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Acetylene-driven superbase-mediated self-organization of (het)arylpyridines from (het)aromatic nitriles

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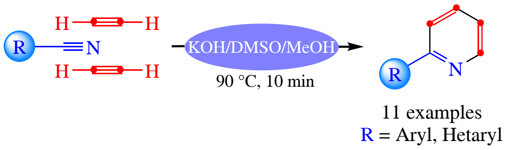
Acetylene gas reacts with (het)aromatic nitriles in the KOH/DMSO/MeOH superbase composition at 90 °C for 10 min to afford 2-(het)arylpyridines in up to 36% yield. The process can be rationalized as the self-organization of two molecules of acetylene and one molecule of nitrile.



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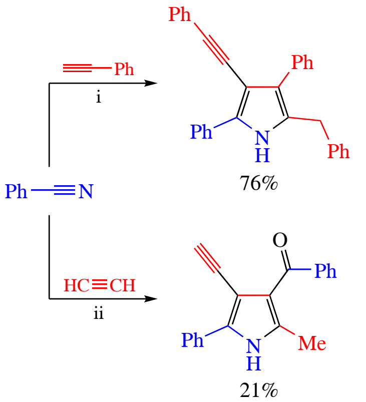
In the last decades, the base-mediated acetylene-driven self-organization of complex molecules on the platform of simple nucleophiles (amines,[1] amides,[2] nitriles,[3,4] ketones[5]) has attracted an even-growing attention of the synthetic community.[6–9] The research in this field was especially accelerated after our discovery of the ketone addition to acetylenes affording β,γ-enones[10] as well as the addition of acetylenic carbanions to the C=N bond leading to new propargylic amines, aza dienes, and pyrrole derivatives.[11] As it appeared, these both reactions occupy a significant place in the self-organization phenomenon.

Recently, we have discovered the addition of acetylenic carbanions to the C≡N bond,[3,4] which also showed the substrate- and condition-dependent divergence. Indeed, when (het)aryl-acetylenes reacted with (het)arene nitriles in the KOBu^t/DMSO superbase system (room temperature, 15 min), tetrasubstituted pyrroles were formed in up to 76% yield (Scheme 1, conditions i, one example is given).[3] This transformation is a typical acetylene-driven self-organization process (three molecules of (het)arylacetylene and one molecule of nitrile), which starts from the parent reaction leading to the isolable acetylenic imines.[3] At the same time, acetylene gas, under even milder conditions (KOBu^t/DMSO/THF, atmospheric pressure, 12–14 °C, 15 min), with arylnitriles yielded (after aqueous work-up) 4-aroyl-2-aryl-3-ethynyl-5-methylpyrroles, the products of the (3 + 2)-self-organization (see Scheme 1, conditions ii, one example is given).[4] Note that in all cases the pyrrole derivatives are formed.



Scheme 1 *Reagents and conditions*: i, KOBu^t, DMSO, room temperature, 15 min; ii, KOBu^t, DMSO, THF, atmospheric pressure of acetylene, 12–14 °C, 15 min.

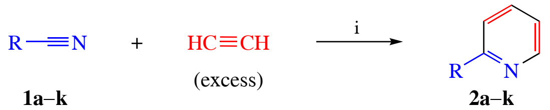
The idea of synthesizing pyridines from acetylene and nitriles in the presence of strongly basic catalyst dates back to 1952, when Cairns *et al*. obtained 2-phenylpyridine in 1.8% yield from the reaction of acetylene with benzonitrile under unusually severe reaction conditions (potassium metal, 170–180 °C, acetylenic pressure of ~13–16 atm, 6 h).[12] In this paper, we report on the reaction of aromatic and heteroaromatic nitriles with acetylene gas under superbasic conditions to deliver 2-aryl-pyridines. Actually, this reaction represents self-organization of two molecules of acetylene and one molecule of nitrile. Our preliminary experiments with benzonitrile **1a** have shown that such switch from the pyrrole to pyridine synthesis is indeed possible. For this it was essential to change the reaction conditions towards a higher temperature and larger excess acetylene.

