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An Intramolecular 1-Azadiene Diels-Alder Approach to the Preparation of Synthetic Equivalents of Pyridine

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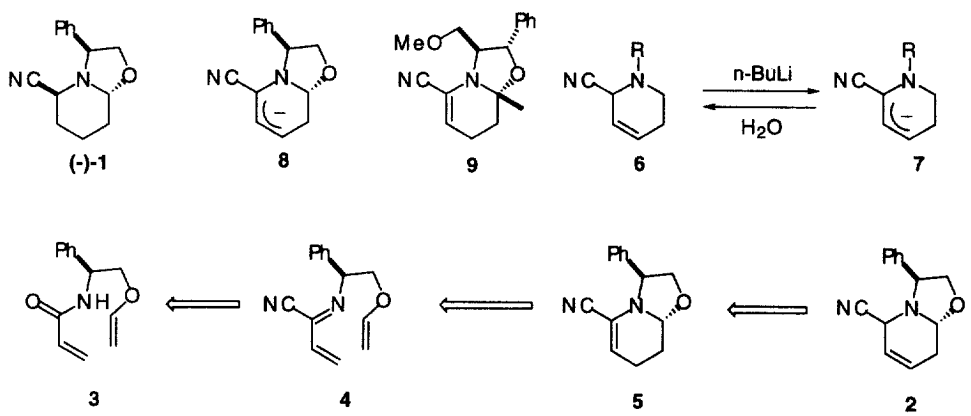
Abstract: *The IMDA reaction of O-vinyl substituted 2-cyano-1-azadienes* ***13a-c*** *provided efficient access to the* Δ^2*-piperideines* ***16a-c****. The reaction of* ***16a*** *with base/electrophile led to formation of the C-4 OH and C-4 OMe substituted compounds* ***19*** *and* ***16b****, rather than to the double bond isomerized product* ***18****. Condensation of the ambident anion* ***17*** *with benzaldehyde as electrophile also occurs preferentially at the C-4 position giving* ***20****.* © 1999 Published by Elsevier Science Ltd. All rights reserved.

The 2-cyano-6-oxazolopiperidine **1**, a chiral 1,4-dihydropyridine equivalent derived from the condensation of (-)-phenylglycinol with glutaraldehyde in the presence of KCN, has proven to be a highly versatile synthon for the construction of a wide range of piperidine systems of natural and non natural origin bearing functionality at all centers except C-4.[1] Based upon the established reactivity of this system toward nucleophiles and electrophiles one can anticipate that the corresponding 3,4-unsaturated compound **2**, a deconjugated form of pyridine, will possess an even larger scope of applications, since, through the correct sequence of reactions, one can envisage construction of piperidine products substituted at all the ring positions.



Scheme 1

Illustrated in Scheme 1, is a concise route envisaged to this novel heterocyclic synthon involving the intramolecular Diels-Alder reaction (IMDA) of the 2-cyano-1-azadiene **4** derived from *O*-vinyl amidoalcohol **3**,

