Study of the Thermal Transformation of 5-*exo*-Methyleneisoxazolidines to 3-Pyrrolidinones

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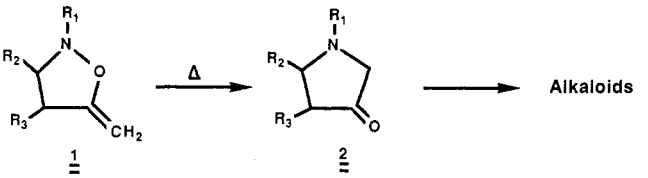
Dipolar cycloaddition of nitrones with electron-deficient allenes gives 5-*exo*-methylene substituted isoxazolidines in high yield. The regiochemistry of the cycloaddition can be attributed to a favorable allene (LUMO)-nitrone (HOMO) interaction. The isoxazolidines obtained undergo smooth rearrangement on thermolysis to produce 3-pyrrolidinones in high yield. The facility of the rearrangement is related to the degree of substitution about the 5-*exo*-methylene double bond. The rate of rearrangement of 4-carbomethoxy-2,3-dimethyl-5-methylene-3-phenylisoxazolidine was found to be 8.75×10^{-6} s^{-1} at 80 °C. The reaction was determined to have an activation energy of 30.2 kcal/mol. The small response of the rate (i.e., less than fivefold) to a variation of the solvent polarity rules out a dipolar intermediate and is more consistent with a diradical species formed by homolytic cleavage of the N-O bond. The thermal rearrangement of several appropriately labeled isoxazolidines was studied and found to produce a mixture of diastereomers. The stereochemical results are consistent with a stepwise mechanism for rearrangement.

The pyrrolidine ring system is a common structural element of a wide variety of alkaloids. This heterocyclic ring has attracted considerable interest in recent years, probably as a consequence of the diverse biological activity exhibited by several polysubstituted pyrrolidines.[1] A variety of pyrrolidine-forming methodologies has emerged in recent years[2-11] including the 1,3-dipolar cycloaddition reaction.[12-17] Through the use of nitrone cycloaddition chemistry, numerous pyrrolidine natural products have been synthesized with excellent stereochemical control.[18] In connection with our ongoing program to develop new methods for alkaloid synthesis,[19] we thought it worthwhile to examine a route to the pyrrolidine ring in which the rearrangement of a 5-*exo*-methyleneisoxazolidine plays a crucial role.[20] This heterocycle can be formed, in principle, by dipolar cycloaddition of a nitrone with an allene.



In contrast to the plethora of examples dealing with the cycloaddition of nitrones with alkenes,[18,21-28] there are only a handful of reports that focus on the bimolecular reactions of nitrones with allenes.[29-33] In an earlier report, Tufariello and co-workers have shown that nitrones react with allene to produce a set of regioisomeric allenes, one of which (**1**) was suggested to undergo spontaneous rearrangement to the pyrrolidinone ring (**2**).[31] Several features of this reaction are imperfectly understood, and we thought that further refinement is necessary if this cycloaddition-rearrangement process is to be used with confidence at a key stage of a total synthesis of an alkaloid. In an attempt to further define the details of the rearrangement reaction, a substituent effect study and a kinetic rate study were undertaken. This article documents the results of these studies.

Results and Discussion

Allenes are an interesting group of substrates since they contain two positions for attack.[34] The ability of allenes

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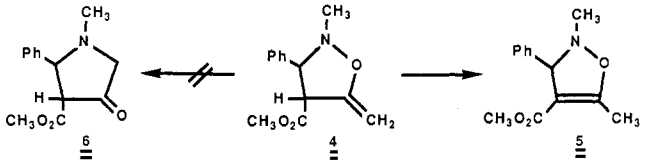
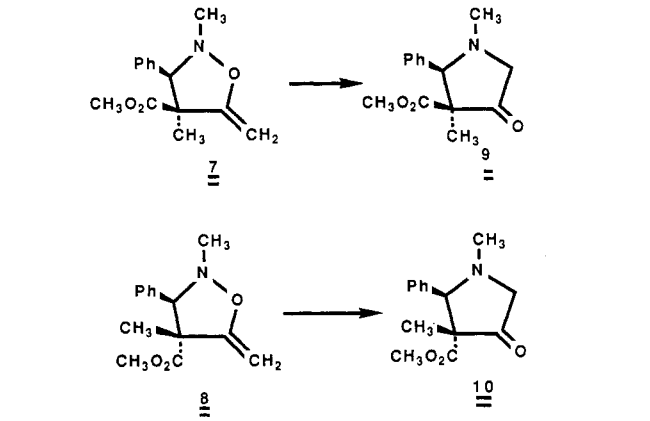
to undergo bimolecular cycloaddition reactions with a variety of unsaturated π-systems has provided the synthetic chemist with a convenient route for the construction of complex ring systems.[35-38] While the Diels–Alder reaction of allenes with dienes has been studied in some detail,[39-41] the use of allenes in 1,3-dipolar cycloadditions has been severely limited as a consequence of their unreactive nature as dipolarophiles.[34] Based on FMO theory,[42] allenes possessing electron-withdrawing substituents are expected to react more readily and to undergo dipolar cycloaddition across the activated π-bond. MNDO calculations indicate that the introduction of a carbomethoxy group causes a significant lowering of the LUMO energy level compared with that of allene, and the largest LUMO coefficient residues on the central carbon and the next on the position bearing the carbomethoxy group. This suggests that the reaction of a typical nitrone with a suitably activated allene will proceed in a highly regioselective fashion and undergo cycloaddition across the activated C_1–C_2 π-bond. This proved to be the case in the reaction of *C*-phenyl-*N*-methylnitrone (**3**) with carbomethoxyallene.

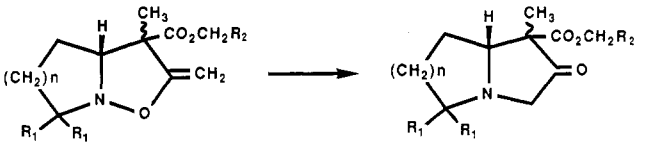
Stirring a solution of *N*-methyl-*C*-phenylnitrone and methyl 2,3-butadienoate in benzene at 40 °C for 6 h gave cycloadduct **4** in 80% yield. The isolation of isoxazolidine **4** is of some interest since related 5-*exo*-methylene substituted isoxazolidines have only been reported as transient species.[32] We have studied the thermolysis of **4** at 90 °C and find that it reacts via a 1,3-hydrogen shift to afford **5** rather than by N–O bond scission to give **6**.



Reaction of methyl 2-methyl-2,3-butadienoate with *C*-phenyl-*N*-methylnitrone (**3**) gave rise to a 5:1 mixture of 3*R**,4*S**- (**7**) and 3*R**,4*R**-4-carbomethoxy-2,4-dimethyl-5-methylene-3-phenylisoxazolidine (**8**) in 88% isolated yield. The two diastereomers were readily separated by silica gel chromatography. These materials cannot rearrange via a 1,3-hydrogen shift. Instead, at 90 °C, in either benzene, DMF, or cyclohexane, both isoxazolidines undergo quantitative reorganization to give pyrrolidinones **9** and **10**, respectively. The isolation of **9** and **10** from the thermolysis of these 5-substituted isoxazolidines provides strong support for the mechanism previously suggested by Tufariello to account for the formation of the pyrrolidinone ring in the cycloaddition reaction of **3** with allene.[31]



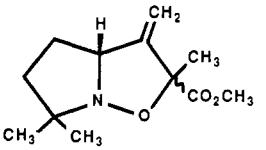
The 5-methyleneisoxazolidine–pyrrolidinone rearrangement was also observed to occur with cycloadducts **11–14**. These compounds were converted to pyrrolidinones **15–18** in good yield upon heating.



11; n=1; R_1=R_2=H
12; n=1; R_1=CH_3; R_2=H
13; n=2; R_1=R_2=H
14; n=2; R_1=H; R_2=CH_3

15; n=1; R_1=R_2=H
16; n=1; R_1=CH_3; R_2=H
17; n=2; R_1=R_2=H
18; n=2; R_1=H; R_2=CH_3

Interestingly, the cycloaddition of 5,5-dimethyl-1-pyrroline *N*-oxide with 1-methyl-1-carbomethoxyallene produced a mixture of the expected 5-substituted isoxazolidine **12** as well as the regioisomeric cycloadduct **19**



(42%). This represents the only exception in regiochemistry that we have encountered with these systems. Clearly, the presence of two methyl groups adjacent to the nitrone atom influences the transition state for cycloaddition. The assignment of structure **19** rests on its spectroscopic properties as well as its chemical behavior. The NMR spectrum ($CDCl_3$, 360 MHz) showed methyl singlets at δ 1.04, 1.37, 1.56, and 3.73 and the vinylic protons at δ 5.03. The appearance of these protons 0.7 ppm downfield from cycloadduct **12** is compatible with this regiochemical assignment. More importantly, all attempts to induce a thermal rearrangement of **19** to the pyrrolidinone ring system failed. This result is fully consistent with the structure assignment. A reasonable explanation to account for the difference in regiochemistry with 5,5-dimethyl-1-pyrroline *N*-oxide is to assume that steric factors play a significant role in controlling the orientation of the reactants in the transition state.[43]

The cycloaddition–rearrangement sequence using the *N*-methylnitrone of acetone and 1-methyl-1-carbomethoxyallene was studied so as to further establish the gen-

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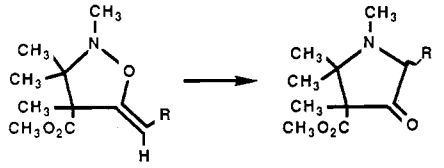
(43) A similar regiochemical crossover was encountered in a study of the reaction of *N*-methyl- and *N*-*tert*-butyl-*C*-phenylnitrone with methyl 2-methyl-2,3-butadienoate. Molecular mechanics calculations showed that the relative energies of the two regioisomeric cycloadducts in the *tert*-butyl system have been switched relative to the methyl system; Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *J. Org. Chem.* **1987**, *52*, 3909.

