Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 999-1002, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02369-0

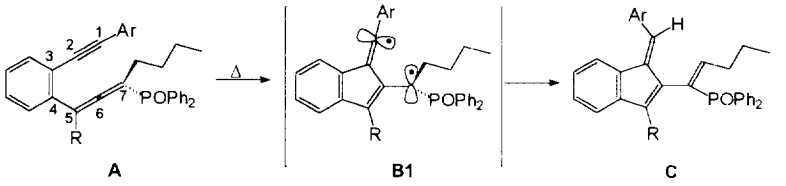
Intramolecular Formal Diels-Alder Reaction in Enyne Allenes. A New Synthetic Route to Benzofluorenes and Indeno[1,2-*g*]quinolines[1]

Michael Schmittel,* Marc Strittmatter, Karl Vollmann and Susanne Kiau

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

Abstract : Through the use of aryl substituents at the acetylene terminus in enyne allenes the reaction mode may be changed from the Myers-Saito cyclization to a C^2-C^6 cyclization resulting in a net intramolecular Diels-Alder reaction. As a consequence, the thermal cyclization of readily accessible acyclic enyne allenes allows for the synthesis of complex benzofluorene and 10H-indeno[1,2-*g*]quinoline derivatives.

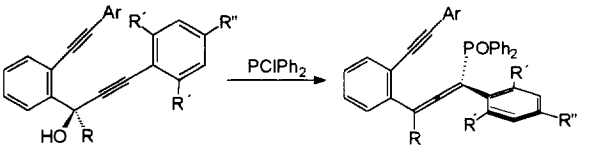
The disclosure of the biradical mechanism in natural enediyne and enyne[3]cumulene antitumor antibiotics[2] not only has spurted an intense search for simple model compounds to trigger DNA cleavage[3] but likewise has initiated investigations to exploit the Bergman and Myers-Saito cyclization protocol for the synthesis of carbocyclic systems via subsequent radical cyclization reactions.[4] In this context we have very recently disclosed a remarkable switch from the well known Myers-Saito C^1-C^6 cycloaromatization[5] to an unprecedented C^2-C^6 cyclization in the thermal reaction of masked[6] enyne allenes **A** affording benzofulvenes **C** in high yield. This mode occurred when the hydrogen at the acetylene terminus was replaced by an aryl group.[7]



Scheme 1. Postulated mechanism of the novel thermal C^2-C^6 cyclization of enyne allenes.[7]

A priori the reaction could have been easily explained by a concerted ene-reaction mechanism,[8] but we have proposed, based on the remarkable aryl substituent effect, an hitherto unprecedented thermal biradical cyclization (**A** → **B1**) being operative in these systems,[7] since aryl groups are known to stabilize vinyl radicals.[9] The occurrence of such a novel biradical cyclization[10] should actually allow to devise a plethora of useful synthetic schemes for the construction of carbocyclic systems. Herein, we would like to report on our investigations indicating that the motif of benzofulvene formation may not only find synthetic application in formal ene-reactions but likewise in formal Diels-Alder (DA) cyclizations.

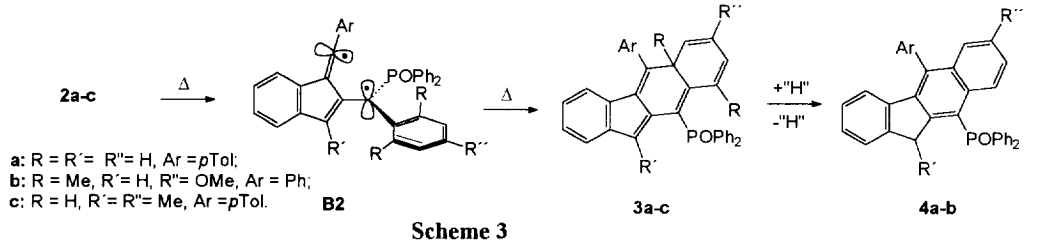
In order to use a putative biradical of type **B1** in a novel carbocyclization reaction, the phenyl substituted enyne allene **1a** was synthesized from the corresponding propargyl alcohol by the $PClPh_2$-method[7] in 51% yield, purified through chromatography and fully characterized.[11]



1a-c **a:** R = R´= R"= H, Ar =*p*Tol; **2a**, 50%
b: R = Me, R´= H, R"= OMe, Ar = Ph; **2b**, not isolated
c: R = H, R´= R"= Me, Ar =*p*Tol. **2c**, 66%

