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Aza Hopf cyclization: synthesis and reactivity of cyclic azadieneynes

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ABSTRACT

Nine- and 10-membered azadieneynes have been synthesized for the first time via an intramolecular aza Wittig reaction. The compounds undergo Hopf cyclization under ambient conditions to the hydroxy dihydroisoquinoline derivatives.

The study of generation of diradicals and their chemical as well as biological reactivity has become an area of intense research in the past two decades.[1] Primarily there are three reasons behind such an interest. The first and foremost is their ability to simultaneously pull off hydrogens from the sugar moiety of opposite strands of a ds-DNA resulting in its cleavage,[2] a process important for cancer chemotherapy.[3] Additionally, these diradicals are useful intermediates for the synthesis of various aromatic compounds[4] including conducting polymers.[5] Their synthesis and methods of generation under ambient conditions are some of the important challenges in this area. The Bergman cyclization[6] of (*Z*)-3-hexene-1,5-diynes (enediynes) to 1,4-didehydrobenzene diradicals and the Myers–Saito cyclization[7] of (*Z*)-1,2,4-heptatriene-6-ynes (enyne-allenes) to α,3-didehydrotoluene diradicals under thermal conditions provide easy entry to a variety of carbon-centered diradicals. Similarly, the Moore cyclization[8] of eneyne–ketenes in which a ketene moiety replaces the allene moiety in the eneyne–allene system leads to a diradical having an aryl and a phenoxy radical. Schmittel[9a,b] has developed several variations of Myers–Saito cyclization using the eneyne carbodiimide in addition to the formation of fulvene diradical[9c,d] from suitably substituted eneyne allenes. Nicolaou et al.[10] in a seminal paper used the chemistry of bisallenic sulfone. These molecules also undergo cyclization to generate diradicals, the reaction is known as the Garatt–Braverman cyclization (GBC).[11] All these cyclization processes leading to diradicals are shown in Scheme 1. In 1969, Hopf and Musso[12] showed that hexa-1,3-dien-5-yne undergoes a thermal cycloisomerization to give rise to benzene. The reaction needs high temperature (>274 °C) and is believed to proceed through the intermediacy of the diradical. A H-shift resulted in the formation of benzene. In this Letter, we have synthesized the nine-membered cyclo 1-aza-1,3-dien-5-yne via an intermolecular aza Wittig reaction. The compound undergoes Hopf cyclization spontaneously at room temperature in $CDCl_3$ solution to a dihydroisoquinoline derivative.

Like BC, Hopf cyclization can also be speeded up by keeping the dieneyne constrained in a cyclic framework which also aides the reaction. Like our earlier work on N-substituted enediyne[13] and also Kerwin's work on azaenediynes,[14] we decided to incorporate a nitrogen atom at the terminal ethylenic carbon and to constrain the moiety in a nine-membered cyclic network and to study its reactivity. Another motivation was to explore the possibility of DNA cleavage by the intermediate for aza Hopf cyclization. It may be pointed out that amongst the various diradical forming processes, Hopf cyclization has a rapid self-quenching mechanism which prevents the intermediate to pull out H from external source. Thus, abstraction of H from sugar phosphate backbone is almost ruled out. In this Letter, we have successfully demonstrated that the nine-membered azadieneyne can cause DNA damage via Hopf cyclization, possibly via a nucleophilic addition.

Before embarking upon the synthesis of the target molecule, we analyzed the possible outcome of a nine-membered azadieneyne system. In case of acyclic systems with a *t*-butyl group attached to imino nitrogen, the molecule undergoes an electrophile-induced intramolecular cyclization to isoquinoline derivative, as demonstrated by Larock and co-workers[15] Similarly, Asao et al.[16a] have also reported the synthesis of 1,2-dihydroisoquinoline derivatives by AgOTf-catalyzed addition of pronucleophiles to o-alkynylaryl aldimine. The same reaction has also been carried via a three-component reaction[16b] using *o*-alkynylbenzaldehyde, primary amine, and pronucleophiles.[16c] The reaction proceeded in the absence of a catalyst and an ionic mechanism was proposed as shown in Scheme 2. We argued that with an appropriately sized cyclic dieneyne, instead of an electrophile or nucleophile-induced cyclization, Hopf cyclization can take place to form a diradical as the first step. Intramolecular electron transfer then leads to a zwitter ion similar to that proposed by Asao et al.[16] Subsequent protonation followed by the addition of a nucleophile will generate the dihydro isoquinoline derivative (Scheme 2). If the reaction is performed in the presence of DNA, then that will act as a nucleophile, and its addition will certainly cause its damage via Maxam–Gilbert pathway.

