Heterocyclic Synthesis via the Reaction of Nitrones and Hydroxylamines with Substituted Allenes

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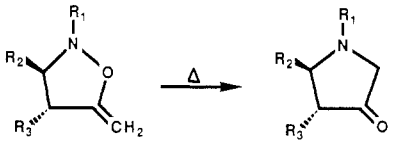
The 1,3-dipolar cycloaddition of *N*-methyl- and *N*-phenyl-*C*-phenylnitrone with several allenes has been investigated. In the case of dimethylallene, a 1:1 mixture of products derived from dipolar cycloaddition across both π-bonds was obtained. The formation of a benzazepinone derivative from this reaction was rationalized in terms of a subsequent rearrangement of a transient 5-methyleneisoxazolidine. In contrast to this result, cycloaddition using methoxyallene proceeded with high regioselectivity, giving rise to a 4-(methoxymethylene)-substituted isoxazolidine. The regioselectivity observed is not in agreement with FMO theory, and steric factors do not seem to play a role in the cycloaddition. The reaction of hydroxylamines with carboalkoxy- and phenylsulfonyl-substituted allenes was also investigated. The reaction encountered is markedly dependent on the nature of the substituent group present at the 1-position of the allene. Carboalkoxy-substituted allenes possessing a methyl group react to produce isoxazolin-5-ones. Simple carboalkoxy-substituted allenes, on the other hand, react with nitrones to give a 2:1 cycloadduct derived from a transient nitrone intermediate. The product distribution is probably related to a competition between tautomerization to a nitrone versus lactonization of the transient vinylhydroxylamine produced by addition of hydroxylamine to the allene.

The 1,3-dipolar cycloaddition reaction has long been recognized as a favored strategy for the synthesis of heterocyclic rings, often with a high degree of stereochemical control.[1] As part of an ongoing program aimed at the development of general methods for the construction of nitrogen-containing heterocycles, we have been investigating the 1,3-dipolar cycloadditions of nitrones with activated allenes.[2-4] In our earlier studies, efforts were focused on probing the potential of utilizing the 5-methyleneisoxazolidine ring system for alkaloid synthesis.[2-8] As an extension of our earlier work, we set out to



investigate the dipolar cycloaddition behavior of nitrones with various allenes with the expectation that the resulting cycloadducts should be of some use in organic synthesis. In this paper we report the results of these studies.

Results and Discussion

Allenes are an interesting group of substrates since they contain two positions for attack.[9] MNDO calculations indicate that the introduction of an electron-withdrawing group on the π-bond causes a significant lowering of the LUMO energy level compared with allene, and the largest LUMO coefficient resides on the position bearing the substituent group.[10,11] This suggests that the reaction of nitrones with electron-deficient allenes 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 various nitrones with allenes possessing cyano, carbomethoxy, or phenylsulfonyl substituents.[3]

As a continuation of our earlier work, we have studied the reaction of nitrones with other substituted allenes. As our first model we investigated the cycloaddition behavior of *C*,*N*-diphenylnitrone with 1,1-dimethylallene. This reaction afforded two products **1** (35%) and **2** (40%), which were identified on the basis of their spectral properties (see the Experimental Section). The formation of the benzazepinone ring system can nicely be accounted for in terms of an initial 1,3-dipolar cycloaddition of the nitrone across the C_2C_3 π-bond to give a transient 5-methyleneisoxazolidine (**3**) (Scheme I). The nitrogen–oxygen bond of the resulting heterocyclic ring is expected to be readily cleaved, since such heteroatom–heteroatom bonds are known to be very weak.[12] The resulting diradical intermediate cyclizes onto the ortho position of the *N*-phenyl group.

In contrast to the low regioselectivity observed with 1,1-dimethylallene, the cycloaddition of *N*,*C*-diphenylnitrone with methoxyallene proceeded with extremely high regioselectivity, giving rise to a single cycloadduct whose structure was assigned as isoxazolidine **5**.[13] Total selectivity was also encountered in the reaction of methoxyallene with *N*-methyl-*C*-phenylnitrone. In this case a 1:1 mixture of the *E* and *Z* isomers of isoxazolidine **6** was produced. Support for the structure of **6** was obtained by LAH reduction to amino alcohol **7**. The structure of **6** was further confirmed by its conversion to enamide **8** upon

(1) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.
(2) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *J. org. Chem.* **1988**, *53*, 2238. Padwa, A.; Craig, S. P.; Chiacchio, U.; Kline, D. N. *J. Org. Chem.* **1988**, *53*, 2232. Padwa, A.; Matzinger, M.; Tomioka, Y.; Venkatramanan, M. K. *J. Org. Chem.* **1988**, *53*, 955.
(3) Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *J. Org. Chem.* **1987**, *52*, 3909.
(4) Padwa, A.; Carter, S. P.; Chiacchio, U.; Kline, D. N. *Tetrahedron Lett.* **1986**, 2683. Padwa, A.; Tomioka, Y.; Venkatramanan, M. K. *Ibid.* **1987**, 755.
(5) Aversa, M. C.; Cum, G.; Sindona, G.; Ucella, N. *J. Chem. Soc., Chem. Commun.* **1971**, 156. Cum, G.; Sindona, G.; Ucella, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 719.
(6) Tufariello, J. J.; Ali, S. A.; Klingele, H. O. *J. Org. Chem.* **1979**, *44*, 4213.
(7) LeBel, N. A.; Banucci, E. *J. Am. Chem. Soc.* **1970**, *92*, 5278.
(8) Bruche, L.; Gelmi, M. L.; Zecchi, G. *J. Org. Chem.* **1985**, *50*, 3206.
(9) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley-Interscience: New York, 1984.
(10) Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512.
(11) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
(12) Kerr, J. A. *Chem. Rev.* **1966**, *66*, 496. Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. B. *J. Am. Chem. Soc.* **1968**, *90*, 5326.
(13) Although a single 4-methyleneisoxazolidine is formed, its stereochemistry is not apparent by examination of its NMR spectrum.

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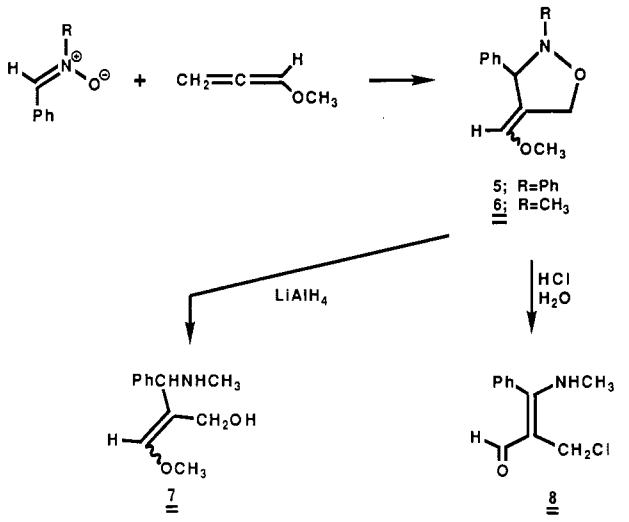
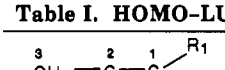


treatment with aqueous hydrochloric acid.