Table I. First-Order Rate Constants and Free-Energy Parameters for the Rearrangement of 5-Methyleneisoxazolidine 7 to Pyrrolidinone 9

solvent	rate (80 °C)	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	E_a
acetonitrile	8.75×10^{-6} s^{-1}	28.83	30.2	4.58	30.8 kcal/mol
methanol	8.85×10^{-6} s^{-1}				
cyclohexane	1.79×10^{-6} s^{-1}				

erality of the process. The cycloaddition reaction proceeded quite smoothly to give isoxazolidine **20**, which cleanly rearranged to pyrrolidinone **21** upon heating at 90 °C. In order to probe the stereochemical aspects of the

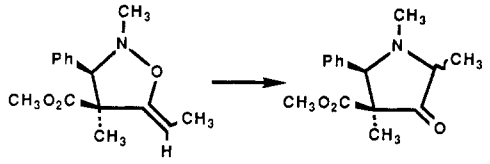


20; R=H
22; R=CH$_3$

21; R=H
23; R=CH$_3$

reaction, we have studied the thermal behavior of isoxazolidine **22**. The stereochemical assignment of the vinyl hydrogen and carbomethoxy groups is based on NOE experiments (8% enhancement). Thermolysis of **22** produced a 2:1 mixture of the (2*S**)- and (2*R**)-pyrrolidinones **23**.

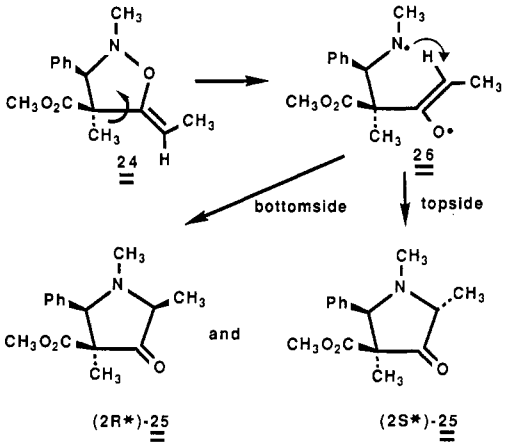
We have also examined the cycloaddition reaction of *N*-methyl-*C*-phenylnitrone with methyl 2,4-dimethyl-2,3-butadienoate. In this case a mixture of diastereomeric cycloadducts was obtained. The major diastereomer was assigned as the 3*R**,4*S** isomer **24** on the basis of its spectroscopic properties and NOE enhancements.



24 25

Heating this compound also gave rise to a mixture (3:1) of the (2*S**)- and (2*R**)-pyrrolidinones **25**. This result clearly establishes that the thermal rearrangement of the 5-*exo*-methyleneisoxazolidine system is a nonstereospecific process.[44] MNDO calculations indicate a 54 kcal/mol difference in the heat of formation of the parent 5-*exo*-methyleneisoxazolidine with the 3-pyrrolidinone ring thereby providing the thermodynamic driving force for the reaction.[45]

The kinetics of the rearrangement of a typical 5-substituted isoxazolidine (i.e., **7** → **9**) was followed by UV spectroscopy.[46] The rearrangement followed first-order kinetics; and the rate was found to be 8.75×10^{-6} s^{-1} at 80 °C in acetonitrile. The activation energy for the rearrangement of **7** was determined from the dependence of the first-order rate constant on temperature and was found to have a value of 30.8 kcal/mol. Most importantly, the small response of the rate (i.e., less than fivefold) (see Table I) to a variation of the solvent polarity rules out the involvement of a dipolar intermediate and is consistent with a mechanism involving homolytic cleavage of the N–O bond.[47] The nitrogen–oxygen bond of these 5-vinyl substituted isoxazolidines is expected to be cleaved readily, since such heteroatom–hetereoatom bonds are known to be relatively weak.[31,48-52] The stereochemical results are consistent with a stepwise mechanism since the initially formed diradical **26** should attack the enol radical from above and below its π-system.[53,54] The predominance (75%) of the 2*S** isomer would require that rotation about the 4,5-bond preferentially occur in a clockwise direction. The preferred direction of rotation is probably due to a preferred topside attack which occurs syn to the smaller carbomethoxy group.



24 26

(2R*)-25 (2S*)-25

We also examined the reaction of 1-carbomethoxy-3-phenylpropadiene with *C*-phenyl-*N*-methylnitrone. Stirring a mixture of these two compounds in benzene at 50 °C for 6 h gave *N*-methyl-1,5-diphenyl-3-carbomethoxypyrrole (**29**) in 67% yield. In this case the initially formed cycloadduct **27** rapidly rearranges since the reaction is facilitated by the conjugative stabilization of the oxygen radical by the phenyl group. The subsequent conversion of the pyrrolidinone to the pyrrole nucleus probably proceeds via a series of proton shifts followed by loss of water.

Having established the experimental feasibility of converting 4-carbomethoxy 5-*exo*-methylene substituted isoxazolidines to pyrrolidinones, we directed our attention to using other allenes in the cycloaddition step. The reaction of *N*-methyl-*C*-phenylnitrone with cyanoallene was found to give the expected cycloadduct **30**. As was the

(44) In our earlier communication,[20] we incorrectly reported that the rearrangement proceeded in a stereospecific manner. The method used to analyze the products (90 MHz, NMR) was not sensitive enough to distinguish between the two diastereomeric pyrrolidinones. The ratio of the diastereomeric pyrrolidinones formed from the thermolysis of isoxazolidines **22** and **24** was now determined by 360 NMR spectroscopy. In addition, we originally assumed that the mixture of diastereomers formed with *N*-methyl-*C*-phenylnitrone with methyl 2,4-dimethyl-2,3-butadienoate was isomeric about the π-bond (i.e., 24*E* and 24*Z*). In fact, NOE experiments indicate that the second most prevalent diastereomer has the phenyl and carbomethoxy groups in a trans relationship and that the stereochemistry about the π-bond still possesses the *Z* configuration.

(45) QCPE no. 506 (Ampac) using the AM1 Hamiltonian.

(46) Identical kinetic results were obtained when the rearrangement was followed by NMR spectroscopy.

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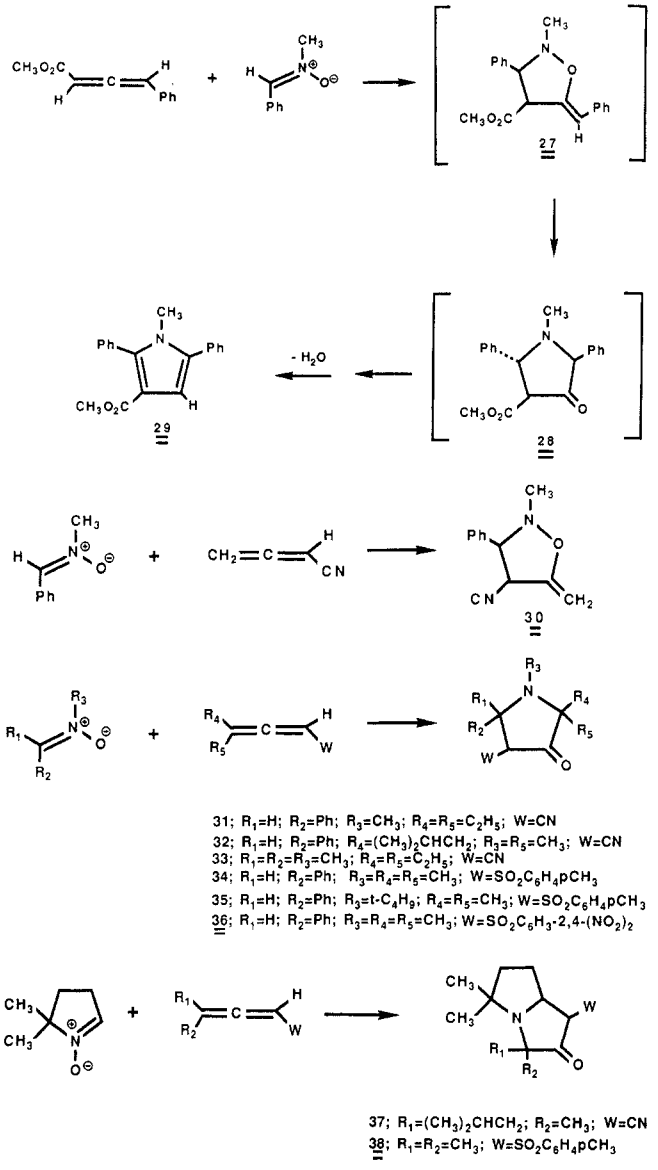
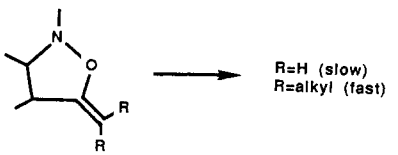


