Organic LETTERS

Letter

pubs.acs.org/OrgLett

Open Access on 08/25/2015

Rates of Hexadehydro-Diels–Alder (HDDA) Cyclizations: Impact of the Linker Structure

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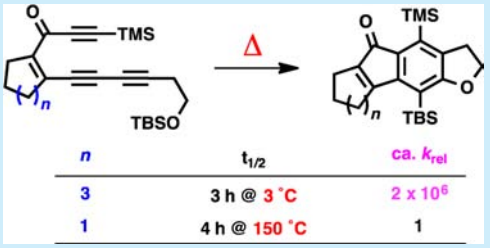
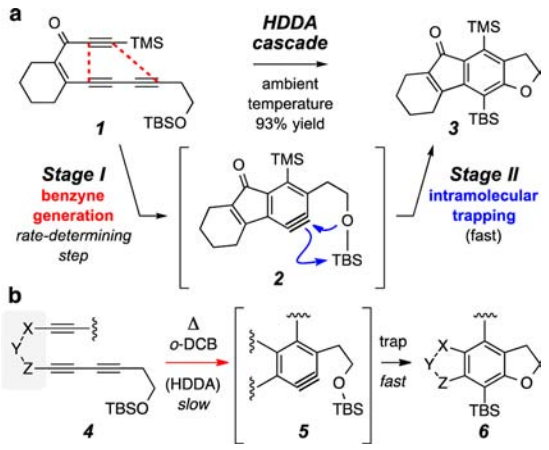
Supporting Information

ABSTRACT: The rates of the hexadehydro-Diels–Alder (HDDA) reaction of substrates containing, minimally, a 1,3,8-triyne subunit are reported. Several series of related substrates, differing in the nature of the three-atom tether that links the 1,3-diyne and diynophile, were examined. Seemingly small changes in substrate structure result in large differences in cyclization rate, spanning more than 8 orders of magnitude. The reactivity trends revealed by these studies should prove useful in guiding substrate design and choice of reaction conditions in future applications.



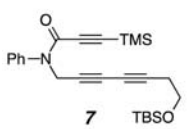
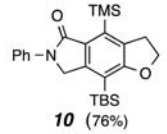
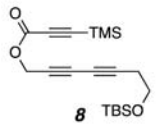
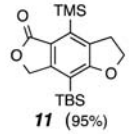
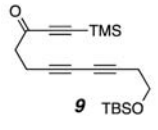
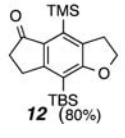
The thermal cycloisomerization of triynes to benzyne[1] intermediates[2] is a powerful process because of its considerable generality.[3] For example, we showed that the triyne **1** isomerized to the indenone product **3** at ambient temperature via the reactive benzyne **2** (Scheme 1a), an overall process that we have termed a hexadehydro-Diels–Alder (HDDA) cascade.[3] This sequence comprises an initial rate-limiting benzyne formation (**1** to **2**, Stage I) followed by a rapid benzyne trapping event (**2** to **3**, Stage II, here with a tethered silyl ether moiety[4]). Because each of the steps in the cascade is purely a thermal process, many opportunities for using this platform for the development of novel chemistries and/or fundamental mechanistic understanding are presenting themselves.[5,6]

Scheme 1. (a) Early Example of a HDDA Cascade (b) Generic Substrates Whose Rates of Cyclization Are Reported Here



Triynes have a wide range of activation barriers for the initial HDDA cycloisomerization event (i.e., Stage I).[2c,3] The structural features that influence the reactivity of dienes and dienophiles in classic [4 + 2] Diels–Alder cycloaddition reactions (including intramolecular variants[7]) have been delineated in manifold reports[8] (including the first[9]). By contrast, the results we report here represent the first systematic study of HDDA cyclization rates. We have examined the reactivities of several sets of related HDDA substrates, all of which share the common generic structure **4** (Scheme 1b). The relative reactivities of the members of each set provide insight about the impact of structure on the rate of the HDDA cyclization. All substrates differ primarily, but in a complementary fashion, in the nature of the "XYZ" atoms that serve to link the diyne to diynophile (Table 1, various carbonyl functional groups; Table 2, various symmetrical tetraynes; and Tables 3 and 4, enones embedded within different

Table 1. HDDA Cycloisomerization Rates of Substrates 7–9, Differing in the Carbonyl Functional Group in the Tether

