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1,3-Dipolar Cycloadditions of Nitrones and Nitrile Oxides.

Yau-min Chang
Louisiana State University and Agricultural & Mechanical College

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1,3-DIPOLAR CYCLOADDITIONS OF NITRONES
AND NITRILE OXIDES.

The Louisiana State University and Agricultural
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Chemistry, organic

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1,3-DIPOLAR CYCLOADDITIONS OF NITRONES AND NITRILE OXIDES

A Dissertation
Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment to the
requirements for the Degree of
Doctor of Philosophy
in
The Department of Chemistry

by
Yau-Min Chang
B.S., Chung-Hsing University, 1968
December, 1975
For Celia and Kevin
ACKNOWLEDGMENTS

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ABSTRACT

Until recently, nitrones and nitrile oxides were thought to add to all monosubstituted alkenes to form 5-substituted adducts, regardless of the electron-donating or electron-withdrawing character of the substituent. Steric arguments have been proposed to account for these results. On the other hand, frontier molecular orbital theory has provided an explanation of this phenomenon in terms of electronic effects, and has predicted that very electron-deficient alkenes and alkynes should show a loss or reversal of regioselectivity in reactions with nitrones and nitrile oxides. To confirm these predictions, reactions of three nitrones (N-t-butylnitrone, C-phenyl-N-methylnitrone, and C-mesityl-N-methylnitrone) and nitrile oxides (benzonitrile oxide, p-nitrobenzonitrile oxide, and mesitylnitrile oxide) with six electron-deficient alkenes and alkynes (methyl acrylate, phenyl vinyl sulfone, nitroethylene, acrylonitrile, methyl propiolate, and cyanoacetylene) have been investigated.

Some of these reactions gave only the normal adducts while many reactions gave mixtures of the 4- and 5-substituted regioisomers. Reactions of C-mesityl-N-methylnitrone with nitroethylene, phenyl vinyl sulfone, methyl propiolate, and cyanoacetylene, as well as reactions of C-phenyl-N-methylnitrone with nitroethylene and cyanoacetylene were regioselective for the formation of the 4-substituted adducts. These results are uniquely compatible with a frontier orbital theory interpretation of regioselectivity.

Mesitylnitrile oxide was also reacted with the following
alkenes and alkynes: isobutyl vinyl ether, styrene, α-methylstyrene, cis-β-methylstyrene, trans-β-methylstyrene, fumaronitrile, divinyl sulfone, methyl vinyl sulfone, tetracyanoethylene, 1,2-bis(trifluoromethyl)fumaronitrile, ethyl propiolate, and 3,3,3-trifluoropropyne.

Rates of mesitylnitrile oxide reactions are correlated with dipolarophile ionization potentials. Both reactivity and regioselectivity are shown to be in accordance with frontier orbital theory.

Solvent effects for reactions of mesitylnitrile oxide with acrylonitrile, tetracyanoethylene, and 1,2-bis(trifluoromethyl)fumaronitrile, were studied. The rates of these reactions are rather insensitive to solvent polarity, compatible with a concerted mechanism.

A few tests of the effects of Lewis acids on 1,3-dipolar cycloaddition regioselectivity were performed by reacting mesitylnitrile oxide with methyl propiolate in the presence of aluminum chloride and boron trifluoride-etherate. The change in the ratio of the regioisomers and the dimerization of mesitylnitrile oxide caused by catalysis are rationalized by frontier orbital considerations.

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I. INTRODUCTION

PART A 1,3-Dipolar Cycloadditions

A 1,3-dipolar cycloaddition is defined as the 1,3-addition of a formally zwitterionic molecule $\text{a}^{+}\text{b}^{-}\text{c} \ (\text{the dipole})$, to a multiple bond system $\text{d}=\text{e} \ (\text{the dipolarophile})$, to form an uncharged five-membered ring.

Because five-membered heterocycles are generated with remarkable stereoselectivity and regioselectivity, the 1,3-dipolar cycloaddition is of great synthetic utility.

Although a few reports of the reactions of ozone, azides and diazoalkanes with alkenes have appeared in the literature during the past sixty years, the general concept of 1,3-dipolar cycloadditions was first recognized by Huisgen. In 1957, Huisgen and his coworkers began a brilliant series of studies which led to a clear classification of dipolar reagents and to a fruitful development of this synthetic principle.

A complete list of 1,3-dipoles and the consideration of the resonance formulation of the electronic structures of these species have been reported by Huisgen, et al. Table I shows the two all-
### TABLE I
THE COMMON 1,3-DIPOLES

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<th>Nitrilium Betaines</th>
<th>Diazonium Betaines</th>
<th>Azomethinium Betaines</th>
<th>Oxygenated Dipoles</th>
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<tr>
<td>R-C≡N–CR₂</td>
<td>N≡N–CR₂</td>
<td>R₂=C=N(R)=CR₂</td>
<td>R₂C=CR₂</td>
</tr>
<tr>
<td>R-C≡N–NR</td>
<td>N≡N–NR</td>
<td>R₂=C=N(R)=NR</td>
<td>R₂C=CR₂</td>
</tr>
<tr>
<td>R-C≡N−O</td>
<td>N≡N−O</td>
<td>R₂=C=N(R)=O</td>
<td>R₂C=CR₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>O=O−O</td>
</tr>
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- **Nitrile ylides**
- **Nitrile imines**
- **Nitrile oxides**
- **Diazocalkanes**
- **Azides**
- **Nitrous Oxide**
- **Azomethine ylides**
- **Azomethine imines**
- **Nitrones**
- **Carbonyl ylides**
- **Carbonyl imines**
- **Carbonyl oxides**
- **Ozone**
The mechanisms of 1,3-dipolar cycloadditions have been thoroughly investigated. Classically, cycloaddition mechanisms have been grouped into three categories: (1) the concerted mechanism, involving simultaneous formation of both new bonds; (2) a stepwise dipolar mechanism, involving a zwitterionic intermediate, and (3) a stepwise diradical mechanism, involving a diradical intermediate. Despite its name, the 1,3-dipolar cycloaddition is generally considered as a single-step, four-center, concerted reaction. The stepwise dipolar mechanism, however, can not be totally rejected for additions involving highly polarized dipolarophiles. The stepwise diradical mechanism has also been postulated, but not accepted. One aspect of this work was designed to test whether mechanisms other than concerted could occur with certain addend pairs not previously studied.

Most 1,3-dipoles lack bisecting planes of symmetry as shown in Table I. Thus, in a 1,3-dipolar cycloaddition reaction involving an unsymmetrical dipolarophile, two modes of approach of the dipole to the 2π electron dipolarophile are possible, as illustrated in Figure 1.

![Figure 1. Modes of Approach of Addends in 1,3-Dipolar Cycloadditions.](image_url)
Selectivity in the direction of addition to an unsymmetrical alkene or alkyne is termed regioselectivity. Until recently, it was believed that reactions of nitrones and nitrile oxides with monosubstituted alkenes gave only the 5-substituted cycloaddition adducts regardless of the nature of the alkene substituent. This experimentally observed regioselectivity of most 1,3-dipolar cycloadditions has been the most difficult phenomenon to explain.

Firestone proposed a stepwise mechanism involving diradical intermediates to account for these observations. Huisgen, on the other hand, has proposed, based on a concerted transition state model, that steric repulsions between a carbon substituent on the nitrone or nitrile oxide and the alkene substituent favor formation of the less sterically hindered 5-substituted adduct.

Houk, et al. have recently applied molecular orbital perturbation theory to the rationalization of reactivity and regioselectivity in all 1,3-dipolar cycloadditions. According to this frontier orbital treatment, the regioselectivity of 1,3-dipolar cycloadditions is produced by electronic rather than steric factors, and the unidirectional addition of many 1,3-dipoles to monosubstituted dipolarophiles should no longer be observed when the dipolarophile is made highly electron-deficient. Experimental results in general accord with these predictions have been obtained for reactions of certain nitrones. Another aspect of this research was to test the generality of these predictions and to place them on a more quantitative basis.
1. Nitrones

In 1889, Beckmann reported obtaining the first azomethine-N-oxides while attempting O-alkylation of oximes. The name "nitrones" was suggested for these N-alkylated oximes by analogy to ketones. Nitrones, as well as other 1,3-dipoles, are isoelectronic with the allyl anion since they contain a resonance stabilized 4π electron system. The two all-octet structures shown in Table I appear to make the most significant contributions to the resonance hybrid.

Aldonitrones (RCH=N(O)R') prefer the trans-orientation of alkyl groups about the C=N double bond. For instance, the structure of the most widely studied nitrone, C-phenyl-N-methylnitrone, is illustrated by structure 1, while Δ¹-piperidene-N-oxide 2, the cis-form of which is dictated by the ring structure, exists in equilibrium with a dimer, 3.

Ketonitrones (RR'C=N(O)R'') may exist as cis and trans isomers, but the cis isomers are readily converted into the trans isomers upon heating.

The syntheses of nitrones were reviewed in 1972 by Sandler and Karo. In addition to alkylation of oximes, nitrones can also be prepared by oxidation of N,N-disubstituted hydroxylamines, reaction of N-substituted hydroxylamines with aldehydes or ketones, or conden-
sation of aromatic nitroso compounds with activated methyl or methylene groups.

The first synthesis of stable methylene nitrones from amines via nitroso compounds was reported by Baldwin.\textsuperscript{18} A modified procedure for the preparation of N-t-butyl nitrone was developed by Sims.\textsuperscript{19}

2. Nitrile Oxides

The history of nitrile oxides began with the description of the mercury salt of fulminic acid (the parent nitrile oxide) in 1800 by Howard.\textsuperscript{20} Many structural formulas had been proposed for fulminic acid until structure 4, formonitrile oxide, was first suggested by Ley\textsuperscript{21} in 1899. Later, Huisgen's concept of the 1,3-dipolar reactivity of nitrile oxides\textsuperscript{22} led to the resonance hybrid formulation, $\overset{\text{+}}{\overset{-}{\text{H}}}{\text{C}}\text{=N}=\overset{\text{-}}{\overset{+}{\text{O}}}$ $\overset{\text{4}}{\overset{\leftrightarrow}{\rightarrow}}$ $\overset{\text{-}}{\overset{-}{\text{R}}}{\text{=C}}\text{=N}=\overset{\text{+}}{\text{O}}$ $\overset{\text{5}}{\text{5}}$, for fulminic acid.

The first member of the higher homologs of fulminic acid prepared was benzonitrile oxide, obtained in pure form by Wieland in 1907.\textsuperscript{23} Since that time, numerous aliphatic and aromatic nitrile oxides have been synthesized.\textsuperscript{8} All are named as N-oxides of the corresponding nitriles.

Most nitrile oxides are unstable at room temperature. As derivatives of fulminic acid, all low molecular weight nitrile oxides are considered as potentially explosive. However, the main difficulties in working with the nitrile oxides are not caused by instability, but by their rapid spontaneous dimerization. Heating a nitrile
oxide above its limit of thermal stability generally initiates two
different, competing, reactions: (a) dimerization to 1,2,5-oxa-
diazoles, 6 (furoxans), and (b) rearrangement to isocyanates, 7.

$$
\begin{align*}
R - C\equiv N &\rightarrow O \\
\text{(a)} &
\end{align*}
$$

$$
\begin{align*}
R - C\equiv N &\rightarrow O \\
\text{(b)} &
\end{align*}
$$

The reaction pathway (a) predominates with lower aliphatic
nitrile oxides, while route (b) is enhanced to some extent for aromatic
nitrile oxides of moderate stability. The mechanism of the thermal
rearrangement of nitrile oxides to isocyanates is unknown.\textsuperscript{24} The
dimerization of nitrile oxides to furoxans is regarded as a 1,3-
dipolar cycloaddition in which one molecule of nitrile oxide adds
onto the C=N bond of another, the latter acting as a dipolarophile.\textsuperscript{25}

Aromatic nitrile oxides can be stabilized by substituting
the o and o'-positions with substituents of large spatial requirements,
such as CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, CH\textsubscript{3}O or CH\textsubscript{3}S, which will block sterically the
dimerization to furoxans. This type of substitution impairs only
slightly the ability of these species to react with other unhindered
systems. In the aliphatic series, a higher degree of steric hindrance
is needed to give thermal stability. Thus, bis-\textit{tert}-butylacetonitrile
oxide is permanently stable at room temperature,\textsuperscript{26} as is triphenyl-
acetonitrile oxide.\textsuperscript{27} This approach has led to the preparation of a
number of nitrile oxides which have unlimited stabilities at room
temperature.

With the exception of fulminic acid, which is generated from its metal salts or halogen derivatives, nitrile oxides are prepared by either the dehydration of primary nitroparaffins or the dehydrogenation of aldoximes. Primary nitroparaffins, in the forms of their acid-salts, react with hydrogen chloride under anhydrous conditions to form hydroxamic chlorides, which are then converted into nitrile oxides by treatment with base.

\[
\begin{align*}
\text{R-CH}_2\text{NO}_2 & \xrightarrow{\theta \text{OH}} \text{R-CH=N-O}^\theta \xrightarrow{\text{2HCl}} \text{R-C=NOH} \xrightarrow{\text{Base}} \text{R-C=N} \rightarrow \text{O} \\
\text{Cl}
\end{align*}
\]

\( R = \text{CH}_3, \text{C}_6\text{H}_5, \text{C}_6\text{H}_5\text{CO}, \text{C}_2\text{H}_5\text{OOC} \)

Some aromatic nitrile oxides have also been prepared by the decomposition of nitrolic acids, which are obtained by reaction of primary nitroparaffins with nitrous acid.

\[
\begin{align*}
\text{R-CH}_2\text{NO}_2 + \text{HNO}_2 & \xrightarrow{\Delta} \text{R-C=NOH} \xrightarrow{\text{NO}_2} \text{R-C=N} \rightarrow \text{O} \\
\text{R} &= \text{C}_6\text{H}_5, 2,4,6(\text{CH}_3)_3\text{C}_6\text{H}_2
\end{align*}
\]

More recently, the dehydration of nitroparaffins to form nitrile oxides was achieved in one step under rather mild conditions using phenylisocyanate as the dehydrating agent in the presence of catalytic amounts of triethylamine. However, all of the above methods are less widely applied. The most important methods for the preparation of nitrile oxides start with aldoximes, from which two hydrogen atoms can be removed by various techniques to form the nitrile oxides.
Aliphatic, aromatic and heterocyclic aldoximes have been dehydrogenated to nitrile oxides in alkaline solution by sodium hypobromite. Aldoximes can also be dehydrogenated to nitrile oxides by means of lead tetraacetate. The reaction, however, has to be carried out at -78°, since only syn-oximes give nitrile oxides.

A milder and more selective dehydrogenation of aldoximes has been achieved with N-bromosuccinimide in the presence of alkali alkoxides or tertiary bases. This modification generally gives good yields, and is probably the most generally applicable procedure for the synthesis of aromatic, heterocyclic, and polyfunctional, nitrile oxides.

Because of their instability, some nitrile oxides are prepared in situ in the study of nitrile oxide reactions. The nitrile oxide is generated from a stable precursor in the presence of a partner with which it will react. Hydroxamic acid chlorides, conveniently prepared from the chlorination of the corresponding aldoximes, are quite stable at room temperature and are therefore most frequently used as precursors of unstable nitrile oxides, which can be generated when needed almost instantaneously by action of base. This in situ preparation technique was first applied successfully by Huisgen, and has been responsible to a considerable degree for the fast developments in the area of nitrile oxide chemistry.
PART C Cycloaddition Reactions of Nitrones and Nitrile Oxides

1,3-Dipoles can undergo 1,3-additions to bases, H-B, or cycloadditions to alkenes and alkynes. Reactions of 1,3-dipoles were reviewed in 1938, 1964, and 1965. Cycloadditions of all 1,3-dipoles were reviewed in 1963. 1,3-Dipolar cycloaddition reactions of nitrile oxides were reviewed in 1971. 1,3-dipolar cycloaddition reactions of nitrones were recently reviewed in 1975.

1. Synthetic Utility

The cycloaddition reactions of nitrones and nitrile oxides with alkenes, alkynes, and other dipolarophiles generally proceed to give good yields and provide a convenient route for the synthesis of five-membered heterocycles. Alkenes and alkynes react with nitrones to give isoxazolidines and \( \Delta^4 \)-isoxazolines, respectively, and with nitrile oxides to give \( \Delta^2 \)-isoxazolines and isoxazoles, respectively. This synthetic approach has been applied to the synthesis of steroid heterocycles which have a wide spectrum of physiological activity. For instance, Culbertson, et al. reported the formation of 9 from the reaction of acetonitrile oxide with 20-oxopregna-5,16-dien-3β-y1 acetate 8.
Benzyne forms stable adducts, 10, with simple nitrones, affording a route to the aromatic indoxazenes, 11, by cycloaddition to nitrile oxides.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \\
\text{Ph} & \quad \text{N} \quad \text{O} + \left[ \begin{array}{c} \text{C} \end{array} \right] \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{N} \quad \text{O} \\
\end{align*}
\]

The cycloadditions of nitrones and nitrile oxides to other multiple bond systems provide convenient syntheses of many classes of heterocycles, which are in some cases otherwise inaccessible. Summaries of the syntheses of heterocyclic systems utilizing cycloadditions of nitrones and nitrile oxides are shown in Tables II and III.

Taking advantage of some unstable cycloadducts, cycloadditions of nitrones and nitrile oxides can be utilized for various carbonyl transformation reactions. In principle, an aldehyde or ketone is converted to a nitrone or nitrile oxide, a cycloaddition reaction carried out on it, and the resulting cycloadduct decomposed in some way to provide a new carbonyl compound. For example, 3-pyrrolidinones, are formed as products of allenes with simple nitrones.

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{O} \\
\text{Ar} & \quad \text{N} \quad \text{O} + \left[ \begin{array}{c} \text{C} \end{array} \right] \quad \rightarrow \quad \text{H} \quad \text{N} \quad \text{O} \\
\end{align*}
\]

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<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;C=C&lt;</td>
<td>isoxazolidines</td>
<td>35,36,37</td>
</tr>
<tr>
<td>—C≡C—</td>
<td>Δ⁴-isoxazolines</td>
<td>35,36,37</td>
</tr>
<tr>
<td>—N=C=O</td>
<td>1,2,4-oxadiazolidin-5-ones</td>
<td>13,39</td>
</tr>
<tr>
<td>—N=C=S</td>
<td>1,2,4-oxadiazolidin-5-thiones</td>
<td>39,40</td>
</tr>
<tr>
<td>—N=C=N—</td>
<td>1,2,4-oxadazolin-5-imines</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>1,4,2-oxathiolizidin-5-thiones</td>
<td>1,4,2-oxathiolizidines</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>42</td>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
</tr>
</tbody>
</table>

Table II (Continued)

S=C=S  
\[ \overset{\text{C}}{\text{S}} \]  
\[ \overset{\text{C}}{\text{S}} \]  
\[ \overset{\text{C}}{\text{C}} \]  
\[ \overset{\text{P}}{\text{S}} \]
Table III  Cycloadditions of Nitrile Oxides (−C≡N → O) With Multiple Bond Systems

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;C=C&lt;</td>
<td>Δ²-isoxazolines</td>
<td>8</td>
</tr>
<tr>
<td>&gt;C≡C&lt;</td>
<td>isoxazoles</td>
<td>8</td>
</tr>
<tr>
<td>&gt;C=O</td>
<td>1,3,4-dioxazoles</td>
<td>34</td>
</tr>
<tr>
<td>&gt;C=S</td>
<td>1,4,2-oxathiazoles</td>
<td>46</td>
</tr>
<tr>
<td>&gt;C=N&lt;</td>
<td>Δ²-1,2,4-oxadiazolines</td>
<td>2</td>
</tr>
</tbody>
</table>
Table III (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>- C≡N</td>
<td><img src="image1" alt="Structure" /></td>
<td>1,2,4-oxadiazoles</td>
<td>34</td>
</tr>
<tr>
<td>- N=N-</td>
<td><img src="image2" alt="Structure" /></td>
<td>1,2,3,5-oxatriazolines</td>
<td>47</td>
</tr>
<tr>
<td>- N=S=O</td>
<td><img src="image3" alt="Structure" /></td>
<td>2-oxo-1,2,3,5-oxathiadiazoles</td>
<td>48,49</td>
</tr>
<tr>
<td>- N=B-</td>
<td><img src="image4" alt="Structure" /></td>
<td>1,3,5,2-oxadiazaboroles</td>
<td>50</td>
</tr>
<tr>
<td>≿ C=Pφ₃</td>
<td><img src="image5" alt="Structure" /></td>
<td>1,2,5-oxazaphosphol-2-ines</td>
<td>51</td>
</tr>
</tbody>
</table>
Polyfunctional nitrones or nitrile oxides provide another interesting method of polymer synthesis. Polymers of type 13 have been obtained from the copolymerization of bis-nitrile oxides and diethynylbenzene, and type 15 from the polymerization of an unsaturated nitrone 14.

Recently, the general 1,3-dipolar cycloaddition principle has also been extended to the preparation of linked and fused ring heterocycles. The general usefulness of this approach has yet to be explored.
2. Reactivity

The rates of 1,3-dipolar cycloadditions are greatly influenced by both the steric and the electronic characteristics of the dipoles and dipolarophiles. Huisgen has attributed the variation in the reactivity of the methylated acrylic esters toward cycloadditions with 1,3-dipoles largely to steric factors. As shown in Table IV, relative rate constant for C-phenyl-N-methylnitrone or benzonitrile oxide cycloaddition reaction decreases as the number of methyl substituents on the dipolarophile increases. For reactions of monosubstituted alkenes shown in Table V, the electronic effects of the substituents apparently have the greatest influence on cycloaddition reactivity.

The substituents on nitrones or nitrile oxides also play an important role in the determination of reaction rates. Steric factors again were proposed to be the cause of the rate variation. Dipolarophiles such as nitriles and carbonyl compounds are generally unreactive in 1,3-dipolar cycloadditions, unless they are "activated." For example, under the normal conditions, benzonitrile oxide reacts only with aromatic nitriles, or with nitriles activated by an electron-attracting substituent²,³ to form oxadiazoles, while aliphatic nitriles are not attacked. Similar limitations apply to carbonyl compounds, both aldehydes and ketones.

