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The domino hexadehydro-Diels-Alder reaction: an elegant way towards polyacenes

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In a recent paper in Nature Chemistry, Thomas Hoyer and coworkers showed the possibility to use hexadehydro-Diels-Alder (HDDA) reactions in a domino process to access functionalized polyacenes in high yields. Up to four consecutive HDDA reactions were employed to build new highly conjugated polyaromatic molecules.

Hexadehydro-Diels-Alder (HDDA) reaction has found a growing interest^{1,2,3} since the original paper from Hoyer group in 2012 where they showed all the potentiality of this reaction by designing *ad hoc* precursors.⁴ This reaction consists of the [4+2] cycloaddition between a 1,3-diyne and an alkyne called a "diynophile" to yield a benzyne, which is subsequently trapped by a nucleophile or a compound able to run a new cycloaddition. Indeed, the HDDA is very close to a classical Diels-Alder reaction with a diene and a dienophile, but here, the C=C double bonds are substituted by C≡C triple bonds. As a consequence, a six-membered cycle including a [3]cumulene and a conjugated alkene functions is formed. This unusual structure is no more than a mesomeric form of the more known aryne moiety, a highly reactive functional group. Since 2012, HDDA reaction is considered as a new way to form arynes.⁵

In principle, the newly formed C≡C triple bond of the aryne is also able to react as a diynophile in another HDDA reaction to form a naphthyne, which is also able to behave as diynophile itself, etc... (scheme 1A). The prerequisite for such a domino process is that the HDDA reaction rates are all significantly higher than the trapping process. This means that HDDA reaction must be an intramolecular process contrary to the trapping reaction that has to occur intermolecularly. The proof of this concept has been published by Ueda and co-

workers at the end of the 90's who generated naphthynes by this methodology.⁶ They could thus synthesize highly functionalized naphthalenes.^{7,8}

Thomas Hoyer and coworkers recently studied in detail the possibility to use this domino HDDA reaction in order to synthesize diverse polyacenes in a controlled manner.⁹ They were able to generate several naphthynes that were trapped by many different compounds such as furane, anthracene, cyclopentadienone, perylene, etc... providing thus interesting polyaromatic hydrocarbons like compound **3** (scheme 1B). More than 20 examples are provided and the yield of the whole sequence is comprised between 44 and 98%. Given the number of steps implied in the transformation and the degree of complexity of the products compared to the reactants, these figures are particularly high. The molecular diversity resulting from this reaction is really impressive. The polyynes precursors are quite diverse and the trapping reagents are significantly varied. In addition to usual [4+2]cycloaddition partners such as furane, pyrrole or anthracene, the generated naphthyne is able to react and dearomatize substituted benzenes such as o-dichlorobenzene. Interestingly, it is also able to undergo a reductive addition of H₂ (formally) by reacting with cyclooctane, a dihalogenation by reaction with Li₂CuCl₄ or 1-iodophenylacetylene, or a dichalcogenation with phenyldisulfide or phenyldiselenide. Moreover, [2+2] or 1,3-dipolar cycloadditions as well as nucleophilic additions are also possible with suitable reagents.

This very large scope and high yields validate the initial hypothesis assuming that the rate of the intramolecular HDDA reactions is much higher than the intermolecular trapping step. This was made possible thanks to the initial design of the substrate. Actually, the authors decided to link each consecutive 1,3-diyne moiety by a two-atom unit, like an ortho-substituted phenyl group or a dimethylene for instance. They showed that by increasing significantly the concentration of the very reactive arynophile furan (like using it as the solvent of the reaction), it was possible to trap the benzyne intermediate before the naphthyne is formed. Indeed, the trapping process, which is bimolecular (first-order in the concentration of furan), is sensitive to the concentration whereas the HDDA reaction is a unimolecular event so that it is obviously not sensitive to the concentration. However, this behavior was only observed with furan as the trapping reagent (since it is one of the most reactive arynophile) and with the flexible dimethylene linker. Because of its rigidity, the ortho-substituted phenyl linker probably increases significantly the rate of the successive HDDA reactions by better preorganizing the cycloaddition partners compared to the