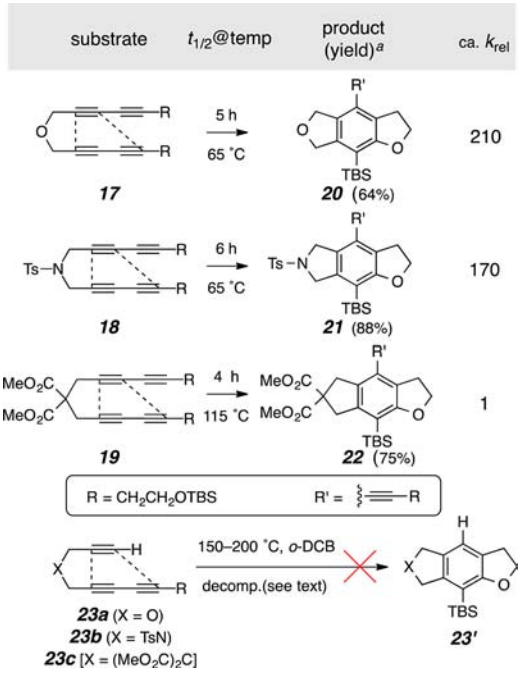
substrate	$t_{1/2}$ @temp	product (yield)[a]	ca. k_{rel}
	5 h, 90 °C		30,000
	5 h, 110 °C		3000
	6 h, 180 °C		1

[a]Yields represent material following chromatographic purification from experiments performed in *o*-DCB on scales of 20–40 mg of substrate.

Received: July 19, 2014
Published: August 25, 2014

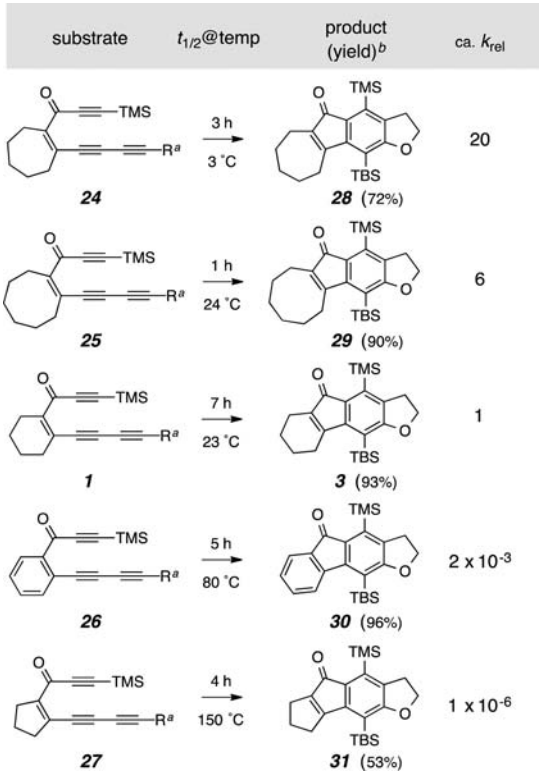
dx.doi.org/10.1021/ol502131r | *Org. Lett.* 2014, 16, 4578–4581

Table 2. HDDA Cycloisomerization Rates of Substrates with No Conjugated Electron-Withdrawing Substituents



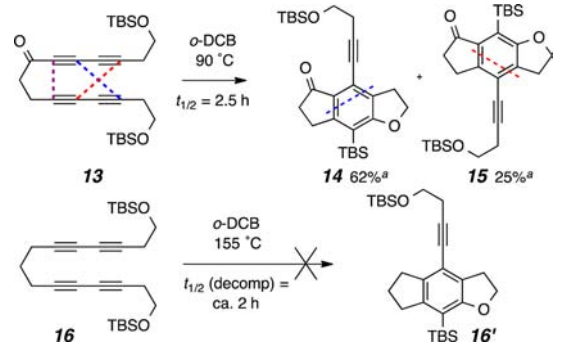
[a]Yields represent material following chromatographic purification and are from experiments performed on scales of 20–40 mg of substrate in 1,2-DCE for **17**, $CDCl_3$ for **18**,[4] and *o*-DCB for **19**.

Table 3. HDDA Cycloisomerization Rates of Substrates Having Various Carbocycles Embedded in the Linker



[a]R = CH_2CH_2OTBS. [b]Yields represent material following chromatographic purification from experiments performed on scales of 20–40 mg of substrate, in various solvents, and for ca. 5 half-lives (see SI).

