Intramolecular Diels−Alder Reaction of 2-Cyano-1-aza-1,3-butadienes

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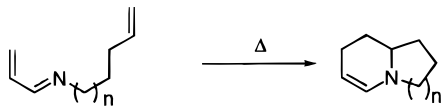
It has been demonstrated that a 2-cyano substituent is sufficient to activate 1-aza-1,3-butadienes with respect to the intramolecular Diels−Alder reaction. This reaction is successful for the preparation of the indolizidine and quinolizidine ring systems. The stereochemistry of the isomeric products was assigned by a careful analysis of their NMR spectral data.

The indolizidine and quinolizidine alkaloids[1] represent a relatively large class of natural products whose importance stems from the potent and useful biological activity of certain of its members.[2−4] The common structural feature of these compounds is a six-membered nitrogen heterocycle incorporated into a bicyclic ring system. Among the heterocyclic ring forming reactions available for the preparation of indolizidines and quinolizidines, nitrogen versions of the Diels−Alder reaction are particularly attractive.[5,6] For example, the intramolecular Diels−Alder reaction (IMDA)[7] of 1-aza-1,3-butadienes can produce, in one step, three stereogenic centers, two σ-bonds, and two new rings. Clearly, synthetic strategies for the preparation of quinolizidine and indolizidine alkaloids incorporating the IMDA reaction of 1-aza-1,3-butadienes will be extremely efficient[8] (Scheme 1).

IMDA reactions of simple alkyl or unsubstituted 1-aza-1,3-butadienes have not been reported, indicating that activation is necessary for the success of this reaction.[9,10] We have reported that substitution on nitrogen by an aromatic ring and by a cyano group at C-2 produces azadienes which react with both electron rich and electron deficient dienophiles with equal ease.[11] These studies have led us to explore the possibility of using a cyano substituent alone to activate 1-aza-1,3-butadienes with respect to the Diels−Alder reaction. Advantages of the cyano group in this role are that it suppresses unwanted side reactions of the imine reactant, stabilizes the reactive enamine in the product, and can be useful for further structural elaboration.[12,13]

Scheme 1. IMDA Reaction of 1-Aza-1,3-butadienes as an Approach to Indolizidines and Quinolizidines



Considering that many indolizidines are substituted on the five-membered ring it was of interest to investigate the IMDA reaction of 1-aza-1,3-butadienes with substitutents on the connecting chain. The 2-cyano-1-aza-1,3-butadienes (e.g. **3**) employed in our studies (Scheme 2) were prepared by treatment of the corresponding amides (e.g. **2**) with triflic anhydride at −60 °C in CH_2Cl_2 containing diisopropylethylamine, followed by reaction of the *in situ* generated imidoyl triflates with lithium cyanide.[11] The starting amide **2** was readily obtained by reduction of the oxime derivative of 5-hexen-2-one **(1)** with LAH followed by reaction with acryloyl chloride.[14,15] In the crucial Diels−Alder step, heating the racemic azadiene **3** in benzene at 110 °C for 24 h led to very clean conversion to product. The desired cycloadducts **4** and

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(1) (a) Michel, J. P. *Nat. Prod. Rep.* **1994**, *11*, 17. (b) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 183.

(2) Examples being the swansonine,[3] slaframine,[3] and the amphibian alkaloids.[4]

(3) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer Verlag: New York, 1986; Vol. 4, p 1. (b) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. *Bioactive Compounds from Plants; Ciba Foundation Symposium 154*; Wiley: Chichester, 1990; p 112.

(4) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S., W., Ed.; Springer Verlag: New York, 1987; Vol. 5, p 1.

(5) Weinreb and co-workers have applied the intramolecular Diels−Alder reaction of *N*-acyl imines to the preparation of piperidine, indolizidine, and quinolizidine alkaloids. For some examples, see Chapter 2 in ref 6.

(6) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987.

(7) For some selective reviews on the intramolecular Diels−Alder reaction, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 513. (b) Craig, D. *J. Chem. Soc. Rev.* **1987**, *16*, 187. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (d) Ciganek, E. *Org. React.* **1984**, *32*, 1.

(8) For an efficient method for the preparation of the quinolizidine alkaloid deoxynupharidine using the intramolecular Diels-Alder reaction of an *N*-acyl-1-azadiene, see: Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719.

