



Attemptd Synthesis of Cyclic Oxa-dieneynes for Studying Self-quenching Hopf Cyclization

Sayantan Mondal

Department of Chemistry, Bankura Zilla Saradamani Mahila Mahavidyapith, Bankura, West

Bengal-722101, India

Email ID: sayantan.saradamani@gmail.com

Abstract: In this paper I have reported an attempted synthesis of cyclic dieneynes having oxygen atom in cyclic framework and their reactivity study. I wanted to incorporate hetero atom (O) in different ways in the carbocyclic dieneyne framework. In type 1, one of the carbons present in the saturated chain is replaced by O atom. The intention was to explore the change towards Hopf cyclization temperature upon incorporation of heteroatom Oxygen in carbocyclic dieneyne framework. Another motivation was to explore the possibility of DNA cleavage by the intermediates for these oxa and aza Hopf Cyclizations as some of the intermediates may have sufficient half-lives so as to interact with external agents like biomacromolecules. Final ring closure reaction even in very high dilution condition resulted dimeric oxa-dieneynes instead of desired monomers and fails to cyclize under ambient conditions.

Keywords: Hopf cyclization, self-quenching, biradical, dimerization

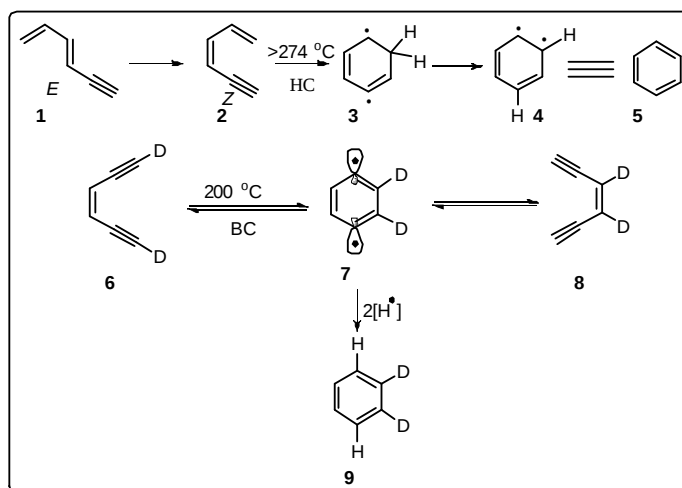
*Corresponding author: Sayantan Mondal

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1. Introduction

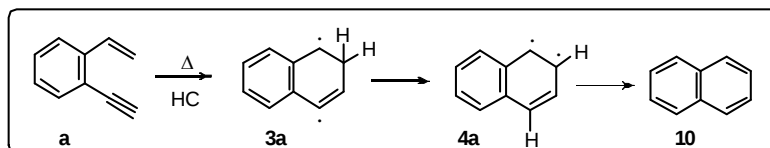
In 1969, Hopf and Musso showed that hexa-1,3-dien-5-yne **1** undergoes a thermal cycloisomerization to give rise benzene.^{1a} The reaction starts above 274 °C, at which point isomerization between *E* isomer and *Z* isomer occurs. From a geometrical point of view, *Z* isomer is the reactive species which readily cyclizes and it is believed to proceed through the formation of a biradical intermediate followed by a H-shift resulting in the formation of benzene.^{1b} This cycloisomerization process is commonly known as Hopf Cyclization (HC).^{1a, b} In the Bergman Cyclization (BC)² of hex-3-en-1,5-diyne **6** the

cycloaromatization requires the addition of external hydrogen atoms (which may be furnished either by simple hydrogen donors, such as cyclohexa-1,4-diene, or also by very complex ones, such as DNA), whereas the substrate **1** required for Hopf Cyclization is self sufficient for leading to a stable product and no external hydrogen source is necessary for its cyclization (**Scheme 1**).