A Lewis-acid catalyzed 1,3-dipolar cycloaddition process has been developed by Morrocchi, et al., to solve these problems. In the presence of boron trifluoride-etherate, nitriles and carbonyl compounds undergo smooth cycloaddition reactions with benzonitrile oxide to give 1,2,4-oxadiazoles and 1,3,4-dioxazoles, respectively, in fairly good yields. However, very few examples have been studied in this respect.
<table>
<thead>
<tr>
<th>Acrylic ester</th>
<th>$k_2$(methyl acrylate)$\equiv100$</th>
<th>$k_2$(methyl acrylate)$\equiv100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Ph} = \text{C} = \text{N} \rightarrow \text{O}$</td>
<td>$100$</td>
<td>$100$</td>
</tr>
<tr>
<td>$\text{H} = \text{C} = \text{C} = \text{CH}_3$</td>
<td>$30$</td>
<td>$43$</td>
</tr>
<tr>
<td>$\text{H} = \text{C} = \text{CH}_3 \text{CO}_2\text{R}$</td>
<td>$8.4$</td>
<td>$10$</td>
</tr>
<tr>
<td>$\text{H}_3\text{C} = \text{C} = \text{H}$</td>
<td>$0.63$</td>
<td>$0.075$</td>
</tr>
<tr>
<td>$\text{H}_3\text{C} = \text{C} = \text{CO}_2\text{R}$</td>
<td>$0.023$</td>
<td>$0.86$</td>
</tr>
</tbody>
</table>

TABLE IV. Relative Rate Constants for Cycloadditions of (a) C-Phenyl-N-methylnitrone, and (b) Benzonitrile Oxide, With Methylated Acrylic Esters. 55,56
TABLE V. Relative Rate Constants for Cycloadditions of (a) C-Phenyl-N-methylnitrone, and (b) Benzonitrile Oxide with $\text{p}$-substituted Styrenes.$^{55,56}$

<table>
<thead>
<tr>
<th>Alkene</th>
<th>$\text{Ph}^-$-$\text{C}=$-$\text{N}^-\text{CH}_3$</th>
<th>$\text{Ph}^-$-$\text{C}\equiv\text{N}$-$\text{O}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{p}$-$\text{CH}_3\text{O}-\text{C}_6\text{H}_4$</td>
<td>0.73</td>
<td>1.48</td>
</tr>
<tr>
<td>$\text{p}$-$\text{CH}_3\text{-C}_6\text{H}_4$</td>
<td>0.79</td>
<td>1.03</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5$</td>
<td>$\equiv$1.00</td>
<td>$\equiv$1.00</td>
</tr>
<tr>
<td>$\text{p}$-$\text{Cl}-\text{C}_6\text{H}_4$</td>
<td>1.68</td>
<td>1.22</td>
</tr>
<tr>
<td>$\text{p}$-$\text{NO}_2\text{-C}_6\text{H}_4$</td>
<td>4.36</td>
<td>2.00</td>
</tr>
</tbody>
</table>
A frontier orbital theory interpretation of the reactivity in 1,3-dipolar cycloadditions is given in Section I D.

3. Mechanistic Interpretations

According to Woodward and Hoffman's classification,\(^6\) the 1,3-dipolar cycloaddition is a \(\left(\pi^4 + \pi^2\right)\) reaction, since four \(\pi\) electrons of the dipole are involved in the reaction. Because of its similarity to the Diels-Alder reaction, the 1,3-dipolar cycloaddition is regarded by Huisgen\(^4,5\) as a single-step, four-center, concerted reaction, in which the two new bonds are formed simultaneously, although not necessarily at equal rates. However, arguments have been raised consistently by Firestone\(^9\) for a two-step diradical mechanism. The confrontation between the two about the possible mechanism of 1,3-dipolar cycloadditions has amazed organic chemists for several years.

Criteria for the concerted and diradical mechanisms are summarized below.
(a) Stereospecificity

The cis-stereospecificity of a reaction means that geometrical relationships among the substituents on both the reactants are preserved in the product. Results of additions of 1,3-dipoles to cis-trans isomeric dipolarophiles showed that all 1,3-dipolar cycloaddition reactions are stereospecifically suprafacial. This represents one of the strongest arguments for a concerted mechanism. However, stereospecificity is necessary, but not sufficient, evidence for concertedness, because two-step mechanisms can also give suprafacial stereochemistry, if the energy barrier for rotation around the single-bond d-e in the intermediate 16 is greater than the activation energy for ring closure or for reversion to reactants. Firestone considered the activation energy for ring closure small or approaching zero, and the energy barrier of rotation relatively large. Huisgen carried out calculations to show that if rotational barriers were normal in 16, the activation barrier for closure would have to be negative, so that only a single step mechanism is likely.

(b) Solvent Effects

Reactions which are accompanied by an increase in charge separation are known to exhibit a strong rate enhancement with increasing solvent polarity. Therefore, a stepwise dipolar mechanism involving a zwitterionic intermediate is characterized by a large solvent effect. On the other hand, a lack of solvent polarity effect on rate would be anticipated for reactions involving concerted mechanisms. The absence or small extent of solvent dependence is typical of 1,3-dipolar cycloadditions. For example, the reaction of
diphenyldiazomethan and dimethyl fumarate in acetonitrile at 40\(^\circ\) is only 1.8 times faster than in benzene.\(^{63a}\) Some 1,3-dipolar cycloadditions have been found to show a small inverse solvent dependence.\(^{19,55}\) As shown in Table VI, the rate of the reaction of C-phenyl-N-methylnitrones and ethyl acrylate at 85\(^\circ\), decreases 5.6 times as the solvent is changed from toluene to ethanol. \(E_T\) is well-known Reichardt empirical solvent polarity parameter which increases as solvent polarity increases.

Huisgen rationalized the solvent effects in Table VI in terms of dipole moments.\(^{4,5}\) Unfortunately, reactions involving diradical intermediates show a similar insensitivity to solvent polarity owing to the lack of appreciable charge separation in the transition state leading to such a species.\(^{64}\) Firestone used the Linnett structure 17c for 1,3-dipoles to make the diradical attribute of 17 apparent, and claimed that the solvent effects on the rate would be expected to be small if the blend of polar and diradical qualities in the transition state leading to the diradical intermediate is about the same as that in 17.\(^{9a}\)

\[
\begin{align*}
-a & \equiv \frac{\ddagger}{\ddagger} - \frac{\ddagger}{\ddagger} \leftrightarrow -\ddagger = \frac{\ddagger}{\ddagger} + \frac{\ddagger}{\ddagger} & \ddagger = \frac{\ddagger}{\ddagger} - \frac{\ddagger}{\ddagger} \\
17a & \quad 17b & \quad 17c
\end{align*}
\]

Firestone also criticized the concerted mechanism by saying that the disappearance of the 1,3-dipole should bring about a strong inverse dependence on solvent polarity. In Huisgen's opinion, the name "1,3-dipole" is misinterpreted by Firestone, because the charge compensation by resonance in 17 is often quite extensive, as shown by the fact that 1,3-dipoles do not necessarily possess high dipole moments. On the other hand, the dipole moments of cycloadducts often approach those of the corresponding 1,3-dipoles or even exceed them.
### TABLE VI. SOLVENT EFFECT DATA FOR THE REACTION OF C-PHENYL-N-METHYLNITRONE AND ETHYL ACRYLATE AT 85°C

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$E_T$</th>
<th>$k_2 \times 10^4$ (1-mol(^{-1})-sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>33.9</td>
<td>4.80</td>
</tr>
<tr>
<td>Benzene</td>
<td>34.5</td>
<td>4.24</td>
</tr>
<tr>
<td>Dioxane</td>
<td>36.0</td>
<td>2.77</td>
</tr>
<tr>
<td>Pyrridine</td>
<td>40.2</td>
<td>2.22</td>
</tr>
<tr>
<td>Acetone</td>
<td>42.2</td>
<td>1.88</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>45.0</td>
<td>1.82</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>46.3</td>
<td>1.65</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>46.0</td>
<td>1.63</td>
</tr>
<tr>
<td>Methoxyethanol</td>
<td>52.3</td>
<td>1.12</td>
</tr>
<tr>
<td>Ethanol</td>
<td>51.9</td>
<td>0.86</td>
</tr>
</tbody>
</table>

(c) Reactivities of Dipolarophiles

The facts that conjugation exerts promoting effect on the dipolarophile activity of all multiple bonds, and that no reactivity difference are found between reactions of benzonitrile oxide with
acrylic esters and with propiolic esters, are used by Firestone to oppose the concerted mechanism, and to support the idea that diradical intermediates are formed in these reactions. From Firestone's point of view, only a dipolar or a diradical intermediate can derive stabilization through conjugation and hence increase the reaction rate. Furthermore, in cycloadditions of some 1,3-dipoles such as benzonitrile oxide, the formation of aromatic systems should bring about greater enhanced reactivity for acetylenic dipolarophiles over their ethylenic counterparts in a concerted process.

Huisgen explained these striking phenomena by two effects: (1) conjugation increases the polarizability of the π-bond of the dipolarophile, (2) concerted formation of the two new σ-bonds is not necessarily synchronous. These phenomena can also be explained in more comprehensible terms by frontier molecular orbital theory, as shown in a later section.

(d) Orientation

Firestone contends that "the electronic factors, when the others are controlled, should direct the course of a concerted cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole." This type of behavior has been observed in azide cycloadditions. Based on this, Firestone argued that concerted mechanism is wrong for cycloadditions of benzonitrile oxide with all monosubstituted alkenes and alkynes, since these additions occur predominantly in one direction whether the substituent be alkyl or aryl, electron withdrawing or electron donating. On the other hand, substituents of different
electronic nature would stabilize the preferred diradical intermediates leading to the observed 5-substituted adducts.

Huisgen pointed out again that "it is not meaningful to assign an electrophilic and a nucleophilic end to a 1,3-dipole" because the formal negative charge of the 1,3-dipole is distributed on either side of the positive center. Instead of the electronic factors, Huisgen suggested that steric effects are the cause of the orientation phenomenon.

However, recent discoveries of the "reversed" 1,3-dipolar cycloadditions of nitrones have proved that the interpretations of the regioselectivity in 1,3-dipolar cycloadditions by either diradical mechanisms or steric effects are incorrect, and electronic factors influencing the concerted transition state can explain these phenomena.

(e) Activation Parameters

The observation of small activation energies and large negative entropies of activation for cycloadditions such as the Diels-Alder reaction is often considered evidence for a concerted mechanism, since the magnitudes of these quantities indicate only small amount of bond breaking and large degree of order in the transition state. 1,3-Dipolar cycloadditions fit this general criterion for concertedness.

For example, $\Delta H^\#$ for the cycloaddition of C-phenyl-N-methyl nitro to methyl methacrylate is found to be 15.7 kcal, while $\Delta S^\# = -32$ e.u. 4

According to Firestone, the large negative entropy of activation may also be expected for a two-step cycloaddition involving a diradical intermediate if the activation energies for both advance and retrograde motion along the reaction coordinate from this inter-
mediate are very small.

All of the above debates on the mechanism of 1,3-dipolar cycloadditions are of value in particular cases. Unfortunately, none provides unequivocal evidence for a particular mechanistic type. However, frontier orbital theory provides a theoretical approach to the problem of reaction mechanism as well as the whole question of reactivity and substituent effects in 1,3-dipolar cycloadditions.

4. Regioselectivity

Cycloadditions of nitrones or nitrile oxides with unsymmetrical dipolarophiles may produce, in principle, two possible regioisomeric products. However, with nitriles, aldehydes, ketones, or monosubstituted alkenes and alkynes as dipolarophiles, cycloadditions to nitrones or nitrile oxides always give only the 5-substituted adducts. This regioselectivity phenomenon has been a puzzle to many organic chemists over the last twenty years. Firestone's free radical theory seems to lack experimental support. Huisgen proposed a principle of maximum gain in σ-bond energy to account for the observations of the exclusive formation of the 5-substituted adducts in the reactions of 1,3-dipoles with dipolarophiles containing hetero-atoms. For example, the addition of benzonitrile oxide to aldehyde, 18, yields exclusively a 1,3,4-dioxazole 19, in which the gain of σ-bond energy is 52 kcal/mole greater than that for the formation of the other structurally isomeric heterocycle 20. This difference in σ-bond energy of the products is sufficient to direct the reaction entirely into the channel leading to the 5-substituted adduct 19.
There are some exceptions, however, in which the maximum gain in $\sigma$-bond energy fail to dictate the direction of addition. One example is the dimerization of nitrile oxides to form furans, whereby one C-N and one N-O bond are closed in contrast to C-N and C-O bond formations in a "normal" fashion. Huisgen suggests that a change in mechanism might be involved in these cases.  

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For reactions of nitrones or nitrile oxides with alkenes or alkynes, whereby both directions of addition produce the same amount of σ-bond energy, Huisgen suggests that the steric substituent effects are responsible for the orientation. In the transition state, steric repulsions between the carbon substituent of the nitrone or nitrile oxide and the alkene or alkyne substituent R' should be greater for the formation of 22. Therefore, steric factors favor the formation of the observed 5-substituted isomers, 21, regardless of the electron-donating or electron-withdrawing character of the R'.

Firestone proposed a diradical mechanism to account for this orientation phenomenon. Presumably the intermediate diradical 23 leading to the formation of 5-substituted adducts 21 is more stable than the intermediate diradical 24 leading to the formation of the 4-substituted isomers 22.

A large number of cycloaddition reactions of nitrones and nitrile oxides with monosubstituted alkenes and alkynes have been studied and only the normal 5-substituted adducts were isolated. Recently, however, a number of reactions have been reported showing "reversal" of nitrone and nitrile oxide cycloaddition regioselectivity. C-Phenyl-N-methylnitron reacts with methyl propiolate to produce 58%
of the 4-carbomethoxy and 42\% of the 5-carbomethoxy Δ^4-isoxazolidines, 25 and 26.\textsuperscript{67} Similarly, 2,4,6-trimethylbenzonitrile oxide reacts with methyl propiolate to give a 72:28 mixture of 27 and 28.\textsuperscript{56}

These observations are contrary to both steric arguments of Huisgen and the free radical theory of Firestone. A frontier molecular orbital theory has been developed to explain regioselectivity phenomena in all 1,3-dipolar cycloadditions, and will be discussed in Section 1 D.
PART D. Perturbation Treatments of 1,3-Dipolar Cycloadditions

Perturbation molecular orbital theory has been developed into a powerful tool for the understanding of a variety of chemical phenomena. Applications of Perturbation theory to all cycloadditions have recently been reviewed by Herndon and Houk. Applications to 1,3-dipolar cycloadditions in particular were reported by Sustmann, Fukui, et al., and Houk, et al.

1. The Frontier Orbital Concept

The interaction of two orbitals results in depression of the energy of the lower energy orbital and raising of the energy of the higher energy orbital, as represented in Figure 2.

![Figure 2. The Interaction of Two Orbitals.](image)

The extent of energy change, \( \Delta E \), is directly proportional to the square of the resonance integral, \( H_{ab} \), and inversely proportional to the energy difference between the two orbitals (\( \epsilon_a - \epsilon_b \)) before the
Interaction, as given by the second-order perturbation expression:

\[
\Delta E = \frac{(H_{ab})^2}{\epsilon_a - \epsilon_b}
\]

In a cycloaddition, only interactions between the π orbitals of both addends are considered since these orbitals will overlap most in the transition state. Interactions between the highest occupied molecular orbital (HOMO) of one addend and the lowest unoccupied molecular orbital (LUMO) of the other, and vice versa, are of most importance because these orbitals are closest in energy, i.e. \((\epsilon_a - \epsilon_b)\) is smallest. A schematic diagram is shown in Figure 3.

![Figure 3. Orbital Interactions of Two Molecules.](image)

The HOMO and the LUMO are defined as the "frontier orbitals". According to Fukui, a chemical reaction should "take place at the position and in the direction of maximum overlapping of the HOMO (or high-lying occupied MO's) and the LUMO (or low-lying unoccupied MO's) of the reacting species". Thus, in 1,3-dipolar cycloadditions, the reactivity and regioselectivity are determined by these orbital inter-
action, although other factors such as closed-shell repulsions, Coulombic terms, and steric effects will exert some influence, also.

Frontier orbital energies can be calculated theoretically or measured experimentally. The HOMO energy of a molecule is defined as the negative of its ionization potential (I.P.), and the LUMO energy is defined as the negative of its electron affinity (E.A.). Ionization potentials can be obtained by photoelectron spectroscopy, while electron affinities have been measured less frequently, but can be estimated from ultraviolet spectral data. Calculated frontier orbital energies may differ from the experimental values, but usually show the same trends for a given series of dipoles or dipolarophiles.\textsuperscript{10,11}

2. Frontier Orbitals of Alkenes and Alkynes

The HOMO energy of ethylene is -10.51eV and the LUMO energy is estimated to be 1.5eV.\textsuperscript{10} Substituents on ethylene will influence the energy of the orbitals and change their coefficients. Calculations using CNDO/2 and EH methods for the orbital energies and coefficients of alkenes have been performed by Houk, et al.\textsuperscript{10,11} Figure 4 shows the generalized orbital energies and coefficients of ethylene and three classes of substituted ethylenes: electron-rich (CH\textsubscript{2}=CH\textsuperscript{X} and CH\textsubscript{2}=CHR), electron-deficient (CH\textsubscript{2}=CHZ), and conjugated (CH\textsubscript{2}=CHC) alkenes.\textsuperscript{10} The size of the orbitals in Figure 4 are roughly proportional to the calculated coefficients for representative members of each class of alkenes.

Electron-rich alkenes have frontier orbitals which are raised in energy with respect to those of ethylene; the HOMO is raised more than the LUMO. Both the LUMO and HOMO of the very electron-rich alkenes (CH\textsubscript{2}=CH\textsuperscript{X}, where as \textsuperscript{X} is amino or alkoxy group) are higher.
Figure 4. Generalized Frontier Orbital Energies and Coefficients for Alkenes.
in energy than those of alkylethylenes (CH$_2$=CHR). The larger coefficient for the HOMO of all electron-rich alkenes is on the carbon removed from the substituent. The larger coefficient for the LUMO of the very electron-rich alkenes is on the carbon adjacent to the substituent. The LUMO coefficients for alkylethylenes are approximately equal in magnitude.$^{10}$

Electron-deficient alkenes have frontier orbitals which are lowered in energy with respect to those of ethylene; the LUMO is lowered more than the HOMO. The larger coefficient in both HOMO and LUMO is on the unsubstituted carbon.$^{10}$

Conjugated alkenes have a higher HOMO and a lower LUMO than the corresponding orbitals of ethylene. Both the LUMO and HOMO have larger coefficient on the unsubstituted carbon.$^{10}$

The general characteristics of the frontier orbitals of alkynes are similar to those of alkenes. The HOMO of an acetylene is lower in energy than the corresponding alkene, while the LUMO of acetylene is slightly higher in energy than that of ethylene.

3. Frontier Orbitals of 1,3-Dipoles

1,3-Dipoles are isoelectronic with allyl anion. A comparison of the calculated (by CNDO/2) $\pi$ orbitals of the parent nitrone and nitrile oxide with those of the allyl anion is given in Figure 5.$^{10}$ Because of the charged nature of the anion, the HOMO of the allyl anion is high in energy. Replacement of carbons by heteroatoms results in lowering of the orbital energies for the parent nitrone and nitrile oxide, due to the electronegativity of the N and O atoms of the 1,3-dipoles. The lowering effect is greater on the HOMO than on the LUMO.
The LUMO energy of formonitrile oxide is slightly higher than that of the allyl anion. This may be attributed to linearity and the shorter bond length of the nitrile oxide, resulting in increased antibonding between the 2p orbitals of C and N atoms.\textsuperscript{10}

As shown in Figure 5, the HOMO's of the parent nitrone and nitrile oxide have larger terminal coefficients on the oxygen atom and smaller coefficients on the carbon atom, while in the LUMO's, larger terminal coefficients are on the carbon and smaller coefficients on the oxygen atom. Other substituted nitrones and nitrile oxides may have different orbital energies, but the relative magnitudes of the terminal coefficients of the HOMO and LUMO are similar. These differences in the magnitudes of the terminal coefficients in the HOMO and LUMO are the origin of the regioselectivity in 1,3-dipolar cycloadditions.\textsuperscript{10}

4. Frontier Orbital Treatment of 1,3-Dipolar Cycloadditions

Reactivity and regioselectivity phenomena in 1,3-dipolar cycloadditions have recently been rationalized very successfully by Houk, et al.\textsuperscript{10,11} In their treatment of 1,3-dipolar cycloadditions, only the frontier orbital interactions are considered. 1,3-Dipolar cycloadditions have been classified by Sustmann\textsuperscript{71} into three types of reactions, depending on the relative intermolecular HOMO-LUMO separations between 1,3-dipole and dipolarophile frontier orbitals. These three types of 1,3-dipolar cycloadditions, shown in Figure 6, are HOMO-controlled reaction (Type I, the interaction of the dipole HOMO with the dipolarophile LUMO is greatest), HOMO,LUMO-controlled reaction (Type II, both frontier orbital interactions are large), and LUMO-controlled reaction (Type III, the interaction of the dipole...
Figure 5. Frontier Orbital Energies and Coefficients for (a) Allyl Anion, (b) CH$_2$NO, the Parent Nitrone, and (c) Formonitrile Oxide.
Figure 5. Three Types of 1,3-Dipolar Cycloadditions.
LUMO with the dipolarophile HOMO is greatest).

Because reactivity in 1,3-dipolar cycloaddition reactions is inversely proportional to the energy gap between interacting orbitals, the large dipole HOMO-dipolarophile LUMO interaction in Type I reactions and dipole LUMO-dipolarophile HOMO interaction in Type III reactions lead to rapid reactions. In Type II reactions, the frontier orbital interactions are smaller and reaction rates should be correspondingly smaller.

Substituents which influence the frontier orbital energies of 1,3-dipoles or dipolarophiles will also influence orbital interactions and thus, reactivity in cycloadditions. Qualitatively, substituents which raise the dipole HOMO energy or lower the dipolarophile LUMO energy will accelerate the HOMO-controlled (Type I) reactions and decelerate the LUMO-controlled (Type III) reactions. Conversely, substituents which lower the dipole LUMO energy or raise the dipolarophile HOMO energy will accelerate the LUMO-controlled reactions and decelerate HOMO-controlled reactions. HOMO,LUMO-controlled (Type II) reactions will be accelerated by an increase of either frontier orbital interaction. Based on these generalizations, several reactivity problems in 1,3-dipolar cycloaddition reactions can now be explained.

In the cycloadditions of C-phenyl-N-methylnitrone with a series of substituted alkenes, both electron-donating and electron-withdrawing groups on alkene enhance the rate of reaction.\(^5\) This can be easily rationalized by considering the cycloaddition of C-phenyl-N-methylnitrone with ethylene as Type II reaction, in which either raising the dipolarophile HOMO energy by an electron-donating substituent or lowering the dipolarophile LUMO energy by an electron-withdrawing substituent would strengthen the dipole-dipolarophile frontier
orbital interaction and increase the reaction rate. Thus, a graph of the ionization potentials of the dipolarophiles versus the rate constants is generally a U shape.  

Another interesting observation is the rate increase through conjugation in the dipolarophile for most 1,3-dipolar cycloaddition reactions. As shown in Figure 4, phenyl or vinyl group tends to compress the frontier orbital energies of ethylene. In other words, extending the π-system will lower the LUMO energy and raise the HOMO energy in comparison with ethylene. Therefore, both frontier orbital interactions will be increased in all types of 1,3-dipolar cycloadditions.

As illustrates in Figure 1 (Section I A), regioselectivity arises when an unsymmetrical 1,3-dipole cycloadds to an unsymmetrical dipolarophile. The preferred regioisomer in a 1,3-dipolar cycloaddition, according to the second-order perturbation expression (Section I, Part D 1), will be the one for which $H_{ab}$ is larger in the transition state; this will be the transition state in which the atoms with the larger terminal coefficients in the most strongly interacting pairs of frontier orbitals are united. Thus, case (a) in Figure 7 results in greater transition state stabilization than case (b).

![Figure 7. Schematic Representation of Greater Stabilization of Transition State (a) than (b) Due to Different Coefficient.](image)
The frontier orbital energies and coefficients of the generalized 1,3-dipoles and monosubstituted dipolarophiles have been shown in Figures 4 and 5. Since the larger terminal coefficient of the dipole LUMO is at the carbon atom (for nitrones and nitrile oxides), and all dipolarophiles have the largest HOMO coefficient on the unsubstituted terminus, a dipole LUMO controlled reaction (Type III) will lead to the predominant product with the substituent near the oxygen atom. In a dipole HOMO (largest coefficient at oxygen atom) controlled reaction (Type I), on the other hand, the predominant product will be the one with the substituent remote from the oxygen atom for all monosubstituted dipolarophiles (larger coefficient at unsubstituted carbon in the LUMO) except electron-rich ones (larger LUMO coefficient at the substituted carbon). This is summarized in Figure 8.

