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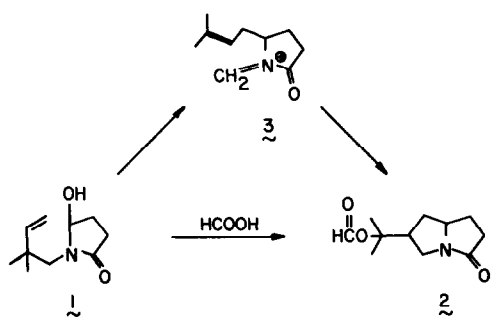
# REARRANGEMENTS OF N-ACYL-2-AZA-1,5-HEXADIENES APPLICATION TO SYNTHESES OF TRAECHELANTHAMIDINE AND SUPINIDINE

David J Hart* and Teng-Kuei Yang
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Summary Efficient syntheses of the pyrrolizidine bases traechelanthamidine (4) and supinidine (5) via an N-acyliminium ion rearrangement-cyclization are described.

During the course of a study of N-acyl-2-aza-1,5-hexadiene rearrangements we found that treatment of carbinolamide 1 with formic acid gave pyrrolizidinone 2 (mp 59-60°C.) as a single stereoisomer in a 81% yield.[2,3] Although the mechanistic details of this transformation

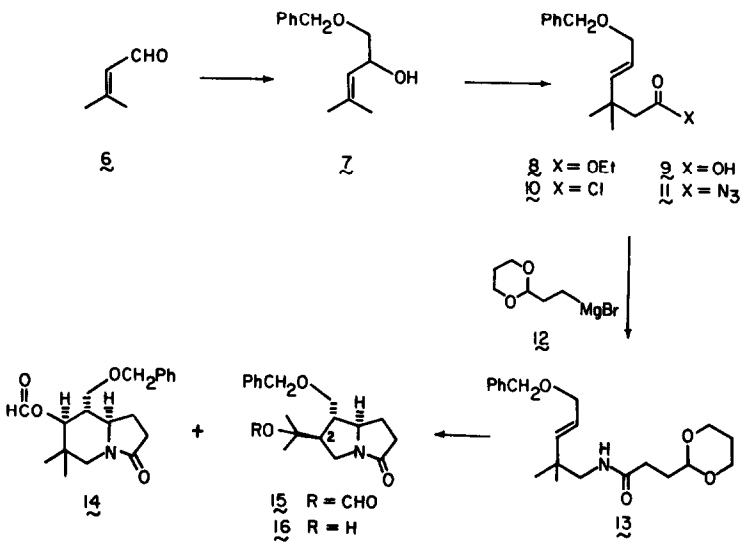



3 1 2

remain to be established, it is conceivable that the reaction involves an initial N-acyl-2-aza-Cope rearrangement[1] to afford N-acyliminium ion 3 followed by cyclization of 3 to formate 2.[4,5] This letter describes the application of this rearrangement to the synthesis of the simple pyrrolizidine bases traechelanthamidine (4) and supinidine (5).[6,7]


4 5

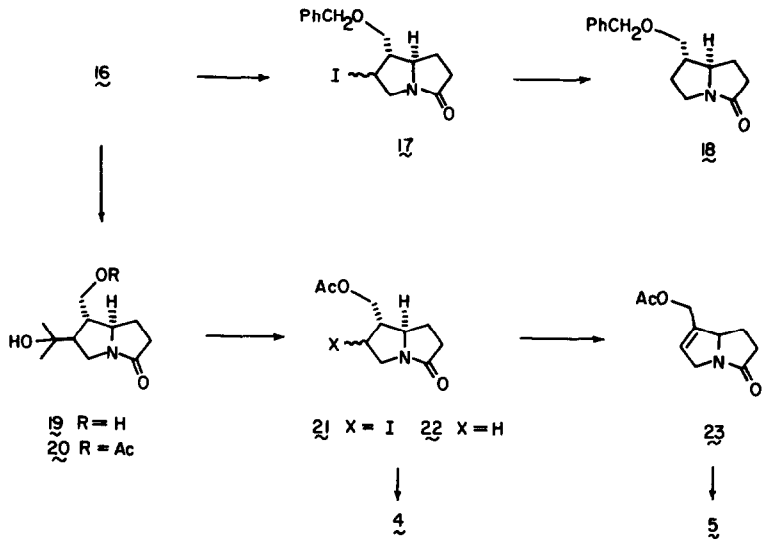
Our plan for adapting this reaction to the synthesis of pyrrolizidine alkaloids called for the preparation of pyrrolizidinone 16 followed by an appropriate degradation of the C-2 sidechain. The synthesis of 16 was accomplished in the following manner. Treatment of




