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THE 1-AZA-COPE REARRANGEMENT

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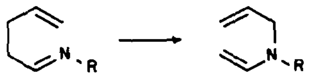
Abstract: N-Acyl-1-aza-1,5-dienes participate in the Cope rearrangement.

In contrast to 2-aza and 3-aza-Cope rearrangements,[1] the 1-aza-Cope rearrangement is not common.[2] One of the few examples of this reaction is the aza analog of the divinylcyclopropane rearrangement,[3] a variation of the Cope rearrangement. The primary reason for the few known examples of the 1-aza-Cope rearrangement is undoubtedly the unfavorable thermodynamic situation that exists for this reaction.[1a] For simple 1-aza-1,5-dienes (1, R=alkyl) the reactants are calculated to be about 7-10 kcal/mole more stable than the products.[4]



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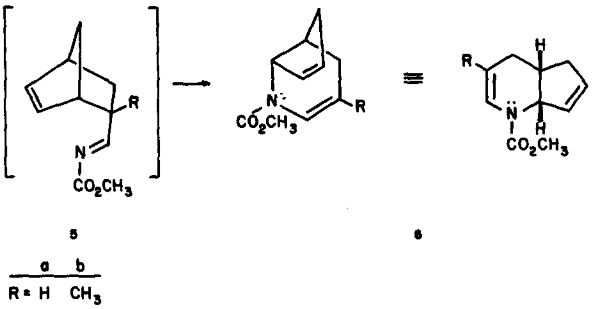
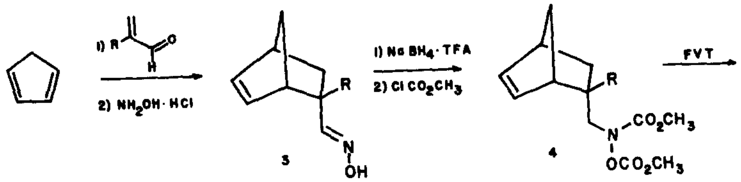
Because of a general interest in new pericyclic reactions and their application to problems in organic synthesis a program was initiated to investigate the 1-aza-Cope rearrangement. It was hypothesized that the large stabilization energy resulting from the interaction of the nitrogen lone pair of electrons with a carbonyl group[5] would be sufficient to induce N-acyl-1-aza-1,5-dienes (1, R = acyl) to undergo the Cope rearrangement. In addition, the electronegativity of the acyl group should lower the LUMO of the imine, allowing for a favorable HOMO-LUMO interaction in the transition state.[6] In order to test the above hypothesis the aza derivatives (5a and b) of the 5-vinylnorbornene ring system[7] were chosen for study. The synthesis of the N-acyl imine was initiated from the oxime derivatives of the cyclopentadiene Diels-Alder adducts. The hydroxamic acid derivatives 4a and b were prepared by reduction of the oximes 3a and b followed by bis acylation. Flash vacuum pyrolysis (FVT)[8] of the hydroxamic acid derivative 4b gave the pyrindine 6b[9] as the major product in 45% yield.[9]

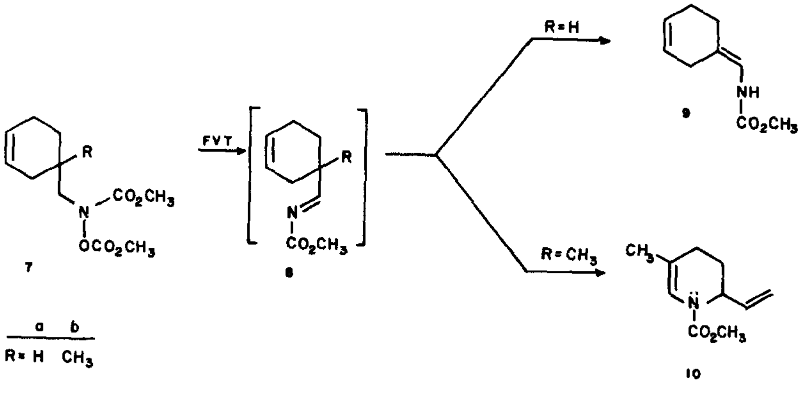
The aza-Cope rearrangement of the methyl derivative 5b was initially studied in order to