<table>
<thead>
<tr>
<th>Nitron or Nitrile Oxide</th>
<th>Monosubstituted Dipolarophile</th>
<th>Preferred Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMO + HOMO</td>
<td>(a)</td>
<td>[Image of reaction product]</td>
</tr>
<tr>
<td>HOMO + LUMO</td>
<td>(b)</td>
<td>[Image of reaction product]</td>
</tr>
</tbody>
</table>

Figure 8. Regioisomer Expected From LUMO or HOMO Control by the Dipole.
Most 1,3-dipolar cycloadditions of nitrones or nitrile oxides with monosubstituted alkenes or alkynes studied previously have been LUMO-controlled (Type III) reactions, in which only the 5-substituted adducts were observed (route a in Figure 8).

Houk, et al., have used this frontier orbital treatment to rationalize the regioslectivity in all 1,3-dipolar cycloadditions, and to predict that 4-substituted adducts should be obtained (route b in Figure 8) with very electron-deficient alkenes or alkynes as the dipolarophiles in nitrone and nitrile oxide cycloadditions. The primary goal of this research was to study these two classes of 1,3-dipolar cycloadditions as a confirmation of these predictions, and to test, on a more quantitative basis, the applicability of molecular orbital perturbation theory to these reactions.
II. RESULTS AND DISCUSSION

PART A Reactivity in Nitrone and Nitrile Oxide Cycloadditions

1. Frontier Orbital Energies of Nitrones, Nitrile Oxides and Dipolarophiles

Frontier molecular orbital treatments of 1,3-dipolar cycloaddition reactions require a knowledge of both the highest occupied molecular orbital (HOMO) energies and the lowest unoccupied molecular orbital (LUMO) energies of the cycloaddends. These data can be obtained theoretically by HMO, CNDO, INDO, MINDO, or ab initio SCF calculations, or experimentally from ionization potentials and electron affinities. Because theoretical calculations generally do not give accurate values, experimental orbital energies have been preferred in several recent papers.10,11,17

From photoelectron spectra, π ionization potentials for five nitrones—N-t-butyl-, C-phenyl-N-methyl-, C-phenyl-N-t-butyl, C-mesityl-N-methyl-nitrone and dihydroisoquinoline-N-oxide, five nitrile oxides—p-chlorobenzo-, p-methoxybenzo-, p-nitrobenzo-, mesityl- and 2,4,6-trimethoxy benzo-nitrile oxide, and sixteen dipolarophiles were obtained. These data along with some measured or estimated electron affinities are shown in Table VII and VIII.

The negative of the ionization potential represents the HOMO energy level of the molecule. The negative of the electron affinity represents the LUMO energy level of the molecule.

For alkenes or dipoles conjugated with aromatic systems, the HOMO is a phenyl orbital mixed in an antibonding sense with some of
### TABLE VII. Ionization Potentials and Electron Affinities of Some Nitrones and Nitrile Oxides

<table>
<thead>
<tr>
<th>1,3-Dipoles</th>
<th>IP, eV</th>
<th>EA, eV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-t-Butynitrone</td>
<td>8.64</td>
<td>-1.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C-Phenyl-N-methylnitrone</td>
<td>7.89, 9.87</td>
<td>-1.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C-Phenyl-N-t-butylnitrone</td>
<td>7.69, 9.66</td>
<td>--</td>
</tr>
<tr>
<td>C-Mesityl-N-methylnitrone</td>
<td>8.08, 9.1</td>
<td>-1.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dihydroisoquinoline-N-oxide</td>
<td>7.81, 9.99</td>
<td>--</td>
</tr>
<tr>
<td>p-Chlorobenzonitrile oxide</td>
<td>8.65, 10.67</td>
<td>--</td>
</tr>
<tr>
<td>p-Methoxybenzonitrile oxide</td>
<td>8.42, 10.16</td>
<td>--</td>
</tr>
<tr>
<td>p-Nitrobenzonitrile oxide</td>
<td>&gt;9.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
</tr>
<tr>
<td>Mesitylnitrile oxide</td>
<td>8.34, 10.24</td>
<td>-1.4&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2,4,6-Trimethoxybenzonitrile oxide</td>
<td>7.95, 9.94</td>
<td>-1.4&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Benzonitrile oxide</td>
<td>(8.7)&lt;sup&gt;d&lt;/sup&gt;, (10.5)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(-1.1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Estimated from EA = IP - ΔE(λ<sub>max</sub>) - 5eV. See reference 10.

<sup>b</sup> Accurate IP's were not obtained due to difficulty of rapid dimerization.

<sup>c</sup> ΔE(λ<sub>max</sub>) values were taken from reference 8.

<sup>d</sup> Estimated on the basis of correlations with model compounds.
TABLE VIII. Ionization Potentials and Electron Affinities of Some Alkenes and Alkynes

<table>
<thead>
<tr>
<th>Dipolarophiles</th>
<th>IP, eV</th>
<th>EA, eV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isobutyl vinyl ether</td>
<td>9.1</td>
<td>-1.80^a</td>
</tr>
<tr>
<td>α-Methylstyrene</td>
<td>8.55, 10.14</td>
<td>-1.55^a</td>
</tr>
<tr>
<td>cis-β-Methylstyrene</td>
<td>8.55, 10.15</td>
<td>-1.60^a</td>
</tr>
<tr>
<td>trans-β-Methylstyrene</td>
<td>8.38, 10.26</td>
<td>-1.58^a</td>
</tr>
<tr>
<td>Styrene</td>
<td>8.48, 10.55</td>
<td>-1.52^a</td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>10.72</td>
<td>0.8^b</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>10.91</td>
<td>0.02^b</td>
</tr>
<tr>
<td>Fumaronitrile</td>
<td>11.15</td>
<td>0.78^b</td>
</tr>
<tr>
<td>Methyl Propiolate</td>
<td>11.15</td>
<td>-0.40^b</td>
</tr>
<tr>
<td>Nitroethylene</td>
<td>11.23</td>
<td>0.8^b</td>
</tr>
<tr>
<td>Phenyl vinyl sulfone</td>
<td>11.4</td>
<td>0.89^a</td>
</tr>
<tr>
<td>Divinyl sulfone</td>
<td>11.45</td>
<td>0.94^a</td>
</tr>
<tr>
<td>Methyl vinyl sulfone</td>
<td>11.52</td>
<td>1.01^a</td>
</tr>
<tr>
<td>Tetracyanoethylene</td>
<td>11.79</td>
<td>2.88^b</td>
</tr>
<tr>
<td>Cyanoacetylene</td>
<td>11.81</td>
<td>0^b</td>
</tr>
<tr>
<td>Bis-trifluoromethylfumaronitrile</td>
<td>11.85</td>
<td>1.83^a</td>
</tr>
<tr>
<td>3,3,3-Trifluoropropyne</td>
<td>12.12</td>
<td>----</td>
</tr>
</tbody>
</table>

^a. Estimated from EA = IP - ΔE(λ_max) - 5eV.

^b. Reference 10.
the CNO or vinyl orbital. The third orbital (next to next to HOMO = N^2HOMO) has more density on the CNO or vinyl moiety, i.e. the reaction site in 1,3-dipolar cycloaddition reactions. In spite of the fact that the HOMO is closer in energy to the electrophile LUMO, the N^2HOMO interaction may contribute more to the stabilization energy because of the larger vinyl coefficients in the N^2HOMO. This greater influence of the N^2HOMO at electrophile LUMO energy arises from the dominance of the numerator of the perturbation expression over the denominator. Sustmann has also assumed this viewpoint, since he uses the third ionization potential of styrene in his correlation between the IP's of alkenes and their reactivities with phenyl azide. Although the lowest IP of styrene (8.48eV) is considerably lower than that of ethylene (10.52 eV), styrene reacts only 1.15 times faster with benzonitrile oxide in ether than ethylene does. The HOMO of styrene has only 35% of its electron density on the vinyl group, whereas the N^2HOMO (-10.55eV) has 65% of its electron density on the ethylenic moiety; obviously the low IP of styrene is a deceptive indicator of reactivity.

Similar conclusions can be made for aryl nitrones and nitrile oxides. For instance, N-t-butylnitrone and mesityl-nitrile oxide have similar ionization potentials; however, the former reacts one-hundred times faster than the latter with acrylonitrile at room temperature. As pointed out above, the 8.64eV IP of N-t-butylnitrone and the 10.24eV IP of mesityl-nitrile oxide (rather than the 8.34eV IP) are those best described as arising from a π^CNO moiety. Therefore, two IP values, the first and third ionization potentials, are given in Table VI and VII for molecules of this type. In later discussions, the N^2HOMO instead of the HOMO will be used for these compounds except
C-phenyl-N-methylnitrone, which HOMO, according to calculations, has more density on the CNO moiety than its N^2HOMO does.

2. Cycloaddition Reactivities of Dipolarophiles

To test the influence of MO energies on reactivity, rate constants for reactions of mesitylnitrile oxide with the sixteen dipolarophiles were measured. Reactions of equimolar quantities of reactants were carried out in sealed nmr tubes under nitrogen, and the disappearance of the nitrile oxide was monitored by nmr spectroscopy. The stability of mesitylnitrile oxide against dimerization allowed both photoelectron spectroscopic and kinetic studies of the cycloaddition of this compound.

The rate expression for a second-order reaction utilizing equal initial concentrations of reactants is \(-d(A)/dt = k(A)^2\). The integrated form of this rate expression is \(1/X - 1/A_0 = kt\), giving \(k = 1/A_0 t^{1/2}\), where \(k\) is the second order rate constant, \(A_0\) is the initial concentration of reactants, \(X\) is the concentration of one reactant at time \(t\), and \(t^{1/2}\) is the reaction half-life. Half-lives were determined from plots of \(X\) versus \(t\), assuming the concentrations of the reactants to be directly proportional to the peak height of the o-methyl proton singlet of mesitylnitrile oxide (2.0-3.0 ppm). The rate constants were determined from both peak height and integrated area data, and the rate constants determined by the two methods differed by less than 5% from the average of the two values. Similarly, rate constants calculated from peak height data for one reaction repeated three times differed by less than 5% from the average of the three measurements. The measured rate constants are estimated to be within ±15% of rate constants that may be determined by a more accurate method.
technique.

Rate constants measured at one temperature were extrapolated to 25\(^0\), 35\(^0\) and 85\(^0\)C by assuming an activation entropy of -24 eu, which was calculated from two measured rate constants at different temperatures (35\(^0\) and 85\(^0\)C) for the reaction of mesitylnitrile oxide and trans-\(\beta\)-methylstyrene. Based on this assumption, activation enthalpies were also calculated.\(^78\) Since activation entropy could be anywhere from -20 to -30 eu, an additional error of ±15\% is estimated to be introduced by this assumption. Therefore, the reported rate constants and activation enthalpies are estimated to be within ±30\% of the correct values. Huisgen made a similar assumption and rate constant extrapolations for the reactions of C-phenyl-N-methylnitrone with several dipolarophiles.\(^55\)

Rate data are given in Table IX.

Figure 9 shows a plot of log \(k_2\) versus the ionization potential of the dipolarophile. An expected U-shaped correlation was obtained with only the points for the \(\beta\)-methyl-styrenes, 3 and 4, far from this correlation. In general, reactions are fast for both electron-rich and electron-deficient dipolarophiles, and slow for conjugated dipolarophiles. This indicates that mesitylnitrile oxide is a HOMO-LUMO controlled 1,3-dipole with "neutral" alkenes.

The U-shape in Figure 9 is far from a perfect correlation, which would only be expected if the coefficients were constant for frontier orbitals of different dipolarophiles and if the changes in I.P. and E.A. were parallel to each other. Due to these limitations, some deviations were observed.

Since steric effects are not taken into account in the frontier orbital treatment, rate constants for reactions of two
<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Solvent</th>
<th>$\Delta H^\circ$ (Kcal)$^a$</th>
<th>Rx. Temp.</th>
<th>$k_2 \times 10^5$ (1-mole$^{-1}$sec$^{-1}$)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>25$^0$</td>
<td>35$^0$</td>
</tr>
<tr>
<td>1. CH$_2$=CH-O-1-BU</td>
<td>CCl$_4$</td>
<td>14.6</td>
<td>35$^0$</td>
<td>53</td>
</tr>
<tr>
<td>2. CH$_2$=C(Me)Ph</td>
<td>CDCl$_3$</td>
<td>16.0</td>
<td>35$^0$</td>
<td>5.4</td>
</tr>
<tr>
<td>3. cis-MeCH=CHPh</td>
<td>CDCl$_3$</td>
<td>18.1</td>
<td>85$^0$</td>
<td>0.14</td>
</tr>
<tr>
<td>4. trans-MeCH=CHPh</td>
<td>CDCl$_3$</td>
<td>17.1</td>
<td>35$^0$</td>
<td>0.84</td>
</tr>
<tr>
<td>5. CH$_2$=CH-Ph</td>
<td>CDCl$_3$</td>
<td>15.3</td>
<td>35$^0$</td>
<td>18</td>
</tr>
<tr>
<td>6. CH$_2$=CH-CO$_2$Me</td>
<td>CCl$_4$</td>
<td>13.8</td>
<td>35$^0$</td>
<td>230</td>
</tr>
<tr>
<td>7. CH$_2$=CH-CN</td>
<td>CCl$_4$</td>
<td>14.9</td>
<td>35$^0$</td>
<td>$34^b$</td>
</tr>
<tr>
<td>8. NC$_2$CH=CH=CN</td>
<td>CDCl$_3$</td>
<td>15.1</td>
<td>35$^0$</td>
<td>$25^b$</td>
</tr>
<tr>
<td>9. CH=C-CO$_2$Me</td>
<td>CCl$_4$</td>
<td>13.0</td>
<td>35$^0$</td>
<td>810</td>
</tr>
<tr>
<td>10. CH$_2$=CH-NO$_2$</td>
<td>CCl$_4$</td>
<td>14.3</td>
<td>35$^0$</td>
<td>98</td>
</tr>
<tr>
<td>11. CH$_2$=CH-SO$_2$Ph$_2$</td>
<td>CDCl$_3$</td>
<td>15.2</td>
<td>35$^0$</td>
<td>22</td>
</tr>
<tr>
<td>12. CH$_2$=CH-SO$_2$-CH=CH$_2$</td>
<td>CDCl$_3$</td>
<td>14.4</td>
<td>25$^0$</td>
<td>85</td>
</tr>
<tr>
<td>13. CH$_2$=CH-SO$_2$Me</td>
<td>CDCl$_3$</td>
<td>14.4</td>
<td>25$^0$</td>
<td>79</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Solvent</td>
<td>$k$</td>
<td>$t$</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>---------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>14</td>
<td><img src="image1" alt="Structure" /></td>
<td>CDCl$_3$</td>
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<td>25</td>
</tr>
<tr>
<td>15</td>
<td>H-C≡C-CN</td>
<td>CCl$_4$</td>
<td>13.1</td>
<td>35</td>
</tr>
<tr>
<td>16</td>
<td><img src="image2" alt="Structure" /></td>
<td>CDCl$_3$</td>
<td>13.9</td>
<td>35</td>
</tr>
</tbody>
</table>

a. Refer to Section II A and III C for an estimate of errors and for experimental details for these data.

b. Addition to C≡N triple bond occurred after first half-life. The reported data measured only the addition to C=C double bond.

c. These data give the maximum rate constants for addition to C=C double bond of TCNE due to the disturbance of the competing addition to cyano triple bond. Products were not isolated.
Figure 9. Plot of $\log k_2$ vs IP(dipolarophile) for Cycloadditions of Mesitylnitrile Oxide.

Numbers refer to reactions in Table VIII.
dipolarophiles which have similar ionization potentials can be quite different if steric effects are much different for the two reactions. α-Methylstyrene (IP's = 8.55, 10.14eV), for example, is 20 times more reactivs than cis-β-methylstyrene (IP's = 8.55, 10.15eV) with mesitylnitrile oxide at 85°. Additional discussion on the styrene series will be given in Section II C.

The cycloaddition of mesitylnitrile oxide with isobutyl vinyl ether is a dipole LUMO controlled reaction, dominated by the interaction between the LUMO of mesitylnitrile oxide and the HOMO of isobutyl vinyl ether. Cycloadditions of mesitylnitrile oxide with dipolarophiles on the upper right-hand side of the U-shaped correlation in Figure 9 are dipole HOMO controlled reactions in which the dipole HOMO-dipolarophile LUMO interaction dominates. The crossover in the control of reactivity is shown in Figure 10 with three representative examples from Table VIII. The HOMO and N2HOMO energies of mesitylnitrile oxide and the dipolarophiles are taken as the negative of their ionization potentials and the LUMO energies as the negative of their electron affinities from Table VII and VIII.

For both LUMO controlled reactions with electron-rich dipolarophiles (e.g. isobutyl vinyl ether) and HOMO controlled reactions with electron-deficient dipolarophiles (e.g. nitroethylene), the interaction of one frontier orbital of mesitylnitrile oxide with one frontier orbital of the dipolarophile is large due to their small energy difference, and the rates of these kinds of reactions are large. For LU,H0 controlled reactions (e.g. α-methylstyrene), the frontier orbital interactions are smaller and reaction rates are correspondingly smaller.
Using the N\textsuperscript{2}HOMO instead of the HOMO energies for conjugated aromatic cycloaddends in frontier orbital treatments of cycloaddition.

Figure 10. Crossover in the Control of Reactivity of Mesitylnitrile Oxide Cycloadditions

reactivity gave better correlations in Figures 9 and 10. This suggests again that the N\textsuperscript{2}HOMO interaction is more important in the consideration of stabilization energy. The results of calculations by a perturbation MO treatment led to a similar conclusion for the effect of aromatic conjugation upon reactivity in 1,3-dipolar cycloadditions.\textsuperscript{79}

According to the perturbation expression, the stabilization energy is inversely proportional to the energy difference between the
two frontier orbitals of a pair of addends. For the HOMO controlled
cycloadditions of mesitylnitrile oxide, a more quantitative correlation
can be obtained by plotting the log of the rate constants against the
reciprocal of the energy differences between the N²HOMO of mesityl-
nitrile oxide and the LUMO's of the dipolarophiles as shown in Figure
11. The correlation coefficient of 0.916, obtained for the least
squares fit, is reasonably good considering that the numerator of the
perturbation expression, along with other factors such as steric
effects, Coulombic effects and closed-shell repulsions, has not
been taken into account. The trend is that the rate of reaction
increases as the energy level of the dipolarophile increases.

It is understandable that reaction of isobutyl vinyl ether
does not fall onto the straight line correlation because this
compound is an electron-rich dipolarophile and its cycloaddition
with mesitylnitrile oxide is a LUMO controlled reaction which does
not belong to the same category. However, the reactions of the
acetylenes, 2 and 10, with mesitylnitrile oxide are unusually fast,
while the reactions of 8-methylstyrenes, 3 and 4, are unusually
slow. To account for these observations, steric effects will be
discussed in Section II C.

3. Cycloaddition Reactivity of Nitrones and Nitrile Oxides

Frontier orbital treatments can also be applied to explain
the relative reactivities of 1,3-dipoles. In principle, the order of
decreasing reactivity should be the same as the order of increasing
dipole ionization potential for HOMO controlled reactions. However,
for the nitrones and nitrile oxides studied here, use of lowest
Figure 11. Plot of \((4 + \log k_2)\) vs \((1/IP - EA)\) for Mesitylnitrile Oxide Cycloadditions
ionization potential alone in perturbation arguments will not give reasonable reactivity correlations, both because of possible difference in the nature of the HO orbitals and because of differences in steric effects in different 1,3-dipoles. For example, the order of decreasing reactivity of nitrones with nitroethylene, where the interaction between the dipole HOMO and the dipolarophile LUMO should be largest, is N-t-butyl-nitrone > C-phenyl-N-methylnitrone ≫ C-mesityl-N-methylnitrone, which is different from the order of increasing lowest ionization potential: C-phenyl-N-methylnitrone (7.89eV) < C-mesityl-N-methylnitrone (8.08eV) < N-t-butyl-nitrone (8.64eV).

Ionization potentials can be adjusted using those that are best described as arising from the π_{CNO} moiety and the predicted reactivity order becomes C-phenyl-N-methylnitrone > N-t-butyl-nitrone > C-mesityl-N-methylnitrene. Furthermore, C-phenyl-N-methylnitrone should be more hindered towards approach of the dipolarophile than is N-t-butyl-nitrone, accounting for its lower reactivity.

In a quantitative treatment of cycloaddition reactivity of 1,3-dipoles, a plot of log of the rate constants for reactions of one dipole versus those for reactions of another should give a linear correlation if reactions are controlled by the same type of orbital interaction, and if the differences in orbital coefficients and steric factors, among others, can be neglected. Figure 12 shows the correlation between cycloaddition reactivities of mesitylnitrile oxide and those of N-t-butyl-nitrone with some dipolarophiles, using rate constants taken from Table VIII and Sims, respectively. A straight line was obtained for six dipolarophiles with a correlation coefficient of 0.966. N-t-Butyl-nitrone reacts extremely rapidly with some of the dipolarophiles at room temperature and only the lower limits of the rate data...
Figure 12. Correlation Between log of Rate constants For Mesitylnitrile Oxide and N-t-Butyl nitro nitrone Cycloadditions With (1) cis-β-Methylst yrene, (2) trans-β-Methylst yrene, (3) α-Methylst yrene, (4) Styrene, (5) Isobutyl vinyl ether, (6) Methyl propiolate, (7) Phenyl vinyl sulfone, (8) Cyanoacetylene, (9) Methyl acrylate, (10) Nitroethylene, and (11) Acrylonitrile.

Slope = 0.890
Correlation Coefficient = 0.966
were used in the graph. These compounds are all very electron-deficient dipolarophiles, and their cycloadditions with both mesitylnitrile oxide and N-t-butyl nitron should be clearly dipole HOMO controlled reactions. If one notices that the HOMO energy (-8.64eV) of N-t-butyl nitron is considerably higher than the N^2HOMO (-10.24eV) of mesitylnitrile oxide, it is not surprising to see that very electron-deficient dipolarophiles are far more reactive with the nitron than with the nitrile oxide.

The slope for the straight line is 0.890, indicating that mesitylnitrile oxide is less sensitive than N-t-butyl nitron towards change of dipolarophiles. This can be explained by use of the perturbation expression. Considering only the dipole HOMO-dipolarophile LUMO interaction for these reactions, the second order perturbation expression can be written as follows:

\[
E = \frac{- (R_{ab})^2}{IP(dipole) - EA(dipolarophile)}
\]

Assuming that the numerator is a constant, K, then the stabilization energies for mesitylnitrile oxide (IP = 10.24eV) and N-t-butyl nitron (IP = 8.64eV) cycloadditions are:

\[
E_{\text{mesitylnitrile oxide}} = K \left(10.24 - EA(\text{dipolarophile})\right)^{-1}
\]

\[
E_{\text{N-t-butylnitrone}} = K \left(8.64 - EA(\text{dipolarophile})\right)^{-1}
\]

Going from a dipolarophile of EA=0eV to another of EA=1eV, the change in stabilization energies, \(\Delta E\), for the two 1,3-dipoles can be calculated as:

\[
\Delta E_{\text{mesitylnitrile oxide}} = K(10.24 - 1)^{-1} - K(10.24 - 0)^{-1}
\]
\[ \Delta E_{\text{N-t-butylnitrone}} = k(8.64 - 1)^{-1} - k(8.64 - 0)^{-1} = 0.015k \]

Comparison of the above two values reveals that change of dipolarophiles should lead to greater change in rates for N-t-butylnitrone reactions than for mesitylnitrile oxide reactions.

