ORGANIC LETTERS

2004
Vol. 6, No. 12
2059−2062

α,5-Didehydro-3-picoline Diradicals from Skipped Azaenediynes: Computational and Trapping Studies of an Aza-Myers–Saito Cyclization

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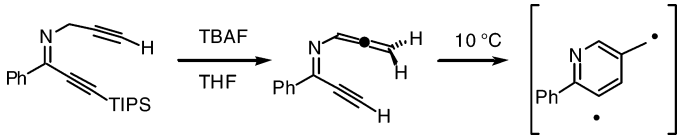
Received April 21, 2004

ABSTRACT



On the basis of density functional calculations, the isomerization of skipped azaenediynes (*C*-alkynyl-*N*-propargylimines) to azaenyne allenes and subsequent rapid aza-Myers–Saito cyclization to α,5-didehydro-3-picoline were predicted. We prepared the *N*-propargylimine of 1-phenyl-3-tri(isopropyl)silylprop-2-yn-1-one, which undergoes proto-desilylation and isomerization to an azaenyne allene when treated with tetrabutylammonium fluoride. In the presence of 1,4-cyclohexadiene, this azaenyne allene affords 6-phenyl-3-picoline and other products corresponding to the trapping of an α,5-didehydro-3-picoline diradical.

The thermal cycloaromatization reactions of enediynes[1] and enyne allenes[2] are of particular importance as a result of both the involvement of these cyclizations in the DNA cleavage mechanism of a large group of natural[3] and designed[4] cytotoxic compounds and the potential synthetic usefulness of these cyclizations, particularly when coupled to free radical cyclization cascades.[5] An aza-variant of the cycloaromatization of enediynes has been reported, which involves aza-substitution of the internal ene double bond of the enediyne. In this case heteroatom substitution has a profound impact on facility of the cyclization and the nature and reactivity of the intermediates involved.[6,7] All of the heteroatom-substituted enyne allene analogues examined to date (Scheme 1) involve heteroatom substitution on the allene or yne termini of the system, including enyne ketenes[8] (**1**, X = CH, Y = O), enyne ketenimines[9] (**1**, X = N, Y = CR′R″), and enyne carbodiimides[10] (**1**, X = N, Y = NR′), which undergo cyclizations analogous to the Myers−Saito or Schmittel cyclizations of enyne allenes (**3a**) to generate diradical or zwitterion

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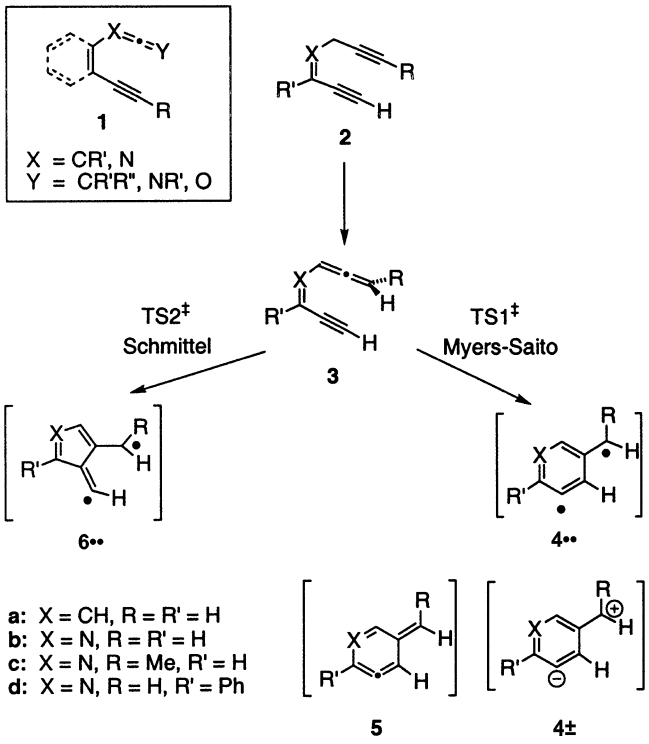
10.1021/ol049266r CCC: $27.50
Published on Web 05/15/2004

