Table I. Crystallography Data for 7

formula	$C_{24}H_{16}O_2N_2$
M	364.4
space group	$P2_1/c$
a, Å	9.688 (3)
b, Å	15.628 (3)
c, Å	12.399 (3)
β, deg	106.37 (2)
V, Å^3	1801.2 (9)
Z	4
ρ, g cm^{-3}	1.34
μ(Mo Kα), cm^{-1}	0.49
no. of unique reflections	2705
reflections used, $>2\sigma(I)$	2160
R	0.054
R_w	0.071
w	$(\sigma_F^2 + 0.000568F^2)^{-1}$

Anal. Calcd for $C_{24}H_{16}N_2O_2$: C, 79.11; H, 4.43; N, 7.69. Found: C, 78.89; H, 4.48; N, 7.36.

1-Ethoxy-1,4-diphenyl-1,4,6,11-tetrahydropyridazino[1,2-*b*]phthalazine-6,11-dione (6). Compound 4 (100 mg) was dissolved in ethanol (20 mL) by heating to reflux. On cooling, compound 6 crystallized out (60 mg, 67%): mp 240–241 °C; IR 1645 cm^{-1} (C=O); NMR (CDCl$_3$) δ 8.32–7.26 (m, 14 H), 6.47 (d, J = 1.9 Hz), 5.80 (d, J = 6.5 Hz), 4.46 (dd, 1 H), 3.73 (q, J = 6.9 Hz, 2 H), 1.23 (t, 3 H); mass spectrum, m/e (relative intensity) 410 (M$^+$, 14), 306 (10), 236 (100), 218 (10), 133 (11), 130 (35), 115 (22), 104 (50), 91 (21), 77 (63). Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N. 6.82. Found: C, 75.71; H, 5.78; N, 6.91.

X-ray Crystal Structure Analysis of 7.[9] Data were measured on an Enraf-Nonius Cad-4 automatic diffractometer. Mo K$_\alpha$ (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The standard CAD-4 centering, indexing, and data collection programs were used. The unit cell dimensions were obtained by a least-squares fit of 25 centered reflections in the range of $10 \leq \theta \leq 14°$.

Intensity data were collected by using the ω–2θ technique to a maximum 2θ of 50°. The scan width, $\Delta\omega$, for each reflection was $(0.80 + 0.35 \tan \theta)°$. An aperture with a height of 4 mm and a variable width, calculated as $(2 + {}^1/_2 \tan \theta)$ mm, was located 173 mm from the crystal. Reflections were first measured with a scan of 8.24°/min. The rate for the final scan was calculated from the preliminary scan results so that the ratio $I/\sigma(I)$ would be at least 40 and the maximum scan time would not exceed 90 s. If in a preliminary scan $I/\sigma(I) < 2$, this measurement was used as the datum. Scan rates varied from 1.03 to 8.24°/min. Of the 96 steps in the scan, the first and the last 16 steps were considered to be background. During data collection the intensities of three standard reflections were monitored after every hour of X-ray exposure. No decay was observed. In addition, three orientation standards were checked after 100 reflections to check the effects of crystal movement. If the standard deviation of the h, k, and l values of any orientation reflection exceeded 0.06, a new orientation matrix was calculated on the basis of the recentering of the 25 reference reflections.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the Multan direct method analysis.[10] After several cycles of refinements[11] the positions of the hydrogen atoms were found and added with a constant isotropic temperature factor of 0.05 Å^2 to the refinement process. Refinement proceeded to convergence by minimizing the function $\Delta w(|F_o| - |F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.2 e/Å^3 scattered about the unit cell without a significant feature.

The discrepancy indices, $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ are presented with other pertinent crystallographic data in Table I.

Registry No. 2a, 102725-66-6; 3, 82141-12-6; 4, 102725-63-3; 5, 891-22-5; 6, 102725-64-4; 7, 102725-65-5; (*E*,*E*)-PhCH=CHCH=CHPh, 886-65-7; $HOCH_2CH_3$, 64-17-5; phthalhydrazide, 253-52-1.

Supplementary Material Available: Complete X-ray data of 7, including positional and thermal parameters, bond distances and angles, and molecular structure (8 pages). Ordering information is given on any current masthead page.

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[9] We wish to thank Dr. S. Cohen for this analysis.

[10] Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. H. "Multan 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", Universities of York, England, and Louvain, Belgium.

[11] All crystallographic computing was done on a Cyber 74 computer at the Hebrew University of Jerusalem, using the Shelx 1977 structure-determination package.

1,3-Dipolar Cycloadditions of Nitrones Derived from the Reaction of Acetylenes with Hydroxylamines

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Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received February 26, 1986

A study of the reaction of hydroxylamines with a variety of acetylenes has been carried out. Methylhydroxylamine readily reacts with methyl propiolate to give methyl 4-carbomethoxy-2-methyl-4-isoxazolidine-3-acetate. Further heating of this material results in the formation of *N*-methyl-2,4-dicarbomethoxypyrrole by a mechanism which involves homolysis of the O–N linkage. The transient aziridine which is suggested to be formed reacts further to give the pyrrole. Formation of the isoxazolidine ring is suggested to proceed by addition of the hydroxylamine onto the triple bond followed by a proton shift to give a nitrone intermediate. This species undergoes 1,3-dipolar cycloaddition across the triple bond. Support for this mechanism was obtained from the reaction of *N*-phenylhydroxylamine with a variety of acyl- and aryl-substituted alkynes bearing a neighboring π-bond. With these systems, the initially formed nitrone was found to undergo smooth intramolecular dipolar cycloaddition to give a variety of substituted isoxazolidines in synthetically useful yields.

The 1,3-dipolar cycloaddition of a nitrone with an olefin is an extremely powerful, yet mild, means of producing carbon–carbon bonds as well as carbon–oxygen and carbon–nitrogen bonds.[1-6] The ring constructive power of this reaction is now well appreciated and has been employed by numerous groups in the total synthesis of al-

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[1] Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Chapter 9.

[2] Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

[3] Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.

[4] Black, D. S.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

[5] Takeuchi, Y.; Furnsaki, F. *Adv. Heterocycl. Chem.* **1977**, *21*, 207.

[6] Freeman, J. P. *Chem. Rev.* **1983**, *83*, 241.

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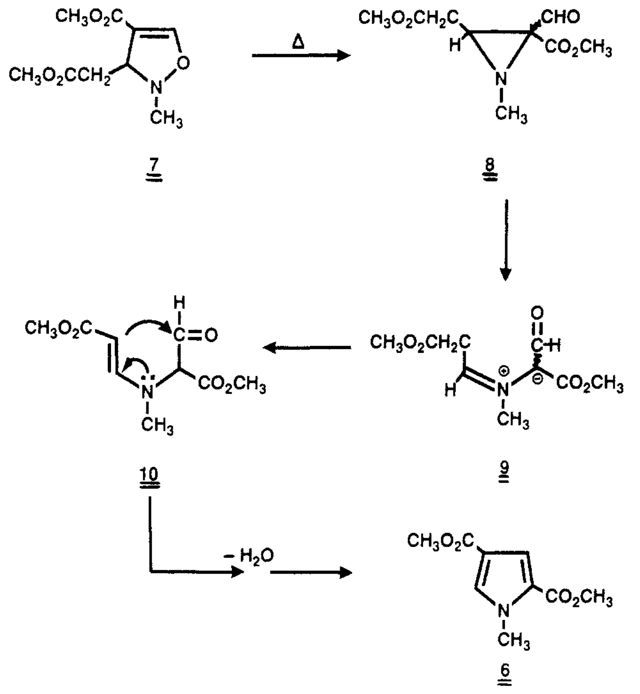
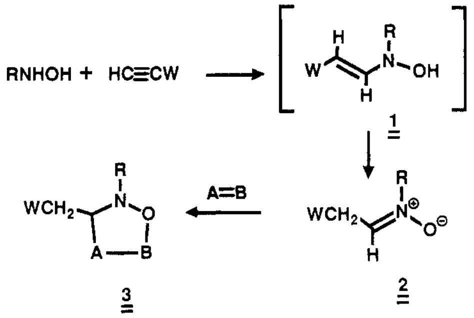
Scheme I



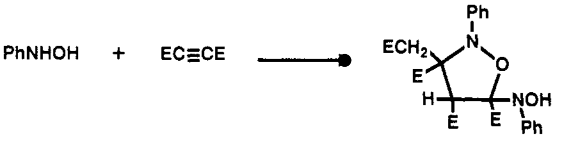
kaloids and other nitrogen-containing natural products.[7-13] Condensation of carbonyl compounds with N-substituted hydroxylamines and oxidation of N,N-disubstituted hydroxylamines represent the most common methods for the synthesis of nitrones.[14] While nitrones are versatile synthetic intermediates especially useful for 1,3-dipolar cycloaddition reactions, they are prone to undergo numerous side reactions. The thermal cycloreversion of isoxazolidines represents another method that has been successfully utilized for nitrone formation.[15] In certain cases, however, drastic conditions are required for the fragmentation to proceed.[16] LeBel and co-workers have recently developed two new methods for the synthesis of nitrones which involve the N-alkylation of *O*-trimethylsilyl oximes[17] and a Grob type fragmentation of *N*-hydroxyamino sulfonates.[18]

