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Steric Effects in Enyne-Allene Thermolyses: Switch from the Myers-Saito Reaction to the C^2-C^6-Cyclization and DNA Strand Cleavage.[1]

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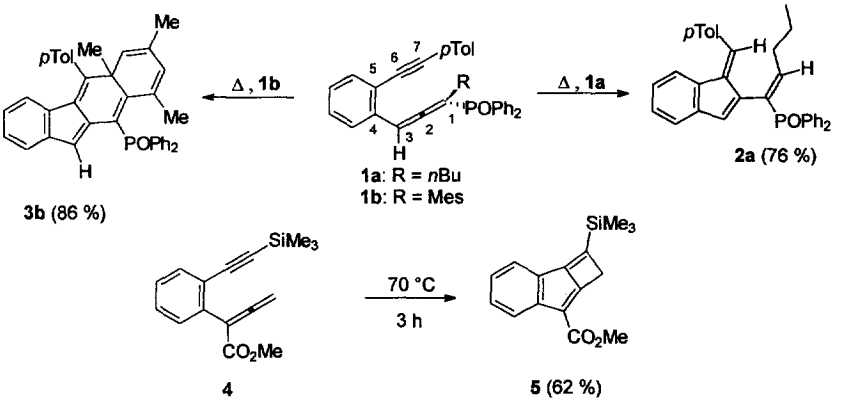
Abstract : The thermal reaction of enyne-allenes **1** with large substituents (*tert.*-butyl, trimethylsilyl) at the acetylene terminus leads to C^2-C^6 cyclization products presumably via an intermediate benzofulvene biradical, whereas with a hydrogen substituent the expected Myers-Saito cycloaromatization product is formed. Effective DNA strand scission can be observed when no intramolecular pathway is available.

Recent results from our laboratory[2,3] and only little later from two other groups[4,5] have unambiguously established that the well-known Myers-Saito cycloaromatization[6,7] of enyne-allenes can be fully suppressed and replaced by a novel C^2-C^6 cyclization through substituent changes at C^7. Accordingly, enyne-allenes **1a,b**[2,3] and **4**[5] afforded various C^2-C^6 cyclization products after heating, *e.g.* **2a**, **3b** and **5**, while with a hydrogen atom at the alkyne terminus solely the Myers-Saito cycloaromatization compounds were obtained.[2,3]

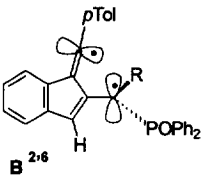


Scheme 1.

As a consequence of this reactivity dichotomy, some earlier claims of Myers-Saito products in thermal reactions of enyne-allenes have been revised just recently[8] and it is to be expected that the C^2-C^6 cyclization is quite a general reaction motif that simply has not been recognized in many cases. Since α,3-didehydrotoluene

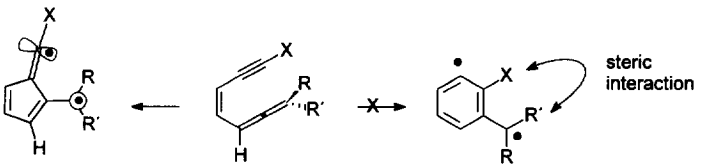
biradical intermediates derived from Myers-Saito cyclization have been invoked in a large amount of enyne-allenes with pharmacological activity[6a,9] it is of considerable importance to clarify which substituents at the alkyne terminus direct the thermal reaction to either of the two cyclization modes.

Our recent mechanistic tests have disclosed for the C^2-C^6-cyclizations of **1a,b** unambiguously the occurrence of a very short-lived benzofulvene biradical **B**[2,6] (R: *n*Bu, Mes),[10] the formation of which seemed to be triggered by the stabilization of the vinyl radical center by the affixed *p*-tolyl group. However, such a biradical stabilizing motif is not recognizable in the formation of benzofulvene **5**, thus posing the question why a C^2-C^6 cyclization has occurred with **4**. Herein, we now describe that the switch from the Myers-Saito to the novel C^2-C^6 cyclization can be brought about solely by *steric effects without the assistance of a radical stabilizing substituent.*



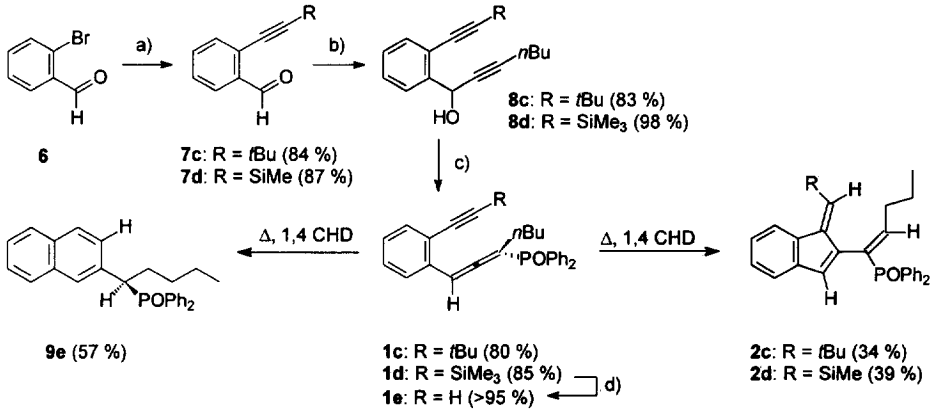
B [2,6]

An inspection of the heat of formation of the two competing biradical intermediates[11] and their transition states in the thermal cyclization of enyne-allenes proposes that the Myers-Saito cyclization should be slowed down or even suppressed by the presence of large groups R, R´ and X.



