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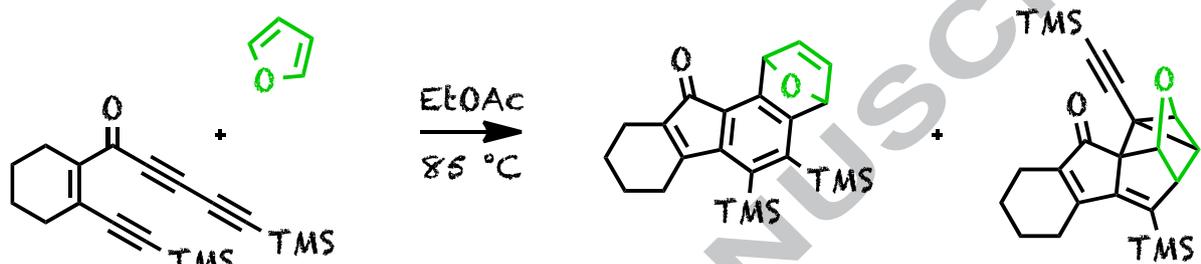
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product ratio depends
on the concentration of furan



Competition between classical and hexadehydro-Diels–Alder (HDDA) reactions of HDDA triynes with furan

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We dedicate this paper to the memory of Harry H. Wasserman, whose amalgamation of scholarship, artistry, and humanity stand as an admirable model for all to emulate.²

Keywords: homo-Diels–Alder; [2+2+2]-cycloaddition; HDDA-cascades; concentration dependence

ABSTRACT

We report here thermal reactions between furan and one of three related triyne substrates. Each triyne is capable of reacting initially in two modes: (i) *unimolecular* hexadehydro-Diels–Alder (HDDA) reaction or (ii) *bimolecular* Diels–Alder reaction between one of its alkynes with furan. The relative rates of these initial events are such that two of the substrates react essentially in only one of modes (i) or (ii). The third is intermediate in behavior; its bifurcation is dependent on the concentration of the furan reactant. These results teach, more generally, principles relevant to the design of efficient HDDA-based reaction cascades. (98 words)

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1. Introduction

In the hexadehydro-Diels–Alder (HDDA) reaction,³ so named⁴ because the triyne reacting components are lacking six hydrogen atoms when compared with the diene and dienophile reactants present in the most common, classic Diels–Alder cycloadditions, the [4+2] cycloisomerization process results in formation of a reactive benzyne intermediate. This benzyne can then be captured, either intra- or intermolecularly with a suitably reactive trapping agent to provide highly functionalized benzenoid products. We also refer collectively to the two consecutive steps of benzyne formation, which is always rate limiting, and benzyne trapping as an HDDA cascade.

We have come to recognize that in order to achieve a successful HDDA cascade, there are two limiting reactivity conditions that must be satisfied. This is a consequence of the importance of properly matching the reactivities of the two principle components in an HDDA cascade. At one extreme, the benzyne trapping agent must capture the benzyne rapidly enough to prevent the benzyne from being intercepted by another molecule of the HDDA triyne substrate. This situation often results in non-specific oligomerization and formation of intractable, darkly colored product mixtures. For example, we reported that numerous bimolecular trapping agents are capable of intercepting benzyne **2** when triyne **1** is heated in their presence (e.g., a chloroform solution of **1** containing acetic acid cleanly gave the acetate ester **3**, Figure 1a).⁴ However, in the

absence of a suitably reactive trap, triynes like **1** give rise to an undecipherable mixture of products when heated in non-participating solvents like CDCl₃, *o*-dichlorobenzene, or acetonitrile.

