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Synthesis of Boron-Substituted Isoxazolidines by Reaction of Nitrones with Alkenyl Boronate Esters

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Synthesis of Boron-Substituted Isoxazolidines by Reaction of Nitrones with Alkenyl Boronate Esters

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Masters of Arts

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Kevin P. Gwaltney

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Approval Sheet

This Thesis is submitted in partial fulfillment of

the requirements for the degree of

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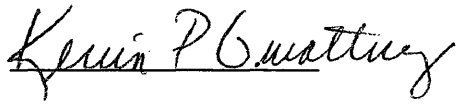

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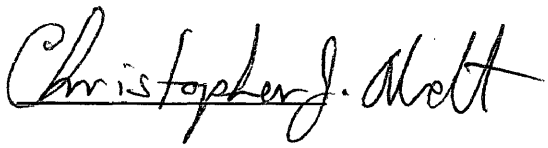
August 18, 1993



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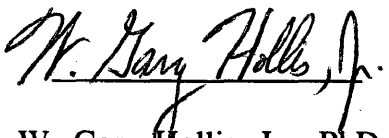

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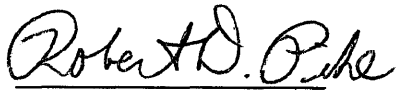

Robert D. Pike, PhD.

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Abstract

1,3-Dipolar cycloaddition was carried between E-B-(1-hexenyl)-1,3-dioxaborolane and 2,3,4,5-tetrahydropyridine-N-oxide. The starting materials were synthesized and fully characterized. Attempts were made to isolate the isoxazolidine product of the cycloaddtion, and these products were partially characterized.

Introduction

The 1,3-dipolar cycloaddition will be examined as an invaluable tool for the formation of heterocycles. The general characteristics of 1,3-dipoles and their participation in cycloadditions will be reviewed, and nitrones will be used as a representative, yet distinct, class of 1,3-dipole. The novelty of this research, however, arises from the creation of boron-substituted isoxazolidines via 1,3-dipolar cycloadditions of alkenyl boronate esters with nitrones. Additionally, hydroboration will be examined as the mode of production of alkenyl boronates.

1,3-Dipolar cycloaddition

The 1,3-dipolar cycloaddition is a [4πs+2πs] addition akin to the well known Diels-Alder reaction. The dipolar cycloaddition differs from the Diels-Alder in that the four electrons of the dipole, analogous to a Diels-Alder diene, are contained in a three atom sequence. These three atoms contain at least one heteroatom and exist in zwitterionic forms as shown in Figure 1 with nitrous oxide as an example. This

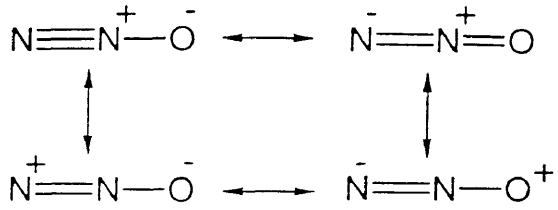


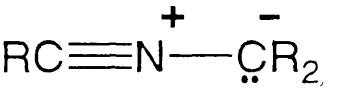
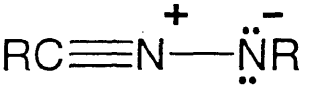
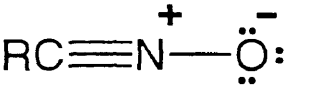
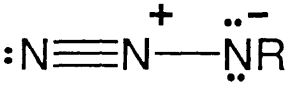
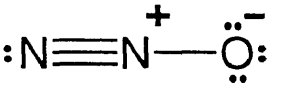
FIGURE 1

structure has several important resonance forms which are also contained in the figure. The name of these compounds originates from the location of the negative charge in the top structures above. These two are the predominant contributors to reactivity and structure because each atom has an octet of electrons while the other two forms leave one atom with a sextet. The two major classes of dipoles are propargyl-allenyl and allyl which are named for the hydrogen carbon analogues that they resemble. Examples of these are shown in Table 1. The reactivity of 1,3-dipoles can be mostly justified by the nucleophilic and electrophilic character of their termini as displayed by the resonance contributors shown earlier. Many of the 1,3-dipoles are unstable or so reactive that they only exist as *in situ* intermediates.(1)

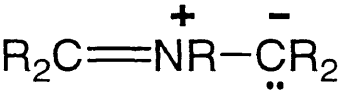
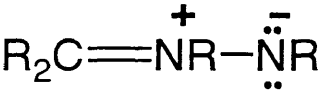
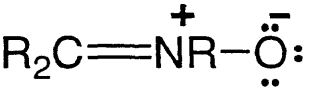
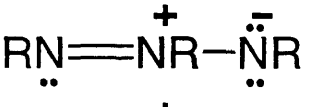
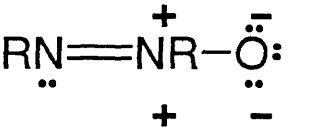
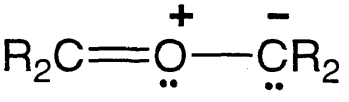
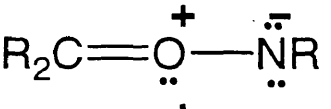
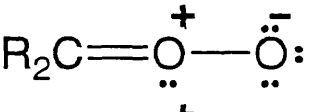
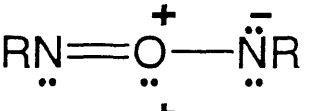
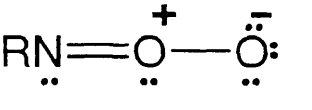
The general 1,3-dipolar cycloaddition occurs between almost any 1,3-dipole

TABLE 1: 1,3-DIPOLES

PROPARGYL-ALLENYL

NITRILE YLIDES	
NITRILE IMINES	
NITRILE OXIDES	
AZIDES	
NITROUS OXIDE	

ALLYL

AZOMETHINE YLIDES	
AZOMETHINE IMINES	
NITRONES	
AZIMINES	
AZOXY COMPOUNDS	
CARBONYL YLIDES	
CARBONYL IMINES	
CARBONYL OXIDES	
NITROSIMINES	
NITROSOXIDES	

and most species containing a multiple bond as shown in Figure 2. The mechanism

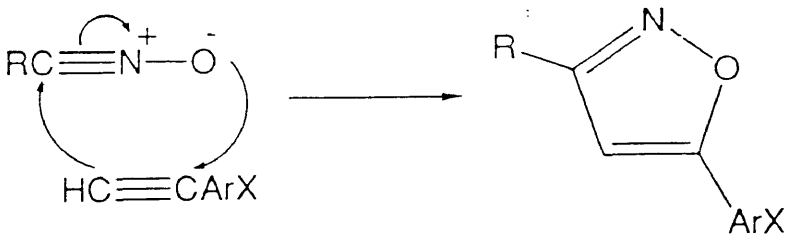


FIGURE 2

is generally accepted to be a concerted process.(1) Another possibility would be a radical mechanism as proposed by Firestone.(2) He suggested that the key intermediate in the cycloaddition is a diradical containing partial charges in an attempt to better explain the transition state, as seen in Figure 3. This explanation

