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Metal-Free Cyclotrimerization for the De Novo Synthesis of Pyridines**

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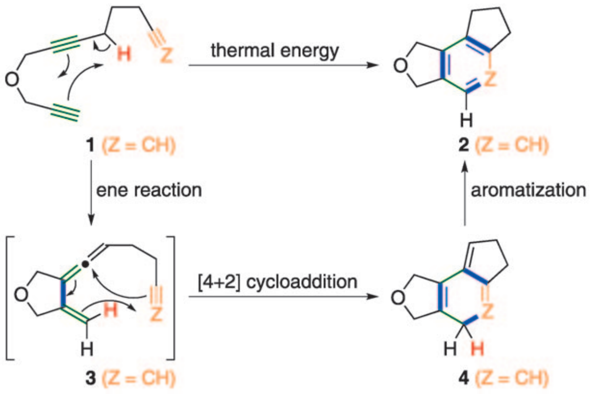
cascade reactions · cycloaddition · ene reactions · nitriles · pyridines

In memory of Keith Fagnou

The de novo synthesis of pyridines from smaller molecules has attracted a lot of interest since pyridine is one of the most important heterocyclic structural motifs in numerous areas of organic chemistry. Many developed syntheses, such as the Kröhnke or the Hantzsch reaction, rely on condensation reactions of smaller molecules, but a number of synthetic approaches including cycloaddition reactions have also been documented.[1] Over the last few decades the use of transition-metal-catalyzed transformations of rather simple alkynes and nitriles to generate pyridines has led to the establishment of the [2+2+2] cycloaddition as an efficient tool to even access complex organic frameworks containing pyridine rings. The cross-cyclotrimerization reaction, which leads to pyridines, can be catalyzed by a large range of early to late transition metals; sometimes, however, two metals are needed to complete the cyclization.[2] The formal mechanism of the reaction comprises two consecutive steps for the intra- as well as the intermolecular case. In the first step two alkynes or a diyne are oxidatively cyclized to give a metallacyclopentadiene. The second step can be imagined as either an insertion or a [4+2] cycloaddition reaction with a nitrile, after which the formation of the pyridine is complete.

While the exclusively intramolecular construction of arenes from tethered triynes or cyanodiynes by transition-metal catalysis is well known, the uncatalyzed reactions, especially of the latter, have not so far been investigated.[3] The thermal reaction of different triynes at rather high temperatures (up to 200 °C) in a microwave indeed yields the expected tricyclic arenes in up to 87 % yield.[4] However, Sakai and Danheiser have now described an interesting version of the uncatalyzed formal [2+2+2] cycloaddition of cyanodiynes that yields functionalized pyridines.[5] The transformation is based on pericyclic cascade reactions and requires thermal energy to proceed successfully, with reaction temperatures higher than 115 °C needed. In a preceding publication, Danheiser and co-workers investigated the formal metal-free, bimolecular [2+2+2] cycloaddition reaction of diynes with electron-deficient alkenes and alkynes (Scheme 1).[6] These investigations led to the proposal that a propargylic–ene/Diels–Alder reaction cascade is responsible for generating the benzene derivative **2** from triyne **1**. The outcome of the reaction, especially the structure of triene **4** from the propargylic–ene and Diels–Alder cycloaddition reaction, provided the key evidence for the reaction mechanism. These findings are in contradiction to earlier proposed mechanisms, including those based on highly strained carbocycles and biradical intermediates, which would result in an isomeric structure of **4**.[4]



Scheme 1. Transition-metal-free cyclotrimerization of triynes (green and orange bonds: original alkyne bonds, blue bonds: newly formed bonds; the arrows highlight the new bond formations).

