Communications to the Editor

Diels-Alder Reaction of 1-Azadienes

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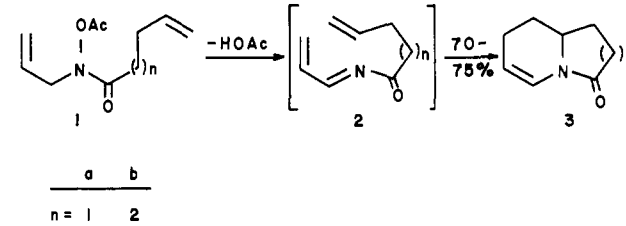
The Diels-Alder reaction has proven to be extremely valuable for the construction of carbocyclic rings. In one step, two new carbon-carbon bonds are formed, and the stereochemistry as well as the regiochemistry can be controlled by the proper choice of reactants. In principle, the Diels-Alder reaction should also be useful for the construction of heterocyclic compounds. The reaction of a diene and dienophile in which one of the carbon atoms of the π system has been replaced by nitrogen would result in a six-membered unsaturated nitrogen heterocycle.

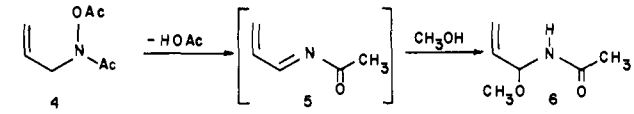
The Diels-Alder reactions of imines are well-known,[1] and the intramolecular version of this reaction has recently been applied to alkaloid total synthesis.[2] Although they have not been as extensively investigated, the Diels-Alder reactions of 2-aza-1,3-dienes are also known and well documented.[3] In contrast, there are only a few isolated reports[4] of little synthetic interest where 1-aza-1,3-dienes behave as dienes in the Diels-Alder reaction. In fact, some earlier claims have recently been reinvestigated and shown to be in error.[5] The 1-aza-1,3-dienes are apparently very reluctant participants in the Diels-Alder reaction. Reasons for the lack of reactivity of these compounds have been previously discussed.[6]

The Diels-Alder reaction of 1-aza-1,3-dienes would be of interest for synthetic chemistry since it produces an endocyclic enamine. These enamines have been long sought because of their value in alkaloid synthesis.[7] We anticipated that the Diels-Alder reaction of 1-azadienes, by analogy to imines,[1] would be possible if the nitrogen atom contained an acyl substitutent. The literature reveals that *N*-acyl-1-aza-1,3-dienes are rare compounds.[8] This is not surprising since the simpler *N*-acylimines are very reactive, frequently being generated only as transient intermediates.[1]

We report that heating *N*-acyl-*O*-acetyl-*N*-allylhydroxylamines (**1a,b**) in the gas phase produce, in addition to acetic acid, the indolizidine **3a** and quinolizidine **3b**.[9] We postulate that this

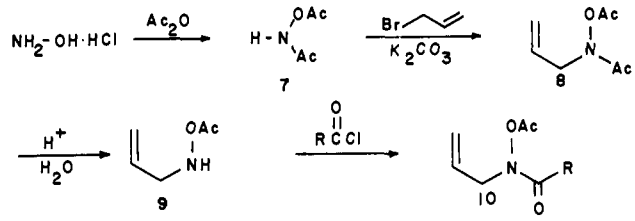


reaction proceeds by initial loss of acetic acid to give the *N*-acylazadienes **2a,b** which then undergo an intramolecular Diels-Alder reaction to give the observed products **3a,b**. To date we have not been able to directly observe the *N*-acyl-1-aza-1,3-dienes, even when the *N*-acyl function does not contain a dienophile. For example, heating *N,O*-diacetyl-1-allylhydroxylamine (**4**) gives acetic acid as the only well-characterized compound.



If **4** was heated and trapped in a flask containing methanol, the amide **6** was observed.[10] Since the addition of methanol to acylimines is known,[11] we believe this experiment provides further support for the existence of *N*-acyl-1-azadienes in these thermal reactions.

An advantage of this approach to nitrogen heterocycles is that the *N*-acyl-1-azadiene precursors are readily prepared from hydroxylamine in a few steps.[12]



Additional examples of this reaction are provided by **11** and **12**.[14] Heating these compounds in the gas phase gave the indolizidines **13** and **14**, respectively. The all "cis" stereochemistry for **13** is apparent from the ^{1}H NMR spectrum,[16] and the ster-

(1) For a recent and excellent reveiw of this reaction see: Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

(2) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073.

(3) (a) Wollweber, H. *Methoden Org. Chem. (Houben-Weyl)* **1970**, *Teil 3*, 1128-1137. (b) J. Hamer, "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967. (c) Chen, K. K.; Bradsher, C. K. *J. Org. Chem.* **1979**, *44*, 4680 and references cited therein.

(4) (a) See: Gladstone, C. M.; Daniels, P. H. and Wong, J. L. *J. Org. Chem.* **1977**, *42*, 1375 and the references cited therein. (b) See ref 3a,b.

