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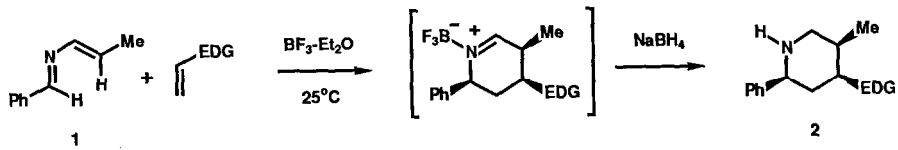
ACID CATALYZED INTRAMOLECULAR 2-AZA-1,3-DIENE DIELS-ALDER CYCLIZATION PROCESSES

Eugene Ho, Yea-Shun Cheng and Patrick S. Mariano*

Department of Chemistry and Biochemistry
University of Maryland, College Park, MD 20742

Abstract. *Preparation and acid-catalyzed Diels-Alder cyclizations of a 1-alkenyl-2-aza-1,3-diene have been explored.*

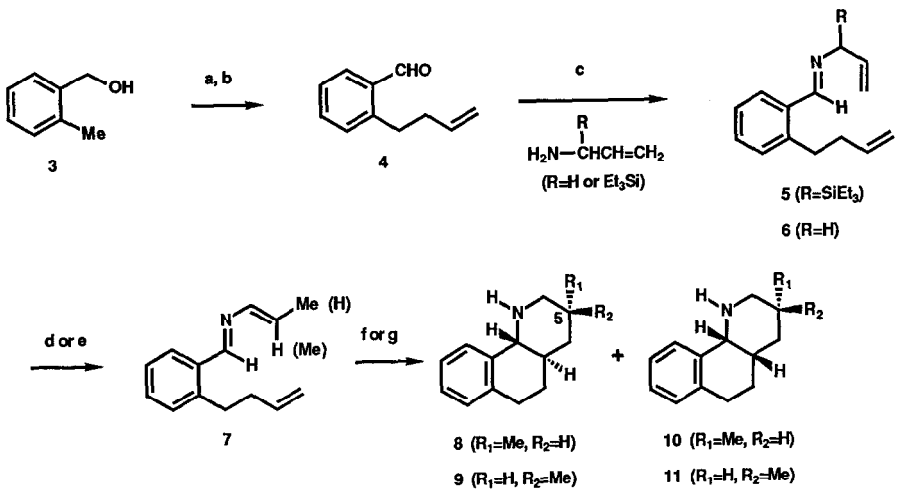
Hetero-Diels-Alder cycloaddition processes have recently received increased attention owing to their obvious use in the area of heterocycle synthesis. The comprehensive review by Boger and Weinreb[1] contains numerous examples demonstrating the broad application of 4+2-cycloadditions with hetero-atom containing dienes and dienophiles. Our interest in this area is concerned with Diels-Alder cycloadditions of 2-aza-1,3-dienes. In an earlier report,[2] we described our initial studies which focused on the development of a mild, protodesilylation-based method for 2-azadiene preparation. In an investigation which followed, we demonstrated that the model azadiene **1** undergoes intermolecular cycloaddition to a variety of electron rich dienophiles under mild (25°C), Lewis-acid (BF_3) catalyzed conditions to produce after $NaBH_4$ reductive work-up the substituted piperidines **2**.[3] The highly regioselective, stereoselective and stereospecific nature of these processes suggested that they occur by concerted mechanisms.[4] While these intermolecular processes show promise as methods for substituted piperidine synthesis, their application would be limited by low yields (25 - 45%), the lack of reactivity of all but electron rich dienophiles (enol ethers, enamines) and of azadienes which can not readily adopt low energy s-cis conformations (*e.g.* E,Z-isomer of **1**), and competitive azadiene dimerizations which occur under the BF_3 reaction conditions.



In order to probe further the synthetic potential of 2-azadiene cycloadditions and to determine if the limitations noted above for the intermolecular reactions can be circumvented, we have initiated efforts to explore intramolecular versions of this process.[5] Initial phases of our studies have focused on the acid catalyzed cyclization chemistry of azatriene **7**. This substance, as a mixture of C-C double bond isomers, was prepared by the sequences shown in Scheme 1 which feature base-catalyzed isomerization[6] and fluoride-induced protodesilylation[2] methods for azadiene formation. The silylallyl-imine **5** can be transformed to a 7:1 **E,E**:**E,Z**

isomeric mixture of **7** by treatment with CsF in THF containing 0.4 equiv. of 18-crown-6. Alternatively, base-catalyzed (KOtBu/THF) isomerization of allyl-imine **6** in the presence or absence of 18-crown-6 provides **7** as respective 8:1 or 1.1:1 mixtures of E,E:E,Z-isomers. The stereoselectivities (or lack thereof) displayed in these processes are discussed in detail elsewhere.[2b]

Scheme 1.



