Tetrahedron Letters,Vol.26,No.30,pp 3527-3530,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# SYNTHESIS OF FUSED PYRROLINES BY THE INTRAMOLECULAR CYCLOADDITION OF AZIDES. APPLICATION TO THE PYRROLIZIDINE ALKALOIDS.

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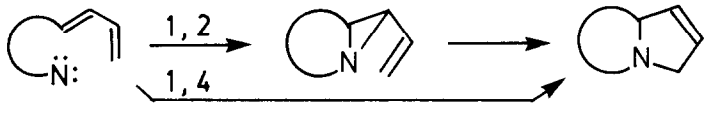
Summary: Intramolecular 1,3-dipolar cycloaddition of azide **4** proceeds through triazoline **5** and vinyl aziridine **6**, resulting in the formation of the 1,5-homodienyl shift product **7** and the tetrahydropyrrolizines **8** and **9**. Compound **8** represents a formal total synthesis of supinidine.

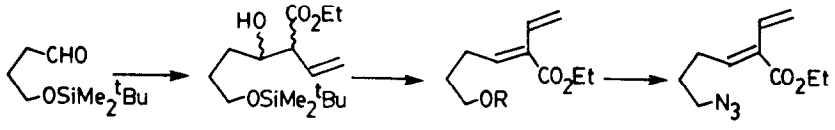
Many diverse classes of alkaloids may be grouped according to a common structural feature, namely a pyrrolidine or pyrroline ring fused to one or more additional rings with the nitrogen atom at the bridgehead position.[2] A general synthetic approach to these compounds is outlined in eq. 1, suggesting the intramolecular 1,2- or 1,4-addition of a nitrene to a diene.[3] To avoid the problems associated with the utilization of an aliphatic nitrene, the synthetic equivalent of a nitrene/diene cycloaddition is required.




eq. 1

Among the several possible equivalents of a nitrene, we have chosen the azido group due to its propensity to undergo 1,3-dipolar cycloadditons with olefins.[4] The intramolecular cyclization of aliphatic azides onto dienes has not been well studied.[3b-d,5] We wish to report some preliminary work using this pathway aimed at the pyrrolizidine alkaloids.[6]

The target azidodiene **4** was prepared as shown in Scheme 1. The known[7] aldehyde **1** was converted to a mixture (1.1:1) of hydroxyesters 2 upon exposure to the lithium enolate of ethyl crotonate.[8] Mesylation in the presence of excess triethylamine (MsCl, 5 eq $NEt_3$, RT, 2h) led smoothly to the diene **3a** (4:1 E:Z, 82% from **1**). Removal of the silyl group (AcOH, THF, $H_2O$, 45°, 4h), mesylation of the resultant alcohol **3b** (MsCl, $NEt_3$, 78% from **3a**) and azide displacement ($NaN_3$, DMSO, RT, 88%) provided azide **4** in excellent overall yield.



