under standard conditions, the yields were 5% and 10%, correspondingly. Thus, the above optimization of the synthesis of **3a** (Table S1) and these results (Scheme 3) show that the reaction can be optimized for each individual acetylene. However, this is a matter for systematic research and is beyond the scope of this priority communication.

To demonstrate the scalability of this synthesis, the reaction of acetylene **1a** and nitrile **2** was performed on a gram scale (Scheme 3). The transformation was successfully scaled up to 33 mmol, furnishing 5-azaindole **3a** in a comparable yield (57%, 1.76 g).

Surprisingly, all the attempts to involve picolinonitrile and isonicotinonitrile in this self-organization met with no success.

The structure of 5-azaindoles **3** was determined by single-crystal X-ray analysis of their representative **3f** and **3h** (Figure 1), and also confirmed by NMR analysis (^{1}H, ^{13}C, and ^{15}N; see SI for details) including 2D techniques (NOESY, COSY, ^{1}H–^{15}N HMBC, ^{1}H–^{13}C HMBC, and ^{1}H–^{13}C HSQC experiments; Figure 2).



3f **3h**

Figure 1 X-ray structure of **3f** and **3h** (from DMSO; CCDC 2550666-2550667)[†]

[†] *Crystal data for* **3f**. $C_{20}H_{13}N_4F$, M_r = 328.35. The integration of the data using a monoclinic unit cell with $P2_1/c$ space group yielded a total of 32932 reflections to a maximum 2θ angle of 53.4, of which 3443 were independent (completeness = 100%, Rint = 5.35%, Rsig = 2.67%) and 2237 were greater than 2σ(F2). The final cell constants of **a** = 13.714(2) Å, **b** = 13.131(2) Å, **c** = 9.1025(12) Å, β = 90.879(8)°, Z= 4, volume = 1639.0(4) Å^3. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.966 and 0.993. The final anisotropic full-matrix least-squares refinement on F2 with 344 variables converged at R1 = 4.19%, for the observed data and wR2 = 11.61% for all data. The goodness-of-fit was 1.05. The largest peak in the final difference electron density synthesis was 0.18 e-/Å^3 and the largest hole was -0.18 e-/Å^3. On the basis of the final model, the calculated density was 1.331 g/cm^3 and F(000), 680 e-.

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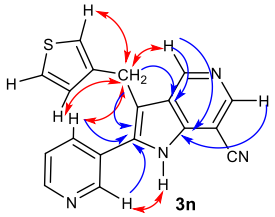
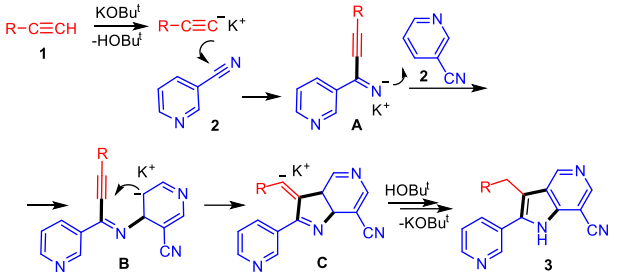


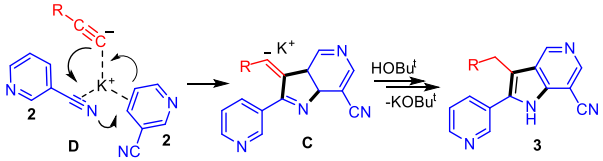
Figure 2 Main NOESY (↔) and ^{1}H-^{13}C HMBC (→) correlations for **3n**.

As to the mechanism of the reaction under study, it is likely triggered by the addition of acetylenic carbanion (accompanied by potassium cation) to the C≡N bond of nicotinonitrile **2** (Scheme 4). The nitrogen-centered anions **A** thus formed attack the second molecule of nicotinonitrile **2** at the position 4 of the pyridine ring. The carbanions **B** then cyclize to the intermediates **C**, which finally aromatize to 5-azaindoles **3** via the corresponding prototropic distribution of hydrogen.