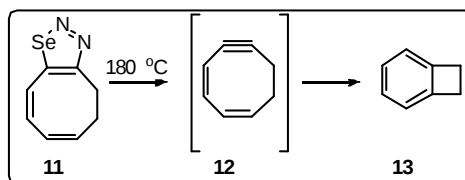
Scheme 1: Hopf Cyclization of diene-yne and Bergman Cyclization of enediyne

For the benzannelated system, experimental values are not yet available. However, computational analysis for the cyclization of **2a** (**Scheme 2**) have been carried out and they are quite useful.^{1c, d} In presence of benzene ring the cyclization barrier (BLYP: 32.1 kcal mol⁻¹, BCCD(T): 36.4 kcal mol⁻¹) is only slightly affected and lies a little higher in energy than in the parent system.^{1c}

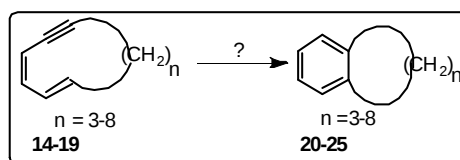


Scheme 2: Hopf Cyclization of benzannelated diene-yne

Research in the last decade or so has enabled us to understand some of the controlling parameters for Hopf Cyclization kinetics.^{1b, c} Like BC, Hopf Cyclization is known to have high activation barriers for acyclic diene-yne (**Scheme 1**). The synthesis of cycloocta-1,3-dien-5-yne **12** from selenadiazol **11** was the first example for cyclic diene-yne.^{1b} After thermolysis of **11** at 180 °C, the highly strained **12** could only be detected in traces because of its short lifetime, but its formation could indirectly be proved by the isolation of its cycloisomerization product benzocyclobutene **13** (**Scheme 3**).

**Scheme 3:** Thermolysis of selenadiazol11

In 2001, Hopf and co-workers synthesized 10-14 membered cyclic dieneynes and studied their thermal reactivity.^{1b} Compared to the acyclic ones, these cyclic dieneynes generally have much lower activation energy so that the same reaction can take place at moderately lower temperature (**Scheme 4**). For example, a 10-membered carbocyclic dieneyne **15** undergoes cyclization at ambient temperature with fairly decent half-life (**Table 1**).

**Scheme 4:** Thermal cyclization of the cyclodieneynes to the benzocycloalkenes

Entry	Compound	Ring Size	T _{cycl.} , °C
1	14 (n = 3)	9	Unknown
2	15 (n = 4)	10	room temperature
3	16 (n = 5)	11	100 °C
4	17 (n = 6)	12	150 °C
5	18 (n = 7)	13	210 °C
6	19 (n = 8)	14	>210 °C

Table 1: Thermal stabilities of 10-14 membered dieneynes

As have been already pointed out, HC has so far failed to draw much attention unlike the apparently similar BC because of its self-quenching nature. The fact that 10-membered Hopf system undergoes the cyclization under ambient conditions is encouraging and offers a scope for further exploitation if the following conditions, one or the other or both, are fulfilled:

- Arrest the self-quenching process and allow the biradicals to react with external agents and

- b) Allow self-quenching but make the product there from reactive enough to interact with external agents.

In this paper, we have attempted the synthesis of cyclicdieneyne having oxygen atom in cyclic framework.

Like BC, Hopf Cyclization can also be speeded up by keeping the dieneyne constrained in a cyclic framework which also aids the reaction. Like earlier work on N-substituted enediynes⁵ and also Kerwin's work on azaenediynes,⁶ we decided to incorporate oxygen atom at cyclic dieneyne network and study its reactivity. We wanted to incorporate hetero atom (O) in three different ways in the carbocyclic dieneyne framework. In type 1, one of the carbons present in the saturated chain is replaced by O atom. In type 2 and 3, one alkenyl carbon in the double bond is replaced by N atom (**Figure 1**).