There is a continuing need to develop mild and versatile procedures for the synthesis of nitrones. As part of our ongoing interest in synthetic applications of nitrone cycloaddition chemistry,[19] we thought it worthwhile to examine a route to nitrones which involves the addition of hydroxylamines to activated acetylenes. The development of this strategy was based on literature reports that primary and secondary amines undergo facile nucleophilic addition to activated alkynes.[20-24] We reasoned that a similar reaction of a hydroxylamine with an activated alkyne might afford nitrone **2**, which could be subsequently trapped by external dipolarophiles to give cycloadducts such as **3**. This paper outlines our successful achievement of this strategy.[24]

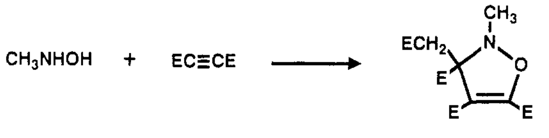


Results and Discussion

The reaction of *N*-phenylhydroxylamine with dimethyl acetylenedicarboxylate has been reported to give a 2:2 cycloadduct whose structure was assigned as compound **4**.[23] In contrast to this result, reaction of *N*-methylhydroxylamine with DMAD produced isoxazolidine **5** as the exclusive product.[24] To better understand the factors controlling the balance between these two pathways, we decided to study the reaction of methylhydroxylamine with several activated alkynes so as to define the scope and possible utilization of this process for natural product synthesis.



4; E=CO$_2$CH$_3$



5 ; E=CO$_2$CH$_3$

We initially examined the reaction of methylhydroxylamine with methyl propiolate. Heating a 1:2 mixture of the two reactants at 80 °C for 12 h gave *N*-methyl-2,4-dicarbomethoxypyrrole (**6**) in 70% yield. When the reaction was carried out at 25 °C, a new compound was formed instead (73%) whose structure was assigned as isoxazolidine **7** on the basis of its spectral properties (see Experimental Section). The regiochemical assignment is based on the chemical shift of the vinyl proton in the NMR

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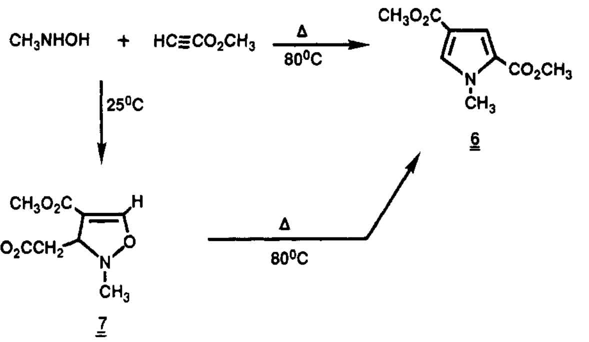
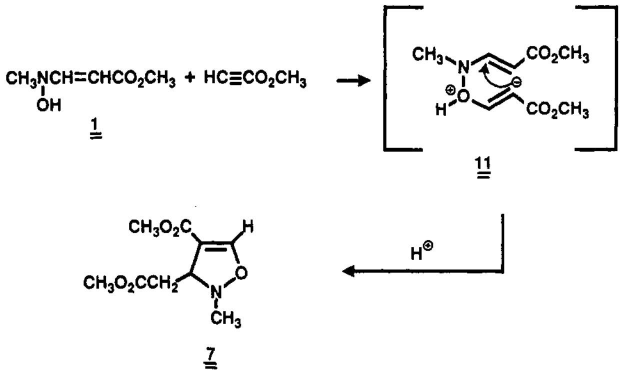
(24) For a related approach, see: Winterfeldt, E.; Krohn, W.; Stracke, H. *Chem. Ber.* **1969**, *102*, 2346.

spectrum (δ 7.27).[25] Thermolysis of isoxazolidine 7 at 80 °C for 12 h produced pyrrole 6 in 95% yield.

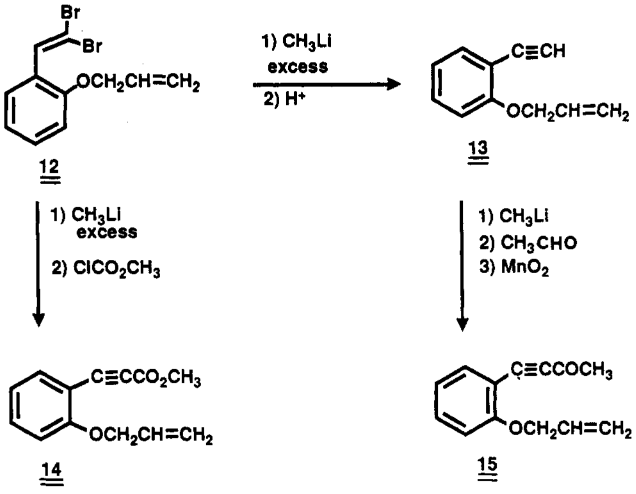


The thermal conversion of 4-isoxazolines into pyrrole derivatives has been previously postulated to involve an aroylaziridine as a transient intermediate.[26-30] The first step of this reaction was suggested to proceed by homolysis of the relatively weak O–N linkage to give a diradical intermediate which recloses to generate the aziridine ring.[28,29] The subsequent conversion of the aziridine to the pyrrole probably proceeds via conrotatory ring opening to give an azomethine ylide intermediate.[31,32] The resulting dipole undergoes an internal proton shift followed by cyclization according to the mechanism outlined above (Scheme I).

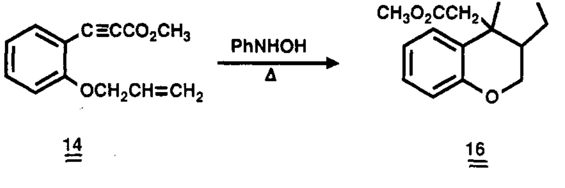
A significant body of information regarding the regiochemistry of nitrone cycloadditions has been collected since the pioneering work of Huisgen.[33-41] With methyl propiolate, nitrones react to give a 2:3 mixture of regioisomeric cycloadducts (4:5 substitution).[25] The fact that only isoxazolidine 7 was isolated from the reaction of methylhydroxylamine with methyl propiolate raises some doubt as to the possible intermediacy of nitrone 2 (W = CO_2CH_3). An alternate mechanism which does not proceed via a nitrone intermediate involves stepwise addition of the oxygen atom of *N*-hydroxy enamine 1 (W = CO_2CH_3) onto the triple bond of the propiolate followed by conjugate addition to the activated olefinic π-bond. Although the exclusive formation of isoxazoline 7 is certainly compatible with the stepwise process, the available data does not eliminate the nitrone mechanism.[42]



Further examples that would distinguish between the above two mechanistic possibilities were sought. With this in mind, we decided to study the reaction of the 2-(2-propylenyloxy)-substituted alkynes 14 and 15 with an appropriate hydroxylamine with the expectation that a nitrone intermediate would undergo rapid intramolecular dipolar cycloaddition across the unactivated π-bond.[43] Treatment of the dibromo-substituted styrene 12 with excess methyllithium followed by quenching with methyl chloroformate afforded the aryl propiolate 14 in high yield. Structure 15 was also prepared from 12 by conversion to acetylene 13 followed by reaction with methyllithium, acetaldehyde, and oxidation of the resulting propargylic alcohol with manganese dioxide.



From the reaction of *N*-phenylhydroxylamine with butynoate 14, a single crystalline solid was isolated in 86% yield and characterized as methyl 3a,4-dihydro-1-phenyl-3*H*-[1]benzopyrano[4,3-c]isoxazole-9b[1*H*]-acetate



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(25) The 5-regioisomeric cycloadduct would be expected to show the vinyl proton at ca. 5.5–6.0 ppm: Seidl, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, *102*, 904. Huisgen, R.; Seidl, H.; Wulff, J. *Chem. Ber.* **1969**, *102*, 915.

