Acid-Catalyzed Nitronate Cycloaddition Reactions. Useful Syntheses and Simple Transformations of 3-Acyl- and 3-Alkenylisoxazolines

Peter A. Wade,* Nayan V. Amin, Hwa-Kwo Yen, David T. Price, and George F. Huhn

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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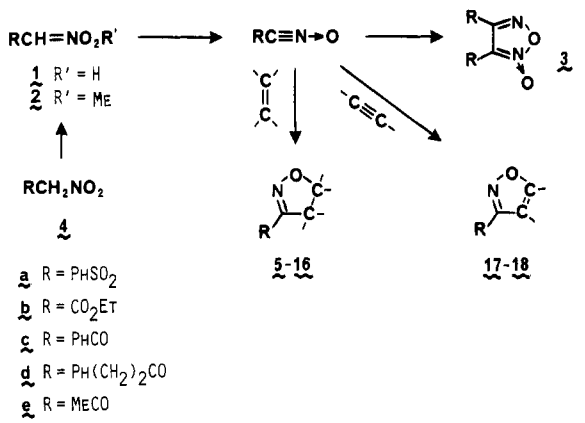
Nitronic esters derived from primary nitro ketones, ethyl nitroacetate, and (phenylsulfonyl)nitromethane react with dipolarophiles in the presence of nonaqueous protic and Lewis acids to give nitrile oxide cycloadducts. α-Nitro ketones, ethyl nitroacetate, and (phenylsulfonyl)nitromethane give nitrile oxide cycloadducts in the presence of *p*-toluenesulfonic acid, although conditions are necessarily more vigorous. The anions of phenylnitromethane and 1-nitropropane react similarly under mild conditions, the latter in poor yield. The methyl nitronic ester of (phenylsulfonyl)nitromethane undergoes direct cycloaddition to 1-hexene in neutral media to give diastereomeric isoxazolidines. 3-(α-Hydroxyalkyl)isoxazolines are readily prepared by reduction of 3-carbethoxyisoxazolines with sodium borohydride and by carbonyl addition to 3-acylisoxazolines with alkyllithium reagents. 3-Alkenylisoxazolines, which can be prepared from either 3-(hydroxyalkyl)isoxazolines or 3-sulfonylisoxazolines, undergo reversible [4 + 2]-cycloaddition with tetracyanoethylene.

The diverse reactions of nitro compounds, nitronate salts, and nitronic esters with aqueous acid have been under study for over a century.[1] Aldehydes and ketones are most commonly obtained (the Nef reaction). Under strongly acidic conditions, hydroxamic acids are formed instead; these may further hydrolyze to carboxylic acids and hydroxylamine (the Meyer reaction). Hydroxamic acid formation has been shown to proceed through hydrolysis of a nitrile oxide intermediate.[2] Surprisingly little synthetic use has been made of this demonstration. Furoxans (1,2,5-oxadiazole 2-oxides) have been prepared from several nitro compounds under strongly acidic conditions,[3] but extensive studies of nitrile oxide cycloadditions to added dipolarophiles are conspicuously lacking.

Nitro compounds and nitronic acids, the aci tautomers of nitro compounds, are both potential 1,3-dipoles. However, there are no documented examples of direct cycloaddition for nitronic acids and only a few examples for nitro compounds.[4] On the other hand, there are many examples where a nitro compound is converted to another more reactive 1,3-dipole prior to cycloaddition. Perhaps best known is Mukaiyama's procedure[5] in which a primary nitro compound reacts via a nitrile oxide intermediate with a dipolarophile. Various other indirect cycloadditions which use nitro compounds have been reported to involve nitrile oxides,[6] nitronic esters,[7,6b] or nitronic anhydrides[8] as the reactive 1,3-dipole. It has been unclear in some cases exactly which 1,3-dipole was responsible for cycloaddition. For example, Levina et al.[6b] report boron trifluoride-catalyzed reaction of the methyl nitronic ester of methyl nitroacetate with 16-dehydro-20-oxosteroids to produce isoxazolines; the authors were unable to decide if the nitronic ester itself underwent cycloaddition or if it was first converted to a nitrile oxide. McKillop and Kobylecki[8] have reported the direct cycloaddition of dipolarophiles and nitronic anhydrides formed from reaction of nitro compounds and acetic anhydride; Kaji et al.[6a] have reported conversion of the same anhydrides to nitrile oxides prior to reaction with dipolarophiles under very similar conditions.

Scheme I



The usual evidence cited for intermediacy of a nitrile oxide in cycloaddition is the formation of a furoxan in the absence of added dipolarophile. The lack of furoxan is taken as evidence against a nitrile oxide intermediate. Of course, it must be assumed that the nitrile oxide does not preferentially undergo a side reaction such as isomerization to an isocyanate or 1,3-addition to give an oxime.

Results and Discussion

Cycloaddition Reactions Using Nitronic Esters. The methyl nitronic esters **2a–e**, substituted with electron-attracting groups, are readily prepared by treatment of the corresponding nitro compounds **4a–e** with ethereal diazomethane. Methylation of α-nitro ketones, which could occur on either the nitro or carbonyl oxygens, has previously been reported to give nitronic esters.[9] This

(1) For reviews see: (a) Breuer, E. In "Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives"; Patai, S., Ed.; Wiley-Interscience: New York, 1982; pp 538–564. (b) Nielsen, A. T. In "The Chemistry of the Nitro and Nitroso Groups"; Feuer, H, Ed.; Wiley-Interscience: New York, 1969; pp. 349–486. (c) Seebach, D.; Colvin, W. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (d) Ioffe, S. L.; Leont'eva, L. M.; Tartakovskii, V. A. *Russ. Chem. Rev. (Engl. Transl.)* **1977**, *46*, 872.

(2) Edward, J. T.; Tremaine, P. H. *Can. J. Chem.* **1971**, *49*, 3483, 3489 and references cited therein.

(3) (a) For a review see: Gasco, A.; Boulton, A. J. In "Advances in Heterocyclic Chemistry"; Katritzky, A., Boulton, A. J., Eds.; Academic Press: New York, 1981; Vol. 29, pp. 251–340. (b) For a recent example, see: Ribo, J. M.; Trull, F. *Liebigs Ann. Chem.* **1983**, 1.

(4) (a) One example of direct cycloaddition by an *aci*-nitro compound has recently been observed: Wade, P. A.; Amin, N. V., unpublished study. (b) Nitro compounds react with strained alkenes to give 1,3,2-dioxazolidines: Leitich, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 372 and references cited therein.

(5) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

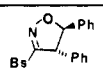
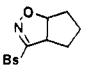
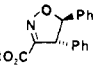
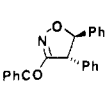
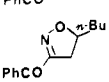
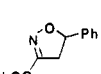
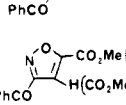
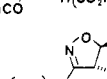
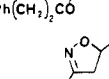
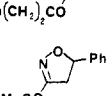
(6) (a) Kaji, E.; Harada, K.; Zen, S. *Chem. Pharm. Bull.* **1978**, *26*, 3254. (b) Levina, I. S.; Mortikova, E. I.; Kamernitzky, A. V. *Synthesis* **1974**, 562. (c) Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971; pp. 51–53. (d) Muller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777.