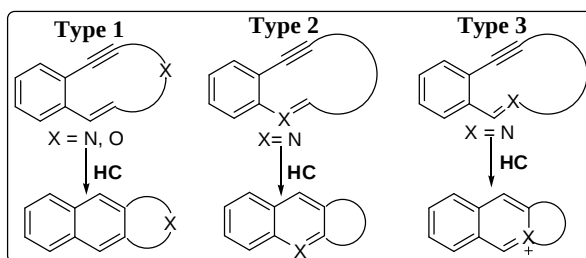
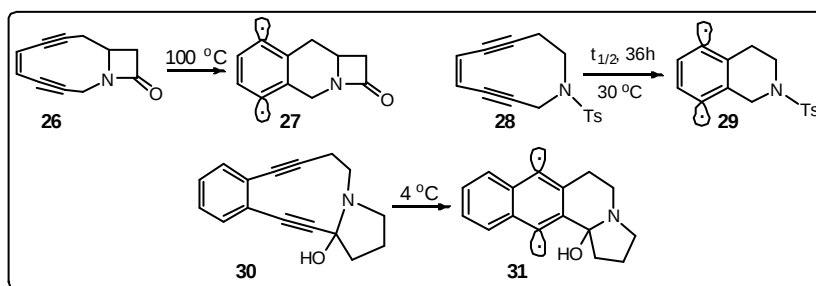


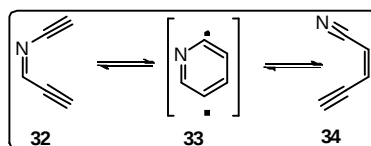
Figure 1: Possible types of heteroatom substituted cyclic dieneynes

Another motivation was to explore the possibility of DNA cleavage³ by the intermediates for these oxa and aza Hopf Cyclizations as some of the intermediates may have sufficient half-lives⁴ so as to interact with external agents like biomacromolecules.

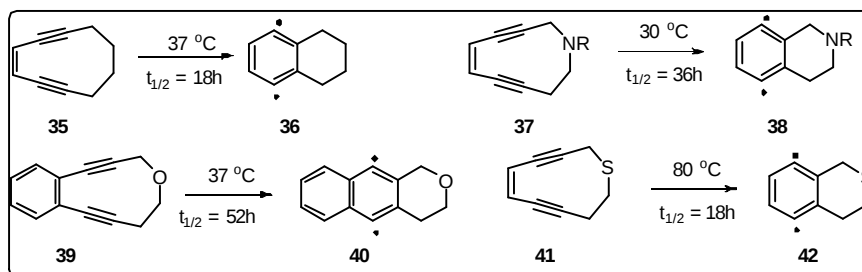
Bargman Cyclization of cyclic enediynes is much more facile than that of acyclic ones.⁷ The effect of incorporation of heteroatom in the cyclic framework of enediyne on the BC kinetics have been quite extensively studied.^{5b, 8} Various N-substituted cyclic enediynes have been synthesized from our laboratory and their reactivity have also been studied.⁵ Kerwin and David have devised an aza-BC route to a pyridine nucleus starting from enediyne where one of the ene carbons has been replaced by a nitrogen atom.⁶ It has been demonstrated from the above two reports that the reactivity of enediynes have been significantly affected by incorporating a heteroatom in an enediyne framework (**Scheme 5, 6 and 7**).



Scheme 5: Reactivity of N-substituted cyclic enediyne

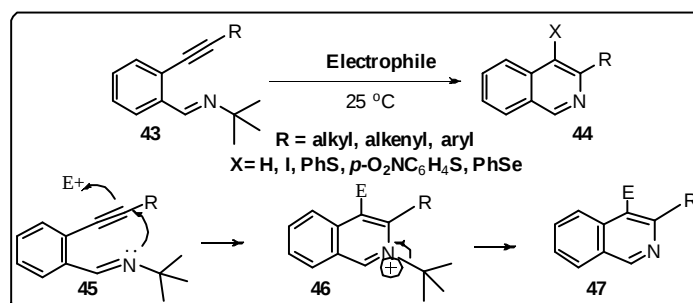


Scheme 6: Aza-Bergman Cyclization



Scheme 7: Stability of enediyne containing heteroatom in cyclic framework.

