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Acetylene-driven multi-molecular assemblies of high complexity: imidazo[1,2-*a*]pyridines and 5-chloro-*N*-[2-(imidazo[1,2-*a*]pyridin-6-yl)vinyl]pyridin-2-amine

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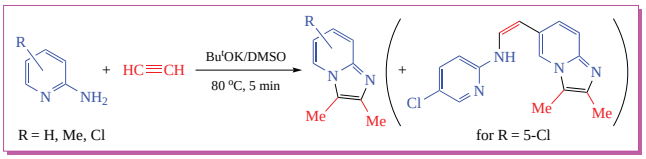
Acetylene reacts with 2-aminopyridines in the superbase system KOBu^t/DMSO (the initial acetylene pressure ~8 atm, 80 °C, 5 min) to give 2,3-dimethylimidazo[1,2-*a*]-pyridines in up to 60% yields. In the case of 2-amino-5-chloropyridine, along with 'normal' product, (*Z*)-5-chloro-*N*-[2-(2,3-dimethylimidazo[1,2-*a*]pyridin-6-yl)vinyl]pyridin-2-amine is formed in 40% yield. These multi-molecular assemblies involve parallel nucleophilic addition of N-centered anions to the triple bond and ethynylation of the forming C=N bond.



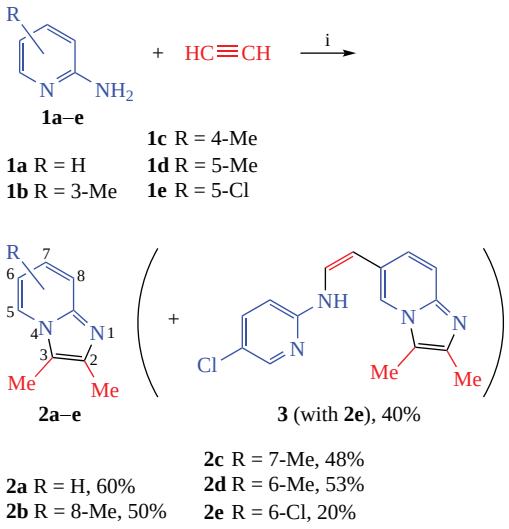
Keywords: acetylene, imidazo[1,2-*a*]pyridines, 2-aminopyridines, superbases, ethynylation, vinylation.

Dedicated to Academician Irina P. Beletskaya on the occasion of her jubilee.

In recent years, multi-molecular assemblies of complex molecules, triggered and driven by acetylenes, proceeding in superbase media gain strength.[1] Among these molecular self-organizations are the assemblies of pyrroles[2] and 1-acetyl-1,3-bis(arylamino)butanes[3] from arylamines and several molecules of acetylene gas. In all these reactions, acetylene simultaneously plays a role of both electrophile and nucleophile that is a ground of this self-organization phenomenon.[1]

In this communication, we share the preliminary results obtained during the investigation of the reaction between substituted 2-aminopyridines **1a**–**e** with acetylene gas in the superbase systems leading to imidazo[1,2-*a*]pyridines **2a**–**e** (Scheme 1).† In the case of 2-amino-5-chloropyridine **1e**, along with 'normal' compound **2e**, (*Z*)-5-chloro-*N*-[2-(imidazopyridin-6-yl)vinyl]pyridin-2-amine **3** was predominating. As follows from the structure of these products, they are assembled from one molecule of 2-aminopyridine and two molecules of acetylene (products **2**) and from two molecules of 2-aminopyridine **1e** and three molecules of acetylene (product **3**).

Earlier,[4,5] imidazopyridine **2a** was isolated in 20% yield from the reaction mixture after the treatment of 2-aminopyridine with acetylene under pressure of 16 atm at 200–210 °C in the presence of equimolar amount of KOH in dioxane. The product of the analogous cyclization, 9-vinyl-1,2-dimethylimidazo[1,2-*a*]benz-imidazole, was obtained in 8–12% yield in the reaction of 2-aminobenzimidazole with acetylene (13–15 atm, 195–210 °C)



Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, DMSO, 80 °C, 5 min (for **1a**–**d**); Bu^{t}OK, Bu^{t}OH, DMSO, 70 °C, 5 min (for **1e**).

