Thermally Induced Intramolecular Oxime Olefin Cycloadditions (IOOC) Leading to N-Bridgehead Systems. Stereochemistry and Molecular Mechanics Calculations[1]

Alfred Hassner* and Rakesh Maurya

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100, Israel

Albert Padwa* and William H. Bullock

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received August 23, 1990

The intramolecular oxime olefin cycloaddition (IOOC) of proline and pipecolinic acid derivatives proceeds thermally with a high degree of stereoselectivity to provide a new route to functionalized pyrrolizidines, indolizidines, or quinolizidines. The ring closure proceeds with simultaneous stereoselective introduction of three or four stereocenters. Molecular mechanics calculations have been refined to accurately predict not only which stereoisomer is preferred but also the syn and anti coupling constants in these tricyclic molecules.

Intramolecular dipolar cycloadditions have recently been of considerable synthetic and mechanistic interest.[2-10] Such reactions generate two new rings, one of which is a five-membered heterocyclic ring, that can be cleaved and can lead to stereospecific introduction of two functional groups. Hence, the stereochemical aspects of these intramolecular cycloadditions are of major importance. Among the most useful systems in this regard are the nitrile oxide olefin[11-18] and nitrone olefin cycloadditions.[19,20] Intramolecular nitrile oxide olefin cycloadditions (INOC) have shown considerable synthetic utility in natural products synthesis.[11-17] They proceed at room temperature but with a variable degree of stereoselectivity.[17] Intramolecular nitrone olefin cycloadditions often require higher temperatures but are usually more stereoselective.[3,19] Conspicuously absent among various nitrones employed until recently have been NH nitrones (2), which are tautomers of the more stable oximes (1).

Over the years there have been scattered examples of oxime olefin cycloadditions.[21-28] More recently, such reactions were shown to proceed by Michael addition of the oxime nitrogen to an acceptor olefin, presumably generating a nitrone intermediate, which underwent dipolar cycloaddition usually to the same olefin.[25,26] The few examples, where unassisted thermal intermolecular cycloaddition between an oxime and an olefin have been observed, did not involve stereochemical studies.[28-32] Recently, we reported on the intramolecular version of the oxime olefin cycloaddition and showed that the stereochemical results were quite promising (e.g. 1→3).[28] It has been assumed that such intramolecular oxime olefin cycloadditions (IOOC) proceed via an NH nitrone intermediate (2) formed by a proton transfer from oxygen to nitrogen in the oxime function.[28,33]

We report here on the utility of IOOC reactions in the synthesis of fused rings containing a bridgehead nitrogen

(1) Cycloadditions 46. For paper 45, see: Hassner, A.; Dehaen, W. *J. Org. Chem.* **1991**, *56*, 896.

(2) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2.

(3) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2. Tufariello, J. J.; Tegler, J. L.; Wong, S. C.; Ali, S. A. *Tetrahedron Lett.* **1978**, 1733. Tufariello, J. J.; Mullen, G. B. *J. Am. Chem. Soc.* **1978**, *100*, 3638. Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866.

(4) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1986**, 757.

(5) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 1688.

(6) Eguchi, S.; Furukawa, Y.; Suzuki, T.; Dondo, K.; Sasaki, T.; Honda, M.; Katayama, C.; Tanaka, J. *J. Org. Chem.* **1985**, *50*, 1895.

(7) Schwartz, M. A.; Willbrand, A. M. *J. Org. Chem.* **1985**, *50*, 1359.

(8) Kametani, T.; Huang, S. D.; Nakayama, A.; Hondu, T. *J. Org. Chem.* **1982**, *47*, 2328.

(9) Oppolzer, W. *Angew Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(10) Wovkulich, P. M.; Uskokovic, M. *J. Am. Chem. Soc.* **1981**, *103*, 3956.

(11) Stevens, R. V.; Christensen, C. G.; Cory, R. M.; Thorsett, E. *J. Am. Chem. Soc.* **1975**, *97*, 5940.

(12) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 6291.

(13) Confalone, P. N.; Pizzolato, G.; Confalone, D. L.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954.

(14) Kametani, T.; Huang, S. P.; Ihara, M. *Heterocycles* **1979**, *12*, 1183.

(15) Jager, V.; Buss, V.; Schwab, M. *Tetrahedron Lett.* **1978**, 3133.

(16) Curran, D. P. *J. Am. Chem Soc.* **1982**, *104*, 4024.

(17) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. Kozikowski, A. P.; Mugrage, B. B. *Tetrahedron Lett.* **1983**, 3705. Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z. B. *J. Am. Chem. Soc.* **1984**, *106*, 1845. Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301. Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1985**, *107*, 2569. Kozikowski, A. P.; Maloneyhuss, K. E. *Tetrahedron Lett.* **1985**, 5759.

(18) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C. Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277.

(19) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

(20) Padwa, A.; Schoffstall, A. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 2–128.

(21) Ochiai, M.; Obayashi, M.; Morita, K. *Tetrahedron* **1967**, *23*, 2641.

(22) Lablache-Combier, A.; Villaume, M. L. *Tetrahedron Lett.* **1968**, *24*, 6951.

(23) Winterfeldt, E.; Krohn, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 709; *Chem. Ber.* **1969**, *102*, 2346.

(24) Agosta, W. C. *J. Org. Chem.* **1961**, *26*, 1724. Huntress, E. H.; Leslie, T. E.; Hearon, W. M. *J. Am. Chem. Soc.* **1956**, *78*, 419.

(25) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125.

(26) Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978**, *31*, 2837. Grigg, R.; Gunaratne, H. Q.; Kemp, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 41. Grigg, R.; Jordan, M.; Tangthongkum, A. *Ibid.* **1984**, 47. Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325. Donegan, G.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1989**, *30*, 609. Grigg, R.; Dorrity, M. R. J.; Heaney, F.; Malone, J. F. M.; Rajvirongit, S.; Sridhararan, V.; Surendrakumar, S. *Tetrahedron Lett.* **1988**, *29*, 4323. Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumur, S.; Warnock, W. J. *Tetrahedron Lett.* **1990**, *31*, 559.

(27) Mihailovic, M. L.; Lorenc, L.; Maksimovic, Z.; Kalvoda, J. *Tetrahedron* **1973**, *29*, 2683; *Heterocycles* **1989**, *28*, 869.

(28) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, *29*, 5313. Hassner, A.; Maurya, R. *Tetrahedron Lett.* **1989**, *30*, 5803.

(29) Grigg, R. *J. Chem. Soc. Rev.* **1987**, *16*, 89. Grigg, R.; Thianpantangul, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 653.

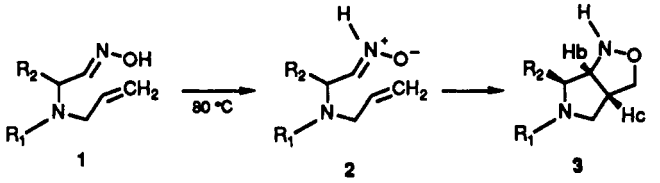
(30) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 1117.

(31) Heathcock, C. H.; Norman, M. H. *J. Org. Chem.* **1987**, *52*, 226.

(32) Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M.; Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1988**, *29*, 4169.

(33) Hassner, A.; Maurya, R. *Tetrahedron Lett.* **1989**, *30*, 2289.