Scheme 2. HDDA Cyclization of the Unsymmetrical Ketotetrayne 13 Showing the Competition between Normal (Blue) and Abnormal (Red) Modes of Reaction



[a]Yields represent material following chromatographic purification.

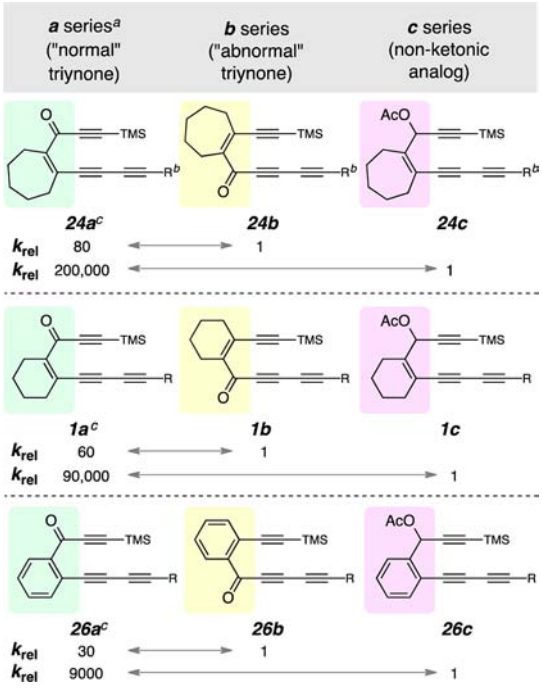
carbocycles). The half-life for the Stage 1 cyclization, the rate-limiting step for all of these unimolecular isomerizations, was determined for each substrate. For the sake of consistency, the same *β*-(*tert*-butyldimethylsilyloxy)ethyl moiety was used as the internal trapping group[4] (cf. **5** to **6**) for each substrate. However, because the intramolecular Stage II trapping event is much faster than the Stage I HDDA reaction, it is safe to presume that the exact choice of the nature of this benzyne trap is not particularly relevant. The range of relative rates of the HDDA reactions described here encompasses more than 8 orders of magnitude. In some instances even seemingly subtle changes within the tether structure were observed to have a relatively large impact on rate.

The triyne (or tetrayne) substrates in each table are listed in order of decreasing reactivity. The first set of triynes is shown in Table 1 (**7**–**9**); each cleanly gave the expected product (**10**–**12**, respectively) upon heating. These triynes differ only in the nature of the carbonyl functional group that is innate to the three-atom tether in each. The reaction temperature and time for the observed half-lives are given in the second column. The approximate relative rates (rightmost column) for the unimolecular HDDA cyclization (the rate-determining step) span more than 4 orders of magnitude (see Supporting Information (SI) for details of how the relative rates and half-lives were determined). The reactivity sequence is amide **7** > ester **8** ≫ ketone **9**. These carbonyl functional groups affect both the electronic character of the diynophile (in this series, the monoyne) as well as the population of the reactive conformation[10] (cf. reactive rotamer effect[11])—the structure depicted for each of **7**–**9**. Intramolecular Diels–Alder (IMDA) reactions have been reported for analogous pairs of classical triene substrates in which the only difference was the presence of an amide vs an ester[10] or of an ester vs a ketone[11] functionality within the tether. Those cases also showed greater reactivity of the amide over the ester and of the ester over the ketone, respectively, which is similar to what we have observed for this series of HDDA reactions.

We proceeded to study the unsymmetrical tetrayne **13** (Scheme 2), in which the linker is the same three-carbon ketone subunit that is present in the triyne **9**. Now two modes of HDDA cyclization are possible. These differ in whether the 1,3-diyne bearing the carbonyl substituent functions as the 2*π* (blue) or the 4*π* (red) HDDA component, that is, the diynophile or the diyne, respectively. The first, which gives product **14**, we call the 'normal' mode, and the second, leading to **15**, is the 'abnormal.' The normal mode of cyclization is favored over the abnormal,

dx.doi.org/10.1021/ol502131r | *Org. Lett.* 2014, 16, 4578–4581

Table 4. Rate Effects of Changing the Location (a[a] Series vs b Series) or the Presence (a[a] Series vs c Series) of an Electron-Withdrawing Group (Carbonyl) within the Triyne Linker



[a]Structures **1a**, **24a**, and **26a** are identical to **1**, **24**, and **26** given in Table 3. [b]R = CH_2CH_2OTBS. [c]The k_{rel} values for **24a**:**1a**:**26a** are 9000:400:1 (data from Table 3).

although only by a factor of ca. 2, as judged from the **14**/**15** product ratio.[12] For comparison we prepared the tetrayne **16**, in which the tether comprises three methylene groups and, therefore, lacks the ketone carbonyl. It proved to be noticeably less reactive, ultimately decomposing at higher temperatures to mixtures that showed no evidence of formation of the expected HDDA product **16**.[13] Thus, the ketone carbonyl group in **13** has a definite activating effect[3] on both the normal (blue) and abnormal (red) pathways.