The synthesis (Scheme 3) started with the protection of 2-iodobenzyl alcohol, prepared from the corresponding acid. Sonogashira

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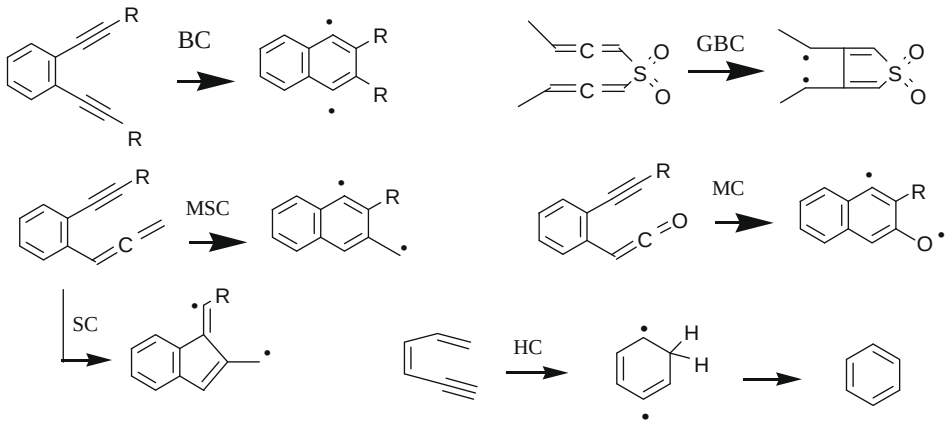
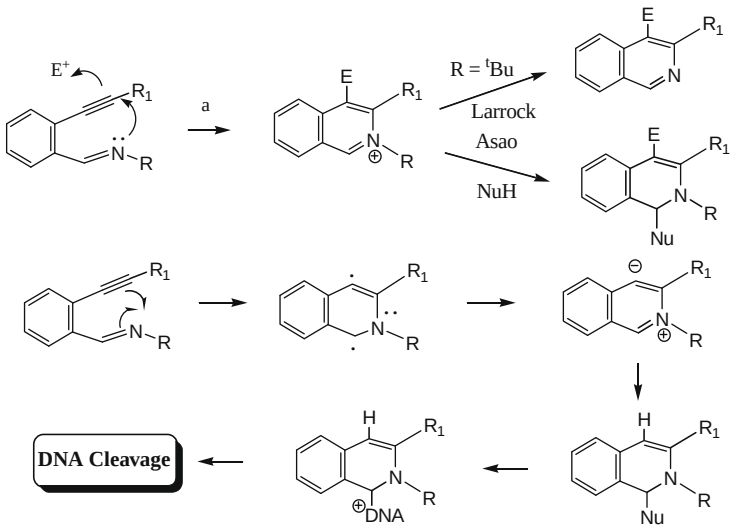
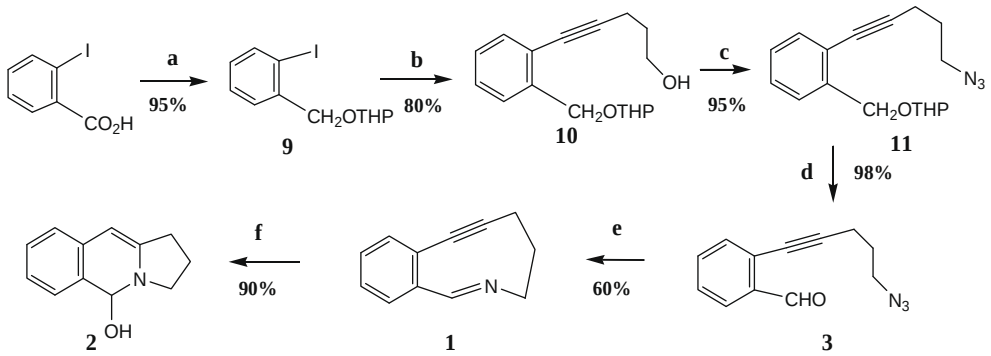