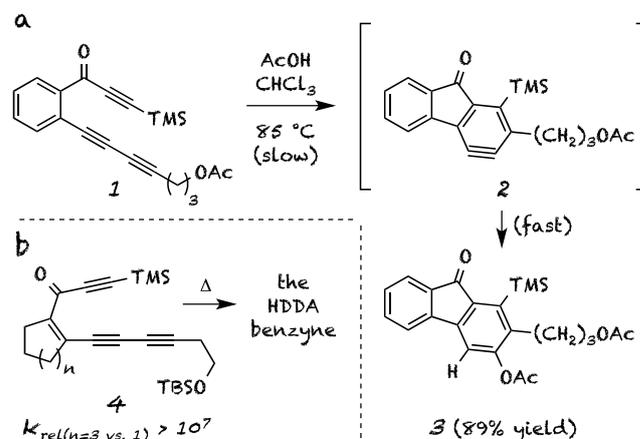


Figure 1. (a) An example of an HDDA substrate that leads to an efficient cascade (e.g., **1** to **3**) using a good trap (e.g., AcOH) but that gives no characterizable products in the absence of any trapping agent (the 3-acetoxypropyl substituent is an innocent, non-participating substituent). (b) HDDA cyclization rates vary widely (cf. **4**).⁷

At the other end of the compatibility spectrum, the trapping agent must not react prematurely with the HDDA triyne before that substrate has had ample time to cycloisomerize to the reactive benzyne. An example of this behavior is the reaction of substrates of type **1** with a prospective primary amine trap. Amines add quite rapidly to ynones to give vinylogous amides, thereby precluding useful HDDA chemistry in this type of experiment.⁶

Of course, the rate of the HDDA cycloisomerization event inherent to the particular substrate under study impacts directly the feasibility of each given trapping agent. We recently reported that the rates of HDDA cyclization can vary substantially, for example, ranging over a factor of $>10^7$ for the series of substrates **4** (cf. Figure 1b).⁷ Collective experience to date with HDDA cascades^{4,5,7,8} clearly indicates that the window of opportunity within which to find suitably matched polyynes and trapping agents is, fortunately, quite wide.

2. Results and Discussion

Here we describe a focused study of the reactions between the potential HDDA triyne substrates **5-7** (reactants in Figure 2, panels a-c, respectively) with furan as the trapping agent, a reactant known to undergo Diels-Alder cycloaddition to both suitably reactive alkynes as well as arynes. We refer to substrates like **5** as 'normal' HDDA triynes because the monoyne (the diynophile) bears the carbonyl activating group. In contrast, diynones **6** and **7** are seen as 'abnormal' HDDA substrates because the carbonyl activating group resides on the 4π conjugated diyne subunit.⁹

Heating triyne **5** in neat furan at 85 °C (sealed vessel) for two days resulted in complete consumption of **5** and clean formation of the HDDA cascade product **8**. This, then, is an example of a process in which the rate-limiting HDDA reaction (to produce the benzyne **9**) has had ample time to proceed prior to engagement with the trapping agent—furan. By contrast, the triyne **6**, after 2 days at 145 °C in furan, gave rise to the interesting and unanticipated polycyclic ketone **10**. None of the product expected from an HDDA cascade was observed. Formation of **10** can be rationalized by the intermediacy of the classic Diels-Alder adduct **11**, formed by addition of furan to the electron deficient ynone. The pendant aryl alkyne in **11** is then poised for an intramolecular [2+2+2] homo-Diels-Alder cyclization to provide **10**.¹⁰ Our assignment of structure **10** to this product was initially based on analysis of HSQC and, especially, HMBC NMR data and subsequently confirmed by a single crystal X-ray diffraction study.¹¹

The intermediate diene **11** was not observed by monitoring the reaction progress by either ¹H NMR spectroscopy or TLC, suggesting that the initial formation of **11** is the rate-limiting event in the transformation of **6** to **10**. This is consistent with expectations from a recent computational study of intramolecular [2+2+2] cycloaddition reactions.¹² The preference of **6** to give **10** is an example where the rate of HDDA cyclization is too slow to be compatible with the inherent reactivity of the trapping agent (i.e., furan) with one of the alkynes in the potential HDDA substrate.