(7) (a) Grêe, R.; Carrié, R. *Tetrahedron* **1976**, *32*, 683. (b) Grêe, R.; Tonnard, F.; Carrié, R. *Ibid.* **1976**, *32*, 675. (c) Torssell, K.; Zeuthen, O. *Acta Chim. Scand., Ser. B* **1978**, *32*, 118. (d) Das, N. B.; Torssell, K. *Tetrahedron* **1983**, *39*, 630.

(8) McKillop, A.; Kobylecki, R. J. *Tetrahedron* **1974**, *30*, 1365.

0022-3263/84/1949-4595$01.50/0

Table I. Cycloadducts Derived from Nitronic Esters 2a–e

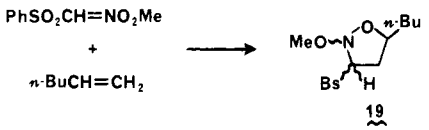
nitronic ester R	alkene or alkyne	cycloadduct		yield,[a] %
$PhSO_2$	Ph–CH=CH–Ph		5	75
	Ph–CH=CH–Ph		6 (◄Ph) / 5 (···Ph)	23 / 13
	n-Bu–CH=CH$_2$		7	73 / 71[b] / 19[c]
			8	80
EtO_2C	Ph–CH=CH–Ph		9	58
			10	56
PhCO	Ph–CH=CH–Ph		11	54
	n-Bu–CH=CH$_2$		12	73 / 35[c]
	Ph–CH=CH$_2$		13	70
	CO_2Me–C≡CH		17 (18)	74 (7)
$Ph(CH_2)_2CO$	Ph–CH=CH–Ph		14	52
			15	67
MeCO	Ph–CH=CH$_2$		16	26 / 22[b]

[a] Using p-TsOH·H_2O, unless otherwise noted. [b] Using BF_3·OEt_2. [c] Using TFA.

matter was carefully reinvestigated for ω-nitroacetophenone (**4c**). After treatment with diazomethane, an NMR spectrum indicated three materials with different methyl absorptions. These could be separated by preparative TLC into an enol ether fraction (22% yield) and nitronic ester fraction (mixture of diastereomers, 72% yield).

The crude nitronic esters **2a–e** were found to react with a variety of alkenes and p-toluenesulfonic acid in refluxing methylene chloride to give isoxazolines **5–16** in 26–80% yield (Table I). In one case, methyl propiolate was employed and isoxazoles **17** and **18** (two regioisomers) were obtained in 81% combined yield. Furoxans **3** were obtained in the absence of added dipolarophile, so it appears that nitrile oxide intermediates were responsible for cycloaddition. The sulfonic acid (1 equiv) was routinely employed in these reactions although as little as 0.4 equiv led to satisfactory results. Boron trifluoride was also highly effective, giving cycloadducts in comparable yield; in the absence of added dipolarophile, furoxans were once again obtained. Trifluoroacetic acid and titanium(IV) chloride were briefly examined, but the yield of cycloadducts was markedly lower. All of the dipolarophiles investigated were stable under the reaction conditions (p-toluenesulfonic acid, 40 °C, 30 min) except for (Z)-stilbene, where some isomerization to the E isomer was noted. Even for (Z)-stilbene a moderate yield of the cycloadduct **6** could be easily prepared.

In the absence of acid, a very slow reaction was noted for 1-hexene with the nitronic ester **2a**; nitronic esters **2b** and **2c** did not react similarly (eq 1). The 250-MHz ^1H

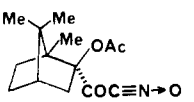


(1)

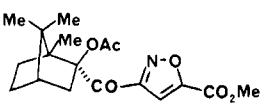
NMR spectrum of the crude reaction product indicated that isoxazolidine **19** was a mixture containing two of the four theoretically possible diastereomers (3:1 ratio). An additional stereoisomer was noted by NMR early in the reaction so it appears that two diastereomers are interconverting under the reaction conditions, possibly through inversion at nitrogen. Isoxazolidine **19** was extremely acid sensitive; standing in commercial deuteriochloroform led slowly to sulfonylisoxazoline **7**. Addition of a trace of acid to solutions of **19** led within a minute at room temperature to **7**. However, heating isoxazolidine **19** in refluxing bicarbonate treated methylene chloride did not result in conversion to **7**. Other workers have noted a similar acid sensitivity for cycloadducts derived from nitronic esters; thermal conversion to isoxazolines has also been documented.[9a,7c] Virtually no furoxan (4.6% yield) was observed when the nitronic ester was heated by itself. We conclude on the basis of these results that a nitrile oxide is generated from the nitronic ester under acidic conditions and is the preferential 1,3-dipole for cycloaddition; under neutral conditions the nitronic ester **2a** itself undergoes cycloaddition but at a much slower rate, at least with typical dipolarophiles.

The nitronic ester **2a** also leads to the corresponding nitrile oxide under strongly basic conditions[10] and other relatively acidic nitronic esters could be expected to do likewise. Thus a cautionary note: indirect cycloaddition of nitronic esters through nitrile oxide intermediates can occur under either acidic or basic conditions. It is only safe to assume that the nitronic ester has directly cycloadded when the isoxazolidine can be isolated or after nitrile oxide formation has been carefully ruled out through the absence of furoxan formation.

The nitronic ester **2c** reacted with methyl propiolate under acidic conditions to give the regioisomeric cycloadducts **17** and **18** (90:10 ratio, respectively). There was no reaction in the absence of acid, so it is concluded that cycloaddition occurs through the intermediacy of a nitrile oxide. For the nitrile oxide **20**, Brittelli and Boswell[11] have



20



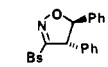
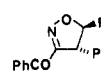
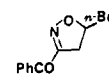
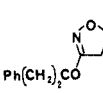
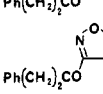
21

reported only the formation of the one regioisomer **21**. They have attributed the high regioselectivity in this cycloaddition to heavily dominant 1,3-dipole NLUMO control. Other nitrile oxides are well-known to give significant amounts of both the 4- and 5-carbomethoxy regioisomers;

(9) (a) Grée, R.; Carrié, R. *Bull. Soc. Chim. Fr.* **1975**, 1319. (b) Arndt, F.; Rose, J. D. *J. Chem. Soc.* **1935**, 1.

(10) Wade, P. A.; Pillay, M. K. *J. Org. Chem.* **1981**, *46*, 5425.
(11) Brittelli, D. J.; Boswell, G. A. *J. Org. Chem.* **1981**, *46*, 316.

