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Beyond Schmittel and Myers–Saito Cyclizations: Rearrangements of 4-Heteroatom-1,2-hexa-diene-5-ynes

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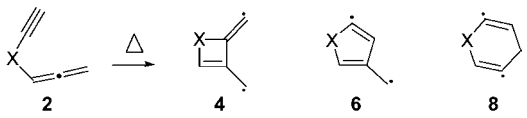
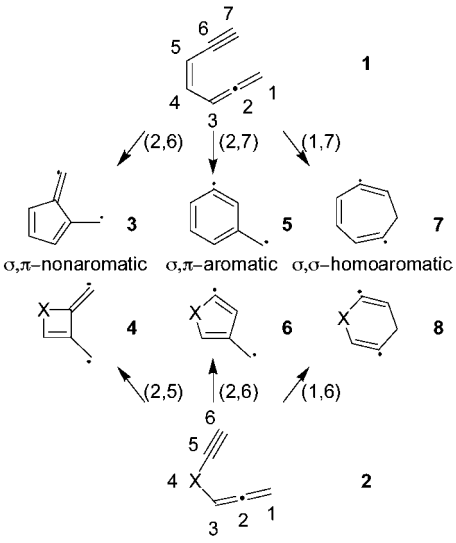
ABSTRACT



The thermal rearrangements of 4-heteroatom-1,2-hexadiene-5-ynes (2) were studied at the BLYP/6-311+G*//BLYP/6-31G* level of theory. Cyclization of 2 to heteroatom-containing cyclopentadienyl structures (6) competes with the Claisen-type rearrangement to acyclic, allenic structures. Cyclizations to cyclobutene (4)- and cyclohexadiene (8)-derived heterocycles are not feasible as a result of high reaction barriers and lower-lying alternative pathways.

The cyclization reactions of enyne-allenes (parent **1**, Scheme 1) lead to biradicals (Myers−Saito C^2-C^7 cyclization[1] and Schmittel C^2-C^6 cyclization[2]) that display antitumor activity (DNA cleavage)[2,3] but also provide access to novel polycyclic materials.[4] The 1,7-cyclization has not yet been observed but seems also viable on the basis of previous computational studies.[5] It is surprising, however, that enyne-allenes with heteroatoms in place of the central olefinic bond (such as **2**) have not been examined. As the driving force in some of the more facile reactions of **1** (such as the formation of **5**) is the aromatic product stabilization, the cyclizations of **2** should be energetically viable if **X** provides a lone pair of electrons.

Scheme 1



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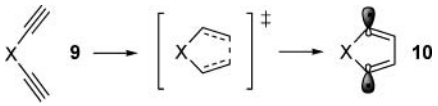
Scheme 2



We could recently show that this is true for the related Bergman-like cyclization of **9** for **X** = OH^+ (Scheme 2) and others.[6]

The present Letter aims at examining the biradical cyclization reactions of **2** in a systematic fashion leading to the formally aromatic hetero-cyclopentadien-di-yl **6**, the homoaromatic cyclohexadiene-di-yl **8**, and the nonaromatic cyclobutene derivative **4** (Scheme 1). Our expectation is that σ-electron-withdrawing, π-electron-donating **X** groups (for our selection see Figure 1) will facilitate the cyclization of

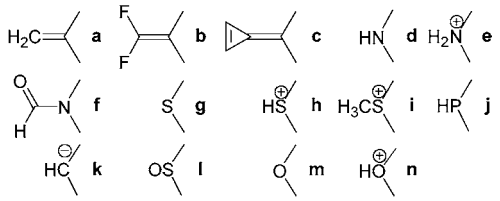


Figure 1. Selection of **X** groups for cyclization reactions of **2**.

