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Two Unusual, Competitive Mechanisms for (2-Ethynylphenyl)triazene Cyclization: Pseudocoarctate versus Pericyclic Reactivity

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Aryl triazenes have been studied over 130 years for their interesting structural, anticancer, and reactivity properties.[1] They have been used in medicinal[2] and combinatorial chemistry,[3] in natural product synthesis,[4] as organometallic ligands,[5] and as precursors to heterocycles.[6] Recently we reported an unusual temperature dependence for the conversion of (2-ethynylphenyl)-triazenes (**1**) into heterocycles.[7] Heating **1i** at 170 °C in *o*-dichlorobenzene (ODCB) gave a ca. 1:1 ratio of an isoindazole aldehyde (**2**) and a cinnoline (**3**) in 95% combined yield (Scheme 1). Heating **1** to 200 °C in ODCB, however, resulted in exclusive formation of **3** in excellent yields (>90%).

To study the generality of these cyclizations for the practical synthesis of heterocycles, we sought to determine the mechanisms for both transformations. The conditions used and the products generated do not support the well-understood mechanisms for isoindazole or cinnoline synthesis,[8] and their concurrent production from the same starting material in the same pot is unique. For the isoindazole product, several factors, such as high temperature and neutral conditions, suggested that cyclization produced carbene **4** (Scheme 2) that could either dimerize or be quenched by oxygen to generate **2**. This cyclization is best described through a *pseudocoarctate* transition state,[9,10] where cyclization and formation of the carbene are simultaneous.[11] Rearrangements similar to this are known,[12] although in the majority of cases they proceed in the opposite direction to give ring-opened products.[13]

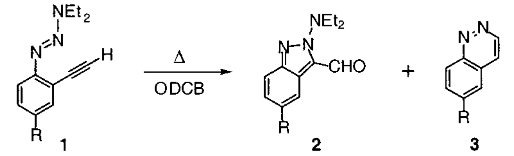
Evidence of carbene **4** was provided by transition state stabilization and trapping studies. Use of Cu salts is known to promote and stabilize carbene (carbenoid) generation;[14] thus, stirring a mixture of CuCl (10 mol %) and **1e** in CH_2Cl_2 at room temperature resulted in slow (96 h) yet nearly quantitative conversion to isoindazole **2e**. Modifying these conditions by heating the mixture of triazene and CuCl (5 equiv) to 50 °C in 1,2-dichloroethane for 12−36 h gave high yields of **2** for nearly every R group on the arene (Table 1). In the case of strongly electron-withdrawing groups (entries i and j), the yields of **2** were lower as dimer formation (**5**) was a competitive side reaction.

To provide additional support for **4**, cyclization to the isoindazole was done in the presence of carbene trapping agents (Scheme 2). Addition of CuCl to a deoxygenated solution of triazene **1c** and 2,3-dimethyl-2-butene (20 equiv) in CH_2Cl_2 gave, after stirring overnight at room temperature, 65% yield of cyclopropane **6**. Intramolecular trapping could be effected by affixing a (1,1′-biphenyl)-2-yl group at the terminus of the acetylenic moiety. Cyclization as above furnished fluorene **7**, the product of intramolecular C−H insertion by the carbene, in 55% yield.

To shed light on the mechanism for **3** and the nature of the intermediates, we performed DFT calculations on a variety of possible cyclization pathways. The reaction energetics for cyclization of the parent triazene (−NH_2) are depicted in Figure 1. Interestingly, a pericyclic reaction to give a planar, six-membered intermediate[15] is the product of thermodynamic control, even though pseudocoarctate cyclization to yield the five-membered ring has a lower barrier. Formation of **4**, however, is reversible, which is consistent with exclusive production of **3** at higher temperatures. NBO analysis[16] showed a notable development of negative charge at C4, going from −0.03 in **1** to −0.22 in **8**. The calculated singlet/triplet gap is 13.6 kcal mol^{-1}. Thus, **8** is most likely a zwitterion with some diradical character.[17]

From these results one could predict the first step after formation of **8** to be protonation at the partially anionic carbon rather than hydrogen abstraction. This was confirmed by using hydrogen donor reagents with differing polarities. Whereas dihydroanthracene-d_4 (5 equiv) gave products with no incorporation of deuterium, reaction of **1e** with benzhydrol-d_2 (4 equiv) gave **3e** where deuteration occurred at *both* the 4-position and 3-position (3:2). No products arising from nucleophilic attack by the benzhydrol oxygen were observed, and relative integration of the protons on benzophenone with those on the cinnoline product showed equimolar formation of both. The deuterium on C3/4 arises from the hydroxyl proton as

Scheme 1



Scheme 2

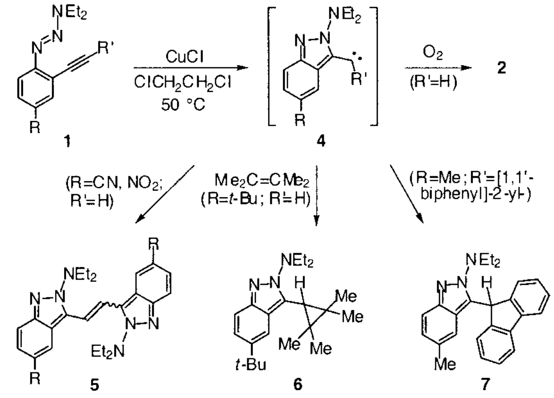


Table 1. Yield of Isoindazole **2** via Cu-Promoted Cyclization of **1**

entry	R	isoindazole **2**	entry	R	isoindazole **2**
a	H	95%	f	Cl	95%
b	Me	90%	g	F	94%
c	*t*-Bu	96%	h	CO_2Me	83%
d	C≡CH	91%	i	CN	60%[a]
e	Br	98%	j	NO_2	54%[b]

[a] Plus 34% yield of **5** (R = CN). [b] Plus 37% yield of **5** (R = NO_2).