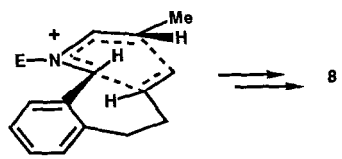
(a) nBuLi, THF/CH_2=CH-CH_2Br (73%); (b) PCC, CH_2Cl_2 (92%); (c) C_6H_6, 3A mol. sieves (*ca.* 95%); (d) for **5** -> **7** CsF, THF, 0.4 eq. 18-crown-6, 25°C 8h (*ca.* 90%); (e) for **6** -> **7** KOtBu, THF, w/wo 18-crown-6, -30°C, 3 min (99%); (f) BF_3-Et_2O (1.1 equiv), C_6H_6 followed by $NaBH_4$, EtOH ; (g) HBF_4 (1.1 equiv.), C_6H_6/ $NaBH_4$.

Diels-Alder cyclization of **7** (8:1 E,E:E,Z) occurs efficiently under mild (25°C) conditions in the presence of Lewis (BF_3-Et_2O) or protic (HBF_4) acid catalysts. The hydrophenanthridines **8** - **11** are isolated in the yields shown in Table 1 after $NaBH_4$ workup and silica gel chromatographic separation. The distributions of stereoisomeric hydrophenanthridines for both the BF_3 and HBF_4 catalyzed processes vary in a regular fashion with time and temperature with the trans-isomer **8** being the major product for short time, lower temperature reactions. Additionally, under these conditions the **8** +**10** / **9** +**11** product ratios are nearly equal to the starting azadiene E,E /E,Z ratio (8:1). These results suggest that both stereoisomers of **7** undergo kinetically controlled, stereospecific cyclization (**7E,E** -> **8** + **10** and **7E,Z** -> **9** + **11**). Moreover, cyclization of **7E,E** is stereoselective, occurring preferentially via an exo-transition state, **12**. This preference appears to result from arene-azadiene conjugation which is maintained to a greater extent in **12** compared to the endo-transition state **13**.[7] Factors similar to this are known to govern the stereochemistry of other intramolecular Diels-Alder cyclizations.[8]

Hydrophenanthridine stereoisomer distributions from reactions of **7** at higher temperatures and longer times favor the trans, cis-isomer **9**. This appears to be due to thermodynamic factors related to the relative energies of iminium cation precursors of **8** - **11**. Thus, transformation of the tricyclic iminium cation **14**, formed initially by exo-cyclization of protonated or BF_3-complexed **7E,E** to its β-Me epimer **16** (the precursor of **9**) should be an exothermic process. Evidence has been gained to support assignment of iminium cation-enamine interconversions[9a] (**14** -> **15**-> **16**) as the major pathway responsible for equilibration of these systems.[9b] Specifically, cyclization of **7** catalyzed by DBF_4 followed by $NaBH_4$ work-up provides hydrophenanthridines **8** and **9**, both of which contain mono-deuterium substitution at the piperidine C-ring, C-5 position. Under the

Table1. Representative Results of Azatriene **7** Cyclizations Catalyzed by BF_3 - Et_2O and HBF_4.

BF_3 - Et_2O						HBF_4					
		Yields						Yields			
Time (h)	Temp. (°C)	**8**	**9**	**10**	**11**	Time (h)	Temp (°C)	**8**	**9**	**10**	**11**
1	25	42	2	8	4	1	5	52	___	3	6
2	25	47	3	7	3	2	25	56	6	5	___
24	25	14	26	13	12	48	25	10	45	___	8
1	45	10	18	9	6	2	45	52	14	4	___
48	45	13	25	5	11	48	45	13	40	___	7



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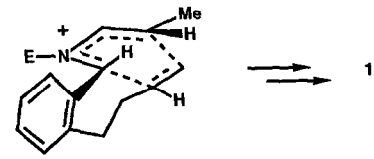