(9) For successful intramolecular Diels−Alder reactions of 1-azadienes, see: (a) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646 and work cited therein. (b) Jun, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729. (c) Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1990**, *31*, 3753. (d) Whitesell, M. A.; Kyba, E. P. *Tetrahedron Lett.* **1984**, *25*, 2119. (e) See also ref 6, Chapter 9, and ref 10c.

(10) Other nitrogen substituents, such as *N,N*-dimethylamino and sulfonyl groups are known to activate azadienes with respect to the Diels−Alder reaction but are not directly produce indolizidines and quinolizidines. (a) See ref 6, Chapter 9. (b) Ghosez, L. *J. Heterocycl. Chem.* **1985**, *22* (Suppl. Issue Lect. Heterocycl. Chem. *8*), 69. (c) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068 and work cited therein.

(11) (a) Sisti, N. J.; Fowler, F. W.; Grierson, D. S. *Synlett* **1991**, 816. (b) For a comparison of nitrogen activating substituents, see: Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075. (c) Sisti, N. J.; Motorina, I. A.; Tran Huu Dau, M.-E.; Riche, C.; Fowler, F. W.; Grierson, D. *J. Org. Chem.* **1996**, *61*, 3715.

(12) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064. (b) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. (c) Shafran, Y. M.; Bakulev, B. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148. (d) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Ind. Ed. Engl.* **1979**, *18*, 917. (e) Zeller, E.; Sajus, H.; Grierson, D. *Synlett* **1991**, 44. (f) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211.

(13) Albrecht, H.; Vonderheid, C. *Synthesis* **1975**, 512.

(14) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

(15) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920.

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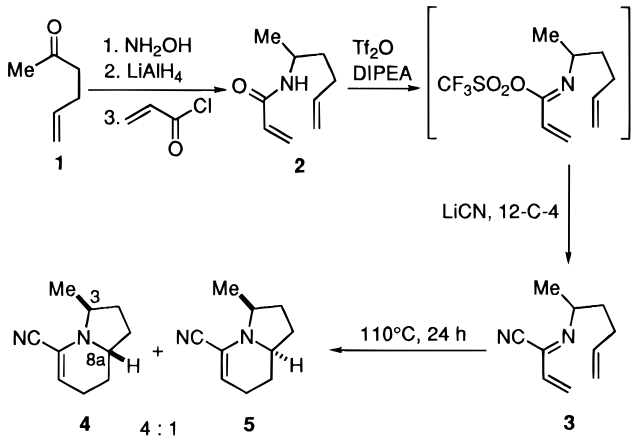
Scheme 2. Preparation of Indolizidines by the IMDA Reaction of 2-Cyano-1-aza-1,3-butadienes



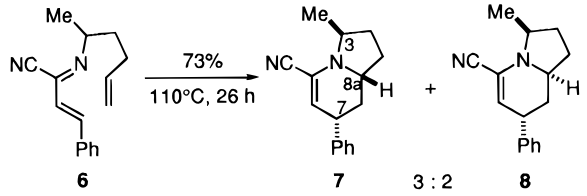
5 were isolated after silica flash column chromatography as an inseparable mixture of diastereomers [**4/5** = 4:1 (R = Me)] in 94% yield. Subsequent rate studies with azadiene **3** showed that cycloaddition is complete after 7−8 h of heating (110 °C sealed tube) in benzene and acetonitrile, whereas the reaction is three times slower in either CH_2Cl_2 or THF.

The above described observation is significant for the following reasons. Simple 1-aza-1,3-butadienes have not been reported to react in the IMDA. The all-carbon diene, 1,6,8-nonatriene, is less reactive being reported to be unreactive upon heating at 140 °C for 10 days.[16] Thus, cyano substitution results in a relatively reactive azadiene (110 °C for 24 h) that undergoes the IMDA to give the Diels−Alder adduct in high yield. This reaction is potentially a useful route to fused nitrogen heterocycles.

