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Isolation of a cyclopropane-containing product from the rearrangement of a 3-aza-3-ene-1,5-diyne under acid catalysis

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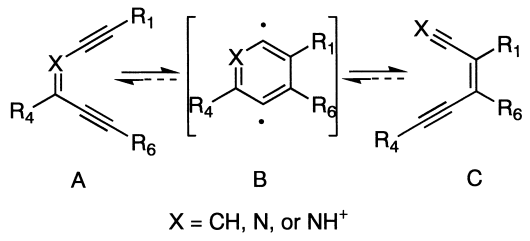
Abstract—A 3-aza-enediyne that undergoes rapid aza-Bergman rearrangement was treated with trifluoromethanesulfonic acid in the presence of 1,4-cyclohexadiene in an attempt to trap the putative 2,5-didehydropyridinium aza-Bergman intermediate. No pyridine products were detected; rather, a cyclopropane derivative of 1,4-cyclohexadiene derived from a 5-oxazolylcarbene was isolated.

Enediynes (Scheme 1, **A**, X = CH) undergo Bergman cyclization[1] to reactive 1,4-didehydrobenzene intermediates (**B**, X = CH), and this process has been the subject of much theoretical,[2] synthetic,[3] and biological interest.[4] The chemistry of 3-aza-enediynes (Scheme 1, **A**, X = N) has not been as widely studied. We have shown that 3-aza-enediynes undergo a rapid aza-Bergman rearrangement through a 2,5-didehydropyridine intermediate (B, X = N) to afford the isomeric β-alkynyl acrylonitrile products (**C**, X = N).[5] Unlike the Bergman cyclization of enediynes, the aza-Bergman rearrangement of 3-aza-enediynes does not afford any products corresponding to trapping of the intermediate diradicals. Theoretical studies[6] have predicted that the parent 2,5-didehydropyridine intermediate (**B**, X = N, $R_1 = R_4 = R_6 = H$) can undergo a rapid retro-aza-Bergman reaction to the nitrile (**C**, X = N, $R_1 = R_4 = R_6 = H$). This, together with the large singlet-state stabilization[7] of the 2,5-didehydropyridine diradical, conspire to make the 2,5-didehydropyridine intermediate an unreactive, very short-lived species. In contrast, the protonated 2,5-didehydropyridinium diradical (Scheme 1, **B**, $X = NH^+$) is predicted to be more resistant to retro-aza-Bergman rearrangement and have a smaller singlet–triplet gap, indicating that this intermediate would more readily undergo trapping reactions.[6] These predictions have led to the proposal that these aza-enediynes might serve as pH-dependent DNA cleavage agents in which the pH-dependence is mediated by the effect of protonation on the reactivity of the intermediate diradical.[6] We recently reported that sterically unencumbered acyclic 3-aza-3-ene-1,5-diynes undergo aza-Bergman rearrangement spontaneously at room temperature and below.[8] This provided an opportunity to examine the effect of protonation on the reactivity of the intermediates formed by aza-Bergman cyclization of these 3-aza-3-ene-1,5-diynes. Here we report our studies on the effect of added acid on the rearrangement chemistry of 3-aza-3-ene-1,5-diynes. Instead of products derived from trapping of the protonated 2,5-didehydropyridine diradical intermediate, one such 3-aza-3-ene-1,5-diyne affords a cyclopropane product apparently derived from a carbene intermediate.



Scheme 1.

