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INTRAMOLECULAR AZIDE-DIENE CYCLOADDITIONS. AN APPROACH TO FUSED BICYCLIC 3-PYRROLINES BASED ON A ONE-POT NITRENE-DIENE CYCLOADDITION EQUIVALENT.

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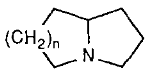
Summary: *Cyclization of heterosubstituted* ω*-azidodienes* **11** *provides fused* bicyclic 3-pyrrolines **12** in one operation. These pyrrolines are potentially useful intermediates for natural products synthesis, as illustrated by further functionalization.

Ring system **1** *is well represented as a structural subfeature in many* alkaloids. An attractive strategy for the assembly of such systems would be an intramolecular 1,4-nitrene/diene cycloaddition, providing bicyclic 3-pyrrolines **2** (eq. 1). We wish to report herein a one-pot equivalent of this cycloaddition (see **3** ⇒ **5** in Scheme 1).



1

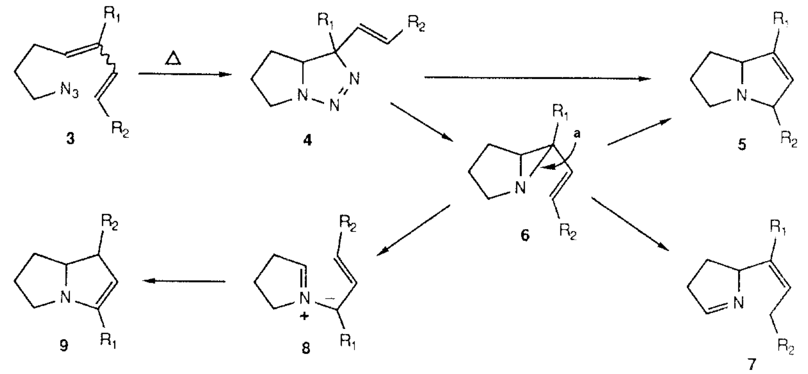
2

(eq. 1)

Recognizing that a nitrene-based strategy would be troublesome, we have reported our initial findings on the intramolecular 1,3-dipolar cycloadditions of azides onto dienes as a formal equivalent of this transformation[2], summarized in Scheme 1. Unfortunately, the desired transformations **3**→**4**(→**6**)→**5** did not constitute the major pathway. Instead, the vinyl aziridine intermediate **6** underwent a 1,5-homodienyl shift (**6**→**7**), or, at high temperatures (>500°), conrotatory opening of the aziridine C-C bond followed by electrocyclic ring closure (**6**→**8**→**9**). We wish to describe herein a method which circumvents these undesired pathways, and provides a direct and potentially general transformation of ω-azidodienes into fused bicyclic 3-pyrrolines (i.e. **3**→**5**).

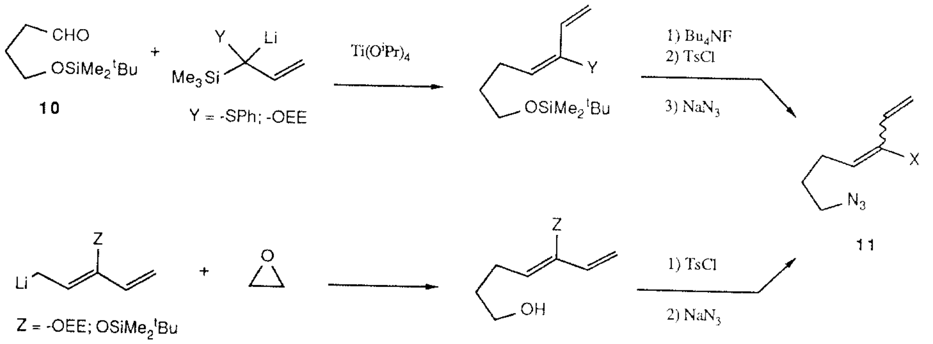
In order to prevent the formation of undesired rearrangement products, we realized that the diverse reaction pathways available to the intermediate vinyl aziridines **6** were the key factor. Since the desired pathway (**6**→**5**) requires cleavage of the allylic C-N bond of the aziridine (bond **a**), we reasoned that factors weakening this bond would facilitate the desired transformation. To accomplish this goal, we have examined the use of heterosubstituted dienes (**3**, R^1 = SR or OR). Should an aziridine be formed, cleavage of bond **a** would be facile, since it is now ketal-like in nature (i.e., two heteroatoms attached to the same carbon), in addition to being allylic and part of a strained ring.

