N-VINYL-2-ETHOXYPYRROLIDINIMIUM TETRAFLUOBORATE: A NOVEL ENOPHILE AND SYNTHETIC EQUIVALENT FOR N-VINYLPYRROLIDINIMINIUM

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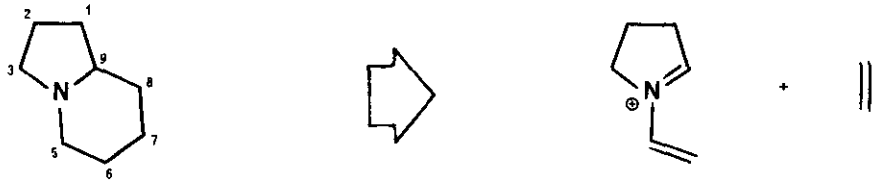
Abstract - Cycloaddition of N-vinyl-2-ethoxypyrrolidiniminium tetrafluoborate, **3**, with alkenes, followed by hydride reduction, yields the 8-alkyloctahydroindolizines, **7 and 8** which would be derived from N-vinylpyrrolidiniminium, **2**. This cycloaddition-reductive elimination sequence offers a new route to indolizidine type alkaloids.

Indolizidine type alkaloids, **1**, comprise a large family of naturally occurring molecules with important medicinal and agricultural properties.[1] Many synthetic approaches have been developed which use cyclization techniques with both electrophilic[2] and nucleophilic[3,4] intermediates in the ring closing process. Alternative synthetic schemes have used the imine-diene Diels Alder reaction[5] and the literature contains several reports of syntheses using a pyrroline derivative as the dienophile in the 4+2 cycloaddition reaction.[6] Iminium and immonium salts have been used as dienophiles, primarily with electron rich alkenes, to form cyclic amines and alkaloids.[7] These salts also function as receptor molecules in Mannich reactions with alkenes.[7d] Also, Grieco has prepared derivatives of **1** from iminium salt dienophiles, via cycloaddition reactions in aqueous media.[8] Kametani has used isoquinoid 1-azadiene derivatives as enophiles in 4+2 cycloaddition reactions to generate complex alkaloids.[9] Tufariello has reported a 3+2 cycloaddition approach[10] in which a nitrone cycloadduct was converted to the desired alkaloid. Finally, Overman[11] has used a cyclization reaction involving pyrroline derivatives which couple to vinyl silanes, via an iminium salt intermediate, to form derivatives of **1**. Photochemically induced cyclizations of immonium salts with alkenes has also been reported.[12]

We have recently reported the preparation of N-vinyl-2-ethoxy pyrrolidiniminium tetrafluoborate, **3**, by treatment of N-vinyl-2- pyrrolidinone with triethyloxonium tetrafluoborate in CH_2Cl_2.[13] It is useful to view **3** as the imidate salt analog of simple 2-azadienes. Although 4+2 cycloaddition reactions using acyclic 2-azadiene derivatives as enophiles have been reported,[14] only the structurally similar aromatic azonia salts[15] are known to give similar cycloaddition reactions, with electron rich alkenes. Similar reaction with iminium salt analogs or imidates was unknown and we hoped to prepare derivatives of **1** via a cycloaddition reaction with imidate salt **3**. A retrosyn-

thetic analysis of octahydroindolizine, 1, in which an iminium salt is used as the enophilic partner, leads to the disconnection shown below and generates 2, N-vinylpyrrolidiniminium. The direct preparation of 2 appeared to be difficult but we believed that 3, which can be prepared in hundred-gram quantities, could act as the synthetic equivalent of 2 in the 4+2 cycloaddition reaction. It is noted that a reductive elimination is required to complete the synthetic equivalency of 3 to 2. This sequence would give an inexpensive 'off the shelf' reagent to generate derivatives of 1 via a simple cycloaddition-reduction sequence.