2 to the electron-rich systems **4**, **6**, and **8**. This analysis is based on the study of the endothermic retro Bergman cyclization of 1,3,4,6-tetrafluorohex-3-ene-1,5-diyne where the forward reaction even becomes exothermic when the ene-diyne substrate is substituted with fluorine in all positions;[7] electron-withdrawing substitutions generally promote the Bergman cyclization.[8]

For three cyclization pathways of **2** (Scheme 1), relative activation and reaction energies as functions of **X** are presented in Figures 2 and 3, respectively. Table 1 includes the relative energies as well as the NICS[9] values for the TSs and products. Additional materials can be found in Supporting Information.

All computations were performed with the Gaussian 98 software package.[10] Optimizations of all ground-state geometries utilized Becke's pure gradient-corrected exchange functional[11] (BLYP) and the Lee−Yang−Parr nonlocal correlation functional[12] (BLYP) with a 6-31G* basis set.[13] A restricted approach was used in the computational analysis for the closed-shell reactants, whereas an unrestricted broken-

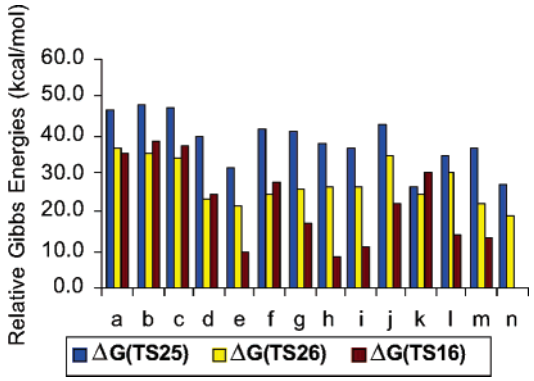


Figure 2. Relative Gibbs activation energies (kcal mol^{-1}, 298 K, at UBLYP/6-31G*) for the thermal cyclization of **2** as a function of **X** to form products **4**, **6**, and **8**.

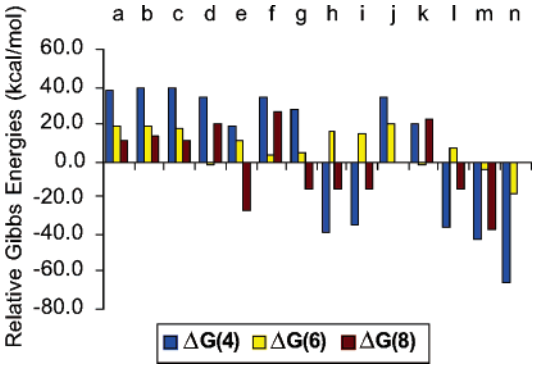


Figure 3. Relative Gibbs reaction energies (kcal mol^{-1}, 298 K, at UBLYP/6-31G*) for the thermal cyclization of **2** as functions of **X** to form products **4**, **6**, and **8**.

spin approach (BS-UBLYP) was used for the open-shell singlet state transition structures (TSs) and products. Analytical vibrational frequencies were calculated for every species to identify the minima and the TSs and to obtain the zero-point vibrational energies (ZPVE) as well as thermal corrections. Additional single-point energies were evaluated using the same level of theory but with a larger basis set (6-311+G*) for all species. As several studies have shown,

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Table 1. Relative Single Point Energies (kcal mol^{-1}) and NICS Values (in the Four-, Five-, and Six-Membered Ring Centers) at BLYP/6-311+G*//BLYP/6-31G* for Transition Structures and Products of the Thermal Cyclization of 4-Heteroatom-1,2-diene-5-ynes (**2**)

	ΔE			NICS		
X	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	50.8	38.3	35.4	−0.8	−5.5	−19.0
b	51.5	36.8	38.0	−2.6	−7.8	−20.4
c	50.6	34.9	37.5	−0.9	−7.9	−19.3
d	41.7	23.6	24.0	−2.1	−12.7	−20.3
e	35.4	23.4	10.6	−5.4	−9.8	−18.3
f	44.2	26.0	28.7	−3.2	−10.8	−18.9
g	42.2	26.1	16.5	−3.2	−13.3	−25.0
h	40.3	27.3	8.1	−3.5	−11.6	−18.9
i	38.9	26.9	10.5	−3.7	−11.2	−22.1
j	45.6	35.3	21.4	−4.2	−9.4	−22.3
k	26.8	22.3	27.3	1.8	−11.0	−15.5
l	36.0	30.6	12.4	−0.9	−11.6	−19.6
m	39.5	24.5	13.9	−1.2	−12.1	−21.8
n	29.5	19.2	na	−8.1	−13.2	na[a]

