Two Novel Thermal Biradical Cyclizations of Enyne-Ketenimines: Theory, Experiment, and Synthetic Potential**

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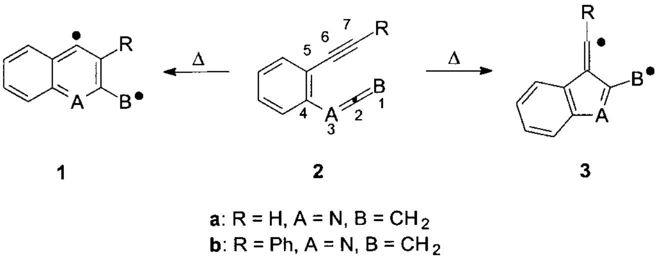
We recently reported a novel thermal C^2-C^6 cyclization of enyne-allenes **2** (A, B = carbon) to biradical **3**[1] that completely displaces the well-known Myers–Saito (C^2-C^7) cycloaromatization[2] to biradical **1** if an aryl substituent (R = phenyl) is attached at the alkyne terminus (Scheme 1). Because biradical intermediate **3** (A, B = carbon) can react in an intramolecular way to give formal [4+2][3] or [2+2][4] cycloadducts and ene products,[5] it is a versatile intermediate for the construction of various ring systems.[6]



Scheme 1. Biradical intermediates **1** and **3** for thermal C^2-C^7 and C^2-C^6 cyclizations, respectively.

The synthetic value of such biradical cyclizations should increase further if CH_n groups in the enyne-allene were replaced by heteroatoms. Indeed, a while ago enyne-ketenes (A = carbon, B = oxygen) were shown to undergo C^2-C^7 and C^2-C^6 cyclizations.[7] We now report theoretical and experimental evidence that points to the occurrence of analogous biradical cyclizations in enyne-ketenimines (A = nitrogen, B = carbon), which makes these compounds interesting precursors for benzocarbazoles and quinolines.

To study the influence of substituents at the alkyne terminus on the reaction behavior of enyne-ketenimines we carried out quantum-chemical calculations. In contrast to our recent calculations on the thermal cyclization of enyne-allenes (A = CH, B = CH_2)[8, 9] it was necessary in the present study to include the annulated benzene ring, because otherwise the biradical intermediates are found to have a different electronic structure.[10] A correct description of the biradical intermediates requires a multireference approach.[11] However, because the biradical nature of the wave function develops only beyond the transition state (TS)—that is, in the density function theory (DFT) calculations $[\boldsymbol{S}^2] = 0$ for all the transition states[8]—the influence of substituents on the activation energy $\Delta E^{\neq}$ in both processes can be determined from DFT calculations. Consequently, activation energies were studied with a density functional approach in combination with a 6-31G* AO basis set, whereas a multireference configuration interaction (MR-CI) approach was used to compute the reaction energies (ΔE^{r}).[12, 13]

Just as in the case of the enyne-allene (*Z*)-1,2,4-heptatrien-6-yne, the theoretical results (Table 1) suggest a change in the regioselectivity of enyne-ketenimine cyclizations as a function of the group R at the alkyne terminus. While the C^2-C^7 cyclization **2a,b** → **1a,b** is exothermic for both systems, the alternative C^2-C^6 biradical cyclization is endothermic for **2a,b** → **3a,b**.[13] Nevertheless, both cyclizations are kinetically controlled, because intra- or intermolecular follow-up reactions ($k > 10^6\,s^{-1}$)[14] of **1** and **3** are much more rapid than a ring-opening of biradical **1** or **3** to the enyne-ketenimine **2** (activation barrier > 17 kcal mol^{-1}).

Table 1. Summary of the calculated data. The energies of the reactants are in Hartree, and those for the other structures relative to the reactants are in kcal mol^{-1}. The energies of transition states are indicated in boldface.

Substituent	**a**: R = H	**b**: R = Ph
reactant **2**[a,b]	– 439.907358	– 670.050551
reactant **2**[a,c]	– 438.526790	–
C^2-C^7 cyclization		
$R_{C^2-C^7}$ = 2.1 Å[b]	23.4	30.0
$R_{C^2-C^7}$ = 2.0 Å[b]	25.3	33.1
$R_{C^2-C^7}$ = 1.93 Å[b]	**25.8**	**34.1**
$R_{C^2-C^7}$ = 1.8 Å[b]	23.9	31.1
$R_{C^2-C^7}$ = 1.43 Å (**1**)[c,d]	– 9.4	– 11[e]
C^2-C^6 cyclization		
$R_{C^2-C^6}$ = 2.0 Å[b]	25.9	23.6
$R_{C^2-C^6}$ = 1.9 Å[b]	29.2	25.3
$R_{C^2-C^6}$ = 1.8 Å[b]	31.5	**25.5**
$R_{C^2-C^6}$ = 1.76 Å[b]	**32.2**	25.3
$R_{C^2-C^6}$ = 1.7 Å[b]	24.9	24.5
$R_{C^2-C^6}$ = 1.50 Å (**3**)[c,d]	15.2	4[e]

[a] $R_{C^2-C^7} = 3.55$ Å, $R_{C^2-C^6} = 3.04$ Å. [b] DFT(B3LYP) in combination with a 6-31G* basis set. [c] MR-CI + Q in combination with a double zeta polarization (DZP) basis set. [d] Biradical intermediate. [e] Reference [13].