Table II. Cycloadducts Derived from Nitro Compounds 4a–d

nitro compound R	alkene	cycloadduct		yield, %
$PhSO_2$[a]			5	53
$EtCO_2$[b]			9	91
PhCO[c]			11	79
			12	78
$Ph(CH_2)_2CO$[c]			14	89
			15	60

[a] At 160–165 °C/15 min. [b] At 80 °C/8 h. [c] At 80 °C/2 h.

occasionally the 4-isomer even dominates.[12] These results have been explained as arising from contribution of both the 1,3-dipole NLUMO (5-isomer) and the 1,3-dipole HOMO (4-isomer). In view of our results, it seems that acylnitrile oxides are clearly NLUMO dominant 1,3-dipoles but certainly not to the exclusion of a significant HOMO contribution in the reaction with methyl propiolate.

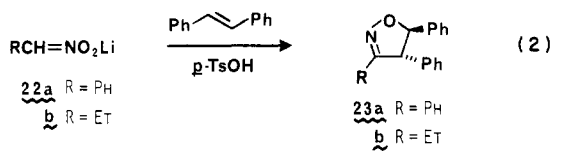
Cycloaddition Reactions Using Nitro Compounds. The availability of nitronic esters is somewhat limited. Also, there is good evidence that nitro compounds, through their aci tautomers under appropriate conditions, can lead to nitrile oxides. Consequently, this approach has also been examined as a potential route to nitrile oxide cycloadducts. When the nitro compound **4a** was heated with *p*-toluenesulfonic acid at 160 °C in the presence of (*E*)-stilbene, a 53% yield of the isoxazoline **5** was obtained. In the absence of stilbene, furoxan **3a** (78% yield) was produced instead and it is therefore concluded that a nitrile oxide intermediate is responsible for cycloaddition. However, these conditions are rather drastic and are not generally suitable for the preparation of cycloadducts. A preliminary examination of cycloaddition to 1-decene gave a mixture of isoxazolines, presumably derived by isomerization of the alkene to 2-decene (and probably 3-, 4-, etc. isomers) followed by competitive cycloaddition.

Ethyl nitroacetate and α-nitro ketones react with *p*-toluenesulfonic acid and alkenes in refluxing benzene to give the corresponding isoxazolines **9**, **11**, **12**, **14**, and **15** (Table II); furoxans are formed in the absence of alkene. 1-Nitropropane, phenylnitromethane, and (phenylsulfonyl)nitromethane do not react under these conditions, so that the procedure is clearly limited. For 1-hexene, competitive addition of *p*-toluenesulfonic acid to give 2-hexenyl tosylate was observed. For the reaction of ethyl nitroacetate and 1-hexene, only the sulfonic acid addition product and no cycloadduct was produced. However, for the reactions of the α-nitro ketones with 1-hexene and 5-hexen-2-one, we obtained only cycloadducts derived from unisomerized alkene. Thus, it is possible to prepare at least a few cycloadducts in very straightforward fashion. The use of α-nitro ketones **4c,d** is particularly well-suited to preparation of nitrile oxide cycloadducts; indeed, a closely related procedure has been reported in the patent literature.[13]

The ease with which ethyl nitroacetate and α-nitro ketones form nitrile oxide cycloadducts likely derives from an enhanced interconversion with the corresponding *aci*-nitro tautomers. Here the aci tautomers would be favored by conjugative stabilization from the adjacent carbonyl group. However, a more important feature may be the ability of the carbonyl group to enolize. Thus, protonation of the acyl oxygen followed by deprotonation of carbon and transfer of the proton to the nitro group may lead to the aci tautomer. Since ester carbonyl groups do not enolize as readily as ketones, this viewpoint is consistent with the observed relative reactivity of ethyl nitroacetate and α-nitro ketones.

Trager et al.[14] have reported the formation of isoxazoles from α-nitro ketones, ketene, and acid and have suggested a pathway involving sequential formation of nitronic anhydrides and nitrile oxides. From our observations, it seems that the *aci*-nitro compound itself might dehydrate to the nitrile oxide in competition with anhydride formation. The reported observation of furoxans indicates a nitrile oxide intermediate, consistent with either explanation.

A potential alternate route to nitrile oxides would involve the use of silyl nitronates. However, treatment of the silyl nitronates[15] derived from (phenylsulfonyl)nitromethane (**4a**) and 1-nitropropane with *p*-toluenesulfonic acid in the presence of (*E*)-stilbene failed to give any cycloadducts. Another alternate route involving the use of nitronate salts was more successful. Addition of the lithium nitronates **22a** and **22b** to a refluxing solution of *p*-toluenesulfonic acid and (*E*)-stilbene in methylene chloride gave the corresponding isoxazolines (eq 2). Stilbene re-



(2)

acted wtih nitronate **22a** to give a 49% yield of cycloadduct **23a** while nitronate **22b** gave only a 7% yield (based on the nitronate) of cycloadduct **23b**. The reaction is clearly more satisfactory for arylcarbonitrile oxides and this is parallel to observations for hydroxamic acid formation under strongly acidic conditions.[16] Perhaps the best feature of this method is the ability to carry out cycloaddition under conditions where a potentially sensitive dipolarophile or cycloadduct is never subjected to base.

The mechanism of nitrile oxide formation from nitro compounds and nitronate salts appears to involve conversion to the *aci*-nitro tautomer 1 as the first step. Indeed, the use of nitro compounds appears to be severely limited because of the difficulty in conversion to aci tautomers under acidic condtions. It is known that very strong protic acid is needed to catalyze this conversion to aci tautomers even under favorable circumstances.[1b] Nitro compounds, in contrast to nitronic esters, do not undergo cycloaddition in the presence of boron trifluoride or trifluoroacetic acid, presumably since these acids fail to generate significant concentrations of the aci tautomer.

(12) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *105*, 3345.

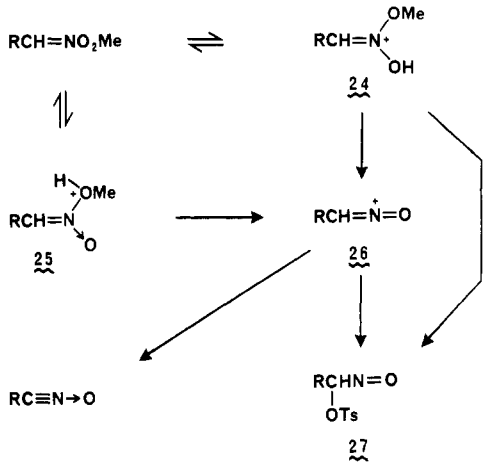
(13) Duranleau, R. G. (Texaco, Inc.) U. S. Patent 4 092 327; *Chem. Abstr.* **1978**, *89*, P146892b.

(14) Nelson, S. D.; Kasparian, D. J.; Trager, W. F. *J. Org. Chem.* **1972**, *37*, 2686.

