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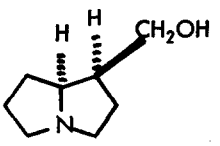
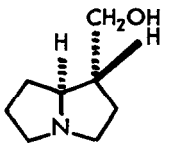
CYCLOPROPYL IMINE REARRANGEMENT: TOTAL SYNTHESIS OF (±)-ISORETRONECANOL AND (±)-TRACHELANTHAMIDINE[1-3]

Harold W. Pinnick* and Yeong-Ho Chang
Department of Chemistry
University of Georgia
Athens, Georgia 30602

The pyrrolizidine alkaloids possess a wide range of physiological properties. Many of them are hepatotoxic or carcinogenic while others have antihypertensive or anticancer activity.[4] We report a new synthesis of the simplest members of this family of alkaloids— (±)-isoretronecanol (1) and (±)-trachelanthamidine (2).

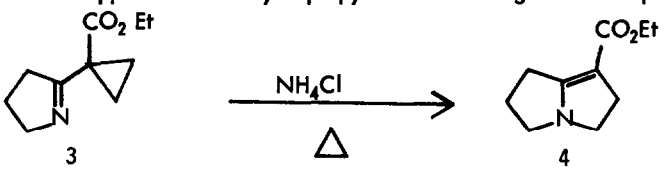


1



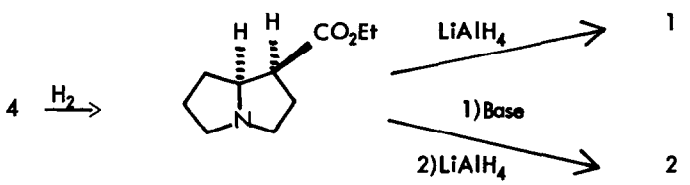
2

The key step in this approach is the cyclopropyl imine rearrangement of equation 1.[5] Thus, when



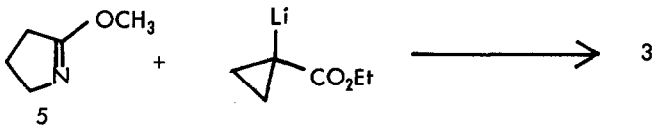
3 4 (1)

the imine 3 is refluxed in xylene containing a catalytic amount of ammonium chloride, the pyrrolizidine 4 is isolated in 76% yield.[6] Catalytic reduction is known to convert compound 4 into ethyl isoretronecanolate which can be reduced with lithium aluminum hydride to give (±)-isoretronecanol[7] or epimerized with base[8] and then reduced to yield (±)-trachelanthamidine (eq. 2).



(2)

The preparation of the critical cyclopropyl imine 3 was not trivial. The initial approach which was attempted was an addition-elimination reaction as in equation 3. In fact, imino ethers are known to react

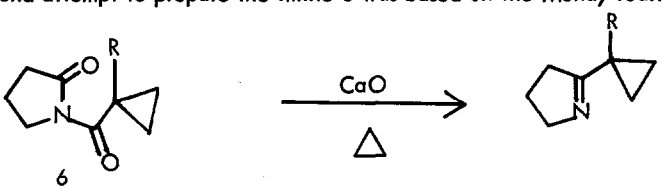


(3)

5

with ethyl acetoacetate[9] and benzylnitrile.[10] Imino ether 5 was prepared easily from pyrrolidone and dimethyl sulfate[9] but the anion of ethyl cyclopropanecarboxylate could not be obtained even by using lithium diisopropyl amide at -78°. Only self-condensation of the ester was obtained. To test the addition-elimination idea, the anion of ethyl acetate was combined with imino ethers but there was no reaction. Apparently, a more stable anion is required as in the documented examples.[9,10]

A second attempt to prepare the imine 3 was based on the Mundy rearrangement (eq 4).[11] Mundy



(4)

6

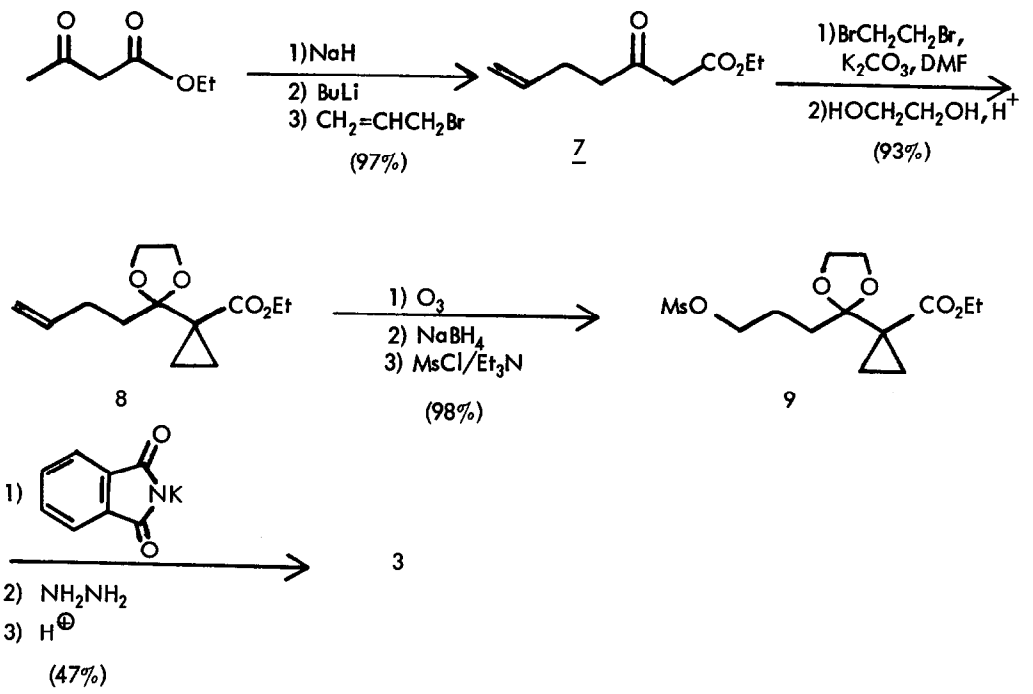
reports that acyl lactam 6 (R=H) rearranges when heated with calcium oxide to give 1-cyclopropyl-1-pyrroline in 73% yield.[11] The ester analogue (R=CO_2Et) was prepared and subjected to a variety of reaction conditions but none of the desired imine 3 was obtained.