Separation of the stereoisomers **4** and **5** was accomplished by HPLC (reverse phase: Hypersel C-8). From the NMR spectra it is possible to assign the relative stereochemistry of the individual stereoisomers with a high degree of certainty (Scheme 2). The methine hydrogen adjacent to the methyl group on C-3 in compounds **4** and **5** have different multiplicities in the proton NMR spectrum. In compound **4** this proton appears as an undefined multiplet (δ 3.61) whereas the analogous hydrogen in compound **5** appears as a quintet (δ 3.85), being coupled to the three hydrogens of the methyl group and one of the hydrogens on the adjacent methylene group. Inspection of molecular models[17] clearly demonstrates that the dihedral angle between the methine hydrogen of compound **5** at the stereogenic center C-3 and one of the adjacent hydrogens on the C-2 methylene group is approximately 90°, resulting in one of the coupling constants being nearly zero. This is consistent with the observation that the quintet collapses to a doublet (J = 6.6 Hz) upon irradiation of the methyl doublet at δ 1.13.

In compound **4** there should be significant coupling of the methine hydrogen at C-3 to both of the hydrogens of the adjacent methylene group.[17] Irradiation of the methyl doublet at δ 1.28 in this compound caused the methine hydrogen on C-3 to collapse to a doublet of doublets (J = 6.8, 4.3 Hz).

Scheme 3. Exo and Endo Reaction Products of the IMDA Reaction



Furthermore, the methyl group at C-3 of the major isomer **4** is shifted downfield (0.15 ppm) compared to the minor isomer **5**. Molecular modeling shows the methyl group of **4** more in the plane of the π system and, consequently, more deshielded than the same methyl group in compound **5**. These assignments were confirmed by the results of a 1D NOE experiments in which a strong NOE was observed between the C-3 methyl group and C-8a hydrogen in **4**, indicating their spatial proximity. Isomer **5** showed no analogous NOE.

Because of the presence of the stereocenter on the connecting chain of **3**, there is the possibility of producing two diastereomeric Diels−Alder adducts, **4** and **5**. The origin of these two stereoisomers is relatively complex since the faces of both diene and dienophile are diastereotopic. This situation allows for *four* possible diastereomeric reaction pathways, two passing through exo transition states and two passing through endo transition states. Because the nitrogen atom rapidly inverts at room temperature, *cis* and *trans* ring fusions are not possible and it is not possible to distinguish between the exo and endo transition states.[18]

When a substituent is present on the terminal carbon atom of the diene, then the four diastereomeric pathways all produce different diastereomers. That is, the exo and endo reaction pathways lead to different diastereomers. For this reason it was of interest to study the 4-phenyl-substituted azadiene **6**. Compound **6** was prepared from 5-hex-2-one in an analogous manner as described above for azadiene **3**. Heating azadiene **6** in benzene for 26 h at 110 °C gave a 3:2 mixture (73%) of only *two* of the four possible stereoisomers, **7** and **8** (Scheme 3), that could be detected by NMR spectroscopy.

Close similarities in the NMR spectra of **4** and **7** as well as **5** and **8** permit the stereochemical assignments for C-8a and C-3 shown in Scheme 3. For example, the ^{13}C chemical shifts of C-8a and C-3 for **4** (δ 57.0, 57.2) and **7** (δ 57.3, 57.4) are nearly identical, whereas the same peaks in the spectra for **5** (δ 55.1, 57.2) and **8** (δ 52.6, 55.5) are located upfield and split by about 2.5 ppm. Also, the methyl groups in **4** and **7** (δ 1.28 and 1.33) are both found downfield with respect to the methyl groups in **5** and **8** (δ 1.13 and 1.19). A similar correspondence is observed in the proton spectra, i.e. a larger separation in the chemical shift for the C-3 and C-8a methine absorptions in the spectrum for **8** than for **7**.

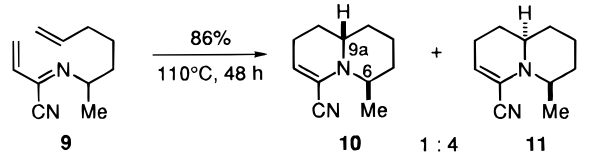
As the predominant conformations **7** and **8** have the hydrogen at C-8a occupying the pseudoaxial position,[19]

(16) Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269. A Diels−Alder adduct was obtained in 85% yield when the nonatriene was heated for 35 h at 190 °C.

(17) These conclusions are supported by MM2 calculations using MacroModel version 4.0 developed by C. Still, Columbia University. These calculations predict that the dihedral angle between the *cis* and *trans* C−H bonds of C-2 and C-3 for **4** are 32 and 153°, respectively. These same bonds for **5** are 39 and 91°.