(15) Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. D.; Sharma, S. C.; Torssell, K.B.G. *Acta Chim. Scand., Ser. B* **1982**, *36*, 1.

(16) Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 1742.

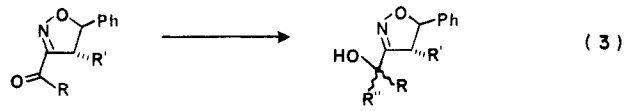
Scheme II



Cycloaddition with *p*-toluenesulfonic acid is much slower for nitro compounds than nitronic esters; this result is also attributed to difficulty in forming the aci tautomer from the nitro compound.

The main features of nitrile oxide formation are relatively straightforward although details of the protonation sequence are somewhat more convoluted (Scheme II). The nitronic ester (or *aci*-nitro compound) should protonate preferentially on its negative O to give species **24**; Lewis acids would be expected to react similarly. However, protonation on the methoxy O to give **25** followed by loss of methanol would produce the α-nitroso cation **26**, a previously postulated[17] intermediate in nitrile oxide formation from nitro compounds. Diprotonation of the *aci*-nitro species could also occur with the very strong *p*-toluenesulfonic acid, but it seems somewhat unlikely that the weaker acids boron trifluoride and TFA would behave similarly. A transient intense blue color was noted in the reaction of *p*-toluenesulfonic acid with lithium propanenitronate but not elsewhere. On this basis, perhaps an α-nitroso tosylate (**27**) has formed as a byproduct in this reaction. Compound **27** could arise if tosylate ion trapped the protonated nitronate **24**, analogous to water in the Nef reaction, or the nitroso cation **26**. A similar reaction has been reported in which α-chloronitroso compounds are formed from nitronate salts using dry hydrogen chloride.[18]

Isoxazoline Transformations. The isoxazolines **9** and **13** readily undergo reduction and carbonyl addition reactions to produce 3-(hydroxyalkyl)isoxazolines. Esters are not usually reduced by sodium borohydride at room temperature;[19] however, smooth reduction of ester **9** with sodium borohydride occurred giving **28** in 78% yield (eq 3).



(3)

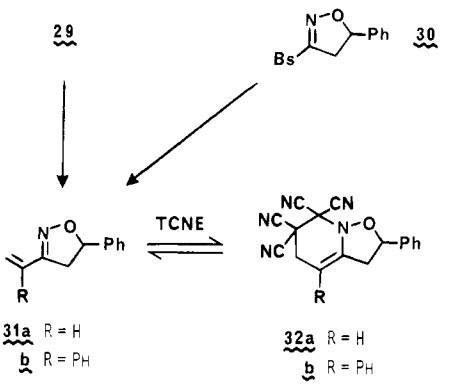
9 R = OEt; R' = Ph
13 R = Ph; R' = H

28 R = R'' = H; R' = Ph
29 R = Ph; R' = H; R'' = Me

Two recent reports have appeared describing a 2-nitroethanol based nitrile oxide route to 3-(hydroxymethyl)-isoxazolines and their hydroxyl-protected derivatives.[20]

(17) Simmons, T.; Kreuz, K. L. *J. Org. Chem.* **1968**, *33*, 836.
(18) Metzger, H.; Meier, H. In "Methoden der Organische Chemie (Houben-Weyl-Muller)"; Georg Thieme Verlag: Stuttgart, 1971; Vol. X/1, p 979.
(19) Hajos, A. "Complex Hydrides"; Elsevier: New York, 1979; p 49.
(20) (a) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603 and reference cited therein. (b) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.

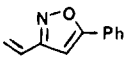
Scheme III



The current procedure seems to be an efficient alternate route to 3-(hydroxymethyl)isoxazolines and can be extended to include more complex 3-(α-hydroxyalkyl)isoxazolines. For example, reaction of acylisoxazoline **13** with methyllithium gave the alcohol **29** as a 59:41 ratio of diastereomers.[21] Further reactions and the stereochemistry of carbonyl addition will be reported separately.

Two routes for the preparation of 3-alkenylisoxazolines have been developed (Scheme III). The first route involves dehydration of a (hydroxyalkyl)isoxazoline using *p*-toluenesulfonic acid. Either diastereomer of alcohol **29** could be transformed to alkenylisoxazoline **31b** in this fashion. The second route involves substitution of the sulfone group of sulfonylisoxazoline **30** by vinylmagnesium bromide. The alkenylisoxazoline **31a** was produced in 72% yield by this means.

The alkenylisoxazolines **31a,b** are formally 1-aza 1,3-dienes and might be expected to behave in a Diels–Alder reaction as the diene component. Accordingly, compound **31a** reacts with a 3-fold excess of TCNE at 190–195 °C (bath temp) for 4 min to give a 28% yield of cycloadduct **32a** and a 16% yield of the isoxazole **33**. Starting **31a**



33

(30% recovery) remains in this reaction; indeed, we have not succeeded in driving cycloaddition to completion. The same cycloadduct can be obtained in 33% yield at 140 °C (bath temperature) along with unreacted starting material (47% recovery). Cycloadduct **32a** was identified by its 250-MHz ^{1}H NMR and infrared spectra. The isoxazole **33** was identified spectroscopically and by elemental analysis; it was also prepared independently from isoxazoline **31a** by using a standard general procedure.[22]

At room temperature, substantial reversion of cycloadduct **32a** to starting materials occurred within a few days. Cycloadduct **32a** reverted to starting materials at 60 °C in dilute solution with a half-life of about 1 h. This cycloreversion proceeded at similar rates in acetonitrile, benzene, and chloroform so it is unlikely that a zwitterionic intermediate was involved. It is therefore concluded that the mechanism of cycloaddition is concerted or possibly diradical in nature, typical of other Diels–Alder reactions. It is further concluded that the starting materials are thermodynamically preferred over the cycloadduct.

The alkenylisoxazoline **31b** reacted with TCNE similar to compound **31a**. However, equilibrium with the cyclo-

(21) Factors affecting the face selectivity of addition to the carbonyl group of acylisoxazolines are under intensive investigation.
(22) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G. *Synthesis* **1977**, 837.

adduct was reached within 4 min at 140 °C whereas **31a** required greater than 15 min. The cycloadduct **32b**, obtained in 52% yield and identified spectroscopically, was largely cycloreverted to starting materials in only 3 h at room temperature. Clearly the phenyl substituent has lowered the activation energy of both cycloaddition and cycloreversion, consistent with its anticipated conjugative effect raising the diene HOMO energy level.