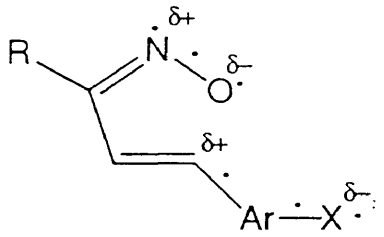


FIGURE 3

has been refuted because it falls short in its explanation of the stereospecifity of the cycloaddition. Also, data from carbon-14 isotope effects confirmed the concerted process and were contrary to the diradical mechanism in several 1,3-dipolar cycloadditions.(3)

Dipolar cycloadditions to alkenes have been experimentally proven to occur through stereospecific suprafacial addition. Solvent selection typically does not affect rates significantly. This experimental observation supports the concerted mechanism since the alternative intermediate- containing mechanism would require

solvents which can stabilize separated charges. The additions typically show small activation enthalpies and large negative activation entropies. Dipoles can also undergo [4πs+6πs] additions to trienes but not [4πs+4πs], which further strengthens the case for a concerted mechanism since the latter is not allowed by a concerted process.(4)

Frontier molecular orbital theory: Woodward-Hoffman rule

Molecular orbital theory has become a dominant factor in investigating reactions, especially rates and regio- and stereoselectivity. The concerted dipolar cycloaddition can be better understood by considering molecular orbital theory. A major rule governing reactivity in pericyclic reactions is known as the Woodward-Hoffman rule. This rule states, "A ground-state pericyclic change is symmetry-allowed when the total number of (4q+2)s and (4r)a components is odd."(5b) Concerted thermal cycloadditions all follow this rule. To further clarify, q and r must be whole numbers. For a reaction to be allowed thermally, the sum of the components which react with suprafacial symmetry having a number of π-electrons which fit the equation 4q+2, and which react with antarafacial symmetry having a number of π-electrons which fit the equation 4r, must be odd. The mode of addition can be determined by examining the products of the reaction. Again, this rule applies for thermal reactions, while photopericyclic reactions are allowed when the sum of the components is even.(5a)

The 1,3-dipolar cycloaddition can be examined using the Woodward-Hoffman

rule. This process has two suprafacial components; bond formation is occurring from the same side of each π-system. One component contains four π-electrons and the other contains two π-electrons. Thus, the 1,3-dipolar cycloaddition is allowed by the Woodward-Hoffman rule because it has one (4q+2)s component, 4*0+2 electrons, and no (4r)a components. The [2πs+2πa] cycloaddition is an example of an allowed process containing an antarafacial component. Here, there are two systems containing two π-electrons, one reacts suprafacially and one reacts antarafacially. Again, the system has one (4q+2)s component and no (4r)a components. However, geometric constraints prevent this reaction from occurring in a concerted manner under thermal conditions.

Frontier orbitals: reaction rates

With the advent of frontier molecular theory, the study of pericyclic processes has been simplified and improved greatly. Here, the frontier orbitals are considered to dominate in bond forming processes thus allowing the other orbitals to be ignored.(5c) These orbitals are the HOMO (highest occupied molecular orbital) and the LUMO (lowest unoccupied molecular orbital). The importance of the frontier orbitals is that they produce the greatest stabilizing interaction between the reacting components. In this way, they eclipse all other orbital interactions therefore having a determining effect on the reaction's outcome. One should note that other orbital interactions between the reactants produce destabilization or reduced stabilization. Figure 4 shows the stabilization of the electrons by removal

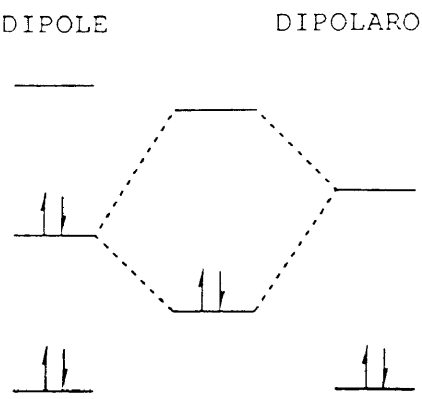


FIGURE 4

to a lower energy orbital created by a HOMO-LUMO interaction of the reactants. This is termed the perturbation of the orbitals supplying two new molecular orbitals, one of higher energy and one of lower energy than the orbitals of the reactants.(5d) The extent of stabilization is determined by the total overlap of the orbitals and the energy difference between the orbitals.

Perturbation theory treats the newly forming molecular orbitals as combinations of the orbitals from the reactants. From examination of the perturbations, the slope of the first portion of the reaction path can be estimated. The nature of the transition state can be predicted by extrapolation to produce a possible reaction diagram. This is especially true for exothermic reactions. For, as the Hammond postulate states, there is a reactant-like transition state in exothermic reactions and a product-like transition state for endothermic reactions.(5e) If the relative energies of the reactants and products are known, the accuracy of the reaction diagram can be increased significantly. Thus, two different pathways from a given set of reactants can be compared, and an estimation of preferred products

can be made rather confidently. In addition, an equation has been formulated to estimate the energy change associated with the overlap of the orbitals of the reactants. For this discussion, a summary of the forces involved in the overlap when reactants collide, as presented by Fleming, will suffice.(5a) Fleming stated that occupied orbitals repel one another, positive charge on a molecule attracts negative charge on the other and repels positive charge, and attraction arises from filled/unfilled orbital interactions.

The frontier orbitals for a general 1,3-dipole and alkene are displayed in Figure 5. The HOMO of the dipole can interact with the LUMO of the

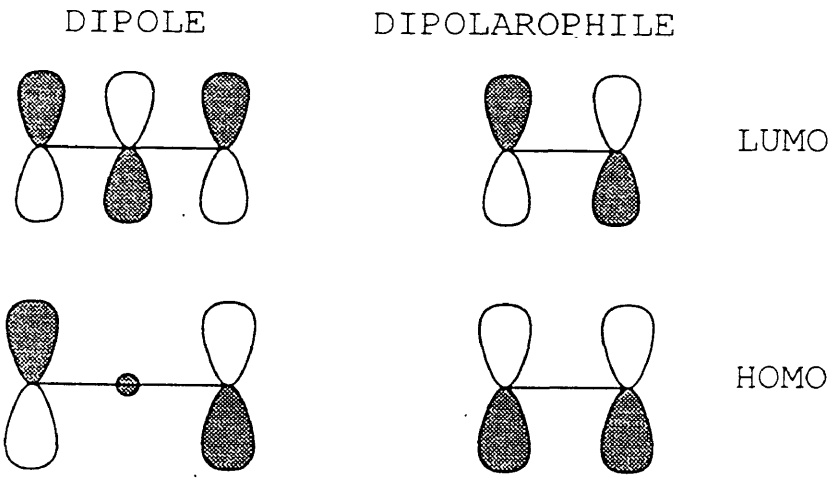


FIGURE 5

dipolarophile or the LUMO of the dipole can interact with the HOMO of the dipolarophile as displayed in Figure 6. The interaction of interest is the HOMO to LUMO with the smallest energy difference between them. The three main types, as proposed by Sustmann(6), are named for the dipole orbital which is involved in this

