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INTRAMOLECULAR [4 + 1] PYRROLINE ANNULATION APPROACH TO PYRROLIZIDINE ALKALOIDS. FORMAL TOTAL SYNTHESIS OF (±)-SUPINIDINE.[1]

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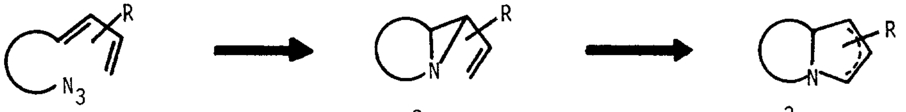
Abstract: Dienic azide 7 was found to yield dehydropyrrolizidines 10 and 11 on thermolysis. The synthesis of these compounds is described and the mechanistic implications as well as synthetic utility of this new annulation sequence is discussed.

The synthetic utility of a carbocyclic [4 + 1] annulation which entails the interaction of a carbenoid species with a conjugated diene and a subsequent vinylcyclopropane - cyclopentene rearrangement has been demonstrated by the generalized synthesis of several sesquiterpenes.[3] The heterocyclic equivalent of this reaction involves the intramolecular union and subsequent rearrangements of an azide and a diene as depicted in eq. 1.



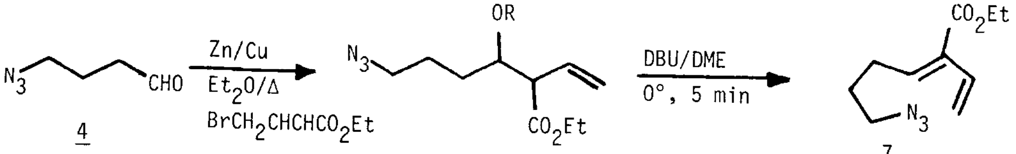
1 2 3

R = H, alkyl, CO_2R

eq. 1

Whereas the outcome of the sequence such as 1→2→3 in the carbocyclic series is quite predictable based on the stability of diradical species, the corresponding nitrogenous anologues can undergo a variety of mechanistically diverse transformations involving either diradical,[4] ionic,[5] or concerted processes.[6] In this report we describe the application of this strategy[1,7] to the synthesis of functionalized pyrrolizidines 10 and 11. Initial model studies involving unsubstituted azide 1 produced marginal evidence of formation of pyrroline 3. An electronically more suitable system was thus envisioned in acrylate 7 (Scheme 1).

The aldehyde 4, prepared by ozonolysis of bromopent-4-ene (CH_2Cl_2/-78°C, Me_2S workup) followed by displacement with sodium azide (NaN_3/DMF/R.T., 12 hours) was subjected to the



4

5, R = H

6, R = Ac

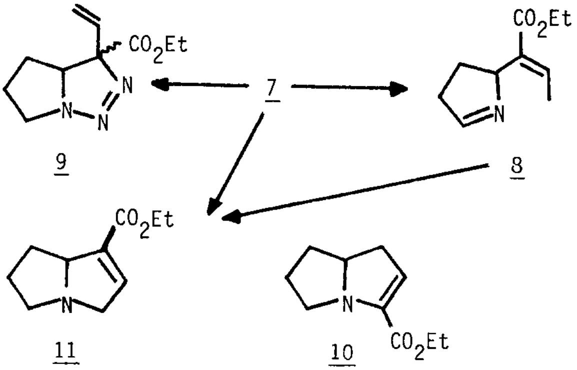
7

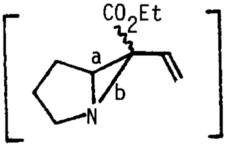
Scheme 1

"α-conditions" of the vinylogous Reformatsky reaction[8,9] (Scheme 1). Hydroxy adduct 5, obtained in 90% yield, was filtered through silica and acetylated (Ac_2O, pyridine, DMAP, 12 hours) to afford 85% yield of acetate 6 which was converted to diene 7 (DME, DBU, 0°C, 5 min.) in 96% yield (2:1 mixture of E/Z).

