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Electronic effects in the thermal C^2–C^6 biradical cyclisation of enyne-allenes

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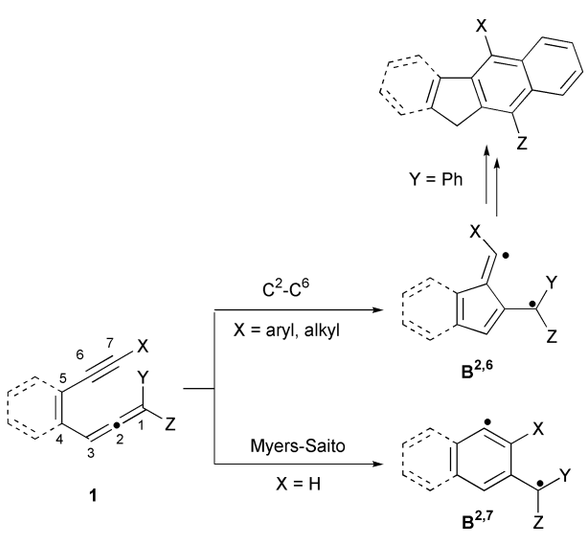
A comprehensive study on the influence of substituents at the alkyne terminus on the thermal biradical cyclisation of enyne-allenes shows a good agreement of the rates with $\sigma^{\cdot}$.

Although the cycloaromatisations of enediynes (Bergman)[1] and enyne-allenes (Myers–Saito)[2] play a fundamental role in the mode of action of the natural enediyne antitumor antibiotics[3] alternative thermal cyclisations with an altered regioselectivity have only been addressed recently. After the discovery of a novel cyclisation of enyne-allenes (C^2–C^6, see Scheme 1) in 1995,[4] this reaction has been studied extensively,[5] and ample evidence for the occurrence of the fulvene biradical **B**[2,6] has been collected through experimental[5f,6] and theoretical investigations.[7]

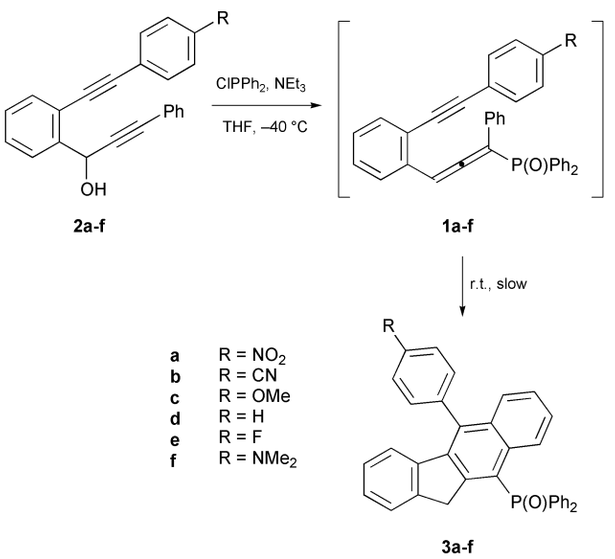
Moreover, the C^2–C^6 cyclisation has become a valuable synthetic tool for the construction of carbocyclic[8] and heterocyclic[9] ring systems as the intermediate biradical can undergo a second C–C bond formation followed by a formal 1,5-H shift to provide a convenient access to polyaromatic systems.

Engels *et al.*[7a] predicted on the basis of calculations that for **1** (Y,Z = H) the thermal C^2–C^6 cyclisation should be extremely accelerated with X = NH_2 in comparison to X = aryl, or ^{t}alkyl due to a special stabilisation of the biradical intermediate. In order to verify their prediction we decided to study the electronic effect of the substituent X in **1** on the thermal behaviour, which should also give some mechanistic insight in the polarity of the transition state. Herein, we describe the synthesis of the novel enyne-allenes **1a**–**f** and their kinetics.