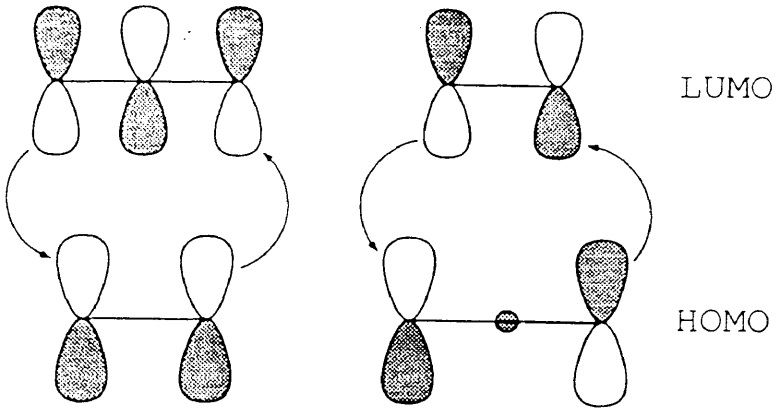


FIGURE 6

interaction. These are HOMO control, HOMO-LUMO control and LUMO control or Type I, II and III, Figure 7. In Type III reactions, the control is effected by

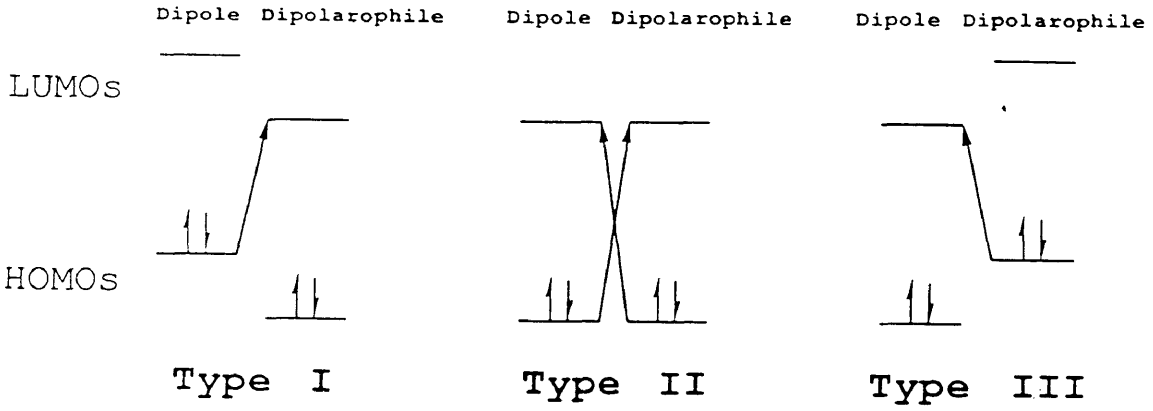


FIGURE 7

small deviations in the HOMOs and LUMOs since the energy differences are of very similar magnitude. Rates can be examined by using the energy gap between the interacting orbitals as an indicator. The gaps are fully dependent on the dipole in use and the substituents on the dipole and dipolarophile. In order to increase

reactivity, the energy difference must be decreased by raising the HOMO or lowering the LUMO. Since the HOMOs vary most, they can be used to give an estimate of reactivity of a particular 1,3-dipole. Figure 8 demonstrates the variety

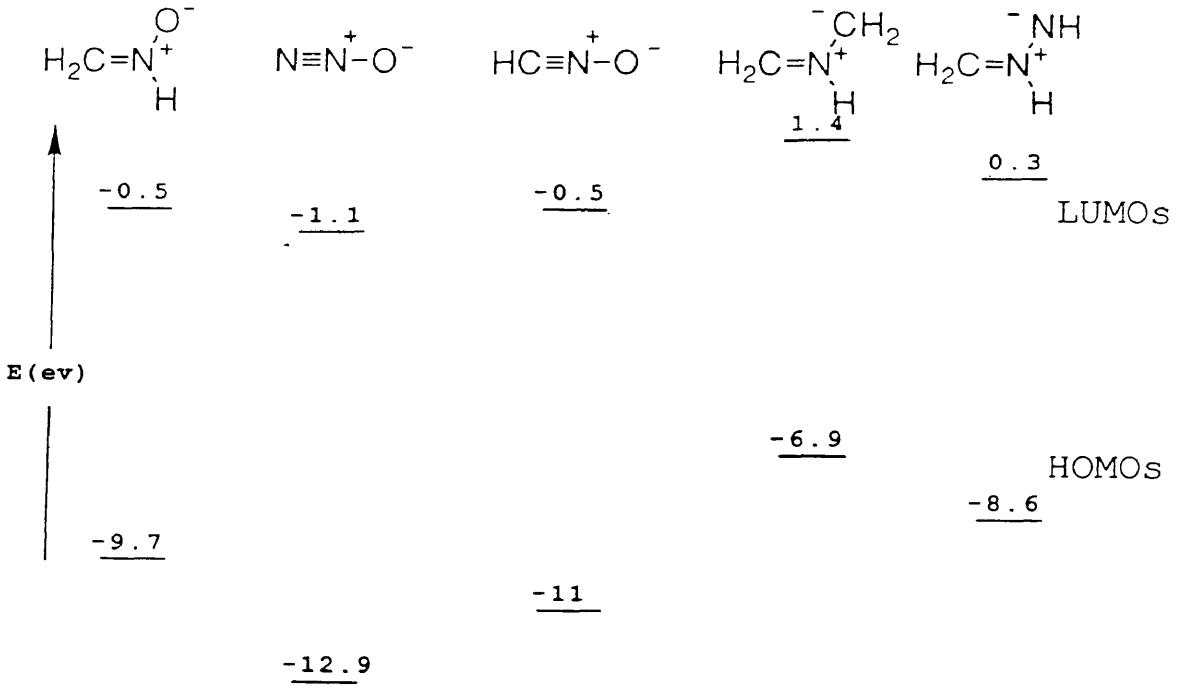


FIGURE 8

of π-system energies associated with some common dipoles. Substituents typically reduce the HOMO\LUMO energy difference when compared to unsubstituted cases. Normally, electron donating groups raise an orbital's energy and electron withdrawing substituents lower it. Rates can also be increased by using a more strained dipolarophile, by conjugated systems, by electron-withdrawing substituents and in some specific cases, by electron-donating substituents.(7)

Frontier orbitals: regiochemistry and stereochemistry

Once one has determined which orbitals are most likely to interact, the

regiochemistry and stereochemistry can be better understood and predicted. First, the dipolar cycloaddition must proceed through syn addition with respect to the dipolarophile which is mandated by its concerted mechanism. The reaction is restricted to syn addition by its concerted suprafacial/suprafacial nature. This results in two possible orientations, again borrowing from the more popular Diels-Alder, named endo and exo. An example of these is demonstrated in Figure 9. Here, one