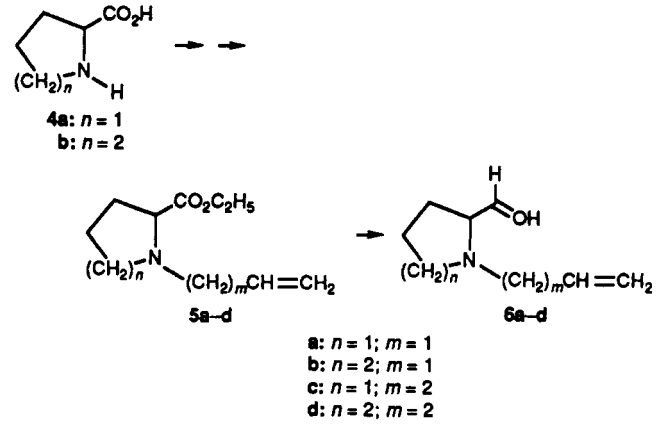
0022-3263/91/1956-2775$02.50/0



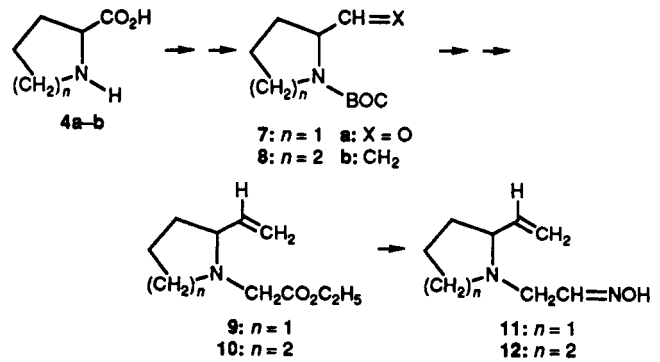
atom, such as pyrrolizidines, indolizidines, and quinolizidines, which occur widely in a number of alkaloids.[34-38] We also discuss the stereochemical aspects of these cyclizations and show how molecular mechanics calculations can be used and refined to predict the stereochemical outcome in such ring closures.

Results and Discussion

Substrates **6a–d**, that possess properly positioned aldoxime and alkene functions, were prepared from proline or pipecolinic acid **4** as shown below. Esterification and introduction of unsaturation on nitrogen by N-alkylation to produce **5** was followed by conversion of the carbethoxy function to an aldoxime using standard procedures. This versatile method allows attachment of various unsaturated side chains that can serve for generation of functionalized five- or six-membered (and possibly even larger) rings.

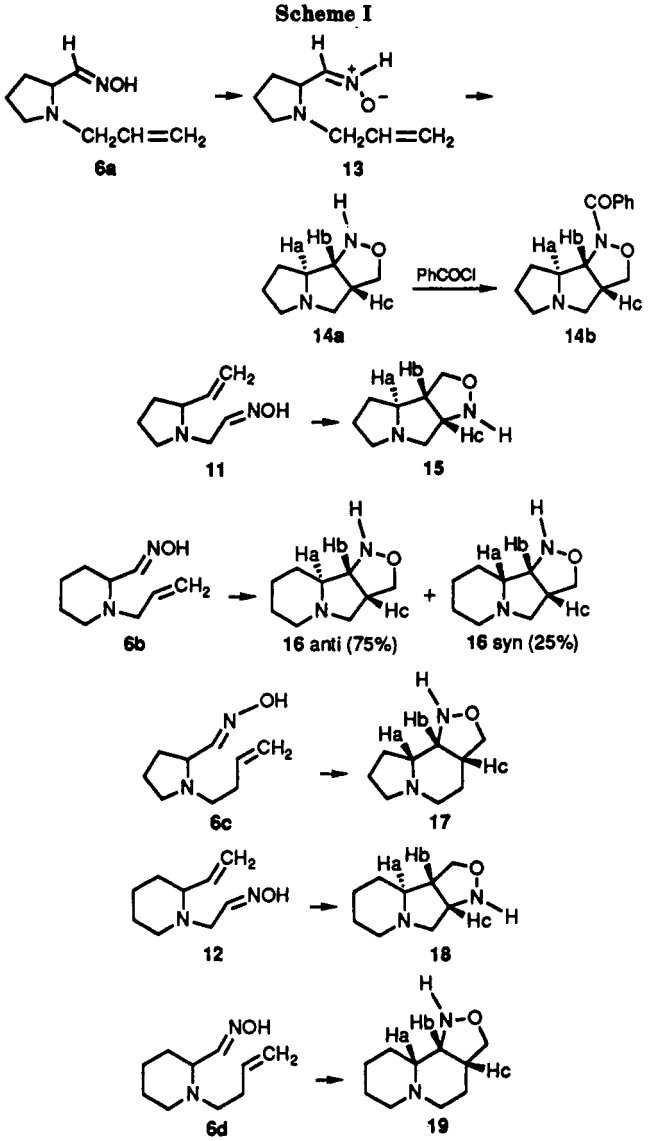


In an alternate approach, the isomeric unsaturated pyrrolidine or piperidine aldoximes **11**, **12** were prepared. To this end, we first synthesized 2-vinylpyrrolidine **7b** or its homologue **8b** by converting the carboxy function of the amino acid **4**, after esterification and *N*-*t*-BOC protection, into a vinyl substituent. This was accomplished



by reduction of the methyl ester to an aldehyde and Wittig olefination. Introduction of a two carbon aldoxime chain

Scheme I

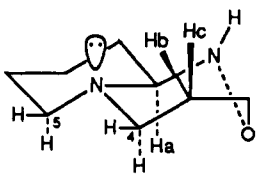


on nitrogen was carried out by alkylation with ethyl α-bromoacetate, after deprotection of the nitrogen atom in **7** or **8**. Reduction and oximation led to **11** or **12**. Though the thermal IOOC reaction can sometimes be accomplished at 80 °C,[28] the oxime olefins **6a–d**, **11**, and **12**, required heating in toluene at 180 °C in a sealed tube. Addition of metal salts did not facilitate the cycloaddition at lower temperature. In this manner the tricyclic pyrrolizidines **14** and **15**, the indolizidines **16**, **17**, and **18** and the quinolizidine **19** were isolated in 60–75% yield (see Scheme I). The intramolecular cycloaddition apparently proceeded via the NH nitrone tautomer (see **13**) which underwent a stereoselective 1,3-dipolar cycloaddition. It is noteworthy that the IOOC products **14**, **15**, **17–19**, were obtained stereochemically pure with no evidence in the NMR spectra or TLC of the crude products of any diastereomers. Indolizidine **16**, on the other hand, was obtained as a 75:25 mixture of anti:syn (H_a:H_b) isomers.

Ring closure to five-membered rings fused to the isoxazolidine, regardless whether part of a pyrrolizidine or of an indolizidine system, led mainly to the cis-anti isomer (see **14**, **16**, **18**), while formation of six-membered fused ring (either as part of an indolizidine or of a quinolizidine system) produced the cis–syn stereoisomer (see **17**, **19**). That the ring junction between the isoxazolidine and the newly formed five- or six-membered ring is always cis is indicated by coupling constants and an examination of

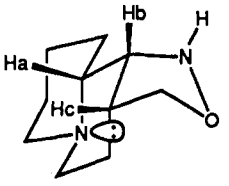
(34) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465.
(35) Zeller, E.; Grierson, D. *Heterocycles* **1988**, *27*, 1575.
(36) Gribble, G. W.; Switzer, F. L.; Soll, R. M. *J. Org. Chem.* **1988**, *53*, 3164.
(37) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325.
(38) Tokuyama, T.; Nishimori, N.; Shimada, A. *Tetrahedron* **1987**, *43*, 643.

molecular models. For instance, in the fused five-membered rings (14, 16, and 18), the coupling constant for the cis ring junction protons ($J_{b,c}$) is 8.5 Hz, indicative of a nearly eclipsed dihedral angle between H_b and H_c (see conformation 20). When the isoxazolidine is fused to a six-membered ring (as in 17 or 19), then $J_{b,c}$ = 4.5 Hz which is indicative of a gauche H_b and H_c relationship (see conformational drawing 21). Furthermore, the indolizidinoisoxazoline 17 or the quinolizidino compound 19 exhibited vicinal coupling constants ($J_{a,b}$) of 3 and 2.8 Hz, respectively, which is indicative of a gauche dihedral angle and therefore of syn stereochemistry between these protons. By contrast, the 8.5-Hz coupling constant between H_a and H_b in 16 or 18 indicates a dihedral angle of ca. 140° and therefore possesses anti stereochemistry. In pyrrolizidine 14 the 3-Hz coupling constant between H_a and H_b is consistent only with anti stereochemistry and a flattened center ring, since in a syn isomer the two hydrogens would be nearly eclipsed and give rise to a much larger coupling constant.