(5) (a) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862. (b) Daniels, P. H.; Wong, J. L.; Atwood, J. G.; Canada, L. B.; Rogers, R. D. *J. Org. Chem.* **1980**, *45*, 435.

(6) See the discussion in ref 4a and 5a.

(7) For some examples, see: (a) Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78. (b) Stevens, R. V. *Ibid.* **1977**, *10*, 193. (c) Kuehne, M. E. *Synthesis* **1970**, 510.

(8) To our knowledge there are no examples of this functional group being characterized in the literature, although there are occasional reports of it being postulated as a transient intermediate. For recent examples, see: (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352. (b) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 587. (c) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 747.

(9) The analytical and spectral data for all new compounds are completely consistent with the proposed structures. In a typical procedure 98.2 mg of **1a** was evaporated through a hot tube previously described (Beeken, P.; Bonfiglo, J.; Hasan, I.; Piwinski, J.; Weinstein, B.; Zollo, K.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677). The pyrolysate was dissolved in ether and passed through a short column of potassium carbonate to remove the acetic acid. Removal of the ether gave 49.9 mg (73%) of **3a**.

(10) The structure of amide **6** was confirmed by reduction ($NaBH_4$-trifluoroacetic acid-benzene) to the known *N*-allylacetamide.

(11) For example, see: Baldwin, J. E.; Urban, F. J.; Cooper, R. D. G.; Jose, F. L. *J. Am. Chem. Soc.* **1973**, *95*, 2401.

(12) Compound **8** was prepared in 68% yield from the known[13] *N,O*-diacetylhydroxylamine and allyl bromide in dimethylformamide at room temperature (24 h) by using potassium carbonate as a base. Selective hydrolysis of **8** to give **9** was accomplished by using 6 N HCl at room temperature for 1 h (28%). Treatment of **9** with the appropriate acid chloride gave the desired azadiene precursors **10** (92%). None of the yields reported above have been optimized.

(13) Exner, O.; Horák, M. *Coll. Czeh. Chem. Commun.* **1959**, *24*, 2992.

(14) These compounds were prepared as described in ref 12 from the commercially available 3-cyclopentenylacetic acid and the known cinnamylacetic acid.[15]

(15) Farmer, E. H.; Hose, C. G. B. *J. Chem. Soc. II* **1933**, 962.

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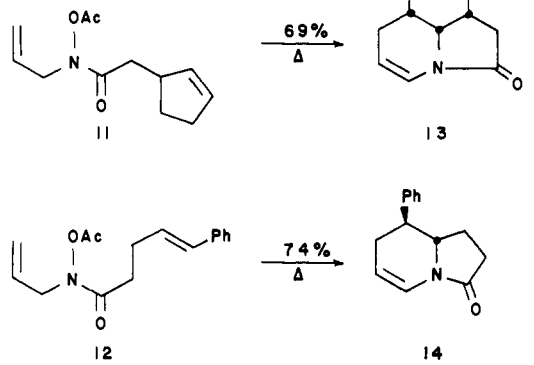
eochemistry of **14** is assumed since the configuration of the double bond in **12** was trans and only one isomer was produced in this reaction.



In summary, we have observed that *N*-acyl-1-azadienes can be prepared by the thermal elimination of acetic acid from *N*-acyl-*O*-acetyl-*N*-allylhydroxylamines and undergo intramolecular Diels–Alder reactions to give the indolizidine and quinolizidine ring systems. This reaction should be particularly useful for the preparation of alkaloids derived from these ring systems, since stereochemistry of substituents on the six-membered ring can be controlled by the proper choice of reactants and enamide functionality can be used for further structural elaboration. We are presently exploring the application of this reaction to the synthesis of the Nuphar and Dendrobatid alkaloids.

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(16) The ^{1}H NMR spectrum shows the bridgehead hydrogen α to the nitrogen atom as a triplet with a coupling constant of 4 Hz. The small coupling constant indicates coupling to only cis hydrogens. When trans hydrogens are adjacent to this hydrogen (e.g. **14**), considerably larger coupling constants are observed.