Scheme 2

Rewardingly, when **2a** was heated in toluene for 18 h at 60 - 70 °C in presence of an excess of 1,4-cyclohexadiene the benzofluorene derivative **4a** was formed in 63%.[12] In absence of a hydrogen donor **4a** was afforded only in 20% yield, although formally hydrogen is not incorporated in the overall reaction. This surprising outcome, however, may be easily explained assuming - after a formal DA reaction - the intermediate formation of benzofulvene **3a**, which must undergo an intermolecular H-addition /H-abstraction in order to provide **4a**.[13]



a: R = R´= R"= H, Ar =*p*Tol;
b: R = Me, R´= H, R"= OMe, Ar = Ph;
c: R = H, R´= R"= Me, Ar =*p*Tol.

B2 **3a-c** **4a-b**

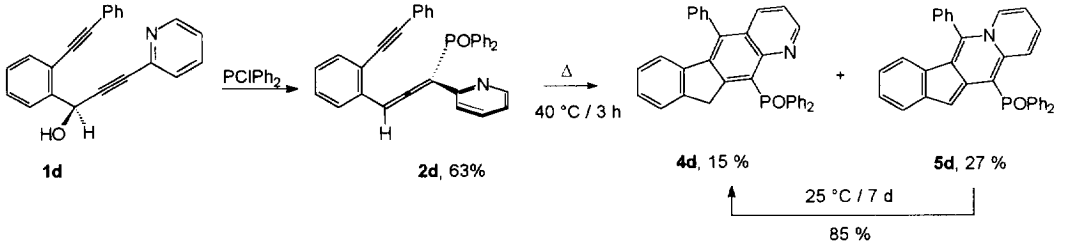
Scheme 3

Likewise, we were able to obtain **4b** in 44% yield, at this time, however, directly from propargyl alcohol **1b** upon reaction with $PClPh_2$. In this case, allene **2b**, which could not be isolated due to its thermal instability, is only a reactive intermediate. The reason for the thermal instability of **2b** may be rationalized on the basis of back-strain effects and conformational equilibria already discussed in the context of our work on the formal ene-reactions in enyne allenes.[7]

As a probe for the steric requirements of this reaction, enyne allene **2c** with the sterically demanding mesityl group replacing the phenyl ring at the allene terminus was synthesized, again from the corresponding propargyl alcohol in 66% yield. Astoundingly, upon heating of **2c** in the presence of triethylamine to 60 - 70 °C for 18 h the same reaction was observed as with **2a**, affording now in 82 % isolated yield the benzofulvene **3c** as a mixture of two rotational isomers (in 50 % and 32 % yield, respectively).[14] The yield of **3c** proved to be independent of whether a hydrogen donor was added nor not, as no follow-up 1,5-hydrogen shift is involved. Certainly, formation of the formal DA adduct **3c** conveys additional evidence for the suggestion, that benzofulvene **3a,b** is indeed an intermediate in the reaction **2a,b** → **4a,b**.

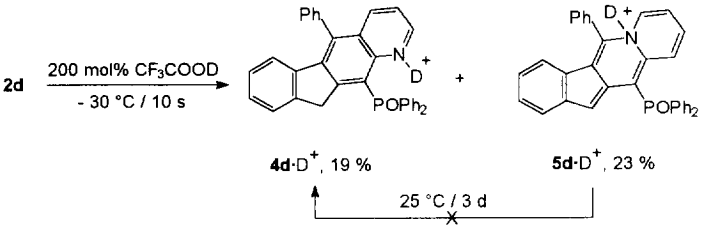
Noticeably, this novel cyclization strategy may also find wide use for the synthesis of heterocyclic ring systems, as exemplified with enyne allene **2d** that could readily be isolated from the corresponding propargyl alcohol **1d** in 63% yield. After heating **2d** at 40 - 50 °C for 18 hours we obtained the carbon-carbon

cyclization product **4d** (analogous to **4a,b**) and also the formal hetero DA adduct **5d** in 42% overall yield. However, the benzofulvene derivative **5d** proved to be unstable at room temperature. In 85% yield it rearranged to the 10H-indeno[1,2-*g*]quinoline **4d** within 7 d.