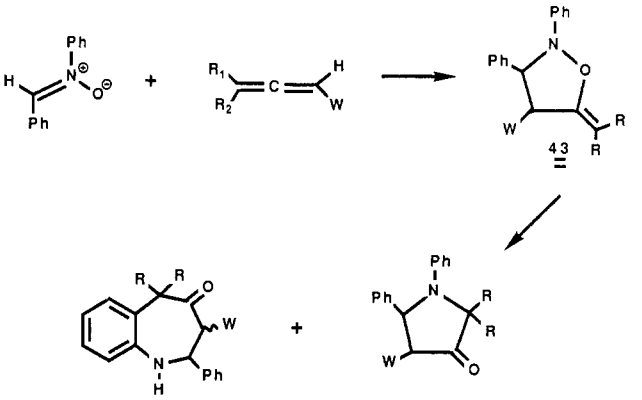
31; R_1=H; R_2=Ph; R_3=CH_3; R_4=R_5=C_2H_5; W=CN
32; R_1=H; R_2=Ph; R_4=$(CH_3)_2CHCH_2$; R_3=R_5=CH_3; W=CN
33; R_1=R_2=R_3=CH_3; R_4=R_5=C_2H_5; W=CN
34; R_1=H; R_2=Ph; R_3=R_4=R_5=CH_3; W=$SO_2C_6H_4pCH_3$
35; R_1=H; R_2=Ph; R_3=t-C_4H_9; R_4=R_5=CH_3; W=$SO_2C_6H_4pCH_3$
36; R_1=H; R_2=Ph; R_3=R_4=R_5=CH_3; W=$SO_2C_6H_3$-2,4-$(NO_2)_2$

37; R_1=$(CH_3)_2CHCH_2$; R_2=CH_3; W=CN
38; R_1=R_2=CH_3; W=$SO_2C_6H_4pCH_3$

case with the analogous carbomethoxy system (i.e., **4**), the thermolysis of **30** results in a 1,3-hydrogen shift rather than in N–O bond scission. In contrast to this observation, we found that reaction of several different nitrones with 3,3-disubstituted cyanoallenes gave pyrrolidinones **31–33** as the exclusive cycloaddition products. All attempts to detect a transient isoxazolidine intermediate failed. This was also the case when substituted (arylsulfonyl)-propadienes were used as the dipolarophiles. With all of these systems, only the pyrrolidinone ring was isolated even though the cycloadditions were carried out at 40 °C. We conclude from this that the rearrangement of 5-*exo*-methyleneisoxazolidines is particularly sensitive to the nature of the substituent groups on the double bond. Apparently, scission of the N–O bond of the isoxazolidine ring is markedly enhanced by groups capable of stabilizing the carbon radical center.



As a further continuation of our work in this area, we have studied the cycloaddition reaction of *N*-phenyl-*C*-phenylnitrone with several disubstituted allenes. In contrast to the results outlined above, the cycloaddition of *N*-phenyl-*C*-phenylnitrone with a disubstituted cyano(or (arylsulfonyl))allene afforded a 1:2 mixture of pyrrolidinone **39** (or **41**) and benzazepine **40** (or **42**). This result is not totally unexpected in that there have been some related reports that show that the initially formed 5-methyleneisoxazolidine adduct (i.e., **43**) can undergo a facile hetero-Cope rearrangement.[31,55–57]



40; R=C_2H_5; W=CN
42; R=CH_3; W=$SO_2C_6H_4pCH_3$

39; R=C_2H_5; W=CN
41; R=CH_3; W=$SO_2C_6H_4pCH_3$

The preference for the seven-membered benzazepine ring is probably related to its greater thermodynamic stability. In support of this suggestion, molecular mechanics calculations were carried out by using the Allinger MM2 force field[58,59] so as to calculate the total energy of the two isomeric ring systems. We assume that the relative energy differences of the lowest energy conformations of both heterocyclic compounds will parallel the energy differences for five- vs seven-membered-ring formation in the transition state. The results obtained demonstrate that the seven-membered benzazepine ring (total energy = 13.05 kcal/mol) is lower in energy than the corresponding pyrrolidinone ring (total energy = 19.29 kcal/mol). MNDO calculations also show that the five- and seven-membered rings differ by 12 kcal in their heat of formation.[45] Some of this energy difference is presumably involved in the transition state for product formation.

In conclusion, the dipolar cycloaddition of nitrones with electron-deficient allenes has been found to give 5-*exo*-methylene substituted isoxazolidines in good yield. FMO considerations account for the fact that these electron-deficient allenes react at the $C_{1,2}$ position. This is presumably due to the favorable LUMO (allene)–HOMO (nitrone) interactions. The facility with which the isoxazolidine system rearranges depends on the degree of substitution about the allene π-bond. The present results show that the rearrangement proceeds in a nonstereospecific fashion involving a stepwise diradical mechanism. Studies of the rearrangement reaction with other systems and its application toward the synthesis of alkaloids are in progress and will be reported on at a later date.

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Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390 and a Nicolet NMC-360 MHz spectrometer. ^{13}CNMR spectra were recorded on an IBM NB 200 SY FT spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Preparation and Thermolysis of (3*R,4*S**)- (7) and (3*R**,4*R**)-4-Carbomethoxy-2,4-dimethyl-5-methylene-3-phenylisoxazolidine (8).** A solution containing 0.65 g of *N*-methyl-*C*-phenylnitrone[60] (3) and 1.32 g of methyl 2-methyl-2,3-butadienoate[61] in 10 mL or benzene was heated at 45 °C for 10 h. Concentration of the solution under reduced pressure followed by silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent gave two fractions. The first fraction contained 180 mg (17%) of a clear oil whose structure was assigned as (3*R**,4*R**)-4-carbomethoxy-2,3-dimethyl-5-methylene-3-phenylisoxazolidine (8) on the basis of its spectra data: IR (neat) 3040, 3000, 2960, 2880, 1740, 1675, 1500, 1458, 1380, 1275, 1145, 1125, 990, 965, 825, 775, 755, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.15 (s, 3 H), 2.70 (s, 3 H), 3.75 (s, 3 H), 3.90 (d, 1 H, J = 4.0 Hz), 4.22 (d, 1 H, J = 4.0 Hz), 4.50 (s, 1 H), and 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 43.75, 52.59, 59.22, 76.27, 76.90, 128.17, 128.32, 134.28, 162.64, and 172.15. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.97; H, 6.94; N, 5.65.

The second fraction contained 770 mg (71%) of a crystalline solid whose structure was assigned as (3*R**,4*S**)-4-carbomethoxy-2,3-dimethyl-5-methylene-3-phenylisoxazolidine (7) on the basis of its spectral data: mp 74–75 °C; IR (KBr) 3005, 2960, 2860, 1730, 1670, 1605, 1445, 1390, 1340, 1285, 1250, 1150, 1130, 990, 930, 810, 760, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 3 H), 2.70 (s, 3 H), 3.45 (s, 3 H), 3.55 (s, 1 H), 3.80 (d, 1 H, J = 4.0 Hz), 4.30 (d, 1 H, J = 4.0 Hz), and 7.30 (s, 5 H); MS m/e 247 (M^+), 188, 145, 132, 91, and 77. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.97; N, 5.66.

A solution containing 100 mg of 7 in 2 mL of dry dimethylformamide was heated at 90 °C for 10 h. At the end of this period, the solution was poured into ice water and extracted with ether. The organic extracts were washed with water and a saturated salt solution and dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to give 95 mg (95%) of clear oil, whose structure was assigned as (4*S**,5*R**)-4-carbomethoxy-1,4-dimethyl-5-phenyl-3-pyrrolidinone (9) on the basis of its spectral data: IR (neat) 3020, 3000, 2960, 2840, 2790, 1760, 1745, 1455, 1315, 1270, 1220, 1030, 740, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (s, 3 H), 2.28 (s, 3 H), 2.95 (d, J = 18.0 Hz, 1 H), 3.60 (d, J = 18.0 Hz, 1 H), 3.70 (s, 3 H), 4.20 (s, 1 H), and 7.20 (s, 5 H). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.03; H, 6.95; N, 5.61.