† *The reaction of 2-aminopyridines* **1** *with acetylene (typical procedure).* A mixture of 2-aminopyridine **1** (10 mmol) and Bu^{t}OK (10 mmol, 1.12 g) in DMSO with 0.05% of water content (50 ml) was placed into a 0.25 dm^3 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 ~ 8 atm) and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again, heated (heating mantle) up to 80 °C within 10–12 min and kept at this temperature for 5 min. Then the heating mantle was switched off and removed from the reactor. After cooling the reactor to room temperature (within 25–30 min), the mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were washed with H_2O (3 × 20 ml) and dried over K_2CO_3. The solvent was evaporated under reduced pressure, and the pure 2,3-dimethylimidazo[1,2-*a*]pyridine **2** was isolated by column chromatography (basic Al_2O_3, hexane–diethyl ether with gradient from 1:0 to 0:1). For characteristics of compounds **2a**–**e** and **3**, see Online Supplementary Materials.

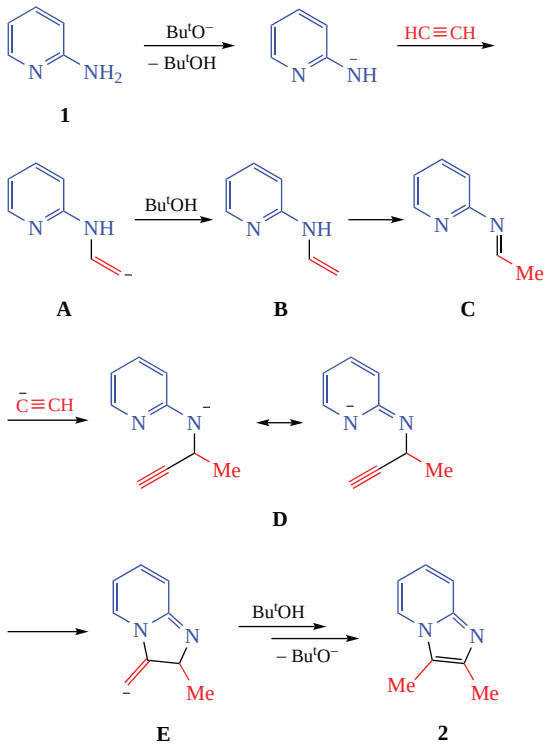
Table 1 Optimization of the reaction conditions for the reaction of 2-aminopyridine **1a** with acetylene.[a]

Entry	Base	*P*/atm	*T*/°C	*t*/min	Conversion of **1a** (%)[b]	Yield of **2a** (%)[c]
1	KOH	8	100	180	100	8[d]
2	KOH	8	80	30	13	traces
3	Bu^{t}OK	12	80	60	100	25[e]
4	Bu^{t}OK	12	60	60	42	traces
5	Bu^{t}OK	8	70	10	63	18
6	Bu^{t}OK	8	80	60	100	48
7	**Bu^{t}OK**	**8**	**80**	**5**	**100**	**60**
8	Bu^{t}OK	8	80	20	100	55
9	Bu^{t}OK	6	80	30	57	12
10	Bu^{t}ONa	8	80	5	5	none
11	Bu^{t}ONa	8	80	60	87	25

