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Synthesis and Unusual Reactivity of *N*-Tosyl-4,5-benzoazacyclodeca-2,6-diyne, Yneamino-Containing Enediyne

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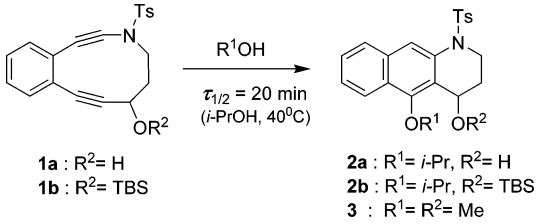
The extreme cytotoxicity of natural enediyne antibiotics is attributed to the ability of the (*Z*)-3-ene-1,5-diyne fragment to undergo Bergman cyclization[1] and produce DNA-damaging *p*-benzyne diradical.[2] It is well-documented that the rate of this process strongly depends on both the ring strain of enediyne-containing cycle[3] and the electronic properties of substituents.[4−6] Recent theoretical studies suggest that repulsion of the in-plane π-orbitals of triple bonds destabilize the cyclization transition state, while overlap of the out-of-plane π-orbitals produces the opposite effect owing to pronounced aromatization.[7] In accordance with this hypothesis, there is theoretical, as well as experimental, evidence that σ-acceptor and π-donor substituents at the acetylenic termini enhance the rate of Bergman cyclization.[3a,8] While replacing one of the carbon atoms in the enediyne system with nitrogen allows for the exploitation of heteroatom electronegativity,[6] nitrogen substituent in the propargylic position potentially allows for benefiting from both rate-enhancing effects.[8c,9]

In this Communication we describe the synthesis and the reactivity of the first cyclic aza-enediyne, in which a nitrogen atom is directly connected to one of the alkyne termini. (Scheme 1).

Scheme 1

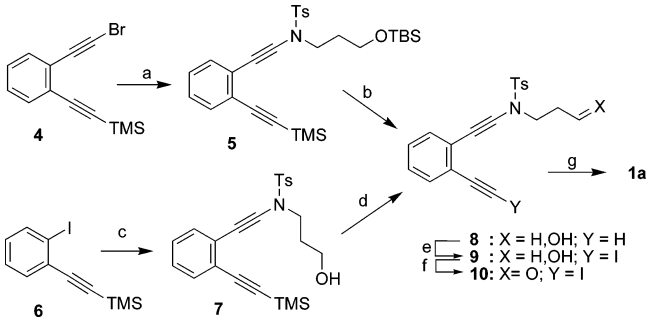


Preparation of the target 8-hydroxy-*N*-tosyl-4,5-benzoazacyclodeca-2,6-diyne (**1a**) is outlined on the Scheme 2.[10] Two methods for the preparation of the key intermediate **8** were employed: Sonogashira coupling of substituted tosyl yneamide with protected *o*-iodophenylacetylene **6** and Cu(II)-mediated amidation[11] of alkynyl bromide **4** with corresponding tosyl amide. Iodination of the terminal acetylene group in **8** followed by the oxidation of the hydroxyl group gave aldehyde **10**. The latter readily underwent cyclization to the target aza-enediyne **1a** under Nozaki−Hiyama−Kishi conditions (Scheme 2).[12]

The rate of cycloaromatization of **1a** at 40 °C was measured using ^{1}H NMR (ca. 25 mM in $CDCl_3$) and UV spectroscopy (ca. 2 × 10^{-4} M in 2-propanol and hexanes). Aza-enediyne **1a** was found be more than 2 orders of magnitude more reactive than its carbocyclic analogue ($\tau_{1/2}$ = 9240 min at 40 °C in neat 1,4-cyclohexadiene[13]). In addition, the rate of cycloaromatization of **1a** was higher in polar solvents, for example, at 40 °C half-life time of **1a** was 105 min in hexane, 65 min in chloroform, and 20 min in 2-propanol.

Surprisingly, the expected Bergman cyclization product (**11**, R = H, Scheme 3) was not detected in thermolyses of aza-enediyne

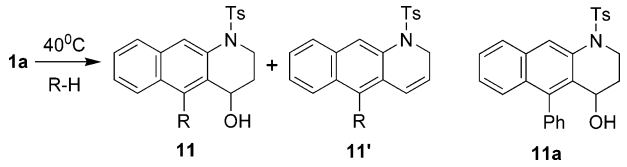
Scheme 2. Synthesis of aza-enediyne **1**[a]



[a] Reagents and conditions: (a) *N*-[3-(*t*-butyldimethylsiloxy)propyl] tosyl amide, $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, toluene, 79%; (b) TBAF, THF, 93%; (c) *N*-ethynyl-*N*-(3-hydroxypropyl) tosyl amide, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, 22%; (d) K_2CO_3, MeOH, 74%; (e) *n*-BuLi, NIS, THF, 79%; (f) Dess−Martin periodinane, CH_2Cl_2, 78%; (g) $CrCl_2$, $NiCl_2$, THF, 61%.

1a in various solvents. Overnight heating of toluene and 1,4-cyclohexadiene solutions of **1a** at 40 °C resulted in the formation of a complex mixture of 1:1 solvent adducts, which mass and NMR spectra corresponded to the general formulae **11** and **11′** (Scheme 3). In benzene under these conditions the single major product **11a** was isolated (Scheme 3).[10] Composition of product mixtures was virtually the same in oxygenated or argon-saturated solvents. While radical addition to 1,4-cyclohexadiene is a known process, the formation of formal C−H insertion products with benzene and toluene as well as regio- and 1:1 selectivity of the process are inconsistent with *p*-benzyne reactivity.