A solution containing 150 mg of 8 in 3 mL of dry benzene was heated in a sealed tube at 90 °C for 9 h. At the end of this time, the solvent was removed under reduced pressure to give 143 mg (93%) of a crystalline solid, whose structure was assigned as (4*R**,5*R**)-4-carbomethoxy-1,4-dimethyl-5-phenyl-3-pyrrolidinone (10), mp 109–110 °C, on the basis of its spectral data: IR ($CHCl_3$) 3010, 2985, 2800, 1775, 1745, 1460, 1440, 1265, 1210, 1110, 1090, 1030, 800, and 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.00 (s, 3 H), 1.90 (s, 3 H), 2.50 (d, J = 18.0 Hz, 1 H), 3.10 (s, 3 H), 3.50 (d, J = 18.0 Hz, 1 H), 6.90 (s, 1 H), and 7.10 (s, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 16.73, 39.92, 51.24, 61.35, 62.57, 79.03, 126.74, 127.76, 135.7, 168.93, and 209.98; MS, m/e 247 (M^+), 188, 176, 162, 145, 132, 91, and 70; HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1203.

Preparation and Thermolysis of Methyl 3-Methyl-2-methylenehexahydroisoxazolo[2,3-*a*]pyrrole-3-carboxylate (11). A solution containing 400 mg of 1-pyrroline 1-oxide[63] and 530 mg of methyl 2-methyl-2,3-butadienoate[61] in 4 mL of benzene was heated with stirring at 50 °C for 2 h. at the end of this time, the solvent was removed under reduced pressure. The resulting oily residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 625 mg (70%) of yellow oil, whose structure was assigned as methyl 3-methyl-2-methylenehexahydroisoxazolo[2,3-*a*]pyrrole-3-carboxylate (11) on the basis of its spectral properties: IR (neat) 2980, 2950, 2870, 1745, 1668, 1260, 1224, 1110, and 967 cm^{-1}; UV (acetonitrile) 218 nm (ϵ 7340); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.51–1.64 (m, 1 H), 1.68 (s, 3 H), 1.76–1.82 (m, 1 H), 1.90–2.07 (m, 2 H), 2.96–3.06 (m, 1 H), 3.49–3.59 (m, 2 H), 3.73 (d, 3 H, J = 0.4 Hz), and 4.28 (dd, 2 H, J = 4.3 and 0.4 Hz). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.86; H, 7.77; N, 6.93.

A solution containing 150 mg of the above material in 2 mL of dimethylformamide was heated with stirring at 80 °C in a sealed tube for 8 h. At the end of this time, the reaction mixture was poured into ice water and extracted with ether. The organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was subjected to silica gel chromatography using a 2% methanol–chloroform mixture as the eluent. The major fraction isolated contained 118 mg (83%) of 1-carbomethoxy-1-methylhexahydropyrrolizidin-2-one (15) as a clear oil: IR (neat) 2960, 2890, 1768, 1740, 1460, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.38 (s, 3 H), 1.58–1.63 (m, 1 H), 1.85–2.0 (m, 4 H), 2.03–2.13 (m, 1 H), 2.82 (m, 1 H), 3.45 (d, 1 H, J = 18.7 Hz), 3.56 (d, 1 H, J = 18.7 Hz), and 3.70 (s, 3 H). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.69; H, 7.83; N, 7.30.

Preparation and Thermolysis of Methyl 3,6,6-Trimethyl-2-methylenehexahydroisoxazolo[2,3-*a*]pyrrole-3-carboxylate (12). A solution containing 1.0 g of 5,5-dimethyl-1-pyrroline 1-oxide[64] and 1.05 g of methyl 2-methyl-2,3-butadienoate[61] in 4 mL of benzene was heated with stirring at 50 °C for 20 h. At the end of this time, the solvent was removed under reduced pressure and the resulting oil was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The first fraction isolated contained 320 mg (14%) of a clear oil, whose structure was assigned as methyl 3,6,6-trimethyl-2-methylenehexahydroisoxazolo[2,3-*a*]pyrrole-3-carboxylate (12) on the basis of its spectral properties: IR (neat) 2980, 2880, 1753, 1675, 1257, 1123, 970, and 815 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.06 (s, 3 H), 1.36 (s, 3 H), 1.54–1.62 (m, 1 H), 1.67 (s, 3 H), 1.76–1.87 (m, 1 H), 1.99–2.12 (m, 2 H), 3.72 (s, 3 H), 3.78 (dd, 1 H, J = 9.0 and 6.4 Hz), 4.28 (d, 1 H, J = 1.9 Hz), and 4.30 (d, 1 H, J = 1.9 Hz). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.69; H, 8.66; N, 5.96.

The second fraction isolated contained 950 mg (42%) of a clear oil, whose structure was assigned as the regioisomeric methyl 3,6,6-trimethyl-3-methylenehexahydroisoxazolo[2,3-*a*]pyrrole-3-carboxylate (19) on the basis of its spectral data: IR (neat) 2975, 2880, 1742, 1675, 1260, 1128, and 910 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.04 (s, 3 H), 1.37 (s, 3 H), 1.56 (s, 3 H), 1.65–1.76 (m, 2 H), 2.05–2.28 (m, 2 H), 3.73 (s, 3 H), 4.20–4.25 (m, 1 H), 5.03 (d, 1 H, J = 2.4 Hz), and 5.04 (d, 1 H, J = 2.4 Hz). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.28; H, 8.72; N, 5.92.

A solution containing 100 mg of 12 in 2 mL of dimethylformamide was heated with stirring at 90 °C in a sealed tube for 8 h. At the end of this time, the reaction mixture was poured into ice water and extracted with ether. The organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was subjected to silica gel chromatography using chloroform as the eluent. The major fraction isolated contained 56 mg (55%) of a clear oil, whose structure was assigned as 1-carbomethoxy-1,4,4-trimethylhexahydropyrrolizidin-2-one (16) on the basis of its spectral data: IR (neat) 2970, 2880, 1763, 1738, 1455, 1382, 12358 1150, 1075, 990, and 765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.02 (s, 3 H), 1.05 (s, 3 H), 1.33 (s, 3 H), 1.4–1.9 (m,

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4 H), 3.17 (d, 1 H, J = 18.0 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 3.66 (s, 3 H), and 3.6–3.8 (m, 1 H); MS, m/e 225 (M^+), 140, 126, 112, 98, and 84; HRMS calcd for $C_{12}H_{19}NO_3$ 225.1364, found 225.1356.

Preparation and Thermolysis of Methyl 3-Methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (13). A solution containing 300 mg of 3,4,5,6-tetrahydropyridine 1-oxide[62] and 340 mg of methyl 2-methyl-2,3-butadienoate[61] in 3 mL of benzene was heated with stirring at 50 °C for 3 h. At the end of this time, the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography using a mixture of 5% ethyl acetate–hexane as the eluent. The first fraction isolated contained 74 mg (12%) of colorless oil, whose structure was assigned as one of the diastereomers of (3*S**)-methyl 3-methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**13a**) on the basis of its spectral properties: IR (neat) 2945, 2860, 1738, 1670, 1280, 1125, 970, and 810 cm^{-1}; UV (acetonitrile) 222 nm (ϵ 5500); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.23–1.38 (m, 2 H), 1.40 (s, 3 H), 1.40–1.48 (m, 1 H), 1.62–1.68 (m, 1 H), 1.70–1.85 (m, 2 H), 2.58–2.66 (m, 1 H), 3.02 (dd, 1 H, J = 2.3 and 0.9 Hz), 3.53–3.58 (m, 1 H), 3.74 (d, 3 H, J = 0.9 Hz), 4.05 (dd, 1 H, J = 2.3 and 0.9 Hz), and 4.27 (dd, 1 H, J = 2.3 and 0.9 Hz). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.69; H, 8.15; N, 6.53.

The second fraction isolated contained 403 mg (63%) of a white crystalline solid, mp 74–75 °C, whose structure was assigned as the second diastereomer of (3*S**)-methyl 3-methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**13b**) on the basis of its spectral data: IR (KBr) 2940, 2860, 1725, 1670, 1257, 1230, 965, and 806 cm^{-1}; UV (acetonitrile) 222 nm (ϵ 7300); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.17–1.42 (m, 2 H), 1.57 (s, 3 H), 1.66–1.96 (m, 4 H), 2.35 (dd, 1 H, J = 11.3 and 2.2 Hz), 2.54 (m, 1 H), 3.60–3.65 (m, 1 H), 3.7 (s, 3 H), 4.38 (d, 1 H, J = 2.6 Hz). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.66; H, 8.13; N, 6.59.

A solution containing 300 mg of **13a** in 3 mL of dimethylformamide was heated with stirring at 90 °C in a sealed tube for 16 h. At the end of this time, the reaction mixture was poured into 6 mL of ice water and extracted with ether. The organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 280 mg (93%) of a clear oil, whose structure was assigned as one of the diastereomers of (1*S**)-1-carbomethoxy-1-methyloctahydroindolizin-2-one (**17a**) on the basis of its spectral properties: IR (neat) 2950, 2870, 2800, 1775, 1746, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.18–1.25 (m, 1 H), 1.37 (s, 3 H), 1.31–1.45 (m, 2 H), 1.56–1.66 (m, 2 H), 1.81–1.88 (m, 1 H), 2.05–2.19 (m, 1 H), 2.77–2.82 (m, 1 H), 2.81 (d, 1 H, J = 16.8 Hz), 3.07–3.12 (m, 1 H), 3.42 (d, 1 H, J = 16.8 Hz), and 3.69 (s, 3 H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.44; H, 7.96; N, 6.51.