In sharp contrast to the fact that **16** is not a competent HDDA substrate, each of the analogously symmetrical tetraynes **17**−**19** smoothly undergoes an HDDA cascade to give essentially a single product, **20**−**22**, respectively (Table 2). The only structural difference among **16**−**19** is the nature of the central atom within the three-atom linker joining the two identical 1,3-diyne moieties. The most reactive of **17**−**19** is the ether-linked tetrayne **17** and the least is the malonate **19**. These three span a relative rate ratio of ca. 200, with the sulfonamide **18** nearly as reactive as the ether **17**. The more reactive ether and amide tetraynes have, perforce, a more electronegative substituent on each of their propargylic carbons as well as a slightly shorter carbon-to-heteroatom bond length compared to the all-carbon linker in the nonproductive substrate **16**. Notably, the rate enhancement from the reactive rotamer/Thorpe−Ingold effect[11] imposed by the malonate substituents in **19** apparently is sufficient to overcome the reluctance of **16** to undergo HDDA cyclization (cf. Scheme 2).

From early reports of these types of cycloisomerization reactions, it can be deduced that tetraynes (i.e., a linked pair of two separated 1,3-butadiyne units) show greater reactivity than their analogous triynes.[14,15] We have now deduced the extent to which the presence of the bystander alkyne in each of the substrates **17**−**19** activates the diynophile to which it is attached. This is perhaps most clearly seen by comparison of the rates of the identically tethered tetrayne and triyne ketones **13** and **9**, respectively. The former (tetrayne) reacted nearly 5 orders of magnitude faster than the latter (triyne) [$k_{rel(\mathbf{13a}\ vs\ \mathbf{9})} = 8 \times 10^4$]. While it might be tempting to assign a significant portion of this difference to a steric effect imposed by the trimethylsilyl group in **9** that becomes more pronounced as the transition structure geometry is approached, we have evidence that this is not a dominant factor. Namely, each of the substrates **23a**−**c** (Table 2, bottom) is a triyne analog of the tetraynes **17**−**19** in which one of the two diyne units has been truncated to a simple terminal monoyne (propargyl) moiety. Each of these triynes proved to be much less reactive than the analogous tetrayne. When finally heated to temperatures where starting material disappeared,[16] decomposition to dark-colored, presumably oligomeric materials was observed without any clear evidence for formation of the product of an HDDA cascade. These observations further emphasize the fact that an alkyne substituent enhances the diynophilicity of the 2π-participant in HDDA cyclizations.

This type of activation of one π-component by a second of its own kind is well-known, of course, in alkene chemistry. For example, 1,3-butadiene enters into a [4 + 2] cycloaddition much faster with itself than with ethylene as the dienophile, which is consistent with the lower HOMO−LUMO gap for the former pair of reactants. We suggest that this same type of behavior is operative in conjugated di-, tri-, and poly-ynes. For example, neat samples of liquid 1,3-butadiyne have been reported to detonate.[17] Moreover, a report of isolation of 1,3,5-hexatriyne (produced by a fungus) gave rise to "colorless crystals...which decomposed slowly at −20° and explosively at room temperature."[18] In the course of defining the boundaries for stability of progressively longer linear conjugated poly-ynes, researchers in the Tykwinski laboratory have established that multiynes are greatly stabilized by the presence of extremely bulky α,ω-terminal substituents that prevent the internal poly-yne chains from associating with one another in parallel fashion.[19] Taken together with the fact that the HDDA cycloaddition of three alkynes to their corresponding benzyne is computed to be exothermic by ca. 50 kcal mol^{-1} (!),[20] we submit that the instability of unhindered, conjugated multialkynes is due to the fact that they enter into HDDA dimerization and, then, oligomerization with sufficiently rapid heating to result in uncontrolled (and typically unwanted) reactions. Moreover, we suggest that carbyne [$(C{\equiv}C)_n$], the elusive missing allotrope of carbon, will most likely never be tamed as a tractable substance because its inherently low HOMO−LUMO gap will necessarily result in facile cross-linking reactions having the nature of an HDDA process.[21]