Scheme 1. Previously Reported Heteroenyne Allenes and Azaenyne Allenes Derived from Skipped Azaenediynes



intermediates (Scheme 1), and 2,4,5-hexatrienenitriles,[11] which do not undergo intramolecular thermal cyclization. The ability of diradical-generating heteroenyne allenes to participate in DNA cleavage chemistry[12] or cascade cyclization reactions[8,9,10,13] provides an impetus to study previously unexplored members of this class of compounds.

The prototropic rearrangement of "skipped" azaenediynes **2b**−**d** represents a potential route to *C*-alkynyl- *N*-allenyl imines **3b**−**d**, representatives of a class of azaenyne allenes that have not yet been reported in the literature (Scheme 1).[14] Here we report our computational and experimental studies of the thermal rearrangements of azaenyne allenes **3b**−**d** derived from rearrangement of skipped azaenediynes **2b**−**d**. We present evidence for an intermediate α,5-didehydro-3-picoline diradical (**4d**••) derived from **3d** and computational studies that support the observed facility of this aza-Myers−Saito cyclization and shed further light on the effect of aza-substitution in this system.

Density functional calculations at the B3LYP/6-31G* level[15] demonstrate that the azaenyne allenes **3b,c** are more stable than the corresponding skipped azaenediynes **2b,c** by 12.0 and 7.3 kcal/mol, respectively, supporting the proposed isomerization. There is only a small predicted energy difference between the less stable (*Z*)-imine isomers **3b,c** and the corresponding (*E*)-isomers (0.1 kcal/mol). Even for the aldimines **3b,c** (X = N, R′ = H), the (*Z*)-isomers required for cyclization should be thermodynamically accessible, and in the case of ketimines **3** (X = N, R′ ≠ H, e.g., **3d**), the reactive imine isomers (corresponding to (*Z*)-**3b,c**) should predominate.

The results of (U)B3LYP/6-31G* calculations (Table 1) indicate that the proposed aza-Myers−Saito cyclization of azaenyne allene **3b** has a slightly lower predicted barrier and is slightly more exothermic than the Myers−Saito cyclization of **3a**. In both cases, the resulting singlet diradical **4**••[16] is much lower in energy than the closed-shell singlet zwitterion **4**±.[17] A non-C_s-symmetric closed-shell singlet **5** lower in energy than **4**± was found for both the Myers−Saito case, as had been previously noted by Squires[18] and Carpenter,[19] and the aza-Myers−Saito case.[20] These results lead to the prediction of a facile aza-Myers−Saito cyclization of azaenyne allenes that may afford products derived from both diradical and ionic reaction pathways. The aza-Schmittel cyclization of **3b** is predicted to be much more facile than the Schmittel cyclization of **3a**, and although the aza-Myers−Saito cyclization is predicted to be favored over aza-Schmittel cyclization of **3b**, the difference between the two pathways is much smaller than in the enyne allene case.[21] In accord with previous computational studies of the Myers−Saito[18,21−23] and Schmittel[20,21,23] cyclizations, the transition states **TS1b** and **TS2b** have little diradical character, indicating that crossing to an open-shell surface occurs after these transition states.

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(16) Despite a certain lack of theoretical rigor in applying UB3LYP calculations to these open-shell singlets, we report these values for comparison with the results in the enyne allene series in refs 2a, 18, and 19. One can reach the same conclusions by comparing the triplet diradical energies.

(17) For the zwitterion **4a**±, we find a structure lower in energy than that reported in ref 19. We note that the wave function is unstable with respect to symmetry breaking for both **4**± and **5** at the B3LYP level.