Exposure of azide 7 to refluxing THF (4 hours) resulted in a clean conversion to imine 8 (82%).[10] On standing at 0°C → R.T. (4-6 days) azide 7 was transformed to triazoline 9.[11] Flash pyrolysis of 7 at 450° or 500° gave a mixture of 8, 10, and 11 (approx. 50:40:10) in 86% yield. Pyrolysis of imine 8 gave similar results as did a sealed tube thermolysis of either azide 7 or imine 8 (toluene, 300°-400°, 2 hours).[12]

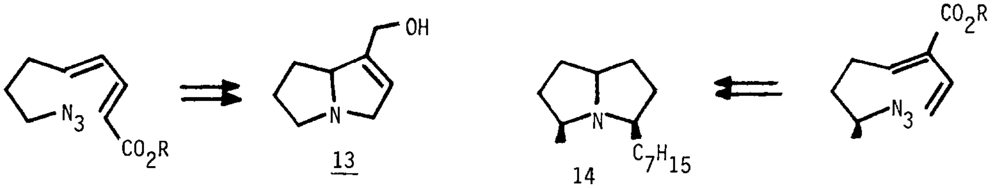
From these observations it is possible to draw certain conclusions about the mechanism of these rearrangements. Although neither vinyl aziridine 12 nor triazoline 9 have been isolated, their existence was detected in ^{1}H-NMR monitoring of reactions and they are presumably intermediates in the formation of 8, 10, and 11.





12a, exo
12b, endo

Vinylaziridine 12 can form two sets of diradicals, depending on the scission of either bond a or b. That the diradical derived from the scission of bond a is the more stable one is supported by the predominant formation of pyrrolizidine 10. In addition, the endo isomer 12b is subject to a 1,5-homodienyl shift which produces imine 8.[13] This behavior is entirely analogous to that of cis-disposed alkyl vinylcyclopropanes, and its reversibility serves to manufacture pyrrolizidines from imine 8 which is obtained in high yield and which is more easily manipulated than azide 7.[12,13] The utility of these transformations lies in their applicability to the synthesis of pyrrolizidine alkaloids such as supinidine 13, whose formal total synthesis has been achieved by the preparation of 11,[14] and of the unusual ant venoms such as 14[15] which could become available through this sequence via modification of precursory azide 4. It should be noted that the regioselectivity of the vinylogous Reformatsky reaction plays an extraordinary role in the design of appropriate precursors to afford pyrrolizidines functionalized at either 1- or 3- position as indicated in eq. 2. If vinylaziridine 12 can be isolated, the previously reported conditions of heterogeneous cleavage[5] will be applied to produce 11 selectively and under mild conditions. Thus both 10 and 11 will be accessible, under different conditions, from the α-regioisomer of 7, as well as from the γ-regioisomer.



13

14

eq. 2

We will report on these and any further applications of this new methodology in due course.

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1. Presented in part at the ACS Southeastern Regional Meeting, Raleigh, NC, October 1986, Abstract no. 431.

2. Fellow of the Alfred P. Sloan Foundation, 1981-85; Recipient of the Research Career Development Award (NIH-AI-00564), 1984-89.

3. For recent applications see B. C. Ranu, M. Kavka, L. A. Higgs, and T. Hudlicky, Tetrahedron Lett., 2447 (1984), and references therein.

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6. Concerted mechanisms are favored in 1,5-homodienyl shift reactions of vinylaziridines (ref. 13), whereas the majority of other rearrangements is explained on the basis of diradical or ionic intermediates. Some photolytic decompositions have been considered as concerted (P. Scheiner, J. Am. Chem. Soc., 90, 968 (1968) and such a possible pathway has not been excluded from further considerations.

7. We have been made aware of a similar study in progress by Prof. William H. Pearson, University of Michigan. Cycloadditions of azides and enones have previously led to the formation of pyrrolines: A. G. Schultz, J. P. Pittami, S. O. Myong, and Chin-Kang Sha, J. Am. Chem. Soc., 105, 3273 (1982); A. G. Schultz and W. G. McMahon, J. Org. Chem., 49, 1676 (1984).

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9. T. Hudlicky, M. G. Natchus, L. D. Kwart, and B. Colwell, *J. Am. Chem. Soc.*, submitted. The conditions yielding α-regiochemistry involve Zn/Cu couple, Et_2O, <1% CH_3CO_2H.

10. Monitoring of this reaction by TLC and ^{1}H-NMR revealed the intermediacy of triazoline **9** and vinylaziridine **12**.

11. The triazoline was not characterized due to its rapid decomposition.

12. The formation of **8** from **12b** is reversible. The sealed tube reactions produced higher content of pyrrolizidines **10** and **11** than the flash vacuum pyrolyses of **7**.

13. Vinylcyclopropanes: T. Hudlicky and F. J. Koszyk, *Tetrahedron Lett.*, 2487 (1980). Vinylaziridines: D. Borel, Y. Gelas-Mialhe, and R. Vessiere, *Can. J. Chem.*, **54**, 1582, 1590 (1976).

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