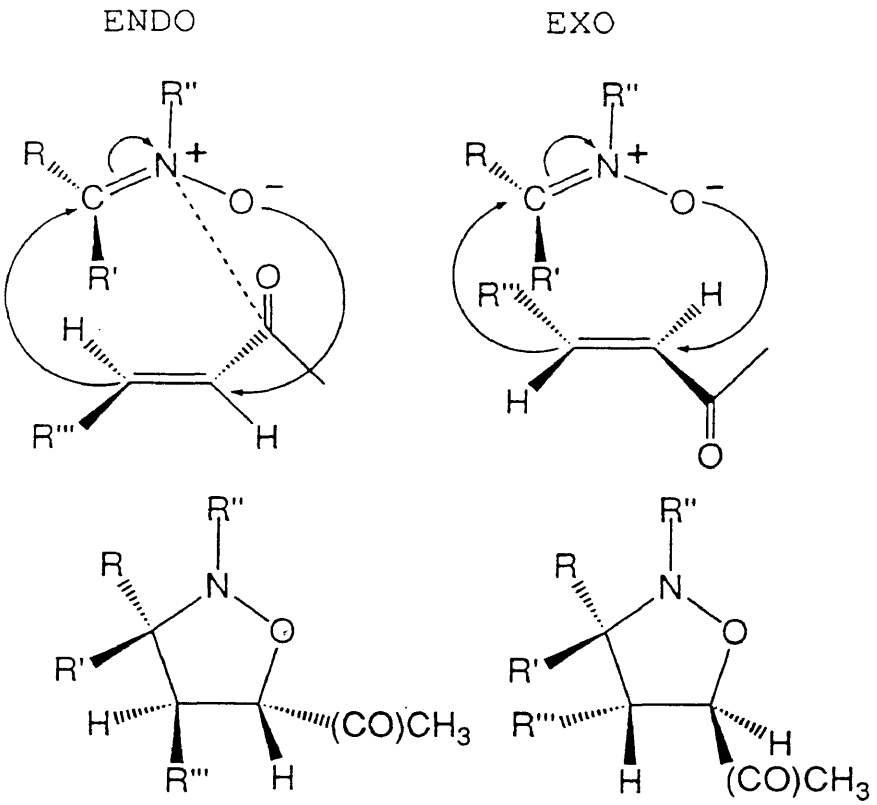


FIGURE 9

can see that there exists a secondary orbital interaction in the first reaction, indicated by the dashed line from the π-orbital of the dipole to the π-system the carbonyl. The products resulting from both reactions are also demonstrated.

The regiochemical outcome in dipolar cycloadditions can also be predicted by considering the frontier orbitals involved in the reaction. For the dipolar cycloaddition, there are two regioisomers per face of the dipolarophile, as shown for one face in Figure 10. The orbitals must be examined closely because the

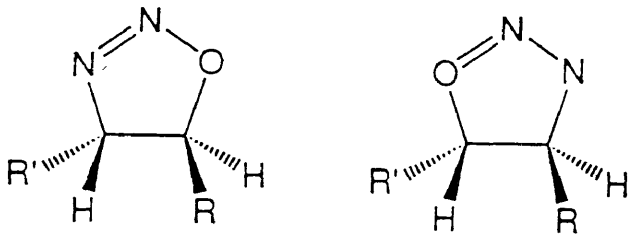


FIGURE 10

regioselectivity is determined by the orbital coefficients of the principal HOMO and LUMO combination. Energy differences as small as 0.1 kcal/mol can change the regioselectivity. Since the orbital coefficients can vary widely for both the dipoles and the dipolarophiles, a general qualitative discussion will be used here. The regioselectivity is determined by maximizing the overlap of the dominant pair of frontier orbitals. Consequently, an orbital will interact best with another orbital having a coefficient of similar magnitude, thus maximizing stabilization and therefore reaction. Dipole HOMOs usually have a larger coefficient on the anionic end of the primary resonance form than on the neutral end, leading to sigma bond formation from the anionic terminus to the more electron-deficient terminus of the dipolarophile in the HOMO-controlled case. In the LUMO-controlled case, the LUMO of the dipole almost always has a larger coefficient on the neutral end giving

rise to the substituted terminus of the dipolarophile being attached to the anionic terminus of the dipole. Figure 11 demonstrates orbital coefficients for nitrous

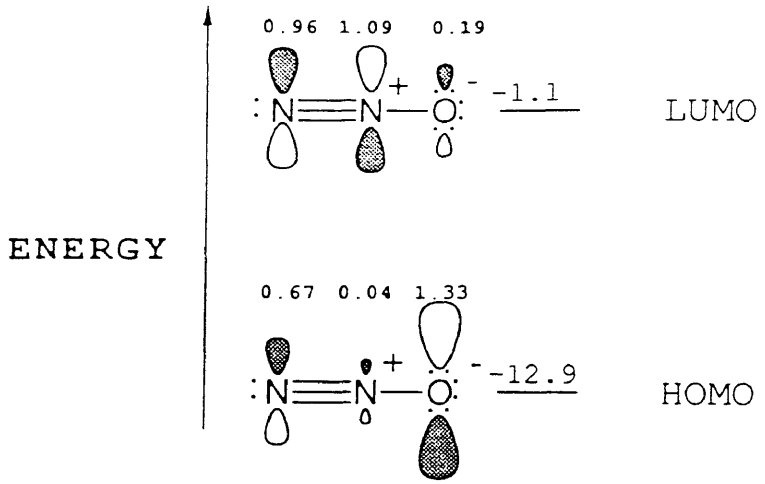


FIGURE 11

oxide.(7) Thus, determining which HOMO-LUMO interaction occurs can allow one to predict the dominant regioisomer of a cycloaddition. However, caution must be exercised in making a definitive prediction without knowing exact properties for a set of compounds. For example, steric interferences can outweigh the mode of reaction predicted by molecular orbital estimates.(4)

Nitrones: preparation

Nitrones are of the general structure $R_2C{=}N(R){\rightarrow}O$ which can also be depicted as $R_2C{=}N^{+}(R)\text{-}O^{-}$ and function quite well as representative 1,3-dipoles. The charges can be delocalized throughout the system, as seen in Figure 1, which contributes significantly to the nitrone's reactivity. The two basic types of nitrones are aldonitrones and ketonitrones depending on whether the α-carbon is monosubstituted or disubstituted as aldehydes or ketones, respectively. Aldonitrones

almost always exist as the Z-isomers due to significant non-bonded interactions between the α-substituent and the oxygen. Z-Isomers in general are more prevalent although a large substituent on the nitrogen can led to E-isomer dominance.(8a)

The preparation of nitrones has been studied extensively. A large number of oxidative pathways exist to produce nitrones from the N,N-disubstituted hydroxylamine, as shown by the general reaction as in Figure 12. One of the

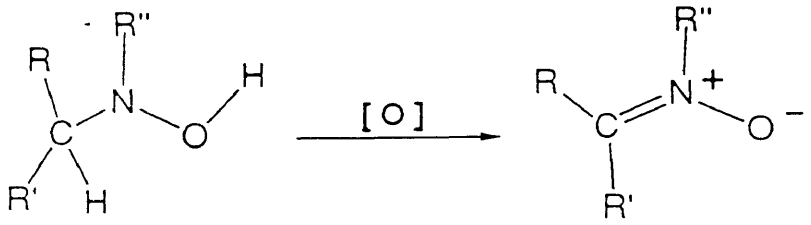


FIGURE 12

earliest methods studied was the bubbling of molecular oxygen through solutions of the hydroxylamines in the presence of aqueous cupric salts.(9) Oxidation can also be performed in alkaline solutions with potassium ferricyanide(10), "active" lead oxide(11), diammino silver nitrate(10), cold potassium permanganate(12), t-butylhydroperoxide(13) or hydrogen peroxide.(14) Yellow mercuric oxide oxidation can be carried out in aqueous acetone suspension or in anhydrous chloroform at room temperature.(15) More recently, N-hydroxy derivatives of cyclic amines have been oxidized electrochemically using halide ion mediators. Also, hydrogen elimination from hydoxylamines has occurred on heating with palladium black to produce the nitrones. In addition, oxidation ensues from reactions with quinones and silver oxide.(16)