(18) In the all carbon intramolecular Diels−Alder reaction the endo reaction pathway leads to the *cis*-fused product whereas the exo reaction pathway leads to the *trans*-fused product. Although *cis*- and *trans*-fused transition states are also involved in the nitrogen analog of this reaction, nitrogen inversion precludes distinguishing their products.

Scheme 4. Preparation of a Quinolizidine by the IMDA Reaction of 1-Azadienes



the coupling constant of the vinyl hydrogen gives the stereochemistry of the carbon bearing the phenyl substituent.[9a] The larger coupling constant of the vinyl hydrogen is due to the pseudoequatorial hydrogen, and the smaller coupling constant is due to the pseudoaxial hydrogen. The compound with the larger coupling constant, **8**, has a *trans* relationship of the hydrogens at C-7 and C-8a and is the product of the reaction proceeding through the exo transition state.

In principle, the use of IMDA reactions with a four-atom connecting chain can allow for the preparation of the quinolizidine ring system. In order to explore this possibility, azadiene **9** was prepared in an analogous manner to that described for the preparation of **3**. Heating azadiene **9** in benzene at 110 °C for 48 h gave a 1:4 ratio of **10** and **11** in 86% yield (Scheme 4).

The structures of **10** and **11** were again assigned from an examination of their NMR spectra. The bridgehead C-9a hydrogen of the minor isomer **10** appeared as a broadened triplet (J = 11 Hz), which is consistent with coupling to two adjacent axial protons. This situation would exist when the two six-membered rings are in the half-chair and chair conformations (Figure 1). Irradiation of the C-6 methyl group resulted in collapse of the C-6 hydrogen multiplet to a doublet (J = 3.3 Hz), showing that the methyl group occupies an axial position.

Although the major isomer, **11**, is epimeric at C-6 with the minor isomer, **10**, molecular modeling indicates that the saturated six-membered ring cannot be in a simple chair conformation and the proton NMR spectrum supports this view. The C-9a bridgehead hydrogen of the major isomer **(11)** appears as a complex multiplet with a chemical shift nearly identical to that of the minor isomer[20,21] with a half-width $w_{1/2}$ = 24 Hz. These data are consistent with an axial position for the C-9a hydrogen anti to two of the adjacent hydrogens. However, irradiation of the C-6 methyl group resulted in collapse of the multiplet to a doublet of doublets (J = 5.6 and 4.5 Hz). This observation is not consistent with the C-6 hydrogen simply occupying an axial position as would be anticipated if compound **11**, like **10**, existed in the half-chair, chair conformation.

In the half-chair, chair conformation, molecule models indicate that there would be a nonbonded interaction between the equatorial methyl and the cyano groups. In agreement with this hypothesis, MM2 calculations[17] predict the most stable conformation to be that shown

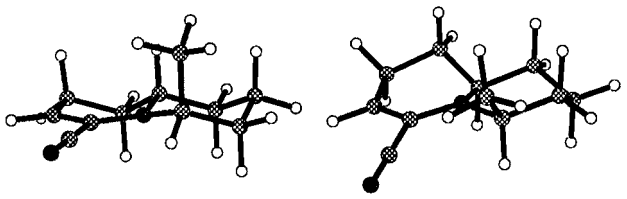


Figure 1. Most stable conformations calculated for **10** and **11**.

in Figure 1. Thus, the NMR spectrum and molecular modeling are consistent with the conformation, shown in Figure 1, playing an important role in the ground state of stereoisomer **11**.

There is a significant change in the stereochemistry of these Diels−Alder reactions as the connecting chain changes from three to four carbon atoms. The major product **(4)** with a three-carbon connecting chain (azadiene **3**) has a *trans* relationship of the hydrogen atoms at the stereogenic centers whereas the major product **(11)** with a four-atom connecting chain (azadiene **9**) has a *cis* relationship of the hydrogen atoms at the stereogenic centers. This change in stereochemistry reflects a change in the reaction pathway from predominantly endo, with azadiene **3**, to the exo reaction pathway, with azadiene **9**. Changes in exo/endo ratios as a function of connecting chain length and substituents have been the focus of much discussion,[7] and a "twist asynchronous" model has been successful for rationalizing the results for all carbon IMDA reaction. A 2-cyano substituent is an important group for the Diels−Alder activation of 1-aza-1,3-butadienes. Although kinetic measurements are not available, cyano activation appears to be comparable to *N*-acyl activation.[22] Possible roles for *N*-acyl activation involve lowering the LUMO of the diene in order to faciliate HOMO−LUMO interactions and stabilizing the transition state by partial amide development. The cyano group lowers the LUMO of the diene[11c] but it cannot directly stabilize the developing lone pair of electrons of the amino substituent. However, the cyano substituent can stabilize the transition state by stabilizing the newly developing bonds. In particular, the presence of a nitrogen atom and an amino substituent on the same carbon[23] can stabilize biradicaloid electronic configurations of the transition state.[24]