BC = Bergman Cyclization, MSC = Myers Saito Cyclization, SC = Schmittel Cyclization, GBC = Garratt Braverman Cyclization, MC = Moore Cyclization, HC = Hopf Cyclization

Scheme 1. Diradical generating processes.



Scheme 2. Electrophile-induced reactivity of ene-yne-imine and predicted reactivity of cyclic systems.



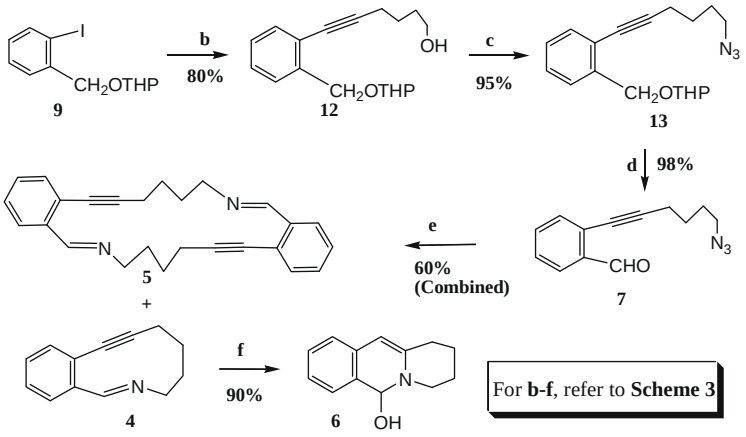
Scheme 3. Synthesis of imine **1** and formation of cyclization product **2**. Reagents and conditions: (i) BH_3–THF, rt, 6 h; (ii) DHP, PPTS, CH_2Cl_2, 12 h; (b) 4-pentyn-1-ol, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, rt, 9 h; (c) (i) MsCl, Et_3N, 0 °C, 10 min; (ii) NaN_3, DMF, rt, 6 h; (d) (i) PPTS, EtOH, rt, 12 h; (ii) Dess–Martin Periodinate, CH_2Cl_2, rt, 3 h; (e) PPh_3, $CHCl_3$, 3days, rt; (f) incubatation at 37 °C for 3 days.

coupling[17] with 4-pentyn-1-ol followed by standard functional group transformations produced the azide. Deprotection followed by oxidation with Dess–Martin reagent[18] gave azido aldehyde **3**. In order to follow the outcome of the intramolecular aza Wittig

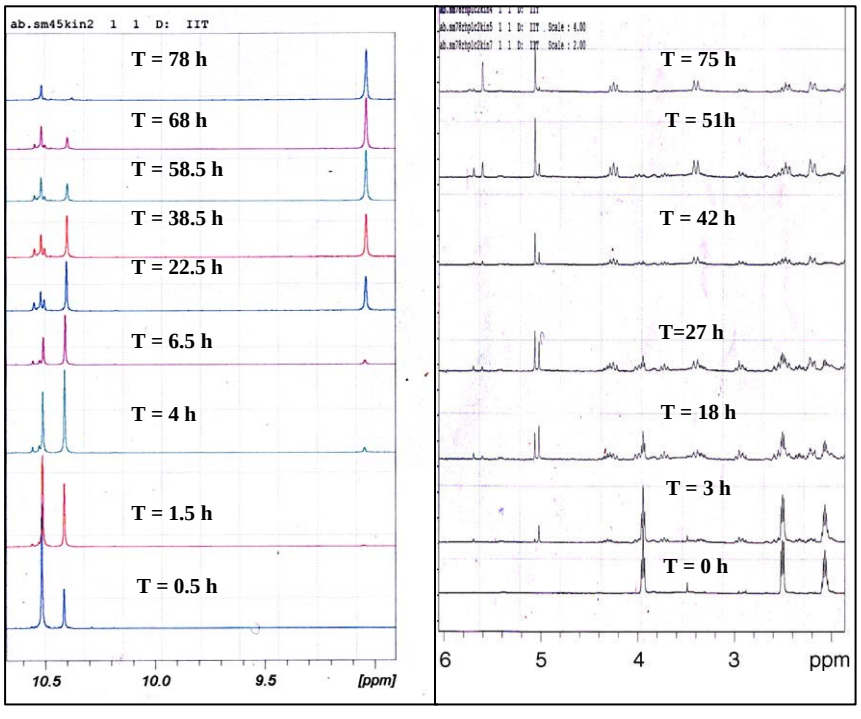
reaction, the azido aldehyde was dissolved in $CDCl_3$ and ^1H NMR was recorded at different time points after adding 1 equiv of PPh_3 in order to determine the course of aza Wittig reaction.[19] The formation of the ylide could be seen within half hour as evidenced from the appearance of a new aldehyde peak at δ 10.45 along with concomitant decrease in the signal for the aldehyde peak.

