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Aza-Enyne Allenes: Thermal Reaction Behavior of 2,4,5-Hexatrienenitriles

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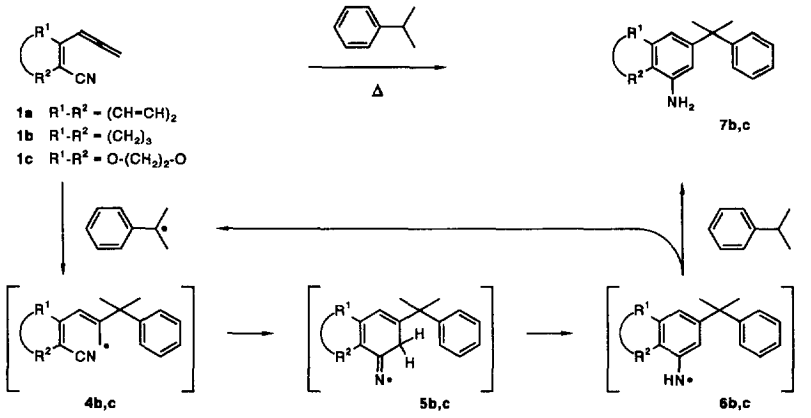
Abstract: *The novel aza-enyne allenes* ***1*** *were found to undergo no thermal isomerization analogous to the cycloaromatization of enyne allenes. Instead, upon heating in cumene,* ***1b*** *and* ***1c*** *cyclized to form amines* ***7b,c****, which appear to arise from an intramolecular 6-exo cyclization of a stabilized allyl radical onto the nitrile functionality.*

The recent interest in the chemistry of enyne allenes derives primarily from their structural and functional relationship to the key intermediate in the activation sequence of the naturally occurring antitumor antibiotic neocarzinostatin.[1] Moreover, the relative ease with which these π-systems undergo a thermally induced cycloaromatization[2] to form a diradical has spurred efforts to trap these reactive intermediates in subsequent radical cyclizations for the construction of multicyclic systems.[3] In light of the fact that the heteroanalogous enyne ketenes undergo a similar cycloaromatization step,[4,5] we have addressed the question of whether the enyne allene cyclization would be a feasible transformation for aza analogues, in which the acetylene moiety is formally replaced by a nitrile functionality. In this communication, we describe the thermal reaction behavior of this novel class of π-systems.

When the aromatic nitrile **1a**[6] (0.1 M) was heated in chlorobenzene in the presence of 1,4-cyclohexadiene (20 equiv.) at 150 °C for 13 h, only polymeric material was formed. On the other hand, when employing a substrate concentration of 0.005 M in cumene, **1a** was found to be stable for 5 d at the same temperature, indicating that the destruction of **1a** arises from its reaction with 1,4-cyclohexadiene. Since the annelation of aromatic ring systems to both enyne allenes[7] and enediynes[8] has been reported to exert a retarding effect on the respective rate of cycloaromatization, we then investigated compounds **1b,c**,[6] which contain an olefinic bond between the nitrile and the allene moiety. Heating substrate **1c** in cumene (0.005 M) for 5 d at reflux afforded the cyclized aniline derivative **7c**[9] in 11% yield. At 185 °C, **1c** was consumed within 7 h, providing **7c** in 10% yield. Applying the same reaction conditions to aza-enyne allene **1b** resulted in the formation of **7b** in a low yield of 2%.