Experimental Section

***N*-[5-(1-Hexenyl)]-cyano-1-azabuta-1,3-diene (3).** To a solution of hydroxylamine hydrochloride (11.3 g) and anhydrous K_2CO_3 (22.5 g) in 26 mL of ethanol and 32 mL of water was added 5-hexene-2-one **(1)** (17.6 g, 130 mmol) over 5 min. The mixture was refluxed for 6 h, and after cooling was extracted with ether (2 × 50 mL). The combined ether layers were washed once with water (20 mL), dried over sodium sulfate, and concentrated *in vacuo*. The 5-hexene-2-one oxime (13.6 g, 93%) was obtained as a pale yellow oil and used without further purification.[14]

Following the method developed by Harding and Burks,[15] the above oxime (3.0 g, 27 mmol) in 20 mL of anhydrous ether was added dropwise over a period of 5 min to a stirred solution

(19) Supporting this assumption, MM2 calculations predict that the conformation of **8** with an axial phenyl substituent at C-7 and an axial hydrogen at C-8a is 2.5 kcal/mol more stable than the conformation of **8** with an equatorial phenyl substituent at C-7 and an equatorial H at C-8a.

(20) The nearly identical chemical shift indicates that the bridgehead hydrogen in both isomers is anti to the nitrogen lone pair of electrons (see ref 21a).

(21) For references related to the structure and NMR spectroscopy of indolizidines and quinolizidines, see: (a) Crabb, T. A.; Newton, R. F. *Chem. Rev.* **1971**, *71*, 109. (b) Tourwe, D.; Binst, G. V. *Heterocycles* **1978**, *9*, 507. (c) Skvortsov, I. M. *Russ. Chem. Rev.* **1979**, *48*, 262. (d) Crabb, T. A. In *Annual Reports in NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: London, 1982; p 60.

(22) For example, an analogous *N*-acyl azadiene requires heating for 6 h at 110 °C, compared to 24 h at the same temperature for azadiene **3**.

(23) Sustman, R.; Korth, H.-G. *Adv. Phys. Org. Chem.* **1990**, *26*, 131.

(24) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682.

of $LiAlH_4$ (3.0 g) in 200 mL of anhydrous ether, under argon at 0 °C. The mixture was refluxed for 23 h and then chilled in a brine/ice bath, and the excess $LiAlH_4$ destroyed by dropwise addition of 6 mL of water, 6 mL of a 15% NaOH solution, and finally 10 mL of water. After being stirred for an additional 2 h, the mixture was treated with 15 g of 1:1 mixture of anhydrous $MgSO_4$ and anhydrous Na_2SO_4, placed under an argon atmosphere, and stirred for 3 h. Acryloyl chloride (2.4 g) was then added dropwise over a period of 10 min, and the reaction mixture was allowed to stir overnight. The resulting mixture was filtered, and the filtrate was concentrated to 50 mL, washed sequentially with 50 mL of saturated $NaHCO_3$ solution, brine, and water, dried over Na_2SO_4, and concentrated under vacuum. Amide **2** was obtained as a colorless oil (2.6 g, 63%) after flash column purification (silica gel, 1:1 heptane/ether): IR (neat) 1656 and 1642 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 1.18 (d, J = 6.6 Hz, 3H), 1.58 (m, 2H), 2.10 (apparent q, J = 7.0, 7.4 Hz, 2H), 4.09 (m, 1H), 5.01 (m, 2H), 5.65 (m, 1H), 5.80 (m, 1H), 6.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 30.4, 36.0, 45.0, 114.9, 126.1, 131.3, 138.0, 164.9; MS m/z 153 (M^+), 138, 125, 98; HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1154.