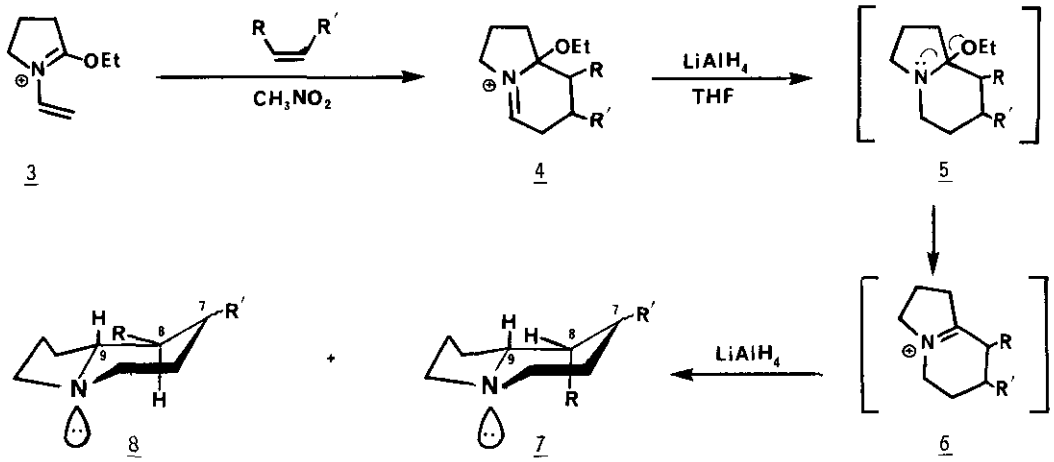
1 2

When 3 was refluxed with styrene in nitromethane, we observed slow formation(48 h) of the 4+2 cycloadduct 4. It was difficult to isolate 4 in pure form although the ^{1}H NMR clearly suggested formation of the cycloadduct. We therefore reduced the crude cycloadduct and isolated 8-phenyloctahydroindolizine, in 39% overall yield. This sequence involved removal of the nitromethane solvent from the crude cycloadduct and dissolution in THF. This solution was added, dropwise, to a slurry of $LiAlH_4$ in THF and refluxed for 24 h. Hydrolysis and chromatographic purification (neutral alumina/pentane - CH_2Cl_2), gave a 1.5:1 mixture of the isomeric 8-phenyloctahydroindolizines **7a:8a**. This yield represents the outcome of four distinct reactions, as shown in Scheme I: the cycloaddition reaction; reduction of iminium salt, 4; elimination of the ethoxy group from amine 5 to a new iminium salt, 6; and, final reduction of 6 to **7/8**. An excess of hydride reagent was required for the two reductions and refluxing the THF solution appeared to facilitate the elimination process.

A variety of alkenes reacted with 3 to give mixtures of 7 and 8, as shown in Table 1. It has been previously reported that iminium salts react with alkenes[7,16] to give coupling products via a cationic, stepwise pathway. The Mannich reaction of immonium salts with alkenes is an example of such a coupling.[7d] This pathway would predict formation of the more stable benzylic cation on reaction of 3, with styrene and subsequent ring closure would generate 7-phenyloctahydroindolizine, **10a**. This is directly analogous with the orientation of the cyclic products observed by Kano[17] in the intramolecular ring closure of N-acyl iminium salts possessing a styryl moiety which proceeds via just such a benzylic cation. We did not observe 7-alkyloctahydroindolizines from any of the alkenes used in Table 1, suggesting a non-cationic cycloaddition pathway. The fact that butyl

vinyl ether and 4-methoxystyrene gave reduced yields of 8-butoxyoctahydroindolizine, **7f/8f**, and 8-(4-methoxyphenyl)-octahydroindolizine, **7c/8c**, respectively, relative to the corresponding reactions with styrene, 1-octene and cyclohexene also supports this contention. The oxygen in these

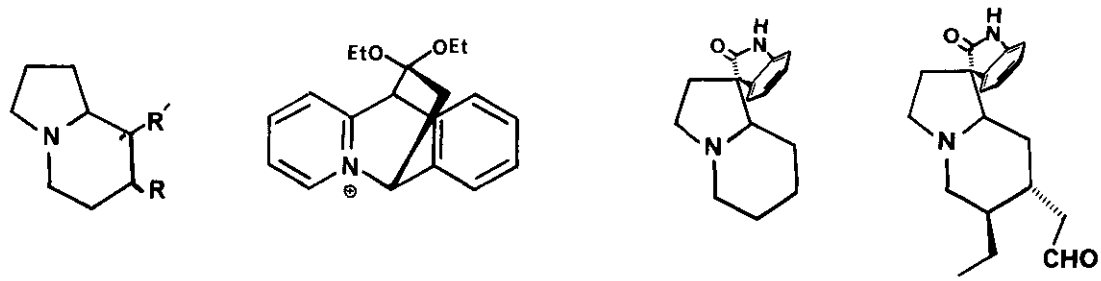
Scheme I



3 4 5 6 7 8

ethers should stabilize a cationic intermediate and, presumably, lead to increased yields of the 7-alkoxyoctahydroindolizine, **10**. The electronic variations of this vinyl iminium salt when compared to iminium and immonium salts can also be illustrated by the previously mentioned reaction of aromatic azonia salts with electron rich alkenes.[15] The cycloadducts derived from this reaction, such as the **bis**-ethoxy derivative **11**, had the relative regiochemistry possessed by **10** rather than that of the observed **7/8**.[15] The formation of **7** and **8** therefore suggests a 'normal' thermal 4+2 cycloaddition but the mechanistic nature of the cycloaddition is not known at this time.