A successful synthesis of the crucial cyclopropyl imine was developed and is outlined in Scheme 1. The dianion of ethyl acetoacetate is alkylated smoothly to give keto ester 7 in 97% yield. Cyclopropanation with ethylene bromide in the presence of potassium carbonate in dimethylformamide (DMF)[12] followed by ketalization gives the olefin 8 in 93% yield. Ozonolysis in 95% ethanol/methylene chloride at -78° followed by reduction with sodium borohydride gives the primary alcohol which is converted into the mesylate 9 with methanesulfonyl chloride (MsCl) in triethylamine. This ester alkylates potassium phthalimide[13] in refluxing benzene containing catalytic benzyltrimethylammonium chloride in quantitative yield. Liberation of the amino group with aqueous hydrazine[14] in refluxing ethanol and acid hydrolysis of the ketal produces the imine 3 in 47% yield. Despite the length of the preparation, the overall yield from ethyl acetoacetate is 42%.

More complex analogues potentially can be produced in a similar manner and this is currently under investigation as well as other approaches to the pyrrolizidine skeleton.

ACKNOWLEDGMENT We wish to thank Hexcel Specialty Chemicals for a gift of benzyl trimethyl ammonium chloride.

Scheme 1



References and Notes

1. Part 2 ofApproaches to the Pyrrolizidine Ring System. For Part 1 see H. W. Pinnick and Y. -H. Chang, J. Org. Chem., in press.
2. Taken in part from the Ph.D. dissertation of Y.-H. Chang, University of Georgia, 1978.
3. Presented at the 30th Southeastern Regional Meeting of the American Chemical Society, Savannah, Georgia, November 8-10, 1978.
4. (a) F. L. Warren in "The Alkaloids—Chemistry and Physiology," R. H. F. Manske, ed., Vol. XII, Academic Press, New York, 1970, p. 319; (b) D. H. G. Crout in "The Alkaloids," Vol. 6, The Chemical Society, London, 1976, p. 84; (c) W. M. Hoskin and D. H. G. Crout, J. Chem. Soc., Perkin I, 538 (1977); (d) E. G. C. Clarke in "The Alkaloids—Chemistry and Physiology," R. H. F. Manske, ed., Vol. XII, Academic Press, New York, 1970, p. 518.
5. Stevens has elegantly applied the cyclopropyl imine rearrangement to the synthesis of a variety of alkaloids: R. V. Stevens, Y. Luh and J. - T. Sheu, Tetrahedron Lett., 3799 (1976) and R. V. Stevens, Accounts Chem. Res., 10, 193 (1977) and references contained therein; however, the present work is the first example of a cyclopropyl imine rearrangement where a cyclic imine is used.

6. All compounds give satisfactory NMR and IR spectra.

7. N. K. Kochetkov, A. M. Likhosherstov and A. S. Lebedeva, J. Gen. Chem. USSR, 31, 3225 (1961).

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9. A. E. Wick, P. A. Bartlett and D. Dolphin, Helv. Chim.Acta, 54, 513 (1971).

10. T. Kametani, T. Takahashi, M. Ihara and K. Fukumoto, J. Chem. Soc., Perkin I, 389 (1976).

11. B. P. Mundy, K. B. Lipkowitz, M. Lee and B. R. Larsen, J. Org. Chem., 39, 1963 (1974).

12. This method was used recently to effect the cyclopropanation of malonic esters: D. A. White, Syn. Comm., 7, 559 (1977). In our hands, the reaction mixture had to be filtered and fresh potassium carbonate added several hours after the initial exothermic reaction in order to get complete conversion to product.

13. P. L. Salzburg and J. V. Supnieski, Org. Syn. Coll. Vol. 1, 119 (1941).

14. (a) L. I. Smith and O. H. Emerson, Org. Syn. Coll. Vol. III, 151 (1955); (b) H. R. Ing and R. H. F. Manske, J. Chem. Soc., 2348 (1926); (c) J. C. Sheehan and V. S. Frank, J. Am. Chem. Soc., 71, 1856 (1950).

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