Larrocket *al.* first synthesized heteroatom containing dienyn **43** where one terminal carbon atom of the double bond is replaced by N-atom.⁹ In case of acyclic systems with a *t*-butyl group attached to imino nitrogen, the molecule underwent an electrophile induced intramolecular cyclization to generate isoquinoline derivative **44** (**Scheme 8**).



Scheme 8: Electrophile induced cyclization of acyclic aza-dieneyne.

2. Experimental Method

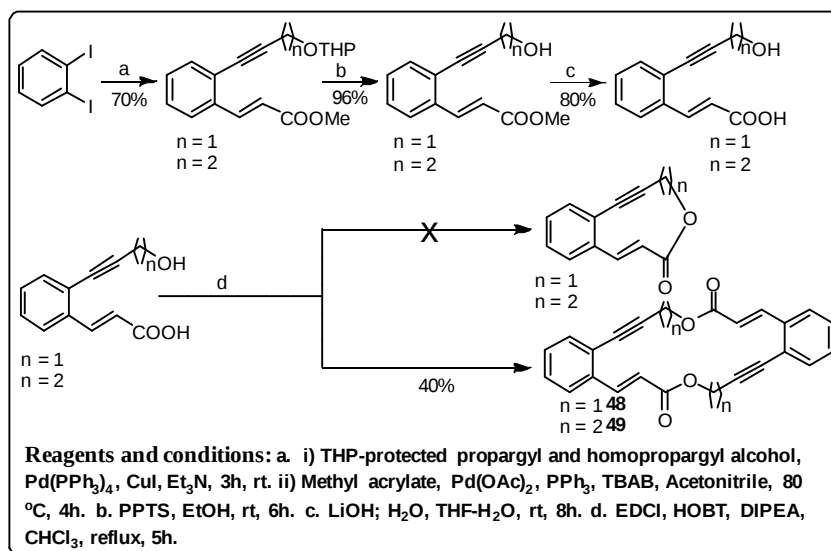
To an ice-cold solution of open chain hydroxy acid dieneyne (60 mg, 0.29 mmol) in dry CHCl_3 (100 mL) EDCI (1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide, 54 mg, 0.35 mmol) and HOBT (Hydroxybenzotriazole, 47 mg, 0.35 mmol) was added successively in 5 minutes interval and the reaction mixture was stirred at 0 °C for 1 h. Then DIPEA (N,N-diisopropylethylamine, 0.15 mL, 0.87 mmol) was

added and the reaction mixture was refluxed at 65 °C for 5 h (Scheme-9). Evaporation of solvent gave a viscous oil from which the product (**48** and **49**) was isolated by column chromatography (Si-gel, PE-EtOAc mixture as eluent). State: off-white semi solid; Yield: 50%.

3. Results and discussion

3.1 Attempted synthesis of oxa-dieneynes (type 1 in Figure 1)

Several attempts were made to synthesize 9- and 10-membered oxa-dieneynes. In the first approach (**Scheme 9**), we started from 1,2-diiodobenzene. Sequential Sonogashira coupling¹⁰ and Heck coupling¹¹ with THP protected alkyne alcohols and methyl acrylate followed by ester hydrolysis followed by THP deprotection gave corresponding hydroxy acids respectively. Attempted intramolecular EDCI coupling¹² of hydroxyl group and acid group at high dilution furnished the dimers **48** and **49** instead of desired dieneyne monomers. The dimeric structure of **49** could be confirmed by single crystal X-ray (Figure 2) which also is an indirect evidence of formation of dimeric structure **48** supported by NMR and Mass spectral data.