Triflic anhydride (4.9 g, new or freshly distilled) was added dropwise over 10 min to a cold (−60 °C, argon atmosphere) solution of amide **2** (2.2 g, 15 mmol) and dry diisopropylethylamine (2.9 g) in 40 mL of anhydrous CH_2Cl_2, and the resulting mixture was stirred at −60 °C for 1 h. A suspension of LiCN (0.7 g, predried for 2 h at 80 °C, 0.01 mmHg) in 40 mL of anhydrous THF containing 12-crown-4 (0.36 g, 0.1 equiv) was then added dropwise over a period of 10 min, and stirring was continued for an additional 1 h at −60 °C. The reaction mixture was warmed to −20 °C over a period of 15 min and quenched with 50 mL of water. After the two layers were separated and the aqueous phase was washed with ether, the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 3:1 pentane/ether) gave azadiene **3** as a volatile yellow liquid (1.0 g, 42%): IR (neat) 2221 (CN), 1651 and 1623 (C═C), 1588 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.2 Hz, 3H), 1.72 (m, 2H), 2.00 (q, J = 7.5, 7.0 Hz, 2H), 3.90 (q, J = 6.3 Hz, 1H), 5.01 (m, 2H), 5.79 (m, 1H), 5.98 (d, J = 10.8 Hz, 1H), 6.16 (d, J = 18.3 Hz, 1H), 6.57 (dd, J = 10.2, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 30.6, 36.7, 63.6, 108.7, 115.2, 127.6, 134.9, 137.7, 141.0; MS m/z 162 (M^+), 147, 107; HRMS calcd for $C_{10}H_{14}N_2$ 162.1157, found 162.1168.

1,2,3,7,8,8a-Hexahydro-3-methylindolizine-5-carbonitrile (4) and 1,2,3,7,8,8a-Hexahydro-3-methylindolizine-5-carbonitrile (5). Azadiene **3** (100 mg, 0.6 mmol) in 4.0 mL of anhydrous benzene was placed in an argon-flushed 10-mL-capacity thick-walled glass tube, equipped with a Rotoflo tap and a stirring bar, and stirred under closed conditions at 110 °C (oil bath temperature) for 24 h. (*CAUTION*: Sealed tube reactions should always be carried out behind a safety shield, using thick-walled glass tubes.) After cooling, the solvent was removed and the residue applied to a flash column (silica gel, 1:1 heptane/ether). Indolizidines **4** and **5**, a 4:1 mixture of diastereomers, were obtained as a yellow oil (94 mg, 94% overall). The mixture of isomers was separated by HPLC (reverse phase: Hypersel C-8; 55:45:0.1 MeOH/H_2O/TEA).

Spectral data for **4**: IR (neat) 2223 (CN), 1639 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 1.20 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.52 (m, 2H), 1.81 (m, 1H), 2.02−2.20 (m, 3H), 3.36 (m, 1H), 3.61 (m, 1H), 5.34 (t, J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 23.1, 26.0, 30.6, 31.3, 57.0, 57.2, 113.7, 117.0, 119.2; MS m/z 162 (M^+), 147, 138, 119, 93, 80, 67; HRMS calcd for $C_{10}H_{14}N_2$ 162.1157, found 162.1159.

Spectra data for **5**: IR (neat) 2223 (CN), 1639 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.5 Hz, 3H), 1.22 (m, 2H), 1.61 (m, 2H), 2.08 (m, 4H), 3.22 (m, 1H), 3.85 (quintet, J = 6.6 Hz, 1H), 5.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 23.7, 29.0, 30.3, 31.2, 55.1, 57.2, 113.4, 116.4, 117.8; MS m/z 162 (M^+), 147, 138; HRMS calcd for $C_{10}H_{14}N_2$ 162.1157, found 162.1155.