In Figure 13, the logs of the rate constants for N-t-butylnitrone cycloadditions were plotted against the logs of the rate constants for C-phenyl-N-methylnitrone cycloadditions at 120°C. Rate data were taken from Sims\textsuperscript{19} and Huisgen, et al.\textsuperscript{55} Again, a linear correlation was obtained. Although all dipolarophiles react faster with N-t-butylnitrone due to greater steric hindrance of C-phenyl-N-methylnitrone, the slope of 0.852 indicates that C-phenyl-N-methylnitrone is more sensitive towards change of dipolarophiles. This is compatible with the fact that C-phenyl-N-methylnitrone has a lower LUMO and a higher HOMO energies than N-t-butylnitrone does.

Huisgen and coworkers\textsuperscript{75} made a similar plot for benzonitrile oxide and diphenylnitrile imine cycloadditions, and grouped dipolarophiles into four categories, namely 1-substituted and 1,1-disubstituted alkenes, 1,2-disubstituted alkenes, cycloalkenes, and alkynes, each giving a linear correlation with a different slope. However, in terms of molecular orbital perturbation theory, if steric effects are negligible, there are only two types of dipolarophiles: those that are electron-rich and those that are electron-deficient. The rates of reactions of a 1,3-dipole with a lower LUMO energy should be more sensitive to an increase in electron-release on the dipolarophiles (LUMO controlled reactions) than a 1,3-dipole with a higher LUMO energy. Similarly, a 1,3-dipole with a higher HOMO energy should be

\[ -2 + \log k_2 (\text{t-Butylnitrone}), 120^\circ \]

Slope = 0.852
Correlation Coefficient = 0.924

log \( k_2 \) (C-Phenyl-N-methylnitrone), 120°
more sensitive towards an increase in electron-withdrawal on the dipolaro-
philes (HOMO controlled reactions) than a dipole with a lower HOMO
energy. Based on this argument, benzonitrile oxide, in comparison
with diphenylnitrile imine, should be more sensitive to electron-
release on the dipolarophile and less sensitive to electron-withdrawal
on the dipolarophile, because both the LUMO and HOMO of benzonitrile
oxide are lower in energy than those of diphenylnitrile imine. By
careful inspection of the plot made by Huisgen and coworkers, two
linear correlations, instead of four, can be observed, with one slope
greater, and the other smaller, than unity, as shown in Figure 14.
Thus, a frontier molecular orbital treatment of reactivity of 1,3-
dipoles is beautifully demonstrated.

Another interesting aspect about the plot in Figure 14 is
the crossover in correlations from p-methoxystyrene, point 9, p-
methyl styrene, point 8, and styrene, point 7, for LUMO controlled
reactions to p-chlorostyrene, point 18, and p-nitrostyrene, point 20,
for HOMO controlled reactions, without going through the intersection
of the two linear correlations. This is explicable by frontier orbital
considerations. As shown in Figure 4, a conjugated alkene CH₂=CH-C,
where C is vinyl or phenyl group, has a lower LUMO and a higher HOMO
than ethylene does. As a result of the compression of the frontier
orbital separation, styrene should always react faster than ethylene
with a given 1,3-dipole, because either the dipole LUMO-dipolarophile
HOMO or the dipole HOMO-dipolarophile LUMO energy gap is always smaller
for styrene than for ethylene. Thus, the p-substituted styrenes
become a class of their own which, in cycloadditions with a HOMO,LUMO
controlled 1,3-dipole, should appear as an independent U-shaped corre-
Figure 14. Correlation Between log of Relative Rate Constants for Benzonitrile Oxide \( k_2(\text{Ethylene}) = 1.0 \) in Ether at 25° and Diphenylnitrile Imine \( k_2(\text{Ethyl Crotonate}) = 1.0 \) in Benzene at 80° Rxns.
Legend for Figure 14

1. Cyclohexene
2. \(\beta\)-Isopropylstyrene
3. Phenylacetylene
4. Cyclopentene
5. 1-Hexene
6. 1,1-Diphenylethylene
7. Styrene
8. \(p\)-Methylstyrene
9. \(p\)-Methoxystyrene
10. Butyl Vinyl Ether
11. Norbornene
12. \(\beta\)-Pyrrolidinostyrene
13. 3,3-Dimethyl Methyl Acrylate
14. Phenyl Methyl Propiolate
15. Ethyl Crotonate
16. Methyl Succinate
17. Dimethyl Maleate
18. \(p\)-Chlorostyrene
19. Methyl Propiolate
20. \(p\)-Nitrostyrene
21. Methyl Methacrylate
22. Ethyl Crotonate
23. Dimethyl Acetylenedicarboxylate
24. Dimethyl Fumarate
ation in plot of the log of the reaction rate versus IP of the styrene, and a crossover in plots like that in Figure 14 is therefore expected.
PART B Regioselectivity in Nitrone and Nitrile Oxide Cycloadditions

1. Nitrile Oxide Cycloadditions

The reaction of mesitylnitrile oxide with phenyl vinyl sulfone at 25° in chloroform gave a 96:4 mixture of the normal and reversed regioisomeric products, 29b and 30b. The structures of these products were assigned by comparisons of their nmr spectra to those of model compounds 29a and 30a obtained as a 93:7 mixture of cycloadducts in a similar reaction reported by Christl and Huisgen.80

\[
\text{Mes}-\overset{\equiv}{\text{N}}\rightarrow\text{O} + \text{CH}_2=\text{CH}-\text{R} \rightarrow \begin{array}{c}
\text{Mes} \begin{array}{c}
\overset{\equiv}{\text{N}} \rightarrow \text{O}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{a. } \text{R} = \text{CO}_2\text{Me} \\
\text{b. } \text{R} = \text{SO}_2\text{ph} \\
\text{c. } \text{R} = \text{NO}_2 \\
\text{d. } \text{R} = \text{CN} \\
\text{e. } \text{R} = \text{ph} \\
\text{f. } \text{R} = \text{i-Bu}
\end{array}
\]

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The nmr spectrum (CDCl₃) of isoxazoline 29b has an ABX octet for the C-4 protons \([\delta(H_A) \ 3.86, \ dd, \ J = 6.5, 19.5 \ Hz, \ 1H; \ \delta(H_B) \ 3.50, \ dd, \ J = 9.5, 19.5 \ Hz, \ 1H]\) and a doublet of doublets at lower field for the C-5 proton \([\delta(H_X) \ 5.53, \ dd, \ J = 6.5, 9.5 \ Hz, \ 1H]\).

The nmr spectrum of the 4-substituted adduct, 30b, was more difficult to analyze, since the spectrum has a complex multiplet at 4.50-5.40 ppm for the three ring protons. No deuterium exchange of the C-4 proton of 30b in NaOEt/EtOH at room temperature was observed after three days. Attempted dehydrogenation with DDQ gave only 3-mesitylisoxazole \([\text{nmr (CCl₄): } \delta 8.40 (\text{OCH -}, \ d, \ J = 2.0 \ Hz, \ 1H); \ \delta 6.85 (\text{Ar-H}, \ s, \ 1H); \ \delta 6.18 (\text{OC=CH}, \ d, \ J = 2.0 \ Hz, \ 1H); \ \delta 2.30 (\text{P-CH₃}, \ s, \ 3H); \ \delta 2.08 (\text{o-CH₃}, \ s, \ 6H)]\). Assignments of the nmr data for 30b could be made, however, upon comparison with the nmr spectrum of 4-carbomethoxy-3-phenylisoxazoline, which has been previously analyzed by Huisgen.⁷⁸ Thus, the C-4 proton, Hₓ, was assigned to \(\delta 5.17 \ (dd, \ J = 6.0, 11.0 \ Hz, \ 1H)\), and the C-5 protons, Hₐ and Hₜ, were assigned to \(\delta 5.22 \ (dd, \ J = 6.0, 13.5 \ Hz, \ 1H)\) and \(\delta 4.73 \ (dd, \ J = 11.0, 13.5 \ Hz, \ 1H)\), respectively. The \text{cis} coupling constant, \(J_{BX} = 11.0 \ Hz\), is greater than the \text{trans} coupling constant, \(J_{AX} = 6.0 \ Hz\). The geminal coupling constant of the methylene protons, \(J_{AB}\), decreases from 19.5 Hz for compound 29b to 13.5 Hz for 30b, a characteristic difference between a 5-substituted and 4-substituted adduct.⁸⁰ The chemical shift separation between \(H_A\) and \(H_B\) increases from 0.36 ppm for 29b to 0.49 ppm for 30b, as compared to 0 ppm to 0.17 ppm change observed for 29a and 30a.

Despite the complications of nmr data assignments for 30b, the identities of compounds 29b and 30b are unambiguous because both regioisomers were isolated and because of the large difference in
chemical shifts of the ring protons. Nmr spectra of 29b and 30b are shown in Appendix A.

Reactions of mesitylnitrile oxide with nitroethylene, acrylonitrile, styrene and isobutyl vinyl ether at 25° in CCl₄ gave only the 5-substituted adducts. The structures of the 5-substituted isoxazolines, 29c-f, were immediately apparent from their nmr spectra. The shifts and splitting patterns in these nmr spectra were all similar. The absorption for the C-5 protons of each product appeared as doublet of doublets in the range of δ5.35-6.20. The absorption for the C-4 protons of each product appeared as an ABX octet in the range of δ2.55-4.10. Spectral data and elemental analysis for new compounds are given in Section III C.

In addition to compound 29d, a small portion (15%) of white crystalline product (mp 91-93°) was also isolated from reaction of mesitylnitrile oxide with acrylonitrile. Based on its nmr spectrum and integration, this product was assigned to compound 31 as shown below. Ms data and elemental analysis were in accordance with this assignment. Reaction of 29d with mesitylnitrile oxide in C₆D₆ at 35° gave quantitatively compound 31 after seven days. The nmr spectrum of 31 is shown in Appendix A.
Reactions of mesityl nitrile oxide with ethyl propiolate, cyanoacetylene and 3,3,3-trifluoropropyne in \( \text{CCl}_4 \) gave both 4- and 5-substituted adducts.

\[
\begin{align*}
\text{Mes} & \equiv \text{C} = \equiv \text{N} \equiv \text{O} \\
\text{HC} = \equiv \text{C} - \text{R} & \quad \rightarrow \\
\text{Mes} & \equiv \text{N} \equiv \text{O} + \text{Mes} & \equiv \text{N} \equiv \text{O} \\
\text{32} & \quad \text{33}
\end{align*}
\]

a. \( R = \text{CO}_2\text{Me} \)  

b. \( R = \text{CO}_2\text{Et} \)  

c. \( R = \text{CN} \)  

d. \( R = \text{CF}_3 \)  

By comparisons of their nmr spectra to those of model compounds 32a, 33a and 3-mesitylisoxazole, structure assignments for isoxazoles 32b-d and 33b-d were especially straightforward. The resonance for the C-5 proton of each 4-substituted adduct appeared as a singlet at low field in the range of \( \delta 8.80-8.94 \). The absorption of the C-4 proton of each 5-substituted adduct appeared as another singlet in the range of \( \delta 6.56-6.81 \). The large difference in the chemical shifts of the C-4 and C-5 protons in the two regioisomers makes these structural assignments unambiguous.

The regiochemical observations for reactions of mesityl nitrile oxide with alkenes and alkynes are summarized in Table X. Dipolarophiles are listed in the order of increasing ionization potential as given in Table VIII. Adduct ratios determined from isolated products or nmr integration of reaction mixtures agreed closely.
<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>% 5-substituted</th>
<th>% 4-substituted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkenes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isobutyl vinyl ether</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Styrene</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Nitroethylene</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Phenyl vinyl sulfone</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>Divinyl sulfone</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Methyl vinyl sulfone</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td><strong>Alkynes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl propiolate</td>
<td>34</td>
<td>66</td>
</tr>
<tr>
<td>Methyl propiolate</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>Cyanoacetylene</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>3,3,3-Trifluoropropyne</td>
<td>57</td>
<td>43</td>
</tr>
</tbody>
</table>

a. See Section III C for experimental details.
b. Reference 80.
c. A. Russo, Unpublished results.
For the purposes of this discussion, reactions are said to have (z)-regioselectivity if the two termini of larger priority are united in the product, and (e)-regioselectivity if the terminal groups of larger priority are not united in the product.

Cycloadditions of mesitylnitrile oxide to isobutyl vinyl ether, styrene, acrylonitrile, nitroethylene and divinyl sulfone gave only the 5-substituted isoxazolines, while additions to other alkenes and alkynes gave both 4- and 5-substituted regioisomers, showing partial reversal of regioselectivity. The results obtained here confirm the prediction made by frontier orbital considerations,\textsuperscript{10,11} that is the unidirectional addition of 1,3-dipoles to monosubstituted dipolarophiles should no longer be observed when the dipolarophile is made highly electron-deficient.

However, according to frontier orbital treatments of these cycloadditions, all electron-deficient dipolarophiles used here, excluding isobutyl vinyl ether and styrene, should give predominantly the 4-substituted or (e) adduct. Because the energy gap between the dipole HOMO and the dipolarophile LUMO is smallest, their interaction should be largest leading to the formation of the (e) adduct when the two larger terminal coefficients of addends are united. In most cases, opposite results were observed despite the fact that some alkynes show reversal of regioselectivity to some extent. Possible explanations are given below.

In a cycloaddition reaction, two pairs of frontier orbital interactions contribute comparable amounts of stabilization energy. Therefore, both interactions need to be considered in predicting regioselectivity. If for some reason, one interaction is reinforced, regioselectivity arising from this interaction will be increased. On
the other hand, if one interaction is prohibited, regioselectivity arising from this interaction will be decreased. As shown in Figure 15, for nitrones and nitrile oxides, the coefficient of the central atom, N, is large in the LUMO, and very small (corresponding to the node for allyl anion) in the HOMO. For electron-deficient dipolarophiles, the relative magnitudes of coefficients are similar in both LUMO and HOMO. In the transition state, the dipole C=N bond and the dipolarophile C=C bond are stretched, resulting in lowering of the LUMO energy due to a decrease in antibonding, and raising of the HOMO energy due to loss of bonding character. However, as a first approximation, the increase of the dipole HOMO energy should be considerably less than the decrease of its LUMO energy, while the dipolarophile LUMO energy decreases and the HOMO energy increases at about the same rate, as illustrated in Figure 15. Thus, in the transition state, the energy gap between the dipole LUMO and the dipolarophile HOMO is narrowed more than the energy gap between the dipole HOMO and the dipolarophile LUMO. If the dipole LUMO-dipolarophile HOMO interaction is strengthened enough, it may become more important than the originally stronger dipole HOMO-dipolarophile LUMO interaction. This bond stretching of addends partially contributes to the high (z)-regioselectivity in cycloadditions of mesitylnitrile oxide to the dipolarophiles.

Another important factor that must be considered is the steric effect. As will be discussed in more detail in Section II C, steric effects disfavor the formation of 4-substituted adducts, especially for reactions of alkenes with nitrones and nitrile oxides. Therefore, although (z)-regioselectivity is favored by frontier orbital
considerations, two other factors, bond stretching and steric effects, operate against it. The net result is that cycloadditions of mesityl-nitrile oxide to alkenes (even those that are highly electron-deficient) show very little reversal of regioselectivity.

Table X also indicates that alkynes always give more reversed adduct than their analogous alkenes do. The (g):(g) ratio is 28:72 for methyl propiolate as compared to 93:7 for methyl acrylate, and is 57:43 for cyanoacetylene as compared to 100:0 for acrylonitrile. Similar results have been observed in other 1,3-dipolar cycloaddition. This higher reversal of regioselectivity of alkynes can be attributed in part to the higher ionization potentials of the
alkynes as compared to the alkenes, but the lesser steric hindrance,
in the alkyne reactions, as compared to the corresponding alkene
reactions, may also contribute to the preferential formation of the (e)
adduct in alkyne reactions.

Benzonitrile oxide and p-nitrobenzonitrile oxide were also
reacted with some of the electron-deficient dipolarophiles in ether.
The structures of the products were conveniently assigned by compari­
sions of their nmr spectra to those of the cycloadducts from reactions
of benzonitrile oxide or p-nitrobenzonitrile oxide with methyl acrylate
and methyl propiolate reported by Christl and Huisgen.\textsuperscript{80} Chemical
shifts and coupling constants for the ring protons of each product
were essentially identical to those of the corresponding mesitylnitrile
oxide cycloaddition adducts. The regiochemical observations for cyclo-
additions of the three nitrile oxides to the electron-deficient alkenes
and alkynes are summarized in Table XI.

Since the ionization potentials for benzonitrile oxide and
p-nitrobenzonitrile oxide are higher than that for mesitylnitrile
oxide, lower reversal is expected. This is indeed the case, as the
order of decreasing reversal in cycloaddition to each dipolarophile--
mesitylnitrile oxide > benzonitrile oxide > p-nitrobenzonitrile oxide--
is generally in accordance with the order of increasing ionization
potential. p-Nitrobenzonitrile oxide, with the lowest nucleophilicity
in the series, gave only the normal adduct in reactions with all
alkenes used.

To quantitatively reveal the relative reversibility, the logs
of the adduct ratios in mesitylnitrile oxide cycloadditions were
plotted against those in benzonitrile oxide cycloadditions, as shown
in Figure 16. A linear correlation was obtained. In plots like this,
<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Adduct Ratio (% 5-substituted : % 4-substituted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R = p$-NO$_2$Ph</td>
</tr>
<tr>
<td><strong>Alkenes</strong></td>
<td></td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>100 : 0</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>100 : 0</td>
</tr>
<tr>
<td>Nitroethylene</td>
<td>100 : 0</td>
</tr>
<tr>
<td>Phenyl vinyl sulfone</td>
<td>100 : 0</td>
</tr>
<tr>
<td><strong>Alkynes</strong></td>
<td></td>
</tr>
<tr>
<td>Methyl propiolate</td>
<td>70 : 30$^b$</td>
</tr>
<tr>
<td>Cyanoacetylene</td>
<td>98 : 2</td>
</tr>
</tbody>
</table>

a. Reference 56. Ether was used as the solvent.

b. Reference 80. Ether was used as the solvent.
Figure 16. Correlation Between Regioselectivities For Nesitylnitrile Oxide and Benzonitrile Oxide Cycloadditions.

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the slope of the linear correlation should be an indication of the relative reversibility. A slope of greater than unity in Figure 16 indicates that the $\%(z):\%(e)$ ratio drops faster, as the dipolarophile changes from acrylonitrile to methyl propiolate, for mesityl-nitrile oxide cycloadditions than for benzonitrile oxide cycloadditions. This is compatible with frontier orbital considerations, since the HOMO of mesitylnitrile oxide is higher in energy than that of benzonitrile oxide. Similar to the reactivity treatment for Figure 12, it can simply be said that for dipole HOMO controlled reactions, the higher the dipole HOMO energy, the more sensitive the reversal of regioselectivity is to a change in dipolarophile LUMO energy.

2. Nitrone Cycloadditions

C-Mesityl-N-methylnitrone was reacted with six electron-deficient alkenes and alkynes. For each alkene reaction, four isomeric products, namely cis-(z), trans-(z), cis-(e), and trans-(e), are possible.

![Diagram of reaction products]

```
C-Mes = O
N
Me

H2C=CHR

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-(z)</td>
<td>trans-(z)</td>
<td>cis-(e)</td>
<td>trans-(e)</td>
</tr>
<tr>
<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
</tr>
</tbody>
</table>

b. R = CN  b. R = CN  b. R = CN
c. R = NO2  c. R = NO2  c. R = NO2
d. R = SO2Ph  d. R = SO2Ph
```
The reaction of C-mesityl-N-methylnitrone with methyl acrylate at 90° in chloroform for ten days gave both (g) and (e) adducts in a 50:50 ratio. The (g) adducts were isolated as a mixture of the cis, 34a, and trans, 35a, isomers which could not be separated by plc. Compound 37a was isolated as the only (e) adduct. Presumably, silica gel of a plc plate caused isomerization of any cis-(g) formed in the reaction to the more stable trans-(e) isomer.19

Reaction of C-mesityl-N-methylnitrone with acrylonitrile gave a 15:85 mixture of the (g) and (e) adducts. The products were not isolated and the ratio was determined by nmr integration.

C-Mesityl-N-methylnitrone reacted with nitroethylene and phenyl vinyl sulfone regioselectively to give only the (g) adducts, and only the trans-(e) isomers was isolated by plc.

Structures of all isoxazolidines were assigned by comparisons of their nmr spectra to those of the corresponding adducts from cycloadditions of C-phenyl-N-methylnitrone to the same dipolarophiles reported by Huisgen, et al.,79 and Sims and Houk.12 Spectral data and elemental analysis are given in Section III C. Nmr spectra of typical 4- and 5-substituted isoxazolidines are shown in Appendix A.

Reactions of C-mesityl-N-methylnitrone with methyl propiolate and cyanoacetylene gave only the 5-substituted 1,4-isoxazoles. Structural assignments for 38a and 38b were straightforward. The nmr spectra of the two compounds were almost identical. Based on the very low field resonance of the olefinic proton (δ7.33 for 38a and δ7.13 for 38b), the identities of the 4-substituted adducts were unambiguous.
The regiochemical observations of C-mesityl-N-methyl-nitrone cycloadditions, along with those for N-t-butylnitrone and C-phenyl-N-methylnitrone cycloadditions, are summarized in Table XII.

Nitrones are generally more electron-rich species than nitrile oxides, as measured by ionization potentials, and their cycloadditions to electron-deficient dipolarophiles show more reversal of regioselectivity as expected. N-t-Butylnitrone, however, has a HOMO with nearly identical terminal coefficients, so that the formation of the (g) adduct never is favored over the formation of the (z) adduct regardless of the high lying HOMO and less steric hindrance of N-t-butylnitrone. Thus, even with cyanoacetylene, a very electron-deficient dipolarophile, the (g)/(z) adduct ratio for N-t-butylnitrone cycloaddition is only 50:50, as compared to 0:100 for both C-phenyl-N-methylnitrone and C-mesityl-N-methylnitrone cycloadditions.

As predicted by frontier orbital considerations, more electron-deficient dipolarophiles show greater tendency to form reversed regioisomers in each nitrone cycloaddition. The reaction of C-phenyl-N-methylnitrone with nitroethylene is the only exception, showing too much reversibility, since only the 4-substituted adduct is
TABLE XII. A Comparison of Regioselectivities in Nitrone (RHC=N) Cycloadditions.

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Adduct Ratio (% 5-substituted : % 4-substituted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R = H, R' = t-Bu</td>
</tr>
<tr>
<td><strong>Alkenes</strong></td>
<td></td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>100 : 0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>100 : 0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nitroethylene</td>
<td>100 : 0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phenyl vinyl sulfone</td>
<td>70 : 30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alkynes</strong></td>
<td></td>
</tr>
<tr>
<td>Methyl propiolate</td>
<td>70 : 30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyanoacetylene</td>
<td>50 : 50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a. Reference 19. Carbon tetrachloride was used as the solvent.
b. Reference 55. Toluene was used as the solvent.
c. This work. Chloroform was used as the solvent.
formed in this reaction.

