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N-ACYLIMINIUM IONS: DETECTION OF A HIDDEN 2-AZA-COPE REARRANGEMENT

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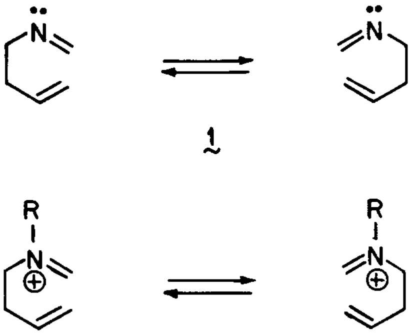
Abstract: A 2-aza-Cope rearrangement underlying the more typical reactions of N-acyl-2-aza-1,5-hexadienes has been detected using triethylsilane as an acyliminium ion trap.

Hetero-Cope rearrangements have previously been reported for substituted 2-aza-1,5-hexadienes 1 and their iminium ion counterparts, 2.[1-4] Although related N-acyliminium ions of type 3 have been investigated extensively throughout the past decade[5], hetero-Cope rearrangements of these systems have remained unknown. We report here an example of a fast 2-aza-Cope rearrangement underlying reactions which are typical of ions of type 3.



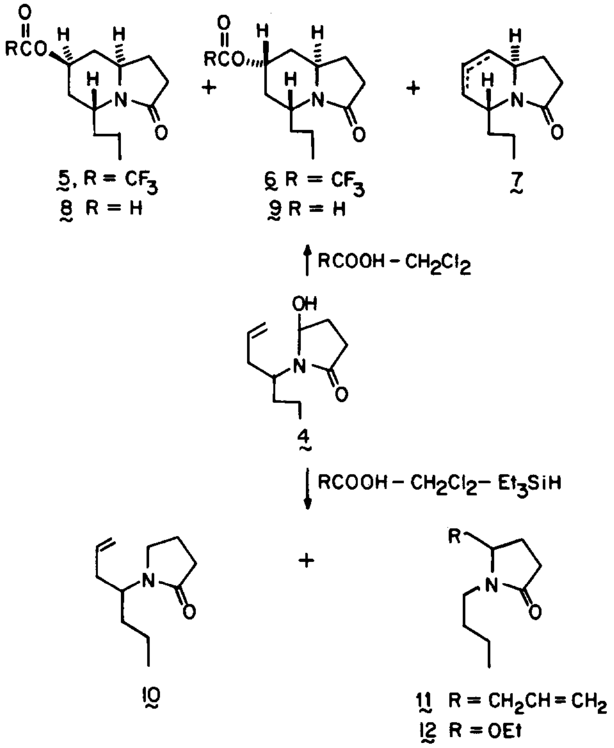
1

2 R = H , alkyl

3 R = acyl

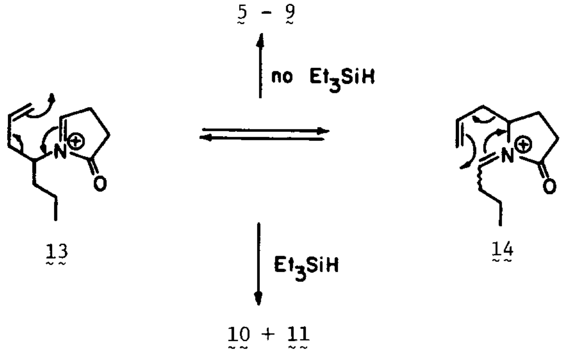
Treatment of carbinolamide 4 with trifluoroacetic acid-dichloromethane (25°C, 5 min) gave a 49% yield of lactam 5[6,7], 13% of lactam 6, and 12% of a mixture of lactams 7.[8,9] Similarly treatment of 4 with formic acid-dichloromethane (25°C, 10 h) gave a 60% yield of formate 8 and trace amounts of lactams 9 and 7.[11]

To our surprise, treatment of 4 with a mixture of trifluoroacetic acid-dichloromethane-triethylsilane (25°C, 5 min)[12] gave no cyclized products. Instead a separable 3:5 mixture of lactams 10 and 11 was obtained in a 73% yield. The structures of 10 and 11 were confirmed by independent synthesis. Thus, reduction of 4 with sodium cyanoborohydride[13] at pH 4 in methanol gave exclusively 10 (84%).[14] The skelatally rearranged lactam 11 was prepared from N-butylsuccinimide by reduction with sodium borohydride in ethanol (85%)[15] followed by treatment of the resulting ω-alkoxylactam 12 with allyltrimethylsilane in the presence of titanium tetrachloride (CH_2Cl_2, 25°C, 7 h, 78%).[16] When 4 was treated with formic acid-dichloromethane-triethylsilane (25°C, 10 h)[12] cyclized formate 8 (29%) was obtained in addition to a 3:5 mixture of lactams 10 and 11, respectively (42%).