20 (corresponds to 16–anti)

$J(H_a, H_b)$ = 8.5 Hz
$J(H_b, H_c)$ = 8.5 Hz



21 (corresponds to 19–syn)

$J(H_a, H_b)$ = 3 Hz
$J(H_b, H_c)$ = 4.5 Hz

In indolizidines 16 and 18 the A/B ring junction is apparently trans, with an axial electron pair on nitrogen. It is known that the vicinal protons oriented anti to the axial electron pair on nitrogen absorb at about 1 ppm higher field than the corresponding syn protons or than protons adjacent to a nitrogen bearing an equatorial pair of electrons.[39] For instance, H_a and the axial protons at C_4 and C_5 in compound 16 (anti isomer) are both vicinal to the bridgehead nitrogen and absorb at higher field (1.69, 2.34, and 2.01 ppm, respectively) than the equatorial proton at C-5 (3.02 ppm) (see 20). By contrast, the pairs of protons vicinal to nitrogen in pyrrolizidine 14 (as the *N*-benzoyl derivative 14b) absorb close to each other (one pair at 3.07 and 3.14, the other at 3.13 and 2.67) and H_a at 3.54 ppm, indicative of an equatorial electron pair on nitrogen.

Compound 15 showed broad resonances, hence stereochemical assignments were very difficult. Inspection of molecular models gave no clear distinction between the two possible stereoisomers. In fact, this problem constitutes a typical example of a more general problem in the conformational analysis of flexible molecules. These molecules can adopt a large number of conformations, involving so many interactions, that the chemist is often more confused than guided when observing molecular models. Does a chemical reaction really occur via the conformation selected by the chemist? Molecular modeling should help in answering this question as it associates energies and conformations.

The molecular mechanics (MM) or force-field method has been shown to be a very reliable, fast, and efficient way of determining molecular properties.[40] There are several force fields for which extensive applications have been reported and are currently in use worldwide.[41-43] We wished to address two issues with such studies. First, we hoped to obtain some precise information on the dynamic properties of these bicyclic N-bridgehead systems in order to help rationalize the stereochemical results obtained from the IOOC reactions. Second, we wished to evaluate the applicability of the MM approach to molecules such as 14–19. While it is true that MM calculations have been applied to molecules that contain heteroatoms, such structures generally have been relatively simple heterocycles. As will be demonstrated below, the extensive flexibility of structures such as 14–19 make them more challenging targets for MM calculations.

We have used several different empirical force fields for the MM calculations. The first is the standard, full MM2 calculation using the Still–Steliou Model 2.94 program.[41] Global minima were found by making use of multiconformer generation in Model (TTY, Conf, Statistical, Coordinate) followed by Batch minimization using Bakmdl. The particular parameters used were those of the NOH (no hydrogen) field developed by Still and implemented by Steliou in the program Model.[44] The resulting lowest energy conformations were then submitted to MMX89 for the calculations of strain energies. Conformational analysis was also carried out using the Amber force field found in Model as well as MMX[42] and Sybyl. In all Sybyl calculations, the default van der Waals factors were employed. These multiplicative factors, VDW, serve to reduce the size of the effective van der Waals radii. The use of the two different molecular modeling software packages required a conversion program for translation of Sybyl and Model coordinate files.[45] Finally, the global Amber minima obtained from Bakmdl were submitted to AMPAC[46] (AM1 Hamiltonian) for a 1SCF determination of the heat of formation of the N-bridgehead system.

Structures within 3 kcal/mol of the lowest (global) energy conformer were retained for study. A Boltzmann distribution of the various conformers for each diastereomer at 25 °C was then established. The calculations indicate that there are several low-energy conformations for these N-bridgehead systems. For example, with compound 16 (anti) we found seven conformers within the global minimimum using Model's MM2 force field but only five conformers using the Amber force field. Consequently, not all of the low-energy structures generated by the MM2 procedure were found using the Amber force field.

We have used the molecular mechanics calculations to model energy differences in the diastereomeric transition states for the IOOC reaction. The stability of the diastereomeric cycloadducts was determined by calculation of their steric energies, the direct sum of the force-field increments. These steric energies represent the thermally averaged energies relative to the same molecule but with all bond lengths, bond angles, and torsional angles set to their strainless values and the atoms having van der Waals and electrostatic interactions corresponding to infinite separation.[47] We assume that the relative energy differ-

(39) Lambert, J. B.; Keske, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 620.
(40) For a review, see: Burkert, U.; Allinger, N. L. *Molecular Mechanics*: American Chemical Society: Washington, DC, 1982.
(41) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L.; Chang, S. H. M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.
(42) MMX is derived from MM2 (1977 Version QCPE 395) with the VESCF π-subroutines from MMP1 (QCPE 318). Gilbert, K. E.; Gajewski, J. J. Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.
(43) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230. Jorgenson, W. L.; Tirado-Rives, *J. Am. Chem. Soc.* **1988**, *110*, 1657.
(44) Still, W. C., unpublished results.
(45) The authors gratefully acknowledge Professor Kosta Steliou of the University of Montreal for providing us with MDLFMTS that effectively interchanges the formats and symbols used in SYBYL and Model coordinate files.
(46) Calculations were performed with the Ampac program (QCPE 506).
(47) Kao, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 975.

Table I. Calculation of J_{AB} for Cycloadduct 16 Based on Model's Force Field

Amber	energy	%	J_{AB}		J_{AB} calcd
1	17.14	61.84	9.2	=	5.69
2	17.88	17.83	8.8	=	1.57
3	18.16	11.02	0.9	=	0.10
4	18.55	5.79	1.1	=	0.06
5	18.84	3.52	0.9	=	0.03
					7.45 calcd
MM2	**energy**	**%**	J_{AB}		J_{AB} calcd
1	25.43	29.12	1.0	=	0.29
2	25.46	27.24	8.7	=	2.36
3	25.75	16.87	0.9	=	0.15
4	25.92	12.67	8.8	=	1.11
5	26.25	7.30	9.5	=	0.69
6	26.50	4.79	8.9	=	0.43
7	27.02	2.01	0.9	=	0.02
					5.05 calcd

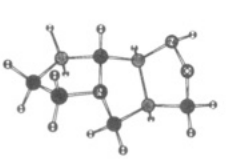
ences of the two lowest energy conformations of the diastereomeric cycloadducts will parallel the energy differences in the transition state. The product ratios can be explained by the calculated energy difference for the various reactive conformers. The lowest energy conformers obtained using Model's Amber force field were found to be most consistent with the NMR data and the observed diastereomeric distribution. Vicinal coupling constants were calculated using standard equations[48] and weighted by the Boltzmann populations of the conformers based on steric energies. As shown in Table II, the correlation is good. The calculated CH_α–CH_β coupling constant is very close to the experimentally measured value when the Amber force field is used. An example which clearly illustrates this can be gleaned from the determination of J_{AB} for the anti stereoisomer of cycloadduct **16** (Table I). The Model MM2 derived coupling constant (J_{AB} = 5.05 Hz) is not in line with the observed 8.5 Hz measured experimentally. The Amber derived coupling constant (J = 7.45 Hz), on the other hand, is in much better agreement. This was essentially the case with all the N-bridgehead systems examined. This observation indicates that the MM2 force field does not respond well to these types of compounds and that the Amber force field does. Thus, the anti conformational preference calculated by Model's MM2 force field is not due to steric repulsion but rather to charge repulsion from the heteroatoms in the syn form.

Comparison of the calculated steric energies of the anti and syn stereoisomers of the N-bridgehead systems (Table II) shows that the best fit of data comes from AMPAC heats of formation (1SCF) using the lowest energy conformer obtained from Model's Amber force field. For example, the calculations reveal a 2.40 kcal difference between the two diastereomeric transition states for isoxazolidine **14** but only a 1.16-kcal difference for isoxazolidine **16**. This accounts for the 3:1 mixture of isomers obtained from **14**, while a single diastereomer was produced from **16**. It should be noted that in both cases, the lower energy isomer corresponds to the anti diastereomer. The calculations also show that the lowest energy anti conformer of **15** is about 1.62 kcal lower in energy than the syn isomer. This fits with the generality that formation of a five-membered ring fused to the isoxazolidine should have the anti configuration.