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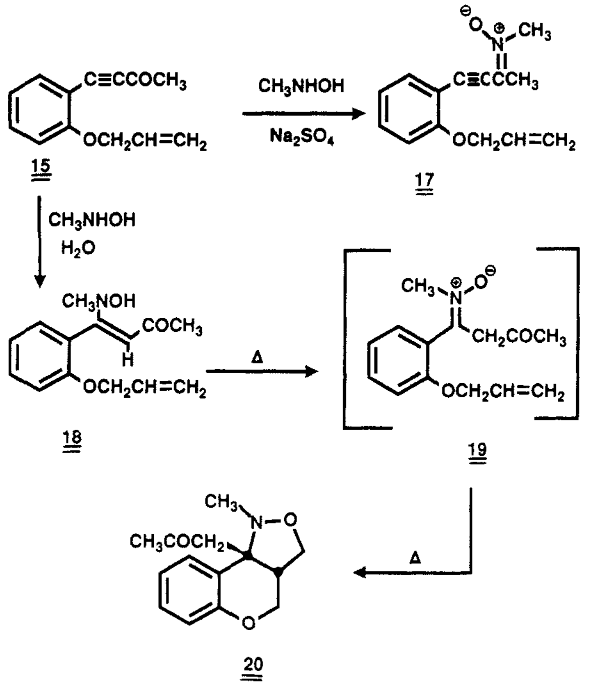
(41) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(42) A referee has suggested that the apparent cycloaddition of the nitrone tautomer of hydroxylamine 1 and methyl propiolate to give 7 might also occur via a stepwise radical process. The oxidation of 1 to the nitroxyl radical should occur readily and its conjugate addition to methyl propiolate seems reasonable. Only a catalytic amount of an oxidant would be required.

(43) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Chapter 12.

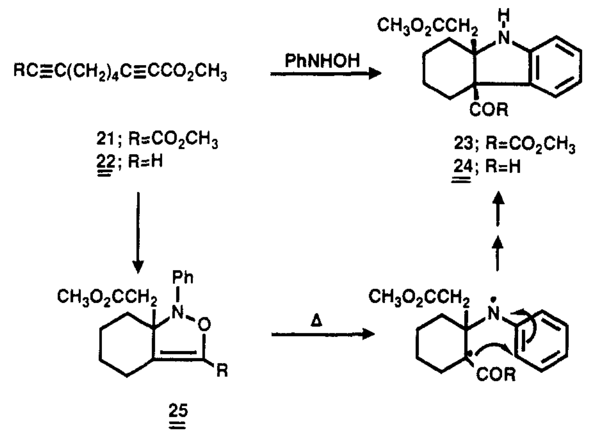
(**16**) on the basis of its spectral properties (see Experimental Section). The formation of **16** is consistent with a nitrone intermediate (i.e., **2**) which undergoes intra molecular dipolar cycloaddition across the neighboring π-bond. Related cycloadducts derived from nitrones have been reported in the literature.[44,45]

A different pattern of reactivity was encountered in the reaction of *N*-methylhydroxylamine with butynone **15**.



When an aqueous solution of the hydroxylamine was added to an ethanolic solution of **15** in the presence of anhydrous sodium sulfate, nitrone **17** was obtained in 60% yield as a mixture of geometric isomers. All attempts to induce an intramolecular cycloaddition of the nitrone failed. Examination of molecular models clearly shows that the dipole and dipolarophile cannot achieve the requisite two-plane orientation approach which is necessary for the cycloaddition to proceed.[43] The reaction followed an entirely different course when water was not removed from the mixture. Under these conditions, a cis–trans mixture of *N*-hydroxyenamides (**18**) was formed. Attempts to isolate this set of compounds failed. We found, however, that when the reaction mixture was heated in benzene, cycloadduct **20** was formed in 80% yield. The above results clearly indicate that the reaction of hydroxylamine with butynone **15** is markedly dependent of the experimental conditions employed. More than likely, the presence of water results in a hydrolysis of the nitrone to regenerate the starting acetylenic ketone. In fact, when a sample of **17** was heated in the presence of water, cycloadduct **20** was formed in good yield.

We also examined the reaction of phenylhydroxylamine with diynes **21** and **22** so as to probe whether an internal cycloaddition of a transient nitrone would occur across the triple bond. Heating a sample of **21** with phenylhydroxylamine gave rise (62%) to a single 1:1 cycloadduct, the structure of which has been assigned as tetrahydro-4a-oxocarbazole diacetate **23** on the basis of its spectroscopic properties (see Experimental Section). Most importantly, three carbonyl resonances were observed in the ^{13}C NMR spectrum. A related cycloadduct (**24**) was obtained when diyne **22** was heated with phenylhydroxylamine at 120 °C for 18 h. Formation of compounds **23** and **24** can be accounted for in terms of the intramolecular cycloaddition process followed by a subsequent rearrangement of the resulting cycloadduct (i.e., **25**). 4-Substituted isoxazolidines are known to readily undergo N–O bond cleavage,[29,46,47] thereby providing good analogy for the formation of **23** (or **24**) from **25**.



The primary spatial requirement for intramolecular dipolar cycloaddition is that the distance between the two reacting centers should be sufficiently short that effective three-center overlap of the 1,3-dipole with the dipolarophile occurs. For concerted 1,3-dipolar cycloaddition to take place, the atoms of the dipolarophile should be arranged in such a way as to allow their p orbitals to lie in a plane parallel to the plane of the 1,3-dipole. In view of the stringent spatial requirements associated with intramolecular dipolar cycloadditions,[43] we thought it worthwhile to determine whether the nitrone derived from the reaction of allyl propiolate (**26**) with phenylhydroxylamine would undergo internal cycloaddition. When the reaction was carried out in benzene at 25 °C, the only product obtained was isoxazolidine acetate **28**. All attempts to detect an intramolecular cycloaddition from a transient nitrone failed. We reasoned that placement of an electron-withdrawing substituent on the olefinic π-bond should lower the dipolarophile LU energy and thereby accelerate the rate of the internal cycloaddition. To this end we examined the reaction of 3-(methoxycarbonyl)allyl propiolate (**27**) with *N*-phenylhydroxylamine. We found, however, that the related isoxazolidine (i.e., **29**) was formed as the exclusive product. The presence of a transient nitrone species could not be detected when the above reactions were monitored by NMR spectroscopy. This would suggest that nitrone **31** rapidly reacts with *N*-hydroxy enamine **30** which is present in tautomeric equilibrium. This reaction could proceed via a 1,3-dipolar cycloaddition or by the alternate mechanism outlined in Scheme II. Certain nitrones formed from the reaction of *N*-phenylhydroxylamines and aldehydes are known to dimerize to produce isoxazolidines which are quite similar in nature to compounds **28** and **29**.[48-51] Recently, Shinkai and coworkers were able to demonstrate the existence of a thermal equilibrium between the isoxazolidine, the *N*-hydroxy enamine, and nitrone.[52] The absence of an in-

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(44) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 1117, 4313. Oppolzer, W.; Weber, H. P. *Tetrahedron Lett.* **1970**, 1121.

(45) Padwa, A.; Ku, H.; Mazzu, A. *J. Org. Chem.* **1978**, *43*, 381.

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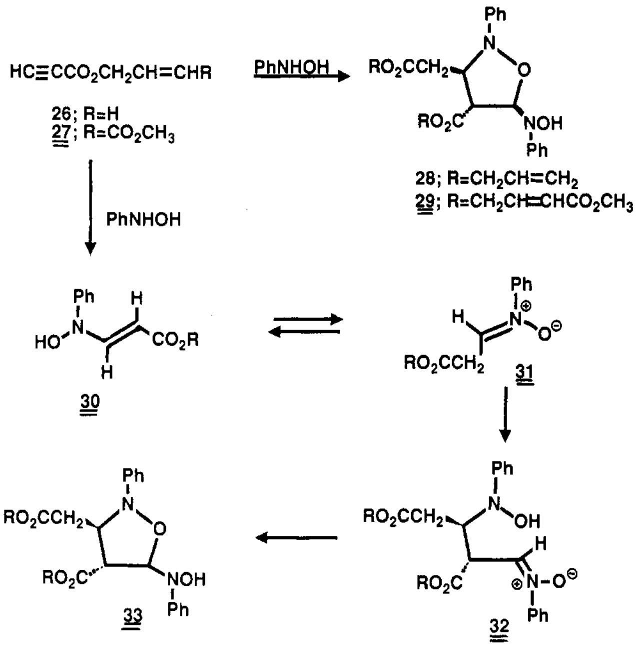
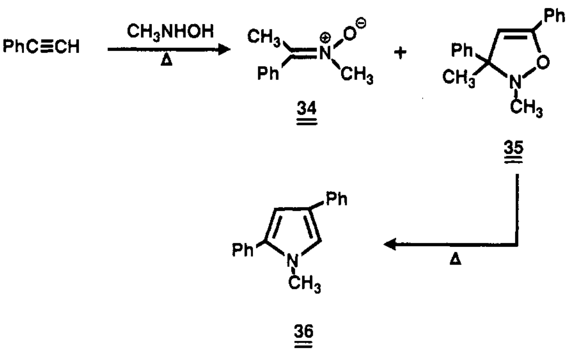
(51) Princ, B.; Exner, O. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2221.