A solution containing 130 mg of **13b** in 2 mL of benzene was heated at reflux in a sealed tube for 72 h. At the end of this time, the solvent was removed under reduced pressure and the resulting crude residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 106 mg (82%) of a yellow solid, mp 58–59 °C, whose structure was assigned as the other diastereomer of (1*S**)-1-carbomethoxy-1-methyloctahydroindolizin-2-one (**17b**) on the basis of its spectral properties: IR (KBr) 2940, 2780, 1760, 1728, and 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.23–1.35 (m, 2 H), 1.28 (s, 3 H), 1.64–1.69 (m, 2 H), 1.80–1.93 (m, 2 H), 2.03–2.11 (m, 1 H), 2.15–2.20 (m, 1 H), 2.68 (d, 1 H, J = 17.5 Hz), 3.13–3.19 (m, 1 H), 3.65 (d, 1 H, J = 17.5 Hz), and 3.72 (s, 3 H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.61; H, 8.14; N, 6.62.

Preparation and Thermolysis of Ethyl 3-Methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (14). A solution containing 500 mg of 3,4,5,6-tetrahydropyridine 1-oxide[62] and 700 mg of ethyl 2-methyl-2,3-butadienoate[61] in 5 mL of benzene was heated with stirring at 40 °C for 5 h. At the end of this time, the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The first fraction isolated contained 168 mg (15%) of clear oil, whose structure was assigned as one of the diastereomers of (3*S**)-ethyl 3-methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**14a**) on the basis of its spectral properties: IR (neat) 2940, 2860, 2830, 1735, 1670, 1275, 1120, 970, and 810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.27 (t, 3 H, J = 9.0 Hz), 1.40 (s, 3 H), 1.60–1.85 (m, 6 H), 2.64 (ddt, 1 H, J = 8.85 and 3.0 Hz), 3.02 (dd, 1 H, J = 11.11 and 2.36 Hz), 3.52–3.60 (m, 1 H), 4.07 (d, 1 H, J = 2.47 Hz), 4.20 (qd, 2 H, J = 9.0 and 3.7 Hz), and 4.26 (d, 1 H, J = 2.45 Hz); MS, m/e 225 (M^+), 183, 154, 137, 124, 111, 97, and 83; HRMS calcd for $C_{12}H_{19}NO_3$ 225.1364, found 225.1366.

The second fraction isolated contained 574 mg (51%) of a white solid, mp 34–35 °C, whose structure was assigned as the second diastereomer of (3*S**)-ethyl 3-methyl-2-methylenehexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**14b**) on the basis of its spectral data: IR (KBr) 2980, 2937, 2860, 2825, 1725, 1670, 1250, 1225, 1102, 970, and 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.25 (t, 3 H, J = 7.08 Hz), 1.40 (s, 3 H), 1.60–1.95 (m, 6 H), 2.35 (dd, 1 H, J = 11.52 and 2.28), 2.50 (dtd, 1 H, J = 10.4 and 3.08 Hz), 3.55–3.65 (m, 1 H), 3.90 (d, 1 H, J = 2.6 Hz), 4.20 (q, 2 H, J = 7.03 Hz), and 4.35 (d, 1 H, 2.60 Hz). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.01; H, 8.53; N, 6.17.

A solution containing 200 mg of **14b** in 3 mL of benzene was heated at reflux in a sealed tube for 48 h. At the end of this time, the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 104 mg (52%) of a clear oil, whose structure was assigned as (1*S**)-1-carbomethoxy-1-methyloctahydroindolizin-2-one (**18b**) on the basis of its spectral properties: IR (neat) 2985, 2935, 2860, 2770, 1758, 1730, and 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.20 (t, 3 H, J = 7.0 Hz), 1.22 (s, 3 H), 1.5–2.3 (m, 8 H), 2.66 (d, 1 H, J = 18.0 Hz), 3.07–3.18 (m, 1 H), 3.66 (d, 1 H, J = 18.0 Hz), and 4.22 (q, 2 H, J = 7.0 Hz); MS, m/e 225 (M^+), 197, 180, 168, 152, 124, 110, and 97; HRMS calcd for $C_{12}H_{19}NO_3$ 225.1364, found 225.1361.

Preparation and Thermolysis of *N*-Methyl-3,3,4-trimethyl-5-methylene-4-carbomethoxyisoxazolidine (20). A solution containing 500 mg of *N*-methyl-*C*,*C*-dimethylnitrone[65] and 640 mg of methyl 2-methyl-2,3-butadienoate[61] in 10 mL of benzene was heated at 45 °C for 48 h. At the end of this time, the solvent was removed under reduced pressure and the resulting oil was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 900 mg (80%) of clear oil, whose structure was identified as *N*-methyl-3,3,4-trimethyl-5-methylene-4-carbomethoxyisoxazolidine (**20**) on the basis of its spectral data: IR (neat) 2990, 2975, 2895, 1730, 1675, 1455, 1435, 1295, 1255, 1125, 970, 900, and 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 6 H), 2.65 (s, 3 H), 3.80 (s, 3 H), 3.90 (d, J = 2.5 Hz, 1 H), and 4.35 (s, J = 2.5 Hz, 1 H); HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1205.

A solution containing 500 mg of the above compound in 2 mL of dry acetonitrile was heated at 90 °C in a sealed tube for 2 days. At the end of this time, the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 450 mg (90%) of clear oil, whose structure was identified as *N*-methyl-4,5,5-trimethyl-4-carbomethoxy-3-pyrrolidinone (**21**) on the basis of its spectral data: IR ($CHCl_3$) 3020, 2980, 2800, 1765, 1725, 1450, 1370, 1260, 1110, 1010, 810, and 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.9 (s, 3 H), 1.04 (s, 3 H), 1.20 (s, 3 H), 2.25 (s, 3 H), 2.96 (s, J = 18.1 Hz, 1 H), 3.44 (s, J = 18.1 Hz, 1 H), and 3.70 (s, 3 H); HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1204.

Preparation and Thermolysis of *N*-Methyl-3,3,4-trimethyl-5-(methylmethylene)-4-carbomethoxyisoxazolidine (22). A solution containing 345 mg of *N*-methyl-*C*,*C*-dimethylnitrone[65] and 500 mg of methyl 2,4-dimethyl-2,3-butadienoate[66] in 10 mL of benzene was heated at 45 °C for 48 h. At the end of this time, the solvent was removed under reduced pressure and

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the resulting oil was subjected to silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 500 mg (60%) of a clear oil, whose structure was assigned as *N*-methyl-3,3,4-trimethyl-5-(methylmethylene)-4-carbomethoxyisoxazolidine (**22**) on the basis of spectra data: IR (neat) 2990, 2950, 1730, 1695, 1460, 1375, 1270, 1225, 1120, 1090, 980, and 805 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.90 (s, 3 H), 1.10 (s, 3 H), 1.45 (d, J = 7.40 Hz, 3 H), 1.50 (s, 3 H), 2.58 (s, 3 H), 3.75 (s, 3 H), and 4.83 (q, J = 7.40 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 11.48, 16.47, 19.04, 19.09, 36.08, 36.43, 51.98, 59.95, 76.61, 91.43, and 155.00; MS, m/e 213 (M^+), 198, 154, 139, 124, 114, 110, 98, and 72; HRMS calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1326.

A solution containing 200 mg of **22** in 3 mL of dry acetonitrile was heated at reflux in a sealed tube for 24 h. At the end of this time, the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 104 mg (52%) of clear oil, whose structure was assigned as a 2:1 diastereomeric mixture of (2*S**)- and (2*R**)-1,2,4,5-pentamethyl-4-carbomethoxy-3-pyrrolidinone (**23**) on the basis of its spectral data: IR ($CHCl_3$) 3010, 2980, 2940, 1760, 1725, 1450, 1360, 1260, 1190, 1110, and 975 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer) δ 0.80 (s, 3 H), 1.10 (s, 3 H), 1.17 (s, 3 H), 1.25 (d, J = 6.70 Hz, 3 H), 2.25 (s, 3 H), 2.63 (q, J = 6.70 Hz, 1 H), 3.60 (s, 3 H), (minor isomer) δ 0.9 (s, 3 H), 1.15 (s, 3 H), 1.19 (s, 3 H), 1.27 (d, J = 6.60 Hz, 3 H), 2.23 (s, 3 H), 2.8 (q, J = 6.60 Hz, 1 H), and 3.63 (s, 3 H); HRMS calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1363.