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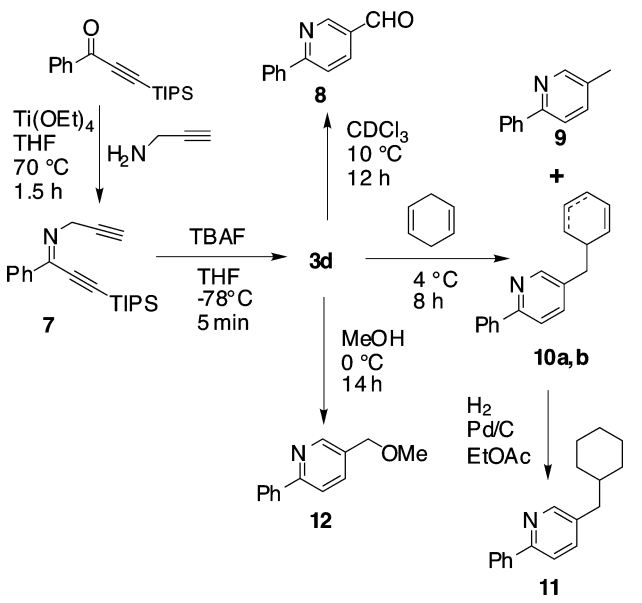
Table 1. Calculated Energies for Myers−Saito and Schmittel Cyclizations of **3a,b**[a]

series	TS1	s**4**••[b]	t**4**••[c]	**4**±[d]	**5**	TS2	s**6**••[b]	t**6**••[c]
a	26.3[e] (23.3 ± 0.5)[f]	−11.6 (−13.5 ± 4)[g]	−10.2	20.9	0.1	34.5[e]	13.1	10.5
b	23.2[e]	−15.4	−14.0	16.5[e]	−2.6	27.7[e]	7.3	5.2

[a] (U)B3LYP/6-31G* energies with zero-point correction relative to the lowest energy, *s-trans* conformer of (*Z*)-**3** in kcal/mol. [b] Open-shell singlet. [c] Triplet diradical. [d] Closed-shell singlet with C_s-symmetry enforced. [e] One imaginary frequency. [f] Experimental data from ref 2a. [g] Experimental data from ref 18.

The skipped azaenediyne **7** was prepared by the condensation of 1-phenyl-3-(triisopropylsilyl)-propynone[6b] with excess propargylamine in the presence of titanium(IV) ethoxide (Scheme 2). When desilylation of **7** to **2d** was carried out

Scheme 2



by treatment with TBAF at −78 °C for 5 min, concomitant isomerization occurred affording azaenyne allene **3d**. Although the instability of **3d** prevented its chromatographic purification, its structure was confirmed by NMR and MS analysis of the reaction mixture after aqueous workup.[24] The ^{1}H NMR of **3d** contains distinctive resonances for the allene moiety: a methylene doublet at 5.36 ppm that couples with a methine triplet at 7.60 ppm (J = 6.0 Hz). The downfield shift of the later is commensurate with the favored (*E*)-*s-trans* conformation of **3d**, in which the allene methine is proximal to and in the deshielding region of the alkyne triple bond. The ^{13}C NMR spectra of **3d** contains the expected resonance for the allene sp carbon [212 ppm], and MS analysis confirms the loss of the triisopropylsilyl group.

Solutions of azaenyne allene **3d** in $CDCl_3$ are unstable, even when refrigerated, and afford complex mixtures from which aldehyde **8** could be isolated (ca. 2% yield). Solutions of **3d** in 1,4-cyclohexadiene (1,4-chd) were allowed to stand at 4 °C for 8 h (TLC monitoring) to afford a complex mixture of products that included 6-phenyl-3-picoline **9** (20%) and a mixture of cyclohexadiene adducts **10a,b** (17%, ∼1:1 ratio), which were characterized as the reduced product **11**.