Scheme II

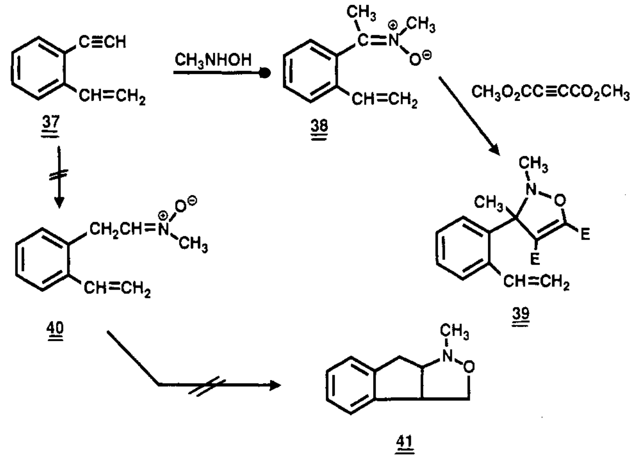


ternal cycloadduct from the reaction of allyl propiolate (**26**) and phenylhydroxylamine can be attributed to a large HOMO–LUMO gap which exists between the transient nitrone and the unactivated π-bond. The fact that the activated (methoxycarbonyl)allyl system does not under cycloaddition suggests, however, that the methylene chain of these systems is not of sufficient length to allow the dipole and dipolarophile to approach each other in parallel planes. Consequently, intramolecular cycloaddition does not occur.

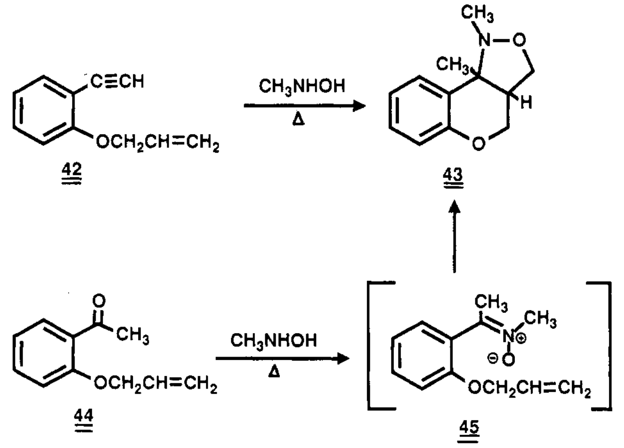
As a continuation of our work in this area, we have also studied the reaction of phenylhydroxylamine with several simple alkynes. Alkyl-substituted 1-alkynes do not react with hydroxylamines even after prolonged heating at elevated temperatures. On the other hand, heating a sample of phenylacetylene methylhydroxylamine afforded a mixture of *N*-methyl nitrone **34**, isoxazolidine **35**, and 2,4-diphenyl-*N*-methylpyrrole (**36**). The structure of isoxazolidine **35** was established on the basis of its spectral properties and by an independent synthesis. Thermolysis of **35** in benzene at 80 °C resulted in the formation of pyrrole **36**. This rearrangement probably occurs by a mechanism similar to that previously outlined in Scheme I. In contrast to the situation with the carbonyl activated alkynes, all of the products formed in the above reaction are derived from attack of the hydroxylamine onto the nonterminal acetylenic carbon atom. No characterizable products could be obtained from the regioisomeric nitrone. More than likely, addition of the hydroxylamine to phenylacetylene proceeds via a concerted syn addition (Markovnikov sense) to generate a transient *N*-vinyl amine oxide which then undergoes tautomerization to the nitrone.



The high directionality of addition to the triple bond was further demonstrated in a study involving the reaction of methylhydroxylamine to *o*-vinyl-1-ethynylbenzene (**37**). Heating a mixture of these two reagents in benzene at 120 °C afforded a single compound whose structure was established as nitrone **38**. Treatment of **38** with dimethyl acetylenedicarboxylate produced the expected dipolar cycloadduct **39**. If addition of methylhydroxylamine had proceeded to give the regioisomeric nitrone **40**, then we would have easily detected the intramolecular cycloadduct adduct **41**. No signs of this material were present in the crude reaction mixture.



The final system that we examined involved the reaction of methylhydroxylamine with (2-(2-propenyloxy)-phenyl)acetylene (**42**). Heating a mixture of these two compounds in benzene at 110 °C gave benzopyrano[4,3-c]isoxazole **43** as the exclusive product in 58% isolated yield (NMR ($CDCl_3$, 360 MHz) δ 1.52 (s, 3 H), 2.69 (s, 3 H), 2.76 (m, 1 H), 3.91 (dd, 1 H, J = 7.9 and 6.1 Hz), 4.14 (dd, 1 H, J = 7.2 and 3.0 Hz), 4.22 (m, 1 H), 4.29 (t, 1 H, J = 7.9 Hz), and 6.8–7.7 (m, 4 H)). The formation of **43** is most easily rationalized in terms of nitrone **45** which is converted to **43** by means of an intramolecular 1,3-dipolar cycloaddition reaction. In support of this suggestion, we have found that heating a sample of aryl ketone **44** with methylhydroxylamine also produced cycloadduct **43** in high yield.



In conclusion, the results reported here clearly show that the reaction of hydroxylamines with aryl and carbomethoxy-substituted acetylenes generate nitrones which un-

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(52) Reamer, R. A.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1980**, *21*, 3447.

dergo 1,3-dipolar cycloaddition. The intramolecular cycloaddition reactions provide ready access to a variety of substituted isoxazolidines in synthetically useful yields. This reaction is currently being used in our laboratory as a method for synthesizing a variety of alkaloids and we will report additional findings at a later date.

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. ^{1}H NMR spectra were obtained on Varian Em-390 and Nicolet FT-360 spectrometers. ^{13}C NMR spectra were recorded on an IBM-200 MHz spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a Finnegan 4000 mass spectrometer at an ionizing voltage of 70 eV. Flash silica gel chromatography was used to separate the various mixtures.

Reaction of Methyl Propiolate with *N*-Methylhydroxylamine. To a sample containing 1.20 g of a 20% sodium hydroxide solution was added 0.5 g of *N*-methylhydroxylamine hydrochloride followed by 1.01 g of methyl propiolate in 20 mL of benzene. The mixture was heated under a nitrogen atmosphere at 80 °C for 12 h. The two layers were separated and the organic layer was washed once with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to chromatography using a 20% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained a white solid (70%), mp 100–101 °C, whose structure was assigned as 2,4-dicarbomethoxy-*N*-methylpyrrole (**6**) on the basis of its spectroscopic properties: IR ($CHCl_3$) 2910, 1720, and 1700 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 3.82 (s, 3 H), 3.93 (s, 3 H), 7.31 (d, 1 H, *J* = 1.5 Hz), 7.38 (d, 1 H, *J* = 1.5 Hz); UV (95% ethanol) 268 nm (ϵ 9120), 263 (9530), 217 (21 800). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.02; H, 5.68; N, 7.07.

When the reaction was carried out at 25 °C for 24 h, 1.90 g (73%) of methyl 4-carbomethoxy-2-methyl-4-isoxazoline-3-acetate (**7**) was obtained: IR (neat) 3060, 2935, 1710, 1620, 1440, 1360, 1120, 1010, and 770 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.37 (dd, 1 H, *J* = 18.0 and 10.5 Hz), 2.80 (dd, 1 H, *J* = 18.0 and 3.0 Hz), 2.86 (s, 3 H), 3.68 (s, 3 H), 3.73 (s, 3 H), 4.32 (ddd, 1 H, *J* = 10.5, 3.0, and 1.8 Hz), and 7.27 (br s, 1 H); UV (95% ethanol) 260 nm (ϵ 1380); MS, *m/e* 215 (M$^+$), 173, 143 (base), 110, and 83. Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.19; H, 6.17; N, 6.49.