Scheme 1



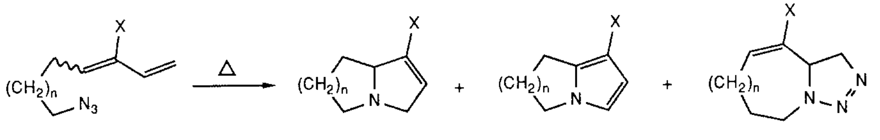
The requisite dienes for this investigation were easily prepared either by an E-selective Peterson olefination of the aldehyde **10**[3] according to the method of Yamamoto[4], or by trapping an (alkoxy)- or (silyloxy)pentadienyl lithium reagent with ethylene oxide.[5] Conversion to the desired azidodienes **11** was straightforward (Scheme 2).

Scheme 2.



Cycloaddition results are presented in Table 1. Our initial investigations were with the phenylthio-substituted diene **11a**. To our delight, heating this diene at 70° in chloroform for ca. 3 days resulted in smooth formation of the desired bicyclic pyrroline **12a** in 50-62% isolated yield. Following the reaction by ^{1}H NMR in deuteriochloroform showed no observable intermediates; only starting diene and product were seen. At higher temperatures (>100^o), the 3-pyrroline ring was converted to a pyrrole (i.e. **13**). Conducting the cycloaddition in nonpolar solvents caused substantial formation of the 1,5-homodienyl shift product **7** (R_1=SPh; R_2=H).

Table 1

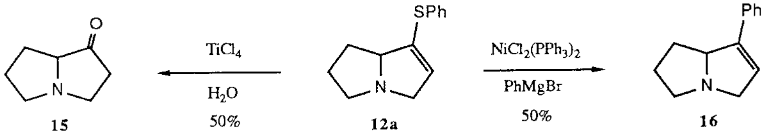


11 **12** **13** **14**

Entry	Diene	n	X	Diene Geometry	Conditions	Products (%isol. yield) 12	13	14
1	**11a**	1	-SPh	E+Z^a	70°,CHCl$_3$,3d	**12a**(50-62)	0	0
2	**11b**	2	-SPh	E+Z^b	95°,CHCl3,6d	**12b**(31)	**13b**(28)	0
3	**11c**	1	-OTBS^c	Z	120°,THF,5d	**12c**(39)^d	trace	0
4	**11d**	1	-OEE	Z	110°,THF,42h	**12d**(55)^e	0	0
5	**11e**	1	-OEE	E	110°,THF,63h	0	0	**14e**(64)
6	**11f**	2	-OEE	E	110°,THF,8d	0	0	**14f**(53)

a) ca. 1:1 mixture of E:Z. The Z isomer cycloadds at a considerably higher rate. b) 1:3 mixture of E:Z. c) TBS=SiMe$_2$^{t}Bu. d) Plus 27% of homodienyl shift product **7** (R^1=OTBS, R^2=H). e) Plus 12% of homodienyl shift product **7** (R^1=OEE, R^2=H).

Cycloaddition of the sulfur-substituted dienes requires less stringent conditions than the oxygen analogs. In addition, the resultant 3-pyrrolines may be functionalized by virtue of the large body of chemistry regarding vinyl sulfides. For example, hydrolysis[6] of **12a** provides the ketone **15**. Nickel-catalyzed cross-coupling of **12a** with Grignard reagents[7] allows C-C bond formation (e.g. **12a**→**16**). *The ability to functionalize pyrrolines such as* ***12*** *enhances the generality of this methodology by obviating the need for individual, target dependent diene syntheses.*



The slower cycloadditions of the oxygen-substituted examples allows an intriguing side reaction to occur. Cyclization of the E dienes **11e** and **11f** provides compounds which are tentatively assigned as the large ring triazolines **14e** and **14f**[8]. The surprising preference for large ring formation may be due to electronic factors as well as diene stereochemistry. The desired cycloaddition onto the internal double bond is regiochemically opposite to that normally observed with electron rich double bonds,[9] and apparently the azide reacts preferentially with the less electron rich terminal olefin when the geometry permits it. Also curious is the stability of these triazolines at the temperatures required for cyclization.[9b]

In summary, *hetero-substituted azidodienes provide a simple one-pot nitrene-diene cycloaddition equivalent,* providing rapid access to ring system **12** and derivatives thereof.

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8. For **14e**, M^+=225.1471, calc. 225.1477; UV (hex): 237 nm (ε=5100), 260 (3100), 320 (1000).

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