Another mode of nitrone production is the reaction of N-substituted hydroxylamines with an aldehyde or ketone, Figure 13, through a condensation

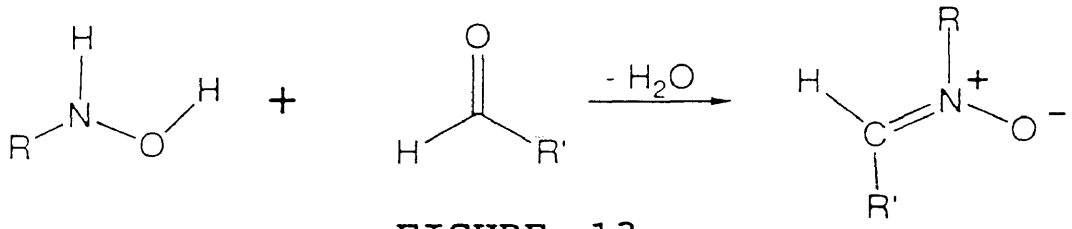


FIGURE 13

reaction. This method works well when the substituents of the carbonyl are not bulky.(17) Nitrones can be prepared by alkylating oximes with haloalkyls, Figure 14.(18) This method, however tends to produce oxime ethers, compound **1**, in

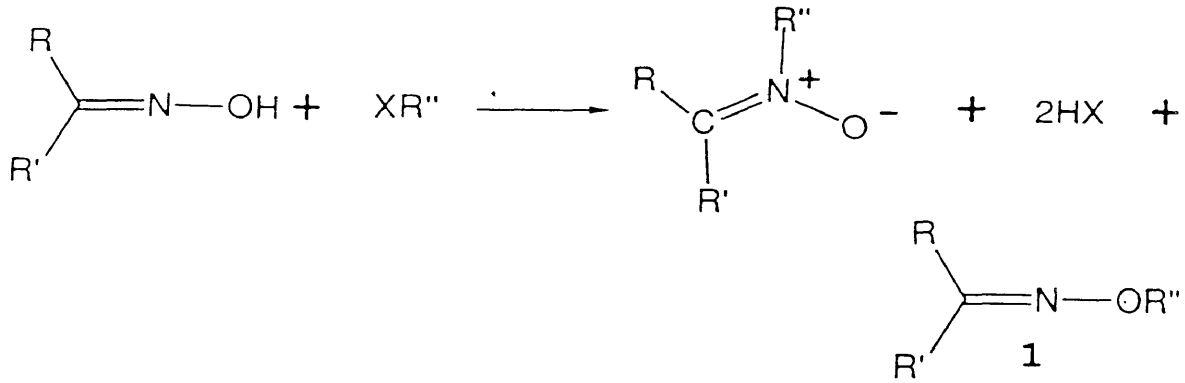


FIGURE 14

competition with the desired nitrones. The yield of nitrones can be increased by using p,p-disubstituted benzophenone oxime salts or smaller alkylating agents such as bromomethane.(16)

Aromatic nitroso compounds provide several methods of nitrone production. When possessing a comparitively acidic methyl substituents, the nitrone can result from catalysis with small amounts of a base such as pyridine, piperidine or sodium

carbonate and reaction with an aromatic nitroso, Figure 15. This method yields a

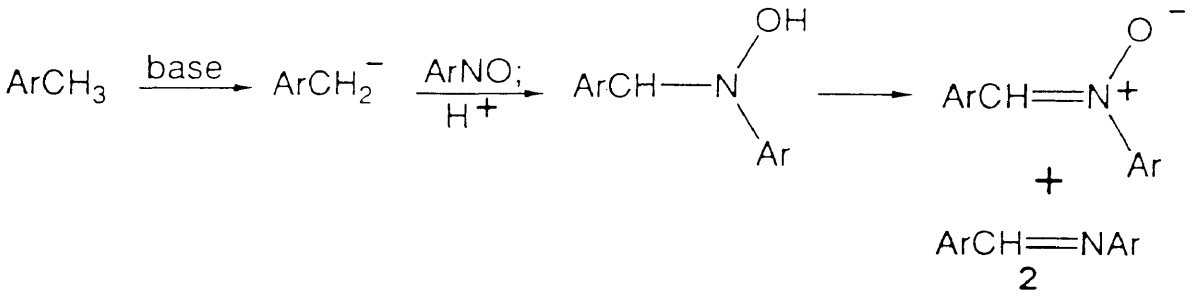


FIGURE 15

nitrone (elimination of HX), imine (elimination of HOX), 2, mixture.(19) With a reactive methylene group, the nitrone can be produced by two methods. First, pyridinium salts can be converted by weak base and reaction with aromatic nitrosos to nitrones, as in Figure 16, producing products uncontaminated by imines.(20)

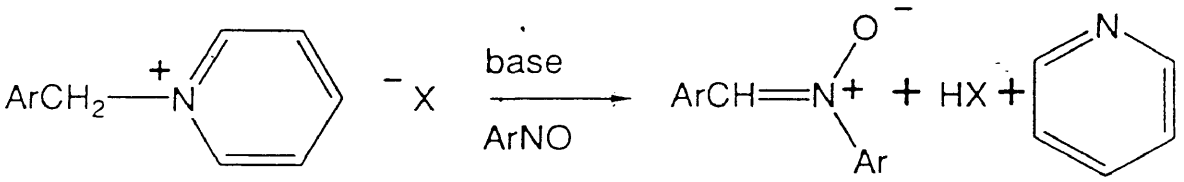


FIGURE 16

Also, treating benzyl derivatives with weak base at low temperature favors production of the nitrone over the imines, Figure 17.(21) Some diazo compounds,

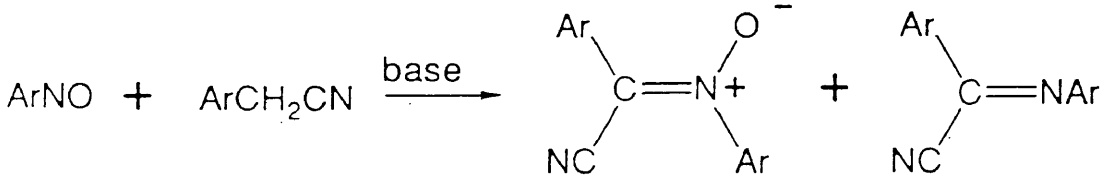


FIGURE 17

sulfur ylides, alkenes and alkynes produce nitrones in reactions with aromatic

nitroso compounds, also.(18,22)

Nitrones: spectroscopy

Nitrones can be characterized by many spectroscopic techniques. In infrared spectroscopy, the N→O stretching appears at 1200 to 1300 cm^{-1} for aromatic ketonitrones and 1050 to 1170 cm^{-1} for aldonitrones. The C=N stretching can be seen 1550 to 1600 cm^{-1} for aromatic nitrones and 1570 to 1620 cm^{-1} for aliphatic and alicyclic nitrones. In the proton-NMR, shifts for the α hydrogen of 7 to 8 ppm for α-aryl substituted and 6.4 to 6.7 ppm for α-alkyl substituted are typical. For α-substituents, the shifts are normally near 2 ppm, while the N-substituents are found to have shifts of 3.4 to 5 ppm. Most nitrones contain an M-16 peak resulting from the loss of oxygen in mass spectra.(8a)