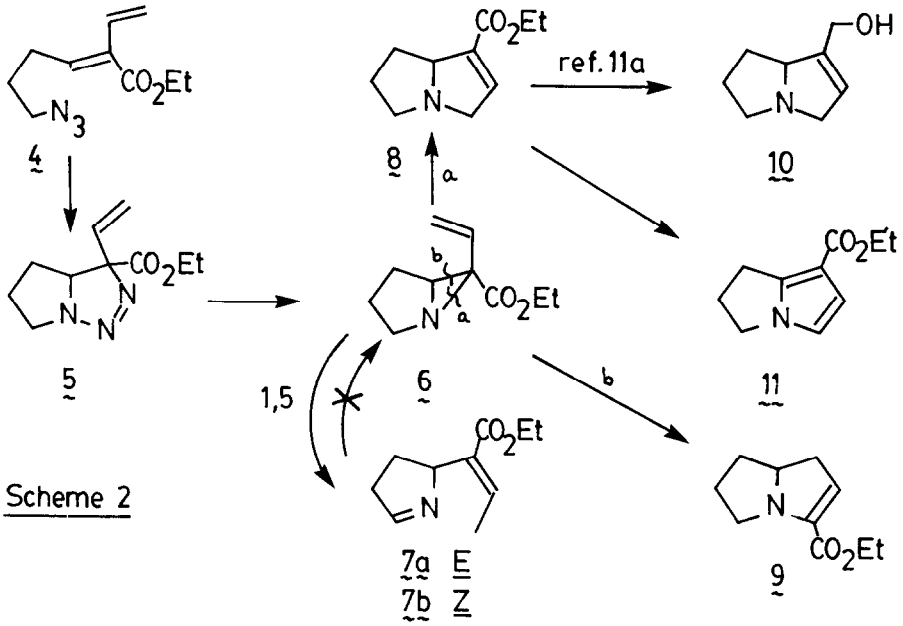

1 2 3a R=SiMe$_2$$^t$Bu 4

b =H

c =SO$_2$Me

Scheme 1

Upon standing at 0° for 1 week, a mixture of starting azide **4**, triazoline **5**,[9] imine **7**[9] and vinyl aziridine **6**[9] was formed in a 17:50:17:17 ratio ($^1$H NMR) Scheme 2. These could be separated by chromatography ($SiO_2$) with the exception of the triazolines, which were too sensitive to isolate in pure form. Imine **7** presumably arises from endo aziridine **6** by a facile 1,5-homodienyl shift.[10] All attempts to cause clean conversion of azide **4** to triazoline **5** without competing decomposition to imine **7** have failed. Alternatively, imine **7** could be formed in good yield by decomposition of the azide at higher temperature. For example, heating **4** at reflux in benzene or THF (4-6h) caused smooth conversion (ca. 90%) to imines **7a,b**, which were now contaminated by two new products (**7a:7b:8:9**, 75:9:6:14). These were isolated and identified as the tetrahydropyrrolizines **8**[11a] and **9**[11b]. Apparently, evolution of nitrogen from the triazoline leads to a diradical[12] which may close to aziridine **6**. At higher temperatures, direct closure to **8** becomes competetive (or, cleavage of bond **a** in **6** occurs). Endo vinyl aziridine **6** may undergo a 1,5-homodienyl shift to **7**, or open to a different diradical[13] (cleavage of bond **b**), leading to **9**.




Scheme 2

The preparation of **8** constitutes a formal total synthesis of supinidine **10**.[14] Attempts to influence the ratios of imine to tetrahydropyrrolizine by changing the solvent led to little variance (MeOH, water, MeCN, DMF). However, supplying the system with more thermal energy met with more success. For example, azide **4**, upon distillation through a 500° hot tube[15] (80° pot, 0.15 torr) led to a mixture of imine **7** and pyrroline **9** (38:62 ratio, traces of **8**, 69%). At these temperatures, one may reasonably expect nitrene formation from azide **4**. However, the clean nature of the reaction led us to believe that nitrenes were not involved to any large extent. To ascertain the nature of the compound actually passing through the hot tube, the azide was simply Kugelrohr distilled under the same conditions (ca. 80°, 0.15 torr). The major component of the distillate was vinyl aziridine **6**,[9] accompanied by imines **7** and a small amount

of starting azide, attesting to the rapid cycloaddition onto this activated diene.[16] Hence, by supplying the vinyl aziridine with more energy, the partitioning of reaction pathways has been influenced to produce a larger amount of tetrahydropyrrolizine.

Since imine **7** was readily available, we speculated that thermolysis may lead back to the vinyl aziridine manifold by an ene reaction, in analogy to work done in the all-carbon series.[10a] To that end, crude imine (containing 8 and 9) was subjected to a wide variety of pyrolysis conditions. Flash vacuum thermolysis and flow thermolysis at temperatures below 500° invariably returned approximately the same ratios of **7**, 8 and **9**. Sealed tube reactions (toluene, 200-300°) selectively destroyed all compounds except the imine **7**. Thermolysis at temperatures above 500° led to the formation of a new product which was identified as the pyrrole **11**.[17] It was shown that this compound arises from the tetrahydropyrrolizine **8**, and not from imine **7**. In fact, thermolysis of pure **7a** resulted in recovery of starting material up to temperatures of about 550°, at which point recovery was low, and the starting material recovered was contaminated with several new compounds, none of which were 8 or **9**.

Although the formal synthesis of supinidine occurs in low yield, the obtention of **8** and **9** is promising for the synthesis of fused pyrrolines. We are currently studying the mechanistic and stereochemical aspects of the reactions presented herein in order to extend this method to more complex alkaloids in a controlled fashion.

**Acknowledgements:** We are grateful to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the University of Michigan (H. H. Rackham Faculty Grant) for the support of this research.

**References and Notes**

1. Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1984-89.

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4. (a) Lwowski, W. in "1,3-Dipolar Cycloaddition Chemistry," Vol. 1, Padwa, A., Ed.; Wiley: New York, 1984, Ch. 5, pp. 559-651. (b) Intramolecular examples: Padwa, A. in ref. 4a, Vol. 2, Padwa, A., Ed.; 1984, Ch. 12, pp. 277-406.

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6. We are aware of a similar investigation by Professor Tomas Hudlicky at Virginia Polytechnic Institute. We thank Professor Hudlicky for communicating his work prior to publication. See: Frazier, J. O.; Short, P. P.; Hudlicky, T., Abstract No. 431, ACS Southeastern Regional Meeting, Raleigh, NC, October 1984.

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8. (a) Rathke, M. W.; Sullivan, D. Tetrahedron Lett. **1972**, 4249. (b) Hermann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. Ibid, **1973**, 2433. (c) Kende, A. S.; Toder, B. H. J. Org. Chem. **1982**, 47, 163.