Scheme 4 Plausible scheme for 5-azaindoles **3** formation

However, the fact that none of the above intermediates are detectable in the reaction mixture, coupled with very high self-organization rate (15 min) at a low temperature (10-22 °C), is inconsistent with the step-wise mechanism. The above experimental features of the reaction rather imply a synchronic circular transfer of electron pairs in a three-molecular complex **D** (Scheme 5). The latter can be organized around the potassium cation, which is brought in with acetylenic carbanion acting as a template.

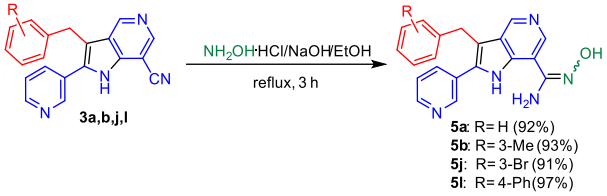


Scheme 5 Alternative scheme for 5-azaindoles **3** formation.

What is unusual in this self-organization process is the dearomatization of the pyridine ring to form the corresponding dihydro species. This is due to a strong electron-withdrawing effect of the nitrile function, which pulls the electron density away from the pyridine moiety.

It is worthwhile to underscore that the remarkable features of the whole process are the nucleophilic addition of the intermediate nitrogen-centred anion **A** to the pyridine core and the double nucleophilic substitution of hydrogen in the heteroaromatic ring in a one synthetic operation at room temperature during minutes.

Overall, this is remarkable that from diversity of possible chaotic transformations, the molecules of acetylene and nicotinonitrile choose the way to 5-azaindole structure, as if these molecules were actually smart. The reaction provides the unique functionalization of 5-azaindole scaffold. The combination of such reactive functions as C≡N and NH allows new facets of azaindole chemistry to be unfolded. As illustration, the addition of hydroxyl amine to the nitrile group of 5-azaindoles **3** to afford amidoximes **5** in almost quantitative yields was realized (Scheme 6).



Scheme 6 Reaction of 5-azaindoles **3** with hydroxyl amine.

In summary, the unique superbase-mediated self-organization of one molecule of (het)aryl acetylene and two molecules of nicotinonitrile to afford functionalized 5-azaindoles has been discovered. The modest and low yields of the target products are compensated by such competitive advantages of the synthesis as very fast, room temperature scalable process, one-pot implementation, available starting materials, simple and readily accessible catalytic superbase composition (KOBu^t/DMSO/THF). The unprecedented features of the process are the nucleophilic addition of the intermediate nitrogen-centred anion to the pyridine core and the double nucleophilic substitution of hydrogen in the heteroaromatic ring in a one synthetic operation. Further investigations towards applications of the reaction and deeper understanding of its mechanism are under way.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8164.

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Crystal data for **3h**. $C_{20}H_{13}ClN_4$, M_r = 344.80. The integration of the data using a orthorhombic unit cell with *Pbca* space group yielded a total of 57675 reflections to a maximum 2θ angle of 53.6, of which 3261 were independent (completeness = 100%, Rint = 10.22%, Rsig = 4.18%) and 2079 were greater than 2σ(F2). The final cell constants of **a** = 13.349(3) Å, **b** = 9.108(2) Å, **c** = 27.934(5) Å, Z= 8, volume = 3396.2(12) Å^3. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.935and 0.979. The final anisotropic full-matrix least-squares refinement on F2 with 226 variables converged at R1 = 5.86%, for the observed data and wR2 = 14.99% for all data. The goodness-of-fit was 1.02. The largest peak in the final difference electron density synthesis was 0.27 e-/Å^3 and the largest hole was -0.41 e-/Å^3. On the basis of the final model, the calculated density was 1.349 g/cm^3 and F(000), 1424 e-.

CCDC 2550666 (**3f**), 2550667 (**3h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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