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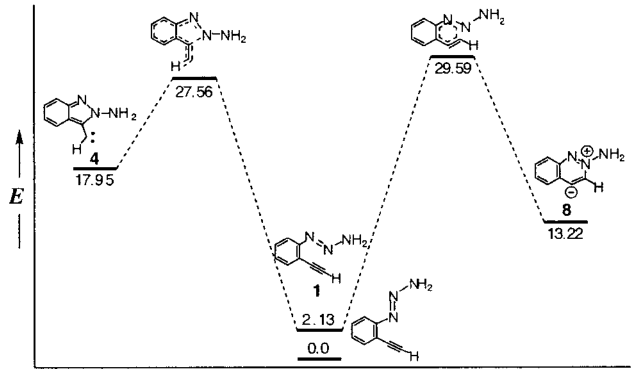
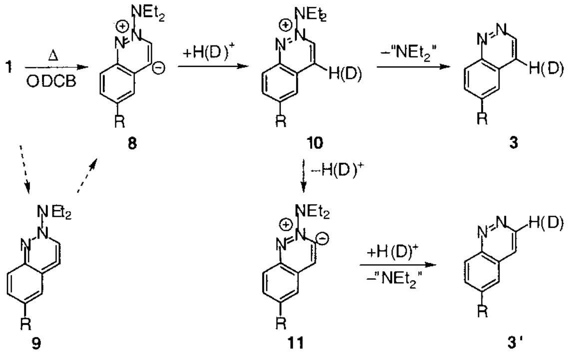
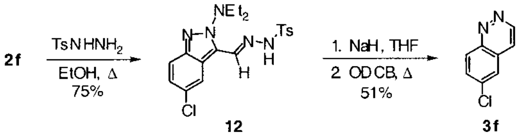


Figure 1. Calculated stationary points for the cyclization of the parent (2-ethynylphenyl)triazene ($-NH_2$); relative energies (kcal mol^{-1}) calculated at the B3LYP/6-31G*(ZPE) level of theory.

Scheme 3



Scheme 4



use of benzhydrol-*d* ($-OD$) furnished a similar C3/4 mixture whereas benzhydrol-*d* ($-OH$) gave *no* deuterated cinnoline.

The above results suggest the mechanism depicted in Scheme 3. Pericyclic ring closure would directly yield **8**, a 3-dehydrocinnolinium ylide, similar to a 3-dehydropyridinium ylide recently described by Shevlin and co-workers.[18] Alternatively, Hopf-type dienyne cyclization[19] might produce allene **9**. Zwitterionic species are known to be one possible structure for highly strained cyclic allenes;[22] however, **9** was not found to be a minimum on the energy hypersurface. Protonation of **8** should lead to **10**. Leakage of the label to C3 in **3′** can be explained by invoking another zwitterionic intermediate (**11**). Similar to Shevlin's system,[18] this appears to be an intermolecular rearrangement where the thermodynamic driving force is greater ylide stabilization by movement of the negative charge closer to the electronegative nitrogen. Indeed, calculations predict **11** to be 12.8 kcal mol^{-1} more stable than **8**.[21]

More complicated is the loss of the $-NEt_2$ moiety from **10**. NMR scale experiments suggest the formation of free Et_2NH. The production of benzophenone clearly indicates a hydride-like transfer must occur at some stage. Although several possible mechanisms can be envisaged, we cannot claim a definitive pathway for $-NEt_2$ loss at this time.[21]

Both experimental and theoretical evidence suggest reversible formation of carbene **4** from the starting triazene, which can regenerate **1** and produce the thermodynamically more stable cinnoline **3** at high temperature. To demonstrate this, we prepared tosylhydrazone **12** (Scheme 4). Alkali metal salts of such hydrazones fragment at 200 °C to furnish carbenes.[22] For our system, generation of **4** at this temperature should induce rearrangement to **1** and thus give **3**. Indeed, deprotonation of **12** and subsequent heating of the resultant anion to 205 °C in ODCB overnight gave 6-chlorocinnoline (**3f**) in 51% yield.

The evidence presented herein strongly supports the reversible generation of carbene **4** as the kinetic intermediate and its transformation into the thermodymanically more stable zwitterion **8**, both of which can furnish useful heterocycles. In addition, the high-yielding, Cu-catalyzed transformation of **1** into **2** represents the first practical synthetic application of a coarctate-type cyclization.[13] Further experiments to show the general utility of these cyclizations as well as to elucidate $-NEt_2$ loss are in progress and will be elaborated shortly.

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Supporting Information Available: Selected spectral data for compounds **1**, **5**−**7** and **12**; NBO analysis for the formation of **8**; ACID plots and Cartesian coordinates for cyclization of **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Formally, the formation of **4** is a coarctate reaction, since at the proximal ethynyl carbon, two bonds are made and two bonds are broken simultaneously. However, the transition state is almost planar and an ACID orbital analysis[10] exhibits a disconnection at the forming σ bond. In analogy to the pericyclic/pseudopericyclic dichotomy, we use the term *pseudocoarctate* to describe the cyclization of **1** to **4**.

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(21) Detailed computational analysis of the transformation of **8** to **11** and of $-NEt_2$ loss will be reported in a full paper.

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