The reversible nature of these cycloadditions and the apparent instability of the cycloadducts are consistent with known chemistry. There are relatively few examples[23] of 1-aza 1,3-dienes which react as the diene component in a Diels–Alder reaction and this matter has received comment.[23a] While these heterodienes seemingly have an appropriate structure for cycloaddition, simple calculations[24] suggest a reduced thermodynamic driving force compared to typical dienes. Also, 1-aza 1,3-dienes can rearrange to conjugated enamines (NHC=CC=C) or to 2-aza 1,3-dienes, either of which undergo preferential cycloaddition.[23a,24]

To our knowledge the cycloadducts **32a,b** are the first examples of the 3,5,6,7-tetrahydro-2*H*-isoxazolo[2,3-*a*]pyridine heterocyclic system as well as the first Diels–Alder products derived from conjugated oxime ethers as dienes.[25] Attempts to extend our studies through the use of other dienophiles are underway, although it has been found that maleic anhydride fails to give a similar reaction with **31a**.

In conclusion, convenient new methods for the generation of nitrile oxides from nitro compounds have been developed. These methods are complimentary to Mukaiyama's procedure; they avoid the presence of base but require acid. The relationship of nitrile oxide and nitronic ester cycloadditions under various conditions has been firmly established. Acylisoxazolines are particularly easy to prepare by the new methods and transformations to (hydroxyalkyl)isoxazolines have been examined. Alkenylisoxazolines are indirectly available from these procedures and their potential as Diels–Alder diene components has been assessed.

Experimental Section

General Methods. Infrared spectra were obtained on a Perkin-Elmer 457 spectrometer. ^{1}H NMR spectra were recorded (in $CDCl_3$ with Me_4Si as internal standard) on a JEOL FX-90Q instrument, unless otherwise noted. Thin-layer chromatography was carried out on Analtech 0.25-mm, precoated, silica gel GF analytical plates with UV and I_2 development or on 1.00-mm, silica gel, preparative plates. Simple column chromatography was caried out on "Baker Analyzed" reagent silica gel, 60–200 mesh. The α-nitro ketones were prepared from the corresponding phenyl esters by reaction with nitromethane and potassium *tert*-butoxide.[26] The dicyclohexylamine salt of 1-nitro-2-propanone was prepared similarly: mp 148.5–149.5°C dec (lit.[26] mp 135–137 °C). Fresh bottles of *p*-toluenesulfonic acid monohydrate (Aldrich, hygrascopic!) were used as received; material dissolved in water, precipitated with concentrated hydrochloric acid, and dried over P_2O_5 (0.2 mm, 12 h) gave similar results. Reactions were routinely run under nitrogen and, unless otherwise noted, were worked up by washing the organic layer with 5% aqueous NaOH (10 mL) followed by water, drying over anhydrous sodium sulfate, and concentrating at reduced pressure.

Preparation of Nitronic Esters 2a–d. General Procedure. Reactions were performed on 0.25–3 mmol of nitro compound and the procedures have been scaled to reflect a typical 1 mmol run. Excess 0.4 M ethereal diazomethane (8 mL) was added to a cold (0–5 °C) solution of the appropriate nitro compound (1 mmol) dissolved in CH_2Cl_2 (2 mL). After stirring for 1 h (only 10 min for **4a**), the solution was concentrated to $^1/_4$ volume. After CH_2Cl_2 (6 mL) was added, the solution was again partially concentrated and the final volume made up to 2 mL with CH_2Cl_2. These solutions of the crude nitronic esters were then used directly for the cycloaddition experiments.

The solution obtained from ω-nitroacetophenone (0.15 g, 0.9 mmol) was fully concentrated and rapidly dissolved in $CDCl_3$; NMR indicated 3 different singlet methyl absorptions: δ 3.96, 3.86, 3.85 (all s, 3:2:1.5 ratio). Preparative TLC gave as the top band enol ether (35.8 mg, 22% yield); IR (film) 1610, 1600 (C=C), 1490, 1345 cm^{-1} (NO_2); NMR δ 6.85–7.50 (m, 6 H) and 3.86 (s, 3 H).

Two additional bands were isolated and contained a partially separated mixture of the nitronic esters (0.12 g, 72% yield). Each band gave the following: IR (film) 1670 (C=O) and 1570 cm^{-1}; NMR δ 7.25–7.95 (m, 6 H) and 3.85, 3.96 (2 s, 3 H) [the δ 3.85 signal was most intense for the lowest band material].

Preparation of Cycloadducts 5–15, 17, and 18. General Procedure Employing Nitronic Esters. The freshly prepared solution of crude nitronic ester in CH_2Cl_2 was treated with excess dipolarophile and *p*-TsOH·H_2O (1 mmol, typical scale). The resulting solution was refuxed for 30 min, cooled, diluted with more CH_2Cl_2 (20 mL), and worked up as described under General Methods. The dipolarophile (scaled quantity), purification procedure, and data used in identifying products are listed for each reaction.

5: from (*E*)-stilbene (1.8 g, 10 mmol); recrystallization from hexane–benzene (53% yield); mp 95–96 °C [lit.[27] mp 94–95 °C]. Preparative TLC (hexane–ethyl acetate, 80:20) on the residue from the mother liquor gave an additional 22% yield.

6 and **5**: from (*Z*)-stilbene (95% pure by NMR, containing 5% of the *E* isomer, 0.19 g, 1.1 mmol). Preparative TLC (CH_2Cl_2–CCl_4, 50:50, and then hexane–ethyl acetate, 80:20) gave 83.5 mg (23% yield) of **6**: mp 130–131 °C [lit.[27] mp 131.5–32.5 °C].

Isolated as upper bands from the second TLC were 47 mg (13% yield) of trans isomer **5** and 9.8 mg of furoxan **3a**.

7: from 1-hexene (0.8 g, 10 mmol); preparative TLC (CH_2Cl_2) followed by Kugelrohr distillation; bp 125–135 °C (0.03 mm) [lit.[10] bp 140–150 °C (0.04 mm)].

8: from cyclopentene (0.7 g, 10 mmol); preparative TLC (CH_2Cl_2) followed by Kugelrohr distillation; bp 130–140 °C (0.08 mm); IR (film) 1330 and 1160 cm^{-1} (SO_2); NMR δ 7.5–8.1 (m, 5 H), 5.1–5.4 (m, 1 H), 3.8–4.2 (m, 1 H), and 1.2–2.5 (m, 6 H). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21. Found: C, 57.09; H, 5.23.

9: from (*E*)-stilbene (0.9 g, 5 mmol); preparative TLC (CCl_4–CH_2Cl_2, 70:30) followed by recrystallization from 95% ethanol; mp 78–79 °C; IR (melt) 1730 cm^{-1}; NMR δ 7.35 (s, 10 H), 5.66 (d, 1 H, J = 6.2 Hz), 4.53 (d, 1 H, J = 6.2 Hz), 4.22 (q, 2 H, J = 7 Hz), 1.24 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 72.90; H, 6.02.

10:[20b] from cyclohexene (1.6 g, 20 mmol); preparative TLC (CH_2Cl_2); bp 142–150 °C (0.25 mm).