aldehyde 6[8] with benzyloxymethyl lithium gave allylic alcohol 7 (89%).[9,10] Alcohol 7 was subjected to the orthoester Claisen rearrangement [$CH_3C(OEt)_3$, $CH_3CH_2COOH$, 145°C, 21h][11] and the resulting ester 8 was saponified (10% aq. NaOH) to afford carboxylic acid 9 (86%). Treatment of 9 with thionyl chloride gave acid chloride 10 (83%) which was converted to acyl azide 11 upon treatment with sodium azide in acetone-water Azide 11 was warmed in benzene (reflux, 1h) and the resulting crude isocyanate was treated with Grignard reagent 12[12] in tetrahydrofuran to afford amide 13 in a 62% overall yield from 10.[13] When 13 was stirred in formic acid at room temperature for 21h, bicyclic lactams 14, 15, and 16 (mp 81.5-82.5°C) were isolated in 9%, 70%, and 10% yields, respectively.[14] The synthesis of 16 was completed by saponification of 15 (94%, NaOH-MeOH-$H_2O$).

With the required ring system in hand, degradation of the C-2 sidechain proceeded as follows. Treatment of 16 with mercuric oxide and iodine in carbon tetrachloride[15] gave a separable mixture of iodides 17 in a 30% yield along with considerable amounts of benzaldehyde as a major side product Even though 17 was converted in a 96% yield to pyrrolidinone 18 (mp 58-59°C) upon treatment with tri-n-butyltin hydride [16], we decided to exchange the benzyl blocking group for one which would be less susceptable to degradation. Thus, hydrogenolysis of 16 ($H_2$, Pd on C, EtOH) followed by selective acylation ($Ac_2O$, pyridine) of the resulting diol 19 gave acetate 20 (mp 108-109°C) in a 94% yield. Degradation of 20 as described for 16 (HgO, $I_2$,$CCl_4$,85°C, 6h) gave a mixture of iodides 21 (89%)[17] which was converted to traechelanthamidine (4) upon treatment with tri-n-butyltin hydride (90%) followed by lithium aluminum hydride (78%).[18] Alternatively, dehydrohalogenation of 21 (67%; DBU, benzene, 80°C, 9h)[19] followed by reduction of the resulting allylic acetate 23 with lithium aluminum hydride gave supinidine (5) in a 93% yield.[20,21,22]

In summary, a new entry to both reduced and 1,2-dehydropyrrolizidine alkaloids has been developed. The route features an N-acyliminium ion rearrangement-cyclization




and couples a Curtius rearrangement with an isocyanate addition reaction as an efficient sequence for generating the iminium ion precursor. The route is stereoselective and, in principle, could be rationally modified to afford C-1 isomeric and C-7 oxygenated pyrrolizidine alkaloids. Studies directed toward this end will appear in the full account of our studies on N-acyl-2-aza-1,5-hexadiene rearrangements.

Acknowledgements We thank the National Institutes of Health for their generous support of this work. We also thank Mr. Richard Weisenberger for performing mass spectral analyses.

## References and Notes

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2 The rearrangement of 1 to 2 was first reported at the 181st National ACS Meeting, Atlanta, Georgia, March 30 - April 3, 1981, Paper No ORGN 13.

3 The stereochemistry of 2 is unknown

4. A similar rearrangement-cyclization was recently reported: Nossin, P.M.M.; Speckamp, W.N. Tetrahedron Lett., 1981, 3289

5. It is noted that the rearrangement-cyclizations reported here and in reference 4 are closely related to the directed 2-azonia [3,3] sigmatropic rearrangements reported by Overman. For examples see: Overman, L.E , Mendelson, L.T. J. Am. Chem. Soc , 1981, 103, 5579 and references cited therein.