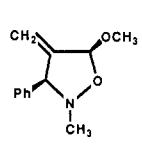
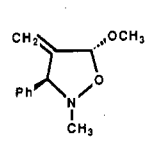
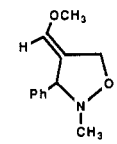
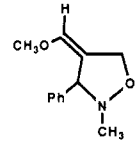
Of the three categories described by Sustmann,[14] type II is particularly common for nitrone cycloadditions.[15] The interaction that dominates in a particular case will depend on the nature of both the nitrone and dipolarophile. Most dipolarophiles react with nitrones to give 5-substituted isoxazolidines with high regioselectivity.[16] As the ionization potential of the nitrone decreases or the electron affinity of the dipolarophile increases,[17] an increasing tendency toward production of 4-substituted isoxazolidines is found.[18] The effect of substituents on the HOMO-LUMO energy levels of allene were determined by using the AMPAC program with the AM1 Hamiltonian.[19] As expected, the electron-releasing methyl and/or methoxy group increases the energy level of one of the degenerate HOMO levels of allene (see Table I).[20] The calculations reveal that dimethylallene has virtually identical orbital coefficients at the C_1–C_2 positions in both the HOMO and LUMO energy levels. This suggests that the cycloaddition will proceed with low selectivity across the more substituted π-bond. This indeed proved to be the case. FMO theory, however, fails to explain the extremely high selectivity encountered with methoxyallene. The AMPAC calculations suggest that the favored cycloadduct should be the result of a LUMO (nitrone)–HOMO (methoxyallene) interaction (i.e. ΔE = 9.06 eV). On the basis of FMO theory, methoxyallene is expected to undergo dipolar cycloaddition across the more substituted π-bond and produce the 4-methylene-5-methoxyisoxazolidine **9**. This prediction of regioselectivity is not, however, in agreement with the experimental results. Thus, the cycloaddition of nitrones with methoxyallene must be related to other factors. One possible explanation could be polar effects in the cycloaddition transition state. However, the lack of a significant solvent-polarity effect on the rate and product distribution diminishes the credibility of this explanation.

Table I. HOMO-LUMO Energies for Substituted Allenes



	HOMO	LUMO	C_1	C_2	C_3
R_1=R_2=H	−10.14		−0.47	−0.56	+0.20
		+1.24	+0.64	−0.62	−0.09
R_1=R_2=CH_3	−9.67		−0.66	−0.63	+0.09
		+0.78	+0.65	−0.66	−0.07
R_1=H; R_2=OCH_3	−9.33		−0.53	−0.63	+0.12
		+1.01	+0.67	−0.63	−0.10
R_1=H; R_2=CN	−10.45		−0.63	−0.55	+0.22
		−0.01	+0.54	−0.65	−0.05
R_1=H; R_2=CO_2CH_3	−10.62		−0.67	−0.53	+0.23
		−0.07	+0.48	−0.63	−0.04

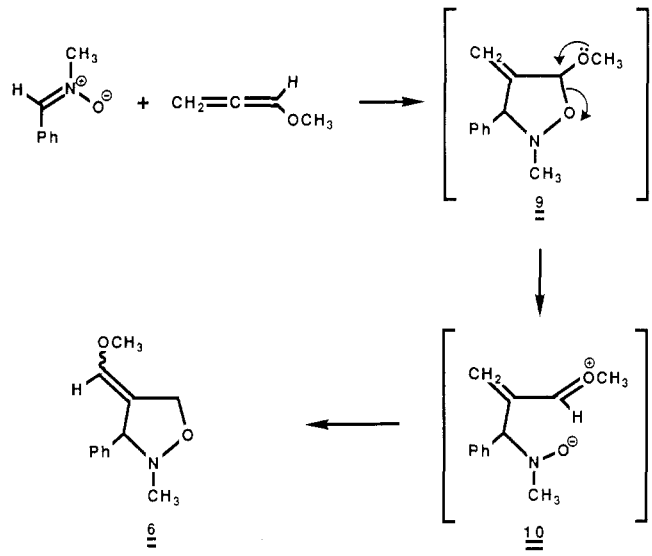
Table II. Molecular Mechanics Calculations of 4-Methylene-Substituted Isoxazolidines

strain energy, kcal/mol			
			
cis	trans	Z	E
21.83	21.17	25.64	25.77

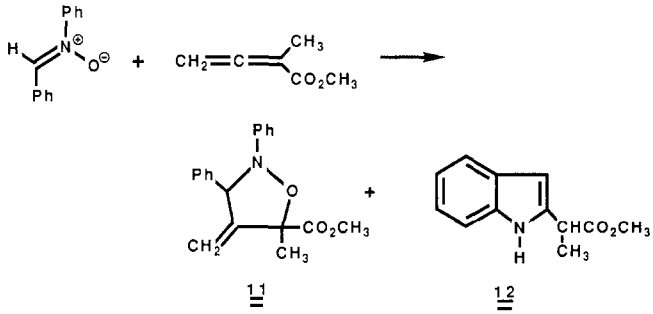
Since the answer to regiochemical control does not seem to be attributable to FMO factors, we examined simple steric effects. Over the past 15 years, molecular mechanics has developed into a powerful tool for the calculation of structures, energies, and sometimes other properties of molecules.[21] The MM2 program does a rather good job of such calculations with hydrocarbons, and it has subsequently been extended to many other functionalized kinds of molecules,[22] including systems as complex as proteins.[23] Molecular mechanics treats molecular strain energy by using a classical model in which the strain energy is expressed as a sum of energies associated with particular molecular deformations. We have used the MMX87 program as parameterized by Gajewski and Gilbert[24] and implemented in the program MODEL 2.93[25] to calculate the strain energy of the two regioisomeric cycloadducts for all the stereoisomers. We assume that the relative energy differences of the lowest energy conformations will parallel the energy differences in the transition state. The relevant strain energies are given in Table II. The results clearly show that steric factors do not play a role here since the more highly strained isoxazolidine ring system (i.e. **6**) is actually produced.[26] One possible explanation to account for the formation of isoxazolidine **6** is that this material is actually derived from the expected cycloadduct **9** followed by an extremely facile rearrangement. The presence of a lone pair of electrons on the methoxy group would be expected to facilitate the 1,3-sigmatropic shift. Further work is necessary to establish this point.

We have also examined the reaction of *C*,*N*-diphenylnitrone with methyl 2-methyl-2,3-butadienoate. In this

(14) Sustmann, R.; Schubert, R. *Tetrahedron Lett.* **1972**, 2739. Sustmann, R.; Trill, H. *Tetrahedron Lett.* **1972**, 4271. Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.
(15) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A.; Ed.; Wiley-Interscience: New York, 1984.
(16) Ali, S. A.; Senaratne, P. A.; Illig, C. R.; Meckler, H.; Tufariello, J. J. *Tetrahedron Lett.* **1979**, 4167.
(17) Houk, K. N.; Bimanand, A.; Mukherjee, D.; Sims, J.; Chang, Y. M.; Kaufman, D. C.; Domelsmith, L. N. *Heterocycles* **1977**, *7*, 293.
(18) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798.
(19) QCPE #506 (AMPAC) using the AM1 Hamiltonian.
(20) For a related set of calculations, see: Yoshida, M.; Hidaki, Y.; Nawata, Y.; Rudzinski, J. M.; Osawa, E.; Kanematsu, K. *J. Am. Chem. Soc.* **1988**, *110*, 1232.
(21) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.
(22) For some leading references, see: Profeta, S.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.
(23) Hagler, A. T.; Hyler, E.; Lifson, S. *J. Am. Chem. Soc.* **1974**, *96*, 5320.
(24) MMX87 is available from Serena software, 489 Serena Lane, Bloomington, IN 47401. Calculations were performed on a Vax 11/785 (version 4.3).
(25) We thank Professor Kosta Steliou of the University of Montreal for many fruitful discussions, helpful advice and providing a copy of the extensively rewritten Still Model program.
(26) Steric factors have been suggested to play an important role in the reaction of diazoalkane cycloadditions to difluoroallene, see: Dolbier, W. R.; Burkholder, C. R.; Winchester, W. R. *J. Org. Chem.* **1984**, *49*, 1518.