For R = H our calculations predict an activation barrier $\Delta E^{\neq}$ of 26 kcal mol^{-1} for the C^2-C^7 cyclization **2a** → **1a**, whereas it is much higher for a C^2-C^6 cyclization to **3a** ($\Delta E^{\neq} = 32$ kcal mol^{-1}). Notably, the activation barrier increases to 34 kcal mol^{-1} for the C^2-C^7 cyclization of **2b** to **1b** when H is replaced by Ph; however, it is decisively decreased for the C^2-C^6 cyclization of **2b** to **3b** ($\Delta E^{\neq} = 26$ kcal mol^{-1}). The calculations confirm that the change from a C^2-C^7 cyclization to a C^2-C^6 ring closure is even more pronounced than with the corresponding enyne-allenes.[9]

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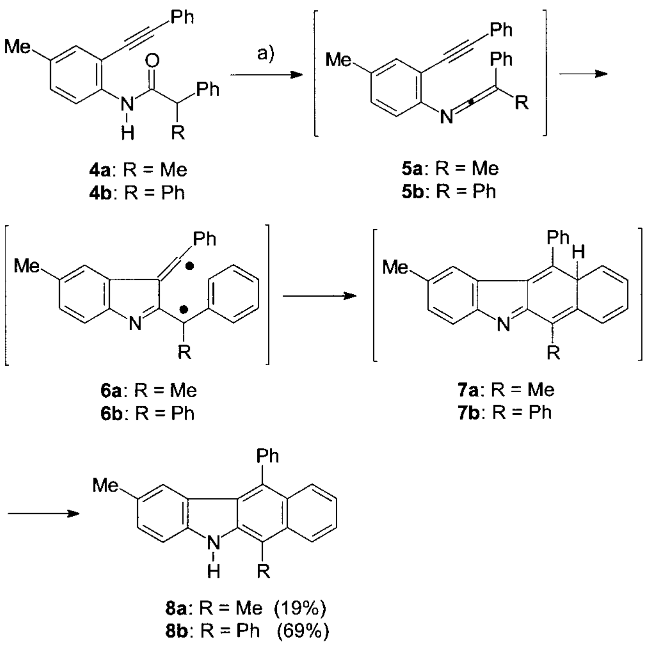
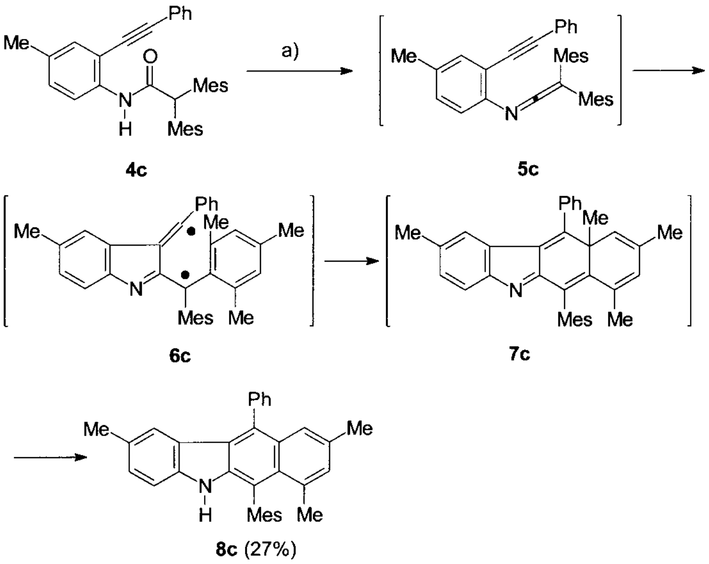
To probe the above predictions, several enyne-ketenimines were prepared from the corresponding amides by standard procedures for simple ketenimines.[15] As reported earlier,[16] however, the desired enyne-ketenimines could not be isolated because under the reaction conditions they underwent rearrangement in the sense of the anticipated thermal biradical cyclizations. Accordingly, when we tried to convert alkynylphenyl amides **4a,b** into enyne-ketenimines **5a,b**, benzocarbazoles **8a,b** were isolated directly (Scheme 2). [17]