The conversion to the ylide was complete in 1 h after which another new peak started to appear at δ 9.05 which grew in intensity at the expense of the aldehyde peak of the ylide. The product corresponding to this new peak was assigned the imine structure. This is the first example of an aza analogue of nine-membered dieneyne and the conversion was almost complete within 3 days with an estimated yield of ~80%. The various time-dependent NMRs are shown in Figure 1.

The imine **1** was, however, unstable to Silica gel chromatographic conditions. It was purified by HPLC (100% methanol, flow rate 0.8 mL/min) and was fully characterized by NMR and mass spectral data. A solution of the imine in $CDCl_3$ was kept at 37 °C in an incubator. It was smoothly converted to the dihydroisoquinoline derivative **2** with a half-life of ~27 h in near quantitative yield (^1H NMR is shown in Fig. 2). The structure of the imine as well as the final cyclization product has been confirmed by ^1H, ^{13}C, and COSY NMR as well as by mass spectral analysis. Thus, the two singlets in the ^1H NMR spectrum at δ 5.61 and δ 5.06 were assigned to be due to the H-1 and H-4, respectively. The ^{13}C NMR spectrum showed the presence of three methylenes and six methine carbons. Mass spectra showed the peak at *m*/*z* 171 corresponding to $[M-OH+H]^+$. In case of the higher homologue (synthesis shown in Scheme 4), the azide **13** upon PPh_3 reduction gave the mono-imine **4** (formed by intramolecular condensation) which was mixed with the intermolecular product, namely, bis-imine **5**. These could not be separated even by HPLC thus prompting us to carry out the Hopf cyclization on the mixture. However unlike in the case of **1**, the temperature had to be raised to 50 °C for mono-imine



Scheme 4. Synthesis of imine **4** and the formation of cyclization product.



Figures 1 and 2. (1) ^1H NMR at different time points after the addition of PPh_3 to the azido aldehyde **3**. (2) ^1H NMR at different time points upon incubation of imine **1**.

Figure 3. DNA cleavage experiment with compound **1** at 37 °C: Lanes **5**: DNA (7 μL) in TAE buffer (pH 7.5) (5 μL) + acetonitrile (6 μL), **4**: DNA (7 μL) in TAE buffer (pH 7.5) (5 μL) + **1** in acetonitrile (6 μL, 2 mM) for 24 h, **3:** DNA (7 μL) in TAE buffer (pH7.5) (5 μL) + **1** in acetonitrile (6 μL, 2 mM) for 48 h, **2:** DNA (7 μL) in TAE buffer (pH 7.5) (5 μL) + **1** in acetonitrile (6 μL, 2 mM) for 72 h, **1:** DNA (7 μL) in TAE buffer (pH 7.5) (5 μL) + **1** in acetonitrile (6 μL, 2 mM) for 96 h.

4 to undergo cyclization to the dihydro isoquinoline derivative **6** in about 45% yield; bis-imine **5** remained intact during the process.