C-Mesityl-N-methylnitrotrone shows complete reversal of regio-
selectivity in cycloadditions to four of the six electron-deficient
dipolarophiles tested. Because of the high lying LUMO and HOMO of
C-mesityl-N-methylnitrotrone, the dipole HOMO-dipolarophile LUMO and inter-
action becomes so much more important than the LUMO-HOMO interaction
that is completely dominates the reactions and leads to the formation
of the 4-substituted adducts. One of the purposes of this research,
i.e. "in search of the reversed regioselectivity in 1,3-dipolar cyclo-
additions", has hereby been accomplished.

In light of the results presented here, it is suggested that
the regioselectivity of 1,3-dipolar cycloadditions is controlled by
electronic considerations, when the dipole is made sufficiently
electron-rich and the dipolarophile highly electron-deficient, rather
than steric factors, which, however, should be considered as the cause
of the low reactivity in some cases.
PART C Electronic Effects vs Steric Effects

The reaction rates of 1,3-dipolar cycloadditions are greatly affected by the electronic and steric nature of dipoles and dipolarophiles. Huisgen and coworkers have amassed a large volume of data to illustrate this point. Huisgen has also proposed that the unidirectional additions of most 1,3-dipoles to many monosubstituted alkenes and alkynes results from steric effects. However, in contrast to these steric arguments, reversal of regioselectivity has been observed for some 1,3-dipolar cycloadditions. Based on frontier orbital treatments, Houk and Sims have argued that regioselectivity in 1,3-dipolar cycloadditions is produced by electronic rather than steric factors.

The influence of electronic effects upon reaction rates and regioselectivity was discussed in the previous section. In this section, the relative influences of steric and electronic factors on reactivity and regioselectivity on some reactions studied here are discussed.

1. Cycloadditions of Methylated dipolarophiles

The point for styrene lies on the right-half side of the U-shape in Figure 9, indicating that cycloaddition of styrene with mesitylnitrile oxide is a dipole HOMO controlled reaction. The cycloaddition of styrene with N-t-butyl nitronate is also a HOMO controlled reaction according to the kinetic studies of Sims. Substitution of a methyl group at the double bond should raise the styrene orbital energies, decreasing the dipole HOMO-alkene LUMO interaction, leading to a decrease in reactivity as styrene is substituted by a methyl on
any position. To verify this idea, cycloadditions of mesitylnitrile oxide and N-t-butyl nitron with three methylated styrenes, α-methylstyrene, cis-β-methyl styrene, and trans-β-methyl styrene, were studied.

Reactions of styrene, α-methylstyrene, and trans-β-methyl styrene with N-t-butyl nitron have been reported by Sims;¹⁹ all of these reactions give only the 5-phenyl substituted adducts. Reaction of cis-β-methyl styrene with N-t-butyl nitron at 85° in CCl₄ gave a 69:31 mixture of 5-phenyl, 39 (the g regioisomer), and 4-phenyl, 40 (the g isomer), adducts.

\[
\begin{align*}
&\text{Mes} \quad + \quad \overset{\text{Me}}{\overset{\text{Ph}}{\text{Me}}} \\
&\text{Ph}\text{Me} \quad \overset{85^\circ}{\text{Me}} \overset{24\text{hrs}}{\text{Ph}} \quad \overset{39}{\text{N}} \overset{40}{\text{O}} \\
&\overset{69\%}{39} \quad \overset{31\%}{40}
\end{align*}
\]

These products could not be separated by plc, but were readily identified by the characteristic chemical shifts and splitting patterns of the C-5 protons in the nmr spectrum of the reaction mixture. The resonance of the C-5 proton of compound 39 appeared as a doublet at δ4.98 (J = 7.0 Hz), and that of the C-5 proton of compound 40 appeared as a doublet of quartets centered at δ4.21 (J = 6.3, 6.3 Hz).

Similarly, the products of mesitylnitrile oxide cycloadditions to styrene were readily identified due to the characteristic nmr chemical shifts of protons on C-5 (δ5.80-4.90) and on C-4 (δ4.40-3.20)
in the isoxazoline products.

Mesitylnitrile oxide reacted with cis- and trans-methylstyrenes in CHCl₃ to give mixtures of the z and e adducts, but the preferred isomer was z for the former and e for the latter reaction. The ratio of the regioisomeric products formed in each of the reactions was determined by integration of the nmr resonances due to H-5 and the saturated methyls in the two adducts. The reactions of the nitrile oxide with methylstyrenes are less regioselective than those of the nitrone, and in the case of the trans compound, opposite regioselectivity is observed for the two 1,3-dipoles.

\[
\begin{align*}
\text{Mes-} & \overset{\text{C==N\rightarrow O}}{\longrightarrow} + \overset{\text{Me}}{\text{Ph}} \quad \overset{85^\circ}{\text{24 hrs}} \quad \overset{57\%}{\text{41}} \quad \overset{57\%}{\text{42}} \\
\text{Mes-} & \overset{\text{C==N\rightarrow O}}{\longrightarrow} + \overset{\text{Me}}{\text{Ph}} \quad \overset{85^\circ}{\text{24 hrs}} \quad \overset{23\%}{\text{43}} \quad \overset{77\%}{\text{44}}
\end{align*}
\]

α-Methylstyrene gave only the z adduct, 45, in reaction with mesitylnitrile oxide.

\[
\text{Mes-} \overset{\text{C==N\rightarrow O}}{\longrightarrow} + \overset{\text{Me}}{\text{Ph}} \quad \overset{35^\circ}{\text{24 hrs}} \quad \overset{\sim}{\text{45}}
\]
Table XIII summarizes products and rates of cycloadditions of styrenes with mesitylnitrile oxide and N-t-butyl nitronitrone.

As expected, rates for all methylated styrene are smaller than that for styrene in reactions with the nitrone or nitrile oxide. Similar results have been reported by Huisgen and coworkers. For example, α-methylstyrene reacts 11 times slower than styrene with C-phenyl-N-methyl nitronitrone at 85° and β-isopropylstyrene reacts 82 times slower than styrene with benzonitrile oxide at 20°.75

However, cis- and trans-β-methyl styrenes exhibited much lower reactivity than α-methylstyrene. Since these three molecules have similar EA's and IP's, the differences in electronic effects between the different methylstyrenes are very small. Thus, steric effects seem to be important in explaining the differences in rates between α- and β-methyl styrenes. In the transition state leading to the formation of the 5-phenyl adduct, steric repulsions involving carbon substituents of the dipoles should be greater in reactions of β-methylstyrenes than for those of α-methylstyrene. This steric repulsion should destabilized the transition states for formation of 5-phenyl adducts from β-methylstyrenes. Thus, for mesityl nitrite oxide cycloadditions, the partial rate constant for the formation of the 5-phenyl adduct decreases 36 and 21 times in going from α-methylstyrene to cis- and trans-β-methyl styrenes, respectively. For N-t-butyl nitronitrone cycloadditions, less steric interference is expected in the transition state (the carbon terminus is substituted only by hydrogens) and the corresponding rate decreasing factors are 3.9 and 5.1 for cis- and trans-β-methyl styrenes, respectively.

The above explanation is compatible with a phenomenon
<table>
<thead>
<tr>
<th>Styrenes</th>
<th>Mesitylnitrile Oxide</th>
<th></th>
<th>N-t-Butynitrone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%5-Phenyl %4-Phenyl k$_2$(85$^\circ$)x10$^5$</td>
<td></td>
<td>%5-Phenyl %4-Phenyl k$_2$(85$^\circ$)x10$^5$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adduct</td>
<td>Adduct (1/mol-sec)</td>
<td>Adduct</td>
<td>Adduct (1/mol-sec)</td>
</tr>
<tr>
<td>Styrene</td>
<td>100</td>
<td>--</td>
<td>1600</td>
<td>--</td>
</tr>
<tr>
<td>$\alpha$-Methylstyrene</td>
<td>100</td>
<td>--</td>
<td>590</td>
<td>--</td>
</tr>
<tr>
<td>cis-$\beta$-Methylstyrene</td>
<td>57</td>
<td>43</td>
<td>29</td>
<td>69</td>
</tr>
<tr>
<td>trans-$\beta$-Methylstyrene</td>
<td>23</td>
<td>77</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>260</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.9</td>
</tr>
</tbody>
</table>
frequently observed in 1,3-dipolar cycloadditions, namely that steric hindrance in 1,1-disubstituted ethylenes is less pronounced than in the 1,2-disubstituted types. For example, 1,1-diphenylethylene reacts faster than stilbene\textsuperscript{75} and methyl methacrylate reacts faster than methyl crotonate\textsuperscript{b} with most 1,3-dipoles. In these cases, the differences in electronic effects of $\alpha$ or $\beta$ methyl substituent may be less significant than differences in steric effects on reactivity. The extent of steric effects differs due to varying spatial requirements of 1,3-dipoles.

It is also frequently observed that cycloadditions of 1,3-dipoles to trans-1,2-disubstituted alkenes are faster than to the geometrically isomeric cis alkenes. The ratios of the rate constants for cycloadditions to dimethyl fumarate and maleate range from 58 for benzonitrile oxide to 2.9 for C-phenyl-N-methylnitrone. This has been explained by Huisgen\textsuperscript{b} in terms of differing van der Waals repulsions between substituents in the transition state. Molecular orbital theory also predicts that the trans isomer will be more reactive than the cis isomer towards reaction with nucleophiles, since the planar trans isomer will have a higher EA and a lower IP than the nonplanar cis isomer. However, when the isomeric compounds have a number of orbitals of similar energy, caution must be taken in predicting the relative reactivity. Because reactivity arises from the stabilization energy resulting from all interacting orbitals of the two addends, there is the possibility that the cis isomer could react faster than the trans isomer. Thus, trans-$\beta$-methylstyrene is four times less reactive than cis with mesitylnitrile oxide, but is two times less reactive than cis with N-t-butylnitron as shown in Table.
XIII. The higher reactivity of cis-β-methylstyrene over its trans isomer in N-t-butyl-nitrone cycloadditions seems to be the only exception to other reported observations in this regard.

The regiochemical observations shown in Table XIII can be rationalized by frontier orbital considerations. As is general with nitrones and nitrile oxides, the dipole LUMO exerts a greater influence on regioselectivity than the dipole HOMO even both interactions are of similar magnitude. This results from the greater difference in LUMO terminal coefficients than HOMO terminal coefficients for both these dipoles. Substitution of an α-methyl group on styrene will raise all the orbital energies, and reinforce the magnitude of the coefficient at the unsubstituted carbon in the styrene HOMO. Thus, the maintenance of regioselectivity with α-methylstyrene is as expected. Substitution of a β-methyl group on styrene will also decrease reactivity, but now the methyl and phenyl groups will have opposite effects on the HOMO coefficients, and reinforcing effects on the LUMO coefficients, leading to diminished regioselectivity. Thus, the β-methylstyrenes are expected to produce mixtures of regioisomers, and, in fact, do so in all cases except the addition of N-t-butyl-nitrone to trans-β-methylstyrene.

The reasons for differences in reactivity and regioselectivity between trans- and cis-β-methyl styrenes are not clear. However, the relative regioselectivity seems to be in harmony with the relative reactivity, since the faster reactions give more (e) adducts with both 1,3-dipoles. Perhaps steric hindrance in the transition state leading to the 4-phenyl adduct is more pronounced for the reaction of cis-β-methylstyrene with mesityl-nitrile oxide because both addends are nonplanar, and for the reactions of methylstyrenes with N-t-butyl-nitrone, only electronic factors determine reactivity.
and regioselectivity.

2. Alkene Versus Alkyne Cycloadditions

Generally, acetylenes possess lower HOMO energies and slightly higher LUMO energies than the corresponding ethylenes. Considering only the orbital energy factors, an alkene should react faster than the corresponding alkyne with a given 1,3-dipole. However, the opposite results have been observed in many cases of 1,3-dipolar cycloaddition reactions. Although aromatic isoxazoles result from cycloadditions of nitrile oxides to acetylenes, the developing aromaticity of product does not substantially stabilize the transition state, in view of the fact that phenyl acetylene reacts 10 times slower than styrene with benzonitrile oxide.

Table XIV gives a comparison of the rate constants for methyl propiolate and methyl acrylate, cyanoacetylene and acrylonitrile, phenylacetylene and styrene, as well as for dimethyl acetylenedi-carboxylate and dimethylfumarate in cycloadditions with nitrones and nitrile oxides. These data show that alkynes are less reactive than their corresponding alkenes in reactions with N-t-butylnitrone and benzonitrile oxide, and more reactive in reactions with C-phenyl-N-methylnitrone and mesitylnitrile oxide. To account for these observations, the transition state geometries will be inspected.

It is believed that all 1,3-dipolar cycloadditions involve the "parallel plane approach" of addends. Figure 17 shows the "two planes" orientation complexes for nitrone cycloadditions, and a slightly different geometry for the nitrile oxide where the nitrogen is bent out of plane of the nitrile oxide.
TABLE XIV. Relativities of Alkynes and Alkenes
in 1,3-Dipolar Cycloaditions

<table>
<thead>
<tr>
<th></th>
<th>$k_2(\text{HC}≡\text{C}-\text{CO}_2\text{Me})$</th>
<th>$k_2(\text{HC}≡\text{C}-\text{CN})$</th>
<th>$k_2(\text{HC}≡\text{C}-\text{Ph})$</th>
<th>$k_2(\text{MeO}_2\text{C}-\text{C}≡\text{C}-\text{CO}_2\text{Me})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_2(\text{H}_2\text{C}=\text{CH}-\text{CO}_2\text{Me})$</td>
<td>&lt;0.11</td>
<td>--</td>
<td>0.46</td>
<td>--</td>
</tr>
<tr>
<td>$\text{C}≡\text{N}→\text{O}$ (25°)</td>
<td></td>
<td>--</td>
<td>0.09</td>
<td>0.51</td>
</tr>
<tr>
<td>$\text{C}≡\text{N}→\text{O}$ (20°)</td>
<td>0.15</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{C}≡\text{N}→\text{O}$ (85°)</td>
<td>4.0</td>
<td>20</td>
<td>--</td>
<td>44</td>
</tr>
<tr>
<td>$\text{C}≡\text{N}→\text{O}$ (35°)</td>
<td>3.4</td>
<td>20</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
As illustrated in Figure 17, when an alkene is the dipolarophile, steric hindrance exists between the alkene substituents and the carbon substituents of nitrone or ortho substituents on the phenyl of nitrile oxide, while the transition state for alkyne cycloaddition is less sterically hindered because there is a single colinear substituent (or H) on each terminus. For reactions of N-t-butynitrone and benzonitrile oxide with alkenes, where \( R_1 = R_2 = H \), steric effects are minimized and the reactivities are controlled only by electronic factors. Thus alkenes behave normally and are more reactive than alkynes in these reactions. For reactions of C-phenyl-N-methylnitrone (\( R_1 = H, R_2 = Ph \)) and mesitylnitrile oxide (\( R_1 = R_2 = Me \)) with alkenes, on the other hand, the greater steric requirements of the transition state slow down the reactions so considerably that their rates are often smaller than those of alkyne reactions.

For reactions which give two regioisomeric products, the rate constant, \( k \), can be divided into two partial rate constants, \( k^z \). 

Figure 17. Approach of Addends in 1,3-Dipolar Cycloadditions.
and $k^e$, for formations of the ($z$) and ($e$) adducts, respectively. The comparisons of the partial rate constants for alkyne vs alkene cycloadditions should reveal more specifically the differences in steric effects in the transition state leading to a particular regioisomer. Table XV shows the ratios of partial rate constants for methyl propiolate vs methyl acrylate cycloadditions with nitrones and nitrile oxides.

In the transition state leading to the ($z$) adduct ($z$ transition state), steric factors are not appreciably different for N-t-butylnitrone and benzonitrile oxide cycloadditions to the alkene ($R_1 = R_2 = R_3 = R_4 = \text{H}$) and alkyne, so that $k^z$ (methyl propiolate) is smaller than $k^z$ (methyl acrylate), as expected by frontier orbital considerations. In the transition state leading to the ($e$) adduct ($e$ transition state), however, steric hindrance for alkene reactions with N-t-butylnitrone and benzonitrile oxide ($R_1 = R_2 = R_3 = \text{H}, R_4 = \text{CO}_2\text{Me}$), begins to show up in the increasing $k^e$ (alkyne)/$k^e$(alkene) ratio. In fact, the ratio becomes approximately unity in the case of benzonitrile oxide reaction, indicating that the electronic preference of alkene is canceled out by its larger steric requirements.

The $k^z$ (alkyne)/$k^z$(alkene) ratio for C-phenyl-N-methyl-nitrone and mesitylnitrile oxide cycloadditions, where the bulky substituents are on the dipoles and the steric hindrance in reactions with the alkene is considered moderate, are 1.91 and 1.02, respectively. The steric effects should be greater in the $e$ transition state for reactions of methyl acrylate with C-phenyl-N-methylnitrone ($R_1 = \text{Ph}, R_2 = R_3 = \text{H}, R_4 = \text{CO}_2\text{Me}$) and mesitylnitrile oxide ($R_1 = R_2 = \text{Me}, R_3 = \text{H}, R_4 = \text{CO}_2\text{Me}$), since the number of bulky substituents increases. This
TABLE XV. Ratios of Partial Rate Constants For Methyl Propiolate and Methyl Acrylate Cycloadditions.

<table>
<thead>
<tr>
<th>Structure</th>
<th>$k^z(H\equiv C-CO_2Me)/k^z(H_2C=CH-CO_2Me)$</th>
<th>$k^e(H\equiv C-CO_2Me)/k^e(H_2C=CH-CO_2Me)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\equiv N\rightarrow O$ (25°)</td>
<td>&lt;0.08</td>
<td>&lt;0.66*</td>
</tr>
<tr>
<td>$\equiv N\rightarrow O$ (20°)</td>
<td>0.11</td>
<td>1.04</td>
</tr>
<tr>
<td>$\equiv N\rightarrow O$ (85°)</td>
<td>1.91</td>
<td>53*</td>
</tr>
<tr>
<td>$\equiv N\rightarrow O$ (35°)</td>
<td>1.02</td>
<td>35</td>
</tr>
</tbody>
</table>

* For reactions from which only one adduct was isolated, a 5% estimate upper limit was used for the other regioisomer in calculating the partial rate constants.
is indeed the case, as the $k^o(\text{alkyne})/k^o(\text{alkene})$ ratios are now 53 and 35 for C-phenyl-N-methylnitrone and mesitylnitrile oxide reactions, respectively.

In cycloadditions of nitrones and nitrile oxides to dimethyl fumarate, only one cycloadduct is possible for each reaction. The alkyne/alkene rate ratios of 0.51 and 44, shown in Table XIV, for benzonitrile oxide and C-phenyl-N-methylnitrone reactions, respectively, are compatible with the above treatments of partial rate constants. Furthermore, the results of cycloadditions of the styrene series with mesitylnitrile oxide mentioned earlier and those of the methylated acrylic esters with C-phenyl-N-methylnitrone and benzonitrile oxide, as shown in Table V of Section I C, are also in accordance with this hypothesis.
PART D Mechanistic Studies

As discussed in Section I C, all of the 1,3-dipolar cycloadditions which have been subjected to mechanistic scrutiny follow concerted pathways as measured by the criteria of stereochemistry, solvent effects, and isotope effects. On the other hand, Firestone has postulated that many 1,3-dipolar cycloadditions occur by stepwise-diradical intermediate mechanisms. The reversals of regioselectivity found in this work, as well as the substituent effects on rate constitute further tacks in the diradical coffin. For example, the diradical hypothesis suggests that regioisomers formed from diradicals should always be preferred over those formed from diradicals. Yet, with strongly electron-withdrawing substituents, products which would have to arise from the less stable diradical are preferred.

If diradical intermediates were formed in endothermic rate determining steps, dipolarophiles might be expected to react with all 1,3-dipoles in a rate order depending only on the ability of a substituent to stabilize a radical center, e.g. \( \text{H}_2\text{C} = \text{CH}_2 \approx \text{H}_2\text{C} = \text{CH-COR} < \text{H}_2\text{C} = \text{CH-} \).
CN < H₂C=CH-CH=CH₂ < H₂C=CH-Ph, where the radical stabilizations provided by these groups are 0, ~0, ~3, 9.6, and 12.5 kcal/mol, respectively. This order is never observed, and the relative reactivities of these dipolarophiles vary with dipole structure in a way in agreement with a concerted mechanism.

On the other hand, the reversals of regioselectivity observed, as well as the increase in reaction rate with electron-withdrawal on the dipolarophile, are, in principle, also compatible with stepwise reactions involving zwitterionic intermediates. That is, the zwitterion 48 is a plausible intermediate in the reactions studied here when the substituent is sufficiently electron-withdrawing. The related Diels-Alder reactions, although usually involving concerted mechanism,

are known in a few highly polar cases to occur via stepwise mechanisms involving zwitterionic intermediates. In order to verify that a mechanistic change was not involved, the effect of solvent polarity on reaction rate, as well as the stereochemistry of a reaction of mesitylnitrile oxide with an extremely electrophilic alkene, were studied.

Huisgen and coworkers have studied the reaction of C-phenyl-N-methylnitrone with ethyl acrylate, and have found that the 5-carboethoxy adduct is formed (Equation 1). By contrast, the more
electron-deficient dipolarophile, cyanoacetylene, reacts with C-phenyl-N-methylnitrone to give only the 4-cyano adduct (Equation (2)). In the nitrile oxide series, the slightly electron-deficient acrylonitrile reacts with mesitylnitrile oxide to give the 5-substituted adduct (Equation (3)), along with slower formation of a 2:1 adduct involving cycloaddition of the nitrile oxide to the adduct cyano group (Section II B). Mesitylnitrile oxide reacts rapidly with tetracyanoethylene to give a single adduct (Equation (4)), which undergoes decomposition, as well as further additions of the nitrile oxide to adduct cyano groups, at rates slower than the initial cycloaddition. The formation of the adduct, 49, was detected by nmr spectroscopy, as the ortho and para methyl resonance in CDCl₃ shift from 82.42 and 2.33, respectively, in mesitylnitrile oxide, to 82.24 and 2.35 in the adduct. Finally, 1,2-bis(trifluoromethyl)fumaronitrile reacts with mesitylnitrile oxide to give a single adduct (Equation (5)), shown by ¹⁹F nmr to be the trans adduct, 50. Thus, two sharp trifluoromethyl resonances are observed at 9.24 and 19.89 ppm (relative to CFCl₃). In cyclobutanes with vicinal trans-trifluoromethyls, the fluorine resonances are unsplit, whereas the corresponding cis compounds show large (J=12Hz) couplings between nonequivalent fluorines.⁶²
The orientation observed in the reactions of unsymmetrical dipolarophiles, the stereospecificity observed in reaction 5, and the rates of these reactions in benzene (k2 : k1 = 30:1 at 85°; k5 : k4: k3 = 11:55:1) can also be explained by concerted mechanisms. However, the orientation observed in reaction 2 and the stereospecificity of reaction 5 could be equally well rationalized by stepwise reactions involving zwitterionic intermediates, because 1,2-bis(trifluoromethyl)fumaronitrile has been found to react stereospecifically with electron-rich alkenes.62

However, the solvent effects measured here rule out such intermediates. Figure 18 shows the logs of the rates of cycloadditions 1-5 in various solvents plotted against the solvent polarity parameter, E_T.66 The data for reaction 1 was reported by Huisgen and coworkers.55 The data for reaction 2 was reported by Sims.19

The two nitrone reactions show very similar rate decelerations by solvents of increasing polarity, regardless of the adduct orientation. The slopes of these lines (Δ log k/ΔE_T = -0.033 and -0.029) are not only much smaller in magnitude, but opposite in sign to that for the cycloaddition of butyl vinyl ether to TCNE (Δlog k/ΔE_T = +0.29), a reaction involving a zwitterionic intermediate.87 The reactions of mesitylnitrile oxide vary in sensitivity to solvent polarity, but the slopes (+0.005, -0.041, and -0.080) are all well within the range expected for concerted reactions.