Products

X	**4**	**6**	**8**	**4**	**6**	**8**
a	42.6	21.4	9.6	2.7	−3.9	na[a]
b	43.1	20.3	11.5	0.6	−6.6	na[a]
c	44.0	18.9	10.2	1.5	−5.0	na[a]
d	34.8	−3.0	19.9	8.1	−2.0	−17.6
e	24.1	13.2	−26.9	−2.3	−8.7	na[a]
f	38.4	4.3	27.5	−0.2	−4.7	−17.3
g	30.9	4.1	−16.0	12.4	−6.1	na[a]
h	−39.6	17.7	−16.9	na[a]	−9.6	na[a]
i	−36.1	15.1	−16.5	na[a]	−8.6	na[a]
j	37.8	21.7	−0.7	1.5	−6.8	na[a]
k	17.9	−6.9	17.9	9.0	5.8	−10.1
l	−39.1	7.2	−19.1	na[a]	−8.4	na[a]
m	−43.3	−3.3	−40.0	na[a]	na[a]	na[a]
n	−69.1	−18.4	na	na[a]	na[a]	na[a]

[a] Unaccounted NICS values for products without ring formation due to either the C^3-X or C^5-X cleavages.

for qualitative purposes this level of theory is well-suited to evaluate the experimental feasibility of the title reactions.[14−16]

The experimental values for the activation barrier and the reaction enthalpy of the Myers−Saito reaction are 23 and −13 ± 4 kcal mol^{-1}, respectively.[15a,17] Our calculated Gibbs activation barriers for the analogous 2,6-cyclization of **2** (**TS_{26}** of **2**) are in the range of 22−37 kcal mol^{-1}. The low activation barriers of 23.3 and 21.8 kcal mol^{-1} for **TS_{26}** when **X** = NH and NH_2^+, respectively, seem therefore experimentally accessible.

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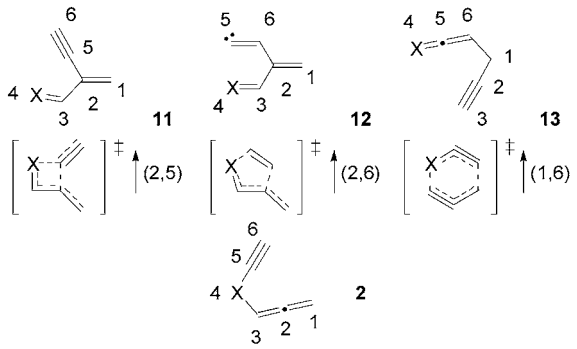
Surprisingly, the supposedly homoaromatic 1,6-reaction of **2** competes with the 2,6-cyclization. As indicated in Figure 2 for **X** = **e**, **g**, **h**, **i**, **j**, **l**, and **m**, the **TS_{16}** barriers (vide infra) are lower than those of **TS_{26}**; the 1,6-reaction also is exergonic (Figure 3). However, this reaction does not result in the expected 1,6-product **8** but instead gives an acyclic product formally resulting from a Claisen-type rearrangement to form the more stable product **13** (Scheme 3).[18,19] The

Scheme 3

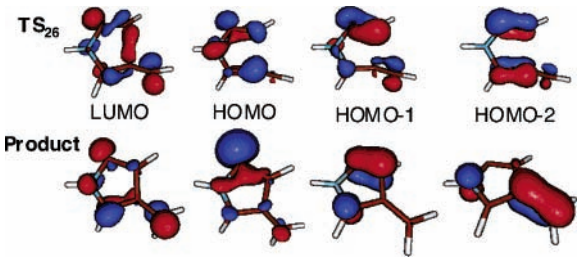


rearrangement is characterized by highly aromatic TSs, as indicated by the negative NICS values at UBLYP/6-311+G* (Table 1).