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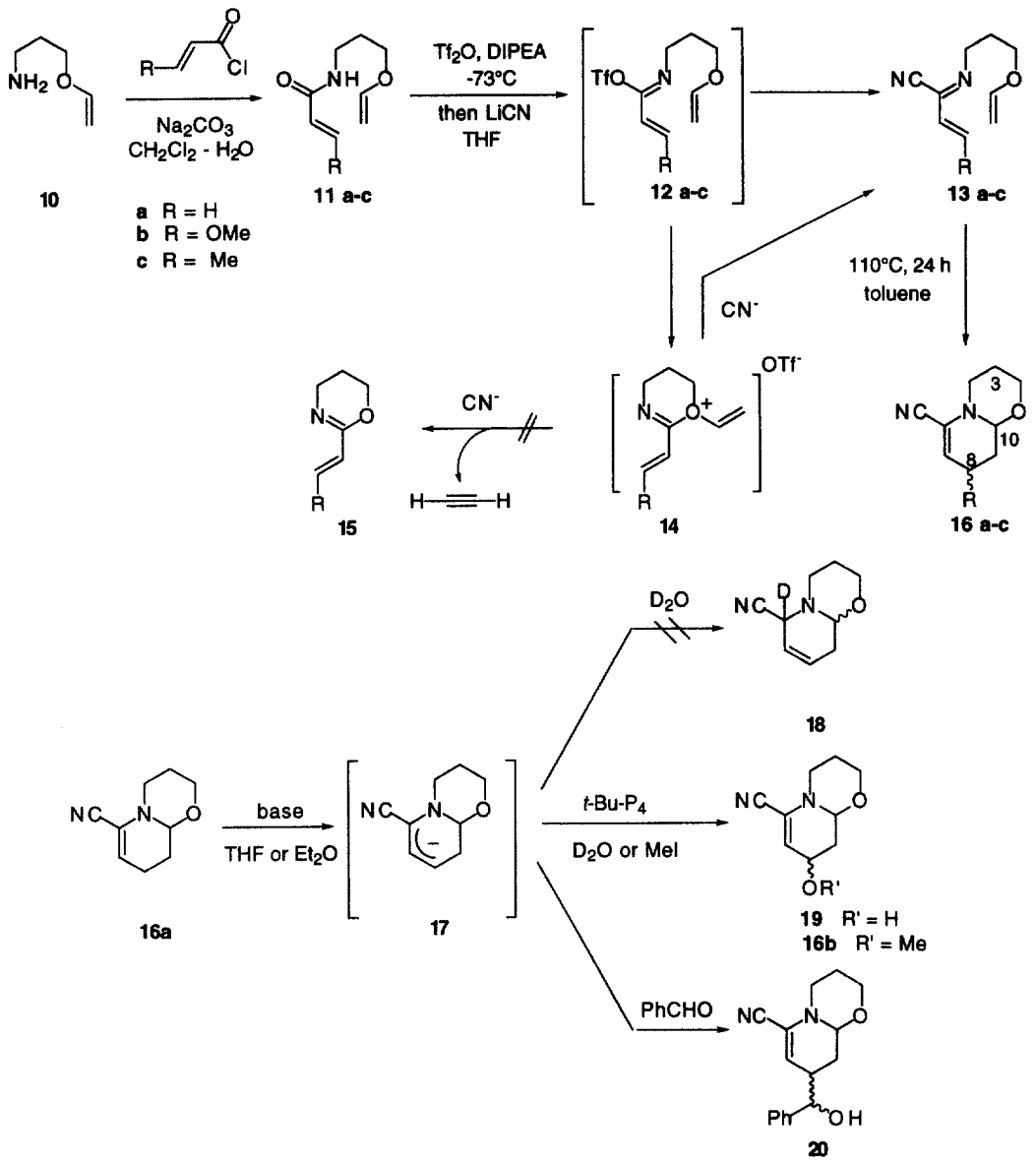
followed by isomerization of the 2,3-double bond in cycloadduct **5**. Our recent study of the IMDA reaction of 1-azadienes provides precedent for this approach,[2] as does earlier work on the reactivity of the ambident anion **7** derived from the related 2-cyano-Δ^3-piperideines **6**,[3] demonstrating that reprotonation/alkylation occurs regioselectively at C-2. Extrapolating this latter observation, one could anticipate that protonation of the delocalized anion intermediate **8**, generated upon treatment of **5** with strong base, would produce the target molecule **2**. However, opposing this logic is the observation by Meyers *et al.* that alkylation of the anion derived from the structurally related bicyclic α-cyanoenamine **9** occurs uniquely at the C-4 position.[4] This preference for formation of the γ-substituted product in this more highly functionalized system was attributed to steric crowding around the piperideine nitrogen center. [4,5] Another important issue was whether or not the protocol we developed to prepare 2-cyano-1-azadienes from acrylamide precursors[6] could be applied to amide **3**, containing a potential nucleophilic oxygen in the dienophile component.