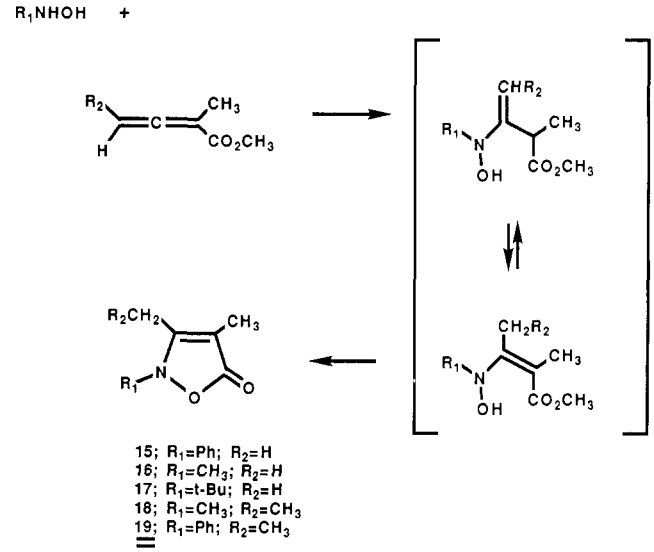
case a mixture of isoxazolidine **11** (32%)[13] and indole **12** (46%) was produced. The formation of **12** represents an



interesting molecular transformation worthy of comment. Two fundamentally different pathways seem possible. One path involves dipolar cycloaddition to produce the 5-methylene-substituted isoxazolidine **13**, which readily rearranges to benzazepinone **14** (path A, Scheme II). This material undergoes a subsequent retro-Mannich reaction followed by hydrolysis and cyclization to produce indole **12**. Blechert has reported a number of related reactions,[27] thereby providing good analogy for this sequence of transformations.

The second possibility (path B, Scheme III) involves hydrolysis of the nitrone to give benzaldehyde and phenylhydroxylamine. Addition of the hydroxylamine across the activated allenyl π-bond followed by a 3,3-sigmatropic shift and subsequent reorganization will produce indole **12**. Independent work by Martin[28] and Blechert[29] has shown that *N*-phenyl-*O*-vinylhydroxylamines undergo a hetero-Cope rearrangement to afford 2,3-unsubstituted indoles in good yield, thereby providing strong precedence for this route.

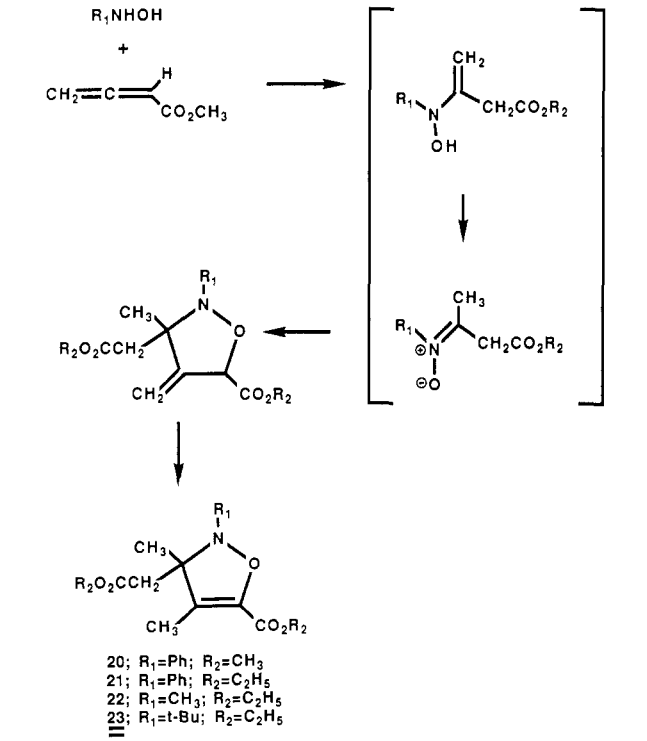
In order to differentiate between the above two pathways, we studied the reaction of phenylhydroxylamine and methyl 2-methylbuta-2,3-dienoate. Interestingly, the only product formed (98%) from this reaction corresponded to *N*-phenyl-3,4-dimethylisoxazolin-5-one (**15**). Similar results were also obtained with methyl- and *tert*-butylhydroxylamine as well as methyl 2-methylpenta-2,3-dienoate as the allene. In all of these cases the only product formed in 81–98% yield corresponded to the isoxazolin-



15; R_1=Ph; R_2=H
16; R_1=CH_3; R_2=H
17; R_1=t-Bu; R_2=H
18; R_1=CH_3; R_2=CH_3
19; R_1=Ph; R_2=CH_3

5-one ring. It's formation can be explained in terms of addition of the nitrogen atoms of the hydroxylamine onto the central carbon of the allene followed by a subsequent lactonization. This result clearly eliminates path B for the formation of indole **12**.

A different pattern of reactivity was encountered in the reaction of phenylhydroxylamine with methyl or ethyl 2,3-butadienoate. From this reaction a single crystalline solid was isolated in 72% yield and characterized as Δ^4-isoxazoline **20** (or **21**) on the basis of its spectral properties (see Experimental Section). A similar process occurred with methyl- and *tert*-butylhydroxylamine giving rise to Δ^4-isoxazolines **22** and **23** in 68% and 78% yield, respectively. Formation of the Δ^4-isoxazoline occurs by addition

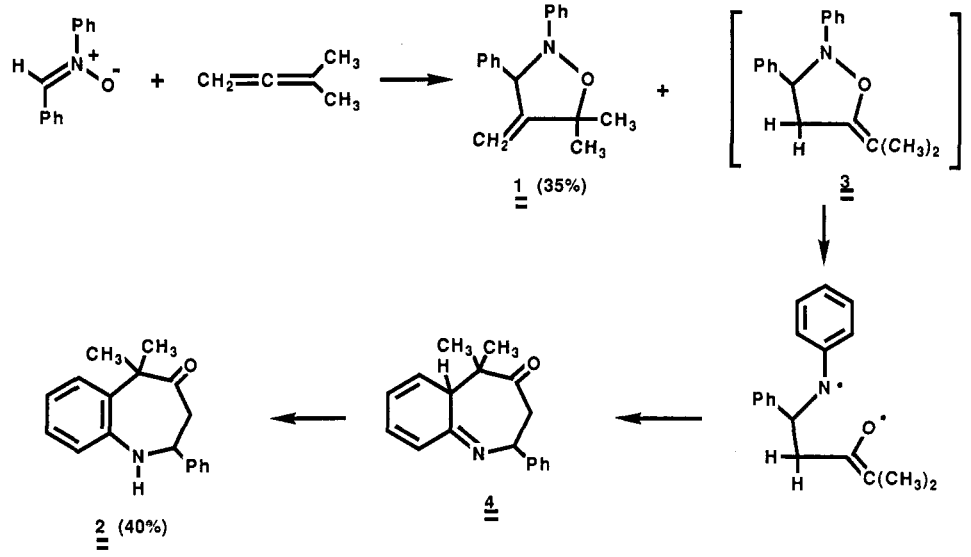


20; R_1=Ph; R_2=CH_3
21; R_1=Ph; R_2=C_2H_5
22; R_1=CH_3; R_2=C_2H_5
23; R_1=t-Bu; R_2=C_2H_5

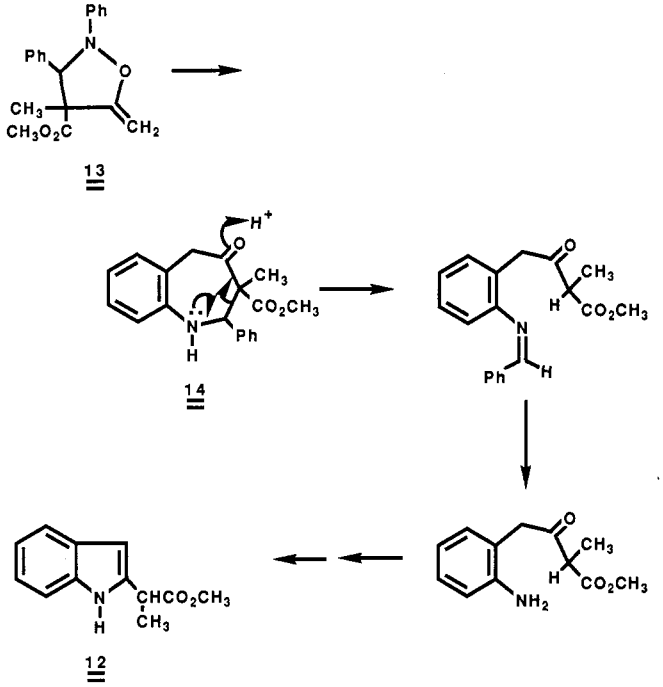
of the hydroxylamine across the activated allenyl π-bond followed by a subsequent tautomerization of the resulting vinylhydroxylamine to a nitrone intermediate. This species undergoes 1,3-dipolar cycloaddition across the allene, and the ensuing cycloadduct rapidly rearranges to the observed product. The reaction of hydroxylamines with several activated alkynes is known to proceed in a related fashion

(27) Blechert, S. *Liebigs Ann. Chem.* **1985**, 673. Wilkens, J.; Kuhling, A.; Blechert, S. *Tetrahedron* **1987**, *14*, 3237.
(28) Martin, P. *Helv. Chim. Acta* **1984**, *67*, 1647.
(29) Blechert, S. *Tetrahedron Lett.* **1984**, 1547.