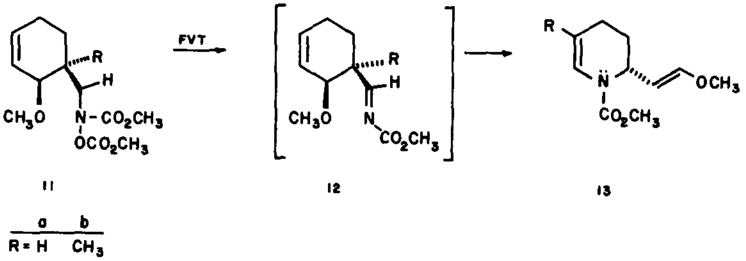
prevent any complications that could result from the facile rearrangement of the N-acyl imine to enamide.[10] Heating 4a to produce N-acylimine 5a, which has the possibility of the aza-Cope rearrangement as well as the isomerization to the enamide, gave the pyrindine derivative 6a in 40% yield.[9] This result, as well as the absence of the retro Diels-Alder reactions[12] of either precursor 4a or 5a, suggests that the Cope rearrangement of N-acyl-1,5-dienes is favorable and competitive with other thermal processes.[13]

The Cope rearrangement of 4-vinylcyclohexene is known to occur with great difficulty (E_a=52.1 kcal/mole)[14] compared to 1,5-hexadiene (E_a=35.5 kcal/mole).[13] The reluctance of the 4-vinylcyclohexene ring system to participate in the Cope rearrangement has been attributed to the reaction passing through a transition state possessing a boat geometry as part of the framework of the strained bicyclo[2.2.2]octane ring system.[15] A severe test for the 1-aza-Cope rearrangement would be the aza derivatives (8a and b) of 4-vinylcyclohexene. Flash vacuum pyrolysis of 7b gave the Cope rearranged product 10b in a 10% isolated yield. In contrast to the result observed previously on the aza derivative (5) of the 5-vinylnorbornene system, heating 7a gave the product 9 in 30% yield,[9] the result of a N-acylimine-enamide isomerization rather than the aza-Cope rearrangement.



The Cope rearrangement is known to be particularly sensitive to substituent effects.[15] For this reason and because the functionalized piperidines could have potential as synthetic intermediates, the 1-aza-Cope rearrangements of 12a and b were studied.

Piperidine 13b was obtained in a clean reaction (55% yield[9]) and at lower temperature (*ca.* 50°C) than was observed for the methyl substituted derivative 7b. In contrast to the unsubstituted derivative 7a, 11a also gave the 1-aza-Cope rearranged product 13a in 25% yield.[9] Although other products were also formed in the latter reaction, these results clearly suggest that the 1-aza-Cope rearrangement is facilitated by a methoxyl group on the 1-aza-1,5-diene.



In summary, N-acyl imines will participate in the 1-aza-Cope rearrangement providing one of the few examples of this reaction. The role of the N-acyl substituent is probably to provide a driving force for this reaction (amide formation) as well as facilitating HOMO-LUMO interaction in the transition state.

Because the 1-aza-Cope rearrangement produces a piperidine derivative containing an endocyclic enamine[16] with control of stereochemistry at the three tetrahedral centers within the six membered ring, the reaction has high potential in organic synthesis. Furthermore, a scheme was developed for preparing the reactants of the 1-aza-Cope rearrangement using the synthetically powerful Diels-Alder reaction. This allows for the preparation of relatively complex heterocycles from simple reactants. Thus, a short sequence, initiating with cyclopentadiene and acrolein, led to the *cis* pyrindine derivative 6[17].

REFERENCES AND FOOTNOTES

(1)(a) Heimgartner, H.; Hansen, H.-J In "Iminium Salts in Organic Chemistry"; Bohme, H.; Viehe, H.; Eds.; Wiley-Interscience: New York, 1979; Part 2 p 655. (b) Winterfeldt, E. *Fortschr. Chem. Forsch.*, 1971, *16*, 75 For reviews of selected Cope rearrangements see: (c) Overman, L. E.; *Angew. Chem., Intern. Ed.*, 1984 *23*, 579. (d)Lutz, R. P. *Chem. Rev.*, 1984, *84*, 205. (e)Gajewski, J. in "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981. (f) Rhoads, S. J.; Raulins, N. R. *Org. React (N. Y.)*, 1975, *22*, 1.