The triisopropylsilyl-substituted aza-enediyne **2** was prepared as previously reported.[8] Briefly, the propynone **1** was converted to the oxime, which was activated as the sulfonate ester followed by addition of a cuprate reagent derived from phenylacetylene to afford the aza-enediyne **2** in modest yield (Scheme 2). The aza-enediyne **2** can be purified by chromatography and isolated as relatively stable yellow oil. However, when a solution of aza-enediyne **2** in chlorobenzene is heated at 150°C for a period of days, the aza-enediyne undergoes

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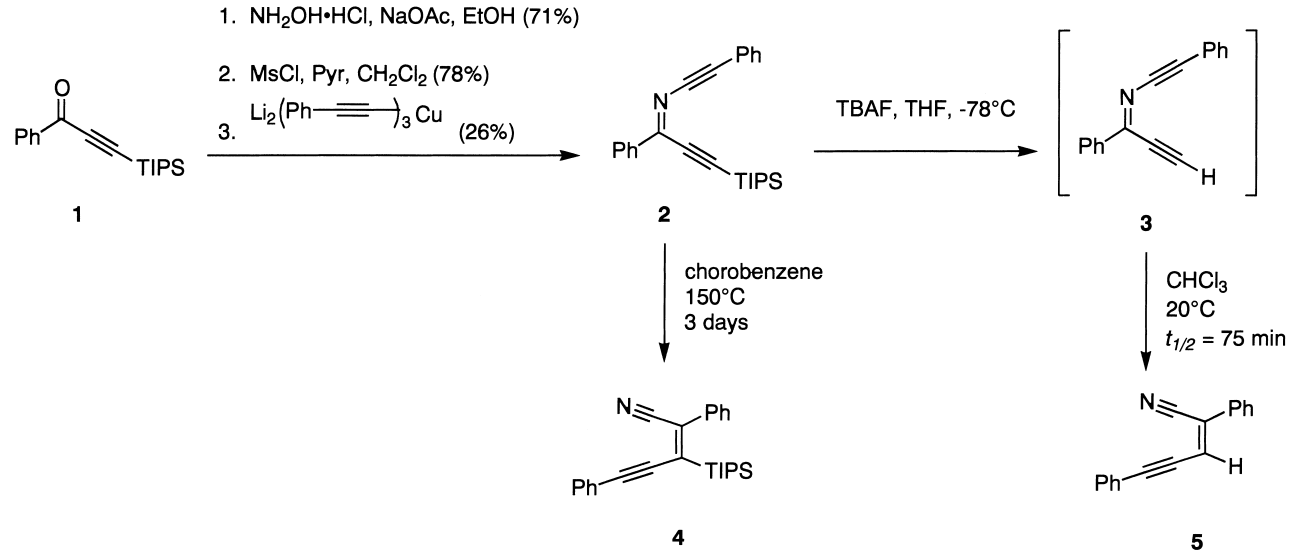
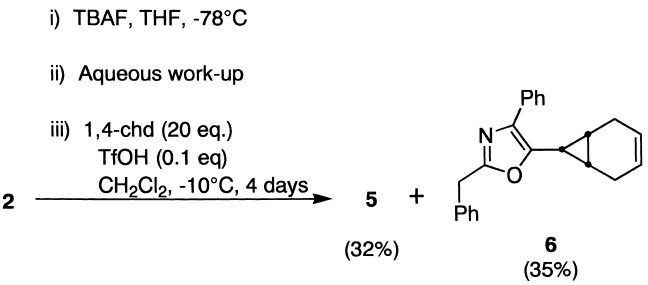


Scheme 2.

aza-Bergman rearrangement to afford the nitrile **4** (Scheme 2). Initial attempts to convert the triisopropylsilyl-substituted aza-enediyne **2** to the desilylated aza-enediyne **3** by treatment with tetrabutylammonium fluoride (TBAF) followed by aqueous work-up and chromatography led instead to the isolation of the aza-Bergman rearrangement product **5** as the sole product in 89% yield. However, treatment of **2** with TBAF followed by rapid aqueous work-up and immediate ^{1}H NMR analysis of the reaction mixture demonstrates the presence of the aza-enediyne **3** as predominantly the (*Z*)-isomer, which undergoes conversion to the nitrile **5** with a first-order half-life of 75 min at 20°C.