Scheme 9: Attempted synthesis of 9- and 10-membered cyclic oxa-dieneynes

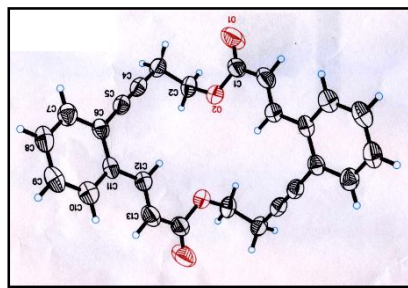
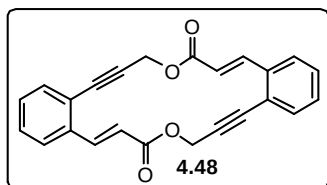


Figure 2: ORTEP diagram of dimer **49**

3.2 Spectral Data of Compound 48:



State: off-white semi solid; **Yield:** 50%. δ_H (200 MHz) 5.13 (4H, s), 6.60 (2H, d, $J = 16.2$ Hz), 7.33-7.38 (4H, m), 7.47-7.52 (2H, m), 7.60-7.64 (2H, m), 8.21 (2H, d, $J = 16.2$ Hz). δ_C 53.3, 84.6, 88.9, 119.5, 122.8, 126.5, 128.9, 129.9, 132.6, 135.5, 142.7, 165.7. HRMS: Calcd. for $C_{24}H_{16}O_4 + H^+$ 369.1127

found 369.1131.

When we attempted thermal cyclization of dieneyne dimer **48**, as expected, under ambient condition it fails cyclize and underwent decomposition over 110 °C. Even if **48** and **49** would cyclize around or above 110 °C, those thermal Oxa-Hopf Cyclizations would fail to find any biological relevance as the cyclization temperature would be way above the biological temperature.

4. Conclusion

The strategy of involving ring closure first, followed by the generation of double bond in the cyclic molecule was successfully executed to prepare the 10- and 11-membered oxa-dieneynes. However both of them failed to undergo HC under ambient conditions. Heating to 110 °C in toluene led to their decomposition. Inspire of failure to produce desired results, this work is probably the first report of macrocyclic Oxa-dieneyne synthesis which can be very useful in synthetical aspect. The dimerization occurred at the final lactonization stage which clearly indicates that the ring closure has to be done through a different reaction other than lactonization and in future we will try the intramolecular ring closure first, followed by the generation of double bond in the cyclic molecule to get a cyclic oxa-dieneyne framework.

