Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6177-6180, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01393-2

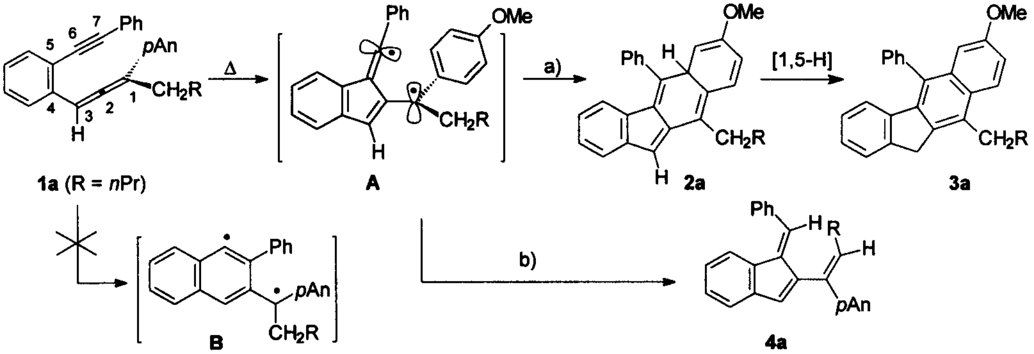
Ring Strain Effects in Enyne-Allene Thermolysis: Switch from the Myers-Saito Reaction to the C^2-C^6 Biradical Cyclization [1]

Michael Schmittel,* Jens-Peter Steffen, Dominik Auer and Michael Maywald

Institut für Organische Chemie der Universität Würzburg,
Am Hubland, D-97074 Würzburg, Germany

Abstract : The mode of the thermal cyclization of enyne-allenes **1** depends on ring strain effects: when the ene functionality is part of a benzene, cyclohexene or cycloheptene ring the novel C^2-C^6 biradical cyclization is observed, while when it is part of a cyclopentene ring the Myers-Saito cycloaromatization is registered.
© 1997 Elsevier Science Ltd.

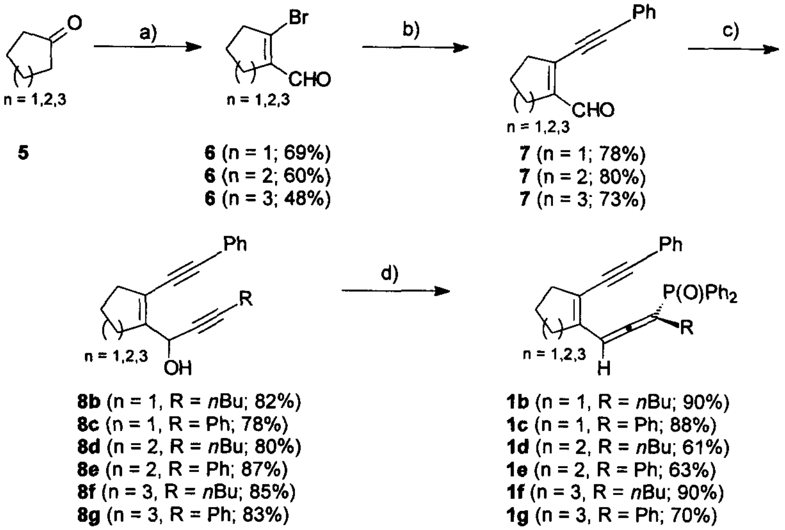
Recent results from our laboratory[2,3] and later from two other groups[4,5] have unambiguously established that the well-known Myers-Saito cycloaromatization[6,7] of enyne-allenes via biradical **B** can be completely replaced by a novel C^2-C^6 cyclization as soon as aryl groups or sterically demanding substituents are affixed to the acetylene terminus. Mechanistic investigations[8] and DFT calculations[9] indicate that the novel cyclization proceeds via intermediate biradical **A** the vinyl radical center of which is stabilized by the attached phenyl group.[3b] After rapid intramolecular follow-up reactions **A** gives rise to either formal Diels-Alder or ene products. For example, after heating enyne-allene **1a** afforded both C^2-C^6 cyclization products **3a** and **4a**, with no Myers-Saito cycloaromatization compounds formed via **B**.[10]



Scheme 1. a) Formal Diels-Alder reaction via biradical **A**; b) formal ene reaction via biradical **A**.