The key step in the preparation of enyne-allenes **1a**–**f** is based on the rearrangement of the propargyl† alcohols[10] **2a**–**f** with $ClPPh_2$. (Scheme 2) Enyne-allenes **1a**–**f** were purified by low-temperature chromatography as far as possible, but their thermal instability precludes any elemental analysis. Some relevant IR and ^{1}H NMR data are presented in Table 1. Rapid cyclisation of **1f** even at rt prevented both isolation and a reliable kinetic analysis.



Scheme 1



Scheme 2 The reaction of **2a**–**f** with $ClPPh_2$, first at −40 °C and then at rt, leads directly to benzofluorenes **3a**–**f** (**3a**: 42%, **3b**: 47%, **3c**: 62%; **3d**: 68%, **3e**: 31%, **3f**: 45%).

Table 1 The IR (allene, alkyne) and ^{1}H NMR data of the desired enyne-allenes **1a**–**f**

	1a	**1b**	**1c**	**1d**	**1e**
IR (allene)/cm^{-1}	1924	1924	1923	1908	1924
IR (alkyne)/cm^{-1}	2216	2199	2215	2212	2227
^{1}H NMR/ppm[a]	6.75	6.26	6.78	6.80	6.83

[a] Allenic proton showing characteristic doublet with J = 10.1–10.7 Hz.

For the kinetic analysis the enyne-allenes were cooled and subjected to three DSC (differential scanning calorimetry) investigations. This method allows the recording of kinetic data over a range of temperatures in a single experiment.[11] To ensure that we monitor indeed the C^2–C^6 cyclisation, product studies were conducted for both preparative and DSC thermolyses. As rate constants determined at very low and very high temperatures proved to be unreliable, we resigned to make an Eyring analysis. Hence, only the cyclisation onset temperatures, reaction rates in the central temperature range (at 50, 60 and 70 °C) and $\Delta G^{\neq}_{60°C}$ are provided in Table 2. Data for enyne-allene **1g** was added for comparison.[12]

According to the data in Table 2 the lowest cyclisation temperature is found for enyne-allene **1f** with R = NMe_2, which unfortunately could not be isolated. The most stable representative is **1e** with R = F. Quite obviously the cyclisation rate constants do not follow a simple picture with electron-withdrawing substituents on one side, and electron-donating substituents on the other.

For a more detailed discussion we will concentrate on the rate constants at 60 °C that constitute the most reliable data due to the form of the DSC curves. In the above analysis we find a rate acceleration of 2.6 (at 60 °C) when going from R = F to NO_2.

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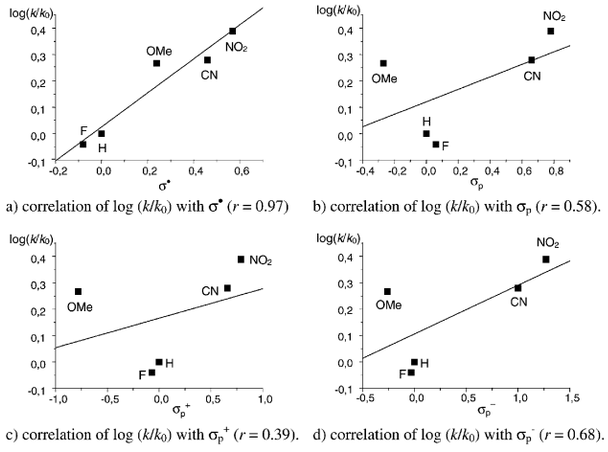
Table 2 Kinetic data of enyne-allenes **1a**–**g** and various σ values[13] for comparison[a]