Finally, it should be noted that reactions 4 and 5 may not follow simple second order kinetics since charge transfer complexes are visually apparent as soon as the reagents are mixed, and it has been found that mesitylnitrile oxide adducts form charge transfer
Figure 18. Plots of $(4 + \log k_2) \text{ vs } E_T$ For Reactions of (1) C-Phenyl-N-methylnitrone With Ethyl Acrylate (85°), (2) C-Phenyl-N-methylnitrone With Cyanoacetylene (85°), (3) Mesitylnitrile Oxide With Acrylonitrile (35°), (4) Mesitylnitrile Oxide With TCNE (25°), and (5) Mesitylnitrile Oxide With 1,2-Bis(trifluoromethyl)fumaronitrile (35°).
complexes with TCNE, undoubtedly involving the electron-rich mesityl group. Nevertheless, the small sensitivity of the rate determining steps of these reactions to solvent polarity rule out the formation of charged intermediates, and lead to the conclusion that all these reactions are concerted.
PART E  Lewis Acid Catalyzed 1,3-Dipolar Cycloadditions

The effects of Lewis acids on the rates, regioselectivity and stereoselectivity of Diels-Alder reactions have been thoroughly investigated.\textsuperscript{88-90} In general, large rate accelerations,\textsuperscript{88} and greatly increased regioselectivity\textsuperscript{89} and stereoselectivity\textsuperscript{90} are observed. These phenomena can be rationalized by the application of frontier orbital theory.\textsuperscript{91} Frontier orbital theory also predicts that Lewis acids will affect rates and selectivities in 1,3-dipolar cycloadditions. However, very few Lewis acid catalyzed 1,3-dipolar cycloaddition reactions have been studied.

Morrocchi, Ricca and Velo\textsuperscript{58} first successfully carried out 1,3-dipolar cycloaddition reactions in the presence of boron trifluoride-etherate. Unactivated nitriles and carbonyl compounds, both aldehydic and ketonic, cycloadd to benzonitrile oxide with BF\textsubscript{3}-etherate as the catalyst to give the corresponding oxadiazoles and dioxazoles respectively. Normally, electron-withdrawing groups are required on the nitrile or carbonyl for reactions with nitrile oxides to occur. Other examples are the cycloaddition of diphenyltrinitrileimine to nitriles catalyzed by AlCl\textsubscript{3},\textsuperscript{59} the dimerization of mesitylnitrile oxide\textsuperscript{92} and the reaction of methyl methoxycarbonylmethanenitronate with 16-dehydro-20-oxosteroids in the presence of BF\textsubscript{3}-etherate.\textsuperscript{38c} All of the above examples give rapid 1,3-dipolar cycloadditions in the presence of a Lewis acid while no reactions are observed in the absence of catalyst.

Unactivated nitriles and carbonyl compounds are unreactive...
towards cycloadditions with many 1,3-dipoles, suggesting that these reactions are HOMO-LUMO controlled, and that the energy difference between the dipole LUMO and the dipolarophile HOMO, or vice versa, is large. The rate enhancement of these reactions by a Lewis acid can be readily explained by frontier orbital considerations. The complexation of a molecule with a Lewis acid results in energy lowering of both the HOMO and LUMO of the molecule. Whether the 1,3-dipole, or the nitrile or carbonyl, is complexed makes no difference. One HOMO-LUMO gap will be decreased, accelerating the reaction. In a catalyzed nitrile oxide cycloaddition reaction, it is expected that complexation will occur preferentially with the oxygen of the nitrile oxide due to the rather large negative charge on oxygen. Thus, as the nitrile oxide orbital energies are lowered upon complexation, the dipole LUMO-dipolarophile HOMO interaction will be strengthened, and the reaction rate will increase. The catalyzed reaction becomes dipole LUMO controlled. This is illustrated in Figure 19, where A represents a Lewis acid.

Figure 19. Frontier Orbital Interactions in Lewis Acid Catalyzed 1,3-Dipolar Cycloadditions.
The preferred regioisomeric product expected for the catalyzed cycloaddition would be the normal adduct, since the larger terminal coefficient on the C of nitrile oxide LUMO and that on the X of the dipolarophile HOMO should become bonded preferentially in the transition state. This is indeed the case, as benzonitrile oxide reacts with nitriles and ketones in the presence of \( \text{BF}_3 \)-etherate to give only 1,2,4-oxadiazoles and 1,3,4-dioxazoles, respectively. On the other hand, complexation with the nitrile or carbonyl compound would also give acceleration, and the same regiochemistry.

In light of the above frontier orbital treatments, it becomes more apparent why thermally stable mesitylnitrile oxide dimerizes readily in the presence of a Lewis acid. The regiochemistry of the mesitylnitrile oxide dimer is as expected by frontier orbital considerations, but in contrast to Huisgen’s principle of maximum gain in \( \sigma \)-bond energy (Section I C). As shown below, both pairs of frontier orbital interactions lead to the formation of the furoxan, in which one C-C and one N-O bond are closed. If a Lewis acid complexation does not change the relative magnitudes of coefficients, regioselectivity in thermal and Lewis-acid catalyzed nitrile oxide dimerizations should remain the same.
However, in a 1,3-dipolar cycloaddition where both regio-isomeric products are formed, complexation of Lewis acid with either the dipole or the dipolarophile should lead to a change in regio-selectivity depending on the site of complexation and the extent of lowering in orbital energies. To verify this idea, reactions of mesitylnitrile oxide and methyl propiolate were carried out in the presence of AlCl$_3$ and BF$_3$-etherate.

In the presence of an 1/10 molar ratio of AlCl$_3$ to cycloaddends, methyl propiolate reacted with mesitylnitrile oxide in benzene at 50° to give 43% of the 5-carbomethoxy and 57% of the 4-carbomethoxy isoxazoles as the reaction products. The ratio of the products were determined from integration of the resonance of the vinyl protons (C-4 at δ6.88, C-5 at δ9.00) and the -OCH$_3$ protons (5-substituted at δ3.90, 4-substituted at δ3.66) in the nmr spectrum of the reaction mixture. Using an equimolar ratio of AlCl$_3$ to the nitrile oxide and the same reaction conditions, two cycloadducts in the ratio of 62% to 38% (for the 5- and 4-substituted isoxazoles, respectively) along with some mesitylnitrile oxide dimer observed. When BF$_3$-etherate was used as the catalyst in equimolar ratio, only the formation of the mesitylnitrile oxide dimer was observed by tlc and nmr spectroscopy.

\[
\text{Mes-}C\equiv N\rightarrow O + \text{HC}≡\text{C-}CO_2\text{Me} \rightarrow \begin{array}{c}
\text{(a) } \text{CCl}_4 \\
\text{(b) 10:1 } \text{AlCl}_3 \\
\text{(c) 1:1 } \text{AlCl}_3 \\
\text{(d) BF}_3\text{-Et}_2\text{O} \\
\text{Benzene} \\
\text{Benzene} \\
\text{Et}_2\text{O}
\end{array} \begin{array}{c}
\text{Mes-} \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C}
\end{array}
\]

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The results are in agreement with predictions of frontier orbital theory.\textsuperscript{91} In the uncatalyzed reaction of mesitylnitrile oxide and methyl propiolate (reaction a), the interaction between the dipole HOMO and the dipolarophile LUMO is strongest, leading preferentially to the (e) adduct, while in the AlCl\textsubscript{3} catalyzed reaction (reaction c), the dipole LUMO-dipolarophile HOMO interaction becomes more important and more (\textgreek{z}) adduct is formed.

In reaction b, a maximum of 10\% of the nitrile oxide is coordinated with AlCl\textsubscript{3}. Under these conditions, three competing reaction pathways are expected: (1) the dimerization of the nitrile oxide, (2) the addition of the uncomplexed nitrile oxide to the dipolarophile (e adduct is favored), and (3) the addition of the complexed dipole to the dipolarophile (\textgreek{z} adduct is favored). All of these contribute to the observed products, i.e. a slight increase in \%(\textgreek{z}) adduct and some amounts of nitrile oxide dimer. The dominant frontier orbital interactions involved in each of these reactions are illustrated in Figure 20.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure20}
\caption{Competing Interactions in Lewis Acid Catalyzed 1,3-Dipolar Cycloadditions.}
\end{figure}
In reaction d, however, only the nitrile oxide dimerization has occurred. This may be attributed to the difference in acid strength of BF$_3$-etherate from that of AlCl$_3$.$^{93}$ The effect of Lewis acid complexation on the reactions studied here is in the direction to decrease the cycloaddition reactivity because the strong dipole HOMO-dipolarophile LUMO interaction is decreased due to lowering of the dipole orbital energies. It is not until the reactivity has passed a minimum that the reaction rate can be enhanced. This crossover in the control of reactivity is similar to that illustrated in Figure 10 (Section II B), except that it is now a dipolarophile reacting with various 1,3-dipoles of different frontier orbital energies. A new U-shaped correlation can therefore be predicted for a plot of reactivity vs IP of the 1,3-dipole. With this in mind, reaction d may be regarded as a HOMO-LUMO controlled reaction for the addition of mesitylnitrile oxide to methyl propiolate, with large energy gaps between both pairs of frontier orbitals, so that the cycloaddition reaction is slow. On the other hand, the dimerization is a HOMO controlled reaction, and is fast, so that it dominates over the cycloaddition with methyl propiolate. AlCl$_3$, a stronger Lewis acid, lowers the dipole energies more, so that the dipole LUMO-dipolarophile HOMO interaction is strong enough to allow the cycloaddition to compete with dipole dimerization.
PART F Summary and Conclusions

Recent applications of perturbation theory have provided a rationalization of 1,3-dipolar cycloaddition reactivity and regioselectivity. Results reported here confirm these ideas for the reactions of nitrones and nitrile oxides with alkenes and alkynes. Nitrones and nitrile oxide reactivities in cycloadditions were shown to be related to the relative disposition of the interacting frontier orbitals, and regioselectivities were shown to be related to the coefficients of the interacting frontier orbitals.

The dominant frontier orbital interaction of nitrones or nitrile oxides and electron-rich monosubstituted alkenes or alkynes is dipole LUMO-dipolarophile HOMO, and regiochemistry is controlled by the terminal coefficients of the dipole LUMO and dipolarophile HOMO. Only the 5-substituted adduct is formed. Both pairs of frontier orbital interactions are important in reactions with conjugated dipolarophiles; however, regiochemistry is controlled by the dipole LUMO due to bond stretching in the transition state and larger differences in relative magnitudes of terminal coefficients in the dipole LUMO. The dominant frontier orbital interaction with electron-deficient dipolarophiles is between the dipole HOMO and the dipolarophile LUMO. When this interaction is sufficiently great, regiochemistry is controlled by the dipole HOMO, and partial or total reversal of regioselectivity (formation of 4-substituted adduct) with nitrones and nitrile oxides is observed, in spite of the fact that steric effect decrease the reaction rate in some cases.
When a 1,3-dipole or dipolarophile is coordinated with a Lewis acid, the orbital energies are lowered, resulting in changes in reactivity and regioselectivity in cycloaddition reactions. Results of the Lewis acid catalyzed 1,3-dipolar cycloadditions studied here also confirm the predictions made by the frontier orbital theory.

The reversals of regioselectivity found in this work, as well as the stereospecificity, the substituent effects on rate, and the small sensitivity of reaction rates to solvent polarity, provide further evidence for concerted mechanisms in 1,3-dipolar cycloadditions.

In general, the successful application of perturbation theory for rationalizing and predicting reactivity and regioselectivity of nitrone and nitrile oxide cycloadditions has been demonstrated. Frontier orbital theory could be applied more quantitatively if more accurate data for frontier orbital energies and coefficients were available.
III. EXPERIMENTAL

PART A. General Information

The reagents and solvents used in all syntheses were reagent grade commerical chemicals. Unless otherwise indicated, these chemicals were used without further purification.

All melting points were measured on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected.

Infrared spectra (ir) were recorded on a Perkin-Elmer Infracord Model 137. Polystyrene was used as the calibration standard.

Electronic spectra (uv) were recorded on a Cary 14 Spectrometer.

Proton nuclear magnetic resonance spectra (nmr) were recorded on a Perkin-Elmer Model R12B (60 MHz) Spectrometer. $^{19}$F nmr spectra were recorded by David Latour on a Varian MA-100 Spectrometer. Chemical shifts are reported in ppm (δ) with tetramethylsilane (TMS) as internal reference, and coupling constants are measured in Hz. The usual notation is used to describe the splitting patterns, i.e., s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, etc.

Mass spectra (ms) were determined by Paula B. Watts and Dr. Paul J. Moses on a Hitachi Perkin-Elmer Model RMS-4 Mass Spectrometer using an ionization energy of 70eV. In general, only parent peaks (m+) and m/e ratios for peaks with intensities greater than 15% of the base peak are given.

Photoelectron spectra (pes) were recorded by Linda Lambert.
on a Perkin-Elmer Model PS-18 Photoelectron Spectrometer using helium discharge lamp (He I, 584 Å = 21.21 eV) as the source.

Microanalysis were performed by Ralph Seab, Louisiana State University, Baton Rouge.
PART B Starting Materials

1. Syntheses of Nitrones

The syntheses of nitrones were reviewed in 1972.9

a. Synthesis of N-t-Butylnitrone

N-t-Butylnitrone was prepared from t-butylamine according to the procedure developed by Sims.19 Diazomethane used in this synthesis was prepared from Diazald utilizing an Aldrich Chemical Company Diazald Kit for the generation of diazomethane.

b. Synthesis of C-Phenyl-N-methylnitrone

C-Phenyl-N-methylnitrone was prepared by the condensation of N-methylhydroxylamine and benzaldehyde as described by Sims.19

c. Synthesis of C-Mesityl-N-methylnitrone

Following the same procedure as that used for the synthesis of C-phenyl-N-methylnitrone, C-mesityl-N-methylnitrone was prepared from N-methylhydroxylamine and mesitaldehyde in 90% yield. Recrystallization from benzene-petroleum ether (30-60°C) gave colorless crystals, mp 169-171°C. Nmr spectrum (CDCl₃): δ2.22 ppm, s, 9H; δ3.83, s, 3H; δ6.84, s, 2H; δ7.50, s, 1H. Anal. calcd. for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.52; N, 7.93.

2. Syntheses of Nitrile Oxides

Nitrile oxide syntheses were reviewed in 1971.8
a. Synthesis of Benzohydroxamic Chloride

Benzohydroxamic chloride was prepared according to the general directions of Pilotz and Steinbock\textsuperscript{95} by passing chlorine gas through the solution of 10 ml of benzaldoxime in 60 ml 8N hydrochloric acid at 0\textdegree for 15-20 min. The colorless product was filtered off (mp 42-48\textdegree, yield 76\%) and used directly for the generation of benzonitrile oxide without further purification.

Benzaldoxime used here was prepared by the following procedure: A quantity of 20 ml of benzoaldehyde was added into a cooled solution of 15 g of sodium hydroxide in 50 ml of water. The mixture was stirred while adding small portions of 15 g of hydroxylamine hydrochloride, cooling the solution from time to time. Stirring was continued until all the benzoaldehyde had gone into solution, and several lumps of dry ice were added. Solid benzaldoxime was filtered off and used without further purification.

b. Synthesis of Mesitylnitrile Oxide

Mesitylnitrile oxide was best prepared by dehydrogenation of 2,4,6-trimethylbenzaldoxime with N-bromosuccinimide and triethylamine in N,N-dimethylformamide according to the procedure described by Grundmann and Richter.\textsuperscript{93}

2,4,6-Trimethylbenzaldoxime used here was prepared according to the general procedure for aldoxime synthesis described by Linsted and Weedon.\textsuperscript{96}

c. Synthesis of p-Nitrobenzonitrile Oxide
$\text{p- Nitrobenzonitrile oxide}$ was synthesized by the dehydrohalogenation of $\text{p-nitrobenzohydroxamic chloride}$ with aqueous sodium carbonate solution as described by Chang and Loue.96

$p$-Nitrobenzohydroxamic chloride was prepared by passing chlorine gas through a solution of 9 g of $p$-nitrobenzaldoxime in 100 ml ether at 0° for 1 hr. The product was filtered off and recrystallized from benzene to give yellow crystals in 60% yield.

$p$-Nitrobenzaldoxime used here was prepared by the same procedure used for the preparation of 2,4,6-trimethylbenzaldoxime.

3. Syntheses of Alkenes and Alkynes

Commercially available alkenes and alkynes were used in these studies without further purification. Bis-trifluoromethylfumaronitrile was obtained as a gift from Dr. H. E. Simmons and Dr. S. F. Proskow of E. I. duPont Nemours & Co., Inc.

a. Synthesis of Nitroethylene

Nitroethylene was prepared by the dehydration of 2-nitroethanol with phthalic anhydride as described by Buckley and Scaife.98

b. Synthesis of Phenyl Vinyl Sulfone

The procedure of Parham, et al.,99 for the oxidation of phenyl vinyl sulfide with hydrogen peroxide in acetic acid was followed verbatim. The overall synthesis of phenyl vinyl sulfone, starting from thiophenol and 2-chloroethanol, has been described by Sims.19

c. Synthesis of Methyl Vinyl Sulfone

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Methyl vinyl sulfone was synthesized in 50% yield by a similar procedure reported by Brown and Moggridge.  

**d. Synthesis of 1-Mesityl-1-phenylethylene**

1-Mesityl-1-phenylethylene was prepared from the reaction of benzoylmesitylene and methylmagnesium iodide by the method of Fuson, et al.  

**e. Synthesis of Adamantylideneadamantane**

Adamantylideneadamantane was prepared in 75% yield from 2,2-dibromoadamantane and magnesium according to the method of Bartlett and Ho.  

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PART C  Cycloadditions of Nitrones and Nitrile Oxides With Alkenes and Alkynes

For cycloadditions of stable nitrones and nitrile oxides (N-t-butylnitrone, C-phenyl-N-methylnitrone, C-mesityl-N-methylnitrone and mesitylnitrile oxide), preparative scale reactions were carried out in sealed test tubes under nitrogen in ~3 ml of solvent. Optimum reaction temperatures and times were determined from small scale reactions carried out in sealed nmr tubes under nitrogen and monitored by nmr spectroscopy or thin layer chromatography (tlc). Benzonitrile oxide and p-nitrobenzonitrile are unstable at room temperature, hence, cycloaddition reactions of these compounds were carried out by generating the nitrile oxides from benzo hydroxamic chloride and p-nitrobenzohydroxamic chloride, respectively, in solutions containing the dipolarophiles.

Most reaction products were isolated by preparative layer chromatography (plc). Preparative and analytical thin layer chromatography (tlc) were performed on glass plates and aluminum sheets, respectively, coated with EM Reagents Silica Gel F-254. The eluent consisted of X% ethyl acetate in cyclohexane, unless otherwise indicated. Selected (by the use of an ultraviolet light) fractions were scraped from the plc plates and eluted with ethyl acetate. The desired fractions were identified by nmr spectroscopy and subsequently purified further by shortpath distillation or recrystallization.

In general, eight kinds of compounds were synthesized in these reactions. Cycloadditions of nitrones with alkenes and alkynes

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gave isoxazolidines and $\Delta^4$-isoxazolines, respectively. Cycloadditions of nitrile oxides with alkenes and alkynes gave isoxazolines and isoxazoles, respectively. Representative nmr spectra for each of these kinds of compounds are included in Appendix A. Detailed descriptions of the nmr spectra of all new compounds are given.

1. Cycloadditions of N-t-Butynitrone

N-t-Butynitrone was used in carbon tetrachloride solution and not isolated in pure form. Concentrations were determined by nmr spectroscopy using benzene as a standard. Numerous cycloadditions of N-t-butynitrone with alkenes and alkynes have been performed by Sims.\(^9\)

**Reaction of cis-β-Methylstyrene and N-t-Butynitrone**

A 354 mg (3.0 mmol) quantity of cis-β-methylstyrene and 2.30 g (3.0 mmol) of N-t-butynitrone solution (CCl₄, 1.3 mmol/g sol'n) were mixed at room temperature, and the solution was heated in a sealed tube under nitrogen at 85° for 24 hrs. Ptc (5% ethyl acetate in cyclohexane as the eluent) gave a mixture of 69% of 2-t-butyl-cis-4-methyl-5-phenylisoxazolidine and 31% of 2-t-butyl-cis-5-methyl-4-phenylisoxazolidine. The products could not be separated by ptc and the ratio was determined by nmr spectroscopy. Total yield after short-path distillation (76 /1.5 mm) was 473 mg (72%). Uv (MeOH): \(\lambda_{\text{max}} 265 \text{ nm} (\varepsilon=320), 258 \text{ nm} (\varepsilon=440), 253 \text{ nm} (\varepsilon=451). \) Nmr (CCl₄):

\begin{align*}
7.18 (\text{Ar-H, s}); & \quad 4.98 (-\text{OCHPh, d, J = 7.0 Hz}); \quad 4.21 (-\text{OCHMe, dq, J = 6.3, 6.3 Hz}); \quad 3.75-2.18 (\text{ring-H, m}); \quad 1.14 (\text{t-butyl, s}); \quad 0.75 (-\text{OCCH₃, d, J = 6.3 Hz}); \quad 0.57 (-\text{CH₃, d, J = 6.3 Hz}).
\end{align*}

**Anal.** Calcd. for C\(_{14}\)H\(_{21}\)NO: C, 76.65; H, 9.67. Found: C, 75.92; H, 9.73.
2. Cycloadditions of C-Mesityl-N-methylNitronc

C-Mesityl-N-methylNitronc was reacted with methyl acrylate, acrylonitrile, nitroethylene, phenyl vinyl sulfone, cyanoacetylene and methyl propiolate. A complete description of the experimental procedure is given for the cycloaddition of phenyl vinyl sulfone and C-mesityl-N-methylNitronc. The procedures for the remaining reactions were similar and the experimental details and product data are summarized in Tables XVI-XVIII.

Reaction of Phenyl Vinyl Sulfone and C-Mesityl-N-methylNitronc

A solution of 504 mg (3.0 mmol) of phenyl vinyl sulfone in 1.5 ml of chloroform was added to a solution of 532 mg (3.0 mmol) of C-mesityl-N-methylNitronc in 1.5 ml of chloroform in a test tube at room temperature. The test tube was sealed under nitrogen and heated at 90° for three days. Tlc of the reaction mixture (20%, 1 elution) revealed only one spot (uv detection), Rf = 0.31. The entire reaction mixture was placed on plc plates and eluted once with 20% ethyl acetate in cyclohexane. The desired fraction was scraped from the plates and the product was extracted with chloroform (125 ml). The solvent was removed at reduced pressure and the product was purified further by recrystallization from petroleum ether (65°) to give 496 mg (49%) of trans-4-benzenesulfonyl-3-mesylyl-2-methyl-isoazolidine as the only product. See Tables XXII and XXIII for analytical data.