Preparation of Methyl 3-[2-(2-Propenyloxy)phenyl]prop-3-ynoate (14). To a solution containing 19.4 g of triphenylphosphine in 150 mL of methylene chloride at 0 °C was added 12.3 g of carbon tetrabromide. After stirring for 10 min, a solution containing 3.08 g of 2-(2-propenyloxy)benzaldehyde[53] in 10 mL of methylene chloride was rapidly added. The mixture was stirred for 30 min at 0 °C and for 1 h at 25 °C. Hexane was added, the precipitate that formed was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed by using hexane as the eluent. The major fraction isolated from the column contained 5.47 g (93%) of 1-(2,2-dibromovinyl)-2-(2-propenyloxy)benzene (**12**) as a clear oil: IR (neat) 3065, 3020, 2910, 2860, 1600, 1575, 1480, 1420, 1390, 1250, 1110, 1000, and 760 cm^{-1}; NMR (90 MHz, CCl_4) δ 4.50–4.60 (m, 2 H), 5.20–5.48 (m, 2 H), 5.83–6.23 (m, 1 H), 6.72–7.33 (m, 3 H), 7.58 (s, 1 H), and 7.60–7.72 (m, 1 H).[54]

To a solution containing 2.0 g of the above compound in 125 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere at −78 °C was added 12.6 mL of a 1.5 M solution of methyllithium in ether. After stirring for 1 h, 1.0 mL of methyl chloroformate was added. The reaction mixture was allowed to warm to −20 °C and was kept at this temperature for 2 h. The reaction mixture was then quenched with water and concentrated under reduced pressure. Standard workup gave a yellow residue which was chromatographed using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 1.29 g (95%) of methyl 3-[2-(2-propenyloxy)phenyl]prop-2-ynoate (**14**) as a clear oil: IR (neat) 2935, 2220, 2185, 1700, 1590, 1490, 1305, 1000, and 760 cm^{-1}; NMR (90 MHz, CCl_4) δ 3.43 (s, 3 H), 4.58 (dt, 2 H, *J* = 4.8 and 1.8 Hz), 5.17–5.47 (m, 2 H), 6.00 (ddt, 1 H, *J* = 17.4, 10.4, and 4.8 Hz), 6.73–7.5 (m, 4 H); UV (95% ethanol) 311 nm (ϵ 7740), 268 (11 600), 257 (10 800), and 221 (18 400); MS, *m/e* 216 (M$^+$), 201, 185, 157, 144, 128 (base), 116, and 88. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.60. Found: C, 72.30; H, 5.61.

Preparation of 4-[2-(2-Propenyloxy)phenyl]but-3-yn-2-one (15). To a solution containing 0.50 g of **12** in 30 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere at −78 °C was added 3.2 mL of a 1.5 M solution of methyllithium in ether. After being stirred for 1 h, the reaction mixture was allowed to warm to 25 °C over a 45-min period. The mixture was quenched with water and concentrated under reduced pressure. The resulting residue was chromatographed using a 2% ethyl acetate–hexane mixture as the eluent. The major component isolated from the column contained 157 mg (63%) of [2-(2-propenyloxy)phenyl]acetylene (**13**) as a clear oil: IR (neat) 3270, 3050, 2900, 2850, 2100, 1590, 1565, 1480, 1440, 1285, 1110, 1000, and 755 cm^{-1}; NMR (90 MHz, CCl_4) δ 3.13 (s, 1 H), 4.55 (dt, 2 H, *J* = 4.8 and 1.8 Hz), 5.24 (dt, 1 H, *J* = 10.2 and 1.8 Hz), 5.43 (dt, 1 H, *J* = 17.3 and 1.8 Hz), 6.02 (ddt, 1 H, *J* = 17.3, 10.2, and 4.8 Hz), and 6.69–7.43 (m, 4 H); UV (95% ethanol) 298 nm (ϵ 5700), 287 (6300), 237 (21 000); MS, *m/e* 158 (M$^+$), 157 (base), 131, 89, and 77. Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.44; H, 6.39.

To a solution containing 1.0 g of the above compound in 75 mL of anhydrous tetrahydrofuran at −20 °C under a nitrogen atmosphere was added 3.95 mL of a 1.6 M solution of methyllithium in ether. After stirring at −20 °C for 30 min, 0.53 mL of acetaldehyde was added. The mixture was allowed to stir for 2 h and was then quenched with water. Standard workup gave 4-[2-(2-propenyloxy)phenyl]but-3-yn-2-ol as a pale yellow oil: IR (neat) 3330, 2960, 2220, 1585, 1480, 1260, and 750 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.52 (d, 3 H, *J* = 7.2 Hz), 2.13 (br s, 1 H), 4.53–4.61 (m, 2 H), 4.82 (q, 1 H, *J* = 7.2 Hz), 5.18–5.58 (m, 2 H), 5.86–6.27 (m, 1 H), and 6.78–7.49 (m, 4 H). This material was used in the next step without further purification.

To a solution containing the above alcohol in 50 mL of methylene chloride was added 5.5 g of activated manganese dioxide. The mixture was allowed to stir at room temperature under a nitrogen atmosphere for 20 h and was then treated with activated charcoal and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was chromatographed using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 1.12 g (88%) of 4-[2-(2-propenyloxy)phenyl]but-3-yn-2-one (**15**) as a clear oil: IR (neat) 3060, 2910, 2100, 2060, 1670, 1490, 1410, 1290, and 1170 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.33 (s, 3 H), 4.57 (dt, 2 H, *J* = 4.68 and 1.32 Hz), 5.18–5.58 (m, 2 H), 6.02 (ddt, 1 H, *J* = 17.4, 10.6, and 4.68 Hz), and 6.77–7.49 (m, 4 H); UV (95% ethanol) 321 nm (ϵ 4600), 280 (5800); MS, *m/e* 200 (M$^+$), 185, 158 (base), 157, and 131. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.98; H, 6.04. Found: C, 77.72; H, 6.16.

Reaction of Methyl 3-[2-(2-Propenyloxy)phenyl]prop-3-ynoate (14) with *N*-Phenylhydroxylamine. A mixture containing 296 mg of **14** and 160 mg of *N*-phenylhydroxylamine in 32 mL of benzene was heated at reflux under a nitrogen atmosphere for 6 h. The solvent was removed under reduced pressure and the residue was chromatographed using a 15% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 328 mg (86%) of a white crystalline solid, mp 91–92 °C, whose structure was assigned as methyl 3a,4-dihydro-1-phenyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazole-9b-(1*H*)-acetate (**16**) on the basis of its spectral data: IR ($CHCl_3$) 2860, 1735, 1610, 1605, and 1580 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 2.95 (d, 1 H, *J* = 15.0 Hz), 3.04 (d, 1 H, *J* = 15.0 Hz), 3.49 (s, 3 H), 3.52–3.58 (m, 1 H), 4.03 (dd, 1 H, *J* = 8.28 and 4.32 Hz), 4.19 (dd, 1 H, *J* = 11.16 and 3.96 Hz), 4.24 (dd, 1 H, *J* = 11.16 and 5.76 Hz), 4.40 (t, 1 H, *J* = 8.28 Hz), and 6.37–7.23 (m, 9 H); UV (95% ethanol) 277 nm (ϵ 3600), 248 (4800); MS, *m/e* 325 (M$^+$), 217 (base), 157, 144, 128, and 116. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 10.14; H, 5.89; N, 4.31. Found: C, 69.98; H, 5.92; N, 4.29.

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(53) Mathur, S. S.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2479.

(54) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

Reaction of 4-[2-(2-Propenyloxy)phenyl]but-3-yn-2-one (15) with *N*-Methylhydroxylamine. To a mixture containing 158 mg of **15** and 1.0 g of sodium sulfate in 6 mL of ethanol at 0 °C was added a mixture containing 69.2 mg of *N*-methylhydroxylamine hydrochloride and 0.17 g of a 20% aqueous sodium hydroxide solution in 3 mL of ethanol. After being stirred for 20 min, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from an ether–pentane mixture to give 167 mg (60%) of *C*,*N*-dimethyl-*C*-(2-(2-propenyloxy)phenylethynyl)nitrone (**17**) as an off-white solid: mp 47–48 °C; IR ($CHCl_3$) 3320, 2910, 2205, 1595, and 1570 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 2.25 and 2.26 (s, 3 H), 4.01 and 4.02 (s, 3 H), 4.60 (dt, 2 H, *J* = 5.28 and 1.35 Hz), 5.31 (ddt, 1 H, *J* = 10.47, 1.44 and 1.35 Hz), 5.46 (ddt, 1 H, *J* = 17.25, 1.44 and 1.35 Hz), 6.05 (ddt, 1 H, *J* = 17.25, 10.47 and 5.28 Hz) and 6.87–7.43 (m, 4 H); UV (methanol) 339 nm (ϵ 20 700), 328 nm (22 000), 300 (19 100), and 234 (11 000); MS, *m/e* 229 (M$^+$), 145, 115, and 56 (base). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 74.43; H, 6.64; H, 6.07.