In analogy to the Schmittel reaction[2] of **1** to **3**, there is the 2,5-cyclization of **2** to the nonaromatic cyclobutadiene derivatives **4** (Scheme 1). The rather high barriers ($\Delta G^{\ddagger}$(**TS_{25}**) = 27−48 kcal mol^{-1}) and endergonicities (ΔG(**4**) = 20−63 kcal mol^{-1}) relative to those of the Schmittel cyclization (35 and 10 kcal mol^{-1}, respectively)[15a] and the availability of alternative pathways render this reaction highly unlikely. As found for the 1,6-reaction of **2**, several four-membered rings do not even form (**4h**, **i**, **l**, **m**, and **n**) because of the facile C^5-X bond cleavage to the more stable dien-ynes (**11h**, **i, l**, **m**, and **n**, Scheme 3).

The frontier molecular orbital (FMO) analysis of the **TS_{26}** family (Scheme 4, **X** = NH) describes the transformation

Scheme 4. Frontier Molecular Orbital Analysis of Transition Structure and Product of 2,6-Cyclization of **2** with X = NH



of the in-plane π-orbitals into the σ-orbitals (HOMO-1); the rotation of the methylene group in the TS accompanies the cyclization. Therefore, the transition structure's active MOs comprise π- (HOMO and HOMO-2) and σ-contributors

(HOMO-1). As a consequence, choice of **X** substituents with σ-accepting ability is crucial for reducing the cyclization barriers. Electronegative substituents lower the barriers by withdrawing in-plane electron density and thus reducing the antibonding character of the $\sigma-\pi$-mixing MO (HOMO-1);[8a] this is evident from the formation of **6d**, **6e**, and **6f** (Figure 2). As found previously, the amplified electron-accepting ability of the nitrogen due to protonation gives the lowest barrier for the protonated amino function **6e**;[6a] this also applies to the lowering of the thiophene reaction barrier (**6h**).

However, unlike the exergonicity observed for the Myers−Saito cyclization, the opposite is found for the 2,6-cyclization of **2** (Figure 3, ΔG(**6**)) with the exception of **X** = NH, where ΔG(**6**) = −1.8 kcal mol^{-1}. Our expectation that the formation of an aromatic sextet would stabilize the product is apparently not met, despite the fact that the computed NICS values indicate appreciable aromaticity in most products **6** (Table 1). For **X** = O, and OH^+, ΔG(**6**) = −3.9 and −17.6 kcal mol^{-1}, respectively, these exergonicities are due to the C^5-X bond cleavage to form the more stable products **12** instead of **6** (Scheme 3).

Hence, the substituent's π-donating ability is insufficient to stabilize the cyclic products **6**. Note that most of the $\mathbf{TS_{26}}$ NICS values are even larger than that of benzene (−7.6) calculated at the same level of theory. The active MO analysis (Scheme 4) supports an early π-delocalized transition structure. Stahl et al.[16] in their study on the aromaticity of the Myers−Saito cyclization reported similar cyclic electron delocalization predominately present in the transition structure π-system that is perpendicular to the molecular plane.

We have examined different reaction pathways of 4-heteroatom-1,2-hexadiene-5-ynes (**2**) depending on **X** functional groups. For **X** = **b**, **c**, **d**, **f**, and **k**, of which **k** seems the most appealing experimental choice, the 2,6-cyclizations of **2** to allylic products **6** should be experimentally accessible as the barriers compare favorably to Myers−Saito reaction of parent **1**. For other functional groups **X** (**a**, **e**, **g**, **h**, **i**, **j**, and **m**) the 1,6-rearrangement of **2** to **13** is energetically preferred. The 2,5-rearrangements have rather high barriers rendering the formations of **4** and **11** unlikely.

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Supporting Information Available: Table of all energies and xyz coordinates of all optimized species. This material is available free of charge via the Internet at http://pubs.acs.org.

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