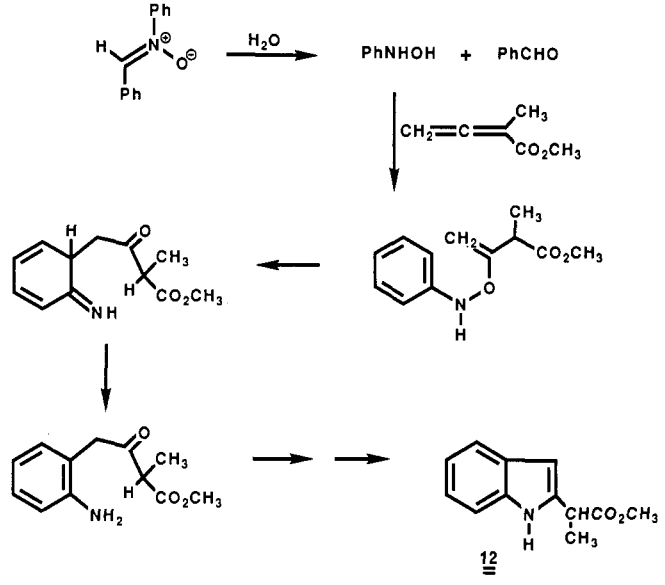
Scheme I



Scheme II. Path A



Scheme III. Path B

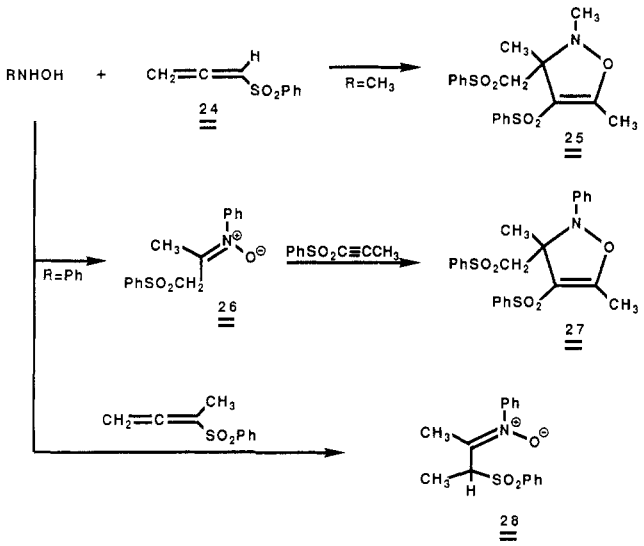


and provides good analogy for the proposed mechanism.[30-34] The above results clearly indicate that the reaction of hydroxylamines with carboalkoxy-substituted allenes is markedly dependent on the nature of the substituent group present on the 1-position of the allene. More than likely this has to do with the competition between tautomerization to the nitrone versus lactonization of the transient vinylhydroxylamine.

We also examined the reaction of methyl- and phenylhydroxylamine with (phenylsulfonyl)propadiene (**24**). This activated allene is known to be extremely susceptible toward nucleophilic addition as a consequence of its markedly lowered LUMO energy, and its reactions with heteronucleophiles have been well investigated.[35-38] We found that the reaction of **24** with methylhydroxylamine proceeded in a related fashion to that encountered with ethyl 2,3-butadienoate and gave Δ^4-isoxazoline **25** in 90% yield. In the case where phenylhydroxylamine was used (equivalent quantities), the only product isolated corresponded to 1-(phenylsulfonyl)-2-propanone *N*-phenylnitrone (**26**) as a 3:1 mixture of *E* and *Z* isomers. A similar reaction occurred on treatment of phenylhydroxylamine with 3-(phenylsulfonyl)-1,2-butadiene giving nitrone **28** as a crystalline solid in 67% yield. Reaction of nitrone **26** with either 1-(phenylsulfonyl)propyne or (phenylsulfonyl)allene **24** gave Δ^4-isoxazoline **27** in 80% yield, thereby providing convincing support for the involvement of a nitrone intermediate in the methylhydroxylamine reaction. It should

(30) Agosta, W. C. *J. Org. Chem.* **1961**, *26*, 1724.
(31) Huntress, E. H.; Leslie, T. E.; Hearon, W. M. *J. Am. Chem. Soc.* **1956**, *78*, 419.
(32) Winterfeldt, E.; Krohn, W.; Stracke, H. *Chem. Ber.* **1969**, *102*, 2346.
(33) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125.
(34) Aurich, H. G.; Hahn, K. *Chem. Ber.* **1979**, *112*, 2769.
(35) Clinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc., Perkin. Trans. 1* **1978**, 247. Clinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1430.
(36) Appleyard, G. D.; Stirling, C. J. M. *J. Chem. Soc. C* **1967**, 2686.
(37) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972; *J. Org. Chem.* **1983**, *48*, 3369; *Tetrahedron Lett.* **1984**, 1543.
(38) Fujii, I.; Ryu, K.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1984**, 844.

be noted that Parpani and Zecchi have isolated Δ^4-isoxazoline **27** by treating a 2:1 mixture of allene **24** with phenylhydroxylamine.[39]



In conclusion, the results reported here show that the reaction of nitrones and hydroxylamines with substituted allenes give rise to a myriad of heterocyclic compounds. In certain cases some of the dipolar cycloadducts rearrange under the experimental conditions used. The further generalization of these findings and their implications for the synthesis of various heterocyclic compounds are the objects of ongoing investigations.

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, a QE-300, and a Nicolet NMC-360 MHz spectrometer. ^{13}C NMR spectra were recorded on an IBM NB 200 SY 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.

Cycloaddition of *C,N*-Diphenylnitrone with 1,1-Dimethylallene. A solution containing 1.97 g of *C,N*-diphenylnitrone and 0.82 g of 1,1-dimethylallene in 5 mL of benzene was heated at reflux for 72 h. At the end of this time the solvent was removed under reduced pressure. The resulting oily residue was subjected to silica gel chromatography with a 5% ethyl acetate–hexane mixture as the eluent. The first fraction isolated contained 0.95 g (35%) of pale yellow clear oil, whose structure was assigned as 4-methylene-5,5-dimethyl-2,3-diphenylisoxazolidine (**1**) on the basis of its spectral properties: IR (neat) 3075, 3040, 2985, 2940, 2860, 1633, 1600, 1495, 1170, 907, 770, 760, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.46 (s, 3 H), 1.58 (s, 3 H), 4.58 (d, 1 H, J = 2.4 Hz), 4.83 (t, 1 H, J = 2.4 Hz), 4.90 (d, 1 H, J = 2.4 Hz), and 6.88–7.54 (m, 10 H). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.20; H, 6.95; N, 5.29.

The second fraction isolated contained 1.07 g (40%) of a white solid, mp 93–94 °C, whose structure was assigned as 5,5-dimethyl-2-phenyltetrahydrobenzazepin-4-one (**2**) on the basis of its spectral properties: IR (KBr) 3340, 3100, 3075, 3040, 2985, 2940, 2920, 1715, 1607, 1470, 1265, 770, and 705 cm^{-1}; UV (acetonitrile) 248 nm (ϵ 7000); ^1H NMR (DMSO-d_6, 360 MHz) δ 1.23 (s, 3 H), 1.3 (s, 3 H), 2.71 (d, 2 H, J = 10.8 Hz), 4.50 (t, 1 H, J = 10.8 Hz), 4.98 (br s, 1 H), 6.80 (dd, 1 H, J = 7.4 and 1.6 Hz), 7.01 (td, 1 H, J = 8.4 and 1.6 Hz), 7.08 (td, 1 H, J = 7.4 and 1.6 Hz), 7.18–7.30 (m, 5 H), and 7.36 (dd, 1 H, J = 8.4 and 1.6 Hz). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.30; H, 7.27; N, 5.26.

