

**N-VINYL-2-ETHOXYPYRROLIDINIUM TETRAFLUORATE: A NOVEL
ENOPHILE AND SYNTHETIC EQUIVALENT FOR N-VINYLPYRROLIDINIUM**

Michael B. Smith* and Hitesh N. Shroff

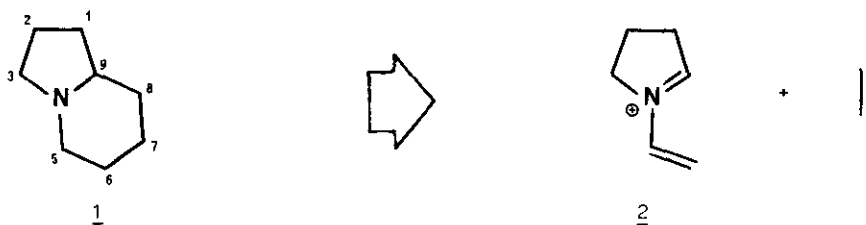
Department of Chemistry, U-60, University of Connecticut
Storrs, Connecticut 06268 U.S.A.

Abstract - Cycloaddition of *N*-vinyl-2-ethoxypyrrolidininium tetrafluoroborate, **3**, with alkenes, followed by hydride reduction, yields the 8-alkyloctahydroindolizines, **7** and **8** which would be derived from *N*-vinylpyrrolidininium, **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 electrophilic² and nucleophilic^{3,4} intermediates in the ring closing process. Alternative synthetic schemes have used the imine-diene Diels Alder reaction⁵ 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 approach¹⁰ in which a nitronc cycloadduct was converted to the desired alkaloid. Finally, Overman¹¹ 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 pyrrolidininium tetrafluoroborate, **3**, by treatment of *N*-vinyl-2-pyrrolidinone with triethyloxonium tetrafluoroborate in CH₂Cl₂.¹³ 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 salts¹⁵ 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.

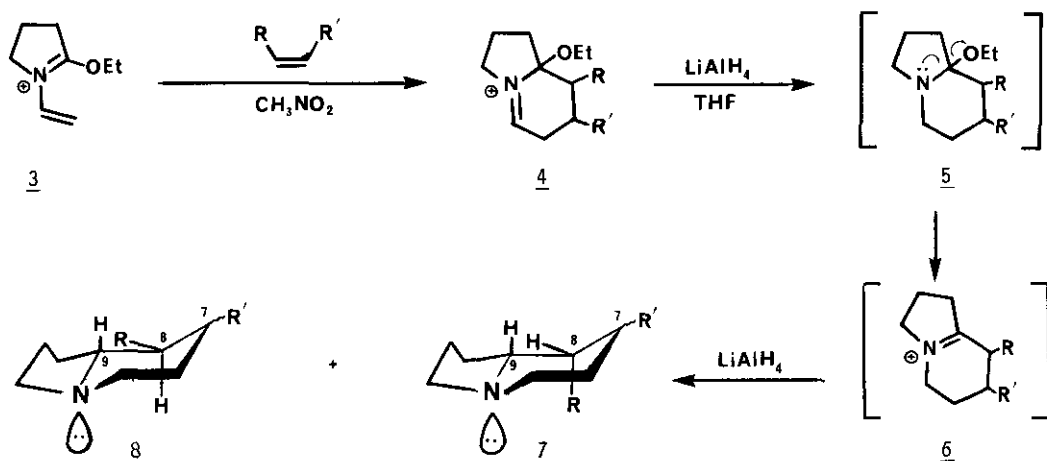


When 3 was refluxed with styrene in nitromethane, we observed slow formation (48 h) of the 4+2 cycloadduct 4. It was difficult to isolate 4 in pure form although the ^1H NMR clearly suggested formation of the cycloadduct. We therefore reduced the crude cycloadduct and isolated 8-phenyloctahydroindolizine, 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 Kano¹⁷ 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

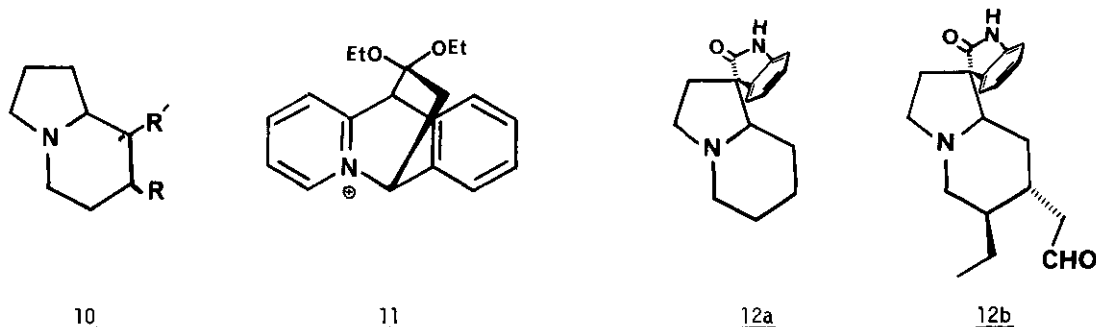
vinyl ether and 4-methoxystyrene gave reduced yields of 8-butoxyoctahydroindolizine, **7f/8f**, and 8-(4-methoxyphenyl)-octahydroindolizine, **7c/8c**, respectively, relative to the corresponding reactions with styrene, 1-octene and cyclohexene also supports this contention. The oxygen in these

Scheme I



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.