Nitrones: reactions

Nitrones have proved useful as general synthetic tools in many reactions other than the 1,3-dipolar cycloaddition. Nitrones are quite susceptible to many types of rearrangement reactions. In certain stabilized cases, oxime O-ethers can be formed by a Martynoff rearrangement, Figure 18.(8b) Another similar case

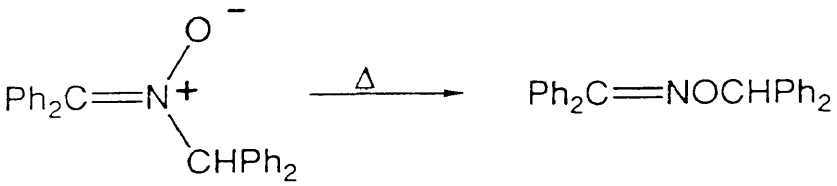


FIGURE 18

involves formation of an oxaziridine ring upon irradiation as seen in Figure 19.(8c)

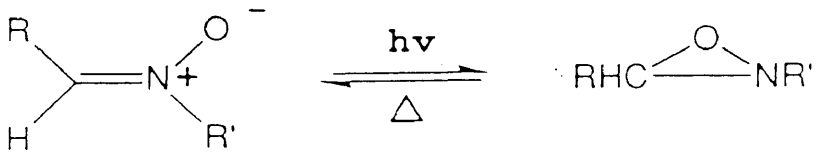


FIGURE 19

Further reactions from this active heterocycle can give alkyl shifts to form beta-lactams and various other amides depending on the substituents, Figure 20.(8d) Base catalyzed removal of water by means of a sodium alkoxide or other reactive

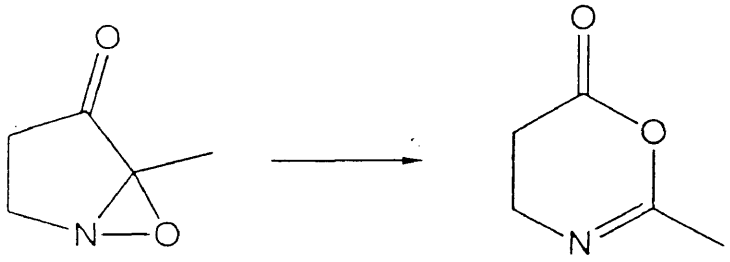


FIGURE 20

organic base followed by hydroxide attack and protonation produces a variety of amides, Figure 21.(8e) Nitrones for which the parent aldehyde contains an electron-

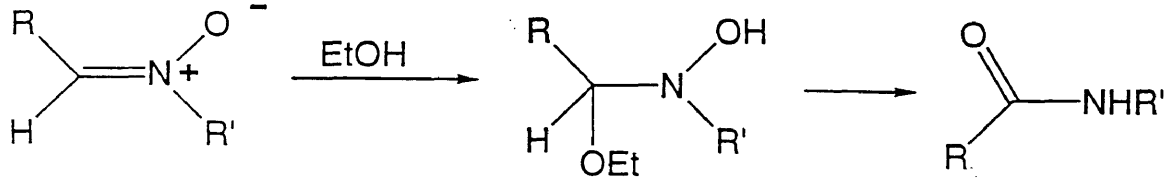


FIGURE 21

withdrawing group can also yield alkenes through a process similar to a Cope elimination, Figure 22.(8f) Nitrones can be further oxidized by a number of oxidizing agents to several α-carbonyl amine ethers and other species, Figure

23.(8a)

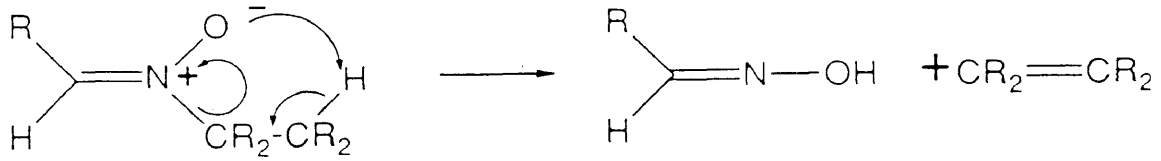


FIGURE 22

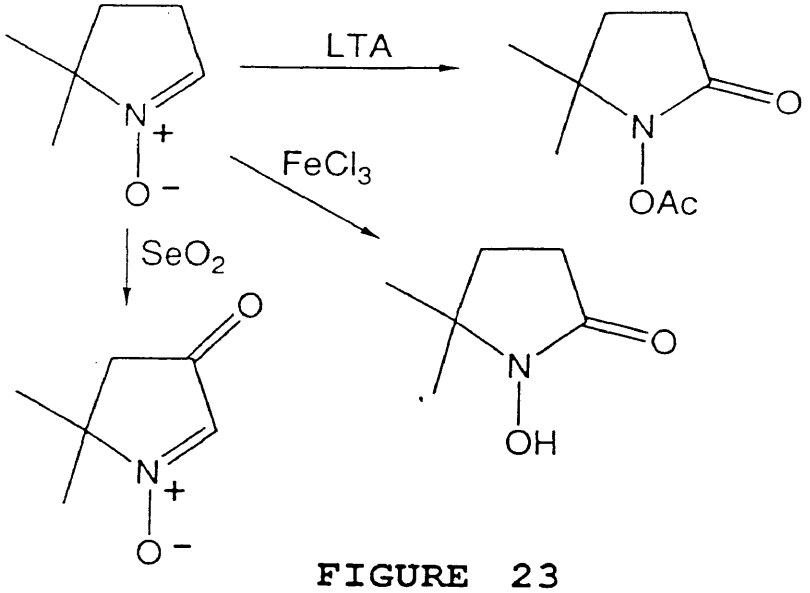


FIGURE 23

In addition, there are several reduction pathways available to nitrones. For instance, they are easily converted to radical anions by sodium metal, Figure 24.

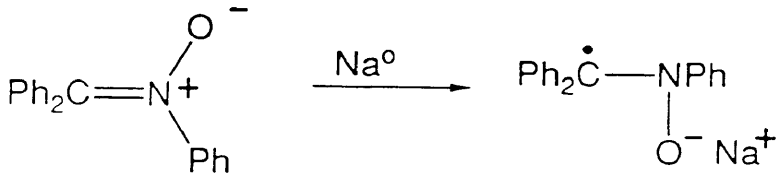


FIGURE 24

The oxygen can be removed from the nitrone to form a variety of amines.(8g) Nitrones react with lithium aluminum hydride, among other hydrides, resulting in

substituted hydroxylamines.(8h) Nitrones can even act as oxidizing agents in a few isolated cases.(8i)

Nitrones, due to the resonance discussed earlier, act as electrophiles and nucleophiles. As nucleophiles, the oxygen can attack carboxylic acid derivative at the electrophilic carbon creating many derivatives most of which are prone to rearrangement. Dimers of nitrones are often formed by nucleophilic reactions through an aldol type mechanism followed by cyclization by attack by a deprotonated β-carbon, Figure 25.(8j) As electrophiles as in the final step of the