9. Satisfactory spectral data have been obtained for **2-6, 7a, 8, 9, 11.** Some relevant partial data are reported below. **5:** A 4:1 mixture of isomers, presumably reflecting the stereochemistry of the diene **4.** Major isomer: $^1$H NMR ($CDCl_3$, 360 MHz): 6.05 (dd, J=17.5, 10.8 Hz, 1H), 5.42 (dd, J=10.8, 1.1 Hz, 1H), 5.50 (dd, 17.2, 1.1 Hz, 1H). Minor isomer: 6.02 (dd, J=17.5, 10.5 Hz, 1H), 5.23 (d, J=10.5 Hz, 1H), 5.30 (d, J=17.5 Hz, 1H). **7:** $^1$H NMR ($CDCl_3$, 360 MHz): 7.62 (bs, 1H), 6.94 (q, J=7 Hz, 1H), 5.05 (m, 1H), 4.12 (q, J=7 Hz, 2H), 2.83 (m, 1H), 2.55 (m, 1H), 2.08 (m, 1H), 1.88 (d, J=7 Hz, 3H), 1.78 (m, 1H), 1.23 (q, J=7Hz, 3H). **6:** Apparently, only one isomer of vinyl aziridine is isolable, presumably the exo isomer: $^1$H NMR ($CDCl_3$, 360 MHz): 5.73 (dd, J=17, 10.5 Hz, 1H), 5.55 (dd, J=10.5, 1.5 Hz, 1H), 5.50 (dd, J=17, 1.5 Hz, 1H), 4.4 (m, 3H), 3.15 (m, 1H), 2.90 (m, 1H), 2.1-1.5 (m, 4H), 1.2 (t, J=7 Hz, 3H).

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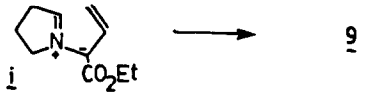
11. (a) Spectral data for **8** agree with the literature data: Robins, D. J.; Sakdarat, S. J. Chem. Soc. Perkin Trans. 1 **1979,** 1734. (b) $^1$H NMR ($CDCl_3$, 300 MHz): 5.84 (t, J=2.9 Hz, 1H), 4.20 (q, J=7 Hz, 2H), 3.97 (m, 1H), 3.28 (m, 1H), 2.98 (dt, J=11, 7 Hz, 1H), 2.73 (ddd, J=18.5, 11, 3 Hz, 1H), 2.45 (ddd, J=18.5, 5, 3 Hz, 1H), 1.97-1.65 (m, 4H), 1.29 (t, J=7 Hz, 3H).

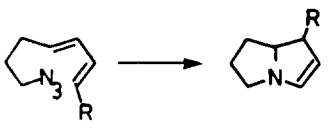
12. Alternatively, a zwitterionic mechanism may operate.

13. Ring opening may also proceed readily via an azomethine ylid **i:**




i 9

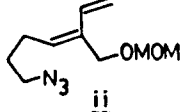
See for example: (a) Borel, D.; Gelas-Mialhe, Y.; Vessiere, R. Can. J. Chem. **1976,** 53, 1590. (b) Pommelet, J. C.; Chuche, J. Ibid **1976,** 54, 1571. The fact that some N-C cleavage occurs leading to **8** indicates that this may become the major route, given proper substitution. Thermal rearrangement of 2-vinylaziridines to 3-pyrrolines by N-C cleavage has precedent: Deyrup, J. A. in "Heterocyclic Compounds," Vol. 42, Part 1; Hassner, A., Ed.; Wiley: New York, 1983, Ch. 1, pp. 1-214. Should C-C bond cleavage continue to be the major reaction process, this methodology could still be used for fused pyrroline synthesis by changing the position of substituents:




14. Robins, D. J. Adv. Het. Chem. **1979,** 24, 247. Recent syntheses: Kametani, T.; Higashiyama, K.; Otomasu, H.; Honda, T. Heterocycles **1984,** 22, 729: Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. J. Am. Chem. Soc. **1984,** 106, 8201.

15. Brown, R. F. C., "Pyrolytic Methods in Organic Chemistry," Academic Press: New York, 1980.

16. In contrast, subjection of the less activated diene **ii** to the same pyrolysis conditions was very complex, perhaps reflecting nitrene formation.

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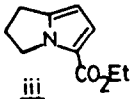
17. Spectral data for **11** agree well with the literature data,[17a] in contrast to that reported for the regioisomeric pyrrole **iii.**[17b] (a) Borch, R. F.; Ho, B. C. J. Org. Chem. **1977,** 42, 1225. (b) Lunig, B.; Trankner, H. Acta Chem. Scand. **1968** 22, 2324.

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(Received in USA 15 April 1985)