Preparation and Thermolysis of *N*-Methyl-4-methyl-5-(methylmethylene)-3-phenyl-4-carbomethoxyisoxazolidine (24). A solution containing 500 mg of *N*-methyl-*C*-phenylnitrone[60] and 680 mg of methyl 2,4-dimethyl-2,3-butadienoate[66] in 10 mL of benzene was heated at 45 °C for 48 h. At the end of this time, the solvent was removed under reduced pressure and the resulting oil was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 760 mg (65%) of a clear oil, whose structure was assigned as (3*R**,4*S**)-*N*-methyl-4-methyl-5-(methylmethylene)-3-phenyl-4-carbomethoxyisoxazolidine (**24**) on the basis of its spectral data: IR (neat) 3020, 3000, 2850, 2780, 1735, 1690, 1500, 1455, 1380, 1260, 1210, 1125, 1090, 985, 750, and 715 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.20 (s, 3 H), 1.50 (d, J = 7.0 Hz, 3 H), 2.80 (s, 3 H), 3.80 (s, 3 H), 4.35 (s, 1 H), 4.85 (q, J = 7.0 Hz, 1 H), and 7.20–7.50 (m, 5 H); MS, m/e 261 (M^+), 202, 146, 118, 91, and 85; HRMS calcd for $C_{15}H_{19}O_3N$ 261.1364, found 261.1394.

A solution containing 300 mg of **24** in 2 mL of dry acetonirile was heated at reflux for 10 h in a sealed tube. At the end of this time, the solvent was removed under reduced pressure and the resulting residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 210 mg (70%) of colorless oil, whose structure was assigned as a 3:1 diastereomeric mixture of 2*S** and 2*R** (4*S**,5*R**)-1,2,4-trimethyl-5-phenyl-4-carbomethoxy-3-pyrrolidinone (**25**) on the basis of its spectral data: IR ($CHCl_3$) 3020, 2960, 2850, 1765, 1735, 1455, 1360, 1200, 1110, and 870 cm^{-1}; ^1H NMR ($CDCl_3$8 360 MHz) δ (major isomer) 0.93 (s, 3 H), 1.30 (d, J = 7.1 Hz, 3 H), 2.33 (s, 3 H), 2.85 (q, J = 7.1 Hz, 1 H), 3.78 (s, 3 H), 4.20 (s, 1 H), and 7.26–7.40 (m, 5 H), (minor isomer) δ 1.02 (s, 3 H), 1.34 (d, J = 6.60, 3 H), 2.26 (s, 3 H), 2.85 (q, J = 6.60, 1 H), 4.20 (s, 3 H), 4.66 (s, 1 H), and 7.20–7.40 (m, 5 H); HRMS calcd for $C_{15}H_{19}NO_3$ 261.1364, found 261.1372.

Cycloaddition of *N*-Methyl-*C*-phenylnitrone with Methyl 4-Phenyl-2,3-butadienoate. A solution containing 1.00 g of *N*-methyl-*C*-phenylnitrone[60] and 926 mg of methyl 4-phenyl-2,3-butadienoate[61] in 10 mL of benzene was heated at 45 °C for 10 h. At the end of this time, the solution was concentrated under reduced pressure and the resulting crude oil was chromatography on a silica gel column using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 500 mg (32%) of crystalline solid, whose structure was assigned as methyl 1-methyl-2,5-diphenylpyrrole-3-carboxylate[67] (**29**) on the basis of its spectral data: mp 97–98 °C (lit.[67] mp 98–99 °C); IR ($CHCl_3$) 3020, 2980, 1725, 1660, 1610, 1490, 1440, 1360, 1285, 1100, 1010, 1030, 920, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.35 (s, 3 H), 3.65 (s, 3 H), 7.25–7.60 (m, 10 H), and 8.10 (s, 1 H).

Reaction of *C*-Phenyl-*N*-methylnitrone with 4-Ethyl-2,3-hexadienenitrile. A solution containing 0.28 g of *C*-phenyl-*N*-methylnitrone[60] and 0.25 g of 4-ethyl-2,3-hexadienenitrile[68] in 20 mL of benzene was heated at 40 °C for 6 h. The solvent was removed under reduced pressure, and the resulting light brown oil was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give 0.42 g (79%) of 4-cyano-2,2-diethyl-1-methyl-5-phenyl-3-pyrrolidinone (**31**) as a light yellow oil: IR (neat) 3080, 3050, 2980, 2940, 2270, 1775, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.83 (t, 3 H, J = 7.55 Hz), 1.46 (dq, 1 H, J = 14.50 and 7.55 Hz), 1.64 (dq, 1 H, J = 14.50 and 7.55 Hz), 1.73 (dq, 1 H, J = 14.50 and 7.55 Hz), 1.80 (dq, 1 H, J = 14.50 and 7.55 Hz), 2.15 (m, 3 H), 3.05 (d, 1 H, J = 9.86 Hz), 4.21 (d, 1 H, J = 9.86 Hz), and 7.36–7.41 (s, 5 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.42, 25.45, 27.32, 28.47, 30.34, 48.71, 67.13, 71.87, 114.36, 126.85, 127.77, 129.09, 138.65, and 205.73; MS, m/e 256 (M^+), 227, 196, 162, 105, and 84 (base); HRMS calcd for $C_{16}H_{20}N_2O$ 256.1576, found 256.1567.

Reaction of *C*-Phenyl-*N*-methylnitrone with 4,6-Dimethyl-2,3-heptadienenitrile. A solution containing 0.50 g of *C*-phenyl-*N*-methylnitrone[60] and 0.50 g of 4,6-dimethyl-2,3-heptadienenitrile[68] in 45 mL of benzene was heated at reflux for 10 h. The solvent was removed under reduced pressure, and the resulting light brown oil was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give 0.94 g (94%) of 4-cyano-1,2-dimethyl-2-(2-methylpropyl)-5-phenyl-3-pyrrolidinone (**32**) as a light yellow oil: IR (neat) 3080, 3030, 2950, 2910, 2250, 1765, 1455, 1370, 1150, 1100, 1030, 760, and 700 cm^{-1} ^1H NMR ($CDCl_3$, 360 MHz) δ 0.83 (d, 3 H, J = 6.45 Hz), 1.02 (d, 3 H, J = 6.45 Hz), 1.12 (s, 3 H), 1.72–1.85 (m, 3 H), 2.14 (s, 3 H), 3.31 (d, 1 H, J = 10.10 Hz), 4.00 (d, 1 H, J = 10.10 Hz), and 7.41–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 15.96, 23.39, 24.01, 24.57, 31.44, 44.70, 47.83, 66.98, 114.57, 127.078 128.97, 129.24, 137.88, and 205.87; MS, m/e 270 (M^+), 255, 213, 113, 105, 98, 91, and 84; HRMS calcd for $C_{17}H_{22}N_2O$ 270.1732, found 270.1713.

Reaction of *N*-Methyl-*C*,*C*-dimethylnitrone with 4-Ethyl-2,3-hexadienenitrile. A solution containing 0.22 g of *N*-methyl-*C*,*C*-dimethylnitrone[65] and 0.30 g of 4-ethyl-2,3-hexadienenitrile[68] in 25 mL of benzene was heated at 45 °C for 7 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 10% methylene chloride–hexane mixture as the eluent to give 0.45 g (87%) of 4-cyano-2,2-diethyl-1,5,5-trimethyl-3-pyrrolidinone (**33**) as a light yellow oil: IR (neat) 3020, 3000, 2980, 2940, 2210, 1765, 1650, 1600, 1465, 865, 820, and 745 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.75 (t, 3 H, J = 7.50 hz), 0.95 (t, 3 H, J = 7.50 Hz), 1.28 (s, 3 H), 1.43 (s, 3 H), 1.63 (q, 2 H, J = 7.50 Hz), 1.72 (q, 2 H, J = 7.50 Hz), 2.35 (s, 3 H), and 3.19 (s, 1 H); MS, m/e 208 (M^+), 193, 179 (base), 149, 84, and 70; HRMS calcd for $C_{12}H_{20}N_2O$ 208.1576, found 208.1563.

Reaction of *C*-Phenyl-*N*-methylnitrone with 3-Methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene. A solution containing 0.37 g of *C*-phenyl-*N*-methylnitrone[60] and 0.60 g of 3-methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene[69] in 40 mL of benzene was heated at 45 °C for 9 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 15% methylene chloride–hexane mixture as the eluent to give a white solid. Recrystallization from methylene chloride–petroleum ether gave 0.92 g (90%) of 5-phenyl-4-(*p*-tolylsulfonyl)-1,2,2-trimethyl-3-pyrrolidinone (**34**) as a white crystalline solid: mp 110–112 °C; IR (KBr) 3070, 3040, 2980, 2960, 2935, 2880, 2805, 1755, 1450, 1320, 1250, 1170, 820, 765, 700, and 655 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.09 (s, 3 H), 1.24 (s, 3 H), 2.08 (s, 3 H), 2.41 (s, 3 H), 3.96 (d, 1 H, J = 8.58 Hz), 4.30 (d, 1 H, J = 8.58 Hz), 7.23–7.38 (m, 7 H), and 7.56 (d, 2 H, J = 8.32 Hz); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.10, 21.51, 23.35, 31.40, 53.27, 64.19, 66.02, 75.14, 127.95, 128.06, 128.42, 129.05, 129.46,

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135.34, 139.75, 145.08, and 205.50. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.23; H, 6.49; N, 3.92. Found: C, 67.22; H, 6.51; N, 3.90.