The reaction was also carried out in the absence of sodium sulfate. To a solution containing 219 mg of **15** in 5 mL of ethanol at 0 °C was added a mixture containing 91 mg of *N*-methylhydroxylamine hydrochloride and 0.22 g of a 20% aqueous sodium hydroxide solution in 3 mL of ethanol. The mixture was stirred at 0 °C for 1.5 h and was then diluted with ether and extracted with water. The ethereal solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to leave behind a yellow oil. The NMR spectrum of the oil showed singlets at δ 1.96, 2.20, 3.25, and 3.49. This material was dissolved in 25 mL of benzene and the mixture was heated at reflux under a nitrogen atmosphere for 15 h. The solvent was removed under reduced pressure and the residue was chromatographed using ether as the eluent. The major fraction isolated from the column contained 86 mg (80%) of a thick oil whose structure was assigned as 3a,4-dihydro-9b(1*H*)-(2-oxopropyl)-1-phenyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazole (**20**) on the basis of its spectral properties: IR (neat) 2950, 2865, 1700, 1600, 1575, 1480, 1220, 1060, and 765 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 2.49 (s, 3 H), 2.92 (d, 1 H, *J* = 14.8 Hz), 3.21 (d, 1 H, *J* = 14.8 Hz), 3.10–3.33 (m, 1 H), 3.77–4.03 (m, 2 H), 4.17 (t, 1 H, *J* = 8.4 Hz), 4.27 (dd, 1 H, *J* = 11.4 and 4.92 Hz), and 6.83–7.33 (m, 4 H); UV (95% ethanol) 283 nm (ϵ 1930), 271 (2150), and 216 (sh, 7600); MS, *m/e* 247 (M$^+$, base), 201, 190, 159, 141, 105, 91, and 77. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 68.04; H, 6.89; N, 5.65.

Preparation of Dimethyl Deca-2,8-diynedioate (21). To a solution containing 1.0 g of 1,7-octadiyne in 150 mL of tetrahydrofuran at −20 °C under a nitrogen atmosphere was added 11.8 mL of a 1.6 M solution of methyllithium in ether. After the addition was complete, the mixture was allowed to stir for 10 min. To the resulting white suspension was added 2.0 mL of methyl chloroformate. After being stirred for 1.5 h, the mixture was quenched with water. Standard workup followed by silica gel chromatography using an ether–hexane (3:1) mixture gave 1.93 g (92%) of dimethyl deca-2,8-diynoate (**21**) as a white solid, mp 38–39 °C: IR ($CHCl_3$) 2910, 2235, 1710, and 1420 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.63–1.87 (m, 4 H), 2.28–2.50 (m, 4 H), 3.77 (s, 6 H); UV (95% ethanol) 215 nm (ϵ 9560); MS, *m/e* 232 (M$^+$), 207, 163, 159, 131, 103 (base), 91, 66, and 59. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.68; H, 6.37.

Preparation of Methyl Nona-1,8-diynoate (22). To a solution containing 1.0 g of 1,7-octadiyne in 100 mL of tetrahydrofuran under a nitrogen atmosphere at −20 °C was added 5.9 mL of a 1.6 M solution of methyllithium in ether. After being stirred for 10 min, 1.45 mL of methyl chloroformate was added to the cloudy solution. The mixture was stirred for 1 h and was then worked up in the standard fashion. Chromatography of the residue using a 5% ether–pentane mixture as the eluent gave 0.93 g (60%) of methyl nona-1,8-diynoate (**22**) as a colorless oil: IR (neat) 3270, 2935, 2860, 2135, 2130, 1725, 1435, 1300, 1085, and 760 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.60–1.85 (m, 4 H), 2.11–2.45 (m, 5 H), 3.69 (s, 3 H); MS, *m/e* 164 (M$^+$), 163, 105 (base), and 79. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.80; H, 7.39.

Reaction of Dimethyl Deca-2,8-diynedioate (21) with *N*-Phenylhydroxylamine. A mixture containing 0.37 g of **21** and 0.18 g of *N*-phenylhydroxylamine in 25 mL of benzene was heated at reflux under a nitrogen atmosphere for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed using a 35% ether–hexane mixture as the eluent. The major fraction isolated from the column contained 0.34 g (62%) of dimethyl 1,2,3,4-tetrahydro-4a-oxacarbazole-4a,9a-diacetate (**23**) as a pale yellow solid, mp 90–91 °C: IR ($CHCl_3$) 3360, 2910, 1730, 1690 and 1610 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.26–2.11 (m, 8 H), 2.80 (d, 1 H, *J* = 15.8 Hz), 2.99 (d, 1 H, *J* = 15.8 Hz), 3.55 (s, 3 H), 3.71 (s, 3 H), 4.91 (s, 1 H), and 6.69–7.26 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.69, 21.12, 27.60, 32.83, 38.19, 51.52, 52.09, 62.70, 67.74, 110.68, 119.05, 124.29, 127.33, 129.29, 150.17, 164.93, 172.26, 199.97; UV (95% ethanol) 298 nm (ϵ 1860), 237 (7850); MS, *m/e* 331 (M$^+$), 244 (base), 170 and 143. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.10; H, 6.42; N, 4.17.

Reaction of Methyl Nona-1,8-diynoate (22) with *N*-Phenylhydroxylamine. A solution containing 148 mg of **22** and 101 mg of *N*-phenylhydroxylamine in 10 mL of benzene was heated at 120 °C in a sealed Carius tube for 18 h. The solvent was removed under reduced pressure and the residue was chromatographed using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 91 mg of methyl 4b-formyl-5,6,7,8-tetrahydrocarbazole-8a(4b*H*)-acetate (**24**). This material was quite labile and was converted to the corresponding tosylhydrazone derivative for characterization purposes.

To a solution of the above aldehyde in 5 mL of methanol was added 62 mg of tosyl hydrazide. The mixture was kept at 40 °C for 1.5 h. After cooling, ether was added and the mixture was extracted with water. The ether layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed using a methylene chloride–acetone (15:1) mixture as the eluent. The major fraction isolated contained 80 mg of a white solid, mp 145–146 °C, whose structure was assigned as methyl 4b,5,6,7,8,9-hexahydro-4b-[[[(4-methylphenyl)sulfonyl]hydrazono]methyl]-8a-acetate: IR ($CHCl_3$) 3360, 2910, 1720, and 1600 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.13–1.33 (m, 2 H), 1.49–1.71 (m, 4 H), 1.82–1.90 (m, 1 H), 1.98–2.05 (m, 1 H), 2.26 (d, 1 H, *J* = 15.5 Hz), 2.45 (s, 3 H), 2.48 (d, 1 H, *J* = 15.5 Hz), 3.68 (s, 3 H), 4.68 (s, 1 H), and 6.65–7.79 (m, 10 H); UV (95% ethanol) 296 nm (ϵ 3350), 230 (25 200); MS, *m/e* 441 (M$^+$), 257, 184 (base), and 105. Anal. Calcd for $C_{23}H_{27}N_3O_4S$: C, 62.56; H, 6.16; N, 9.52. Found: C, 62.46; H, 6.21; N, 9.49.

Preparation of Allyl Propiolate (26). To a solution containing 15.0 g of propiolic acid and 35 g of diethyl azodicarboxylate in 150 mL of anhydrous ether was added a solution containing 11.25 g of allyl alcohol and 50.5 g of triphenylphosphine in 250 mL of anhydrous ether. A mild exothermic reaction took place. The mixture was allowed to stir at room temperature for 24 h and the precipitate that formed was filtered. The filtrate was concentrated by distillation and the residue was distilled to give 10.1 g (48%) of allyl propiolate (**26**) as a colorless liquid, bp 133–134 °C: IR (neat) 3260, 2935, 2130, 1710, 1450, 1425, 1210, 990, and 765 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.90 (s, 1 H), 4.63 (ddd, 2 H, *J* = 5.7 and 1.2 Hz), 5.20–5.43 (m, 2 H), 5.91 (ddt, 1 H, *J* = 17.3, 10.8, and 5.7 Hz). Anal. Calcd for $C_6H_6O_2$: C, 65.54; H, 5.49. Found: C, 65.32; H, 5.51.

Preparation of 3-Carbomethoxyallyl Propiolate (27). To a solution containing 1.34 g of propiolic acid and 3.16 g of diethyl azodicarboxylate in 20 mL of ether was added a mixture containing 210 g of γ-methylhydroxycrotonate[55] and 4.56 g of triphenylphosphine in 25 mL of ether. After the addition was complete, the mixture was stirred for 20 h. The precipitate that formed was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed using a 50% ether–hexane mixture as the eluent. The major fraction contained 2.14 g (74%) of 3-carbomethoxyallyl propiolate (**27**): mp 60–61 °C; IR (KBr) 3185, 2110, 1720, 1660, 1445, 1250, 1020, and 780 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.83 (s, 1 H), 3.70 (s, 3 H), 4.79 (dd, 2 H, *J* = 4.8 and 1.8 Hz), 5.98 (dt, 1 H, *J* = 15.6 and 1.8 Hz), 6.85 (dt, 1 H, *J* = 15.6 and 4.8 Hz); MS, *m/e* 168 (M$^+$), 167 (base), 149, 115, 99, 83, and 53. Anal. Calcd for $C_8H_8O_4$: C,

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57.14; H, 4.79. Found: C, 57.22; H, 4.81.