The triyne **7** has a cyclohexenyl enone tether, which we have shown leads to a rate enhancement of ca. 200–400 fold for its HDDA cycloisomerization vs. that of a substrate with an aryl ketone linker like that in **5**. Triyne **7** showed intermediate behavior compared to that of the extreme cases of **5** and **6**. Namely, when heated in neat furan, at 85 °C both the HDDA cascade product **12** and the polycyclic ketone **13** were formed and to a nearly equal extent. Thus, this example represents a case

where the rate limiting HDDA and premature trapping events were essentially equally competitive. Because the former involves a unimolecular rate-determining step (r.d.s.) and the latter a bimolecular r.d.s., the concentration of trapping agent should impact the ratio of products **12** and **13**. A concentration dependence study was performed and the key results are summarized in Figure 2c. Indeed, as the amount of furan was reduced, the preference for formation of the HDDA cascade product **12** was increased. By limiting the furan to only five (entry 3) or one (entry 4) equivalents, the benzenoid **12** was formed exclusively within the limits of our analysis. Reducing the concentration of an external trapping agent, then, represents a strategy for improving an HDDA outcome that is being compromised by premature trapping of a polyyne substrate.¹³

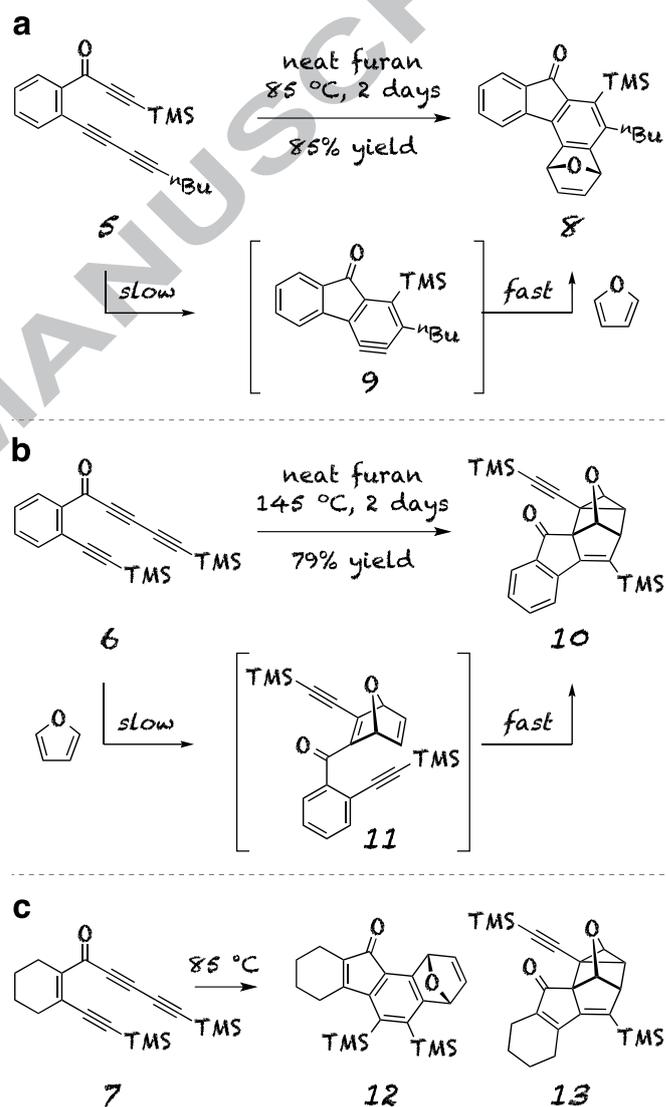


Figure 2. Reactions in panels a and b were performed in neat furan as solvent at an initial concentration of triyne of 0.03 M. The initial concentration of **7** (panel c experiment) in EtOAc/furan was 0.05 M; the ratios of **12**:**13** are initial ratios, measured (by ¹H NMR spectroscopy) at <40% conversion of **7**.