Since the thermal Myers-Saito biradical cyclization has been invoked in a large amount of enyne-allenes with pharmacological activity[6a,7,11] it is of considerable importance to clarify which structural motifs will direct the thermal reaction to either of the two cyclization modes. 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 *ring strain effects with all other substituents kept identical* as demonstrated by the thermolysis results of the novel enyne-allenes **1b-g**.

After formation of the 1-(2-bromo-1-cycloalkenyl)carboxaldehydes **6** from the corresponding cyclic ketones **5**,[12] subsequent Pd-catalyzed cross coupling of **6** with phenylacetylene furnished aldehydes **7**. Alcohols **8b,c** were prepared by addition of BrMg-C≡C-R to **7**, while alcohols **8d-g** could be afforded after reaction of aldehyde **7** with the appropriate sodium diethyldialkynylaluminates (SDAA).[13] Finally the rearrangement of propargylalcohols **8** with chlorodiphenylphosphine produced enyne-allenes **1b-g** that were isolated and fully characterized.[14]



5

6 (n = 1; 69%)
6 (n = 2; 60%)
6 (n = 3; 48%)

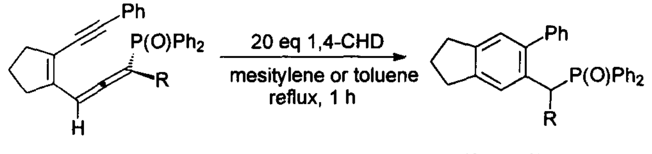
7 (n = 1; 78%)
7 (n = 2; 80%)
7 (n = 3; 73%)

8b (n = 1, R = *n*Bu; 82%)
8c (n = 1, R = Ph; 78%)
8d (n = 2, R = *n*Bu; 80%)
8e (n = 2, R = Ph; 87%)
8f (n = 3, R = *n*Bu; 85%)
8g (n = 3, R = Ph; 83%)

1b (n = 1, R = *n*Bu; 90%)
1c (n = 1, R = Ph; 88%)
1d (n = 2, R = *n*Bu; 61%)
1e (n = 2, R = Ph; 63%)
1f (n = 3, R = *n*Bu; 90%)
1g (n = 3, R = Ph; 70%)

Scheme 2. Synthesis of enyne-allenes **1b-g**. a) PBr_3, DMF, $CHCl_3$; b) Ph-C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF / $Cl_2Pd(PPh_3)_2$, CuI, NEt_3; c) BrMg-C≡C-R, Et_2O / SDAA, toluene; d) $PClPh_2$, NEt_3, THF, -80 °C.

After heating in presence of 1,4-cyclohexadiene (1,4-CHD) enyne-allenes **1b,c** furnished the Myers-Saito cyclization products in 29% (**9b**; mesitylene) and 38% (**9c**; toluene) yield despite the presence of a phenyl substituent at the alkyne terminus (*cf.* scheme 1) that was expected to favor biradical **A** over **B**.[3b]

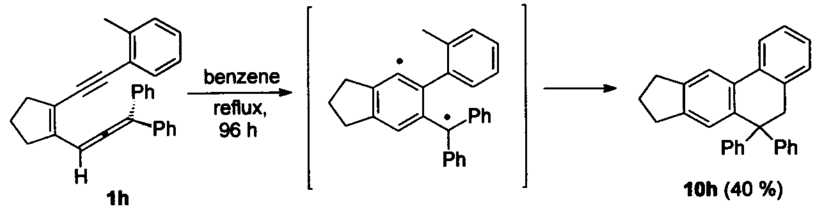


1b (R = *n*Bu)
1c (R = Ph)

9b (29%)
9c (38%)