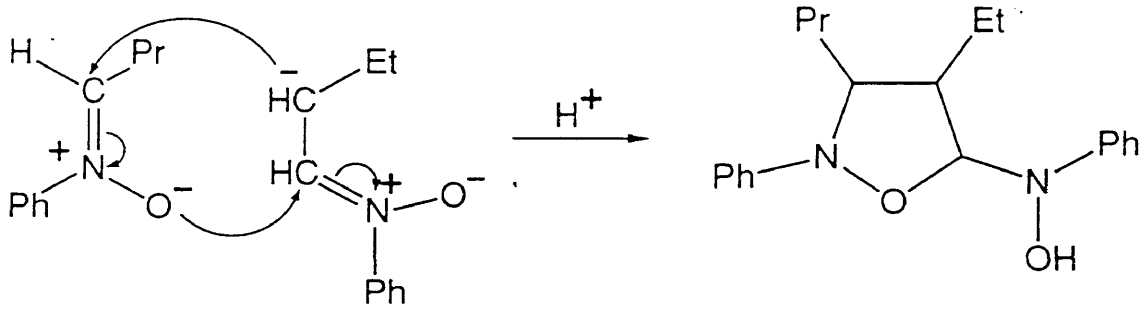


FIGURE 25

Kroehnke aldehyde synthesis, nitrones are hydrolyzed furnishing the parent carbonyl and parent hydroxylamine as in Figure 26.(8k) Likewise, nitrones are subject to

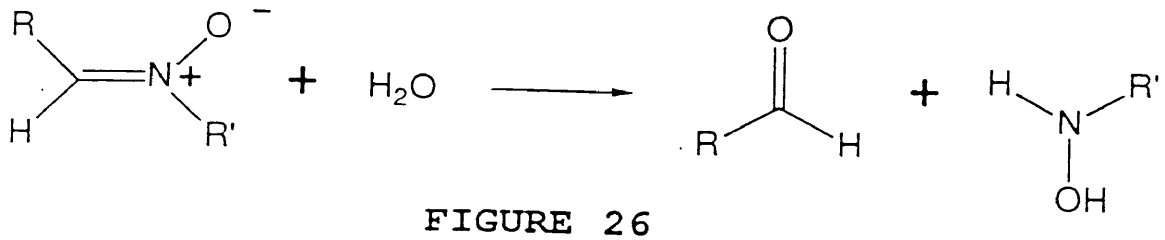


FIGURE 26

attack, regularly at the α-carbon, by numerous electrophilic compounds.(8b)

Nitrones: dipolar cycloadditions and their products

Of paramount importance to this work, nitrones participate as representative dipoles in 1,3-dipolar cycloadditions. These reactions construct heterocycles of the isoxazolidine class when using carbon-carbon multiple bonds as dipolarophiles. The product heterocycles are typically of the 5-substituted variety with an occasional 4-substituted case when highly electron-deficient alkenes are used as dipolarophiles, Figure 27. This can be rationalized by the gradual conversion of the reactivity of

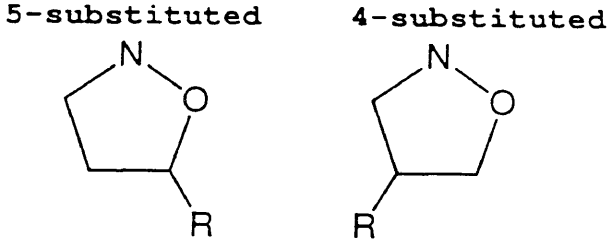


FIGURE 27

nitrones from LUMO control for electron-rich dipolarophiles to HOMO control for electron-deficient dipolarophiles. In illustrative form, Figure 28 displays the energy differences for C-phenyl-N-methyl nitrone to an assortment of general dipolarophiles. In the LUMO controlled reactions, the best orbital overlap as determined by coefficient match provides the 5-substituted isoxazolidine while in HOMO control, the 4-substituted case furnishs the best overlap. Nitrones are susceptible to changes in control induced by a comparatively narrow HOMO-LUMO separation. Moreover, unlike most dipoles, almost any substituent on the nitrone, whether electron withdrawing or donating, accelerates the dipolar reaction.(7)

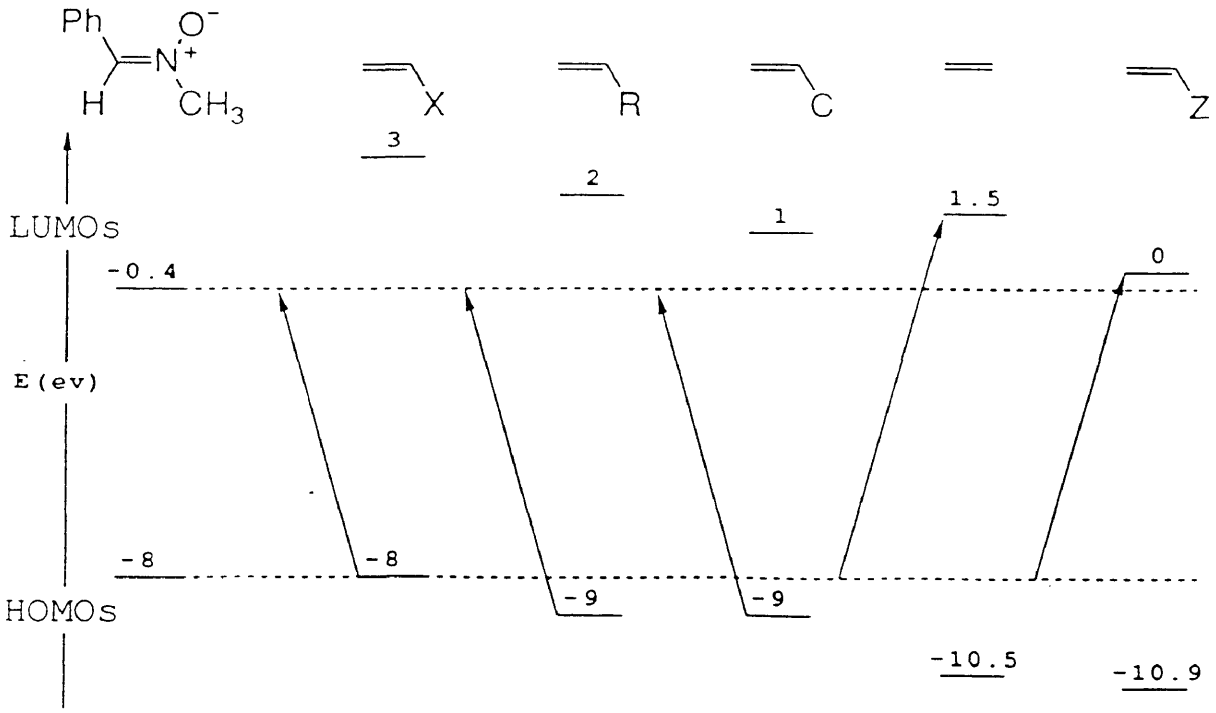


FIGURE 28

Nitrones have been found to be quite useful in intramolecular synthesis as well as many other molecular building applications. Their general usefulness extends to many degradation routes from the resulting heterocycles of the cycloaddition. The main focus of the derivatization of isoxazolidines arises from the easily cleaved nitrogen-oxygen bond. Since the cycloaddition is stereoselective, products can be synthesized which contain high ratios of a desired stereoisomer in acyclic forms after cleavage.(23)