To address these problems the synthesis of the 2-cyano-1-azadiene **13a**, which lacks the bulky phenyl substituent next to nitrogen, was undertaken (Scheme 2). Commercially available *O*-vinyl aminoalcohol **10** was thus converted to acryloylamide **11a**, and this intermediate was treated with Tf_2O and DIPEA at -73°C, followed by LiCN.[6] In the amide to azadiene transformation the major concern was that the enol ether oxygen would react preferentially with the imodyl triflate system in the *in situ* generated intermediate **12a**.[7] In the reaction of the derived oxazinium salt **14** with CN^- ion two alternatives were considered possible: formation of **13a** via addition of cyanide-OTf displacement, or base induced loss of a molecule of acetylene and formation of the dihydro-1,3-oxazine **15**. In the experiment, the desired azadiene product **13a** was obtained, isolated in 60-83% overall yield after silica flash column chromatography. In view of the success of this reaction the azadienes **13b** (33%) and **13c** (74%), already bearing a substituent at C-4, were similarily prepared. It was not anticipated that the subsequent IMDA reactions of these azadienes would pose problems, and indeed, on heating in toluene at 110-130°C for 24 h the cyanoenamine products **16** were obtained [**16a**, 80%; **16b**, 59% (14 : 1 separable mixture of 8,10-*trans*/*cis* isomers); **16c**, 63-71%].[8] It is noteworthy, however, that under these thermal conditions some product degradation was observed, particularily for **16b** (up to 40% loss of material), indicating that these molecules are inherently fragile.

To examine the double bond migration cycloadduct **16a** was treated with alkyllithium bases (n-BuLi, sec-BuLi, MeLi) or LDA in THF or Et_2O (with or without added HMPA) at -78°C to -20°C, followed by quenching with D_2O. However, there was no sign of formation of the expected product **18**, and deuterium was not present in the recovered starting material (20-80% depending on conditions). These results were surprizing, both in view of the work by Meyers,[4] and by the fact that the alkyllithium reagents did not even react with the cyano substituent in **16a**. In further experiments in which compound **16a** was reacted with the phosphazene base (*t*-Bu-P_4)[9] in THF at -78°C, followed by treatment with D_2O, evidence was obtained in favour of formation of ambident anion **17**. Under these conditions double bond migration was again not observed, but a new product, identified as **19**, was formed in up to 53% yields. Further, under the same conditions the corresponding C-4 methoxy substituted enaminonitriles **16b** were isolated (10 - 37% yield) when MeI was added as the electrophile. The structure of **16b** was deduced from the $^1H/^{13}C$ NMR spectra,[10] and confirmed by comparison with the data for the same compound and the C-4 methyl substituted product **16c** obtained from IMDA reaction of azadienes **13b** and **13c**, respectively. Interestingly, although this parasite oxidation process could be effectively suppressed by rigorous exclusion of O_2 (multiple freeze-thaw cycles) from the medium, the yield of **19/16b** was not improved when dry O_2 was bubbled directly into the reaction during base addition. However, it remains probable that the formation of these products results from reaction of an anion intermediate with molecular oxygen.



10 11 a-c 12 a-c 13 a-c 14 15 16 a-c 16a 17 18 19 R' = H 16b R' = Me 20

Scheme 2

In view of the apparent lack of reactivity of anion **17** with D_2O and MeI, the reaction of enaminonitrile **16a** with benzaldehyde as the electrophile was examined using either LDA or *t*-Bu-P_4 as the base (THF, -78°C). In this reaction the formation of all four diastereomers of the C-4 condensation product **20** (2:1:1:2 for LDA or 1:3:3:1 for *t*-Bu-P_4) was observed in moderate 30 - 35% yield. Two of these isomers were isolated pure by flash chromatography and characterized by NMR/mass spectroscopy, whereas the structures of the two minor components were inferred from the data obtained for the mixture. The regiochemistry in this reaction correlates with the results obtained by Meyers, [4] but the possibility that a kinetic C-2 addition product initially forms, and undergoes isomerization to the observed product **19** can not be excluded at the moment. [3]

The results obtained during the preliminary exploration of the azadiene Diels-Alder/double bond migration strategy to the pyridine equivalent **2** indicate that there is a fundamental problem to be resolved concerning the reactivity of the bicyclic enaminonitrile system **16** relative to **9**. Further work is in progress to both harness the reactivity of compounds **16** and to direct it toward our synthetic objective.