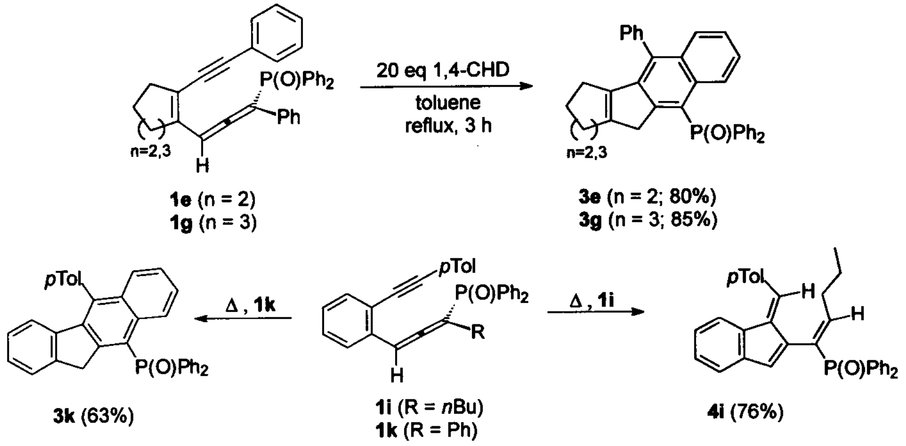
Scheme 3. Thermolysis of enyne-allenes **1b,c**.

Importantly, in both thermolyses no C^2-C^6 cyclization products could be detected, a result reminescent of the thermolysis of another five-membered ring enyne-allene reported by Wang (**10h**).[15]



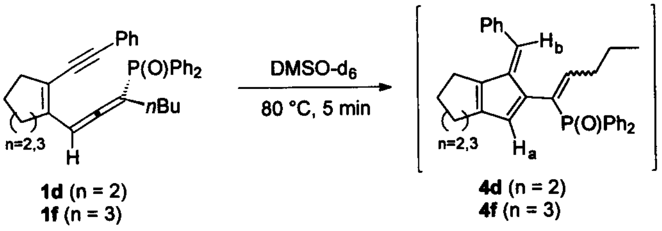
Scheme 4. Thermolysis of enyne-allene **1h**.

On the contrary, the thermolysis of the cyclohexene and cycloheptene derived enyne-allenes **1e,g** (3 h, toluene) resulted in the formation of the formal Diels-Alder products in 80% (**3e**) and 85% (**3g**) yield, respectively, in line with earlier results on the thermal rearrangement of benzene derived enyne-allene **1k**.[3a]



Scheme 5. Thermolysis of enyne-allenes **1e,g,i,k**.

In analogy, we expected the C^2-C^6 cyclization of **1d,f** to result in net ene products as such a reaction has been observed for **1a** and **1i**. However, thermolysis of **1d,f** under various conditions (different temperatures, flash pyrolysis) always afforded complex mixtures of products that could not been identified. We hypothesized that vinyl fulvenes **4d,f** are thermally unstable in line with results on simple fulvenes[16] and 1-vinylfulvenes,[17] and consequently followed their reaction by ^{1}H-NMR. Indeed, after 5 min (80 °C) signals could be observed indicative of **4d,f** as judged by the known signals of **4i**.[3b] After prolonged heating **4d,f** finally decomposed.

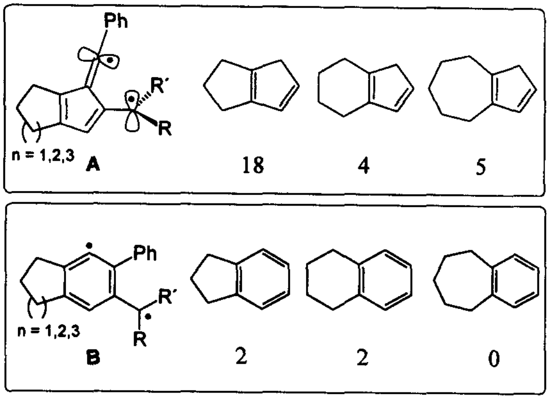


n	δ(H_a)*	δ(H_b)
2	5.53	6.48
3	5.68	6.62

*(d, $J_{H\text{-}P}$ = 3.5 Hz)

Scheme 6. C^2-C^6 cyclization of enyne-allenes **1d,f**. Selected ^{1}H NMR data of **4d,f** (in ppm).