(2) The 1-aza-Cope rearrangement is the [3,3]-sigmatropic shift of 1-aza-1,5-dienes. The [3,3]-sigmatropic shifts of imidate esters[1] and imino vinyl ethers (Lipowitz, K. B.; Scarpone, S.; McCullough, D.; Barney, C. *Tetrahedron Lett.*, 1979, 2241) are more correctly considered aza-Claisen rearrangements since the driving force of the reaction is the formation of a carbonyl group.

(3) For a discussion of these reactions see Maier, G.; "Valenzisomerisierungen," Verlag Chemie GmbH: Weinheim, 1972 pp. 197ff.

(4) The greater stability of the 1-aza-1,5-diene 1 over the 3-aza-1,5-diene is due primarily to the C-C and C=N of the reactant being more stable than the C-N and C=C of the product. (For typical bond energies see Sandorfy, C. in "The Chemistry of the Carbon-Nitrogen Double bond", Patai, S. Ed,; Wiley-Interscience: New York, 1970, p. 1. and for the enamine resonance energy see Doering, W. von E.; Birladeanu, L.; Andrews, D. W.; Pagnotta, M. J. Am. Chem. Soc., 1985, 107, 428.) For a calculation of this rearrangement using enthalpy increments see reference 1a.

(5) Amide stablization energy can be estimated from amide rotational barriers to be about 15-20 kcal/mole (Testa, B. "Principles of Organic Stereochemistry," Marcel Dekker: New York, 1979, p.106.

(6) Delbecq, F.; Anh, N. T. Nouv. J. Chim., 1983, 7, 505.

(7) Because of strain and geometric constraints it was anticipated that this compound should be particularly reactive in the 1-aza-Cope rearrangement (see Burnier, J. S.; Jorgensen, W. L. J. Org. Chem., 1984, 49, 3001).

(8) The temperature of the reaction tube has been estimated to be approximately 500^{o}C. For recent reviews of the flash vapor phase thermolysis technique see: Wiersum, U. E. Recl. Trav. Chim. Pay-Bas, 1983, 101, 317 and 365.

(9) All yields are for products purified by flash chromatography. None of the yields of these reactions have been maximized. The structures of all new compounds reported have been fully characterized. The following is a typical procedure. To the oxime derivative 3 (5 mmol) in dry THF(2 mL) and cooled in an ice bath was added a solution of a sodium borohydride-trifluoroacetic acid complex (2.5 mmol) in 8 mL of dry THF. The reaction mixture was stirred for 10 min and methyl chloroformate (6 mmol) was added. The mixture was stirred for 6 h and was worked up by adding water, extracting with ether and drying the ether extracts with sodium sulfate. Removal of the ether in vacuo gave the N-acyl hydroxylamine derivative in 75% yield. Further treatment of this compound with methyl chloroformate and triethylamine in dry ether gave the diacylhydroxylamine derivative 4 in 95% yield. Evaporation of 4 through the pyrolysis apparatus gave the pyrindine 6 in 40-45% yield.

(10) Lenz, G. Synthesis, 1978, 489.

(11) In the all carbon Cope rearrangement a methyl group results in a lowering of the E_a of about 1.3 kcal/mole ("Chemical Kinetics", Bamford, C. H. and Tipper, C. F. H., eds.; Elsevier Scientific Publishing Company: Amsterdam, 1973, p 455.

(12) The activation energy for the retro Diels-Alder reaction of the cyclopentadiene-acrolien adduct is 33.6 kcal/mole (see reference 13).

(13) Willcott, M.. R.; Cargill, R. L.; Sears, A. B. Prog. Phy. Org. Chem., 1972, 9, 25.

(14)(a) Doering, W. von E.; Franck-Neumann, M.; Hasselmann, D.; Kaye, R. L. J. Am. Chem. Soc., 1972, 94, 3833.

(15) Gajewski, J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981, p174.

(16)(a) Stevens, R. V. Accounts Chem. Res., 1977, 10, 193. (b) Wenkert, E. ibid., 1968, 1, 78.

(17) A reduced pyrindine analogous to 6 was a key intermediate in the recent total synthesis of Streptazolin. Kozikowski, A. P.; Pyeong-uk, P. J. Am. Chem. Soc., 1985, 107, 1763.

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