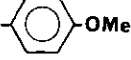
Identification of the octahydroindolizine products, **7/8**, was accomplished primarily by ^{13}C NMR. The 1H NMR at 200 MHz gave the expected signals between 2.0-3.0 ppm as previously reported¹⁻¹¹ but



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. Aaron¹⁹ 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 ¹³C NMR shows two carbon signals which correspond to C₉, at 67.9 ppm and 72.3 ppm. The parent, octahydroindolizine, shows a signal for C₉ at 64.1 ppm.²⁰ By analogy with the usual effect^{21ef} observed in substituted cyclic derivatives, substitution at C₇ should induce no shift for an equatorial and a 5.4 ppm upfield shift at C₉ for an axial substituent. This would lead to a predicted signal at C₉ 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.

<u>3</u>		+	RCH=CHR'	→	<u>7</u>	+	<u>8</u>
<u>R</u>	<u>R'</u>				% <u>7/8</u>		
(a) 	H				39		
(b) 	H				33		
(c) 	H				16		
(d) -(CH ₂) ₅ CH ₃	H				20		
(e) -CH ₂ CH ₂ CH ₂ CH ₂ -					20		
(f) -O-nBu	H				14		

substitution at C₇ of 12b induces a 0.9 ppm downfield shift at C₉ (74.5 vs. 75.4 ppm, respectively).^{21,20b} 7-Alkyloctahydroindolizines, 10, are not, therefore, expected to exhibit signals at C₉ as far downfield as those of the observed products. This contrasts with substitution at C₈ 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 C₇. Further proof of the significant downfield shift for substitution at C₈ comes from 12a in which the signal at C₈ appears at 25.6 ppm whereas the C₈ 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.

ACKNOWLEDGEMENTS

We thank the University of Connecticut Research Foundation for partial funding of this work.

REFERENCES

- (a) "The Alkaloids", Specialist Periodical Report, The Chemical Society, London, Vol. 1-10;
(b) "The Alkaloids, Chemistry and Physiology", R.H.F. Manske, Ed., Vol. I-XV, Academic Press, New York.
- D.L. Boger, Tetrahedron, 1983, 39, 2869.

3. (a) D.J. Hart, J. Org. Chem., 1981, 46, 367; (b) D.J. Hart, ibid., 1981, 46, 3576; (c) R.V. Stevens and Y. Luh, Tetrahedron Lett., 1977, 979; (d) M.T. Pizzorno and S.M. Abonico, J. Org. Chem., 1977, 42, 909.
4. (a) S. Yasuda, H. Hanaoka and Y. Arata, Heterocycles, 1977, 6, 391; (b) L. Faber and W. Wiegrebem, Helv. Chim. Acta, 1973, 56, 2882; (c) F. Bohlmann, N. Oltaur and R. Keller, Ann. Chem., 1954, 587, 162.
5. (a) W. Oppolzer, Angew. Chem., Int. Ed., Engl., 1972, 11, 1031; (b) S.M. Weinreb and R.R. Staib, Tetrahedron, 1982, 38, 3087; (c) S.M. Weinreb and J.I. Levin, Heterocycles, 1979, 12, 949; (d) T.R. Bailey, R.S. Garigipati, J.A. Morton, and S.M. Weinreb, J. Am. Chem. Soc., 1984, 106, 3240; (e) W. Oppolzer, Angew. Chem., Int. Ed., Engl., 1971, 11, 1; (f) M. Lora-Tomayo, "1,4-Cycloaddition Reactions", J. Homer, Ed., Academic Press, New York, 1967, pp. 127-142; (g) F. Bohlmann, D. Hobek, E. Poetsch, and D. Schuman, Chem. Ber., 1967, 100, 2742.
6. (a) F. Bohlmann, D. Habeck, E. Pletsch and D. Schuman, Chem. Ber., 1967, 100, 2742. (b) V. Boekelheide and S. Rothchild, J. Am. Chem. Soc., 1949, 71, 870. (c) E. Vedejs, M.J. Arco, D.W. Powell, J.M. Renga, and S.P. Singer, J. Org. Chem., 1978, 43, 4831. (d) M.A. Anderson, R.C.F. Jones, and J. Saunders, J. Chem. Soc., Chem. Commun., 1982, 2821. (e) R. Grewe and A. Mondon, Chem. Ber., 1948, 81, 279. (f) O. Schnider and A. Crussner, Helv. Chim. Acta, 1949, 32, 821.
7. (a) H. Bohme, K. Hartke, and A. Muller, Chem. Ber., 1963, 96, 607; (b) R. Mertenand and G. Muller, Angew. Chem, 1962, 74, 866; (c) J. Marchand-Brynaert and L. Chosez, Tetrahedron Lett., 1974, 377; (d) S. Danishefsky, T. Kitahara, R. McKee, and P.F. Schuda, J. Am. Chem. Soc., 1976, 98, 6715.
8. S.D. Larsen and P.A. Crieco, J. Am. Chem. Soc., 1985, 107, 1768.
9. T. Kametani and K. Fukumoto, Accts. Chem. Res., 1976, 9, 319.
10. (a) J.J. Tufariello, J. Am. Chem. Soc., 1979, 101, 7114; (b) J.J. Tufariello and J.J. Tegeler, Tetrahedron Lett., 1976, 4037; (c) J.J. Tufariello, Accts. Chem. Res., 1979, 12, 396.
11. (a) L.E. Overman and S.W. Goldstein, J. Am. Chem. Soc., 1984, 106, 5360; (b) L.E. Overman, K.L. Bell, and F. Ito, ibid., 1984, 106, 4192; (c) L.E. Overman and K.L. Bell, ibid., 1981, 103, 1851; (d) L.E. Overman, T.C. Malone, and G.P. Meier, ibid., 1983, 105, 6993.