Scheme 4

The different reaction conditions indicate that cyclization of **2d** is more rapid than the one of **2a,c**. However, we found that the cyclization of **2d** was markedly slowed down upon addition of pyridine as base, while the reaction proceeded much more rapidly in the presence of a proton source. For example, in the presence of d_1-trifluoroacetic acid (200 mol%) **2d** was completely consumed within 10 s at - 30 °C affording the deuterated products **4d•D**$^+$ and **5d•D**$^+$ in 42% yield. No thermal isomerization between the two isomers was observed.



Scheme 5

The acceleration of reaction **2d** → **4d** + **5d** proposes that the C^2-C^6 cyclization is initiated by protonation at the pyridine ring of **2d** and proceeds via a polar intermediate. In contrast, no acid catalysis could be detected for the thermal reaction of **2a** making it much more difficult to formulate a mechanistic hypothesis. Although any final conclusion has to await the outcome of our radical clock experiments, we favor a stepwise over a concerted DA reaction. Certainly, the occurrence of biradical[15] intermediate **B**[16] is highly likely as it would be very difficult to reconcile a concerted DA mechanism[17] with the formation of **4c**.

In conclusion, it can be stated that the simple exchange of a hydrogen at the alkyne terminus with an aryl group[18] redirects the thermal reaction mode in **2** from the well-known Myers-Saito rearrangement to a novel DA cyclization in enyne allenes, thus constituting the second example of a C^2-C^6 cyclization.

Acknowledgments. Generous financial support from the Volkswagen-Stiftung 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 3; for part 2 see M. Schmittel, S. Kiau, *Chem. Lett.* **1995**, 953-954.

[2] For reviews, see: M. E. Maier, *Synlett* **1995**, 13-26. - K. C. Nicolaou, W.-M. Dai, *Angew. Chem.* **1991**, *103*, 1453 - 1481; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387-1416.

[3] K. Iida, M. Hirama, *J. Am. Chem. Soc.* **1995**, *117*, 8875-8876. - T. Takahashi, Y. Sakamoto, H. Yamada, S. Usui, Y. Fukazawa, *Angew. Chem.* **1995**, *107*, 1443-1446; *Angew. Chem. Int. Ed. Engl.* **1995**, *43*, 1345-1348. - K. Yoshida, Y. Minami, T. Otani, Y. Tada, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 5253-5256. - K. C. Nicolaou, P. Maligres, J. Shin, E. de Leon, D. Rideout, *J. Am. Chem. Soc.* **1990**, *112*, 7825-7826. - A. G. Myers, *Tetrahedron Lett.* **1987**, *28*, 4493-4496.

[4] J. W. Grissom, D. Huang, *Angew. Chem.* **1995**, *107*, 2196-2198; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2037-2039. - J. W. Grissom, B. J. Slattery, *Tetrahedron Lett.* **1994**, *35*, 5137-5410. - J. W. Grissom, D. Huang, *J. Org. Chem.* **1994**, *59*, 5114-5116. - Y. W. Andemichael, Y. G. Gu, K. K. Wang, *J. Org. Chem.* **1992**, *57*, 794 -796. - Y. W. Andemichael, Y.Huang, K. K. Wang, *J. Org. Chem.* **1993**, *58*, 1651-1652.

[5] R. Nagata, H. Yamanaka, E. Murahashi, I. Saito, *Tetrahedron Lett.* **1990** , *31*, 2907-2910. - A. G. Myers, E. Y. Kuo, N. S. Finney, *J. Am. Chem. Soc.* **1989**, *111*, 8057 - 8059.

[6] In our model systems the ene functionality is replaced by a phenyl group.

[7] M. Schmittel, M. Strittmatter, S.Kiau, *Tetrahedron Lett.* **1995**, *36*, 4975 - 4978.

[8] For intermolecular ene-reaction of allenes and acetylenes, see H.-A. Chia, B. E. Kirk, D. R. Taylor, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1209-1213.

[9] J. E. Bennett, J. A. Howard, *Chem. Phys. Lett.* **1971**, *9*, 460.

[10] So far, only indirect proof for the biradical cyclization could be obtained: M. Schmittel, M. Strittmatter, S. Kiau, *J. Am. Chem. Soc.*, manuscript in preparation.

