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First Intramolecular Benzyne Diels-Alder Reaction with an Acyclic Diene. Unusual Effect of Diene Geometry on the Course of the Reaction.¹

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Abstract: The first intramolecular benzyne Diels-Alder reaction with an acyclic diene is reported. The course of the reaction is dependent on the diene geometry. Trans dienes afford [4+2] cycloadducts; cis dienes apparently give [2+2] cycloadducts followed by further rearrangement, a mechanistic course which is supported by deuterium labeling experiments.

Intramolecular Diels-Alder reactions involving benzynes are rare. Indeed, the literature records few cases, all involving furans or arenes as the four-electron component.² In view of the preeminent position occupied by the normal intramolecular Diels-Alder reaction³ in the arsenal of tools available to the synthetic organic chemist and the impressive list of complex natural products synthesized by this method, the lack of attention to the benzyne counterpart seems surprising. This surprise is underscored by the fact the *inter*molecular benzyne Diels-Alder reaction, although well-established,⁴ is notorious for its lack of regioselectivity.⁵ Complete control of regiochemistry should therefore be possible by connecting the reactive ends of the system with a tether of suitable length. In connection with several total synthesis objectives in this laboratory, there was occasion to employ the heretofore unknown intramolecular benzyne Diels-Alder reaction (IMBDA) with a simple acyclic diene. This paper describes the first example of such a process.

The study employed simple tethered dienes derived from sorbic acid (Scheme 1). The Grignard reagent prepared from (*E*)-1-bromo-3,5-hexadiene⁶ was condensed with the known aldehyde 2^7 to give in 83% yield the benzylic alcohol which was quantitatively oxidized with Dess-Martin periodinane⁸ and the resulting ketone protected as its 1,3-dioxolane ketal (88%).^{9,10} Treatment with LDA generated the benzyne¹¹ and, to our gratification, afforded the cycloadduct $4a^{12}$ in 20-28% yield, presumably derived from a concerted [4+2] reaction. To our knowledge, this is the first example of an intramolecular benzyne Diels-Alder reaction with a non-aromatic diene. Hydrogenation and hydrolysis gave the corresponding hexahydrophenalen-1-one. The previous lack of success in this type of reaction is no doubt due to the combination of high benzyne reactivity and low concentration of the reactive s-cis diene conformation.¹³ That the yield is low is not surprising; that any [4+2] product forms is significant. A possible explanation for the observation with the ketal involves an increase of the reactive s-cis diene conformation which facilitates some cycloaddition, a phenomenon which might be yet another manifestation of the gem-dimethyl effect.¹⁴ Indeed, **3b** reacts similarly with LDA to give the corresponding Diels-Alder product in



Scheme 1. Reagents and Reaction Conditions (a) 1. Mg/THF/RT, then add to 2 in THF at 0°C. 2. Dess-Martin periodinane/CH₂Cl₂/RT. 3. For 3a: TMSOCH₂CH₂OTMS/TMSOTf/CH₂Cl₂/-78°C. For 3b: Tebbe reagent (excess)/PhMe/RT. (b) LDA/ -78°C ---> RT.

about 25% yield. No product corresponding to an intramolecular cycloaddition was observed when the benzylic position is monosubstituted (e.g., 3c), an observation that has been previously noted.¹⁵

Intramolecular benzyne cycloaddition with cis dienes, however, followed an entirely different course (Scheme 2). The benzyne intermediate **6** was prepared from 3-butyn-1-ol in the manner described above. Treatment with LDA now gave a new cycloadduct 7^{16} in 64% yield in which the olefin is conjugated with the aromatic ring.



Scheme 2. Reagents and Reaction Conditions (a) 1. TBDPSCl/imidazole/CH₂Cl₂/RT. 2. CH₂=CHBr/(*i*-Pr)₂NH/(Ph₃P)₄Pd/CuI/THF/RT. 3. H₂/Lindlar catalyst/PhH/RT. 4. TBAF/IHF/RT. 5. PPh₃/NBS/cat. pyridine/CH₂Cl₂/RT/1 h. (b) Scheme 1, (a), as for 3a. (c) Scheme 1, (b).

It is conceivable that this process involved an initial [4+2] cycloaddition followed by isomerization to give the conjugated isomer. However, inspection of models reveals that, whereas a trans diene can adopt an unexceptional Diels-Alder transition state with the diene and aromatic components in perpendicular planes, it is very difficult for a cis diene to do so. In order to account for the results, we propose the following mechanism outlined in Scheme 3. An initial non-concerted [2+2] addition⁴ of the cis olefin to the benzyne **8** would produce the strained benzocyclobutene intermediate **9**, which should



Scheme 3

undergo a rapid concerted conrotatory electrocyclic ring opening to the *o*-quinomethide **10**, followed by spontaneous electrocyclic ring closure to the product. The intermediate **9** could not be isolated.

In an attempt to provide further evidence for this mechanistic course, the intermediate **11** was synthesized. The methyl group would function as as a probe; the position of the methyl group in the cycloadduct **13** would support the proposed mechanism. Compound **11** was prepared as a mixture of cis



Scheme 4

and trans isomers from a procedure analogous to that described in Scheme 2.¹⁷ Attempted cycloaddition under the usual conditions afforded neither the product 13 nor the product derived from a [4+2] addition, namely, 15, but rather a compound tentatively identified as the benzocyclooctene 16 in low yield, presumably derived from an intramolecular ene rearrangement. The mechanism is however supported by a labeling experiment in which deuterium placed across the cis olefin of the starting diene 12 was found incorporated at the C.4 and C.7 positions in the product 14. It is also known from studies with intermolecular benzyne Diels-Alder reactions that dienes which can readily achieve an unstrained transition state react predominantly in the [4+2] manifold: otherwise [2+2] or ene processes are observed.¹⁸

Further mechanistic investigations as well as synthetic applications of these heretofore unknown reaction types are in progress.

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