12. (a) S.F. Chen, J.W. Ullrich, and P.S. Mariano, J. Am. Chem. Soc., 1983, 105, 6160; (b) P.S. Mariano, Accts. Chem. Res., 1983, 16, 130; (c) K. Ohga and P.S. Mariano, J. Am. Chem. Soc., 1982, 104, 617.
13. (a) M.B. Smith and H.N. Shroff, J. Org. Chem., 1984, 49, 2900. (b) M.B. Smith and H.N. Shroff, Tetrahedron Lett., 1983, 2091.
14. (a) D.L. Boger, Tetrahedron, 1983, 39, 2869. (b) Y. Cheng, F.W. Fowler, and A.T. Lupo, J. Am. Chem. Soc., 1981, 103, 2090. (c) A. Demoulin, H. Goussen, A-M. Hesbain-Frisque, and L. Ghosez, ibid., 1975, 97, 4409. (d) reference 6 in F. Sainte, B. Serckx-Poncin, A-M. Hesbain-Frisque, and L. Ghosez, ibid., 1982, 104, 1428.
15. (a) D.L. Fields, T.H. Regan, and J.C. Dignan, J. Org. Chem., 1968, 33, 390. (b) N.A. Porter, I.J. Westerman, and C.K. Bradsher, J. Am. Chem. Soc., 1974, 96, 5104. (c) I.J. Westerman and C.K. Bradsher, J. Org. Chem., 1971, 36, 969. (d) C.K. Bradsher and J.A. Stone, ibid., 1969, 34, 1700.
16. (a) A.R. Chamberlin, H.D. Nguyen, and J.Y.L. Chung, J. Org. Chem., 1984, 49, 1682. (b) W.M. Speckamp, Recl. Trav. Chem. Pays Bas, 1981, 100, 345. (c) H. Rapoport, Lect. Heterocycl. Chem., 1978, 4, 41. (d) S.W. Fallig and H. Rapoport, J. Org. Chem., 1980, 45, 1260.
17. S. Kano, T. Yokomatsu, H. Nemoto, and S. Shibuya, Tetrahedron Lett., 1985, 26, 1531.
18. F. Bohlmann, Chem. Ber., 1958, 91, 2157.
19. (a) H.S. Aaron and C.P. Ferguson, Tetrahedron Lett., 1968, 6191. (b) H.S. Aaron, Chem. Ind.(London), 1965, 1338.
20. (a) P.E. Sonnet, D.A. Netzel, and R. Mendoza, J. Heterocycl. Chem., 1979, 16, 1041. (b) E. Wenkert, J.S. Bindra, C.-J. Chang, D.W. Cochran, and F.M. Schell, Accts. Chem. Res., 1974, 47.
21. (a) F.A.L. Anet, C.H. Bradley, and G.W. Buchanan, J. Am. Chem. Soc., 1971, 93, 258. (b) D.K. Dalling and D.M. Grant, ibid., 1967, 89, 6612. (c) D.M. Grant and D.V. Cheney, ibid., 1967, 89, 5315. (d) G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, pp. 43-49.

Received, 28th May, 1985