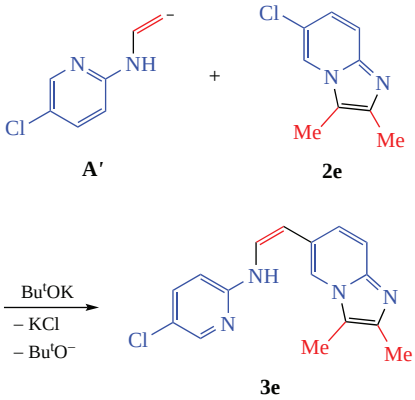
[a] 2-Aminopyridine **1a** (10 mmol), base (10 mmol), DMSO (50 ml), closed stirred reactor. [b] According to ^{1}H NMR data of the crude product. [c] Isolated yield after column chromatography (Al_2O_3, *n*-hexane/diethyl ether, with gradient from 1 : 0 to 0 : 1). [d] Low yield is associated with unoptimized work up and chromatographic isolation. [e] Tar formation.

in the presence of CuCl in dioxane.[6] These works were not further continued probably due to the harsh reaction conditions.

The selected representative experiments on optimization of this reaction are illustrated in Table 1. We have focused our main efforts on minimization of the tar formation (due to the acetylene oligomerization) and elaboration of the isolation procedure, including the work up and the chromatography of the crude material. The variable parameters were superbase systems, initial acetylene pressure, reaction temperature and time. Most of the parameter combinations tested proved to be inefficient or low efficient. For example, when the reaction was carried out at 70 °C (10 min), the yield of the target product dropped to 18% (entry 5). The variation of the temperature in the range of 75–80 °C within 2–10 min led to just insignificant unstable change (± 2%) of the product yield. In all the runs, ^{1}H NMR



Scheme 2



Scheme 3

spectra of the crude materials contained weak signals of pyrroles similar to those reported.[2]

The assembly of imidazopyridines **2** (1 : 2 adduct) likely starts with the nucleophilic addition of 2-aminopyridine **1** to acetylene *via* carbanions **A** (Scheme 2). The thus formed (vinylamino)-pyridines **B** rearrange to imines **C**, which are then attacked by acetylenide anions to generate nitrogen-centered anions **D** (the recently discovered *aza*-Favorsky reaction).[7] The latter are actually diazaallyl anions, wherein the negative charge is also translated to the pyridine ring. The pyridine nitrogen site of anions **D** undergoes the ring closure *via* the intermolecular nucleophilic addition to the triple bond and, after protonation of the anionic adducts **E** and prototropic rearrangement, affords the final imidazopyridines **2**.

In the case of 2-aminopyridine **1e**, (*Z*)-5-chloro-*N*-[2-(imidazopyridin-6-yl)vinyl]pyridin-2-amine **3e** in 40% yield was unexpectedly obtained, though under milder conditions (see Scheme 1). This 2 : 3 adduct is obviously a result of the interception of the initial anions **A′** by imidazopyridine **2e** *via* the nucleophilic substitution of its chlorine atom (Scheme 3). It could be expected that anions **A′** were capable of interception by other halogen containing electrophiles. *e.g.*, chlorobenzene or 2-chloropyridine, but that was not the case as the special experiments showed. This can be rationalized in terms of aromaticity loss in the pyridine ring of imidazopyridine **2e**, in which chlorine atom became more reactive.

Imidazo[1,2-*a*]pyridines attract a growing attention owing to their close relation to pharmaceuticals (see reviews[8]). There are mainly prepared by the three-component reaction between 2-aminopyridines, aldehydes and acetylenes (A^3 condensation) in the presence of transition metal-tailored catalysts (see reviews[9]), also, metal-free synthesis now being rapidly developed (see recent reviews[10]). However, the yields of imidazopyridines available by the known protocol (32–50%)[11] are comparable with those of this work.

In conclusion, apart from the major topic of this paper (multi-molecular assemblies driven by acetylene), the two-component transition metal-free and pot-atom-step economical synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines and acetylene gas, elaborated in this work, may be considered as an alternative approach to the synthesis of the same special imidazo[1,2-*a*]-pyridines. The question if this reaction is possible with monosubstituted acetylenes is now under our investigation.

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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.2023.02.005.

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