[11] **2a**: pale yellow solid, m.p. 67-68 °C (decomposition); ^{13}C-NMR ($CDCl_3$) δ 219 (C=C=C), 104.8 (d, J_P = 75 Hz, HC=C=C), 96.4 (d, J_P = 12 Hz, CH=C=C,), 93.0, 84.9 (C≡C); IR (KBr) (cm^{-1}) 2212 (C≡C), 1923 (C=C=C); **2c**: redish solid, m.p. 70-73 °C (decomposition); ^{13}C-NMR ($CDCl_3$) δ 210.2 (C=C=C), 102.9 (d, J_P = 140 Hz, HC=C=C), 94.3(C≡C), 93.3 (CH=C=C, J_P = 13 Hz), 86.2 (C≡C); IR (KBr) (cm^{-1}) 2204 (C≡C), 1928 (C=C=C); **2d**: greenish solid, ^{13}C-NMR ($CDCl_3$) δ 215.2 (C=C=C), 106.3 (d, J_P = 106 Hz, HC=C=C), 96.9 (CH=C=C, J_P = 10 Hz), 94.0, 86.4 (C≡C); IR (KBr) (cm^{-1}) 2208 (C≡C), 1928 (C=C=C), 1632 (C=N).

[12] The characterization has been undertaken using IR, ^{31}P-, ^{1}H-, ^{13}C-NMR, MS, HRMS, and 2D-NMR methods (COSY). Some selected data are presented: **4b**: yellow solid, m.p. 162 °C (decomposition), ^{1}H-NMR ($CDCl_3$) δ 1.41 (d, J = 7.1 Hz, 3H), 3.59 (s, 3H), 5.09 (q, J = 7.1 Hz, 1H), 6.31 (d, J = 7.9 Hz, 1H), 6.73 (dd, J_1 = 9.4 Hz, J_2 = 2.8 Hz, 1H), 6.83 (m, 1H), 6.96 (t, J = 7.9 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.35-7.39 (m, 3H), 7.41-7.53 (m, 5H), 7.56-7.66 (m, 6H), 7.68 (d, J = 9.4 Hz, 1H), 7.89-7.93 (m, 2H); ^{31}P-NMR ($CDCl_3$) δ 29.95 (s); HRMS ($M^+/C_{34}H_{31}OP$) 536.1906; **4a**: ^{1}H-NMR ($CDCl_3$) δ 3.99 (s, 2H); **4d**: ^{1}H-NMR ($CDCl_3$) δ 4.87 (s, 2H); **3d** (*1. rotational isomer*): ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.61 (d, J = 1.5 Hz, 3H), 1.93 (d, J = 1.5 Hz, 3H), 2.43 (s, 3H), 6.04 (s, 1H) **3d** (*2. rotational isomer*): ^{1}H-NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.77 (br s, 3H), 1.94 (br s, 3H), 2.34 (s, 3H), 6.73 (s, 1H); **5d**: ^{1}H-NMR ($CDCl_3$) δ 5.43 (m, 1H), 6.31 (m, 1H), 6.71 (m, 1H); **4d**·H$^+$: ^{1}H-NMR ($CDCl_3$) δ 3.10 (s, 2H); **5d**·H$^+$: ^{1}H-NMR ($CDCl_3$) δ 3.28 (s, 2H).

[13] Since an intramolecular 1,5-hydrogen shift is highly unlikely, we suggest that this reaction is taking place via an intermolecular H-addition /abstraction mechanism in between two molecules of **3** or in between **3** and the thc added hydrogen donor. R. L. Danheiser, A. E. Gould, R. F. de la Pradilla, A. L. Helgason, *J. Org. Chem.* **1994**, *59*, 5514 - 5515.

[14] The two rotational isomers could be separated by chromatography allowing to unequivocally establish their structures on the basis of their spectral data.

[15] A biradical **B** (scheme 3) or alternatively a Zwitterion are thought to constitute the postulated intermediate in the formal Diels-Alder reaction.

[16] A related C^2-C^8 biradical cyclization has been reported by S. W. Scheuplein, R. Machinek, J. Suffert, R. Brückner, *Tetrahedron Lett.* **1993**, *34*, 6549 - 6552.

[17] In concerted Diels-Alder reactions *ortho* substituents are usually prohibitive, see R. Brückner, R. Huisgen, J. Schmid, *Tetrahedron Lett.* **1990**, *31*, 7129 - 7132.

[18] To the best of our knowledge thermal cyclizations of enyne allenes carrying aryl or vinyl groups at the alkine terminus are not reported in the literature, although for few examples the synthesis was reported: K. K. Wang, Z. Wang, *Tetrahedron Lett* **1994**, *35*, 1829-1832. - K. K. Wang, *J. Chin. Chem. Soc.* **1995**, *42*, 745-749.

(*Received in Germany* 10 *November* 1995; *accepted* 5 *December* 1995)