(39) Parpani, P.; Zecchi, G. *J. Org. Chem.* **1987**, *52*, 1417.

Dipolar Cycloaddition of *C,N*-Diphenylnitrone with Methoxyallene. A solution containing 2.30 g of *C,N*-diphenylnitrone and 2.0 g of methoxyallene in 20 mL of dichloromethane was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the resulting oil was chromatographed on a silica gel plate with a 5% ethyl acetate–hexane mixture as the eluent. The major band contained 480 mg (43%) of a pale yellow solid, mp 95–96 °C, whose structure was assigned as 4-[(*Z*)-methoxymethylene]-*N*-phenyl-3-phenylisoxazolidine (**5**) on the basis of its spectral properties: IR (KBr) 3060, 3030, 2950, 2920, 2860, 2840, 1700, 1600, 1480, 1450, 1300, 1230, 1215, 1200, 1180, 1160, 1120, 1025, 985, 960, 910, 860, 775, 755, 700, 660, and 610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3 H), 4.60 (d, J = 10 Hz, 1 H), 4.67 (d, J = 10 Hz, 1 H), 5.52 (s, 1 H), 6.08 (d, J = 2 Hz, 1 H), and 6.96–7.63 ppm (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.9, 67.1, 70.0, 115.1, 119.3, 122.0, 127.1, 127.2, 128.3, 125.8, 139.3, 140.7, and 151.0; *m/e* 267, 236, 162, 159, 129, 115, 105, 85, and 77 (base); HRMS calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1251.

Dipolar Cycloaddition of *N*-Methyl-*C*-phenylnitrone with Methoxyallene. A mixture containing 1.00 g of *N*-methyl-*C*-phenylnitrone and 1.00 g of methoxyallene in 5 mL of benzene was heated at 90 °C for 72 h. The solution was concentrated under reduced pressure, and the resulting brown oil was distilled at 150 °C (0.1 mm). The clear oil obtained was chromatographed on silica gel with a 5% ethyl acetate–hexane mixture as the eluent. The first band contained 0.71 g (28%) of a clear oil whose structure was assigned as 4-[(*E*)-methoxymethylene]-2-methyl-3-phenylisoxazolidine (**6E**) on the basis of its spectral properties: bp 120 °C (0.1 mm); IR (neat) 3010, 2970, 2940, 2850, 1725, 1500, 1455, 1440, 1235, 1205, 1185, 1140, 1125, 1020, 990, 830, 770, and 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3 H), 3.44 (s, 3 H), 3.94 (s, 1 H), 4.58 (d, 1 H, J = 12 Hz), 4.62 (d, 1 H, J = 12 Hz), 5.50 (s, 1 H), and 7.24–7.34 ppm (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.1, 59.7, 67.3, 74.2, 123.5, 127.8, 127.9, 128.3 and 128.5 and 140.3; *m/e* 205 (base), 174, 160, 159, 145, 144, 129, 128, 117, 115, 103, 91, and 77; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1102.

The second fraction contained 0.76 g (30%) of a clear oil whose structure was assigned as 4-[(*Z*)-methoxymethylene]-2-methyl-3-phenylisoxazolidine (**6Z**): bp 125 °C (0.1 mm); IR (neat) 3020, 2980, 2950, 2860, 1715, 1610, 1505, 1465, 1225, 1140, 1030, 1000, 870, 710, and 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 3 H), 3.48 (s, 3 H), 4.45 (s, 1 H), 4.52 (d, 1 H, J = 10 Hz), 4.56 (d, 1 H, J = 10 Hz), 6.10 (s, 1 H), and 7.20–7.45 ppm (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.2, 59.7, 66.6, 71.9, 120.9, 127.1, 127.7, 128.1, 128.5, and 139.6; *m/e* 205 (base), 174, 160, 159, 145, 144, 129, 128, 117, 115, 103, 87, 84, and 65; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1101.

Support for the structure of the above compounds was obtained by lithium aluminum hydride reduction. In a sealed tube equipped with a magnetic stirrer was placed 93 mg of 4-[(*Z*)-methoxymethylene]-2-methyl-3-phenylisoxazolidine (**6Z**) in 5 mL of tetrahydrofuran. To this was added 46 mg of lithium aluminum hydride, and the mixture was heated at 85 °C for 24 h. After the mixture was cooled to 25 °C, the reaction was quenched with 1 mL water and then 1 mL of a 10% sodium hydroxide solution. The mixture was filtered, and the solution was concentrated under reduced pressure to give a yellow oil. Chromatography of this material on silica gel with ethyl acetate as the eluent gave 90 mg (96%) of a yellow oil whose structure was assigned (*Z*)-2-(hydroxymethyl)-1-methoxy-3-(methylamino)-3-phenylpropene (**7**): IR (neat) 3350 (broad), 3060, 3020, 2930, 2840, 1670, 1605, 1495, 1455, 1240, 1135, 1020, 910, 760, and 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.63 (s, 3 H), 3.84 (d, 1 H, J = 12 Hz), 3.88 (d, 1 H, J = 12 Hz), 4.70 (b s, 2 H), 4.93 (s, 1 H), 6.13 (s, 1 H), and 7.20–7.42 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.3, 60.2, 61.0, 114.0, 126.9, 127.7, 128.3, 128.7, 138.1, and 148.5; UV (95% ethanol) 268 nm (ϵ 1900); *m/e* 207, 206, 205, 188, 176, 158, 142, 131, 120 (base), 115, 112, 105, 103, 91, 77, and 65; HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1257.

Further support for the regiochemical assignment of isoxazolidine **6** was obtained from an acid-induced hydrolysis reaction. A solution containing 100 mg of **6E** (or **6Z**) was heated at 85 °C for 2 h in a 90% aqueous dioxane solution, which contained two drops of concentrated hydrochloric acid. After cooling, the re-

action mixture was extracted with ether, and the ethereal solution was dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was chromatographed on a silica gel plate with a 20% ethyl acetate–hexane mixture as the eluent. The major fraction contained 80 mg (72%) of a white solid, mp 119–120 °C, whose structure was assigned as 3-(methylamino)-2-(chloromethyl)-3-phenyl-2-propenal (**8**) on the basis of its spectral data: IR (KBr) 3320, 3060, 3030, 2940, 1740, 1650, 1620, 1545, 1500, 1450, 1410, 1300, 1260, 1190, 1160, 1095, 1070, 1020, 910, 700, and 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 1.35 H), 2.99 (s, 1.65 H), 4.48 (s, 2 H), 6.22 (b s, 1 H), 7.32–7.50 (m, 5 H), and 7.55 ppm (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.9, 40.0, 128.8, 129.1, 132.1, 134.3, 138.6, 138.7, and 167.8; UV (95% ethanol) 260 nm (ϵ 15 240); *m/e* 209, 179, 174, 173, 160, 151, 143, 131, 120, 117, 116, and 115 (base); HRMS calcd for $C_{11}H_{12}NOCl$ 209.0607, found 209.0589.

Cycloaddition of *C,N*-Diphenylnitrone with Methyl 2-Methyl-2,3-butadienoate. A solution containing 1.97 g of *C,N*-diphenylnitrone and 1.35 g of methyl 2-methyl-2,3-butadienoate[40] in 5 mL of carbon tetrachloride was heated with stirring at 50 °C for 72 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 0.99 g (32%) of pale yellow clear oil whose structure was assigned as 5-carbomethoxy-5-methyl-4-methylene-2,3-diphenylisoxazolidine (**11**) on the basis of its spectral properties: IR (neat) 3070, 3040, 3000, 2960, 2850, 1742, 1601, 1495, 1250, 1128, 918, 757, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.82 (s, 3 H), 3.71 (s, 3 H), 4.79 (dd, 1 H, J = 2.5 and 1.0 Hz), 5.01 (t, 1 H, J = 2.5 Hz), 5.27 (dd, 1 H, J = 2.5 and 1.0 Hz), and 6.94–7.45 (m, 10 H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.85; H, 6.23; N, 4.48.

