

A STUDY OF THE HETERO DIELS-ALDER REACTION OF *N*-ALKYL-2-CYANO-1-AZADIENES WITH 2-VINYLINDOLE

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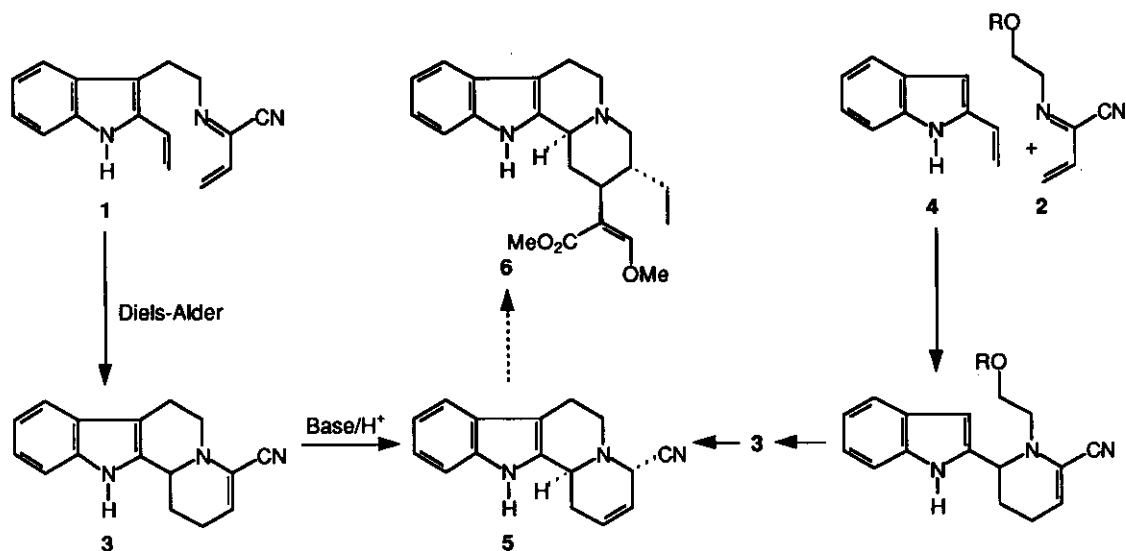
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Abstract - The *N*-alkyl-2-cyano-1-azadienes (**2a**) and (**2b**) derived from ethanolamine react with 2-vinylindole under thermal conditions to give the Michael addition adducts (**9**) and (**9'**) as the principle product. In the reaction of **2a** with vinylindole the Diels-Alder product (**11**) was also isolated. In the reaction with **2b**, formation of compounds (**9**) was accompanied by the cyclized product (**10**) and the Diels-Alder adduct (**13**).

It has been demonstrated that activation of 1-azadienes toward the Diels-Alder reaction and concomitant stabilization of the derived Δ^2 -piperidine cycloadducts is achieved by substitution of the azadiene nitrogen by electron donating ($R = NAlk_2$) and electron withdrawing substituents ($R = COR', SO_2R'$).¹⁻³ Work from our laboratories has focused upon the role that a cyano group at the adjacent C-2 carbon center can play in both promoting the Diels-Alder reactivity of these heterodienes, and in providing versatile functionality for further elaboration of the enamionitrile system in the derived cycloaddition products.⁴ Recently, we have found that the intramolecular Diels-Alder reaction of *N*-alkyl-2-cyano-1-azadienes is particularly efficient (>90% yields) giving access to simple indolizidines and quinolizidine derivatives. Continuing in this direction we envisaged that the indoloquinolizidine system characteristic of the Yohimbine family of indole alkaloids, represented by dihydrocorynantheine (**6**), could be readily constructed in either an intra- or intermolecular fashion from the 2-cyano-1-azadienes (**1**) and (**2**) (Scheme 1). It was further anticipated that the enamionitrile double bond in **3** could be deconjugated giving intermediate(**5**).^{5,6} Condensation of allylic aminonitriles related to **5** with 1,3-dicarbonyl anions is well documented.⁶ Even though the route to compound (**3**) *via* azadiene (**2**) appears longer we have concentrated our initial efforts in this direction in order to obtain information concerning the behaviour of *N*-alkyl-2-cyano-1-azadienes in intermolecular Diels-Alder reactions. In particular, we wanted to determine which of the two reacting partners (**2**) or (**4**) will react as the diene, and further, in the case where 2-vinylindole (**4**) reacts as the 2π -electron component, to study the competition between the indole $\Delta^{2,3}$ and exocyclic double bonds.