***N*-[5-(1-Hexenyl)]-2-cyano-4-phenyl-1-azabuta-1,3-diene (6).** Following the procedure described for the preparation of azadiene **3**, 5-hexene-2-one oxime (2.0 g, 17 mmol) was reduced using $LiAlH_4$ in anhydrous ether. *N*-[5-(1-Hexenyl)]-cinnamide was obtained as a colorless solid (3.2 g, 80%) after flash column purification (silica gel, 1:1 heptane/CH_2Cl_2, then CH_2Cl_2): mp 69−71 °C; IR (Nujol) 3276 (NH), 1656 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6.5 Hz, 3H), 1.59 (m, 2H), 2.11 (q, J = 7.3 Hz, 2H), 4.16 (quintet, J = 7.0, 7.7 Hz, 1H), 4.97 (m, 2H), 5.79 (m, 1H), 6.31 (N-H), 6.51 (d, J = 15.5 Hz, 1H), 7.28 (m, 3H), 7.46 (m, 2H), 7.62 (d, J = 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 30.4, 36.1, 45.2, 114.9, 121.4, 127.7, 128.7, 129.5, 135.0, 138.0, 140.6, 165.4; MS m/z 229 (M^+), 175, 146, 131, 103, 84, 77.

The derived amide (0.5 g, 2.2 mmol) was treated with triflic anhydride (0.74 g, 1.2 equiv) in anhydrous CH_2Cl_2 containing diisopropylethylamine (0.39 g) at −60 °C and then with LiCN (0.1 g) and 12-crown-4 (0.05 g). Azadiene **6** was obtained as a light yellow oil (0.22 g, 43%) after flash column purification (silica gel, 9:1 heptane/ether): IR (neat) 2221 (CN), 1629 (C═C), 1578 cm^{-1}; (C═N); ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.2 Hz, 3H), 1.75 (m, 2H), 2.03 (q, J = 7.0, 7.9 Hz, 2H), 3.96 (m, 1H), 5.01 (m, 2H), 5.80 (m, 1H), 6.96 (d, J = 16.3 Hz, 1H), 7.38−7.55 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 21.8, 30.6, 36.9, 63.4, 109.1, 115.1, 126.0, 127.7, 129.0, 130.1, 134.6, 137.7, 140.7, 142.2; MS m/z 238 (M^+), 223, 140, 129, 102, 91, 77; HRMS calcd for $C_{16}H_{18}N_2$ 238.1470, found 238.1463.

1,2,3,7,8,8a-Hexahydro-3-methyl-7-phenylindolizine-5-carbonitrile (7) and 1,2,3,7,8,8a-Hexahydro-3-methyl-7-phenylindolizine-5-carbonitrile (8). Azadiene **6** (150 mg) in 2 mL of anhydrous benzene was placed in an argon-flushed 10-mL capacity thick-walled glass tube, equipped with a Rotoflo tap and a magnetic stirring bar, and heated under closed conditions at 110 °C for 26 h. (*CAUTION*: Sealed tube reactions should always be carried out behind a safety shield, using thick-walled glass tubes.) After cooling, the solvent was removed under vacuum and the residue was applied to a flash column (silica gel, 5:1 heptane/ether). Indolizidines **7** and **8** (a 3:2 mixture of diastereomers) were obtained as a yellow oil (110 mg, 73%). The mixture of isomers was separated by HPLC (silica, 97:3.0:0.1 heptane/EtOAc/TEA).

Spectral data for **7**: IR (neat) 2225 (CN), 1602 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 6.2 Hz, 3H), 1.54 (m, 2H), 2.12 (m, 4H), 3.65 (m, 3H), 5.33 (s, 1H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.3, 30.9, 32.3, 36.7, 41.0, 57.3, 57.4, 116.6, 126.9, 127.2, 128.9, 144.0; MS m/z 238 (M^+), 223, 140, 115, 91; HRMS calcd for $C_{16}H_{18}N_2$ 238.1470, found 238.1466.

Spectral data for **8**: IR (neat) 2224 (CN), 1602 cm^{-1} (C═C). ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.4 Hz, 3H), 1.58 (m, 2H), 1.99 (m, 4H), 3.13 (m, 1H), 3.63 (t, J = 5.6 Hz, 1H), 3.97 (m, 1H), 5.44 (d, J = 5.5 Hz, 1H), 7.14−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.8, 30.0, 31.3, 37.4, 39.1, 52.6, 55.5, 112.8, 116.3, 118.8, 126.6, 128.4, 128.5, 146.0; MS m/z 238 (M^+), 223, 199, 161, 140, 115, 91; HRMS calcd for $C_{16}H_{18}N_2$ 238.1470, found 238.1471.