Having accomplished the synthesis and the chemical reactivity study of azadieneyne toward Hopf cyclization, we checked its DNA cleavage activity. Thus incubation of compound **1** in acetonitrile (6 μL) and ds-plasmid DNA in aqueous buffer (7 μL) at 37 °C led to the moderate cleavage of DNA after 48 and 72 h (Fig. 3) in millimolar concentrations.

In conclusion, we have synthesized the aza analogue of the 9- and 10-membered dieneyne for the first time. The compounds showed cyclization to form dihydroisoquinoline derivatives. The nine-membered imine showed moderate DNA cleaving activity.

Selected spectral data: All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz, respectively.

For **3***: State*: Oily liquid; yield: 95%: δ_H 10.51 (1H, s), 7.89 (1H, d, J = 7.6 Hz), 7.53–7.50 (2H, m), 7.43–7.39 (1H, m), 3.50 (2H, t, J = 6.8 Hz), 2.62 (2H, t, J = 6.8 Hz), 1.95–1.88 (2H, m); δ_C 191.8, 135.9, 133.7, 133.4, 128.1, 127.2, 127.1, 95.7, 77.30, 50.2, 27.7, 16.9; MS (ESI) m/z 213 (M^+).

For compound **1**: *State*: Oily liquid; yield: 60%: δ_H 9.04 (1H, s), 8.07–8.05 (1H, m), 7.46–7.43 (1H, m), 7.37–7.26 (2H, m), 3.94 (2H, t, J = 6.4 Hz), 2.50 (2H, t, J = 6.0 Hz), 2.10–2.04 (2H, m); δ_C 160.6, 136.3, 132.7, 130.3, 127.9, 125.8, 125.0, 95.0, 78.4, 60.0, 28.5, 16.5; MS (ESI) m/z 170 (MH^+).

For compound **2**: *State*: Oily liquid; yield: 98%: δ_H 7.39 (1H, d, J = 7.6 Hz), 7.36–7.31 (1H, m), 7.17 (1H, t, J = 7.6), 7.07 (1H, d, J = 7.6 Hz), 5.61 (1H, s), 5.06 (1H, s), 4.29–4.22 (1H, m), 3.40 (1H, d, J = 16.0 Hz), 2.48–2.43 (1H, m), 2.20 (1H, d, J = 12.8 Hz), 1.86–1.83 (1H, m), 1.77–1.74 (1H, m): δ_C 144.2, 134.7, 129.7, 128.9, 124.4, 123.1, 121.4, 100.7, 76.8, 49.4, 27.0, 23.2; MS (ESI) m/z 171 (MH^+−OH).

For compound **7**: *State*: Oily liquid; yield: 95%: δ_H 10.52 (1H, s), 7.89 (1H, d, J = 8.0 Hz), 7.53–7.51 (2H, m), 7.43–7.39 (1H, m), 3.36 (2H, t, J = 6.4 Hz), 2.55 (2H, t, J = 6.4 Hz), 1.80–1.73 (4H, m): δ_C 191.9, 135.9, 133.7, 133.3, 128.0, 127.4, 127.0, 96.9, 76.9, 50.9, 28.0, 25.6, 19.1; MS (ESI) m/z 227 (M^+).

For 1:1 mixture of compounds **5** *and* **6***: State*: Oily liquid; δ_H 8.80 (1H, s), 7.98–7.95 (1H, m), 7.36–7.30 (4H, m), 7.26–7.23 (1H, m), 7.12–7.09 (1H, m), 6.99 (1H, d, J = 7.6 Hz), 5.62 (1H, s), 4.93 (1H, s), 4.01–3.89 (2H, m), 3.60–3.54 (1H, m), 3.32–3.25 (1H, m), 2.60–2.54 (1H, m), 2.42–2.30 (3H, m), 2.12–2.08 (1H, m), 1.90–1.85 (1H, m), 1.73–1.43 (6H, m); δ_C 160.7, 144.0, 136.6, 135.0, 132.1, 130.2, 129.7, 128.8, 128.0, 126.1, 124.6, 124.2, 122.1, 106.2, 103.7, 95.6, 59.9, 55.0, 30.7, 28.9, 28.3, 25.6, 23.4, 19.4.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.168.

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