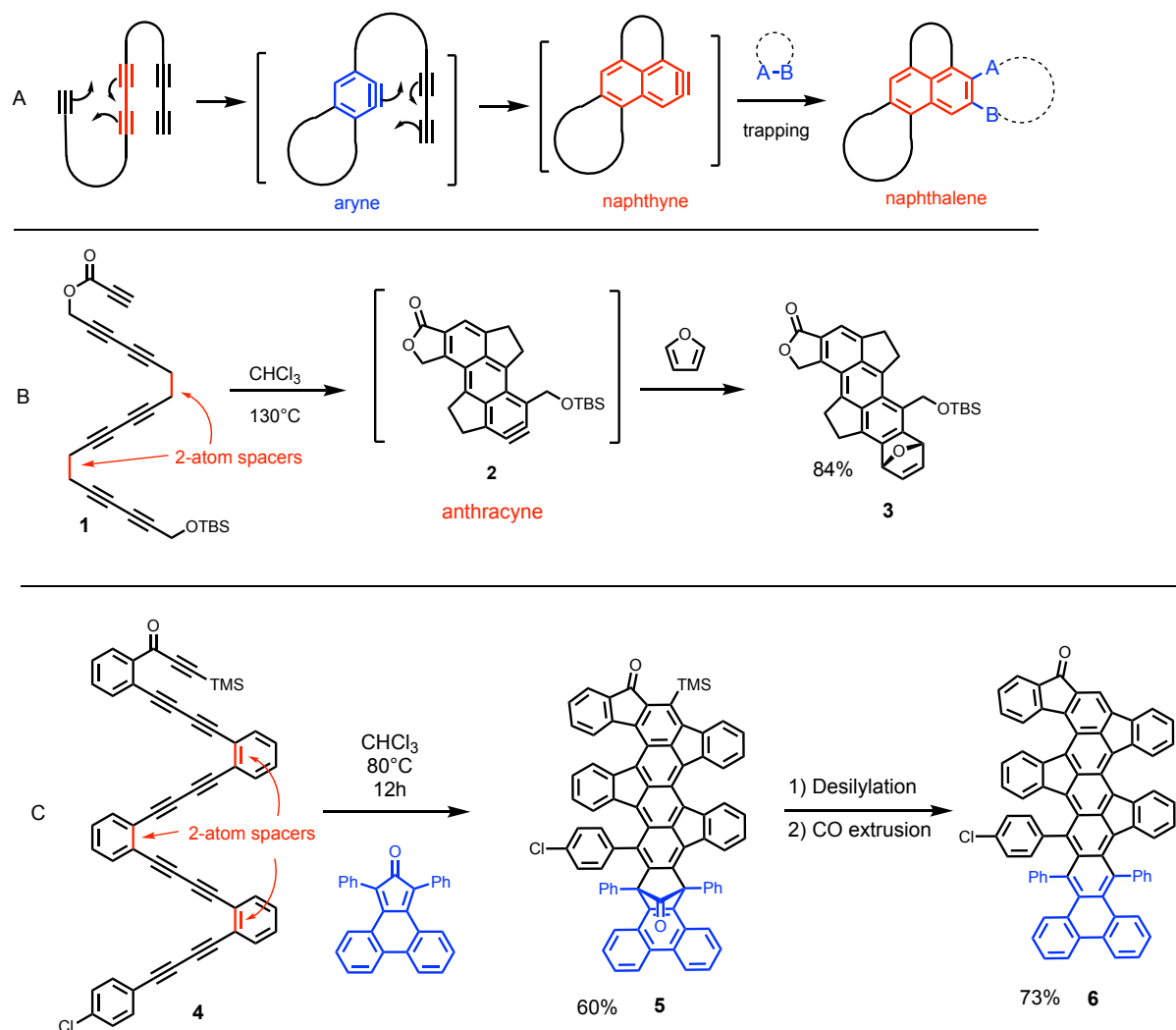
dimethylene linker, which allows for a higher degree of freedom. Another significant difference between these two kinds of linkers is the reactivity of the resulting naphthyne with perylene. Indeed, with dimethylene linker, the naphthyne added (as expected on the bases of examples from the literature) to the bay-region diene of the perylene. Subsequently, hydrogen ejection occurred thermally to rearomatize the system. In the case of the ortho-substituted phenyl linker, the addition does not occur on the bay region but on one benzenic ring, dearomatizing thus the system without possible rearomatization. This difference is essentially due to the steric demand imposed by the larger aryl linker, as suggested by theoretical calculation.

Anthracynes could also be generated, meaning that three HDDA reactions are at stake before the trapping process. Three examples are reported (51 to 84% yield). The trapping proceeded with furan or diethyl 3,4-furandicarboxylate. Again, two-atom linkers between the 1,3-diyne units were used. The introduction of one three-atom linker in the center of the polyynes completely prevents the formation of the anthracyne. Only the benzyne or the naphthyne intermediate could be formed before the trapping event. This example illustrates well the necessity to use two-atom linkers in order to induce multiple intramolecular HDDA reactions.

Furthermore, the authors pushed their methodology successfully to the formation of tetracynes in order to get tetracenes in high yields (60 to 88% yield) after trapping with anthracene or a cyclopentadienone (scheme 1C). It means that four HDDA reactions are at stake in addition to the trapping reaction, which is a genuine *tour de force*. In addition to this elegant sequence, they induced a desilylation and a CO extrusion with cyclopentadienone adduct **6** to produce a highly conjugated compound that absorbs light in the whole visible range until 1000 nm with a significant extinction coefficient (mainly above $10^3 \text{ mol}^{-1} \cdot \text{L} \cdot \text{cm}^{-1}$). This kind of panchromatic chromophores absorbing in the near-infrared range are very appreciated in the field of organic electronic devices.¹⁰ Considering the easiness of the domino HDDA reaction, the essential effort of synthesis was focused on the formation of the polyynes that requires several classical steps (twelve steps for compound **4** but no more than seven steps for the previous polyynes leading to naphthyne or anthracynes).

To conclude, domino HDDA reactions represent a new efficient method to synthesize functionalized polyacenes in high yields. On a fundamental point of view, the authors of this article revealed a completely novel strategy towards polyaromatic molecules. They show it

was possible to control the reactivity of the precursors by designing them properly. There is no doubt that organic chemists willing to synthesize such compounds for various applications will abundantly use this methodology in a near future.



Scheme 1. Examples of the domino HDDA reaction

(A) The general concept with two consecutive HDDA reactions.

(B) The formation of an anthracene derivative.

(C) The formation of a tetracene derivative followed by desilylation and CO extrusion.

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