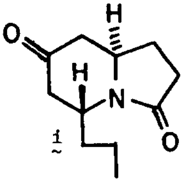
The observations outlined above suggest that treatment of carbinolamide 4 with acid gives N-acyliminium ion 13 which rearranges to ion 14, presumably via a 2-aza-Cope process. In the presence of triethylsilane, 13 and 14 are reduced to lactams 10 and 11, respectively.[17,18] In the absence of an ion trap[19] cyclized products, typical of those observed upon generation of ions of type 3 in nucleophilic media,[5] are formed.[20]

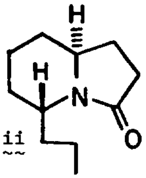
Since the ratio of lactams 10 and 11 does not vary with reduction media it is tempting to suggest that an equilibrium mixture of 13 and 14 is rapidly established, followed by slower secondary processes such as reduction and cyclization. In trifluoroacetic acid, reduction is faster than cyclization. In the more nucleophilic formic acid media, cyclization and reduction take place at comparable rates. We have not, however, generated ion **14** independently and thus the exact meaning of the observed **10**:**11** ratio remains uncertain.[21,22] We are currently examining the effect of substituents on the relative rates of cyclization and rearrangement for a variety of ions of type **3**.[23]



References and Notes

1. R. M. Holowitz and T. A. Geissman, *J. Am. Chem. Soc.*, **72**, 1518 (1950).
2. For a review of the area see: E. Winterfeldt, *Fortschr. Chem. Forsch.*, **16**, 75 (1971).
3. See also: H. Bohme and H. G. Viehe, Ed., "Iminium Salts in Organic Chemistry, Part 2", Wiley, New York, 1978.
4. For a recent example see: L. E. Overman and M. Kakimoto, *J. Am. Chem. Soc.*, **101**, 1310 (1979).
5. H. E. Schoemaker, J. Dijkink and W. N. Speckamp, *Tetrahedron*, **34**, 163 (1978).
6. Trifluoroacetate **5** and all other new compounds reported herein gave ^1H NMR, IR, mass spectral, exact mass, and in some instances ^{13}C NMR data consistent with the assigned structures.
7. The stereochemistry of **5** was determined by appropriate ^1H NMR decoupling experiments performed at 300 MHz and follows from earlier stereochemical observations reported from these laboratories: D. J. Hart, *J. Am. Chem. Soc.*, **102**, 397 (1980).
8. The stereochemical relationship between **5** and **6** was established in the following manner. Trifluoroacetate **5** was hydrolyzed (NaOH-MeOH-H_2O, 100%) and oxidized (Jones, 53%) to give ketolactam **i**. Ketolactam **i** was reduced ($NaBH_4$, EtOH) and the resulting mixture of alcohols was esterified [$CF_3CO)_2O$, Et_3N)] to give a separable mixture of **5** (13%) and **6** (35%).


i


ii

9. The structure of 7 was confirmed by reduction (H_2, Pd-C, 86%) to lactam ii which was prepared independently [1. NaOH; 2. NaH; 3. CS_2; 4. CH_3I; 5. $\underline{n}Bu_3SnH$[10]] from 5.

10. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc. Perkin I*, 1574 (1975).

11. The relationship between 8 and 9 was established via a sequence of reactions similar to those described in reference 8.

12. The relative concentrations of 4: acid (TFA or HCOOH) and molar concentration 4 were held constant for all experiments.

13. C. F. Lane, *Synthesis*, 135 (1975).

14. To our knowledge this represents a new and general method for reducing carbinolamides to amides and lactams.

15. J. C. Hubert, J. B. P. A. Wijnberg, and W. N. Speckamp, *Tetrahedron*, **31**, 1437 (1975).

16. To our knowledge this is the first example of an acyliminium ion being used to alkylate an allylsilane.

17. For a review of ionic reductions with silanes see: D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 633 (1974).

18. For reduction of *N*-acyliminium ions with triethylsilane-TFA see: J. Auerbach, M. Zamose, and S. M. Weinreb, *J. Org. Chem.*, **41**, 725 (1976).

19. For the use of silanes as carbonium ion traps see: F. A. Carey and H. S. Tromper, *J. Am. Chem. Soc.*, **91**, 2967 (1969).

20. The cyclized products 5-9 are stable to the reaction conditions.

21. Previous work (ref. 7) suggests that ion 14 should be born as the E geometrical isomer. Isomerization of E-14 to Z-14 via an addition-elimination process should be possible under current reaction conditions. These factors make it difficult to enter the $13 \rightleftarrows 14$ manifold from the side of 14 in a meaningful way.

22. We do not know the relative rates of reduction of 13 and 14.

23. Financial support from the donors of The Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM27647-01) is gratefully acknowledged.

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