Reaction of Allyl Propiolate (26) with *N*-Phenylhydroxylamine. To a stirred solution containing 0.20 g of allyl propiolate (**26**) in 20 mL of benzene under a nitrogen atmosphere was added 0.20 g of *N*-phenylhydroxylamine. After being stirred for 2 h, the solvent was removed under reduced pressure. The resulting residue was recrystallized from ethyl acetate–hexane to give 0.29 g (73%) of 2-propenyl 5-(hydrophenylamino)-2-phenyl-4-[(2-propenyloxy)carbonyl]-3-isoxazolidineacetate (**28**) as a crystalline solid, mp 104–105 °C: IR (KBr) 3185, 1720, 1590, 1485, 1380, 1230, 930, and 780 cm^{-1}; NMR (360 MHz, CDCl$_3$) δ 2.84 (dd, 1 H, J = 16.2 and 5.76 Hz), 3.16 (dd, 1 H, J = 16.2 and 8.64 Hz), 3.76 (dd, 1 H, J = 5.1 and 3.6 Hz), 4.40–4.42 (m, 2 H), 4.59–4.61 (m, 2 H), 4.70 (ddd, 1 H, J = 8.64, 5.76, and 3.6 Hz), 5.09–5.36 (m, 4 H), 5.63 (ddt, 1 H, J = 18.0, 9.72, and 5.76 Hz), 5.74 (s, 1 H), 5.91 (ddt, 1 H, J = 17.3, 10.4, and 5.76 Hz), 6.11 (d, 1 H, J = 5.1 Hz), and 6.99–7.34 (m, 10 H); UV (95% ethanol) 318 nm (ϵ 26 500), 224 (12 200); MS, *m/e* 279, 258, 219, 161 (base), 134, 119, and 104. Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.52; N, 6.39. Found: C, 65.85; H, 5.54; N, 6.33.

Reaction of 3-Carbomethoxyallyl Propiolate (27) with *N*-Phenylhydroxylamine. To a stirred solution containing 0.20 g of **27** in 20 mL of benzene under a nitrogen atmosphere was added 0.13 g of *N*-phenylhydroxylamine. After being stirred for 2 h, the solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate–hexane to give 0.23 g (70%) of 4-methoxy-4-oxo-2-butenyl 5-(hydroxyphenylamino)-4-[[(4-methoxy-4-oxo-2-butenyl)oxy]carbonyl]-2-phenyl-3-isoxazolidineacetate (**29**): mp 96–97 °C; IR (KBr) 3160, 1720, 1590, 1490, 1380, 1175, and 780 cm^{-1}; NMR (360 MHz, CDCl$_3$) δ 2.90 (dd, 1 H, J = 16.6 and 5.76 Hz), 3.20 (dd, 1 H, J = 16.6 and 8.28 Hz), 3.74 (s, 3 H), 3.75 (s, 3 H), 3.80 (dd, 1 H, J = 5.04 and 3.24 Hz), 4.55 (dd, 2 H, J = 4.86 and 1.8 Hz), 4.72 (ddd, 1 H, J = 8.28, 5.76, and 3.24 Hz), 4.78 (dd, 2 H, J = 4.86 and 1.8 Hz), 5.82 (dt, 1 H, J = 15.5 and 1.8 Hz), 5.83 (s, 1 H, 6.05 (dt, 1 H, J = 15.5 and 1.8 Hz), 6.09 (d, 1 H, J = 5.04 Hz), 6.67 (dt, 1 H, J = 15.5 and 4.68 Hz), 6.93 (dt, 1 H, J = 15.5 and 4.68 Hz), 6.99–7.37 (m, 10 H); UV (95% ethanol) 319 nm (ϵ 66 700), 223 (sh, 33 600). Anal. Calcd for $C_{28}H_{30}N_2O_{10}$: C, 60.64;, H, 5.45; N, 5.05. Found: C, 60.54; H, 5.48; N, 5.00.

Reaction of *N*-Methylhydroxylamine with Phenylacetylene. To a suspension containing 1.0 g of *N*-methylhydroxylamine hydrochloride and 2.45 g of phenylacetylene in 10 mL of benzene was added 2.40 g of a 20% sodium hydroxide solution. The mixture was heated at reflux under a nitrogen atmosphere for 21 h. After cooling, the reaction mixture was washed with a saturated sodium chloride solution and was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed using a 5% ethyl acetate–hexane mixture. The major component contained 1.1 g of an oil which consisted of three components. Chromatography of the oil gave 40% of a white solid, mp 100–101 °C, whose structure was assigned as 2,3-dimethyl-3,5-diphenyl-4-isoxazoline (**35**) on the basis of its spectral properties: IR (KBr) 3050, 2940, 1610, 1450, 1405, 1390, 1360, 1230, and 960 cm^{-1}; NMR (90 MHz, CDCl$_3$) δ 1.67 (s, 3 H), 2.60 (s, 3 H), 5.48 (s, 1 H), 7.18–7.63 (m, 10 H); UV (95% ethanol) 274 nm (ϵ 8280), 225 (14 300), 218 (15 000); MS, *m/e* 251 (M$^+$), 237, 175, 141 (base), and 105. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.98; H, 6.86; N, 5.54. This material was independently synthesized by heating a sample of (1-phenylethylidene)methanamine *N*-oxide[56] with phenylacetylene at 80 °C for 24 h.

The second compound obtained from the column was identified as the *N*-methylnitrone of acetophenone by comparison with an authentic sample.[56] The last material to be eluted (29%) was a white solid, mp 108–109 °C (lit.[57] 109–110 °C) whose structure was assigned as *N*-methyl-2,4-diphenylpyrrole (**36**) on the basis of its spectral data: IR (KBr) 3000, 2970, 2850, 1605, 1485, 1450, 1390, 1360, 1185, 1060, and 915 cm^{-1}; NMR (90 MHz, CDCl$_3$) δ 3.59 (s, 3 H), 6.42 (d, 1 H, J = 2.0 Hz), 6.86 (d, 1 H, J = 2.0 Hz), and 7.1–7.6 (m, 10 H). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.46; H, 6.40; N, 5.87. Heating a sample of isoxazolidine **35** in benzene at 120 °C for 24 h produced pyrrole **36** in 83% isolated yield.

Reaction of *o*-Vinyl-1-ethynylbenzene (37) with *N*-Methylhydroxylamine. To a mixture containing 83 mg of *N*-methylhydroxylamine and 128 mg of *o*-vinyl-1-ethynylbenzene (**37**)[58] was added 0.2 g of a 20% sodium hydroxide solution. The mixture was heated at 120 °C for 27 h. After cooling, the two layers were separated and the organic layer was washed with a saturated sodium chloride solution and was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was chromatographed. Elution of the column with a methanol–chloroform mixture gave 76 mg (44%) of 1-(2-vinylphenylethylidene)methanamine *N*-oxide (**38**): NMR (90 MHz, CDCl$_3$) δ 2.36 and 2.37 (s, 3 H), 3.46 and 3.47 (s, 3 H), 5.38 (d, 1 H, J = 11.1 Hz), 5.72 (d, 1 H, J = 16.5 Hz), 6.57 (dd, 1 H, J = 16.5 and 11.1 Hz), 7.06–7.68 (m, 5 H). The structure of this material was further established by its cycloaddition with dimethyl acetylenedicarboxylate.

A solution containing the above nitrone and 0.05 mL of dimethyl acetylenedicarboxylate in 10 mL of benzene was heated at reflux under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was chromatographed using a 20% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 58 mg (42%) of a clear oil whose structure was identified as dimethyl 2,3-dimethyl-3-(2-vinylphenyl)-isoxazoline-4,5-dicarboxylate (**39**) on the basis of its spectral properties: IR (neat) 2940, 1740, 1700, 1635, 1430, 1300, 1090, and 760 cm^{-1}; NMR (90 MHz, CDCl$_3$) δ 1.78 (s, 3 H), 2.71 (s, 3 H), 3.60 (s, 3 H), 3.88 (s, 3 H), 5.20 (d, 1 H, J = 10.2 and 1.8 Hz), 5.40 (d, 1 H, J = 17.1 and 1.8 Hz), and 7.23–7.77 (m, 5 H); UV (95% ethanol) 282 nm (sh, ϵ 10 600); MS, *m/e* 317 (M$^+$), 305, 258, 214, 158, 110, and 77. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.42. Found: C, 64.52; H, 6.09; N, 4.41.