Scheme 2.

Hence, in order to investigate the steric effects of various substituents at the alkyne terminus on the mode of cyclization the enyne-allenes **1c-e** were synthesized.[12,13] After Pd-catalyzed alkynylation of *o*-bromobenz-aldehyde **6** with the appropriate acetylene R-C≡CH, and after addition of BrMg-C≡C-*n*Bu to **7c,d**, the rearrangement of propargylalcohols **8c,d** with chlorodiphenylphosphine finally afforded **1c,d**, the latter of which gave rise to **1e**.

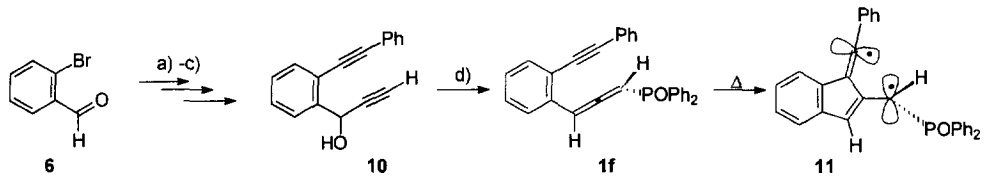


Scheme 3. Synthesis and thermolysis of enyne-allenes **1c-e**. a) R-C≡CH, $PdCl_2(PPh_3)_2$, CuI, NEt_3; b) BrMg-C≡C-*n*Bu, Et_2O; c) $PClPh_2$, THF, NEt_3, -60 °C; d) KOH, MeOH.

In contrast to enyne-allene **1e** that furnished the Myers-Saito cyclization product **9e** in 57 % yield (scheme 3) after heating (50 °C, $t_{1/2}$ = 1 h),[2] the thermolysis of **1c** (40 h, 90 °C) and **1d** (18 h, 90 °C) in toluene with excess of 1,4-cyclohexadiene (1,4-CHD) afforded the benzofulvene derivatives **2c** (34 %) and **2d** (39 %). Their structure[14] could be unambiguously assigned on the basis of their spectral data by comparison with those of X-ray characterized benzofulvenes.[15] Importantly, in the latter two reactions no Myers-Saito cyclization product could be detected at all.

The present thermolysis results demonstrate that the switch from the Myers-Saito to the novel C^2-C^6 cyclization cannot only be effected with aryl substituents but also with sterically large groups such as *t*Bu or $SiMe_3$ at the alkyne terminus. In line with our suggestion of a rate determining benzofulvene biradical formation (*cf.* **B**[2,6]), the thermal cyclization of **1c** (90 °C, 40 h) proceeds slower than that of **1d** (90 °C, 18 h) and that of **1a** (84 °C, $t_{1/2}$ = 1 h) thus following roughly the radical stabilizing abilities of *t*Bu < $SiMe_3$ < Ph.

But what happens if no intramolecular follow-up reaction after C^2-C^6 cyclization to the benzofulvene biradical is possible? To answer this question we have synthesized the enyne-allene **1f**. The reduced steric bulk at the allene terminus in **1f** proposed to us that the derived biradical intermediate **11** should be accessible for intermolecular radical trapping agents.



Scheme 4. Synthesis and thermolysis of enyne-allenes **1f**. a) Ph-C≡CH, $PdCl_2(PPh_3)_2$, CuI, NEt_3, 94%; b) H-C≡C-$SiMe_3$, SDDA, benzene, 85 %; c) KOH, MeOH, 98 %; d) PPh_2Cl, NEt_3, -78 °C, 67 %.

Unfortunately, thermolysis of **1f** (70 °C, 22 h) in presence of PhSH, $(Me_3Si)_3SiH$, or 1,4-CHD as hydrogen donors only furnished complex product mixtures, which could not be separated by chromatography because of decomposition on various stationary phases. Importantly, the mass spectral analysis of these mixtures indicates the presence of several species with molecular weights of $M+H_2$ and $M+H_4$ as main products, whereas the ^{1}H NMR spectra unambiguously exclude the formation of the Myers-Saito cycloaromatization product.[16]

The postulated formation of biradical **11** is additionally suggested by our observation that thermolysis of enyne-allene **1f** induces DNA strand cleavage as demonstrated by the formation of the open circular DNA (form II), when incubated with closed supercoiled pBR322 DNA (form I) at pH 7.0 and 37 °C. As a consequence, enyne-allenes undergoing the novel C^2-C^6 biradical cyclization may constitute compounds with pharmacologically interesting properties.