Desilylation of aza-enediyne **2** was carried out at −78°C for 5–10 min, and the reaction mixture subjected to rapid aqueous work-up. The organic extracts were cooled in a dry ice bath, dried over Na_2SO_4, and passed through a plug of silica gel to remove the tetrabutylammonium species. After evaporation of the solvent, the resulting oil consisting of aza-enediyne **3** along with variable amounts of the nitrile **5** was dissolved in CH_2Cl_2 and treated with catalytic trifluoromethanesulfonic acid (TfOH) in the presence of an excess of 1,4-cyclohexadiene (1,4-chd) at −10°C for 4 days. Monitoring of the progress of the reaction by TLC demonstrated the disappearance of aza-enediyne **3** and the appearance of two products, the aza-Bergman rearrangement product **5** and a more polar product **6** (Scheme 3). These products were isolated after evaporation of the reaction mixture and chromatography. The structural characterization of the cyclopropane **6** was carried out by NMR and single-crystal X-ray diffraction studies (Fig. 1).[9]

When the reaction was carried out in the presence of stoichiometric TfOH, complete consumption of the aza-enediyne was observed in 30 min at −78°C, and the cyclopropane derivative **6** was isolated in 30% yield,



Scheme 3.

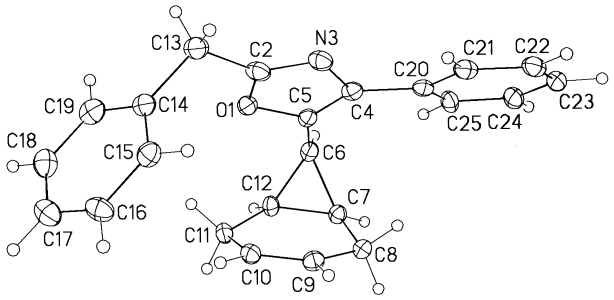
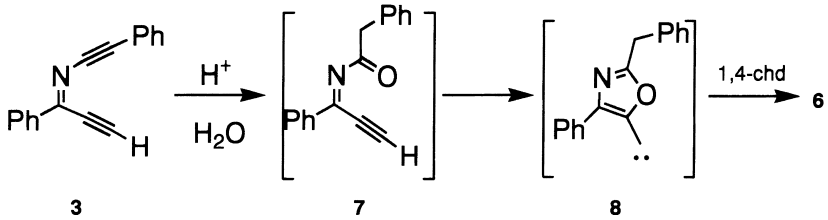


Figure 1. X-Ray structure of **6** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 30% probability level. The hydrogen atoms are drawn to an arbitrary size.

along with a 15% yield of the nitrile **5**. In the absence of added acid, only nitrile **5** was isolated in 89% yield. Re-subjecting nitrile **5** to the reaction conditions resulted only in recovered starting material; there was no evidence of conversion of nitrile **5** to the cyclopropane **6** under these reaction conditions.

The cyclopropanyl oxazole **6** appears to be the trapping product of an intermediate carbene **8** (Scheme 4). Although the origin of this carbene is uncertain, a possible route involves the acid-catalyzed addition of



Scheme 4.

water to the ynamine functionality[10] of the 3-aza-enediyne **3** to afford an intermediate *N*-acyl-*C*-alkynyl imine **7**. The presence of adventitious water in the crude desilylated 3-aza-enediyne **3** would be expected, given the procedures employed in the work-up of the desilylation reactions, which involved storing solutions of **3** on dry-ice during work-up and isolation in order to minimize conversion to the nitrile **5**. The proposed cyclization of the *N*-acyl-*C*-alkynyl imine **7** to the 5-oxazolylcarbene **8** is related to the observations of Schecter and co-workers,[11] who found that certain 5-oxazolylcarbenes, generated by thermolysis or photolysis of the corresponding diazo compounds, undergo C–H insertion and cyclopropanation reactions as well as ring-opening to *N*-acyl-*C*-alkynyl imines. The facile ring opening of related 2-furylcarbenes is well known,[12] and there are examples of the reverse reaction in which a heteroatom-substituted dieneyne system undergoes thermal cyclization to a carbene intermediate.[13] We propose that the reversible formation of the carbene **8** from the *N*-acyl imine **7** followed by addition of **8** to the double bond of 1,4-chd leads to consumption of the *N*-acyl imine species and formation of **6** (Scheme 4).