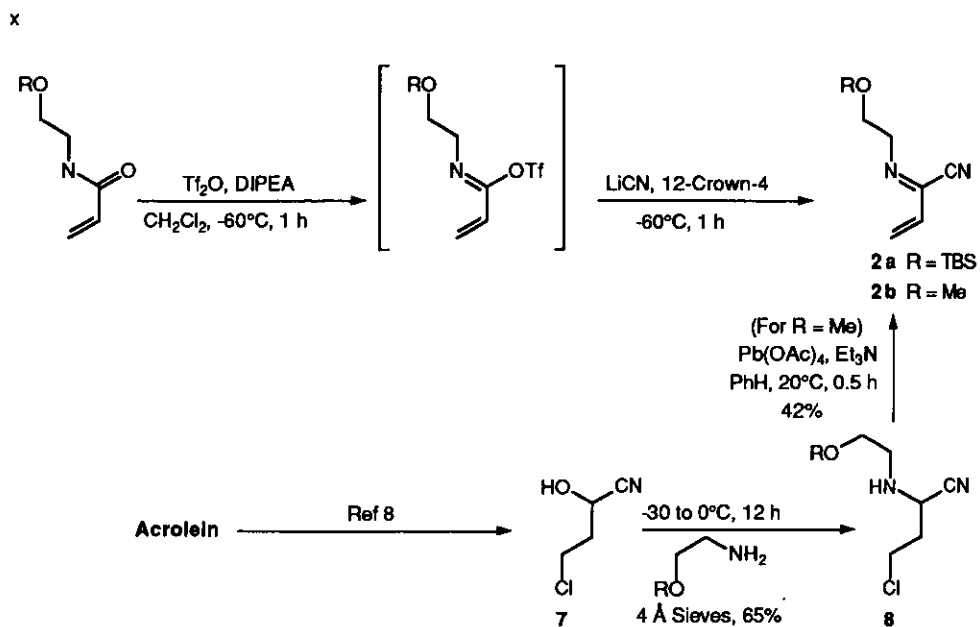
Azadienes (**2**) (**a** $R = TBS$, **b** $R = Me$) were prepared (Scheme 2) by conversion of the *O*-TBS and *O*-Me ethers of 2-aminoethanol to their corresponding acryl amides using a two phase reaction system (acryloyl chloride,