The preferred stereoisomer in the formation of the six-membered-ring heterocycle (i.e. **17** and **19**) is syn whereas in the five-membered-ring amines (**14**–**16**; **18**) the anti isomer predominates. This coincides with the more stable isomer in each set (as revealed by Amber–AMPAC calculations (see Table II)) and thus can be explained on conformational grounds. In the six-membered-ring amine, transition state **22** with the oxime side chain in the equatorial position is expected to be more stable. The calculations of the energy relationships between the syn

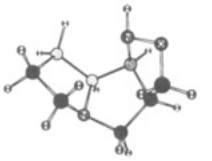
(48) Haasnoot, C. A. G.; de Leeue, F. A.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

Table II. Molecular Mechanics Calculations of the IOOC Reaction of Unsaturated Pyrrolidine or Piperidine Aldoximes



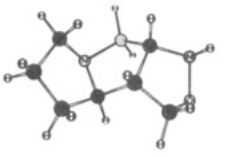
14 -anti

MM2	29.57 kcal		-3.05 kcal
Amber	22.99 kcal	Jab Calcd.=1.3 Hz	-1.05 kcal
MMX	37.74 kcal	Jab Exp.=3.0 Hz	-2.31 kcal
Sybyl	22.49 kcal		-0.30 kcal
Ampac	23.12 kcal		**-2.40 kcal**



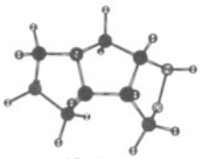
14 -syn

MM2	32.62 kcal	
Amber	24.04 kcal	Jab Calcd.=6.2 Hz
MMX	40.05 kcal	
Sybyl	22.79 kcal	
Ampac	25.52 kcal	



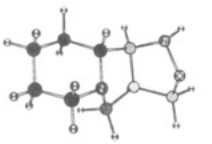
15 -anti

MM2	31.24 kcal		-1.53 kcal
Amber	24.37 kcal	Jab Calcd.=8.3 Hz	+2.12 kcal
MMX	39.65 kcal		+0.37 kcal
Sybyl	19.86 kcal		-3.79 kcal
Ampac	24.66 kcal		**-1.62 kcal**



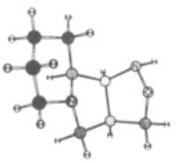
15 -syn

MM2	32.77 kcal	
Amber	22.25 kcal	Jab Calcd.=9.3 Hz
MMX	39.28 kcal	
Sybyl	23.65 kcal	
Ampac	26.28 kcal	



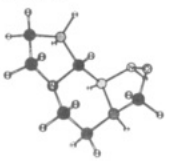
16 -anti

MM2	25.43 kcal		+2.04 kcal
Amber	17.13 kcal	Jab Calcd.=7.5 Hz	+0.25 kcal
MMX	33.99 kcal	Jab Exp.=8.5 Hz	+2.17 kcal
Sybyl	15.04 kcal		-1.71 kcal
Ampac	15.53 kcal		**-1.16 kcal**



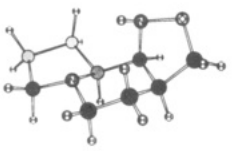
16 -syn

MM2	23.41 kcal	
Amber	16.88 kcal	Jab Calcd.=5.0 Hz
MMX	31.82 kcal	
Sybyl	16.75 kcal	
Ampac	16.69 kcal	



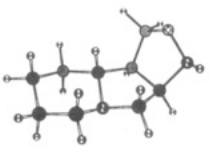
17 -anti

MM2	28.36 kcal		+1.23 kcal
Amber	17.47 kcal	Jab Calcd.=10.4 Hz	+0.06 kcal
MMX	32.38 kcal		+2.35 kcal
Sybyl	17.60 kcal		+0.54 kcal
Ampac	17.29 kcal		**+3.29 kcal**



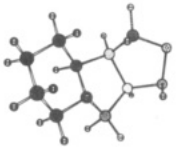
17 -syn

MM2	27.13 kcal	
Amber	17.41 kcal	Jab Calcd.=3.0 Hz
MMX	30.03 kcal	Jab Exp.=2.8 Hz
Sybyl	17.06 kcal	
Ampac	14.04 kcal	



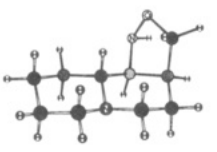
18 -anti

MM2	23.98 kcal		-0.87 kcal
Amber	17.19 kcal	Jab Calcd.=10.1 Hz	-1.17 kcal
MMX	32.02 kcal	Jab Exp.=8.5 Hz	-0.89 kcal
Sybyl	14.73 kcal		-0.66 kcal
Ampac	16.57 kcal		**-2.96 kcal**



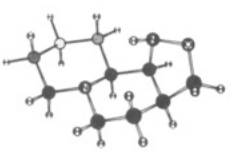
18 -syn

MM2	24.85 kcal	
Amber	18.36 kcal	Jab Calcd.=6.6 Hz
MMX	32.91 kcal	
Sybyl	15.39 kcal	
Ampac	19.53 kcal	



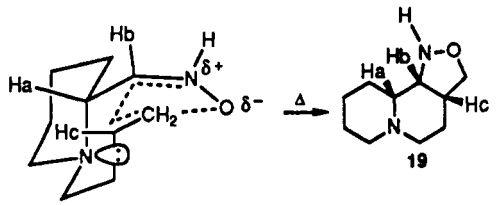
19 -anti

MM2	23.83 kcal		+1.38 kcal
Amber	11.68 kcal	Jab Calcd.=10.4 Hz	+1.45 kcal
MMX	27.93 kcal		+2.77 kcal
Sybyl	9.60 kcal		+0.69 kcal
Ampac	4.04 kcal		**+2.63 kcal**



19 -syn

MM2	22.45 kcal	
Amber	10.23 kcal	Jab Calcd.=2.9 Hz
MMX	25.16 kcal	Jab Exp.=2.8 Hz
Sybyl	8.91 kcal	
Ampac	1.41 kcal	



22 19

and anti isomers of **17** and **19** (3.29 and 2.63 kcal) are also in agreement with the isolation of a single product.

In conclusion, the work reported herein establishes the utility of the IOOC reaction for the construction of fused heteroisoxazolidines. Force field calculations help rationalize the observed stereoselectivity. Extensions of the scope and synthetic potential of these cyclizations are being further investigated.

Experimental Section

Methyl *N*-allyl-2-pyrrolidinecarboxylate (5a) was obtained by treatment of proline with 1:1 equiv of thionyl chloride in methanol at 0 °C. After evaporation of the solvent under vacuum, the crude hydrochloride salt was treated with 1 mmol each of triethylamine and allyl bromide in 1 mL of benzene. Stirring at 20 °C for 16 h and subsequently at 60 °C for 3 h followed by evaporation of the solvent and chromatography (SiO_2, ether–petroleum ether, 40:60) gave **5a** in 83% yield.

Methyl *N*-(3-Butenyl)-2-pyrrolidinecarboxylate (5c). To proline methyl ester (387 mg, 3 mmol) in 5 mL of benzene were added 300 mg of triethylamine and 405 mg (3 mmol) of 1-bromo-3-butene. The mixture was stirred at 20 °C for 16 h and evaporated under reduced pressure. Chromatography of the residue (silica gel, ether–petroleum ether, 30:70) gave 403 mg (73%) of **5c**: ^{1}H NMR δ 5.72–5.90 (m, C*H*=CH_2, 1 H), 4.95–5.12 (m, CH=CH_2, 2 H), 3.72 (s, CO_2CH_3, 3 H), 3.12–3.25 (m, 2 H), 2.70–2.82 (m, 1 H), and 1.75–2.03 (m, 4 H).

Methyl *N*-(3-Butenyl)pipecolinate (5d). To 2.0 g (15.5 mmol) of pipecolinic acid in 50 mL of dry methanol was added 300 mmol of $SOCl_2$, and the mixture was heated at reflux for 16 h. After evaporation of the solvent under vacuum, the crude hydrochloride salt was treated with 1 mmol each of triethylamine and 1-bromo-3-butene in 1 mL of benzene. Stirring at 20 °C for 16 h and subsequently at 60 °C for 3 h followed by evaporation of the solvent and chromatography (SiO_2, ether–petroleum ether, 5:95) gave 0.866 g of **5d**: ^{1}H NMR δ 5.68–5.85 (m, C*H*=CH_2, 1 H), 4.94–5.10 (m, C*H*=CH, 2 H), 3.73 (s, OMe, 3 H), 3.02–3.14 (m, 2 H), 2.54–2.66 (m, 1 H), 2.15–2.43 (m, 4 H), 1.56–1.85 (m, 6 H), and 1.28–1.43 (m, 1 H).