Identification of the octahydroindolizine products, **7/8**, was accomplished primarily by ^{13}C NMR. The ^{1}H NMR at 200 MHz gave the expected signals between 2.0-3.0 ppm as previously reported[1-11] but



10 11 12a 12b

did not provide sufficient resolution to allow one to distinguish the site of alkylation, C_8 or C_7, or the relative stereochemistry of the alkyl group and the bridgehead hydrogen. All products isolated exhibit the Bohlmann bands in the infra-red(ca. 2800 cm^{-1}),[18] indicating a trans ring junc-

ture. Aaron[19] has shown that the trans ring juncture in octahydroindolizine, **1**, is at least 2.4 kcal/mole more stable than the corresponding cis ring juncture and we have shown octahydroindolizines **7** and **8** exclusively with the trans geometry. In all cases examined only two products were isolated although a significant amount of intractable and polymeric material remained. The verification of the position of the alkyl group on the octahydroindolizine skeleton, shown in Scheme I, can be illustrated with **7e/8e** which were isolated in 20% overall yield from 1-octene. The ^{13}C NMR shows two carbon signals which correspond to C_9, at 67.9 ppm and 72.3 ppm. The parent, octahydroindolizine, shows a signal for C_9 at 64.1 ppm.[20] By analogy with the usual effect[21ef] observed in substituted cyclic derivatives, substitution at C_7 should induce no shift for an equatorial and a 5.4 ppm upfield shift at C_9 for an axial substituent. This would lead to a predicted signal at C_9 in **7/8**, of 64.1 and 58.7 ppm, respectively. To test this prediction, we examined 3,7-dimethyloctahydroindolizine, which shows a signal at 65.4 ppm, only 1.3 ppm downfield from octahydroindolizine.[20a] Likewise, the oxindole alkaloids, **12a** and **12b** show that relative to **12a**,

Table 1: Reaction of **3** with Alkenes.

3 + RCH=CHR' ⟶ **7** + **8**

	R	R'	% 7/8
(a)		H	39
(b)		H	33
(c)		H	16
(d)	$-(CH_2)_5CH_3$	H	20
(e)	$-CH_2CH_2CH_2CH_2-$		20
(f)	-O-nBu	H	14

substitution at C_7 of **12b** induces a 0.9 ppm downfield shift at C_9 (74.5 vs. 75.4 ppm, respectively).[21,20b] 7-Alkyloctahydroindolizines, **10**, are not, therefore, expected to exhibit signals at C_9 as far downfield as those of the observed products. This contrasts with substitution at C_8 which should induce a shift of 8.9 ppm downfield for an equatorial substituent and 5.6 ppm downfield for an axial substituent.[21ef] These values lead to a prediction of 76 and 70 ppm, respec-

tively, for 8 and 7, relative to octahydroindolizine. This is very close to the observed values which is significant only with respect to the previous prediction for substitution at C_7. Further proof of the significant downfield shift for substitution at C_8 comes from **12a** in which the signal at C_8 appears at 25.6 ppm whereas the C_8 signal for **12b** appears at 32.0 ppm, a 6.4 ppm downfield shift. We have, therefore, assigned the structure of the isolated products in reactions of 3 with alkenes as the 8-alkyloctahydroindolizines, 7 and 8.

Apparently, 3 functions as an enophile in 4+2 cycloaddition reactions with alkenes containing electron releasing groups since similar reaction with ethyl acrylate, maleic anhydride and tetracyanoethylene gave no cycloaddition but only recovered starting material and a small amount of oil which resisted characterization. It is noted that two equivalents of 3 were required for the results shown in Table 1. When a 1:1 molar ratio of imidate to alkene was utilized, the yields were in the 5-8% range.

This cycloaddition constitutes the preliminary report of a new synthetic entry to indolizidine alkaloids and should compliment the highly useful imine-diene cycloaddition reactions previously described. Imidate 3, by virtue of the lability of the ethoxy group on reduction of the cycloadduct, functions as the synthetic equivalent of 2, which is currently unknown and appears accessible only with great difficulty. This new and unusual imidate salt reacts as an enophile in 4+2 cycloaddition reactions and gives rapid access to an important class of alkaloids, via reduction, from a readily available starting material. Indeed, this reaction offers the possibility of an 'indolizidine reagent' allowing direct formation of the alkaloid from an alkene. It opens the possibility of such reactions with a wide variety of simple alkenes and imidates possessing ring skeletons larger than 3 as well as the intramolecular cycloaddition from a suitable derivative of 3.

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