The second fraction isolated contained 0.94 g (46%) of a white crystalline solid, mp 89–90 °C, whose structure was assigned as methyl 2-(2-indolyl)propionate (**12**) on the basis of its spectral data: IR (KBr) 3365, 3090, 3060, 2990, 2960, 1721, 1208, 790, and 760 cm^{-1}; UV (acetonitrile) 272 nm (ϵ 7850) and 290 nm (ϵ 5330); ^1H NMR ($CDCl_3$, 360 MHz) δ 1.62 (d, 3 H, J = 7.2 Hz), 3.74 (s, 3 H), 3.96 (q, 1 H, J = 7.2 Hz), 6.36 (d, 1 H, J = 2.2 Hz), 7.07 (td, 1 H, J = 7.9 and 0.2 Hz), 7.15 (td, 1 H, J = 7.9 and 0.2 Hz), 7.33 (dd, 1 H, J = 7.9 and 0.2 Hz), 7.55 (dd, 1 H, J = 7.9 and 0.2 Hz), and 8.51 (br s, 1 H). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.47; N, 6.87.

Reaction of *N*-Phenylhydroxylamine with Methyl 2-Methylbuta-2,3-dienoate. A mixture containing 151 mg of *N*-phenylhydroxylamine and 155 mg of methyl 2-methylbuta-2,3-dienoate in 10 mL of carbon tetrachloride was heated to 50 °C for 24 h. The solvent was removed under reduced pressure and chromatographed using a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 260 mg (98%) of a white solid whose structure was assigned *N*-phenyl-3,4-dimethylisoxazolin-5-one (**15**): IR (KBr) 3090, 3030, 2970, 2935, 2880, 1730, 1610, 1590, 1500, 1490, 772, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (s, 3 H), 2.08 (s, 3 H), 7.25 (m, 2 H), and 7.40 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.8, 120, 99.2, 124.3, 128.7, 129.5, 138.9, 159.3, and 171.6; UV (methanol) 276 nm (ϵ 11 000). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.64; H, 5.92; N, 7.37.

Reaction of *N*-Methylhydroxylamine with Methyl 2-Methylbuta-2,3-dienoate. A mixture containing 87 mg of *N*-methylhydroxylamine hydrochloride and 42 mg of a 10% aqueous sodium hydroxide solution was added to a solution containing 104 mg of methyl 2-methylbuta-2,3-dienoate in 5 mL of benzene. The mixture was heated to 80 °C in a sealed Carius tube for 18 h. After cooling, the mixture was washed with a 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 116 mg (98%) as a yellow oil whose structure was assigned as 2,3,4-trimethylisoxazolin-5-one (**16**): IR ($CHCl_3$) 3010, 2930, 2900, 2400, 1750–1700, 1640, 1520, 1475, 1435, 1390, 1370, 1130, 1050, 930, and 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78 (s, 3 H), 2.11 (s, 3 H), and 3.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.7, 10.9, 38.7, 99.6, 162.3, and 171.9; *m/e* 127 (M^+), 98, 68, and 56; HRMS calcd for $C_6H_9NO_2$ 127.0633, found 127.0629.

Reaction of *N*-tert-Butylhydroxylamine with Methyl 2-Methylbuta-2,3-dienoate. A mixture containing 189 mg of *N*-*tert*-butylhydroxylamine hydrochloride and 60 mg of a 10% aqueous sodium hydroxide solution was added to a solution containing 169 mg of methyl 2-methylbuta-2,3-dienoate in 5 mL of benzene. The mixture was heated to 80 °C in a sealed Carius tube for 18 h. After cooling, the mixture was washed with a 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 239 mg (94%) of a yellow oil whose structure was assigned as *N*-*tert*-butyl-3,4-dimethylisoxazolin-5-one (**17**): IR ($CHCl_3$) 3010, 2990, 2930, 2260, 1745, 1700, 1630, 1460, 1410, 1370, 1100, 950, 910, and 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 9 H), 1.64 (s, 3 H), and 2.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.8, 13.9, 27.2, 62.8, 101.5, 160.2, and 171.5; MS *m/e* 169 (M^+), 113, and 57; HRMS calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1101.

Reaction of *N*-Methylhydroxylamine with Methyl 2-Methylpenta-2,3-dienoate. A mixture containing 165 mg of *N*-methylhydroxylamine hydrochloride and 79 mg of a 10% aqueous sodium hydroxide solution was added to a solution containing 250 mg of methyl 2-methylpenta-2,3-dienoate[41] in 5 mL of benzene. The mixture was heated to 80 °C in a sealed Carius tube for 18 h. After cooling, the solution was washed with 10% sodium carbonate and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed with an ethyl acetate–hexane (1:4) mixture as the eluent. The major fraction contained 246 mg (88%) of a colorless oil whose structure was assigned as 2,4-dimethyl-3-ethylisoxazolin-5-one (**18**): IR ($CHCl_3$) 3000, 2980, 2940, 1750–1710, 1630, 1465, 1440, 1390, 1130, and 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3 H, J = 7.7 Hz), 1.53 (s, 3 H), 2.28 (q, 2 H, J = 7.7 Hz), and 3.00 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.3, 11.7, 18.6, 38.4, 97.9, 167.1, and 171.8; HRMS calcd for $C_7H_{11}NO_2$ 141.0789, found 141.0788.

Reaction of *N*-Phenylhydroxylamine with Methyl 2-Methylpenta-2,3-dienoate. A mixture containing 102 mg of *N*-phenylhydroxylamine and 118 mg of methyl 2,4-dimethylpenta-2,3-dienoate in 10 mL of carbon tetrachloride was heated to 50 °C for 24 h. The solvent was removed under reduced pressure, and the residue was chromatographed with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 154 mg (81%) of a yellow oil whose structure was assigned *N*-phenyl-3-ethyl-4-methylisoxazolin-5-one (**19**): IR ($cHCl_3$) 3020, 2980, 2605, 1750–1710, 1640, 1595, 1500, 1425, 1050, 930, 915, 700, and 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, 3 H, J = 7.6 Hz), 1.88 (s, 3 H), 2.42 (q, 2 H, J = 7.6 Hz), 7.26 (m, 2 H), and 7.41 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.7, 12.1, 19.4, 98.6, 125.0, 129.2, 129.5, 138.9, 164.9, and 172.1; UV (methanol) 276 nm (ϵ 11 000); HRMS calcd for 203.0946, found 203.0947.

Reaction of *N*-Phenylhydroxylamine with Methyl 2,3-Butadienoate. A solution containing 0.76 g of phenylhydroxylamine and 0.77 g of methyl 2,3-butadienoate[41] in 3 mL of carbon tetrachloride was heated with stirring at 50 °C for 10 h. At the end of this time the solvent was removed under reduced pressure, and the resulting residue was subjected to silica gel chromatography with hexane as the eluent. The major fraction isolated contained 1.52 g (72%) of a yellow solid, mp 164–165 °C, whose structure was assigned as 2-phenyl-3,4-dimethyl-3-(carbomethoxymethyl)-5-carbomethoxy-Δ^4-isoxazoline (**20**) on the basis of its spectral properties: IR (KBr) 3050, 3020, 2990, 2975, 2940, 1768, 1736, 1592, 1482, 1355, 1210, 775, and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.22 (s, 3 H), 2.26 (s, 3 H), 2.67 (d, 1 H, J = 15 Hz), 6.67 (d, 1 H, J = 15 Hz), 3.60 (s, 3 H), 3.70 (s, 3 H), and 7.06–7.27 (m, 5 H). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.92; H, 6.28; N, 4.59. Found: C, 62.84; H, 6.07; N, 4.68.