***N*-Allyl-2-pyrrolidinecarboxaldoxime (6a).** Diisobutylaluminum hydride (DIBAL) (1 mM in hexane, 5.54 mL) was added dropwise with a syringe to a solution containing 0.78 g (4.62 mmL) of methyl *N*-allylpyrrolidine-2-carboxylate (**5a**) in 12 mL of dry toluene at −78 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until TLC showed the absence of **5a** and was then quenched with 0.5 mL of methanol. The mixture was poured over 5% aqueous hydrochloric acid and ice, extracted with ether, washed with brine, and concentrated under reduced pressure.

The resulting crude aldehyde was treated with 1.0 g of hydroxylamine hydrochloride in 5 mL of water, 4 mL of 10% aqueous sodium hydroxide, and 0.5 mL of ethanol and heated on a water bath for 5 min. The mixture was diluted with water and extracted with ether. The extracts were washed, concentrated, and chromatographed (silica gel, diethyl ether–petroleum ether, 1:1) to yield 500 mg (70%) of oxime **6a** as a syn–anti mixture (major isomer): ^{13}C NMR δ 152.1 (d, C=N), 134.9 (d, CH=CH_2), 117.7 (t, CH_2=C), 63.4 (d, CHN), 56.7 (t, NCH_2CH=C), 53.1 (t, N=CH_2), 29.2 (t, CH_2), 22.3 ($CH_2CH_2CH_2$); ^{1}H NMR δ 9.31 (br, OH, 1 H), 7.31 (d, J = 8 Hz, CH=N), 5.8–5.9 (m, C*H*=CH_2, 1 H), 5.07–5.26 (m, CH=CH_2, 2 H), 3.32–3.49 (m, NCH_2CH=C, 1 H), 3.09–3.20 (m, CH_2N, 1 H), 2.88–3.06 (m, NCH_2CH=C, 1 H), 2.81, dd, J = 13 and 8.0 Hz, 1 H), 2.11–2.30 (m, 1 H), 1.94–2.10 (m, 1 H), and 1.62–1.93 (m, 3 H); (minor isomer) ^{13}C NMR δ 153.3 (d, C=N), 134.7 (d, *C*H=CH_2), 117.9 (t, CH_2=C), 63.37 (d, CHN), 58.8 (NCH_2CH=C), 57.8 (t, NCH_2), 28.5 (t), and 22.7 (t); ^{1}H NMR δ 9.31 (br, OH, 1 H), 6.85 (d, J = 7 Hz, 1 H); all other resonances as for major isomer.

***N*-Allyl-2-piperidinecarboxaldehyde Oxime (6b).** Methyl pipecolinate was treated with allyl bromide followed by reduction with DIBAL and then treatment with hydroxylamine hydrochloride as described for **6a** gave, after chromatography (SiO_2, ether–petroleum ether, 30:70), 210 mg (82%) of **6b**: ^{1}H NMR δ 9.22 (br, NOH, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 5.78–5.95 (m, C*H*=CH_2, 1 H), 5.07–522 (m, CH=CH_2, 2 H), 3.35 (ddt, J = 14.0, 5.0, and 1.0 Hz, NCH_2CH=CH_2, 1 H), 2.88–3.04 (2 H, m), 2.83 (dd, J = 14 and 8.0 Hz, NCH_2CH_2=CH_2, 1 H), 2.06 (td, J = 11.5 and 4.0 Hz, 1 H), 1.50–1.80 (5 H, m), 1.23–1.42 (m, 1 H); ^{13}C NMR: δ 152.6 (C=N), 134.0 (C=C), 118.0 (C=CH_2), 61.6 (d), 59.0 (CH_2C=C), 51.8 (CH_2N), 30.4 (t), 24.9 (t), and 23.1 (t).

***N*-(3-Butenyl)-2-pyrrolidinecarboxaldehyde Oxime (6c).** From 400 mg of **5c** and DIBAL as described for **6a** followed by oximation there was obtained, after chromatography on silica gel (ether–petroleum ether, 40:60), 220 mg (60%) of **6c** as a 19:1 mixture of anti:syn isomers (by NMR) which was purified by bulb-to-bulb distillation. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.28; H, 9.52. Found: C, 64.70; H, 9.80. ^{1}H NMR ($CDCl_3$) [**6c**-*anti* (major isomer)] δ 9.02 (br, NOH, 1 H), 7.32 (d, J = 8 Hz, CH=N, 1 H), 5.70–5.86 (m, C*H*=CH_2, 1 H), 4.92–5.13 (m, CH=CH_2, 2 H), 3.15–3.30 (m, 1 H), 3.00 (q, J = 8 Hz, 1 H), 2.72–2.90 (m, 2 H), 2.15–2.35 (m, 4 H), 1.70–2.05 (m, 4 H); [**6c**-*syn* (minor isomer)] δ 9.02 (br, NOH, 1 H), 6.86 (d, J = 6 Hz, CH=N, 1 H), and all other resonances as for major isomer; ^{13}C NMR δ (**6c**-*anti*) 152.0 (d), 136.8 (d), 115.7 (t), 64.1 (d), 53.7 (t), 53.3 (t), 32.7 (t), 29.1 (t), and 22.4 (t); (**6c**-*syn*) δ 153.4 (d), 136.1 (d), 115.8 (t), 64.14 (d), 54.7 (t), 53.3 (t), 32.7 (t), 28.4 (t), and 22.0 (t).

***N*-(3-Butenyl)-2-piperidinecarboxaldehyde Oxime (6d).** Reduction of 0.85 g (4.31 mmol) of **5d** in 12 mL of toluene with 8.6 mmol of DIBAL for 45 min as shown for **6a** followed by hydroxylamine treatment gave after chromatography (SiO_2, ether–petroleum ether, 40:60) 436 mg (56%) of oxime **6d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (br, NOH, 1 H), 7.92 (d, J = 8 Hz, CH=N), 6.20–6.38 (m, C*H*=CH_2, 1 H), 5.46–5.65 (m, CH=CH_2, 2 H), 3.42–3.60 (m, 2 H), 3.16–3.30 (m, 1 H), 2.60–2.92 (m, 4 H), 2.02–2.34 (m, 5 H), and 1.78–1.96 (m); ^{13}C NMR δ 152.5 (d), 136.2 (d), 115.7 (t), 61.2 (d), 55.1 (5), 51.7 (t), 30.4 (t), 29.8 (t), 25.0 (t), and 22.9 (t).

Ethyl (2-Vinylpyrrolidinyl)acetate (9). Methyl triphenylphosphonium bromide (3.73 g, 10.47 mml) was suspended in 50 mL of dry THF under argon and cooled to 0 °C. *n*-Butyllithium (6.98 mL of 1.5 M in hexane, 10.47 mmol) was added slowly, and the mixture was stirred at 0 °C and for 15 min at 20 °C for 30 min. The red solution was cooled to 0 °C, and 1.82 g (9.16 mml) of *t*-BOC-prolinal[49] in 5 mL of dry THF was added dropwise at 0 °C. Stirring was continued for 1 h and then at 20 °C for 16 h. The mixture was diluted with pentane and cooled to 0 °C, triphenylphosphine oxide was filtered off, and the filtrate was concentrated to give *N*-(*tert*-butoxycarbonyl)-2-vinylpyrrolidine (**7b**) as a thick air-sensitive syrup. Chromatography (SiO_2, hexane–ethyl acetate, 15:5) yielded 0.97 g (54% overall) of **7b**, an unstable liquid that was used immediately in the next step.