***N*-[6-(1-Heptenyl)]-2-cyano-1-azabuta-1,3-diene (9).** Using the procedure described for the preparation of the azadiene **3**, the *syn*- and *anti*-6-hepten-2-one oximes (1.7 g, 13.9 mmol) prepared from 6-hepten-2-one[15] were reacted with acryloyl chloride. The derived amide was obtained as a colorless oil (1.6 g, 70%) after flash column purification (silica gel, 1:1 heptane/ether): IR (neat) 3276 and 3077 (NH), 1629 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.4 Hz, 3H), 1.45 (m, 4H), 2.05 (q, J = 6.5, 7.0 Hz, 2H), 4.06 (quintet, J = 7.0, 8.1 Hz, 1H), 4.98 (m, 2H), 5.60 (dd, J = 2.2, 8.0 Hz, 1H), 5.78 (m, 1H), 5.92 (NH), 6.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.4, 33.6, 35.4, 45.3, 114.8, 126.0, 131.3, 138.5, 164.9; MS m/z 167 (M^+), 152, 143, 134, 126; HRMS calcd for $C_{10}H_{17}NO$ 167.1309, found 167.1309.

The above amide (1.5 g, 9.0 mmol) was treated with triflic anhydride (3.0 g, 1.2 equiv) in anhydrous CH_2Cl_2 containing diisopropylethylamine (1.7 g, 1.5 equiv) at −60 °C and then with LiCN (0.4 g, 1.4 equiv) and 12-crown-4 (0.2 g, 0.1 equiv). Azadiene **9** was obtained as a light oil (0.7 g, 43%) after flash column purification (silica gel, 3:1 heptane/ether): IR (neat) 2221 (CN), 1588 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 1.24 (d, J = 6.2 Hz, 3H), 1.33 (m, 2H), 1.63 (m, 2H), 2.06 (q, J = 7.0 Hz, 2H), 3.87 (q, J = 6.3 Hz, 1H), 4.99 (m, 2H), 5.78 (m, 1H), 5.95 (d, J = 10.6 Hz, 1H), 6.15 (d, J = 17.6 Hz, 1H), 6.56 (dd, J = 10.6, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 33.6, 37.1, 64.1,

108.8, 114.9, 127.6, 134.9, 138.4, 140.8; MS *m*/*z* 176 (M^+), 161, 107; HRMS calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1307.

1,6,7,8,9,9a-Hexahydro-6-methyl-2*H*-quinolizine-4-carbonitrile (10) and 1,6,7,8,9,9a-Hexahydro-6-methyl-2*H*-quinolizine-4-carbonitrile (11). Azadiene **9** (100 mg) in 2 mL of anhydrous benzene was placed in an argon-flushed 10-mL capacity thick-walled glass tube, equipped with a Rotoflo tap and a magnetic stirring bar, and heated under closed conditions at 110 °C for 48 h. (*CAUTION*: Sealed tube reactions should always be carried out behind a safety shield, and using thick-walled glass tubes.) After cooling, the solvent was removed under vacuum and the residue was applied to a flash column (silica gel, 20:1 heptane/ether). Quinolizidines **10** and **11** were obtained as a yellow oil in a 1:4 ratio (86 mg, 86%). The mixture of isomers were separated by HPLC (reverse phase: Hypersel C-8; 55:45:0.1 MeOH/H_2O/TEA).

Spectral data for **10**: IR (neat) 2223 (CN), 1614 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 6.8 Hz, 3H), 1.41−1.83 (m, 8H), 2.10 (m, 2H), 2.92 (broad triplet, J = 11 Hz, 1H), 3.90 (m, 1H), 5.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 18.8, 22.3, 29.4, 30.5, 32.6, 49.6, 51.6, 116.0, 116.4, 122.6; MS *m*/*z* 176 (M^+), 161, 133, 107; HRMS calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1313.

Spectral data for **11**: IR (neat) 2223 (CN), 1614 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.8 Hz, 3H), 1.44−1.85 (m, 8H), 2.16 (m, 2H), 3.00 (m, 1H), 3.45 (m, 1H), 5.55 (t, J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 22.0, 23.0, 28.9, 29.2, 31.0, 53.5, 55.2, 117.3, 119.6, 121.7; MS *m*/*z* 176 (M^+), 161, 133, 107; HRMS calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1307.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**−**11**, as well as the amide precursors to azadienes **6** and **9** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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