The present thermolysis results demonstrate that a switch from the Myers-Saito to the novel C^2-C^6 cyclization can be brought about solely by ring strain effects. When comparing the ring strain in the annulated biradicals **A** and **B** as approximated by simple model compounds, it becomes obvious that the Myers-Saito cyclization is not affected by ring strain energies, while the C^2-C^6 cyclization is strongly impeded in case of n = 1.



Scheme 7. (right) Ring strain energies of simple models of biradicals **A** and **B** (in kcal•mol^{-1}).[18]

Acknowledgments. Generous financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

[1] Thermal and electron transfer induced reactions of enediynes and enyne-allenes, part 11; for part 10 see M. Schmittel, J.-P. Steffen, I. Bohn, *Heterocycl. Commun.* **1997**, in press.

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

[3] a) M. Schmittel, M. Strittmatter, K. Vollmann, S. Kiau, *Tetrahedron Lett.* **1996**, *37*, 999. - b) M. Schmittel, M. Keller, S. Kiau, M. Strittmatter, *Chem. Eur. J.* **1997**, *3*, 807.

[4] J. G. Garcia, B. Ramos, L. M. Pratt, A. Rodríguez, *Tetrahedron Lett.* **1995**, *36*, 7391.

[5] T. Gillmann, T. Hulsen, W. Massa, S. Wocadlo, *Synlett* **1995**, 1257.

[6] a) R. Nagata, H. Yamanaka, E. Murahashi, I. Saito, *Tetrahedron Lett.* **1990**, *31*, 2907. - b) A. G. Myers, E. Y. Kuo, N. S. Finney, *J. Am. Chem. Soc.* **1989**, *111*, 8057.

[7] For reviews, see: a) M. E. Maier, *Synlett* **1995**, 13. - b) K. C. Nicolaou, W.-M. Dai, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387. - c) K. K. Wang, *Chem. Rev.* **1996**, *96*, 207. - d) J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453.

[8] M. Schmittel, M. Strittmatter, S. Kiau, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1843.

[9] B. Engels (University of Bonn, Germany), private communication.

[10] M. Schmittel, M. Maywald, M. Strittmatter, *Synlett* **1997**, 165.

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

[12] Z. Arnold, A. Holý, *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059.

[13] Diethyldialkynylaluminates were obtained by reacting sodium diethyldihydroaluminate in toluene with the corresponding alkynes: J. H. Ahn, M. J. Joung, N. M. Yoon, *J. Org. Chem.* **1995**, *60*, 6173.

[14] Some selected data of the enyne-allenes: e.g. **1d**: ^{1}H-NMR ($CDCl_3$; 200 MHz): $\delta = 0.85$ ppm (t, $J = 7.4$ Hz, 3H), 1.24-1.43 (m, 4H), 1.47-1.55 (m, 4H), 1.70 (bs, 1H), 1.95 (bs, 1H), 2.18-2.30 (m, 2H), 2.35 (dt, $J = 7.4$ Hz, $J = 3.2$ Hz, 2H), 6.66 (dt, $J_{P\text{-}H} = 11.2$ Hz, $J = 3.2$ Hz, 1H), 7.29-7.34 (m, 2H), 7.36-7.52 (m, 9H), 7.63-7.83 (m, 4H); IR (neat): $\tilde{\nu} = 2197$ cm^{-1} (C≡C), 1920 (C=C=C).

[15] B. Liu, K. K. Wang, J. L. Petersen, *J. Org. Chem.* **1996**, *61*, 8503.

[16] a) K. Hafner, K. H. Häfner, C. König, M. Kreuder, G. Ploss, G. Schulz, E. Sturm, K. H. Vöpel, *Angew. Chem.* **1963**, *75*, 35. - b) M. Neuenschwander, *Pure Appl. Chem.* **1986**, *58*, 55.

[17] A. Pauli, H. Kolshorn, H. Meier, *Chem. Ber.* **1987**, *120*, 1611.

[18] Ring strain energies were evaluated from AM1 calculated heats of formation (M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902) and strainless heat of formation increments (N. Cohen, S. W. Benson, *Chem. Rev.* **1993**, *93*, 2419).

(*Received in Germany* 20 *June* 1997; *accepted* 8 *July* 1997)