Table 1 represents the results illustrating the effects of the reaction conditions on the yield of pyridine **2a** from benzo-

Table 1 Reaction of benzonitrile **1a** with acetylene: optimization of the conditions.[a]

Entry	Base	Additive	*T*/°C	*t*/min	Yield of **2a** (%)[b]
1	NaOH	none	90	10	traces
2	KOH	none	90	10	14
3	KOH	MeOH	90	10	36 (28[c])
4	KOH	MeOH	100	5	31
5	KOH	MeOH	70	20	18
6	KOH	ButOH	90	10	14
7	NaOBu^t	none	90	10	3[d]
8	NaOBu^t	MeOH	90	10	23
9	KOBu^t	none	90	10	traces[d]
10	KOBu^t	MeOH	90	10	18

[a] Benzonitrile **1a** (5 mmol, 0.516 g), base (5 mmol), additive (5 mmol), DMSO (50 ml), closed stirred reactor, acetylene pressure of ~4–5 atm. [b] Isolated yield after column chromatography (Al_2O_3, eluent *n*-hexane–diethyl ether, gradient from 1 : 0 to 1 : 1). [c] With 2.5 mmol of MeOH. [d] Tar formation.



1a–k **2a–k**

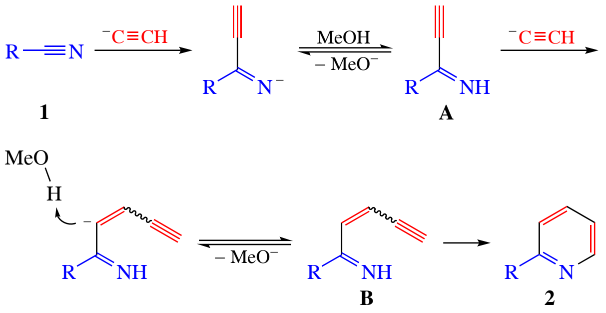
a R = Ph (36%)
b R = 3-MeC_6H_4 (31%)
c R = 4-MeC_6H_4 (30%)
d R = 3-$MeOC_6H_4$ (28%)
e R = 4-$MeOC_6H_4$ (29%)
f R = 4-FC_6H_4 (15%)
g R = 4-ClC_6H_4 (18%, with 13% of **2e**)
h R = 4-BrC_6H_4 (19%, with 10% of **2e**)
i R = 4-$Me_2NC_6H_4$ (19%)
j R = 2-thienyl (13%)
1k R = 1*H*-indol-5-yl
2k R = 1-vinyl-1*H*-indol-5-yl (14%)

Scheme 2 *Reagents and conditions*: i, KOH · $0.5H_2O$, DMSO, MeOH (Bu^tOH for **2f**), 90 °C, 10 min.

nitrile **1a** and acetylene (Scheme 2). The reaction was carried out in the presence of DMSO-tailored superbase composition under acetylenic pressure of ~4–5 atm (that ensures large excess acetylene) at 70–100 °C. The best achievable yield of pyridine **2a** was 36% (entry 3) when the reaction was performed in the presence of KOH/DMSO/MeOH composition at 90 °C for 10 min. The major result-determining factor in this pyridine synthesis is the nature of a base: the sodium bases [NaOH (entry 1), $NaOBu^t$ without the MeOH additive (entry 7)] happened to be inert, while KOH was active (entry 2). Also, a strongly influencing parameter was the additive of MeOH in equimolar amount to nitrile **1a** that allowed the yield of the target pyridine **2a** to be sharply increased from 14 to 36% (*cf.* entries 2 and 3). At a lower content of MeOH (0.5 equiv.), the yield of pyridine **2a** droped to 28% (see entry 3). The positive effect of MeOH additive was observed both at higher temperature (entry 4) and even when, instead of KOH, $NaOBu^t$ and $KOBu^t$ were employed (entries 8, 10). This MeOH effect is probably associated with the basicity tuning to the level optimal for the pyridine self-organization. The modest yields in all the cases are obviously due to oligomerization and co-oligomerization processes involving both acetylene and intermediates (Scheme 3 depicting mechanistic rationale).