Reaction of 2-(2-Propenyloxy)phenylacetylene (42) with *N*-Methylhydroxylamine. A mixture containing 23 mg of *N*-methylhydroxylamine hydrochloride and 0.11 g of a 10% aqueous sodium hydroxide solution was added to a solution containing 36 mg of **42** in 2 mL of benzene. The mixture was heated at 110 °C in a sealed Carius tube for 46 h. After cooling, the mixture was washed once with a saturated sodium chloride solution and was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed using an ethyl acetate–hexane (1:2) mixture as the eluent. The major fraction contained 14 mg (49%) of a clear oil whose structure was assigned as 3a,4-dihydro-1-methyl-9b-(1*H*)-methyl-3*H*-[1]-benzopyrano[4,3-*c*]isoxazole (**43**): IR (neat) 2960, 2860, 1610, 1580, 1490, 1430, 1235, and 770 cm^{-1}; NMR (360 MHz, CDCl$_3$) δ 1.52 (s, 3 H), 2.69 (s, 3 H), 2.76 (m, 1 H), 3.91 (dd, 1 H, J = 7.92 and 6.12 Hz), 4.14 (dd, 1 H, J = 7.2 and 3.06 Hz), 4.22 (m, 1 H), 4.29 (t, 1 H, J = 7.92 Hz), 6.84–7.40 (m, 4 H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 23.13, 38.65, 46.85, 46.93, 63.41, 65.05, 67.13, 117.05, 121.28, 128.45, 128.67, and 128.77; UV (95% ethanol) 282 nm (ϵ 1920), 273 (21 600); MS, *m/e* 205 (M$^+$, base), 190, 159, 145, 131, 115, 91, and 77. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 69.43; H, 7.39; N, 6.60.

Reaction of 2-(2-Propenyloxy)acetophenone with Methylhydroxylamine. To a solution containing methylmagnesium iodide (prepared from 0.79 g of magnesium and 2.03 mL of methyl iodide) in 150 mL of ether at 0 °C was added a solution containing 5.0 g of 2-(2-propenyloxy)benzaldehyde in 30 mL of ether. The mixture was stirred at room temperature for 4 h and was quenched with an ammonium chloride solution. The two layers were separated and the ether extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 1-[2-(2-propenyloxy)phenyl]ethanol as a pale yellow oil: NMR (90 MHz, CDCl$_3$) δ 1.50 (d, 3 H, J = 6.0 Hz), 2.80 (br s, 1 H), 4.56 (br d, 2 H, J = 5.4 Hz), 5.0–5.5 (m, 3 H), 5.84–6.25 (m, 1 H), and 6.77–7.4 (m, 4 H). Jones oxidation of the crude alcohol in acetone followed by chromatography using a 5% ethyl acetate–hexane mixture as the eluent gave 4.13 g (76%) of 2-(2-propenyloxy)acetophenone: IR (neat) 3060, 2970, 2910, 2850, 1670, 1590, 1480, 1450, 1295, 1240, and 760 cm^{-1}; NMR (90 MHz, CCl$_4$) δ 2.5 (s, 3 H), 4.58 (dt, 2 H, J = 5.28 and 1.35 Hz),

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5.2–5.53 (m, 2 H), 6.07 (ddt, 1 H, J = 17.7, 10.7, and 5.28 Hz), 6.80–7.73 (m, 4 H); UV (95% ethanol) 305 nm (ϵ 3620), 247 (8060); MS, m/e 176 (M^+), 161 (base), 133, 119, 105, 91, and 77. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.94; H, 6.92.

To a solution containing 0.5 g of this material in 10 mL of absolute alcohol was added a mixture containing 1.20 g of *N*-methylhydroxylamine hydrochloride and 2.84 g of a 20% aqueous sodium hydroxide solution in 10 mL of absolute alcohol. The mixture was heated at reflux and the condensate was passed through a column of 3-Å molecular sieves. After being heated for 36 h, the reaction mixture was cooled and worked up in the usual manner. Chromatography of the residue using an ethyl acetate–hexane mixture gave 0.45 g (78%) of 3a,4-dihydro-1-methyl-9b(1*H*)-methyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazole (**43**) as the exclusive product. This material was identical in every detail with the sample obtained from the reaction of [2-(2-propenyloxyl)phenyl]acetylene (**42**) with *N*-methylhydroxylamine.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health. Use of the high-field NMR spectrometer used in these studies was made possible through a NSF equipment grant.

Registry No. 6, 29182-34-1; **7**, 29182-33-0; **12**, 102851-74-1; **13**, 66021-96-3; **14**, 102851-75-2; **15**, 102851-77-4; **16**, 102851-78-5; **17**, 102851-79-6; (*E*)-**18**, 102851-80-9; (*Z*)-**18**, 102851-81-0; **20**, 102869-63-6; **21**, 102851-82-1; **22**, 5828-16-0; **23**, 102851-83-2; **24**, 102851-84-3; **26**, 14447-00-8; **27**, 102851-86-5; **28**, 102851-87-6; **29**, 102869-64-7; **34**, 10557-03-6; **35**, 62772-79-6; **36**, 17165-01-4; **37**, 90766-20-4; **38**, 102851-88-7; **39**, 102851-89-8; **42**, 66021-96-3; **43**, 102869-65-8; **44**, 53327-14-3; *N*-methylhydroxylamine hydrochloride, 4229-44-1; methyl propiolate, 922-67-8; 2-(2-propenyloxy)benzaldehyde, 558-13-4; methyl chloroformate, 79-22-1; acetaldehyde, 75-07-0; 4-[2-(2-propenyloxy)phenyl]but-3-yn-2-ol, 102851-76-3; *N*-phenylhydroxylamine, 100-65-2; 1,7-octadiyne, 871-84-1; methyl 4b-[[[(4-methylphenyl)sulfonyl]hydrazonono]-methyl]-4b,5,6,7,8,9-hexahydrocarbazole-8a-acetate, 102851-85-4; phenylacetylene, 536-74-3; dimethyl acetylenedicarboxylate, 762-42-5; 1-[2-(2-propenyloxy)phenyl]ethanol, 28752-82-1; 2-(2-propenyloxy)acetophenone, 82315-95-5.

The Synthesis of Substituted [[3(*S*)-(Acylamino)-2-oxo-1-azetidinyl]thio]acetic Acids

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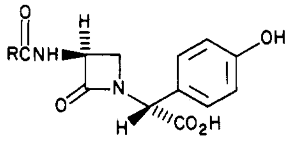
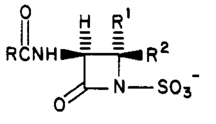
Received November 18, 1985

The synthesis of substituted [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]thio]acetic acids (**6**, thiamazins) is described. Various substituted 3(*S*)-(acylamino)-2-azetidinones were sulfenylated with *tert*-butyl (phthalimidothio)acetate. Deprotection of the *tert*-butyl ester with trifluoroacetic acid provided the title compounds. In sharp contrast to their oxygen analogues (oxamazins), the thiamazins were devoid of biological activity.

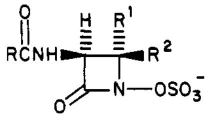
The recent discovery of the nocardicins **1**[1] and the monobactams **2**[2] (sulfazecins)[3] has generated considerable interest in the synthesis of novel monocyclic β-lactam antibiotics. In addition, the realization that the β-lactam ring could be activated toward nucleophilic attack by the presence of an electronegative atom on the azetidinyl nitrogen led to the development of the synthetic monosulfactams **3**[4,5] and oxamazins **5**.[6] The significant antibacterial properties inherent in these monocyclic β-lactams demonstrated that oxygen-induced chemical activation could be used to provide new biologically active compounds. As part of an effort examining the scope of heteroatom activation of β-lactam antibiotics, we have determined the effect that replacement of the oxygen with a sulfur atom has on chemical and biological activity. Herein, we report our attempts that ultimatley led to the synthesis of [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]thio]-acetic acids **6** (thiamazins).[7]



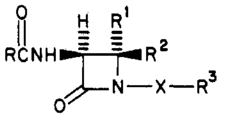
1, nocardicins



2, monobactams



3, monosufactams



4, X = O, R^3 = H
5, X = O, R^3 = CH_2CO_2H, oxamazins
6, X = S, R^3 = CH_2CO_2H, thiamazins

Since *N*-hydroxy-2-azetidinones **4** have proven to be useful intermediates in the synthesis of the oxamazins **5**[6] our first attempt to prepare the thiamazins centered on the synthesis of the unknown *N*-(thiohydroxy)-2-azetidinones **15**. Conceptually, these thiols were available by utilizing an approach analogous to the hydroxamate-mediated β-lactam synthesis developed in our laboratory[8] (Scheme I). However, attempts to separately couple both phenyloxomethane-[9] and triphenylmethanesulfenamides[10] **9a,b** with *N*-(carbobenzyloxy)-L-threonine (**7**) under standard conditions (WSC; DCC; DCC/*N*-hydroxysuccinimide; EEDQ) failed. Alternatively, conversion of

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