Reaction of *C*-Phenyl-*N*-*tert*-butylnitrone with 3-Methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene. A solution containing 0.48 g of *C*-phenyl-*N*-*tert*-butylnitrone[70] and 0.60 g of 3-methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene[69] in 50 mL of benzene was heated at 50 °C for 7 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 15% methylene chloride–hexane mixture as the eluent to give a white solid. Recrystallization from methylene chloride–petroleum ether gave 1.01 g (94%) of *N*-*tert*-butyl-2,2-dimethyl-5-phenyl-4-(*p*-tolylsulfonyl)-3-pyrrolidinone (**35**) as a white crystalline solid: mp 59–60 °C; IR (KBr) 3055, 3005, 2980, 2975, 2965, 2910, 1750, 1600, 1360, 1310, 1140, 1080, 830, 810, 750, and 660 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.21 (s, 9 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 2.45 (s, 3 H), 3.64 (d, 1 H, J = 3.55 Hz), 5.30 (d, 1 H, J = 3.55 Hz), 7.18–7.32 (m, 5 H), 7.36 (d, 2 H, J = 8.35 Hz), and 7.69 (d, 2 H, J = 8.35 Hz); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 1.33, 21.62, 24.91, 30.56, 30.73, 56.21, 58.42, 68.34, 125.64, 126.85, 128.62, 129.05, 129.72, 134.47, 145.35, 148.46, and 208.85. Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51. Found: C, 68.87; H, 7.18; N, 3.48.

Reaction of *N*-Methyl-*C*-phenylnitrone with 1-[(2,4-Dinitrophenyl)sulfonyl]-3-methyl-1,2-butadiene. A solution containing 0.50 g of *N*-methyl-*C*-phenylnitrone[60] and 1.10 g of 1-[(2,4-dinitrophenyl)sulfonyl]-3-methyl-1,2-butadiene[71] in 50 mL of benzene was heated at 50 °C for 12 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 10% methylene chloride–hexane mixture as the eluent to give 1.48 g (93%) of 4-[(2,4-dinitrophenyl)sulfonyl]-5-phenyl-1,2,2-trimethyl-3-pyrrolidinone (**36**) as a white crystalline solid: mp 175–176 °C; IR (KBr) 3100, 3040, 2980, 2960, 1760, 1610, 1565, 1540, 1360, 1340, 1155, 915, 845, and 765 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.24 (s, 3 H), 1.30 (s, 3 H), 2.15 (s, 3 H), 4.46 (d, 1 H, J = 8.90 Hz), 4.94 (d, 1 H, J = 8.90 Hz), 7.34–7.38 (m, 3 H), 7.41–7.46 (m, 2 H), 7.33–7.36 (m, 1 H), and 7.55–7.59 (m, 2 H); MS, m/e 433 (M^+), 418, 371, 267, 212, 187, and 77; HRMS calcd for $C_{19}H_{19}N_3O_7S$ 433.0944, found 433.0917.

Reaction of 5,5-Dimethyl-1-pyrroline 1-Oxide with 4,6-Dimethyl-2,3-heptadienenitrile. A solution containing 0.42 g of 5,5-dimethyl-Δ^1-pyrroline 1-oxide[64] and 0.50 g of 4,6-dimethyl-2,3-heptadienenitrile[68] in 40 mL of benzene was heated at reflux for 36 h. The solvent was removed under reduced pressure, and the resulting brown oil was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give 0.59 g (64%) of 4,4-dimethyl-3-isopropyl-3-methyl-2-oxopyrrolizidine-1-nitrile (**37**) as a yellow oil: IR (neat) 3040, 2960, 2180, 1770, 1480, and 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.59 (d, 3 H, J = 6.74 Hz), 0.87 (d, 3 H, J = 6.74 Hz), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.33 (s, 3 H), 1.62 (dd, 2 H, J = 14.50 and 9.00 Hz), 1.80 (m, 1 H), 1.95 (m, 2 H), 2.11 (m, 2 H), 3.02 (d, 1 H, J = 10.35), and 3.51 (ddd, 1 H, J = 10.35, 9.00, and 5.77 Hz); MS, m/e 248 (M^+), 233, 220, 205, 191 (base), 180, 164, 122, and 82; HRMS calcd for $C_{15}H_{24}N_2O$ 248.1889, found 248.1871.

Reaction of 5,5-Dimethyl-1-pyrroline 1-Oxide with 3-Methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene. A solution containing 0.31 g of 5,5-dimethyl-1-pyrroline 1-oxide[64] and 0.60 g of 3-methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene[69] in 50 mL of benzene was heated at 40 °C for 12 h. The solvent was removed under reduced pressure, and the resulting oil was subjected to silica gel chromatography using a 15% methylene chloride–hexane mixture as the eluent to give a light yellow solid. Recrystallization from methylene chloride–petroleum ether gave 0.76 g (84%) of 3,3,4,4-tetramethyl-2-oxopyrrolizidinyl *p*-tolyl sulfone (**38**) as a white crystalline solid: mp 111–112 °C; IR (KBr) 3020, 2980, 2940, 2880, 1755, 1600, 1365, 1320, 1150, 1090, 820, 720, and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.02 (s, 3 H), 1.18 (s, 3 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 1.51 (m, 1 H), 1.70 (m, 2 H), 2.01 (m, 2 H), 2.48 (s, 3 H), 3.61 (d, 1 H, J = 8.70 Hz), 3.95 (ddd, 1 H, J = 8.70, 8.45, and 6.15 Hz), 7.35 (d, 2 H, J = 8.35 Hz), and 7.65 (d, 2 H, J = 8.35 Hz); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 20.12, 21.58, 24.42, 27.10, 28.51, 29.73, 43.30, 57.79, 58.20, 64.29, 74.22, 129.10, 129.61, 135.67, 145.04, and 206.99. Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18. Found: C, 64.37; H, 7.55; N, 4.17.

Reaction of *C*,*N*-Diphenylnitrone with 4-Ethyl-2,3-hexadienenitrile. A solution containing 0.40 g of *C*,*N*-diphenylnitrone[72] and 0.25 g of 4-ethyl-2,3-hexadienenitrile[68] in 25 mL of benzene was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give two fractions. The first fraction contained 0.34 g (52%) of an inseparable 1:2 mixture of *cis*- and *trans*-3-cyano-5,5-diethyl-4-oxo-2-phenyl-2,3-dihydro-1*H*-1-benzazepine (**40**) as a light yellow oil: IR (neat) 3340, 3080, 3040, 2970, 2940, 2880, 2260, 1720, 1620, 1600, 1500, 1465, 920, 760, 740, and 705 cm^{-1}; MS, m/e 318 (M^+), 289, 250, 222 (base), 212, 206, 183, 160, 91, and 77; HRMS calcd for $C_{21}H_{22}N_2O$ 318.1732, found 318.1723.

The *trans*-benzazepine showed the following ^1H NMR spectral data: ($CDCl_3$, 360 MHz) δ 0.58 (t, 3 H, J = 7.55 Hz), 0.96 (t, 3 H, J = 7.55 Hz), 1.59 (br s, 1 H), 1.71 (dq, 1 H, J = 13.85 and 7.55 Hz), 1.83 (dq, 1 H, J = 13.85 and 7.55 Hz), 1.94 (dq, 1 H, J = 13.85 and 7.55 Hz), 2.12 (dq, 1 H, J = 13.85 and 7.55 Hz), 4.28 (d, 1 H, J = 11.20 Hz), 4.77 (d, 1 H, J = 11.20 Hz), 6.58 (dd, 1 H), 7.09 (m, 2 H), and 7.15–7.45 (m, 6 H). The *cis*-benzazepine showed the following ^1H NMR spectral data: ($CDCl_3$, 360 MHz) δ 0.70 (t, 3 H, J = 7.55 Hz), 0.93 (t, 3 H, J = 7.55 Hz), 1.71 (dq, 1 H, J = 13.85 and 7.55 Hz), 1.83 (dq, 1 H, J = 13.85 and 7.55 Hz), 1.94 (dq, 1 H, J = 13.85 and 7.55 Hz), 2.12 (dq, 1 H, J = 13.85 and 7.55 Hz), 3.38 (br s, 1 H), 4.41 (d, 1 H, J = 7.75 Hz), 4.79 (d, 1 H, J = 7.75 Hz), 6.58 (m, 1 H), and 7.05–7.45 (m, 8 H).

The second fraction contained 0.17 g (26%) of 4-cyano-2,2-diethyl-1,5-phenyl-3-pyrrolidinone (**39**) as a white crystalline solid: mp 134–136 °C; IR (KBr) 3070, 3040, 2980, 2960, 2240, 1775, 1665, 1610, 1505, 1460, 770, 750, and 710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.75 (t, 3 H, J = 7.45 Hz), 1.19 (t, 3 H, J = 7.45 Hz), 1.68 (dq, 1 H, J = 14.43 and 7.45 Hz), 1.82 (dq, 1 H, J = 14.43 and 7.45 Hz), 1.95 (dq, 1 H, J = 14.43 and 7.45 Hz), 2.11 (dq, 1 H, Jj = 14.43 and 7.45 Hz), 3.41 (d, 1 H, J = 10.52 Hz), 5.19 (d, 1 H, J = 10.52 Hz), and 8.28–8.86 (m, 10 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.02, 9.32, 28.53, 33.39, 49.78, 63.49, 75.17, 113.95, 121.74, 122.55, 126.34, 128.50, 128.72, 129.20, 138.79, 143.17, and 205.36; MS, m/e 318 (M^+), 289 (base), 180, 161, 132, 113, 104, and 77; HRMS calcd for $C_{21}H_{22}N_2O$ 318.1732, found 318.1722.