11: from (*E*)-stilbene (0.7 g, 4 mmol); preparative TLC (CCl_4–CH_2Cl_2, 50:50) followed by recrystallization from 95% ethanol; mp 95–97 °C; IR (KBr) 1655 cm^{-1} (C=O); NMR δ 7.3–8.3 (m, 15 H), 5.66 (d, 1 H, J = 6.2 Hz), 4.84 (d, 1 H, J = 6.2 Hz). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.72; H, 5.23. Found: C, 80.90; H, 5.63.

12: from 1-hexene (1.7 g, 20 mmol); preparative TLC (hexane–ethyl acetate, 90:10) followed by Kugelrohr distillation: bp 140–145 °C (0.05 mm); IR (film) 1645 cm^{-1} (C=O); NMR δ 7.3–8.3 (m, 5 H), 4.5–4.9 (m, 1 H), 3.35 (dd, 1 H, J = 17.4, 10.8 Hz), 2.94 (dd, 1 H, J = 17.4, 8.8 Hz), 0.7–1.8 (m, 9 H). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.91; H, 7.60.

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(24) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862.

(25) See ref 23b for an unsuccessful attempt to use oximes as heterodienes in the Diels–Alder reaction.

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(27) Wade, P. A.; Yen, H.-K.; Hardinger, S. A.; Pillay, M. K.; Amin, N. V.; Vail, P. D.; Morrow, S. D. *J. Org. Chem.* **1983**, *48*, 1796.

13: from styrene (0.4 g, 4 mmol); preparative TLC (CH_2Cl_2–CCl_4, 50:50 then hexane–ethyl acetate, 80:20) followed by Kugelrohr distillation; bp 140–145 °C (0.25 mm) [lit.[28] bp 185 °C (3.5 mm)].

14: from (*E*)-stilbene (0.4 g, 2 mmol); preparative TLC (CCl_4–CH_2Cl_2, 50:50) followed by Kugelrohr distillation; bp 170–175 °C (0.05 mm); NMR δ 7.0–7.4 (m, 15 H), 5.63 (d, 1 H, J = 5.9 Hz), 4.55 (d, 1 H, J = 5.9 Hz), 3.15–3.3 (m, 2 H), 2.8–3.0 (m, 2 H). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.11; H, 5.95. Found: C, 80.90; H, 5.93.

15: from 5-hexen-2-one (0.4 g, 4 mmol); preparative TLC (CH_2Cl_2–ethyl acetate, 95:5) followed by Kugelrohr distillation; bp 190–195 °C (0.03 mm); IR (film) 1685, 1710 cm^{-1} (C=O); NMR δ 7.21 (s, 5 H), 4.6–5.0 (m, 1 H), 2.57 (t, J = 7 Hz) on 2.5–3.4 (m) [8 H total], 2.13 (s, 3 H), 1.7–2.0 (m, 2 H). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.32; H, 7.00. Found: C, 69.97; H, 6.96.

17 and 18: from methyl propiolate (0.3 g, 3.4 mmol); preparative TLC (CH_2Cl_2). Compound **17** was isolated as the upper band and was recrystallized from methanol: mp 97–98 °C; IR (KBr) 1730, 1655 cm^{-1} (C=O); NMR δ 7.5–8.4 (m) and 7.44 (s) [6 H total], 4.03 (s, 3 H). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92. Found: C, 62.12; H, 3.88.

Compound **18** was isolated as the lower band: mp 73–75 °C; IR (melt) 1720 cm^{-1} (br, C=O); NMR δ 9.03 (s, 1 H), 7.4–8.4 (m, 5 H), 3.76 (s, 3 H).

Preparation of 3-Ethanoyl-4,5-dihydro-5-phenylisoxazole (16). A cold (0–5 °C) solution of the dicyclohexylamine salt of 1-nitro-2-propanone (0.34 g, 1.20 mmol) in CH_2Cl_2 (4 mL) was treated with excess ethereal diazomethane. After stirring for 1 h at 0–5 °C, volatiles were removed at reduced pressure and the residue was dissolved in CH_2Cl_2 (4 mL). Styrene (1.0 g, 10 mmol) and p-TsOH·H_2O (0.45 g, 2.37 mmol) were added and the mixture was refluxed for 30 min. Methylene chloride (10 mL) was added and the reaction worked up as described in General Methods. Preparative TLC (CH_2Cl_2) on the crude product followed by Kugelrohr distillation gave 58 mg (26% yield) of pure **16**: bp 95–105 °C (0.04 mm) [lit.[29] bp 101–102 °C (0.15 mm)].

The reaction was repeated using boron trifluoride etherate (0.3 mL, 3.4 mmol) in place of p-TsOH·H_2O. Compound **16** was obtained in 22% yield.

Preparation of Furoxans from Nitronic Esters 2a and 2c. Freshly prepared solutions of the nitronic esters were treated with p-TsOH·H_2O (0.19 g, 1 mmol) and refluxed for 30 min. Methylene chloride (10 mL) was added and the reaction worked up as described in General Methods. The crude products were recrystallized from 95% ethanol. Furoxan **3a** was obtained in 76% yield: mp 156–157 °C [lit.[30] mp 155–156 °C]. Furoxan **3c** was obtained in 64% yield: mp 84–85 °C [lit.[31] mp 87 °C].

Preparaton of Cycloadducts and Furoxans from Nitro Compounds 1b–d. General Procedure. A solution of the nitro compound (1 mmol, typical scale), p-TsOH·H_2O (0.19 g, 1.0 mmol), and dipolarophile (if used) in benzene (6 mL) was heated at reflux. The resulting solution was diluted with CH_2Cl_2 (20 mL) and worked up as described under General Methods. The quantity of added dipolarophile (if used), reflux time, purification procedure, and product identification data are listed for each reaction.

3b: 8 h; 89% yield after preparative TLC (CH_2Cl_2) followed by Kugelrohr distillation; bp 110–115 °C (2 mm) [lit.[31] bp 120 °C (5 mm)].

3c: 2 h; 93% yield after recrystallization from 95% ethanol; mp 84–85 °C.

9: from (*E*)-stilbene (0.7 g, 4 mmol); 8 h; preparative TLC (CCl_4–CH_2Cl_2, 50:50) followed by recrystallization from 95% ethanol; mp 78–79 °C.

11: from (*E*)-stilbene (0.7 g, 4 mmol); 2 h (15 h in CH_2Cl_2); mp 94–96 °C.

12: from 1-hexene (1.7 g, 20 mmol); 2 h; preparative TLC (hexane–ethyl acetate, 90:10); bp 140–145 °C (0.05 mm). Also obtained from a lower TLC band was 110 mg (43% yield) of 2-hexenyl tosylate.

14: from (*E*)-stilbene (0.7 g, 4 mmol); 2 h; preparative TLC (CCl_4–CH_2Cl_2, 50:50) followed by Kugelrohr distillation; bp 170–180 °C (0.05 mm).

15: from 5-hexen-2-one (0.2 g, 2 mmol); 2 h; preparative TLC (CH_2Cl_2–ethyl acetate, 95:5) followed by Kugelrohr distillation; bp 190–195 °C (0.03 mm).