We next examined the influence of the size and/or the nature of the carbocycle upon which the diyne and diynophile are templated. The series of five triyne substrates **1** and **24**−**27** was studied, and their reactivities are shown in Table 3. Variation of the carbocycle embedded within the diyne-to-ynone linker results in HDDA-cyclization rates that, remarkably, span ca. 7 orders of magnitude. The most reactive of all HDDA substrates we have studied to date[3,4,6] is the cycloheptene-containing triyne **24**, which cyclizes within hours at 0 °C. In contrast the cyclopentene substrate **27** requires heating at 150 °C to achieve 50% conversion in 4 h.

The intraring bond angles at the alkene carbons differ across this series of substrates. This impacts the angles at which the diyne and ynone substituents are splayed with respect to the cycloalkene, which, in turn, dictates the distance between the proximal pair of terminal diyne/diynophile carbons in each

dx.doi.org/10.1021/ol502131r | Org. Lett. 2014, 16, 4578−4581

reactant. This splay angle (and resulting distance) is largest for the cyclopentene and smaller (and more similar) for the 6-, 7-, and 8-membered cycloalkenes (see SI). These subtle changes in geometry translate into the large differences in reactivity. This acute sensitivity to small geometric changes is reminiscent of observations made for Bergman (enediynes[22]) and Hopf (dienyne[23]) electrocyclizations.

Finally, we studied the effect of (i) reversing the relative orientation of the enone in a set of otherwise identical substrates [cf. the **a** ("normal") series vs the **b** ("abnormal") series in Table 4] and (ii) interrupting the contiguous conjugation by replacement of the ketone carbonyl with a reduced carbinol derivative (cf. the **a** series vs the **c** series in Table 4). Each normal member of the isomeric pair of enones reacted faster than the abnormal analog, although only by a factor ranging from 30−80. This is not dissimilar to the result presented earlier for the two modes of reaction within ketotetrayne **13**.[12] Finally, each normal enone reacted faster than its acetate analog by a considerably larger rate factor (ca. 10^3 to 2×10^5), again emphasizing the significant acceleration afforded by an electron-withdrawing carbonyl group.

In conclusion, the results presented here provide useful insight into both electronic and structural factors that affect the rate of HDDA cyclization. For example, substrates having a heteroatom within the three-atom tether joining the 1,3-diyne to the diynophile cyclize faster than their methylene analogs (Table 2). Even minor geometric differences within the linker can have a dramatic effect on cyclization rates (cf. cyclic enones in Table 3). The presence of an additional bystander alkyne (cf. tetrayne substrates) provides a rate enhancement (several orders of magnitude) similar to that of a carbonyl substituent (cf. Table 2 with 13 vs 9). These studies should help guide the planning of future applications of HDDA processes for the synthesis of benzenoid target structures. These results expand the scope of product types accessible by an HDDA strategy, especially when considered in conjunction with the growing body of HDDA-derived benzyne trapping reactions.[3−6]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the General Medical Institute of the National Institutes of Health (GM65597) for support of this research.

■ REFERENCES

(1) We adopt here the following terminology: (i) *o*-aryne (or aryne): any aromatic ring containing an adjacent pair of sp-hybridized carbon atoms (this includes any of the subfamilies of, for example, benzynes, pyridynes, naphthalynes, or indolynes); (ii) *o*-benzyne (**2**): the parent 1,2- or *o*-dehydrobenzene; (iii) a benzyne derivative (collectively, "benzynes"): any substituted *o*-benzyne analog; this may or may not be fused to an additional, nonaromatic ring. Thus, the arynes described here from HDDA cycloisomerization of a triyne subunit are "benzynes".

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(12) We also studied two close structural analogs of the ketotetrayne **13** in which one of the two siloxyethyl substituents was replaced by a siloxypropyl group on the top and on the bottom diyne, respectively. Each reacted at essentially the same rate and to give the same ratio of normal to abnormal products as **13**. See SI (pp 20−26) for details.

(13) When **16** was heated at 165 °C for 1 h, only a few percent of **16** remained, and no HDDA-derived product was seen. We judged that substantial oligomerization of **16** was occurring.

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