The formation of **8**, **9**, and **10a,b** are all commensurate with the intermediacy of the previously unreported α,5-didehydro-3-picoline diradical **4d**••. Rapid cyclization of **3d** to diradical **4d**•• (compare Myers cyclization of **3a** with $t_{1/2}$ of 20.5 h at 39 °C),[2a] followed by hydrogen atom abstraction from 1,4-chd affords a radical pair that can recombine to give **10a,b** or undergo subsequent hydrogen atom abstraction to afford **9**. Aldehyde **8** presumably arises from interception of adventitious oxygen by diradical **4d**••. Further support for the intermediacy of **4d**•• was obtained from analysis of solutions of **3d** in d_8-THF, which afforded dideuterated **9**.[25]

When solutions of **3d** in methanol were stored at 0 °C, 5-methoxymethyl-2-phenylpyridine (**12**, 20%) was isolated. A similar methanol addition product has been observed in thermolyses of **3a**, in methanol, and this has been attributed to a partitioning between diradical and ionic reaction pathways.[2a,19] Despite the overall similarity in trapping products from the thermal rearrangements of **3a** and **3d**, there are differences between these two systems. In general, the isolated yields of trapped products from **3d** are lower than those reported for **3a**. It may be that a competing aza-Schmittel pathway in the case of **3d** leads to more complex reaction mixtures and lower isolated yields. Also in contrast to the case of **3a**, which upon thermolysis in methanol gives rise to mixtures of products derived from hydrogen atom abstraction and methanol addition, we failed to isolate any hydrogen atom abstraction product **9** from methanolic solutions of **3d**. This observation may be related to the modest isolated yields of trapping products from reaction of the diradical **4d**•• with 1,4-chd. Perhaps **4d**•• is less reactive as a hydrogen atom abstraction agent toward 1,4-chd and methanol when compared to **4a**••. Alternatively, the methoxymethyl pyridine **12** may arise from a different mechanism involving methanol addition to the aminoallene functionality of **3d**, followed by cyclization of the resulting azadienyne.[26]

In conclusion, the formation of α,5-didehydro-3-picoline diradical intermediates from skipped azaenediynes via isomer-

(24) Data for **3d**, isolated as a yellow oil: R_f 0.45 (ethyl acetate/hexanes, 1:9); ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 1H), 5.36 (d, 2H, J = 6.0 Hz), 7.38−7.41 (m, 3H), 7.60 (t, 1H, J = 6.0 Hz), 8.07 (dd, 2H, J = 7.6, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 75.35, 81.06, 89.72, 110.11, 127.99, 128.54, 131.12, 136.72, 147.10, 213.72; CIMS m/z 168 (MH^+).

(25)) The **9** that was isolated (∼2% yield) consisted of ∼33% dideuterated material by ^{1}H NMR and MS analysis. Similarly low yields of **9** were obtained from reactions in THF, which is apparently a poor hydrogen atom donor towards **4d**••.

(26) We thank one of the reviewers for bringing this possibility to our attention.

ization to azaenyne allenes and aza-Myers−Saito cyclization has been predicted on the basis of DFT calculations. Skipped azaenediynes are easily prepared, and their facile aza-Myers cyclization provides a route to the previously unreported picolinyl diradicals. In addition, the isomerization of skipped azaenediynes and their subsequent rapid aza-Myers cyclization may have relevance to the recently reported DNA-cleavage ability of cationic heterocyclic skipped azaenediynes.[27] The potential modifications of azaenyne allenes such as **3d** by, for example, nitrogen atom protonation, are of particular interest, and we are currently investigating the potential of nitrogen atom protonation as a means to increase the reactivity of the α,5-didehydro-3-picoline diradical, as has been observed for the related aza-Bergman cyclization-derived 2,5-didehydropyridine diradical.[7]

Acknowledgment. We thank Dr. Shuhua Ma from University of Minnesota for helpful discussions. This work was supported by grants from the Robert Welch Foundation (F-1298) and the Petroleum Research Fund, administered by the American Chemical Society (AC-34115).

Supporting Information Available: Coordinates and energies of (U)B3LYP/6-31G* calculations and experimental data for compounds **7**, **3d**, **8**, **9**, **10a,b**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049266R

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