3. Summary

Triynes **5**, **6**, and **7** react by divergent pathways when heated in the presence of furan. The first undergoes an initial, rate-limiting HDDA cycloisomerization to the benzyne intermediate **9**, which is then rapidly trapped by furan to give the HDDA cascade product **8** [mode (i)]. The abnormal analog of **5**, namely **6** is a less reactive HDDA substrate. As such it reacts first with furan at its central alkyne to give the intermediate diene **11**, which then undergoes an intramolecular homo-Diels-Alder reaction to give **10** [mode (ii)]. Triyne **7** is intermediate in behavior, giving rise, competitively, to products of both modes (i) and (ii) (i.e., **12** and **13**, respectively) and the product ratio is affected by the bulk concentration of furan that is present.

Collectively, the three case studies reported here bring to light relative reactivity conditions that need to be met in order to allow for an effective HDDA cascade process. At one extreme, if the trapping agent is too slow at capturing the benzyne—a function of both the inherent rate constant for that event as well as the amount of that agent present in the reaction medium—,¹³ the benzyne will encounter and react with additional copies of the triyne substrate, usually in manifold ways resulting in intractable oligomer formation. We would call this the slow trapping regime. The efficient capture of the benzyne enroute to **12** by furan, even at a unimolar ratio of the two reactants (entry 4, Figure 2c), shows that furan is an exceptionally good trap. Thus, the limitation of the slow trapping regime is not breached by any of the examples studied here. At the other extreme, if the trapping agent, by its nature, is so highly reactive that it captures an alkyne in the HDDA substrate prior to the initial cycloisomerization, then an HDDA cascade process will have been thwarted. This is the case for the reaction of **6** (Figure 2b). Fortunately, the window of opportunity between these extremes is quite wide, which contributes, no doubt, to the broad generality of HDDA cascade chemistry.

Acknowledgments

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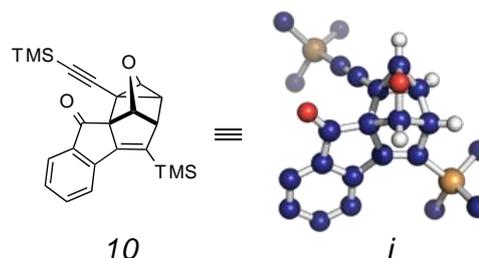
References and notes

1. Present address: Department of Chemistry, IIT Madras, Chennai, 600036, INDIA
2. (a) One of Harry Wasserman's (HHW) many lasting legacies, well-remembered by me, the corresponding author (TRH), is his use of hand-lettered graphics in many of the slides and schemes he created to accompany his scientific lectures and papers. Being calligraphically challenged, I instead surveyed all of the fonts available in popular structure-drawing programs and elected to use "Chalkduster" as the font in the graphics for this paper; it most closely mirrors what I remember of HHW's distinctive handiwork. To my delight, I then learned from the lead author of this paper (QLN) about a popular song that he had learned at a very young age. Nearly all schoolchildren in Vietnam learn this verse, which reverses the time-honored traditions of teaching and learning. It is titled "Bụi Phần." The English translation?—Chalkdust (!). (b) I also am pleased to note (i) that HHW and TRH are academic siblings, having both carried out our Ph.D. thesis research in the laboratory of Professor R. B. Woodward and (ii) that HHW also contributed to the field of benzyne chemistry [Wasserman, H. H.; Solodar, J. *J. Am. Chem. Soc.* **1965**, *87*, 4002–4003; Wasserman, H. H.; Solodar, A. J.; Keller, L. S. *Tetrahedron Lett.* **1968**, *9*,

5597–5600; Wasserman, H. H.; Fernandez, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 5322–5323.] (c) Finally, I share here a memorable encounter with HHW in the late 1990s. I found him at a desk in Tucson, AZ intently inspecting different arrays of paper tetrahedra of various sizes and hues that were artistically strewn in front of him. He was deep in contemplation, mentally and visually revamping the design of the covers of the family of *Tetrahedron* journals. The outcome?—the artistic rebranding that we enjoy to this day. As per usual, HHW was genuinely interested in hearing my opinion of the various options as well as my suggestions for alternative views and approaches.



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Supplementary Material

Preparation procedures and characterization data for each new compound and a copy of the ¹H and ¹³C NMR spectrum of each.