Preparation of Cycloadduct 5 and Furoxan 3a from (Phenylsulfonyl)nitromethane (4a). A mixture of **4a** (0.1 g, 0.5 mmol), (*E*)-stilbene (0.33 g, 1.8 mmol), p-TsOH·H_2O (96 mg, 0.5 mmol), and m-dichlorobenzene (0.3 g) was heated at 160–165 °C for 15 min. The resulting solution was diluted with CH_2Cl_2 (20 mL) and worked up as described under General Methods. Preparative TLC (CH_2Cl_2) gave 95 mg (53% yield) of **5**, with spectra identical with an authentic sample.

When the reaction was repeated without (*E*)-stilbene, 72 mg (78% yield) of furoxan **3a** was obtained. This was recrystallized from 95% ethanol: mp 156–157 °C.

Preparation of *trans*-4,5-Dihydro-3,4,5-triphenylisoxazole (23a). The lithium salt of α-nitrotoluene (0.46 g, 3.2 mmol, prepared from reaction of Li^0 and methanol followed by addition of a slight excess of α-nitrotoluene) was added to a refluxing solution of (*E*)-stilbene (1.12 g, 7 mmol) and p-TsOH·H_2O (0.77 g, 4.0 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at reflux for 1 h, cooled, diluted with CH_2Cl_2 (20 mL), and worked up as described under General Methods. Preparative TLC (CH_2Cl_2–CCl_4, 50:50) followed by recrystallization from 95% ethanol gave 0.45 g (49% yield) of pure **23a**: mp 139–140 °C (lit.[27] mp 137–138 °C).

Preparation of *trans*-4,5-Dihydro-4,5-diphenyl-3-ethylisoxazole (23b). 23b was prepared from the lithium salt of 1-nitropropane similar to **23a**. Pure **23b** was obtained in 7% yield after chromatography followed by Kugelrohr distillation: bp 115–120 °C; NMR δ 7.32 (s, 10 H), 5.43 (d, 1 H, J = 7 Hz), 4.20 (d, 1 H, J = 7 Hz), 2.1 (m, 2 H), 1.07 (t, 3 H, 7 Hz).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.25; H, 6.81. Found: C, 81.13; H, 6.87.

Isolation of Isoxazolidine 19. A solution of nitronic ester derived from **4a** (0.2 g, 1 mmol) was treated with sodium bicarbonate (2 mg) and 1-hexene (1.36 g, 16 mmol). The resulting mixture was refluxed for 18 h and volatiles were removed at reduced pressure. Preparative TLC (alumina, CH_2Cl_2–CCl_4, 50:50 elution) of the crude product gave 0.22 g (73% yield) of **19** as an oil. Isoxazolidine **19** did not give a correct C analysis but did give spectra consistent with the assigned structure: IR (film) 1320 and 1140 cm^{-1} (SO_2); 250-MHz NMR[32] ($NaHCO_3$ treated $CDCl_3$) δ 7.5–8.0 (m, 5 H), 4.81 (dd, J = 2.7, 9.7 Hz, major) and 4.70 (dd, J = 6.3, 9.0 Hz, minor) [1 H total], 4.3–4.4 (m, 1 H), 3.38 (s, major) and 3.35 (s, minor) [3 H total], 2.99 (ddd, major) and 2.72 (ddd, minor) [1 H total], 2.46 (ddd, major) and 2.25 (ddd, minor) [1 H total], 1.2–1.8 (m, 6 H), 0.88 (skewed t, 3 H).

Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.17; H, 7.06. Found: C, 54.57; H, 6.77.

Reduction of 3-(Ethoxycarbonyl)-4,5-dihydro-4,5-diphenylisoxazole (9). Sodium borohydride (0.15 g, 4 mmol) was added to a cold (0–5 °C) solution of **9** (37 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) and methanol (5 mL). The reaction was stirred at ambient temperature for 90 min and more $NaBH_4$ (57 mg) was added. After an additional 30 min 10% aqueous KH_2PO_4 (8 mL) was added and then CH_2Cl_2. The organic layer was separated, washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated at reduced pressure. Preparative TLC (hexane–ethyl acetate, 50:50) of the resulting residue followed by Kugelrohr distillation gave 24 mg (78% yield) of pure **28** as an oil: bp 90–100 °C (0.2 mm); IR 3200–3600 cm^{-1} (br, OH); NMR δ 7.43 (m, 10 H), 5.52 (d, 1 H, J = 6.8 Hz), 4.38 (d, J = 6.8 Hz) on 4.0–4.5 (m, collapses to dd on D_2O exchange) [3 H total], 2.2 (br s, 1 H, disappears on D_2O exchange).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.97. Found: C, 75.48; H, 6.14.

Reaction of 3-Benzoyl-4,5-dihydro-5-phenylisoxazole (13) with Methyllithium. Methyllithium (16 mL of a 2.45 M solu-

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(32) We thank K.-Y. Jen and R. Zipkin [University of Pennsylvania] for obtaining these spectra.

tion) was added dropwise over 5 min to a cold (−78 °C) solution of **13** (2.46 g, 9.8 mmol) in THF (80 mL). The resulting solution was stirred 15 min (−78 °C) and then wet THF and water were added sequentially. The mixture was allowed to warm (>0 °C), was diluted with CH_2Cl_2, and was worked up as in the previous procedure. Column chromatography (hexane–ethyl acetate, 70:30) of the crude product followed by recrystallization from 95% ethanol gave 1.0 g (38% yield) of one pure diastereomer of **29**: mp 79–80 °C; IR (KBr) 3200–3500 cm^{-1} (br, OH); NMR δ 7.3–7.5 (m, 10 H), 5.56 (dd, 1 H, J = 9.1, 10.2), 3.19 (dd, J = 10.2, 18 Hz) overlapping 2.95 (dd, J = 9.1, 18 Hz), 2.64 (br s, 1 H), 1.91 (s, 3 H).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.29; H, 6.41.

Continued elution followed by recrystallization from 95% ethanol gave 1.44 g (55% yield) of the second diastereomer of **29**: mp 104–105 °C; IR (KBr) 3200–3500 cm^{-1} (br, OH); NMR δ 7.25–7.5 (m, 10 H), 5.58 (dd, 1 H, J = 8.7, 10.8 Hz), 3.41 (dd, 1 H, J = 10.8, 17.2 Hz), 2.71 (dd on br s, 2 H, J = 8.7, 17.2 Hz), 1.89 (s, 3 H).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.00; H, 6.43.