The role of adventitious water in the formation of **6** was established by carrying out the isolation of crude **3** and the TfOH-catalyzed rearrangement in the presence of 1,4-chd under strictly anhydrous conditions and in the presence of 4 Å molecular sieves. Under these conditions, no cyclopropane **6** is observed; instead, only nitrile **5** is isolated in 87% yield.

The isolation of the cyclopropyloxazole **6** from aza-enediyne **3** under acidic conditions contrasts with the results of Chen and co-workers,[6a] who report that the aza-enediyne **9** (Scheme 1, **A**, X = N, $R_1 = R_6 =$ Ph, $R_4 =$ Me) affords primarily the hydrolysis products 4-phenyl-but-3-yn-2-one and phenylacetonitrile under acidic conditions. When aza-enediyne **2** is subjected to similar reaction conditions as employed in the conversion of **3** to **6**, the hydrolysis product 1-phenyl-3-triisoproylsilyl-propynone is obtained. No pyridine products corresponding to trapping of a reactive 2,5-didehydropyridinium species were detected in the crude ^{1}H NMR spectra of any of the acidic reactions involving either **2** or **3**, which is also in contrast with Chen's report of a pyridine product from the thermolysis of aza-enediyne **9** under acidic conditions.[6a] We note, however, that our analysis would not be able to detect the extremely low yields ($\sim$0.05%) of pyridine product reported by Chen.

The substitution of nitrogen for carbon in the enediyne system can have a profound impact on the facility of the Bergman rearrangement and on the nature of the intermediates that are involved. Here we demonstrate that certain 3-aza-enediynes can also undergo reaction under acidic aqueous conditions to afford carbene intermediates that can be efficiently trapped. The generality of this reaction and its application to pH-dependent DNA cleavage reactions are under investigation.

Acknowledgements

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9. The product **6** was re-crystallized in hexanes and afforded colorless lathes and needles: mp = 85.0–86.4°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.5, 1.4 Hz, 2H, H21/25), 7.37 (t, J = 8.1 Hz, 2H, H16/18), 7.29 (dd, J = 7.1, 1.0 Hz, 2H, H15/19) 7.28–7.15 (m, 4H, H22/24 and H23 and H17), 4.89 (s(br), 2H, H9/10), 4.04 (s, 2H, H13), 2.22 (d(br), J = 19.8 Hz, 2H, H_{eq}8/11), 2.18–2.00 (m, 3H, H_{ax}8/11 and H6), 1.60 (dd, J = 7.7, 4.5 Hz, 2H,

H7/12); ^{13}C NMR ($CDCl_3$) δ 13.77 (C6), 15.79 (C7/12), 20.78 (C8/11), 34.85 (C13), 123.15 (C9/10), 126.00 (C21/25), 126.83 (C17 or C22/24), 126.84 (C17 or C22/24), 128.39 (C15/19 or C16/18), 128.45 (C15/19 or C16/18), 128.86 (C23), 132.77 (C4), 135.67 (C20), 136.01 (C14), 145.72 (C5), 160.45 (C2); HRMS m/z 328.1711 (calcd 328.1702, $C_{23}H_{21}NO$). The data crystal was cut from a long lathe and had approximate dimensions; 0.27×0.17×0.04 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ=0.71073 Å). A total of 400 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 136 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Crystallographic data for this structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 204592 and can be obtained, free of charge, from CCDC at deposit@ccdc.cam.ac.uk.

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