Reaction of *N*-Phenylhydroxylamine with Ethyl 2,3-Butadienoate. A mixture containing 76 mg of *N*-phenyl-

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hydroxylamine and 157 mg of ethyl 2,3-butadieneoate[42] in 10 mL of carbon tetrachloride was heated to 50 °C for 24 h. The solvent was removed under reduced pressure and chromatographed with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 156 mg (73%) of a yellow oil whose structure was assigned as 2-phenyl-3,4-dimethyl-3-(carboethoxymethyl)-5-carboethoxy-Δ^4-isoxazoline (21) on the basis of the following spectral data: IR ($CHCl_3$) 3010, 2090, 2600, 1730, 1695, 1645, 1525, 1425, 1380, 1340, 1100, 1040, 935, and 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3 H, J = 7.20 Hz), 1.29 (t, 3 H, J = 7.11 Hz), 1.47 (s, 3 H), 2.16 (s, 3 H), 2.63 (d, 1 H, J = 14.3 Hz), 2.75 (s, 3 H), 2.80 (d, 1 H, J = 14.3 Hz), 4.09 (q, 2 H, J = 7.4 Hz), and 4.19 (q, 2 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 14.0, 14.1, 14.3, 19.7, 39.2, 43.6, 59.6, 60.2, 61.2, 70.3, 164.2, and 170.5; HRMS m/e calcd for 333.1576, found 333.1574.

Reaction of *N*-Methylhydroxylamine with Ethyl 2,3-Butadienoate. A mixture containing 78 mg of *N*-methylhydroxylamine hydrochloride and 37 mg of a 10% aqueous sodium hydroxide solution was added to a solution containing 210 mg of ethyl 2,3-butadienoate in 5 mL of benzene. The mixture was heated to 80 °C in a sealed Carius tube for 18 h. After cooling, the mixture was washed with a 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 173 mg (68%) of a yellow oil whose structure was assigned as *N*-methyl-3,4-dimethyl-3-(carboethoxymethyl)-5-carbethoxy-Δ^4-isoxazoline (**22**): IR ($CHCl_3$) 3010, 2090, 2600, 1730, 1695, 1645, 1525, 1425, 1380, 1340, 1100, 1040, 935, and 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3 H, J = 7.2 Hz), 1.29 (t, 3 H, J = 7.2 Hz), 1.47 (s, 3 H), 2.16 (s, 3 H), 2.63 (d, 1 H, J = 14.3 Hz), 2.75 (s, 3 H), 2.80 (d, 1 H, J = 14.3 Hz), 4.09 (q, 2 H, J = 7.4 Hz), and 4.19 (q, 2 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 14.0, 14.1, 14.3, 19.7, 39.2, 43.6, 59.6, 60.2, 61.2, 40.3, 164.2, and 170.5; m/e 271 (M^+), 256, 184, 156, and 84; HRMS calcd for $C_{13}H_{21}NO_5$ 271.1420, found 271.1423.

Reaction of *N*-*tert*-Butylhydroxylamine with Ethyl 2,3-Butadienoate. A mixture containing 142 mg of *N*-*tert*-butylhydroxylamine hydrochloride and 45 mg of a 10% aqueous sodium hydroxide solution was added to a solution containing 254 mg of ethyl 2,3-butadienoate in 5 mL of benzene. The mixture was heated to 80 °C in a sealed Carius tube for 18 h. After cooling, the mixture was washed with a 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 276 mg (78%) of a yellow oil whose structure was assigned as *N*-*tert*-butyl-3,4-dimethyl-3-(carboethoxymethyl)-5-carboethoxy-Δ^4-isoxazoline (**23**): IR ($CHCl_3$) 2915, 2870, 2830, 2300, 1730, 1645, 1420, 1280, 1230, 1020, 935, and 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, 3 H, J = 7.0 Hz), 1.24 (t, 3 H, J = 7.0 Hz), 1.25 (s, 9 H), 1.49 (s, 3 H), 2.10 (s, 3 H), 2.51 (d, 1 H, J = 13.4 Hz), 3.26 (d, 1 H, J = 13.4 Hz), 4.04 (q, 2 H, J = 6.9 Hz), and 4.14 (q, 2 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 14.2, 14.3, 23.6, 27.7, 44.1, 59.2, 59.6, 56.7, 71.7, 107.7, 162.3, 164.6, and 170.5; m/e 313 (M^+), 242, 226, 196, 170, 142, and 84; HRMS calcd for $C_{16}H_{27}NO_5$ 313.1889, found 313.1895.

Reaction of *N*-Methylhydroxylamine with (Phenylsulfonyl)propadiene. To a solution containing 128 mg of sodium hydroxide in 2 mL of water was added 250 mg of *N*-methylhydroxylamine hydrochloride followed by a solution containing 1.08 g of (phenylsulfonyl)propadiene[43] dissolved in 10 mL of benzene. The reaction mixture was heated at 50 °C for 12 h in a sealed tube. The organic layer was separated, washed with a 10% hydrochloride acid solution, and a sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by recrystallization from chloroform–hexane gave *N*-methyl-3,5-dimethyl-3-[(phenylsulfonyl)methyl]-4-(phenylsulfonyl)-Δ^4-isoxazoline (**25**) as colorless crystals (90%): mp 124–125 °C; IR (KBr) 3070, 2990, 2930, 1630, 1440, 1300, 1260, 1150, 1090, 780, 745, 730, and 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3 H), 2.30 (s, 3 H), 2.51 (s, 3 H), 3.45 (d, 1 H, J = 14.5 Hz), 3.55 (d, 1 H, J = 14.5 Hz), 7.49–7.66 (m, 6 H), and 7.80–7.93 (m, 4 H). Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.06; H, 5.15; N, 3.43. Found: C, 55.90; H, 5.23; N, 3.37.

Reaction of *N*-Phenylhydroxylamine with (Phenylsulfonyl)propadiene. A solution containing 0.70 g of *N*-phenylhydroxylamine and 1.15 g of (phenylsulfonyl)propadiene in 70 mL of benzene was stirred at room temperature for 4.5 min. Removal of the solvent under reduced pressure followed by silica gel chromatography with a 30% methanol–ethyl acetate mixture as the eluent afforded a mixture of (*E*)- and (*Z*)-1-(phenylsulfonyl)-2-propanone *N*-phenylnitrone (70%) as a colorless oil (3:1 ratio), which crystallized on standing. Fractional crystallization of the oil with a chloroform–ether–hexane mixture resulted in the isolation of the major stereoisomer, which showed the following spectral properties: mp 117–118 °C; IR (KBr) 3060, 2990, 2920, 1560, 1490, 1450, 1310, 1150, 780, 760, and 695 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.18 (s, 3 H), 4.78 (s, 2 H), 6.93–6.98 (m, 2 H), 7.35–7.41 (m, 3 H), 7.60 (t, 2 H, J = 8.0 Hz), 7.70 (t, 1 H, J = 8.0 Hz), and 8.07 (d, 2 H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 58.1, 122.7, 123.2, 128.2, 129.0, 129.5, 1296, 134.2, 136.0, 139.7, and 145.0. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.18; H, 5.28; N, 4.79.

A solution containing 186 mg of 1-(phenylsulfonyl)propyne and 119 mg of the above nitrone was stirred in 25 mL of dry benzene at room temperature for 24 h. The solution was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography with a hexane–ethyl acetate–methanol mixture as the eluent (20:30:1). Recrystallization of the major product from ether–hexane gave 2-phenyl-3,5-dimethyl-4-(phenylsulfonyl)-3-[(phenylsulfonyl)methyl]-Δ^4-isoxazoline (**27**) (80%): mp 119–120 °C; IR (CCl_4) 3070, 3000, 2930, 2850, 1640, 1600, 1590, 1495, 1450, 1325, 1150, 730 and 695 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.19 (s, 3 H), 2.50 (s, 3 H), 3.75 (s, 2 H), 7.01 (d, 2 H, J = 7.8 Hz), 7.08 (t, 1 H, J = 7.5 Hz), 7.21 (d, 2 H, J = 7.8 Hz), 7.42–7.60 (m, 5 H), 7.61 (t, 1 H, J = 7.5 Hz), 7.80 (d, 2 H, J = 7.5 Hz), and 7.97 (d, 2 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.0, 20.5, 64.5, 73.0, 111.2, 122.4, 126.7, 127.0, 127.8, 128.6, 129.1, 129.2, 133.2, 133.4, 141.7, 142.5, 144.9, and 167.7; m/e 451 (M − 18), 250, 218, 144, 125, 109, 94, and 77; HRMS calcd for $C_{24}H_{23}NO_5S_2$ 451.0912, found 451.0903.