6 For a recent review see Robin, D.J. in "Advances in Heterocyclic Chemistry", Katritzky, A.R , Boulton, A J.,Eds., Academic Press New York, 1979. Vol. 24, p. 247.

7. For some syntheses of pyrrolizidine alkaloids reported after the appearance of Robins' review see Iwashita, T., Kusumi, T., Kakisawa, H. J. Org. Chem., 1982, 47, 230. Takano, S., Ogawa, N.; Ogasawara, K. Heterocycles, 1981, 16, 915. Robins, D J., Sakdarat, S. J. Chem. Soc., Perkin I, 1981, 909. Flitsch, W.; Wernsmann, P Tetrahedron Lett., 1981, 719. Wilson, S.R., Sawicki, R.A., Huffman, J C. J. Org. Chem., 1981, 46, 3887. Vedejs, E., Martinez, G R. J. Am Chem. Soc., 1980, 102, 7993. Keck, G.E., Nickell, D.G. J. Am. Chem. Soc., 1980, 102, 3632. Kraus, G.A., Neuenschwander, K. Tetrahedron Lett., 1980, 3841. Tufariello, J.J., Lee, G.E. J. Am Chem. Soc., 1980, 102, 373 Iwashita, T.; Kusumi, T., Kakisawa, H. Chem Lett., 1979, 1337. Robins, D.J , Sakdarat, S. J. Chem. Soc , Chem Commun., 1979, 1181. Wilson, S.R , Sawicki, R A J Org Chem , 1979, 44, 287 Nossin, P.M M , Speckamp, W N Tetrahedron Lett. 1979, 4411.

8. Prepared by PCC oxidation (Corey, E J , Suggs, J W. Tetrahedron Lett., 1975, 2647) of 3-methyl-2-buten-1-ol

9 Still, W.C J. Am. Chem. Soc , 1978, 100, 1481.

10. All new compounds reported herein gave satisfactory $^{1}$H-NMR, IR, mass, and in some cases carbon-13 NMR spectra.

11. Johnson, W.S., Werthemann, L.; Bartlett, W.R , Brockson, T.J , Li, T., Faulkner, D J ; Peterson, M.R. J. Am. Chem. Soc., 1970, 92, 741.

12. Stowell, J.C. J. Org Chem., 1976, 41, 560.

13. LeBel, N.A , Cherluck, R M., Curtis, E.A Synthesis, 1973, 678 and references cited therein.

14. The stereochemical assignment at C(2) in 15 and 16 is tentative.

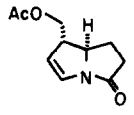
15. Greene, F D., Savitz, M.L., Osterholtz, F.D., Lau, H.H.; Smith, W.N., Zanet, P.M. J. Org. Chem., 1963, 28, 55. Macdonald, T L., O'Dell, D E J. Org Chem., 1981, 46, 1501 and references cited therein.

16. Kuivila, H G. Synthesis, 1970, 499.

17. Iodides 21 were contaminated by 1-4% of olefin 23.

18 The 200 MHz $^{1}$H-NMR spectrum of 4 and the melting point of its picrate (173.5 - 174.5°C ) corresponded satisfactorally with those reported by others Danishefsky, S., McKee, R., Singh, R.K J. Am. Chem. Soc., 1977, 99, 4783 and references cited therein.

19. In addition, unstable enamide 1 was obtained in a 31% yield




20 The $^{1}$H-NMR spectrum of 5 and the melting point of its picrate (124 - 125°C ) coressponded satisfactorally with those reported by others.[21,22]

21. For other syntheses of dl-supinidine see Robins, D J., Sakdarat, S. J. Chem Soc , Perkin I, 1979, 1734. Tufariello, J J.; Tette, J.P. J. Org. Chem., 1975, 40, 3866 and references cited therein.

22. For $^{1}$H-NMR data on 5 see Culvenor, C.C.J., Woods, W.G Aust J. Chem., 1965, 18. 1625

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