Scheme 3



In methanol and 2-propanol at 40 °C aza-enediynes **1a**,**b** underwent rapid and clean conversion to the product of formal insertion into O−H bond of the solvent (**2a**,**b**, Scheme 1). No hydrogen abstraction products (**11** or **11′**, R = H) were detected. While the formation of O−H insertion byproducts in the course of Myers−Saito cycloaromatization of allene-eneynes was reported in a couple of cases,[14] such clean and efficient reaction is unknown for enediyne compounds. Furthermore, cycloaromatization of aza-enediyne **1a** to 5-alkoxy-1,2,3,4-tetrahydrobezo[g]quinoline (**2a**) exhibits strong acid catalysis. Thus, in the presence of 1.5 × 10^{-4} M of toluenesulfonic acid the half-life time of **1a** in 2-propanol at 25 °C dropped down to 5 min. This observation is in a sharp contrast with carbocyclic enediynes, where the rate of cyclization is independent of the acid concentration.[15] Cycloaromatization of **1a**

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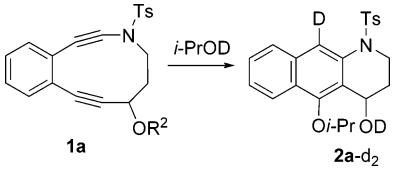
in methanol was also accompanied by etherification of the hydroxy group (**3**, Scheme 1).

Cycloaromatization of **1a** was ca. two times slower in 2-propanol-d_1 and in methanol-d_1. The substantial solvent isotope in normal direction ($k_H/k_D \approx 2$) indicates that proton transfer is at least partially rate-determining. Incorporation of deuterium into the reaction product (**2a**-d_2, Scheme 4) provides further evidence against diradical mechanism since *p*-benzene should preferentially abstract protium from the methine group of the solvent.

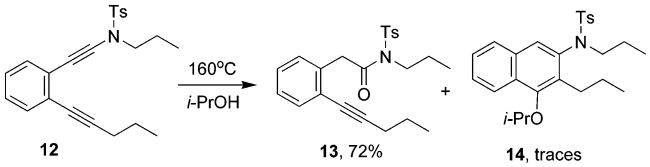
Scheme 4



1a **2a**-d_2

In contrast to **1a**, only traces of the O−H insertion product **14** were detected in the thermolysis of acyclic enediyne-sulfonamide **12** in 2-propanol, while imide **13** was isolated in 72% yield (Scheme 5).[10] The acyclic compound is less reactive and requires 4 h heating at 160 °C in 2-propanol to achieve full conversion. The product of conventional Bergman reaction, 2-(*N*-propyl-*N*-tosyl)-3-propylnaphthalene, has not been detected in reaction mixtures.

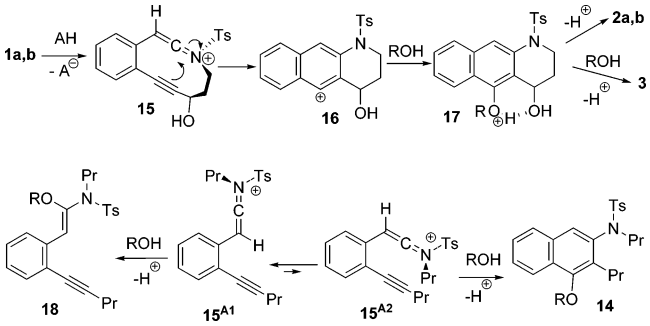
Scheme 5



12 **13**, 72% **14**, traces

The fact that cycloaromatization of aza-enediynes **1a**,**b** and **12** is accompanied by O−H insertion in hydroxylic solvents and not hydrogen abstraction suggests that this reaction proceeds by the polar rather than diradical pathway. Experimental observation described above can be accommodated by the following reaction mechanism (Scheme 6).

Scheme 6



Acid catalysis of cycloaromatization reaction, as well as pronounced solvent isotope and deuterium incorporation, provides strong support for the rate-determining protonation of the nucleophilic yneamine carbon of **1a**. Resulting ketenimmonium cation **15** undergoes very facile, as evident by the absence of addition products, nucleophilic attack by the second acetylenic moiety to give phenyl cation **16**, which is in turn trapped by the solvent yielding intermediate **17**. The latter can be deprotonated to **2a** or, in the case of small nucleophiles such as methanol, suffer subsequent S_N2 substitution of a protonated hydroxy group. We believe that the formation of **11a** in benzene also proceeds via a Friedel−Crafts-type reaction of the cation **16** with the solvent.

Acyclic ketenimmonium cation $\mathbf{15^A}$ formed by the protonation of **12** should exist predominantly in the less hindered conformation $\mathbf{15^{A1}}$, which cannot cyclize but rather adds alcohol to give **18**. The unstable imide enol ether **18** is hydrolyzed upon workup to imide **13**. Traces of the cyclization product **14** are, apparently, produced from the minor conformer $\mathbf{15^{A2}}$.

In conclusion, the replacement of a propargylic carbon in 3,4-benzocyclodeca-1,5-diyne with a nitrogen atom resulted in dramatic enhancement of the enediyne reactivity. The cycloaromatization reaction of aza-enediynes **1a**,**b** proceeds by a new polar mechanism via the intermediate formation of ketenimmonium cation. The latter undergoes rapid cyclization to give phenyl cation, which is trapped by a solvent.

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Supporting Information Available: Experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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