Trifluoroacetic acid (TFA) (0.5 mL) was added dropwise under an argon atmosphere to 400 mg of **7b** at 0 °C. The mixture was stirred at 20 °C for 1 h, the excess TFA was evaporated in vacuum at room temperature, and the residue was dissolved in 5 mL of acetone. To this solution at 0 °C was added 2 g of dry K_2CO_3 and dropwise 1.0 g (6 mmol) of ethyl bromoacetate. The mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. Evaporation of the acetone, dilution with 20 mL of water, extraction with ether, workup, and chromatography (SiO_2, ether–petroleum ether, 20:80) gave 200 mg (54% yield) of **9**: ^{1}H NMR δ 5.62–5.80 (m, C*H*=CH_2, 1 H), 5.08–5.24 (m, CH_2=CH, 2 H), 4.1–4.28 (m, OCH_2CH_3, 2 H), 3.53 (d, J = 16 Hz, NCH_2CO_2Et, 1 H), 3.31 (dt, J = 8.0 and 3.0 Hz, 1 H), 3.01 (d, J = 16 Hz, NCH_2CO_2Et, 1 H), 1.61–2.05 (m, 6 H), and 1.27 (t, J = 7 Hz, 3 H).

(49) Miles, N. J.; Peter, G. S.; Konnewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299.

1-(2-Vinylpyrrolidinyl)acetaldoxime (11). The ester **9** (200 mg, 1.09 mml) in 2 mL of tolune was reduced with 1.8 mmol of DIBAL as indicated for **6a** to give after chromatography (SiO_2, ether–petroleum ether, 40:60), 80 mg (48%) of **11** as an oil containing a 79:21 mixture of anti:syn oximes: ^{1}H NMR [**11**-*anti* (major)] δ 7.48 (dd, J = 8.0 and 5.0 Hz, CH=N, 1 H), 5.65–5.82 (m, C*H*=CH_2, 1 H), 5.05–5.25 (m, CH=CH_2, 2 H), 3.52 (dd, J = 14 and 4.5 Hz, NCH_2CH=N, 1 H), 3.10–3.32 (m, 1 H), 2.90 (dd, J = 14.0, 7.0 Hz, NCH_2CH=N, 1 H), 2.75–2.85 (m, 1 H), 2.18–2.32 (m, 1 H), and 1.50–2.06 (m, 5 H); [**11**-*syn* (minor)] δ 6.90 (dd, J = 4.5 and 3.0 Hz, NCH_2CH=N, 1 H), 5.65–5.82 (m, C*H*=CH_2), 5.05–5.25 (m, CH=CH_2, 2 H), 3.62 (dd, J = 14.0 and 3.5 Hz, NCH_2CH=N), 3.10–3.32 (m, 1 H), 2.90 (dd, J = 14.0 and 7.0 Hz, NCH_2CH=N, 1 H), 2.75–2.85 (m, 1 H), 2.18–2.32 (m, 1 H), and 1.50–2.06 (m, 5 H). Anal. Calcd for $C_8H_{14}N_2O$: C, 62.34; H, 9.09. Found: C, 62.60; H, 9.23.

***N*-(*tert*-Butoxycarbonyl)-2-vinylpiperidine (8b).** Pipecolinic acid **4b** (2.0 g) was converted to methyl *N*-(*tert*-butoxycarbonyl)pipecolinate using first methanol and thionyl chloride and then triethylamine (1:1 equiv) and chloro *tert*-butyl carbonate (1.2 equiv) as shown for **5d**. The crude ester carbamate 3.2 g (13.16 mmol) was reduced with 2 molar equiv of DIBAL at −78 °C as shown for **6a**. Workup with 1 M aqueous sodium potassium tartrate and ether extraction provided the crude aldehyde **8a** (2.8 g, 13.1 mmol). The latter was immediately reacted with methyltriphenylphosphonium bromide (19.7 mmol) and *n*-butyllithium (19.7 mmol) at 0 °C as described for **7b**, to give after chromatography (SiO_2, ether–petroleum ether, 5:95), 1.5 g (54%) of **8b** as an oil. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.25; H, 9.95. Found: C, 68.81; H, 10.10. ^{1}H NMR δ 5.75 (ddd, J = 14.5, 10.5, and 4.0 Hz, C*H*=CH_2, 1 H), 4.98–5.22 (m, CH_2=CH, 2 H), 4.78 (br s, 1 H), 3.94 (br d, J = 14 Hz, 1 H), 2.82 (td, J = 12.0 and 3.0 Hz, 1 H), 1.32–1.77 (m, 8 H), and 1.45 (s, CH_3, 9 H).

1-(2-Vinylpiperidinyl)acetaldoxime (12). Ethyl 1-(2-vinylpiperidinyl)acetate was first prepared from 211 mg (1 mmol) of **8b** and 1 mL of TFA then with 1 mmol of ethyl bromoacetate as shown for **9**. After chromatography (SiO_2, ether–petroleum ether, 10:90) 125 mg of the acetate (63%) was obtained: ^{1}H NMR δ 5.65–5.83 (m, C*H*=CH_2, 1 H), 5.03–5.24 (m, CH_2=CH, 2 H), 4.15 (q, J = 7 Hz, 2 H), 3.46 (d, J = 17 Hz, CH_2CO_2Et, 1 H), 3.14 (d, J = 17 Hz, CH_2CO_2Et, 1 H), 2.8–3.0 (m, 2 H), 2.28–2.4 (m, 1 H), 1.2–1.8 (m, 8 H), and 1.26 (t, J = 7 Hz, 1 H).

DIBAL reduction of 125 mg (0.63 mmL) of the foregoing ester followed by treatment with hydroxylamine as described for **6a** led after chromatography (SiO_2 ether–petroleum ether, 80:20) to 63 mg (59%) of **12**, mp 81–82 °C, as a 4:1 mixture of anti and syn isomers by NMR: ^{1}H NMR δ [**12**-*anti* (major)] 7.46 (dd, J = 5.8 Hz, CH_2-CN=N, 1 H), 5.70–5.88 (m, C*H*=CH_2, 1 H), 5.05–5.24 (m, CH=CH_2, 2 H), 3.50 (dd, J = 5, 14 Hz, CH_2CH=N, 1 H), 2.94 (dd, J = 8, 14 Hz, CH_2CH=N, 1 H), 2.90–3.02 (m,1 H), 2.68 (dt, J = 10.0 and 3.0 Hz, 1 H), 2.09 (dt, J = 10.5 and 4.0 Hz, 1 H), 1.20–1.79 (m, 6 H); [**12**-*syn* (minor)] δ 6.87 (dd, J = 3.5 Hz, CH_2C*H*=N, 1 H), 5.70–5.88 (m, C*H*=CH_2, 1 H), 5.05–5.24 (m, $CHCH_2$, 2 H), 3.63 (dd, J = 16.5 and 3.0 Hz, CH_2CH=N, 1 H), 3.17 (dd, J = 16.5 and 5.0 Hz, CH_2CH=N, 1 H), 2.90–3.02 (m, 1 H), 2.68 (dt, J = 10 and 3.0 Hz, 1 H), 2.09 (dt, J = 10.5 and 4.0 Hz, 1 H), 1.20–1.79 (m, 6 H); ^{13}C NMR [**12**-*anti* (major)] δ 149.1 (d), 140.8 (d), 116.7 (t), 66.6, 53.8, 52.7, 53.1, 24.5, and 23.6; [**12**-*syn* (minor)] δ 149.6 (d), 140.3 (d), 117.1 (t), 67.0, 53.6, 51.2, 33.0, 25.4, and 23.6; MS m/e (CI) 169 (100, MH^+), 151 (4, M − OH), 124 (5, M − (CH=NOH)).