3. Cycloadditions of Benzonitrile Oxide

Benzonitrile oxide was generated from benzohydroxamic chloride
and reacted with phenyl vinyl sulfone, nitroethylene and cyanoacetylene. A complete description of the experimental procedure is given for the cycloaddition of phenyl vinyl sulfone and benzonitrile oxide. The procedures for the remaining reactions were similar and the experimental details and product data are summarized in Tables XIX and XX.

Reaction of Phenyl Vinyl Sulfone and Benzonitrile Oxide

A quantity of 776 mg (5 mmol) of benzohydroxamic chloride dissolved in 25 ml of ether was cooled to \(-20^\circ\) in acetone-dry ice bath. A solution of 505 mg (5 mmol) of triethylamine in 20 ml of ether was added dropwise while stirring. The reaction mixture was then filtered into a solution of 840 mg (5 mmol) of phenyl vinyl sulfone in 20 ml of ether, allowed to slowly warm up to room temperature and left standing for one hour. Analysis of the mixture by tlc revealed the presence of one spot. Plc separation followed by recrystallization from chloroform-petroleum ether gave 950 mg (66.2%) of 5-benzenesulfonyl-3-phenyl-isoxazoline, mp 138-139\(^\circ\).

4. Cycloadditions of Mesitylnitrile Oxide

Mesitylnitrile oxide was reacted with a variety of alkenes and alkynes. The experimental procedure of the cycloaddition of phenyl vinyl sulfone and mesitylnitrile oxide is given as a representative reaction. The procedures for most of the remaining reactions were similar and the experimental details and product data are summarized in Tables XXI-XXIII. Other cycloadditions and related reactions are described separately.
Reaction of Phenyl Vinyl Sulfone and Mesitylnitrile Oxide

A 336 mg (2.0 mmol) quantity of phenyl vinyl sulfone was dissolved in 1 ml of chloroform and added to a solution of 322.5 mg (2.0 mmol) of mesitylnitrile oxide in 1 ml of chloroform. After standing at room temperature for 5 hrs., tlc of the reaction mixture (20%, 1 elution) revealed two spots (uv detection), $R_f = 0.49, 0.38$. Plc separation and chloroform extraction gave 524 mg of 5-benzene-sulfonyl-3-mesityl-isoxazoline and 23 mg of 4-benzenesulfonyl-3-mesityl-isoxazoline in 83% total yield. The products were purified further by recrystallization from petroleum ether (65°C) to give analytically pure samples.

a. Reaction of 3,3,3-Trifluoropropyne and Mesitylnitrile Oxide

A solution of 361 mg (2.2 mmol) of mesitylnitrile oxide in 2 ml of carbon tetrachloride was placed in a steel bomb connected to a cylinder containing liquid 3,3,3-trifluoropropyne on a top-loading balance. The steel bomb was cooled to dry ice/acetone temperature, and a quantity of 2.0 g (22 mmol) of 3,3,3-trifluoropropyne was then allowed to diffuse into the mesitylnitrile oxide solution by opening the inlet valve of the steel bomb. The reaction mixture was allowed to slowly warm up to room temperature and left standing for three days. After carefully opening up the steel bomb, the entire reaction mixture was placed on a 20 x 40 cm Silica Gel plc plate and eluted with 5% ethyl acetate in cyclohexane. Uv detection showed two separated fractions which were scraped from the plc plate and eluted with ethyl acetate. The solvent was removed at reduced pressure to give 80 mg of 3-mesityl-
4-trifluoromethylisoxazole and 50 mg of 3-mesityl-5-trifluoromethylisoxazole as pale yellow oils in 24% total yield. The products were identified by nmr spectroscopy without further purification.

b. Reaction of Bis-trifluoromethylfumaronitrile and Mesitylnitrile Oxide

A solution of 177 mg (0.83 mmol) of bis-trifluoromethylfumaronitrile in 0.5 ml of chloroform was added to a solution of 120 mg (0.74 mmol) of mesitylnitrile oxide in 0.5 ml of chloroform. The reaction mixture turned yellow and the color faded away after standing at room temperature for 3 hrs. Tlc (20% ethyl acetate in cyclohexane) revealed only one spot. Plc separation followed by chloroform extraction gave 125 mg of the cycloadduct in 45% yield. The stereochemistry of the product was identified by $^{19}$F nmr spectroscopy which showed only the trans adduct was obtained.

c. Lewis Acid Catalized Reaction of Methyl Propiolate and Mesitylnitrile Oxide

A solution of 484 mg (3.0 mmol) of mesitylnitrile oxide in 5 ml of benzene was added over a period of 10 min. to a stirred suspension of 40 mg (0.3 mmol) of AlCl$_3$ in 5 ml of benzene warmed to 50$^\circ$. AlCl$_3$ rapidly dissolved to form a slightly yellow clear solution. A solution of 252 mg (3.0 mmol) of methyl propiolate in 5 ml of benzene was then added dropwise during a period of 20 min., and the reaction mixture was stirred at 50$^\circ$ for three hrs. After allowing to cool to room temperature, the reaction mixture was washed with dilute hydrochloric acid and then with water. The organic layer was separated
and dried over anhydrous sodium sulfate. The solvent was removed with reduced pressure. The nmr spectrum of the residue showed two cycloaddition adducts in the ratio of 57% to 43% for 3-mesityl-4-methylcarboxyisoxazole and 3-mesityl-5-methylcarboxyisoxazole, respectively. The product ratio was determined from integration of the resonances of the vinyl protons (C-4 at δ6.88, C-5 at δ9.00) and the -OCH₃ protons (5-substituted at δ3.90, 4-substituted at δ3.66) in the isoxazole products.

Using an equimolar ratio of AlCl₃ to nitrile oxide and the same reaction conditions, two cycloaddition adducts in the ratio 38% to 62% (for 4- and 5-substituted isoxazoles respectively) along with some mesitylnitrile oxide dimer were observed.

d. Attempted Reaction of 3,3,3-Trifluoropropene and Mesitylnitrile Oxide

The attempted reaction of 3,3,3-trifluoropropene and mesitylnitrile oxide was performed with 2.3 mmol of the nitrile oxide and five fold excess of the alkene by the same procedure as described above. After standing at room temperature for two weeks, mesitylnitrile oxide was recovered and no cycloaddition product was observed in the nmr spectrum.

e. Attempted Reaction of 1-Mesityl-l-phenylethylene and Mesitylnitrile Oxide

A solution of 161 mg (1.0 mmol) of mesitylnitrile oxide in 0.5 ml of CDCl₃ was added to a solution of 222 mg (1.0 mmol) of 1-mesityl-l-phenylethylene in 0.5 ml of CDCl₃ in an nmr tube. The reaction
tube was purged with nitrogen, sealed, and heated in an oil bath at 80° for 48 hrs. Periodically recorded nmr spectra showed no change for the alkene signals and only partial dimerization of mesitylnitrile oxide had occurred.

Numerous attempts to react 1-mesityl-1-phenylethylene with benzonitrile oxide (25°, 3 hrs, Et₂O), p-nitrobenzonitrile oxide (25°, 4 hrs, Et₂O) C-phenyl-N-methylnitrone (80°, 48 hrs, CDCl₃), and C-mesityl-N-methylnitrone (80°, 48 hrs, CDCl₃) were also without success.

f. Attempted Reaction of Adamantylideneadamantane and Mesitylnitrile Oxide

No cycloaddition reaction was observed when chloroform solutions of adamantylideneadamantane and mesitylnitrile oxide were mixed in an nmr tube and heated at 80° for three days. Again, mesitylnitrile oxide dimerized slowly at high temperature. Adamantylideneadamantane remained unreacted and was recovered by plc.

Efforts to react adamantylideneadamantane with other nitrones and nitrile oxides were totally unsuccessful.

5. Cycloadditions of p-Nitrobenzonitrile Oxide

The experimental details and product data of the cycloadditions of p-nitrobenzonitrile oxide with phenyl vinyl sulfone, nitroethylene and cyanoacetylene are summarized in Tables XXIV-XXVI. The procedures for all reactions were similar and only that for the cycloaddition of phenyl vinyl sulfone and p-nitrobenzonitrile oxide is given.
Reaction of Phenyl Vinyl Sulfone and p-Nitrobenzonitrile Oxide

A solution of 2.0 g (0.01 mol) of p-nitrobenzohydroxamic chloride in 120 ml of ether was extracted with a cold 5% aqueous sodium carbonate solution (13 ml, 0.01 mol) in a separatory funnel. The organic layer containing p-nitrobenzonitrile oxide was then removed, washed with 10 ml of cold water, dried over anhydrous calcium chloride for 2 min., and treated with 1.69 g (0.011 mol) of phenyl vinyl sulfone in 20 ml of ether. The reaction mixture was stirred at room temperature for 3 hrs. and precipitate was filtered off and recrystallized from acetone to give 2.78 g (84%) of white crystalline 5-benzene-sulfonyl-3-p-nitrophenylisoxazoline.

6. Kinetic Measurements and Solvent Effect Studies

Reactivities and relative reactivity orders for reactions of dipolarophiles with N-t-butylnitrone and mesitylnitrile oxide were sought. Bimolecular rate constants were determined by monitoring small scale reactions with nmr spectroscopy. Most reactions employed equal concentrations of reactants (~0.75 mmol) in approximately one milliliter of solvent sealed in nmr tubes under nitrogen. For very fast reactions and for reactants with low solubilities, more dilute solutions were used. For studies above room temperature, the reaction mixture was heated in an oil bath (±0.3°C), periodically removed and rinsed with acetone to quench the reaction and clean the nmr tube, and the nmr spectrum was recorded. The concentrations of reactants were assumed to be directly proportional to the peak height of the methylene
proton singlet of N-t-butylnitrone (6.0-7.0 ppm) or the o-methyl proton singlet of mesitylnitrile oxide (2.0-3.0 ppm). Five or more spectra for the first half-life of each reaction were recorded. Data were obtained in most cases for only one sample of a given reaction. Ratios of the regioisomeric products were determined by the integration of the nmr spectra taken after allowing the reactions to proceed to completion. Adduct ratios determined from nmr integration of the reaction mixtures or from isolated products closely agreed.

Reaction solvents, temperatures, calculated enthalpies, and extrapolated rate constants for N-t-butylnitrone and mesitylnitrile oxide cycloadditions are reported and discussed in Section II A.

Experiments for solvent effect studies were carried out in the same way for the cycloadditions of mesitylnitrile oxide with acrylonitrile, tetracyanoethylene and bis-trifluoromethylfumaronitrile in various solvents with different solvent polarities. Kinetic data were reported and discussed in Section II D.

Attempted measurements of the rates of the reactions of tetracyanoethylene and bis-trifluoromethylfumaronitrile with N-t-butylnitrone in all solvents failed. The nmr spectra revealed that the products with resonances expected for 1:1 adducts were formed but these decomposed at room temperature as these reactions were proceeding. The reaction mixtures turned from yellow to orange, and eventually to dark brown. Broad and complex nmr signals were always observed, so that these reactions were not studied further.
<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Nitrone (mmol)</th>
<th>Alkene or Alkyne (mmol)</th>
<th>Reaction Conditions</th>
<th>Pile Separation Eluent</th>
<th>bp or mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C=CH-CO₂CH₃</td>
<td>50</td>
<td>0.75</td>
<td>0.78</td>
<td>CHCl₃, 90°</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>cis + trans A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans B</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂C=CH-CN</td>
<td>50</td>
<td>0.75</td>
<td>0.81</td>
<td>CHCl₃, 90°</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>cis + trans A</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not isolated</td>
</tr>
<tr>
<td>trans B</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂C=CH-NO₂ trans B</td>
<td>90</td>
<td>0.75</td>
<td>0.77</td>
<td>CHCl₃, 35°</td>
<td>10</td>
<td>120°/0.9 mm</td>
</tr>
<tr>
<td>H₂C=CH-SO₂Ph trans B</td>
<td>49</td>
<td>0.75</td>
<td>0.75</td>
<td>CHCl₃, 90°</td>
<td>20</td>
<td>mp 163–165°</td>
</tr>
<tr>
<td>HC≡C-CN trans B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC≡C-CO₂CH₃ B</td>
<td>81</td>
<td>1.00</td>
<td>1.00</td>
<td>CHCl₃, 25°</td>
<td>20</td>
<td>116°/0.25 mm</td>
</tr>
</tbody>
</table>
a. All reactions were carried out in ~3 ml of solvent.

b. Separations were carried out on plc plates (EM Reagents Silica Gel-F254) using uv detection.

The eluent was XX ethyl acetate in cyclohexane, v/v.
TABLE XVII

Reactions of C-Mesityl-N-Methylnitrone With Alkenes and Alkynes: Analytical Data

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidine or Δ^4-Isoxazolines

<table>
<thead>
<tr>
<th>Product</th>
<th>UV Spectrum</th>
<th>IR Spectrum</th>
<th>NMR Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MeOH</td>
<td>λ_max nm(ε)</td>
<td>λ(microns)</td>
</tr>
<tr>
<td>CH2=CHCO2CH₃</td>
<td>A</td>
<td>259(1,350)</td>
<td>(film): (C=O), 5.68(s); 5.75(s); 6.87(s); 6.97 (s); 8.30(b); 8.99(m); 9.32(m); 9.72(b); 11.77 (s).</td>
</tr>
<tr>
<td>(cis and trans mixture)</td>
<td>Not obtained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(trans) B</td>
<td>259(1,350)</td>
<td>(film): (C=O), 5.68(s); 5.75(s); 6.87(s); 6.97 (s); 8.30(b); 8.99(m); 9.32(m); 9.72(b); 11.77 (s).</td>
<td>(CDCl3): 66.82(Ar-H, s,2H); 4.50-3.40(ring-H,m,4H); 3.65(-OCH3, s,3H); 2.55(-NCH3, s,3H); 2.44(o-CH3, s,6H); 2.24(p-CH3, s,3H).</td>
</tr>
<tr>
<td>CH2=C=CHN</td>
<td>B</td>
<td>265(12,460)</td>
<td>(film): (C≡N), 4.45(m); 5.91(s); 6.19(s); 6.86 (b); 8.43(m); 9.01(m); 9.62(s); 11.69(s); 12.21(s).</td>
</tr>
<tr>
<td>Compound</td>
<td>ν (film) (cm⁻¹)</td>
<td>ν (Nujol) (cm⁻¹)</td>
<td>ν (CDC) (δ ppm)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>CH₂=CH-NO₂ (trans)</strong></td>
<td>265 (13,350)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(CDC) : 66.84 (Ar-H, s, 2H); 5.43 (-CHNO₂, ddd, J=3.0, 6.0, 7.0 Hz, 1H); 4.55 (-OCHNO₂-cis, ddd, J=3.0, 11.0 Hz, 1H); 4.33 (-OCHNO₂-trans, ddd, J=6.0, 11.0 Hz, 1H); 4.50 (-CH₃, d, J=7.0 Hz, 1H); 2.59 (-NCH₃, s, 3H); 2.39 (-CH₃, s, 6H); 2.24 (-CH₃, s, 3H).</td>
</tr>
<tr>
<td><strong>CH₂=CHSO₂Ph (trans)</strong></td>
<td>272 (3,360)</td>
<td>265 (3,780)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>259 (3,000)</td>
<td></td>
<td>(CDC) : 68.00-7.30 (Ar-H, m, 5H); 6.85 (Ar-H, s, 2H); 4.60-4.30 (ring-H, m, 4H); 2.85 (-NCH₃, s, 3H); 2.65 (-CH₃, s, 6H); 2.24 (-CH₃, s, 3H).</td>
</tr>
<tr>
<td><strong>CH≡C-CN</strong></td>
<td>300 (21,470)</td>
<td>265 (58,280)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(CDC) : 67.13 (vinyl-H, d, J=2.0 Hz, 1H); 6.83 (Ar-H, s, 2H); 5.45 (PhCH-, d, J=2.0 Hz, 1H); 2.95 (-NCH₃, s, 3H); 2.38 (-CH₃, s, 6H); 2.24 (-CH₃, s, 3H).</td>
</tr>
<tr>
<td><strong>CH≡C-CO₂CH₃</strong></td>
<td>265 (53,400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(CDC) : 67.33 (vinyl-H, d, J=2.0 Hz, 1H); 6.79 (Ar-H, s, 2H); 5.47 (PhCH-, d, J=2.0 Hz, 1H); 3.56 (-OCH₃, s, 3H); 2.95 (-NCH₃, s, 3H); 2.39 (-CH₃, s, 6H); 2.22 (-CH₃, s, 3H).</td>
</tr>
<tr>
<td>Product</td>
<td>Mass Spectral Data</td>
<td>Elemental Analysis</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_2=\text{CH-}$</td>
<td>$\text{CO}_2\text{CH}_3$</td>
<td>$\text{B}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{M}^+,263(52);218(11);178(10);163(14);$</td>
<td>$\text{C}_1\text{H}_7\text{NO}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$162(100);160(39);158(10);157(19);$</td>
<td>$\text{C}_68.42%;\text{H},8.04$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$146(14);145(15);144(36);129(9);$</td>
<td>$\text{Found: C}_68.41%;\text{H},8.23$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$115(7);91(9);77(6);42(9).$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_2=\text{CHC}≡\text{N}$</td>
<td>$\text{(trans)}$</td>
<td>$\text{B}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{M}^+,230(20);184(14);163(13);162(100);$</td>
<td>$\text{C}<em>1\text{H}</em>{18}\text{N}_2\text{O}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$160(22);148(14);147(24);146(10);$</td>
<td>$\text{Calcd: C}_73.01%;\text{H},7.88$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$145(13);144(13);119(17);115(14);$</td>
<td>$\text{Found: C}_73.35%;\text{H},7.93$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$105(11);91(22);77(18);51(11);$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$42(13);41(16).$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_2=\text{CH-}\text{NO}_2$</td>
<td>$\text{(trans)}$</td>
<td>$\text{B}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{M}^+,250(100);204(35);203(80);202(94);$</td>
<td>$\text{C}<em>1\text{H}</em>{18}\text{N}_2\text{O}_3$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$162(66);160(46);159(82);158(32);$</td>
<td>$\text{Calcd: C}_62.38%;\text{H},7.25$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$157(39);147(36);146(28);145(47);$</td>
<td>$\text{Found: C}_62.75%;\text{H},7.47$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$144(55);143(30);129(44);128(35);$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$115(33);91(41);77(30).$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_2=\text{CHSO}_2\text{Ph}$</td>
<td>$\text{(trans)}$</td>
<td>$\text{B}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{M}^+,345(84);204(100);203(73);173(19);$</td>
<td>$\text{C}<em>1\text{H}</em>{13}\text{NO}_3\text{S}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$162(35);160(21);159(21);158(16);$</td>
<td>$\text{Calcd: C}_66.06%;\text{H},6.72%;\text{N},4.05$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$157(22);146(19);145(20);1144(21);$</td>
<td>$\text{Found: C}_66.41%;\text{H},6.83%;\text{N},3.94$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$129(22);77(23).$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Mass Spectrum</td>
<td>Elemental Analysis</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>-------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| CH≡C-C≡N   | M+ 228(88); 213(22); 211(30); 199(21); 185(35); 160(24); 148(70); 147(100); 119(50); 115(20); 109(76); 105(23); 91(30); 77(27); 39(23). | C_{14}H_{16}N_{2}O
Calcd: C, 73.66; H, 7.06
Found: C, 73.86; H, 7.24 |
| CH≡C-CO_{2}CH_{3} | M+ 261(29); 148(39); 147(63); 142(100); 119(35); 115(20); 110(20); 105(20); 90(31); 77(25). | C_{15}H_{19}NO_{3}
Calcd: C, 68.94; H, 7.33
Found: C, 69.37; H, 7.52 |
**TABLE XIX**

Reactions of Benzonitrile Oxide

A = 5-Substituted Adducts; B = 4-Substituted Adducts

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Nitrile oxide (mmol)</th>
<th>Alkene or Alkyne (mmol)</th>
<th>Reaction Conditions</th>
<th>Solvent recryst. from</th>
<th>mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{C}=$CH–NO$_2$</td>
<td>52</td>
<td>5.0</td>
<td>5.0</td>
<td>Et$_2$O, 25° 1 hr</td>
<td>CHCl$_3$/Pet. Ether(60°)</td>
<td>102–103°</td>
</tr>
<tr>
<td>$\text{H}_2\text{C}=$CH–SO$_2$Ph</td>
<td>66</td>
<td>5.0</td>
<td>5.0</td>
<td>Et$_2$O, 25° 1 hr</td>
<td>CHCl$_3$/Pet. Ether(60°)</td>
<td>138–139°</td>
</tr>
<tr>
<td>HCC=C-CN</td>
<td>53</td>
<td>5.0</td>
<td>5.0</td>
<td>Et$_2$O, 25° 1 hr</td>
<td>plc separation Eluent : 5%</td>
<td></td>
</tr>
</tbody>
</table>

A 82 CHCl$_3$/Pet. Ether (60°) 65–68°

B 18 Not isolated in pure form

---

a. See Section III C for experimental details.
<table>
<thead>
<tr>
<th>Product</th>
<th>NMR Spectrum</th>
<th>Mass Spectral Data</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{H}_2\text{C}=\text{CH}-\text{NO}_2 )</td>
<td>((\text{CDCl}_3)): 6.95-8.10(\text{Ar}-\text{H}, \text{m}, 5 \text{H}); 6.06(\text{CHNO}_2, \text{dd}, J=3.0, 6.0 \text{ Hz}, 1\text{H}); ) (ABX octet: 4.20(\text{CHNO}_2-\text{trans}, \text{dd}, J=6.0, 19.0 Hz, 1\text{H}); 3.85(\text{CHNO}_2-\text{cis}, \text{dd}, J=3.0, 19.0 Hz, 1\text{H}))</td>
<td></td>
<td>( \text{C}_9\text{H}_8\text{N}_2\text{O}_3 )</td>
</tr>
<tr>
<td>( \text{H}_2\text{C}=\text{CH}-\text{SO}_2\text{Ph} ) A</td>
<td>((\text{CDCl}_3)): 6.70-8.20(\text{Ar}-\text{H}, \text{m}, 10 \text{H}); 5.50(\text{CHSO}_2\text{Ph}, \text{dd}, J=3.8, 6.6 \text{ Hz}, 1\text{H}); ) (ABX octet: 4.00(\text{CHSO}_2\text{Ph-cis}, \text{dd}, J=38, 12.0 Hz, 1\text{H}); 3.22(\text{CHSO}_2\text{Ph-trans}, \text{dd}, J=6.6, 12.0 Hz, 1\text{H}))</td>
<td>( \text{M}^+ , 287(2); 147(33); 146(100); 145(44); 144(40); 118(94); 117(21); 91(40); 78(40); 77(95); 76(18); 51(85); 50(28). )</td>
<td>( \text{C}<em>{12}\text{H}</em>{13}\text{NO}_3\text{S} )</td>
</tr>
<tr>
<td>( \text{HC}=\text{C}-\text{CN} ) A</td>
<td>((\text{CDCl}_3)): 6.75-8.15(\text{Ar}-\text{H}, \text{m}, 5 \text{H}); 7.06(\text{vinyl-H}, \text{s}, 1\text{H})</td>
<td></td>
<td>( \text{C}<em>{14}\text{H}</em>{16}\text{N}_2\text{O} )</td>
</tr>
<tr>
<td>( \text{HC}=\text{C}-\text{CN} ) B</td>
<td>((\text{CDCl}_3)): 6.75-8.15(\text{Ar}-\text{H}, \text{m}, 5 \text{H}); 8.80(\text{vinyl-H}, \text{s}, 1\text{H})</td>
<td></td>
<td>( \text{N} )</td>
</tr>
</tbody>
</table>