References and Notes

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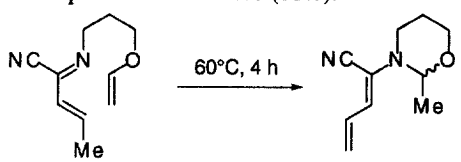
7. For analogous intramolecular reaction of nucleophilic nitrogen with trifloyl imidates, see: Goulaouic-Dubois, C.; Adams, D.; Sisti, N.J.; Fowler, F.W.; Grierson, D.S. *Tetrahedron Lett.*, **1998**, *39*, 4283-4286.
8. Azadiene **13c**, bearing a C-4 methyl group was heated at different temperatures and times to study its reactivity with respect to imine to enamine tautomerization. Thus, on heating a 0.02 M solution of **13c** in benzene at 110°C for 24 h the Diels-Alder product **16c** (4,6-*trans*/4,6-*cis* : 2/1) was obtained (71%) along with some amount of the cyclized enamine **21** (11%), whereas, on heating at 60°C for 24h only a slow conversion to the enamine product **21** occurred (11%).



12c **21**

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10. **16b** : **major isomer:** yellow oil; R_F 0.50 (heptane/EtOAc; 1/1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (m, 1H, 3-H), 1.88-2.11 (m, 3H, 3-H+9-H), 3.09 (dt, J=3.0, 12.9 Hz, 1H, 4-H), 3.36 (s, 3H, OMe), 3.71 (dt, J=2.4, 11.9 Hz, 1H, 4-H), 3.82 (m, 1H, 2-H), 3.98 (ddd, J=3.7, 5.4, 6.8 Hz, 1H, 8-H), 4.09 (m, 1H, 2-H), 4.43 (dd, J=3.1, 6.8 Hz, 1H, 10-H), 5.62 (d, J=3.7 Hz, 1H, 7-H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 24.87 (C3), 32.67 (C9), 48.62 (C4), 56.04 (OMe), 67.69 (C2), 69.54 (C8), 84.29 (C10), 114.84 (CN), 115.76 (C7), 121.54 (C6); IR (neat) 2931, 2853, 2228 (CN), 1616, 1420, 1096 cm^{-1}; MS (CI, isobutane, 170°C): 251 (M+57), 195 (M+H), 163 (M-MeOH); HRMS (CI, isobutane, 170°C): calc'd for $C_{10}H_{15}N_2O_2$ ([M+H]): m/e 195.1133, found 195.1134. **minor isomer:** yellow oil; R_F 0.31 (heptane/EtOAc; 1/1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (d, J=13.6 Hz, 1H, 3-H), 1.92-2.12 (m, 2H, 3-H+9-H), 2.23 (dt, J=14.4, 4.7 Hz, 1H, 9-H), 3.13 (dt, J=3.0, 13.1 Hz, 1H, 4-H), 3.38 (s, 3H, OMe), 3.70 (dt, J=2.4, 12.2 Hz, 1H, 4-H), 3.88 (m, 2H, 2-H+8-H), 4.17 (m, 1H, 2-H), 4.53 (dd, J=3.3, 5.1 Hz, 1H, 10-H), 5.68 (d, J=4.2 Hz, 1H, 7-H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 24.83 (C3), 32.79 (C9), 49.29 (C4), 56.49 (OMe), 68.32 (C2), 68.90 C8), 84.17 (C10), 114.93 (CN), 115.30 (C7), 121.85 (C6).