Intramolecular Oxime Olefin Cycloaddition (IOOC). General Procedure. Synthesis of 1-Benzoyl-1,1a,3,3a-tetrahydropyrrolizidino[3,2-*c*]isoxazole (14b). A solution containing 50 mg (0.324 mmol) of oxime **6a** in 5 mL of dry toluene was heated in a sealed tube at 180–185 °C for 18 h, with TLC monitoring every 6 h until oxime **6a** had been consumed. The solution was poured onto a column of alumina (packed in chloroform), the product was eluted with chloroform, and 1,1a,3,3a-tetrahydropyrrolizidino[3,2-*c*]isoxazole (**14a**) (30 mg, 60%) was obtained as a light yellow oil upon evaporation of the solvent: ^{1}H NMR ($CDCl_3$) δ 4.85–5.54 (br s, NH, 1 H), 3.58–4.00 (m, 2 H), 3.15–3.33 (m, 2 H), 2.81–3.14 (m, 3 H), 2.50–2.76 (m, 1 H), and 1.52–2.18 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ all broad peaks 77.3, 71.8, 71.1, 57.9, 52.9, 48.6, 29.1, 24.2; MS m/e (EI) ($C_8H_{14}N_2O$, MW 154) 155 (12, MH^+), 154 (5), 136 (25), 125 (11), 124 (98), 123 (100), 108 (39), 96 (79), and 81 (22). Anal. Calcd for $C_8H_{14}N_2O$: C, 62.33; H, 9.09. Found: C, 62.47; H, 9.41.

To a solution of **14a** (30 mg, 0.194 mmol) in 0.5 mL of pyridine, cooled to 0 °C, was added 0.1 mL of benzoyl chloride. The mixture was stirred for 1 h, the solvent was removed in vacuum, and ether was added. The resulting solution was washed with brine and chromatographed (SiO_2, chloroform–methanol, 95:5) to afford 30 mg (60%) of the *N*-benzoylisoxazolidine (**14b**): ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2 H), 7.44 (m, 3 H), 4.80 (dd, J = 8.5 and 3.0 Hz, 1 H), 3.94 (dd, J = 8.5 and 2.0 Hz, 1 H), 3.85 (dd, J = 8.5 and 6.0 Hz, 1 H), 3.54 (ddd, J = 8.0, 6.0, and 3.0 Hz, 1 H), 3.36 (dddd, J = 8.5, 7.5, 6.0, and 2.0 Hz, 1 H), 3.14 (dd, J = 12 and 7.5 Hz, 1 H), 3.07 (dd, J = 12 and 6.0 Hz, 1 H), 3.13 (ddd, J = 10.5, 6.0, and 2.5 Hz, 1 H), 2.67 (dt, J = 10.5 and 7.0 Hz, 1 H), 2.24 (m, 1 H), and 1.8–2.0 (3 H, m); MS m/e ($C_{15}H_{18}N_2O_2$, MW 258) 259 (12.06, MH^+), 257 (2, $(M-1)^+$), 228 (26), 173 (23), 153 (9), 151 (85), 123 (84), 108 (87), 105 (100), 83 (60.5); ^{13}C NMR δ 169.4 (C=O), 133–127.9 (4 peaks aromatic), 74.7 (t), 72.0 (d), 67.8 (d), 57.2 (t), 53.4 (t), 46.3 (d), 29.6 (t), and 21.7 (t).

1,1a,3,3a,4,5,6,7,8,8a-Decahydropyrrolo[1,2-*a*]isoxazolo-[3,4-*c*]pyridine (17). From 100 mg (0.595 mmol) of **6c** in 8 mL of toluene at 185–190 °C for 10 h, as described for **14b**, was obtained after chromatography, 74 mg (74%) of **17**: ^{1}H NMR δ 5.96 (NH), 3.93 (dd, J = 7.0 and 5.5 Hz, 1 H, CH_2O), 3.75 (dd, J = 7.0 and 1.0 Hz, CH_2O, 1 H), 3.45 (dd, J = 4.5 and 3.0 Hz, C*H*NH), 3.06 (dm, J = 9.0 Hz, 1 H, CH_2N, 5-ring), 3.02 (ddd, J = 11.5, 3.5, and 3.5 Hz, 1 H, CH_2N, 6 ring), 2.42 (ddddd, J = 10, 6.0, 5.5, 4.5, and 1 Hz, 1 H, C*H*CH_2O), 2.34 (dd, J = 9.5, 6.5, and 3 Hz, 1 H, CHN), 2.06 (ddd, J = 9.0, 9.0, and 9.0 Hz, 1 H, CH_2N, 5-ring), 2.01 (ddd, J = 11.5, 11.5, and 3.5 Hz, 1 H, CH_2N, 6-ring), 1.6–1.9 (m, 6 H); ^{13}C NMR δ 74.8, 62.4, 60.3, 54.0, 51.5, 41.2, 27.2, 26.9, and 20.8. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59. Found: C, 64.06; H, 9.24.

1,1a,3,3a,4,5,6,7,8,8a-Decahydropyridino[1,2-*a*]isoxazolo-[3,4-*c*]pyrrole (16). From 45 mg (0.267 mmL) of **6b** in 5 mL of toluene at 110 °C for 24 h as described for **14b** was obtained, after chromatography (Al_2O_3, petroleum ether–chloroform, 1:1), 34 mg of **16** (75%) as two isomers in 3:1 ratio. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.13; H, 9.37; N, 16.44. MS m/e (CI) 169 (100, MH^+), 137 (22.5), 122 (69); ^{1}H NMR [**16**-*anti* (major)] δ 3.94 (dd, J = 9.0 and 1.0 Hz, CH_2O, 1 H), 3.62 (ddd, J = 8.5, 8.5, and 4.5 Hz, CHNH), 3.42 (dd, J = 9.0 and 6.5 Hz, CH_2O, 1 H), 3.33 (dd, J = 8.5 and 8.5 Hz, $CHCH_2N$, 1 H), 3.09 (dddd, J = 8.5, 8.5, 8.5, and 6.5 Hz, C*H*CH_2O, 1 H), 3.01 (ddd, J = 11.0, 4.0, and 3.0 Hz, CH_2CH_2N, 1 H), 2.00 (ddd, J = 12.5, 11.0, and 3.0 Hz, CH_2CH_2N, 1 H), 1.98 (dd, J = 8.5 and 8.5 Hz, $CHCH_2N$, 1 H), 1.69 (ddd, J = 11, 8.5, and 2.5 Hz, NC*H*CH, 1 H), 1.60 (m), 1.50 (m); ^{13}C NMR δ 75.7 (t, CH_2O), 71.2 (d), 66.6 (d), 60.3 (t, CH_2N), 52.9 (t, CH_2N), 46.1 (d), 29.9 (t), 25.1 (t), and 24.2 (t); [**16**-*syn* (minor)] δ broad lines; ^{13}C NMR δ 78.2 (t, CH_2), 66.3 (br), 58.9 (br), 53.1 (br), 26.1 (t), and 24.4 (t).

(1a,3a-*cis*-1a,9a-*syn*)-1a,3,3a,4,5,6,7,8,9,9a-Decahydro-1*H*-pyridino[1,2-*a*]isoxazolo[3,4-*c*]pyridine (19). From 175 mg (0.96 mmol) of oxime **6d** in 10 mL of toluene at 180–185 °C for 8 h and chromatography as described for **14** was obtained 120 mg (69%) of **19** as an oil: ^{1}H NMR δ 3.89 (dd, J = 7.0 and 5.5 Hz, 1 H, CH_2O), 3.70 (dd, J = 7.0 and 1.0 Hz, 1 H, CH_2O), 3.17 (dd, J = 4.5 and 3.0 Hz, 1 H, CHNH), 2.83 (ddd, J = 12, 11.5, and 4.0 Hz, 1 H, CH_2N, A ring), 2.70 (ddd, J = 12.0, 3.5, and 3.5 Hz, 1 H, CH_2N, B ring), 2.41 (ddddd, J = 10.5, 8.0, 5.5, 4.5, and 3.7 Hz, 1 H, CH_2CHCH_2), 2.24 (ddd, J = 11.5, 3.0, and 2.5 Hz, 1 H, CHN), 2.04 (dd, J = 8.0 and 3.5 Hz, 1 H, CH_2CH_2CH), 1.97 (ddd, J = 12, 11.5, and 3.5 Hz, 1 H (ax), CH_2N, A ring), 1.75 (ddd, J = 4.0, 4.0, and 3.5 Hz, 1 H, $CH_2CH_2CH_2$), 1.70 (dd, J = 10.5 and 3.5 Hz, 1 H, CH_2CH_2CH), 1.22 (m), 1.49 (m), 1.51 (m), 1.64 (m), and 1.69 (m); ^{13}C NMR δ 74.6, 62.7, 60.9, 56.5, 55.3, 41.0, 30.6, 26.3, 25.7, and 25.0; MS m/e (EI) 182 (23, M^+), 152 (31), 151 (75), 150 (27), 136 (85), 135 (35), 134 (18), 123 (20), 96 (100).