Preparation of 4,5-Dihydro-3-ethenylisoxazole (31a). A solution (7.5 mL, 1.3 M) of vinylmagnesium bromide in THF was added dropwise over 3 min to a slightly cooled solution of sulfonylisoxazoline **30** (0.7 g, 2.45 mmol) in THF (25 mL). The resulting solution was stirred at room temperature for 5 h and then THF–water (50:50, 20 mL) was cautiously added. The mixture was diluted with CH_2Cl_2 (50 mL) and worked up as in the two previous procedures. Preparative TLC (hexane–ethyl acetate, 70:30) of the crude product followed by Kugelrohr distillation gave 0.30 g (72% yield) of **31a**: bp 45–55 °C (0.2 mm); NMR δ 7.33 (s, 5 H), 6.74 (dd, 1 H, J = 11.2, 20 Hz), 5.35–5.85 (m, 3 H), 3.50 (dd, 1 H, J = 10.5, 16.7 Hz), and 3.15 (dd, 1 H, J = 8.6, 16.7 Hz).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40. Found: C, 75.98; H, 6.32.

Preparation of 4,5-Dihydro-3-(1-phenylethenyl)-5-phenylisoxazole (31b). A solution of the first diastereomer of **29** (1.01 g, 4 mmol) and p-TsOH·H_2O (2.16 g, 12 mmol) in benzene (100 mL) was refluxed for 1 h. The reaction was worked up according to the procedure in General Methods. The crude product was column chromatographed (hexane–ethyl acetate, 80:20) and recrystallized from absolute alcohol to give 0.66 g (74% yield) of alkene **31b**: mp 58–59 °C; NMR δ 7.36 (s, 10 H), 5.68 (dd, J = 8.3 Hz) on 5.58, 5.48 (2 s) [3 H total], 3.65 (dd, 1 H, J = 11.0, 16.5 Hz), 3.19 (dd, 1 H, J = 8.3, 16.5 Hz).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06. Found: C, 81.85; H, 6.10.

Similar treatment of the second diastereomer of **29** gave alkene **31b** in 73% yield.

Cycloaddition of Alkenylisoxazoline 31a and TCNE. Alkenylisoxazoline **31a** (31 mg, 0.18 mmol) and TCNE (138 mg, 1.1 mmol) were placed in a 25-mL round-bottom flask. The flask was dipped into an oil bath kept at 140 ± 3 °C for 15 min and was then rapidly cooled. Preparative TLC (hexane–ethyl acetate, 80:20) on the crude products gave 17.2 mg (33% yield) of cycloadduct **32a** as the lowest isolated band: IR ($CHCl_3$) 2260 cm^{-1}; 250-MHz NMR[32] δ 7.41 (s, 5 H), 5.41 (dd, 1 H, J = 6.8, 9.4 Hz), 5.17 (m, 1 H), 3.3–3.5 (m, 1 H), 3.25 (m, 2 H), 3.0–3.2 (m, 1 H).

Starting material **31a** (14.9 mg, 47% recovery) was obtained from a middle TLC band. An upper band contained 1.8 mg (6% yield) of isoxazole **33**.

After only 4 min at 140 ± 3 °C bath temperature, 2.6 mg (5% yield) of cycloadduct **32a** could be isolated. After 4 min at 190–195 °C bath temperature, **32a** (28% yield), **31a** (30% recovery), and **33** (16% yield) were obtained. Isoxazole **33** was prepared in 76% yield by refluxing a mixture of **31a** (0.8 g, 4.6 mmol), γ-MnO_2 (4 g), and benzene (30 mL) for 24 h: mp 55–56 °C; NMR δ 7.4–7.8 (m, 5 H), 6.66 (s) on 6.82 (dd, J = 6.8, 11 Hz) [2 H total], 5.5–6 (m, 2 H).

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30. Found: C, 77.37; H, 5.54.

Cycloaddition of Alkenylisoxazoline 31b and TCNE. Alkenylisoxazoline **31b** (45 mg, 0.18 mmol) and TCNE (139 mg, 1.1 mmol) were placed in a 25-mL round-bottom flask. The flask was dipped into an oil bath kept at 140 ± 2 °C for 4 min and was then rapidly cooled. Preparative TLC (hexane–ethyl acetate, 70:30) on the crude products gave 39.1 mg (57% yield) of cycloadduct **32b** as the lowest isolated band: IR ($CHCl_3$) 2250 cm^{-1}; 250-MHz NMR[32] δ 7.2–7.6 (m, 10 H), 5.43 (dd, 1 H, J = 6.7, 9.3 Hz), 3.54 (m, 2 H), 3.46 (dd, 1 H, J = 6.7, 10.6 Hz), 3.12 (dd, 1 H, J = 9.3, 10.6 Hz).

After 2 days at −20 °C or 1 h at room temperature, some cycloreversion to **31b** was noted.

Solvent Effects on Cycloreversion of 32a. A solution of cycloadduct **32a** (29 mg, 0.1 mmol) in the specified solvent (2 mL) was heated for 55 min at 60 ± 1 °C (bath temperature). The reaction mixture was rapidly cooled and the products were separated by preparative TLC (hexane–ethyl acetate, 70:30). The mole ratio **31a**:**32a** and combined recovery of **31a** and **32a** are listed for each solvent: benzene, 34:66 (77% recovery); $CHCl_3$, 42:58 (78% recovery); CH_3CN, 35:65 (67% recovery).

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Registry No. 2a, 57359-33-8; **2b**, 57777-62-5; **2c**, 92241-09-3; **2d**, 92241-10-6; **2e**, 92241-11-7; **3a**, 66074-00-8; **3c**, 6635-54-7; **4a**, 21272-85-5; **4b**, 626-35-7; **4c**, 614-21-1; **4d**, 67333-73-7; **5**, 85355-68-6; **6**, 85355-67-5; **7**, 70367-25-8; **8**, 70367-27-0; **9**, 92241-12-8; **10**, 40499-70-5; **11**, 92241-13-9; **12**, 92241-14-0; **13**, 7064-02-0; **14**, 92241-17-3; **15**, 92241-18-4; **16**, 7064-03-1; **17**, 92241-15-1; **18**, 92241-16-2; **19**, 92241-21-9; **22a**, 92241-19-5; **22b**, 74601-45-9; **23a**, 4894-25-1; **23b**, 92241-20-8; **28**, 92241-22-0; **29** (isomer 1), 92241-23-1; **29** (isomer 2), 92241-24-2; **30**, 70367-29-2; **31a**, 84817-45-8; **31b**, 92241-25-3; **32a**, 92269-45-9; **32b**, 92241-26-4; **33**, 5376-55-6; (*E*)-PhCH=CHPh, 103-30-0; TCNE, 670-54-2; (*Z*)-PhCH=CHPh, 645-49-8; CH_2=$CH(CH_2)_3CH_3$, 592-41-6; PhCH=CH_2, 100-42-5; HC≡CC(O)OMe, 922-67-8; CH_2=CH-MgBr, 1826-67-1; MeLi, 917-54-4; CH_2=N_2, 334-88-3; CH_2=C-$H(CH_2)_2C(O)CH_3$, 109-49-9; cyclopentene, 142-29-0; cyclohexene, 110-83-8.