Enyne-allene R	**1a** NO_2	**1b** CN	**1c** OMe	**1d** H	**1e** F	**1f** NMe_2	**1g** Me
T_{DSC}/°C[b]	43	45	46	51	53	—	50
$k^{50°C}/s^{-1} \times 10^{-3}$	2.06 ± 0.46	1.42 ± 0.43	1.40 ± 0.10	0.86 ± 0.24	0.69 ± 0.05	3.07[c]	0.95[c]
$k^{60°C}/s^{-1} \times 10^{-3}$	5.65 ± 0.98	4.36 ± 1.04	4.23 ± 0.37	2.29 ± 0.49	2.13 ± 0.04	8.20[c]	2.54[c]
$k^{70°C}/s^{-1} \times 10^{-2}$	1.55 ± 0.21	1.22 ± 0.26	1.08 ± 0.08	0.59 ± 0.17	0.56 ± 0.05	2.11[c]	0.66[c]
$\Delta G^{\neq 60°C}$/kJ mol^{-1}	96.27	96.96	97.04	98.74	98.94	95.21[c]	98.46[c]
$\sigma^{\cdot}$	0.57	0.46	0.24	0	−0.08	0.90	0.11
σ_p	0.81	0.70	−0.28	0	0.15	−0.63	−0.14
σ_p^+	0.79	0.66	−0.78	0	−0.07	−1.70	−0.31
σ_p^-	1.27	1.00	−0.26	0	−0.03	−0.12	−0.17

[a] Measured by DSC. [b] Onset temperature in the DSC. [c] Calculated from the correlation of the rate constants with $\sigma^{\cdot}$ (see Fig. 1a).



a) correlation of log (k/k_0) with $\sigma^{\bullet}$ (r = 0.97) b) correlation of log (k/k_0) with σ_p (r = 0.58).

c) correlation of log (k/k_0) with σ_p^+ (r = 0.39). d) correlation of log (k/k_0) with σ_p^- (r = 0.68).

Fig. 1 Correlation of the log (k/k_0)-values with the different substituent constants.[13]

Such accelerations are characteristic for radical reactions (2- up to 5-fold acceleration),[13] but much too low for reactions involving polar intermediates where the rates typically change over 2–7 orders of magnitude.

To further evaluate the data we correlated the log (k/k_H) values against the well-known substituent constants, $\sigma^{\cdot}$ (for radical reactions), and σ_p, σ_p^+ and σ_p^- (for polar reactions).[14]

The poor correlation with the polar substituent constants σ_p, σ_p^+ and σ_p^- (Fig. 1) clearly contradicts any polar intermediate in the thermal C^2–C^6 cyclisation, such as a zwitterion. On the contrary, a good correlation is obtained using $\sigma^{\cdot}$ values (reaction constant ρ = 0.643).[15] The latter correlation is strong support, together with earlier mechanistic evidence,[6] that the C^2–C^6 cyclisation is a biradical cyclisation. Moreover, it enables a good insight into the electronic structure of the transition state, as even *bona fide* radical reactions, but with a polar transition state, correlate with polar substituent constants, such as σ_p, σ_p^+ and σ_p^-.[13] Thence, the C^2–C^6 cyclisation of **1** proceeds *via* an extremely unpolar transition state (TS), in contrast to the Myers–Saito cyclisation, where the occurrence of unpolar and polar TS's is discussed.[16]

The reaction constant now allows us to predict the cyclisation rate and the free activation energy of **1f** and **1g** at various temperatures (Table 2). The higher rate constant for **1f** is in agreement with the fact that we have not been able to isolate it. The difference $\Delta\Delta G^{\neq 60°C}$ = −3.5 kJ mol^{-1} when going from R = H to R = NMe_2 is drastically smaller than predicted for **1** (no benzoannelation, Y,Z = H) upon changing from X = H to NH_2 ($\Delta\Delta G^{\neq 25°C}$ = −57 kJ mol^{-1}).[7a] Obviously, the substituent effect in our study is heavily attenuated because of the phenyl spacer between R and the alkynyl group.

In summary, the present study definitely rules out zwitterionic intermediates in the C^2–C^6 cyclisation and supports the biradical hypothesis. For the first time, a thermal biradical cyclisation was demonstrated to follow the radical substituent constant $\sigma^{\cdot}$. This finding is notable as calculations have as yet described the TS to contain no biradical character.[7]

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Notes and references

† The IUPAC name for propargyl is prop-2-ynyl.

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