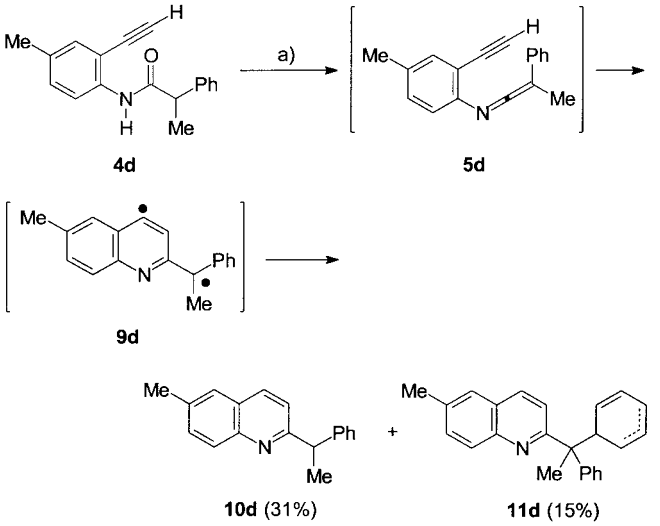
Scheme 2. Synthesis of benzocarbazoles **8a,b**. a) **8a**: Ph_3P, Br_2, NEt_3, CH_2Cl_2, reflux, 15 h; **8b**: Ph_3P, Br_2, NEt_3, chlorobenzene, 80 °C, 21 h.

Although formation of **8a,b** from **4a,b** was expected based on our calculations, isolation of these products cannot be taken as a rigorous proof of a biradical cyclization via **6**, because it could also be the result of a concerted Diels–Alder reaction **5**→**7**. Indeed, a similar cyclization was reported by Ghosez and Differding,[16] although they did not recognize it to be a biradical cyclization, which prevented full exploitation of the reaction's synthetic potential. To demonstrate experimentally that biradical **6** is an intermediate, both phenyl groups in enyne-ketenimine **5b** were replaced by mesityl substituents. It is well established that concerted Diels–Alder reactions are prevented by *ortho*-alkyl substituents because of steric hindrance;[14a, 18] therefore, the only option available to **5c** is a stepwise formal Diels–Alder cycloaddition. Transformation of **4c** into enyne-ketenimine **5c** produced benzocarbazole **8c** as the only low-weight product, which constitutes rather strong evidence for biradical intermediate **6c** (Scheme 3). This biradical subsequently closes to the formal Diels–Alder cycloadduct **7c**, from which a methyl group is then lost. The latter reaction can be explained by the assumption that after protonation at the nitrogen atom in **7c** the methyl group is eliminated in an S_N2-type reaction, a transformation driven by the gain in aromatization energy.



Scheme 3. Synthesis of benzocarbazole **8c**. a) Florisil, P_2O_5, 1,4-cyclohexadiene, pyridine, reflux, 30 h (61 % of **4c** recovered).

We also investigated the thermal cyclization of enyne-ketenimine **5d** with a hydrogen atom at the alkyne terminus to test experimentally the theoretical prediction of a preferred C^2-C^7 cyclization of **2a** (Scheme 4). After converting amide **4d** into enyne-ketenimine **5d** we obtained the quinolines **10d** (31 %) and **11d** (15 %); the latter is a product of addition of biradical intermediate **9d** to 1,4-cyclohexadiene.[19] Both compounds clearly indicate a C^2-C^7 biradical cyclization for enyne-ketenimines, whereas no C^2-C^6 cyclization product has yet been detected.



Scheme 4. Cyclization of **5d** to quinolines **10d** and **11d**. a) Florisil, P_2O_5, 1,4-cyclohexadiene, pyridine, reflux, 3 d.

We have thus provided both theoretical and experimental evidence for two novel thermal biradical cyclizations of enyne-ketenimines. The C^2-C^6 cyclization pathway also opens the way to a straightforward synthesis of benzocarbazoles via azafulvenemethyl biradicals. The present results have encouraged us to engage in further investigations of heteroenyne-allenes in which other CH_n groups are replaced by hetero units (e.g., B = NH in **2**).

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X-Ray Absorption Spectroscopy of Dimethylcuprates: Evidence for Solvent-Dependent Aggregation[**]

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Organocopper reagents are widely used in organic synthesis. Although their properties depend on experimental conditions, with solvent often a key factor,[1] only limited information is available on the solvent dependence of organocopper structures.[2, 3] Vapor pressure depression and X-ray scattering measurements have suggested that lithium dimethylcuprate derived from cuprous halide is dimeric $(Me_2CuLi)_2$ in Et_2O;[4a] this structure is supported by theoretical calculations.[4b, 5] In contrast, recent cryoscopic measurements suggest that monomeric lithium dimethylcuprate is the major species in THF.[3] Dimethylcuprates derived from cuprous halide give different ^1H and ^7Li NMR signals in THF and Et_2O,[2b] consistent with a solvent-dependent difference in structure. However, to date there have been no direct data

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