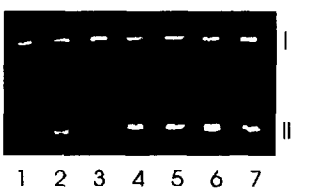


Figure 1. DNA cleavage with enyne-allene **1f**; pBR322 DNA (10 μg/ml) was incubated for 37 h at 37 °C with the enyne-allene **1f**; lane 1-3: DNA without enyne-allene; lane 4-7, **1f** (350 μM in 20 % ethanol in phosphate buffers, pH 7.0, 500 μM). Analyzed by gel electrophoresis (agarose, ethidium bromide).

In conclusion, the present results indicate that the C^2-C^6 cyclization is apparently a general thermal reaction pathway for enyne-allenes that may be triggered by aryl substituents or bulky groups at the alkyne terminus. The benzofulvene biradical intermediate thus generated may be utilized to effect DNA strand cleavage similar to the biradical intermediate in the Myers-Saito cycloaromatization protocol.

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References and Notes:

[1] Thermal and electron transfer induced reactions of enediynes and enyne-allenes, part 6; for part 5 see ref. M. Schmittel, S. Kiau, *Chem. Ber.*, submitted for publication.

[2] M. Schmittel, M. Strittmatter, S. Kiau, *Tetrahedron Lett.* **1995**, *36*, 4975.

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[7] For reviews, see: a) M. E. Maier, *Synlett* **1995**, 13. - b) K. C. Nicolaou, W. M. Dai, *Angew. Chem.* **1991**, *103*, 1453; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

[8] N. Krause, M. Hohmann, *Synlett* **1996**, 89 and 590.

[9] K. C. Nicolaou, P. Maligres, J. Shin, E. de Leon, D. Rideout, *J. Am. Chem. Soc.* **1990**, *112*, 7825.

[10] M. Schmittel, M. Strittmatter, S. Kiau, *Angew. Chem.* **1996**, *108*, 1952.

[11] M. Schmittel, S. Kiau, unpublished results. The energetics of the biradical formation was evaluated using the AM1 semiempirical method. It has been demonstrated that AM1 calculations with configuration interaction (CI = 6) reproduce rather well the experimental heat of the 1,4-dehydrobenzene biradical: H. A. Brummel, G. C. Shields, *Int. J. Quantum Chem., Quantum Biol. Sympos.* **1995**, *22*, 51. In our hands, AM1 calculation on the α,3-didehydrotoluene provided ΔH_f° = 110 kcal•mol^{-1}, close to the experimental value ΔH_f° (exp.) = 108 kcal•mol^{-1} determined in the gas phase: P. G. Wenthold, S. G. Wierschke, J. J. Nash, R. R. Squires, *J. Am. Chem. Soc.* **1993**, *115*, 12611.

[12] The synthesis of enyne-allene **2e** by another, less efficient strategy has been described in reference 2.

[13] Some selected data of the enyne-allenes: e.g. **1d**: ^{1}H-NMR ($CDCl_3$; 200 MHz): δ = 0.31 (s, 9H), 0.92 (t, *J* = 7.1 Hz), 1.28 (m, 2H), 1.62 (m, 2H), 2.48 (m, 2H), 6.72 (dt, $J_{H\text{-}P}$ = 11.2 Hz, *J* = 3.4 Hz, 1H), 7.18 (m, 1H), 7.27 (m, 1H), 7.41-7.58 (m, 8H), 7.73-7.88 (m, 4H); IR (neat): $\tilde{\nu}$ = 2154 (C≡C), 1931 (C=C=C).

[14] **2c**: ^{1}H-NMR ($CDCl_3$; 200 MHz): δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 1.46 (m, 2H), 2.01 (m, 2H), 5.79 (s, 1H), 6.16 (d, $J_{H\text{-}P^*}$ = 3.2 Hz, 1H), 7.06-7.17 (m, 3H), 7.18-7.30 (m, 2H), 7.34-7.50 (m, 6H), 7.62-7.74 (m, 4H); **2d**: ^{1}H-NMR ($CDCl_3$; 200 MHz): δ = 0.11 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H), 1.48 (sext, *J* = 7.4 Hz, 2H), 2.06 (m, 2H), 5.83 (s, 1H), 6.34 (d, $J_{H\text{-}P^*}$ = 3.2 Hz, 1H), 7.03-7.16 (m, 3H), 7.21-7.30 (m, 2H), 7.34-7.51 (m, 6H), 7.57-7.81 (m, 4H).

[15] M. Schmittel, M. Keller, S. Kiau, M. Strittmatter, unpublished results.

[16] In analogy to known Myers-Saito cyclization products (*cf.* ref. 2) the CH_2POPh_2 group in the putative Myers-Saito cyclization product from thermolysis of **1f** would be expected to show up as a doublet at 3.5 ppm with a characteristic $J_{H\text{-}P} \approx 11$ Hz in the ^{1}H-NMR spectrum.

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