Asymmetric Reductions with 1,4-Dihydropyridines Contained in Chiral Macrocycles

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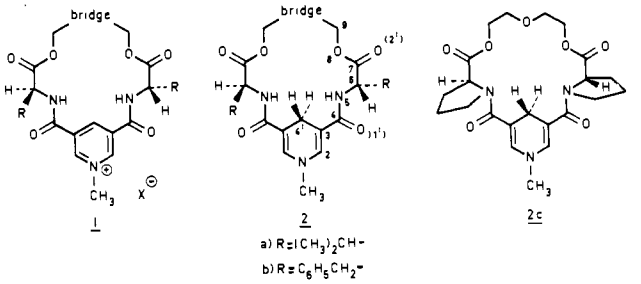
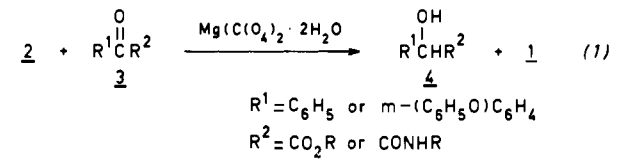
Activated carbonyl compounds at room temperature in the presence of Mg^{2+} ions are reduced to the corresponding alcohols by **2a** [bridge = $-(CH_2)_2O(CH_2)_2-$] in enantiomeric excesses ranging from 64 to 86% depending on the compound.[1] A ternary complex of **2a**, Mg^{2+}, and carbonyl substrate was suggested to be responsible for the reduction. We have now prepared structural analogues of **2a** in which the amino acid, in all cases but one having the L configuration (see Table I), and length and form of the bridge have been varied. The results of reductions (Table I) carried out with these analogues support and extend our previous observations and allow us to distinguish stereochemical features that govern the transfer of chirality.

Bridged pyridines were prepared in 50–70% yields by the synthetic route described earlier,[1,2] using the cesium salt method[3] for ring closure. Alkylation provides the bridged pyridinium salts (**1a–c**), which are reduced with $Na_2S_2O_4$ to **2a–c**. The yields

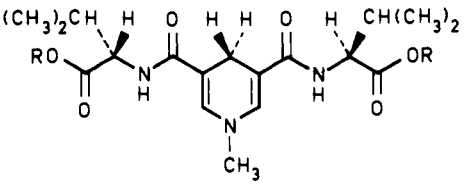


of the latter two reactions are nearly quantitative.[4] The reductions of ketones (**3**) to alcohols (**4**) shown in eq 1 and listed in Table



I proceed at 17–20 °C in acetonitrile in the presence of 1 equiv of $Mg(ClO_4)_2 \cdot 2H_2O$.[5,6] Tetrahydrofuran can be used as solvent with comparable results. Times for complete conversion are 1–2 days, although compounds with very long bridges or without a bridge react more slowly. The dihydropyridines (**2a,b**) are all believed to be optically pure.[7] The alcohols (**4**) were purified by using methods known not to lead to optical enrichment.[8]

In order to evaluate the effect of a cyclic structure in the bridged dihydropyridine on the enantiomeric excesses of **4**, the "open" compounds **5** were prepared. Results of reductions with these compounds are also given in Table I.



Good to excellent enantiomeric excesses of **4** are obtained for a wide range of bridges for **2a,b**.[9] Note especially the *consistent* formation of an excess of the *S* enantiomer of **4** (the relative priorities of the groups are the same in all cases allowing direct comparison). As expected the D enantiomer of **2a** [bridge = $-(CH_2)_6-$] affords the *R* enantiomer of ethyl mandelate (entry 11). The proline derivative (**2c**) is the one example (entry 16) so far examined that fails to transfer chirality. Another point of special interest is that the open derivatives **5** give the *R enantiomer* of ethyl mandelate in low enantiomeric excess.

(1) de Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.

(2) The synthetic approach involving protection of the amino acids as described in ref 1 has been replaced by a simpler synthesis more amenable for large scale work. The amino acid (40 mmol) is dissolved in 50 mL of 2 N NaOH, and the solution is cooled to ca. 5 °C. The diacid chloride of pyridine-3,5-dicarboxylic acid (20 mmol) in 50 mL dry CH_2Cl_2 is added dropwide to the vigorously stirred amino acid solution. The temperature is kept below 10 °C. The aqueous layer is acidified to pH 4–5 with formic acid and the bis-coupled products usually precipitate in 70–85% yield.

(3) See, for example: Kruizinga, W. H.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 286. Buter, J.; Kellogg, R. M. *Ibid.* **1980**, 466.

(4) All new bridged pyridines have been characterized completely by analytical and spectroscopic methods. Owing to instability some of the 1,4-dihydropyridines were characterized only by chromatographic methods and ^{1}H NMR spectroscopy.

(5) Smith, G. F.; Koch, E. G. *Z. Anorg. Chem.* **1935**, *223*, 17.

(6) The use of $Mg(ClO_4)_2$ has been pioneered by others. For examples, see: (a) Ohno, A.; Ikeguchi, M.; Kimia, T.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1978**, 328. (b) Gase, R. A.; Pandit, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 7059.

(7) Compound **2b** [bridge = $(CH_2)_2O(CH_2)_2-$] was digested in 5.7 N HCl for 24 h and the phenylalanine was assayed with L-amino acid oxidase; 99.8% of the theoretical amount of L-phenylalanine was detected by using this method.

(8) de Vries, J. G. Thesis, Groningen, 1979.

(9) For related work on asymmetric inductions, see references in ref 1. Also: (a) Baba, N.; Oda, J.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 815. (b) Baba, N.; Makino, T.; Oda, J.; Inouye, Y. *Can. J. Chem.* **1980** *58*, 387. (c) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. (d) Ohno, A.; Ushida, S.; Oka, S. *Tetrahedron Lett.* **1980**, 2969.

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