Reaction of *N*-Phenylhydroxylamine with 3-(Phenylsulfonyl)-1,2-butadiene. A solution containing 0.59 g of *N*-phenylhydroxylamine and 1.04 g of 3-(phenylsulfonyl)-1,2-butadiene in 70 mL of benzene was stirred at room temperature for 2 h. Removal of the solvent under reduced pressure followed by silica gel chromatography with a 50% methanol–ethyl acetate mixture as the eluent afforded an oil, which crystallized on standing. Recrystallization from ethyl acetate–hexane gave 3-(phenylsulfonyl)-2-butanone *N*-phenylnitrone (**28**) in 67% yield: mp 141–142 °C; IR (KBr) 3070, 2960, 1590, 1540, 1490, 1450, 1310, 1160, 780, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, 3 H, J = 7.2 Hz), 1.97 (s, 3 H), 5.80 (q, 1 H, J = 7.2 Hz), 6.75–6.85 (m, 2 H), 7.30–7.39 (m, 3 H), 7.58 (t, 2 H, J = 7.4 Hz), 7.68 (t, 1 H, J = 7.4 Hz), and 8.05 (d, 2 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.1, 15.9, 58.2, 128.5, 128.6, 128.9, 129.0, 129.4, 129.5, 129.6, 134.1, 138.8, 141.0, and 145.2. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.49; H, 5.71; N, 4.59.

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Registry No. 1, 120610-09-5; **2**, 120610-10-8; **5**, 120610-11-9; (*E*)-**6**, 120610-12-0; (*Z*)-**6**, 120610-17-5; **7**, 120610-13-1; **8**, 120610-14-2; *cis*-**9**, 120610-29-9; *trans*-**9**, 120610-30-2; **11**, 120610-15-3; **12**, 120610-16-4; **15**, 120610-18-6; **16**, 7713-68-0; **17**, 120610-19-7; **18**, 74272-45-0; **19**, 120610-20-0; **20**, 120610-21-1; **21**, 120610-22-2; **22**, 120610-23-3; **23**, 120610-24-4; **24**, 2525-42-0; **25**, 120610-31-3; (*E*)-**26**, 120610-25-5; (*Z*)-**26**, 120610-26-6; **27**, 120610-27-7; **28**, 120610-28-8; CH_2=C=$C(CH_3)_2$, 598-25-4;

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CH_2=C=CHOMe, 13169-00-1; PhNHOH, 100-65-2; MeNHOH·HCl, 4429-44-1; *t*-BuNHOH·HCl, 57497-39-9; CH_2=C=C-$CH_3CO_2CH_3$, 18913-37-6; CH_3CH=C=$CCH_3CO_2CH_3$, 57585-04-3; CH_2=C=$CHCO_2CH_3$, 18913-35-4; CH_2=C=$CHCO_2CH_2CH_3$, 14369-81-4; $PhSO_2C$≡CCH_3, 2525-41-9; CH_2=C=CCH_3SO_2Ph, 13603-90-2; CH_2=C=CH_2, 463-49-0; CH_2=C=CHCN, 1001-56-5; *C,N*-diphenylnitrone, 1137-96-8; *N*-methyl-*C*-phenylnitrone, 3376-23-6.

Synthesis of Polynitrocyclobutane Derivatives

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The synthesis of polynitrocyclobutanes was studied. Oxidation of oximinocyclobutanes with hypochlorite followed by Zn reduction gave ethyl 3-nitrocyclobutanecarboxylate (**4a**), diethyl 3-nitrocyclobutane-1,1-dicarboxylate (**4b**), and 2,5,8,10-tetranitrodispiro[3.1.3.1]decane (**4d**) in 20–90% yields. Oxidation of aminocyclobutanes with *m*-chloroperbenzoic acid gave 1-nitrocyclobutane (**4e**), 1,3-dinitrocyclobutane (**4f**), and 2,8-dinitrodispiro[3.1.3.1]decane (**4c**) in 20–40% yields. Bromination of **4f** gave 1,3-dibromo-1,3-dinitrocyclobutane (**5**). Addition of N_2O_4 to methyl or ethyl bicyclo[1.1.0]butane-1-carboxylates gave methyl or ethyl 1,3-dinitrocyclobutanecarboxylates (**7a,b**) in 17% and 40% yields. Oxidative nitration of nitrocyclobutanes **4a,d,e** gave the corresponding *gem*-dinitrocyclobutanes in 15–78% yield. 1,1,3,3-Tetranitrocyclobutane (**8f**) and 1,1,3-trinitrocyclobutane (**11**) were obtained by similar oxidative nitration of **4f** or **7a,b** in 20–40% yields. Dispirane **4c** was converted similarly to 5,5,10,10-tetranitrodispiro[3.1.3.1]decane in 64% yield.

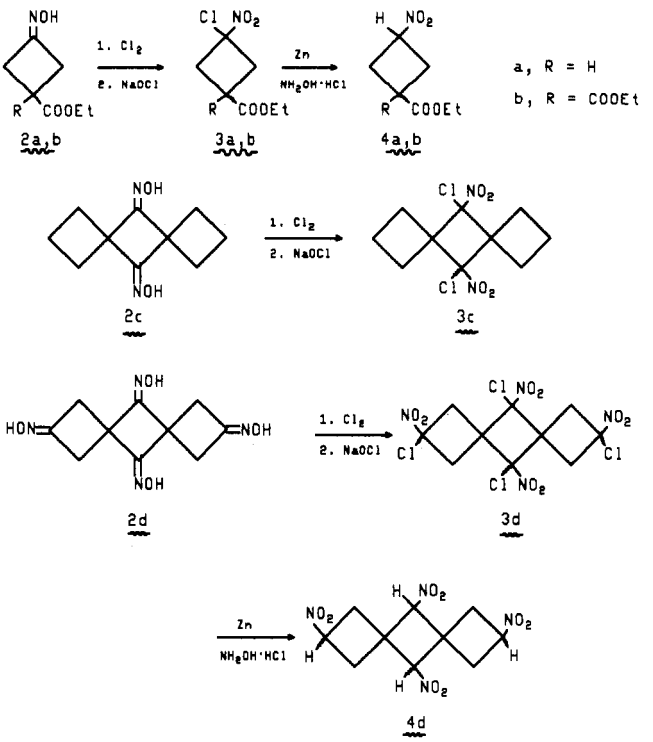
Introduction

Although there has been considerable current interest in the synthesis of cyclic polynitro compounds,[1] nitrocyclobutanes are relatively unstudied. Reported examples of this class of compounds are 1-nitrocyclobutane[2] and several phenyl-substituted derivatives.[3] The preparation of nitrocyclobutanes is complicated by the fact that standard nitrite ion displacements of cyclobutyl halides or tosylates is too slow to be of practical synthetic value.[4] We report here the synthesis of several highly nitrated cyclobutane derivatives, including the first examples of *gem*-dinitrocyclobutanes and nitro derivatives of dispiro-[3.1.3.1]decane.

Results and Discussion

Ethyl 3-oxocyclobutanecarboxylate[5] (**1a**), diethyl 3-oxocyclobutane-1,1-dicarboxylate[6] (**1b**), 5,10-dioxo-

Scheme I



dispiro[3.1.3.1]decane[7] (**1c**), and 2,5,8,10-tetraoxodispiro-[3.1.3.1]decane (**1d**) were prepared and converted to the corresponding oximes in 56–90% yields. The oximes **2a–d** were converted to the *gem*-chloronitro derivatives, **3a–d**, in 89–90% yields (Scheme I), employing chlorine gas and subsequent oxidation of the unisolated *gem*-chloronitroso intermediates with alkaline chlorine bleach under phase-transfer conditions.[8] The reduction of **3a**, **3b**, and **3d** with

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