**TABLE XX**

Reactions of Benzonitrile Oxide: Analytical Data

A = 5-Substituted Adducts; B = 4-Substituted Adducts
### TABLE XXI
Reactions of Mesitylnitrile Oxide With Alkenes and Alkynes

**A = 5-Substituted Δ²-Isoxazolines or Isoxazoles**

**B = 4-Substituted Δ²-Isoxazolines or Isoxazoles**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Nitrile Oxide (mmol)</th>
<th>Alkene or Alkyne (mmol)</th>
<th>Reactions Conditions</th>
<th>plc separation Eluent</th>
<th>Dist. Temp. or mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C=CHO-ιBu</td>
<td>91</td>
<td>0.76</td>
<td>0.81</td>
<td>CHCl₃, 25°C, 1 hr</td>
<td>5%</td>
<td>125°C/0.8mm</td>
</tr>
<tr>
<td>H₂C=CH-Ph</td>
<td>96</td>
<td>2.0</td>
<td>2.0</td>
<td>CHCl₃, 35°C, 24 hrs</td>
<td>10</td>
<td>130°C/2.4mm</td>
</tr>
<tr>
<td>H₂C=C(Me)Ph</td>
<td>95</td>
<td>3.0</td>
<td>3.0</td>
<td>CHCl₃, 35°C, 24 hrs</td>
<td>Cryst. from pet. Ether (60°C)</td>
<td></td>
</tr>
<tr>
<td>cis-MeHC=CHPh</td>
<td>88</td>
<td>3.0</td>
<td>3.0</td>
<td>CHCl₃, 85°C, 24 hrs</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>trans-MeHC=CHPh</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-MeHC=CHPh</td>
<td>90</td>
<td>3.0</td>
<td>3.0</td>
<td>CHCl₃, 85°C, 24 hrs</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>trans-MeHC=CHPh</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Time</td>
<td>Tmp</td>
<td>Temp</td>
<td>Product</td>
<td>Yield</td>
<td>Mp</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----</td>
<td>------</td>
<td>---------------------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>( H_2C=CH-CN )</td>
<td></td>
<td>3.0</td>
<td>3.1</td>
<td>( CC_1_4 ), 25°</td>
<td>10</td>
<td>118°/0.8 mm</td>
</tr>
<tr>
<td>( H_2C=CH-SO_2Ph )</td>
<td></td>
<td>2.0</td>
<td>2.0</td>
<td>( CHC_1_4 ), 25°</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>( H_2C=CH-NO_2 )</td>
<td>A</td>
<td>75</td>
<td>3.0</td>
<td>( CC_1_4 ), 25°</td>
<td>10</td>
<td>105°/0.9 mm</td>
</tr>
<tr>
<td>( HC≡C-CN )</td>
<td>A</td>
<td>55</td>
<td>3.0</td>
<td>( CC_1_4 ), 25°</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>( HC≡C-CF_3 )</td>
<td>A</td>
<td>24</td>
<td>2.2</td>
<td>( CC_1_4 ), 25°</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>( NC\ C≡C\ CF_3 )</td>
<td>B</td>
<td>45</td>
<td>0.74</td>
<td>( CDCl_3 ), 25°</td>
<td>20</td>
<td>128°/0.5 mm</td>
</tr>
</tbody>
</table>

a. All reactions were carried out in ~3 ml of solvent.
b. Separations were carried out on plc plates using uv detection. The eluent was X% ethyl acetate in Cyclohexane, v/v.
### TABLE XXII
Reactions of Mesitylnitrile Oxide With Alkenes and Alkynes: Analytical Data

**A = 5-Substituted Λ²-Isoxazolines of Isoxazoles**

**B = 4-Substituted Λ²-Isoxazolines or Isoxazoles**

<table>
<thead>
<tr>
<th>Product</th>
<th>UV Spectrum</th>
<th>NMR Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MeOH</td>
<td>λ max</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂C=CH-i-Bu</td>
<td>not obtained</td>
<td>(CDCl₃); 66.78(Ar-H, s, 2H); 5.42(-CHOBu, J=1.8, 5.0 Hz, 1H); 3.62, 3.20(-OCH₂,dd, J=7.0, 9.5 Hz, 2H); [ABX octet: 3.24(CH-COBu-trans, dd, J=5.0, 17.0 Hz, 1H); 2.72(CHCBOu-cis, dd, J=1.8, 17.0 Hz, 1H); 2.23(p-CH₃, s, 3H); 2.16(o-CH₃, s, 6H); 1.5-2.2(-CH₂Me₂, 1H); 0.91(CMe₂, d, J=6.0 Hz, 6H).</td>
</tr>
<tr>
<td>H₂C=C(Me)Ph</td>
<td>201.3(41,800)</td>
<td>(CDCl₃); 67.62-7.16(phenyl Ar-H, m, 5H); 6.81(mesityl Ar-H, s, 2H); 3.24(CH, s, 2H); 2.24(p-CH₃, s, 3H); 2.10(o-CH₃, s, 6H); 1.81 (-OCH₃, s, 3H).</td>
</tr>
<tr>
<td>H₂C=CH-Ph</td>
<td>199.5(239,000)</td>
<td>(CDCl₃); 7.38(phenyl Ar-H, s, 5H); 6.87 (mesityl Ar-H, s, 2H); 5.74(-OCHPh, dd, J=8.5, 10.5 Hz, 1H); [ABX octet: 3.59(-OCHPh-CH-trans, dd, J=10.5, 17.0 Hz, 1H); 3.05 (O-CPhCH-cis, dd, J=8.5, 17.0 Hz, 1H); 2.26 (p-CH₃, s, 3H); 2.19(o-CH₃, s, 6H).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>cis-MeHC=CH-Ph</strong></td>
<td><strong>A</strong> 201.3(43,000)</td>
<td>(CDCl$_3$):67.36(phenyl Ar-H,s,5H);6.89(mesityl Ar-H,s,2H); 5.78(-OCHPh, d, J=1.00 Hz,1H); 3.78(CHMe, d,q, J=10.0 Hz,1H); 2.27(α-CH$_3$, s,6H); 2.22(p-CH$_3$,s,3H); 0.63(CCH$_3$,d, J=7.5 Hz,3H).</td>
</tr>
<tr>
<td></td>
<td><strong>B</strong> 200.5(140,000)</td>
<td>(CDCl$_3$):7.21(phenyl Ar-H,s,5H);6.76(mesityl Ar-H,s,2H); 5.00(-OCHMe,d,q, J=8.7,6.2 Hz,1H); 4.36(CHPh,d,J=8.7 Hz,1H); 2.27(α-CH$_3$,s,6H); 22.2(p-CH$_3$,s,3H); 1.19(CCH$_3$,d, J=6.2 Hz,3H).</td>
</tr>
<tr>
<td><strong>trans-MeHC=CH-Ph</strong></td>
<td><strong>A</strong> 201.5(43,000)</td>
<td>(CDCl$_3$):67.40(phenyl Ar-H,s,5H);6.88(mesityl Ar-H,s,2H); 5.21(-OCHPh,d,J=8.4 Hz,1H);3.48 (CHMe,d,q,J=8.4,7.0 Hz,1H); 2.20(p-CH$_3$,s,3H); 2.07(α-CH$_3$,s,6H); 1.18(CCH$_3$,d, J=7.0 Hz,3H).</td>
</tr>
<tr>
<td></td>
<td><strong>B</strong> 202.0(68,000)</td>
<td>(CDCl$_3$):67.16(phenyl Ar-H,s,5H);6.74(mesityl Ar-H,s,2H); 4.97(-OCHMe,d,q, J=6.0 Hz,1H); 4.16(CHPh,d,J=6.0 Hz,1H); 2.20(p-CH$_3$,s,3H); 2.07(α-CH$_3$,s,6H); 1.51(CCH$_3$,d, J=6.0 Hz,3H).</td>
</tr>
<tr>
<td><strong>H$_2$C=CH-CN</strong></td>
<td><strong>A</strong> 197.5(142,000)</td>
<td>(CCl$_4$):66.84(Ar-H,s,2H);5.27(CHCN,dd, J=6.0, 9.0 Hz,1H); ABX octet: 3.60(CHCCN-trans,dd, J=9.0,17.0 Hz,1H); 3.24(CHCCN-cis,dd, J=6.0, 17.0 Hz,1H); 22.4(p-CH$_3$,s,3H); 2.17(α-CH$_3$,s,6H).</td>
</tr>
<tr>
<td><strong>H$_2$C=CH-SO$_2$Ph</strong></td>
<td><strong>A</strong> (CHCl$_3$):2405 (5,700)266.0(2,300); 273.5(1,730)</td>
<td>(CDCl$_3$):67.3-8.3(phenyl Ar-H,m,5H);6.83 (mesityl Ar-H,s,2H); 5.53(CHSO$_2$Ph,dd,J=6.5,9.0 Hz,1H); ABX octet: 3.70(CHCSO$_2$Ph-cis,dd,J=6.5, 19.5 Hz,1H); 3.65(CHCSO$_2$Ph-trans,dd,J=9.5,19.5 Hz,1H); 2.23(p-CH$_3$,s,3H); 2.14(α-CH$_3$,s,6H).</td>
</tr>
<tr>
<td>Compound</td>
<td>Location</td>
<td>Spectral Data</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>H₂C=CH-SO₂Ph</td>
<td>B</td>
<td>(CHCl₃): 238.0(8,800); 240.5(8,450); 252.0 (7,650)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CDCl₃): 67.27.7(phenyl Ar-H, m, 5H); 6.69 (mesityl Ar-H, s, 2H); ABX octet: 5.22(CH CSO₂Ph-cis, dd, J=6.0, 13.5 Hz, 1H); 4.73 (CHCSO₂Ph-trans, dd, J=11.0, 13.5 Hz, 1H); 5.17(CHSO₂Ph, dd, J=6.0, 11.0 Hz, 1H); 2.22 (o-CH₃, s, 6H); 2.18 (p-CH₃, s, 3H).</td>
</tr>
<tr>
<td>H₂C=CH-NO₂</td>
<td>A</td>
<td>197.5(178,000)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>(CDCl₃): 56.80(Ar-H, s, 2H); 6.09(CHNO₂-dd, J=3.0, 7.0 Hz, 1H); ABX octet: 3.85(CHCNO₂-trans, dd, J= 7.0, 19.0 Hz, 1H); 3.45(CHCNO₂-cis, dd, J=3.0, 19.0 Hz, 1H); 2.23(p-CH₃, s, 3H); 2.09(o-CH₃, s, 6H).</td>
</tr>
<tr>
<td>H₃C-C-CN</td>
<td>A</td>
<td>197.5(712,000)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>(CDCl₃): 58.93(vinyl-H, s, 1H); 6.90(Ar-H, s, 2H); 2.30(p-CH₃, s, 3H); 2.09(o-CH₃, s, 6H).</td>
</tr>
<tr>
<td>NC</td>
<td>CF₃</td>
<td>not obtained</td>
</tr>
<tr>
<td>F₃C-CN</td>
<td></td>
<td>(CDCl₃): 66.99(Ar-H, s, 2H); 2.31(o-and p- CH₃, s, 9H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C₆D₆): 6.40(Ar-H, s, 2H); 2.06(o-CH₃, s, 6H); 191(p-CH₃, s, 3H).</td>
</tr>
<tr>
<td>H₃C-C-F₃</td>
<td>A</td>
<td>not obtained</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>(CDCl₃): 66.93(Ar-H, s, 2H); 6.61(vinyl-H, s, 1H); 2.31(p-CH₃, s, 9H); 2.11(o-CH₃, s, 6H).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CDCl₃): 68.84(vinyl-H, s, 1H); 6.92(Ar-H, s, 2H); 2.30(p-CH₃, s, 3H); 2.04(o-CH₃, s, 6H).</td>
</tr>
<tr>
<td>Product</td>
<td>Mass Spectral Data</td>
<td>Elemental Analysis</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>( \text{H}_2\text{C}^=\text{CH-O-\text{Bu}} ) A</td>
<td>( \text{M}^+ ), 261(64);189(100);162(47);161(22);160(47);159(33);146(19);145(22);131(16);120(16);91(19);57(44);41(34).</td>
<td>( \text{C}<em>{16}\text{H}</em>{23}\text{NO}_2 ) Calcd: C,73.53;H,8.87 Found: C,73.62;H,9.02</td>
</tr>
<tr>
<td>( \text{H}_2\text{C}^=\text{CH-Ph} ) A</td>
<td>( \text{M}^+ ), 265(91);250(17);248(31);161(100);159(31);158(24);145(25);144(24);130(30);115(18);105(24);104(31);91(51);77(36);51(18).</td>
<td>( \text{C}<em>{16}\text{H}</em>{19}\text{NO} ) Calcd: C,81.48;H,7.22 Found: C,80.98;H,7.16</td>
</tr>
<tr>
<td>( \text{H}_2\text{C}^=\text{C(\text{Me})Ph} ) A</td>
<td>( \text{M}^+ ), 279(89);264(95);161(100);159(32);158(25);118(68);117(31);115(23);105(100);103(28);91(42);77(65);51(23).</td>
<td>( \text{C}<em>{18}\text{H}</em>{21}\text{NO} ) Calcd: C,81.68;H,7.58;N,5.01 Found: C,81.63;H,7.29;N,4.90</td>
</tr>
<tr>
<td>( \text{cis-\text{MeHC=CHPh}} ) A</td>
<td>( \text{M}^+ ), 279(43);202(42);173(28);172(31);161(21);158(59);140(20);130(26);118(79);117(59);115(34);105(44);103(26);91(100);78(30);77(100).</td>
<td>( \text{C}<em>{18}\text{H}</em>{21}\text{NO} ) Calcd: C,81.68;H,7.58;N,5.01 Found: C,81.81;H,7.53;N,4.98</td>
</tr>
<tr>
<td>B</td>
<td>( \text{M}^+ ), 279(36);264(31);235(21);161(24);145(94);134(34);130(100);118(56);117(35);105(38);91(60);90(67);89(39);77(38);51(28).</td>
<td>( \text{C}<em>{19}\text{H}</em>{21}\text{NO} ) Calcd: C,81.68;H,7.58;N,5.01</td>
</tr>
</tbody>
</table>
| trans=MeHC=CHPh | A | \( \mathrm{H^+}, 279(4); 145(92); 134(35); 130(100); 118(34); 117(28); 105(42); 91(53); 89(38); 77(33); 63(23); 51(34). \) | \( \text{C}_{13}\text{H}_{21}\text{NO} \)  
Calcd: C, 81.68; H, 7.58; N, 5.01  
Found: C, 81.66; H, 7.69; N, 4.84 |
|---|---|---|---|
| B | \( \mathrm{H^+}, 279(31); 264(24); 235(16); 161(18); 145(34); 130(40); 119(17); 118(100); 117(29); 105(15); 91(38); 90(29); 89(19); 77(18); 51(14). \) | \( \text{C}_{13}\text{H}_{21}\text{NO} \)  
Calcd: C, 81.68; H, 7.58; N, 5.01  
Found: C, 82.10; H, 7.51; N, 5.01 |
| H\(_2\)C=CH-CN | A | not obtained | \( \text{C}_{13}\text{H}_{14}\text{N}_{2}\text{O} \)  
Calcd: C, 72.87; H, 6.59  
Found: C, 73.05; H, 6.70 |
| H\(_2\)C=CH-NO\(_2\) | A | not obtained | \( \text{C}_{13}\text{H}_{14}\text{N}_{2}\text{O} \)  
Calcd: C, 81.53; H, 6.02  
Found: C, 61.65; H, 6.11 |
| H\(_2\)C=CH-SO\(_2\)Ph | A | \( \mathrm{H^+}, 329(8); 188(100); 160(14); 158(19); 146(25); 145(25); 144(15); 130(12); 119(22); 91(19); 77(23); 51(10). \) | \( \text{C}_{15}\text{H}_{19}\text{NO}_{3}\text{S} \)  
Calcd: C, 65.63; H, 5.81; N, 4.25  
Found: C, 65.66; H, 5.76; N, 4.13 |
| B | not obtained | \( \text{C}_{15}\text{H}_{19}\text{NO}_{3}\text{S} \)  
Calcd: C, 65.63; H, 5.81; N, 4.25  
Found: C, 65.37; H, 5.72; N, 4.09 |
<p>| NC-(\text{CF}_3)- | | ( \mathrm{H^+}, 375(23); 286(24); 279(26); 183(16); 161(72); 145(40); 130(37); 115(20); 91(40); 77(28); 69(100). ) | Analysis not obtained |</p>
<table>
<thead>
<tr>
<th>TABLE XXIII (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC≡C-CN</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
TABLE XXIV
Reactions of $p$-Nitrobenzonitrile Oxide
A = 5-Substituted Adducts; B = 4-Substituted Adducts

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Nitrile Oxide (mmol)</th>
<th>Alkene or Alkyne (mmol)</th>
<th>Reaction Conditions</th>
<th>Solvent recryst. from</th>
<th>mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$C=CH-NO$_2$ A</td>
<td>80</td>
<td>5.0</td>
<td>5.0</td>
<td>Et$_2$O, 25 2 hrs</td>
<td>Acetone</td>
<td>143-144°d</td>
</tr>
<tr>
<td>H$_2$C=CH-SO$_2$Ph A</td>
<td>84</td>
<td>10.0</td>
<td>11.0</td>
<td>Et$_2$O, 25 3 hrs</td>
<td>Acetone</td>
<td>178-179°d</td>
</tr>
<tr>
<td>HC=CH-CN</td>
<td></td>
<td>90</td>
<td>5.0</td>
<td>Et$_2$O, 25 1 hr</td>
<td>Acetone</td>
<td>--</td>
</tr>
<tr>
<td>A</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td>Acetone</td>
<td>112-113°d</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>not isolated</td>
<td>--</td>
</tr>
</tbody>
</table>

a. See Section III C for experimental details.
### TABLE XXV

Reactions of **p**-Nitrobenzonitrile Oxide: Analytical Data

**A** = 5-Substituted Adducts; **B** = 4-Substituted Adducts

<table>
<thead>
<tr>
<th>Product</th>
<th>NMR Spectrum</th>
<th>Mass Spectral Data</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H₂C=CH-NO₂ A</strong></td>
<td>(Acetone-d₆): (A₂B₂ pattern: 6A=8.39, 6B=8.09, JₐB=9.0 Hz, 4H); 6.75(CHNO₂, dd, J=5.0, 6.2 Hz, 1H); ABX octet: 4.55(CH-CN-O₂-trans, dd, J=6.2, 19.0, 1H); 4.23(CH-CN-O₂-cis, dd, J=5.0, 19.0, 1H)</td>
<td>M⁺, 237(0.1); 190(100); 189(52); 148(16); 143(19); 116(18); 102(34); 90(20); 89(51); 76(36); 75(37); 74(16); 63(27); 62(17); 51(23); 50(41).</td>
<td>C₅H₅N₃O₅</td>
</tr>
<tr>
<td><strong>H₂C=CH-SO₂Ph A</strong></td>
<td>(Acetone-d): (A₂B₂ pattern: 6A=8.29, 6B=7.93, JₐB=9.0 Hz, 4H); 7.50-8.13 (phenyl Ar-H, m, 5H); 5.98(CHSO₂Ph, t, J=7.8 Hz, 1H); 4.13(CH₂SO₂Ph, dd, J=7.8 Hz, 2H)</td>
<td>M⁺, 332(0.1); 191(100); 190(54); 189(36); 163(57); 145(21); 117(61); 89(31); 78(35); 77(62); 76(40); 75(22); 51(29).</td>
<td>C₁₅H₁₁N₂O₅S</td>
</tr>
<tr>
<td><strong>HC≡C-CN A</strong></td>
<td>(Acetone-d₆): (A₂B₂ pattern: 6A=8.42, 6B=8.21, JₐB=9.0 Hz, 4H); 8.10(vinyl-H, s, 1H)</td>
<td>M⁺, 237(0.1); 190(100); 189(52); 148(16); 143(19); 116(18); 102(34); 90(20); 89(51); 76(36); 75(37); 74(16); 63(27); 62(17); 51(23); 50(41).</td>
<td>C₁₉H₅N₃O₅</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Product</th>
<th>NMR Spectrum</th>
<th>Mass Spectral Data</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H₂C=CH-NO₂ B</strong></td>
<td>(Acetone-d₆): (A₂B₂ pattern: 6A=8.38, 6B=8.16, JₐB=9.0 Hz, 4H); 9.77(vinyl-H, s, 1H)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>H₂C=CH-SO₂Ph B</strong></td>
<td>(Acetone-d): (A₂B₂ pattern: 6A=8.39, 6B=8.09, JₐB=9.0 Hz, 4H); 6.75(CHNO₂, dd, J=5.0, 6.2 Hz, 1H); ABX octet: 4.55(CH-CN-O₂-trans, dd, J=6.2, 19.0, 1H); 4.23(CH-CN-O₂-cis, dd, J=5.0, 19.0, 1H)</td>
<td>M⁺, 237(0.1); 190(100); 189(52); 148(16); 143(19); 116(18); 102(34); 90(20); 89(51); 76(36); 75(37); 74(16); 63(27); 62(17); 51(23); 50(41).</td>
<td>C₅H₅N₃O₅</td>
</tr>
<tr>
<td><strong>HC≡C-CN B</strong></td>
<td>(Acetone-d₆): (A₂B₂ pattern: 6A=8.42, 6B=8.21, JₐB=9.0 Hz, 4H); 8.10(vinyl-H, s, 1H)</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
REFERENCES


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references therein.

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Nmr Spectra of Compounds Number 32c and 33c.
Nmr Spectra of Compounds Number 34a and 35a.
NMR Spectrum of Compound Number 36.
Nmr Spectrum of Compound Number 43.
Nmr Spectrum of 5-Benzenesulfonyl-3-p-nitrophenylisoxazoline.
Ir Spectrum of Compound Number 29c.
$\text{Ir Spectrum of Compound Number 31.}$
Yau-Min Chang was born March 25, 1944 in Chiayi, Taiwan. He was educated in Chiko Elementary School and graduated from Chiayi High School in 1962. He attended Taiwan Christian College in Chung-Li from 1963 to 1964, and transferred to Chung Hsing University in Taichung from which he received his Bachelor of Science degree in 1968. He was commissioned as a second lieutenant in The Chinese Air Force and completed his military service in July of 1969. He attended the Graduate School of the University of Detroit in Detroit, Michigan in 1969 and transferred to the Graduate School of the Louisiana State University in Baton Rouge, Louisiana in 1971. He is currently a candidate for the degree of Doctor of Philosophy in the Department of Chemistry, Louisiana State University.

He married Celia Hui-Fen Shih in 1971, and they are the parents of a son, Kevin Jeffrey Chang, who is one year old.
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Major Field: Chemistry

Title of Thesis: 1,3-Dipolar Cycloadditions of Nitrones and Nitrile Oxides

Approved:

[Signature]
Major Professor and Chairman

[Signature]
Dean of the Graduate School

EXAMINING COMMITTEE:

[Signature]

[Signature]

[Signature]

Date of Examination:

September 22, 1975