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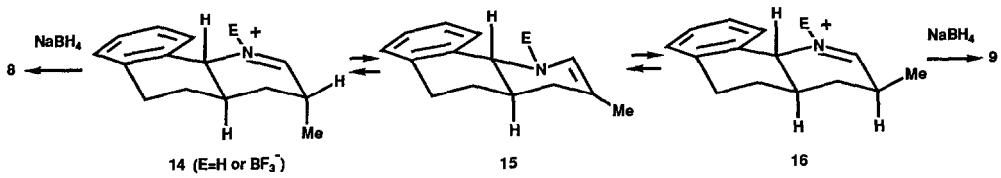
reaction conditions, deuterium is not incorporated into unreacted **7**.[10] This result in conjunction with the observation that stereoisomeric azadienes related to **7** are only slowly isomerized under the BF_3 - Et_2O and HBF_4 cyclization reaction conditions,[3,11] allows us to rule out an alternate route as the major pathway for the **14** -> **16** interconversion involving reversible cycloaddition and **7E,E** -> **7 E,Z** isomerization.

The above results demonstrate that intramolecular Diels-Alder cyclizations can serve as efficient methods for stereocontrolled synthesis of N-heteroatom containing, fused polycyclic systems. The yields of these processes, catalyzed by proton or Lewis acids, are modestly high even in this case where a non-electron donating substituted dienophile moiety participates. The stereochemistry of the cyclization reactions appears to be controlled in a



predictable way by kinetic (transition state preferences) and thermodynamic (equilibration via iminium cation -> enamine) factors. Finally, the product iminium cation functions in the products of these cyclizations (*e.g.* **14** and **16**) can potentially serve as a site for the introduction of additional functionality.[12] Thus, the use of this chemistry in alkaloid synthesis appears promising.

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(1) Boger, D.L.; Weinreb, S.M., " Hetero-Diels-Alder Methodology in Organic Synthesis," Org. Chem. Series, Vol. 47, Academic Press, N.Y., **1987**.

(2) (a) Chen, S.F.; Mariano, P.S. *Tetrahedron Lett.*, **1985**, 47; (b) Chen, S.F.; Ho, E.; Mariano, unpublished results.

(3) Cheng, Y.S.; Ho, E.; Mariano, P.S.; Ammon, H.L. *J. Org. Chem.*, **1985**, *50*, 5678.

(4) (a) Gupta and Franck (ref. 4b) have gained evidence in support of a nonconcerted mechanism for related 4+2-cycloadditions between olefins and N-arylisoquinolinium salts; (b) Gupta, R.B.; Franck, R.W. *J. Am. Chem. Soc.*, **1987**, *109*, 5393.

(5) (a) Isolated examples of intramolecular azadiene-olefin cycloaddition are found in the acid catalyzed cyclizations of 4-aryl-1,4-dihydropyridines (ref 5b); (b) Hartman, G.D.; Halczenko, W.; Phillips, B.T. *J. Org. Chem.*, **1985**, *50*, 2427.

(6) (a) Wender, P.A.; Schaus, J.M. *J. Org. Chem.*, **1978**, *43*, 782; (b) Worley, S.D.; Taylor, K.G.; Venugopalan, B; Clark, M.S. *Tetrahedron*, **1978**, *34*, 833.

(7) Owing to the small amounts of **9** and **11** generated, it is difficult to accurately determine the exo *vs.* endo transition state preferences for kinetically controlled cyclization of **7E,Z**.

(8) See for example Stork, G.; Morgans, D.J. *J. Am. Chem. Soc.*, **1979**, *101*, 7110.

(9) (a) For an example of a related yet slower iminium cation epimerization process see Evans, D.A.; Mitch, C.H.; Thomas, R.C.; Zimmerman, D.M.; Robey, R.L. *J. Am. Chem. Soc.*, **1980**, *102*, 5955; (b) the increase in yields of **10** and **11** in the BF_3-catalyzed reaction of **7** suggests that another equilibration pathway involving reversible Diels-Alder cyclization is also operating.

(10) ^1H NMR analysis of the N-arylmethyl-N-propyl amine $NaBH_4$ reduction product of unreacted **7** from reaction catalyzed by DBF_4 (1 equiv) at 25°C for 1h showed no D-incorporation.

(11) Isomerization of azadiene **1** or its E,Z-isomer with HBF_4 (C_6H_6, 25°C) is slow.

(12) Work up of the reaction mixture from BF_3-catalyzed cyclization of **7** with NaCN (2 equiv.) gives α–cyanoamine analogs of **8-11**.

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