Reaction of *C*,*N*-Diphenylnitrone with 3-Methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene. A solution containing 0.53 g of *C*,*N*-diphenylnitrone[72] and 0.60 g of 3-methyl-1-(*p*-tolylsulfonyl)-1,2-butadiene[69] in 50 mL of benzene was heated at reflux for 8 h. The solvent was removed under reduced pressure, and the resulting yellow oil was subjected to silica gel chromatography using a 15% methylene chloride–hexane mixture as the eluent to give two fractions. The first fraction contained 0.8 g (65%) of an inseparable (1:2) mixture of *cis*- and *trans*-3-(*p*-tolylsulfonyl)-5,5-dimethyl-4-oxo-2-phenyl-2,3-dihydro-1*H*-1-benzazepine (**42**): IR (neat) 3375, 3100, 3070, 3020, 2980, 2920, 1730, 1600, 1500, 1460, 1150, 860, 820, 760, and 810 cm^{-1}. The trans isomer showed the following ^1H NMR spectral data: ($CDCl_3$, 360 MHz) δ 1.37 (s, 3 H), 1.43 (s, 3 H), 1.81 (s, 3 H), 4.22 (d, 1 H, J = 11.05 Hz), 4.91 (d, 1 H, J = 11.05 Hz), and 6.80–7.75 (m, 13 H). the cis isomer showed the following spectral data: ^1H NMR ($CDCl_3$, 360 MHz) δ 1.36 (s, 3 H), 1.40 (s, 3 H), 1.83 (s, 3 H), 4.21 (d, 1 H, J = 7.50 Hz), 6.23 (d, 1 H, J = 7.50 Hz), and 6.80–7.75 (m, 13 H); HRMS calcd for $C_{25}H_{25}NO_3S$ 419.1555, found 419.1548.

The second fraction was a white solid. Recrystallization from methylene chloride–petroleum ether gave 0.62 g (35%) of 2,2-dimethyl-1,5-diphenyl-4-(*p*-tolylsulfonyl)-3-pyrrolidinone (**41**) as a white crystalline solid: mp 153–154 °C; IR (KBr) 3060, 3040, 2980, 2960, 1750, 1600, 1495, 1320, 1150, 1080, 815, 770, 705, and 670 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.00 (s, 3 H), 1.51 (s, 3 H), 2.46 (s, 3 H), 4.10 (d, 1 H, J = 7.11 Hz), 5.55 (d, 1 H, J = 7.11 Hz), 6.96–7.40 (m, 12 H), and 7.75 (d, 2 H, J = 8.30 Hz); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.64, 21.55, 26.11, 59.59, 67.38, 75.54, 123.14, 123.84, 127.51, 127.69, 128.39, 128.50, 129.23, 129.62, 135.00, 140.01, 142.39, 145.41, and 205.35. Anal. calcd for $C_{25}H_{25}NO_3S$: C, 71.57;

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H, 6.02; N, 3.34. Found: C, 71.47; H, 6.03; N, 3.29.

Kinetic Measurements. All thermolysis experiments were carried out in a TAMSON TC-9 constant-temperature oil bath. All solvents used were purified and freshly distilled prior to use. A stock solution was prepared by dissolving 5.363 mg of 7 in 25 mL of the appropriate solvent. One milliliter of the above solution was diluted by a factor of 10. The resulting solution was distributed to six different sample tubes which were degassed and sealed. The tubes were inserted into a constant-temperature oil bath and were withdrawn at periodic intervals. Their UV spectra were determined by using a Hewlett-Packard 8451A diode array spectrophotometer. Absorbance data were acquired for at least four half-lives. First-order rate constants were calculated from a computer-assisted linear least-squares regression analysis of ln $[A - A_0]$ vs time. At least three runs were averaged for each data point. Agreement between runs was to within 10%. Correlation coefficients were generally >0.99. Erying and Arrhenius parameters were determined by least-squares analysis, by using rate constants for three different temperatures.

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The 1-Aza-Cope Rearrangement[1]

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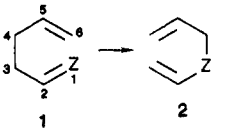
The 1-aza-Cope rearrangements of azavinylcyclohexene derivatives were investigated. It was observed that an *N*-acyl substituent on the 1-aza 1,5-diene provides a sufficient driving force for this normally contrathermodynamic process. Although simple derivatives have high activation energies proceeding in relative low overall yield, a methoxy substituent at C-4 of the aza diene as well as its incorporation into strained bicyclic ring systems facilitates the 1-aza-Cope rearrangement. Because the aza diene precursors are readily available by using the Diels–Alder reaction with acrolein derivatives, this process has synthetic potential for the preparation of nitrogen heterocycles. This scheme is illustrated with the preparation of a hydrolulolidine providing a formal total synthesis of (±)-aspidospermine.

It has been over 45 years since the 3,3-sigmatropic shift of 1,5-dienes (the Cope rearrangement) has been recognized as a general transformation in organic chemistry.[2,3] This reaction has continued to attract the attention of organic chemists, particularly with respect to studies directed to understanding the reaction pathway. At least two geometries,[4] chair and boat, and three mechanisms have often been proposed and are possibly operative among the various Cope rearrangements.[3a,b]

Uncertainties about the mechanism of the Cope rearrangement have not prevented this reaction from being exploited by synthetic chemists. It has been valuable for the alteration of the connectivity to produce new structures that would not be readily accessible with other methods.[5]

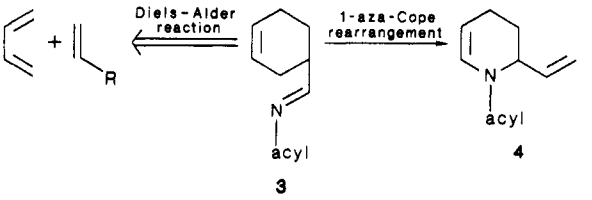
Heteroatomic versions of the Cope rearrangement, Z = O or NR, are known. Primarily because of the greater stability of carbon–heteroatom π-bonds[6] these reactions are usually driven from right to left (**2** → **1**) (Scheme I). When Z = O this reaction is the well-known Claisen rearrangement and has taken on considerable importance

Scheme I



1 2

Scheme II



3 4

as a synthetic transformation[7] as well as being the focus of a number of mechanistic studies.[8]

The 3-aza-Cope rearrangement (**2** → **1**, Z = NR) is also well-known.[9] Because this sigmatropic shift is accelerated

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(2) (a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. (b) Cope, A. C.; Hofmann, C. M.; Hardy, E. M. *Ibid.* **1941**, *63*, 1852. (c) Cope, A. C.; Levy, H. *Ibid.* **1944**, *66*, 1684.

(3) For reviews concerned with various aspects of the Cope rearrangement, see: (a) Gajewski, J. J. *Hydrocarbon Thermal Isomerization*; Academic: New York; pp 163–176. (b) Wehrli, R.; Hansen, H.-J.; Schmid, H. *Chimia* **1976**, *30*, 416. (c) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (d) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (e) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.

(4) For a more complete analysis of possible geometries for the Cope rearrangement, see: Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7149.

(5) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; ACS Monograph 189; American Chemical Society: Washington, DC, 1983; p 443.

(6) The π-bond strengths for $CH_2{=}CH_2$, $CH_2{=}O$, and $CH_2{=}NH$ have been calculated to be 59.4, 72.4 and 74.3 kcal/mol, respectively (Shaw, R. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; p 131).

(7) (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (b) Bennett, G. B. *Synthesis* **1977**, 589. (c) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.

(8) For recent examples, see the following references and the work cited therein: (a) Coates, R. M.; Robers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (b) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. (c) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636.

(9) Although the terms 3-aza-Cope and 1-aza-Cope rearrangement are the most commonly used when Z = N, the term aza-Claisen has also been used for this process. This latter designation would be a misuse of the "replacement nomenclature" (For example, see: *Nomenclature of Organic Compounds. Principles and Practice*; Fletcher, J. H., Dermer, O. C., Fox, R. B., Eds.; American Chemical Society: Washington, DC, 1974; Chapter 7) since it would imply there is *both* a nitrogen and oxygen atom present in the six-atom chain. These latter compounds are known and undergo the Claisen rearrangement, but they are distinct from the class of compounds discussed in this paper. (a) Heimgartner, H.; Schmid, H. in *Advances in Organic Chemistry*; Taylor, E. C., Ed.; Academic: New York, 1979; Vol. 9, Part 2, p 656. (b) Winterfeldt, E. *Fortshr. Chem. Forsch.* **1971**, *16*, 75.

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