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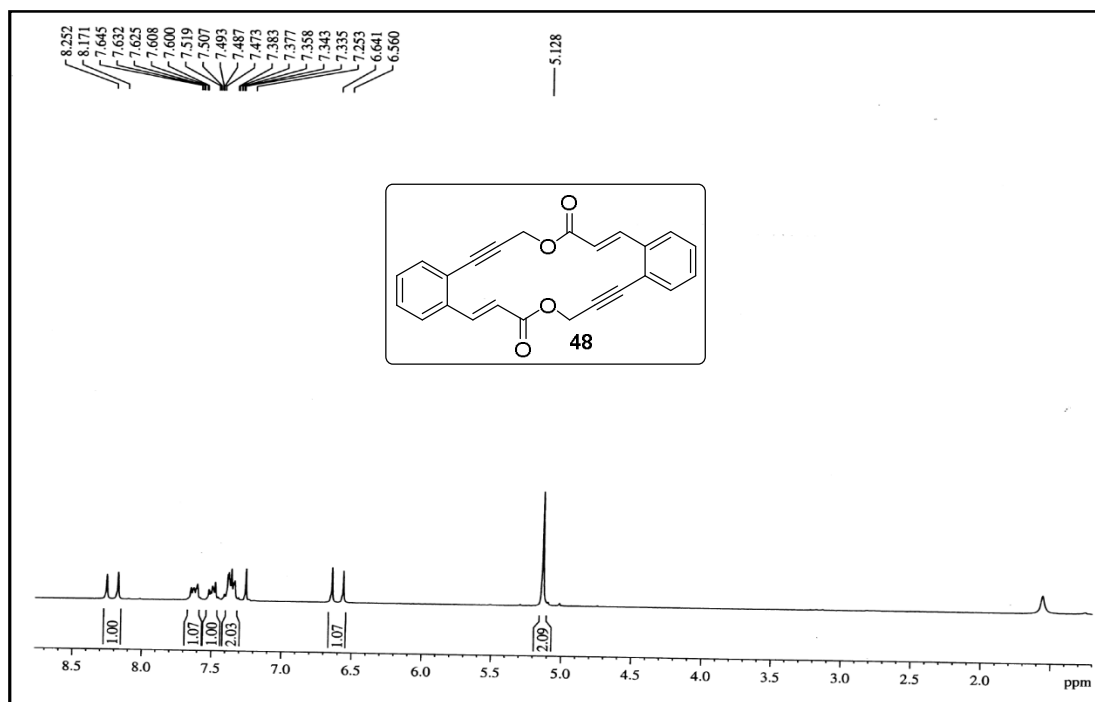
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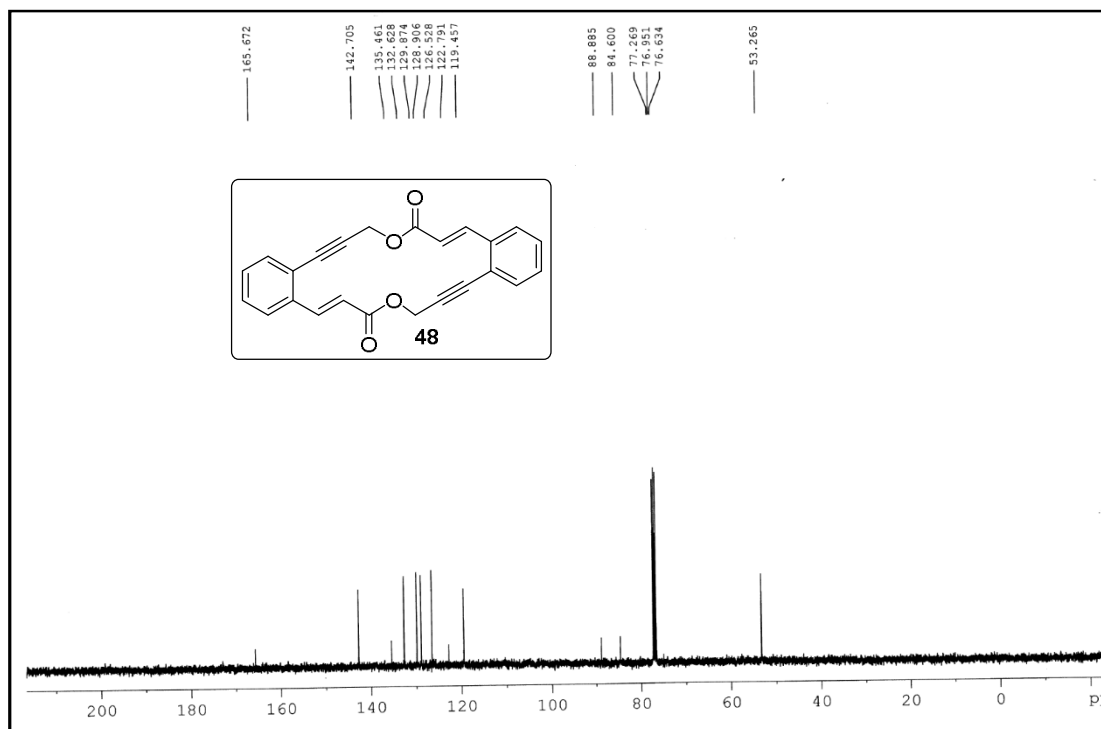
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Appendix

^1H and ^{13}C NMR spectra of selected compounds



^1H NMR (200 MHz, CDCl_3)



^{13}C NMR (100 MHz, CDCl_3)