We then addressed the question of whether the formation of **7** reflects a thermo*isomerization* of the aza-π-systems as the key step with subsequent trapping of the diradical intermediate by the solvent cumene. In light of the fact that attempts to trap potential radical intermediates by hydrogen transfer from 1,4-cyclohexadiene were unsuccessful, a thermoisomerization pathway similar to the enyne allene cyclization appears to be rather unlikely. A more plausible mechanism that would account for the observed product formation is depicted in Scheme 2. Initial addition of a cumyl radical to the sp-carbon of the allene, followed by an intramolecular addition of the resulting radical **4** onto the nitrile would generate the iminyl radical **5**.[10] Subsequent aromatization to give aminyl radical **6** and hydrogen abstraction from the solvent to regenerate the cumyl radical completes the radical chain with the formation of product **7**. When we heated **1c** in cumene (0.005 M) at 150 °C in the presence of di-*tert.*-butyl peroxide as a radical initiator, product **7c** was formed in 20% yield after a reaction time of 40 h.[11] The observed acceleration of the process together with the higher yield seems to support the postulated radical chain mechanism outlined above.



In conclusion, heating the novel aza-enyne allene analogues **1** in cumene gives rise to the aromatic amines **7**. Mechanistically, an unprecedented intramolecular addition of a *stabilized* allyl radical onto the nitrile functionality is proposed as the key cyclization step.

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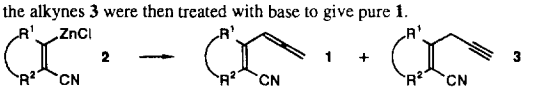
5. For an unsuccessful attempt to cyclize an aza-enyne ketene, see: Yamamoto, Y.; Nunokawa, K.; Ohno, M.; Eguchi, S. *Synlett* **1993**, 781-783.
6. The aza-enyne allenes **1** were prepared by a CuI-catalyzed reaction of organozinc chlorides **2** with propargyl bromide. The resulting mixtures of the allenes **1** and the alkynes **3** were then treated with base to give pure **1**.



Typical procedure: *n*-Butyllithium (1.6 M in hexane, 1.06 equiv.) was added dropwise to a solution of 2-bromobenzonitrile (1.00 mmol) in THF (2.5 mL) at -100 °C. After 15 min of stirring, $ZnCl_2$ (1.0 equiv.) in THF was introduced dropwise and the mixture was allowed to warm to -55 °C within 25 min. Then propargyl bromide (1.00 mmol), dissolved in THF (2.0 mL), and CuI (0.10 mmol) were added. After warming to -10 °C during 2 h, work-up (sat. NH_4Cl-sol., extraction with ether) provided a crude which was purified by flash chromatography (hexane/ethyl acetate 97.5/2.5) to give a 14:86 mixture of **1a** and **3a** (0.103 g, 73%). This mixture was then dissolved in $CHCl_3$ (2.0 mL) and powdered NaOH (1.5 equiv.) was added with stirring for 14 h. Silica was then added and the solvent removed in vacuo. The residue was subjected to flash chromatography (hexane/ethyl acetate 92.5/7.5) to afford pure **1a** (0.091 g, 88%).

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9. **7c**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 6H), 3.62 (bs, 2H), 4.21-4.27 (m, 4H), 6.12 (d, *J*=2.2 Hz, 1H), 6.26 (d, *J*=2.2 Hz, 1H), 7.13-7.17 (m, 1H), 7.24-7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 42.4, 64.4, 64.5, 05.7, 107.3, 125.4, 126.7, 127.9, 129.5, 135.2, 142.9,143.8, 150.7; IR (film) 3456, 3380, 1615, 1517 cm^{-1}; MS (EI) *m/z* (%) 269 (M^+, 75), 254 (100). HRMS calcd for $C_{17}H_{19}NO_2$ (M^+) *m/z* 269.1416, found 269.1436.
10. To our knowledge, a cyclization of a *stabilized* radical onto a nitrile function has not been reported previously. Nitriles as radical acceptors are sometimes problematic. For unsuccessful or low yield attempts of ε-cyano radical cyclizations, see: (a) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409-5410. (b) Yeung, B.-W. A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160-1162. (c) Knapp, S. Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397-5400. For successful examples, see: (d) Shono, T.; Kise, N. *Tetrahedron Lett.* **1990**, *31*, 1303-1306. (e) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322-326. (f) Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666-6672.
11. The peroxide was added in portions of 10 mol% each at 2 h intervals.

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