The analogous reaction for the construction of pyridines from cyanodiynes is more complicated because the nitrile group rarely adopts the role of the enophile or dienophile in electrocyclization reactions, such as the Alder–ene or Diels–Alder reaction, respectively, which is required to either start or complete the cyclization cascade. There are few examples of successful cyano–ene reactions with olefins, but in these cases either strong Lewis acids such as BCl_3 are necessary to activate the nitriles[7] or an in situ generated nitrile oxide acts as the enophile to yield cyclic oximes from acyclic precursor compounds.[8]

In the present study, the formation of the pyridines can proceed through two distinct cascade pathways, depending on

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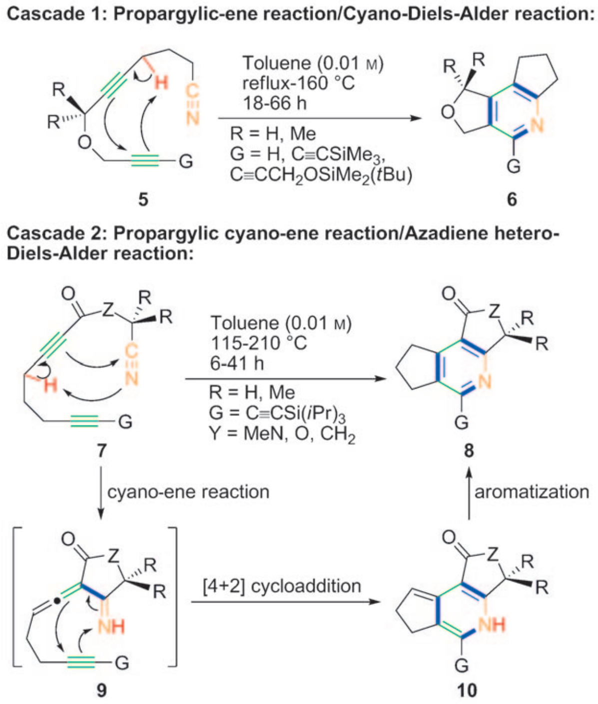
the structure of the cyanodiyne substrate, both being very different from the transition-metal-catalyzed case (Scheme 2). Cascade 1 starting from **5** is comparable to the mechanism shown in Scheme 1 for triyne **1** (with Z = N). The ene reaction leading to intermediate **3** is more facile than the corresponding cyano–ene reaction and would dominate in the case when both pathways are possible. The high reactivity of the vinylallene (**3**) in Diels–Alder reactions makes it possible for the nitrile to react as the dienophile to form dieneimines analogous to **4**. After aromatization of the corresponding dieneimine, pyridine **6** can be isolated in yields ranging from 30 to 96 %.



Scheme 2. Formal [2+2+2] cycloaddition reactions of cyanodiynes, which proceed through two different pathways (green and orange bonds: original alkyne and nitrile bonds, blue bonds: newly formed bonds; the arrows again highlight the new bond formations).

In cascade 2 the propargylic–ene reaction is blocked, because no hydrogen atom is available at the required position; in **7** this position is blocked by a carbonyl group. Here, the cyano–ene mechanism becomes operative, with a hydrogen atom on the opposite side of the triple bond being attacked, which leads to the allenylimine **9**. The following hetero-Diels–Alder reaction of the azadiene moiety with the second triple bond yields the triene **10**, which furnishes the pyridine **8** after aromatization. Again, high reaction temperatures are necessary for this alternative pathway. Further experiments confirmed the feasibility of the cyano–ene reaction, including the isolation of a tautomerization product from an assumed intermediate. The reaction of a cyanoalkyne with an enol ether as an alkyne equivalent hints at the general possibility of an intermolecular reaction pathway. In this case, an enamine results from the cascade reaction, which needs to be transformed to the pyridine by acid catalysis.[9]

These investigations, despite requiring rather high reaction temperatures, open the door to new approaches for the synthesis of substituted pyridines by a formal [2+2+2] cycloaddition without the need for transition-metal complexes as catalysts. The utilization of the cyano group in unusual reaction modes is particularly noteworthy. The possibility of switching between two different pathways might be a convenient way to direct the reaction outcome, depending on the structure of the starting material. However, in this context, the synthesis of the starting materials such as **5** and **7** requires particular attention, because the complete intramolecular reaction fixes the configuration of the pyridine ring. Moreover, hydrogen atoms adjacent to the triple bond are a necessity to start the ene reaction, a requirement that the metal-catalyzed cycloaddition reactions does not need. Further examination might be directed at the possibility of using gentler reaction conditions, maybe by the use of Lewis acid catalysts. Connecting two cyanodiynes or a cyanodiyne and a triyne at the terminal alkyne moieties might be a possibility for the preparation of biaryls by this approach. In summary, the described method establishes an interesting alternative approach for [2+2+2] cycloaddition reactions without the need for transition-metal catalysts.

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