Notably, in none of the cases the expected pyrrole (see Scheme 1, conditions ii) was detected. This is obviously due to the different conditions, under which the both reactions were conducted. For the pyrrole synthesis, the conditions were $KOBu^t$/DMSO/THF, 12–14 °C, atmospheric pressure of acetylene,[4] whereas for the synthesis of pyridine **2a** those were found to be absolutely different ones (see Table 1, entry 3).

Then, we have extended the above provisionally optimum conditions over the synthesis of other pyridine derivatives **2** from a series of aromatic and heteroaromatic nitriles **1a–k** (see Scheme 2). The expected 2-(het)arylpyridines **2a–k** were synthesized in 13–36% yields, the reaction tolerated the alkyl, alkoxy, amino, and halo substituted arylnitriles **1a–i** as well as 2-cyanothiophene **1j** and 5-cyanoindole **1k**. Interestingly, in the case of 4-fluorobenzonitrile **1f**, only 4-methoxybenzonitrile **1e** was isolated, indicating the complete substitution of fluorine atom by the MeO-group prior to the pyridine formation. At the same time, with 4-chloro- and 4-bromobenzonitriles, the substitution of halogen mainly occurred in the 4-halophenylpyridines to deliver the mixtures of the corresponding 2-(4-halophenyl)pyridines **2g**,**h** and 2-(4-methoxyphenyl)pyridine **2e**. 2-(4-Fluorophenyl)pyridine **2f** was accessed in 15% yield when equimolar amount of Bu^tOH was added to the reaction mixture. The conversion of 5-cyanoindole **1k** to pyridine **2k** took place simultaneously with vinylation of the indole NH-function.



Scheme 3

As to the mechanistic rationalization, the pyridine self-organization obviously starts from the formation of acetylenic imines **A**, the products of the acetylenic carbanion addition at the C≡N bond of nitriles **1** followed by MeOH neutralization (Scheme 3). These stable intermediates **A** were previously isolated and characterized.[3,13] Further, the triple bond of imines **A** is attacked by the second acetylenic carbanion to produce, after protonation, vinyl acetylenic imines **B** as *E*- and *Z*-isomers. The latter are capable of undergoing the ring-close affording pyridines **2**, while the former remain intact. Note here that nucleophilic addition to the triple bond in the presence of proton suppliers, which synchronically stabilize *trans*-anions emerged in the transition state, proceeds to stereoselectively deliver *Z*-isomers.[14] In aprotic solvents, this stereoselectivity is usually breached in favor of less sterically strained *E*-isomers. This explains the pronounced effect of MeOH on the increase in pyridine **2** yield: MeOH facilitates the formation of *Z*-isomers capable of cyclizing into pyridines **2** *via* the intramolecular nucleophilic hydroimination of the triple bond. The remaining *E*-isomers, which are incapable of intramolecular cyclization, likely undergo the intermolecular head-to-tail dimerization, thereby being a cause of the decrease in the pyridine yield. Since in DMSO the pK_a values of MeOH (29.0)[15] and acetylene (28.8)[16] are almost equal, in the reaction mixture there are enough non-dissociated MeOH molecules to provide electrophilic assistance during the formation of intermediates **B**.

Here it is appropriate to emphasize that 2-arylpyridines are the privileged players in the pharmaceutical scene (see recent reviews[17–19]). Their derivatives are also crucial in bio-imaging applications for the diagnostics of various diseases.[20–22] In recent decades, the 2-arylpyridine-based metal complexes have been extensive utilized as components of OLEDs,[21] dye sensitized solar cells,[23] and photocatalysts.[24] Therefore, no wonder that the syntheses of 2-arylpyridines are still being developed.[25–29]

Thus, the reaction of nitriles with acetylene gas in KOH/DMSO/MeOH superbase media to give pyridine represents a new case of base-mediated acetylene-driven self-organization (two molecules of acetylene and one molecules of nitrile) of complex heterocyclic compounds. Despite the modest yields of the target pyridines, this one-pot synthesis may be preparatively useful because the insufficient reaction efficiency is compensated by the simplicity of the operation and availability of the starting compounds and auxiliaries. From theoretical point of view, the result of this work contributes to better knowledge and understanding of the above multi-molecular self-organization phenomenon.

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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.7801.

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