(1a,3a-*cis*-3a,4a-*anti*)-1,1a,3,3a,4,4a,5,6,7,8-Decahydropyridino[1,2-*a*]isoxazolo[4,3-*c*]pyrrole (18). From 30 mg of oxime **12** in 5 mL of toluene heated in a sealed tube at 180–185 °C for 3 h after chromatography (as described for **14**) resulted 24 mg (80%) of **18**: ^{1}H NMR δ 5.1 (NH), 4.09 (ddd, J = 9.5, 8.5, and 7.5 Hz, CH_2C*H*N), 3.95 (dd, J = 9.0 and 0.5 Hz, CHO), 3.37 (dd, J = 9.5 and 8.0 Hz, NCH_2CH), 3.32 (dd, J = 9.0 and 6.0 Hz, CHO), 3.03 (ddd, J = 11.5, 4.0, and 4.0 Hz, CH_2N), 2.70 (ddd,

J = 8.5, 6.0, and 0.5 Hz, C*H*CH_2O), 2.06 (dd, J = 9.5 and 7.5 Hz, NCH_2CH), 2.03 (ddd, J = 11.5, 5.0, and 3.0 Hz, CH_2N), 1.70 (ddd, J = 10.5, 8.5, and 2.5 Hz, NC*H*CH), 1.54 (ddd, J = 11.5, 4.0, and 3.0 Hz, CH_2), 1.6–1.9 (m, 3 H), and 1.2–1.3 (m, 2 H); ^{13}C NMR: δ 74.5 (t), 69.0 (t), 63.2 (d), 60.9 (t), 54.8 (d), 52.4 (t), 30.5 (t), 25.1 (t), 24.3 (t); MS m/e (EI) ($C_9H_{16}N_2O$) 168 (m, 87), 167 (M – 1, 23), 150 (M – H_2O, 7), 137 (M – CH_2OH, 100), 122 (69), and 110 (89).

Acknowledgment. Support of this research by Grant 87-00299 from the United States–Israel Binational Science Foundation is gratefully acknowledged. A.P. acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are grateful to Dr. H. E. Gottlieb for help with the NMR spectra.

Formation and Electrophilic Reactions of Benzeneselenenyl *p*-Toluenesulfonate. Preparation and Properties of Addition Products with Acetylenes

Thomas G. Back* and K. Raman Muralidharan

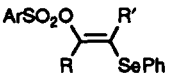
Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Received October 2, 1990

Benzeneselenenyl *p*-toluenesulfonate (**1**) was generated in situ by the reaction of silver *p*-toluenesulfonate with benzeneselenenyl chloride in acetonitrile. The reagent reacted with acetylenes by electrophilic 1,2-addition to afford the β-(phenylseleno)vinyl *p*-toluenesulfonates **2–12**, generally in high yield. The latter were formed preferentially by anti addition, but with poor regioselectivity, unless a strongly orienting group (e.g., phenyl) was present. Selenenyl sulfonate **1** was also unexpectedly produced via radical pathways by heating *p*-toluenesulfonic acid with AIBN in the presence of diphenyl diselenide, or from the pyrolysis of sulfinyl sulfone **15** with the diselenide. The regioisomeric adducts **3** and **4** were prepared from **1** and 1-decyne, and both underwent elimination with potassium *tert*-butoxide to afford the acetylenic selenide **19** initially, which isomerized to a 6:1 mixture of the propargylic and allenic selenides **20** and **21** upon further equilibration. A Fritsch–Buttenberg–Wiechell rearrangement is proposed for the elimination of **4**. The syn elimination of the selenoxide of **4** required forcing conditions and afforded only ca. 20% of the corresponding allenic sulfonate **22**. The electrophile **1** induced the efficient cyclization of 5-hexen-1-ol and 4-pentenoic acid to the corresponding pyran **24** and lactone **25**, respectively. It failed to cyclize alkynols, but afforded the lactones **28** and **29** from 4-pentynoic acid in low yield.

The reactions of electrophilic selenium compounds are both synthetically important and mechanistically interesting.[1] The majority of such species are selenenyl halides or pseudohalides (RSeX, where X = a leaving group) that are formally related to selenenic acids (RSeOH). For instance, selenenyl chlorides (RSeCl) and bromides (RSeBr) and diselenides (RSeSeR) are well-known, often commercially available compounds, with numerous applications. Examples of less frequently encountered selenenic electrophiles include benzeneselenenyl acetate (PhSeOAc)[2] and trifluoroacetate,[2j,3] selenocyanates (RSeCN),[4] benzeneselenenyl fluoride (PhSeF)[5] and iodide (PhSeI),[6] *N*-(phenylseleno)phthalimide[7] and -succinimide,[7a,8] sele-

Table I.[a] **Preparation, from RC≡CR′, of**



no.	R	R′	method[b]	yield,[c] %
2	H	H	A	51
3	n-C_8H_{17}	H	A	81 (3:4 = 57:43)
4	H	n-C_8H_{17}	B	85 (3:4 = 55:45)
			C	68 (3:4 = 53:47)
5	Ph	H	A	62
			B	40
			C	23
6	Ph	Me	A	75
7	Ph	n-Bu	A	65
8	Ph	Ph	A	60
9	n-Bu	n-Bu	A	84
			B	56
			C	52
10	$ClCH_2$	CH_2Cl	A	80
11	H	CO_2Me	A	42
12	MeO_2C	CO_2Me	A	25

[a] Ar = *p*-tolyl. [b] Method A: $AgOSO_2Ar$, PhSeCl, RC≡CR′; MeCN; room temperature. Method B: $ArSO_3H$, AIBN, PhSeSePh, RC≡CR′; C_6H_6; Δ. Method C: $ArS(O)SO_2Ar$, PhSeSePh, RC≡CR′; C_6H_6; Δ. [c] Isolated yields are reported except for **12** (see Experimental Section).

(1) For a review of electrophilic reactions of selenium compounds, see: (a) Back, T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; Chapter 1. For other recent reviews of organoselenium chemistry, see: (b) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1986 (Vol. 1), 1987 (Vol. 2). (c) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986. (d) Nicolaou, K. C.; Petasis, N. A. In *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1984.

(2) For examples of this and other selenenyl acetates, see: (a) Behaghel, O.; Müller, W. *Ber. Dtsch. Chem. Ges.* **1935**, *68B*, 1540. (b) Jenny, W. *Helv. Chim. Acta* **1953**, *36*, 1278. (c) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429. (d) Reich, H. J.; Renga, J. M. *J. Org. Chem.* **1975**, *40*, 3313. (e) Miyoshi, N.; Takai, Y.; Murai, S.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1265. (f) Garratt, D. G.; Ryan, M. D.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 2329. (g) Arunachalam, T.; Caspi, E. *J. Org. Chem.* **1981**, *46*, 3415. (h) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *Chem. Pharm. Bull.* **1981**, *29*, 105. (i) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K.; Hamada, Y.; Kotera, K.; Iitaka, Y. *Tetrahedron* **1984**, *40*, 1783. (j) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.

(3) (a) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. (b) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (d) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 274. (e) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861.

(4) For a review, see: Toshimitsu, A.; Uemura, S. In ref 1b, Vol. 2, Chapter 14.

(5) Although this electrophile has not been characterized, it is a possible intermediate in several recent procedures: (a) Tomoda, S.; Usuki, Y. *Chem. Lett.* **1989**, 1235. (b) McCarthy, J. R.; Matthews, D. P.; Barney, C. L. *Tetrahedron Lett.* **1990**, *31*, 973. (c) Saluzzo, C.; Alvernhe, G.; Anker, D. *Tetrahedron Lett.* **1990**, *31*, 2127. (d) Uneyama, K.; Kanai, M. *Tetrahedron Lett.* **1990**, *31*, 3583.

0022-3263/91/1956-2781$02.50/0