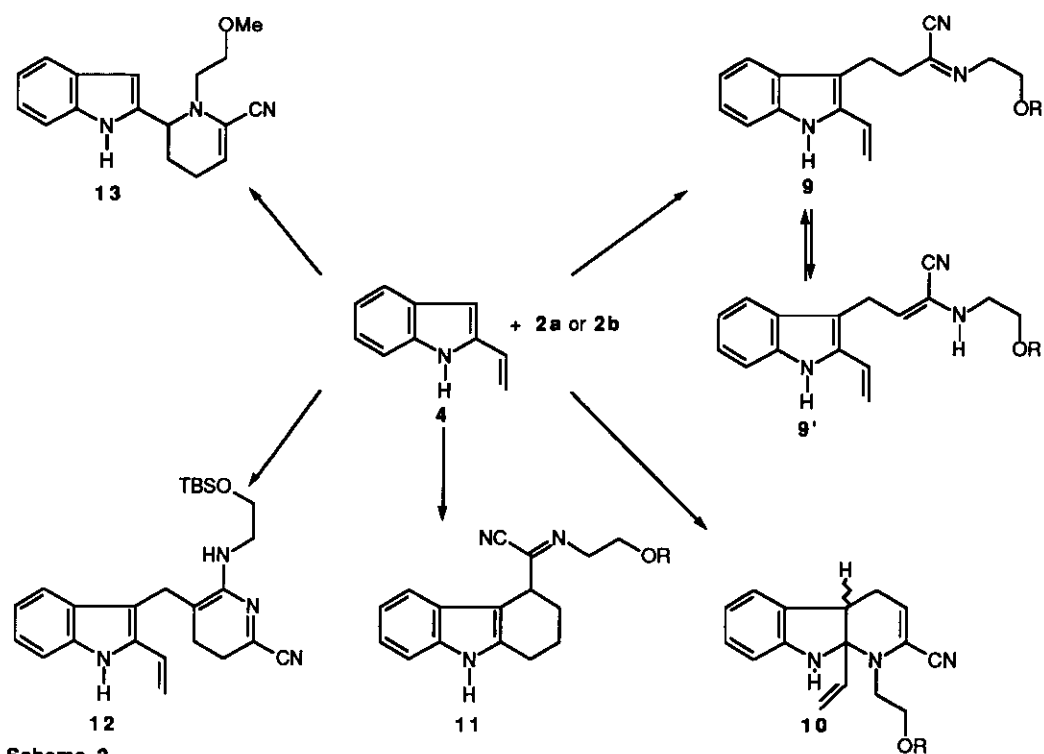
Scheme 1

$\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$, K_2CO_3 , 20°C ; 80-94%), followed by treatment of the amide derivatives with triflic anhydride in CH_2Cl_2 containing Hünigs base at -60°C (1 h), and reaction of the *in situ* generated imodyl triflates with LiCN .^{4b} Compounds (2a) (pale yellow oil) and (2b) (colourless oil) were isolated pure (42-50% yields) by flash column chromatography using heptane - EtOAc (or Et₂O) (4:1).⁷ Special attention had to be paid to using EtOAc rather than Et₂O as the co-eluting solvent to isolate 2b in order to avoid its spontaneous decomposition on the column (probably promoted by trace peroxides in Et₂O). Alternatively, azadiene (2b) was prepared by the second route illustrated in the scheme. Our objective in this case was to determine whether cyanohydrin (7), available on a large (>100 g) scale,⁸ could be used as a convenient precursor to a whole range of azadienes through aminonitrile formation and oxidation. Intermediate (7) was thus reacted with *O*-methyl-2-aminoethanol and the resulting aminonitrile (8) was oxidized ($\text{Pb}(\text{OAc})_4/\text{Et}_3\text{N}$) to give the desired azadiene (2b) in 42% yield after column purification. The present oxidation conditions were not amenable to preparation of the more labile *O*-TBS protected azadiene (2a).

Exploration of the Diels-Alder reactivity of azadienes (2) began with the reaction of 2a with 2-vinylindole in toluene at 110°C for 36 h (Scheme 3). Tlc revealed the formation of a number of products, and the presence of substantial amounts of unreacted vinylindole. The principle component, isolated with considerable difficulty by repetitive column chromatography (heptane-EtOAc gradient) was determined to correspond to a mixture of compounds (9a) and its enamine tautomer (9a') (23%).⁷ Trace amounts of compound (10a), derived either by Diels-Alder reaction of 2a with the electron rich "enamine" double bond of 2-vinylindole or by cyclization of the Michael addition product (9a), was also isolated from this reaction. Interestingly, the cycloaddition product (11a) arising from the process in which the azadiene reacts as the dienophile was isolated in 10% yield.⁷ It is



Scheme 2



Scheme 3

probable that the imine double bond in this product does not isomerize to enter into conjugation with the indole ring as a result of the strong peri interaction with the C-6 hydrogen that would be generated.

By lowering the temperature and shortening the reaction time (toluene, 80°C, 20 h) the yield of the Michael addition products (**9**) was increased to 42%. Compound (**11a**) (3%) was also detected in these reactions as well as the interesting dihydropyridine (**12**).⁷ Formation of this product is envisaged to arise by a hetero Diels-Alder reaction between the azadiene and enamionitrile (**9a'**), followed by loss of CN⁻ to give an intermediate iminium ion which in turn undergoes a β -elimination reaction (liberating the OTBS enol ether of acetaldehyde), and double bond reorganization, generating the observed product.

Using azadiene (**2b**), and by varying the temperature of the reaction [25°C (4 h) $\rightarrow$ 80°C (16 h)] the product (**10b**) of reaction of the azadiene with the indole enamine system could be isolated (16%) along with compounds (**9b/9b'**) (9%) and a small amount of the desired cycloadduct (**13**) (2%).⁷ In the reaction of **2b** with *N*-benzenesulfonyl-2-vinylindole addition to the $\Delta^{2,3}$ double bond was suppressed. In this instance the *N*-benzenesulfonyl derivative of **13** was the only cycloaddition product formed. The isolated product yield was again low (5-10%) due to extensive decomposition of the azadiene. This problem should, in principle, be of less importance in future studies of the intramolecular reaction of azadiene (**1**).

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Dedicated to Prof. Alan Katritzky on the occasion of his 65 birthday

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