There are several other reactions and uses of nitrone dipolar cycloadditions. Isoxazoles react with methyliodide which attachs the nitrogen giving the ammonium salt. Reductive cleavage at the nitrogen-oxygen bond can then be achieved by a

number of methods including zinc/acetic acid or lithium aluminum hydride, Figure 29.(8l) Mesylate protected methyl alcohol at the fiveposition of an isoxazolidine

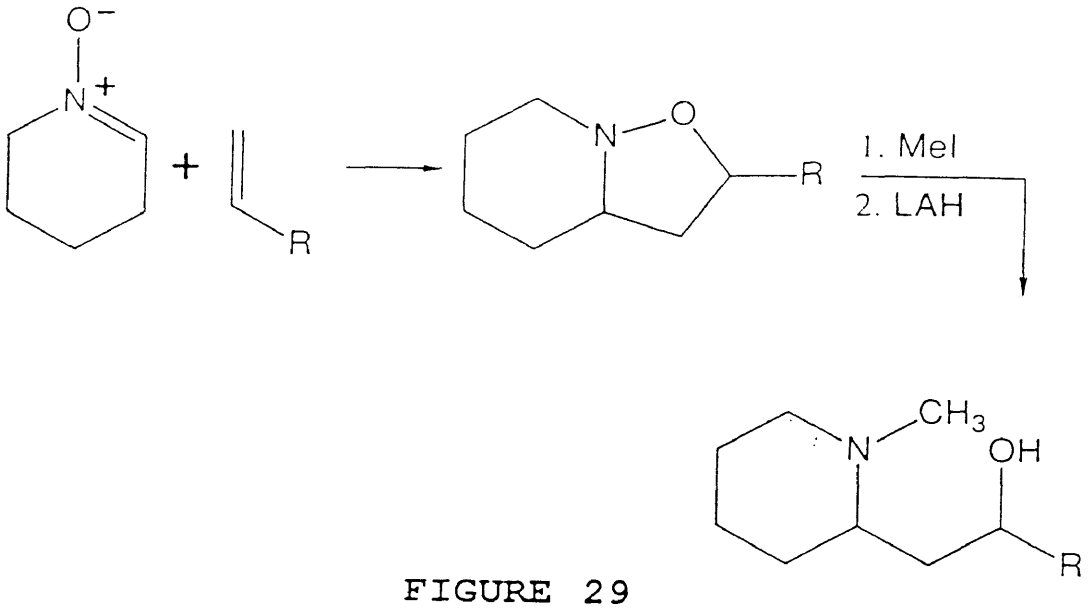


FIGURE 29

rearranges when hydrogenated to return the pyrolidin-4-ol which, depending on other substituents, can undergo further useful reactions, Figure 30.(8m) Most

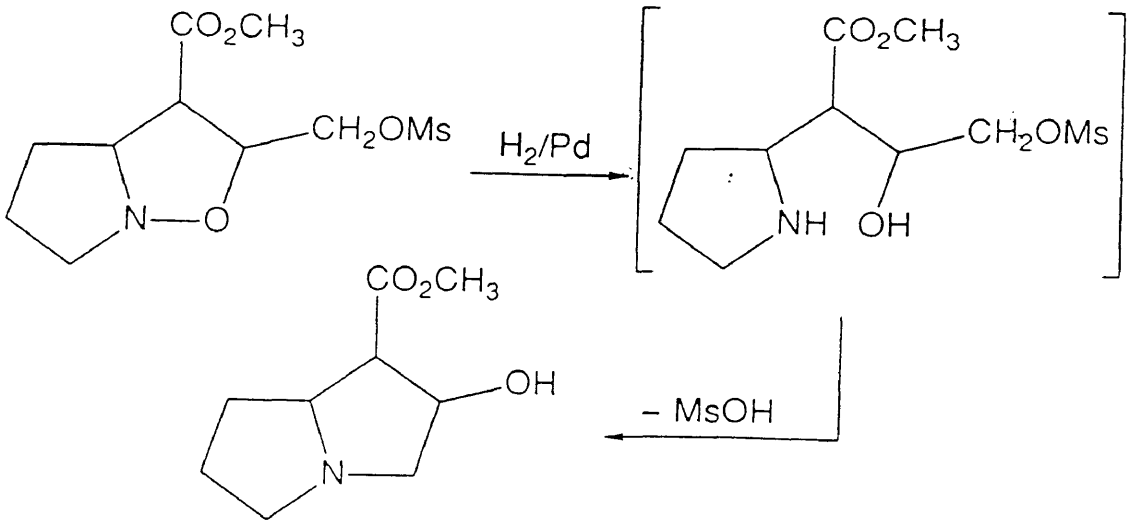


FIGURE 30

alkynes decompose when reacted as dipolarophiles. The isoxazoline formed is quite unstable, but the degradation patterns are usually predictable.(24)

In part due to the ease with which nitrones can be synthesized, there are many intramolecular uses of the dipolar cycloaddition. Cocaine has been formed through the use of a isoxazolidine seen in Figure 31 by performing a

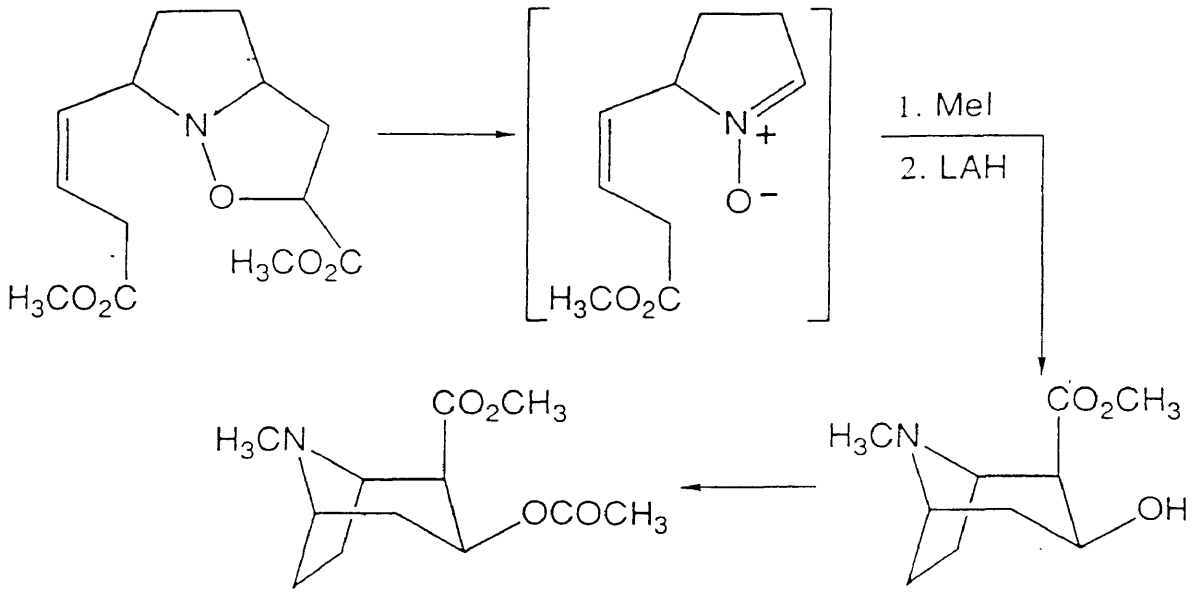


FIGURE 31

retrocycloaddition followed by intramolecular trapping of the nitrone with subsequent methylation, reduction and derivatization of the resulting alcohol.(8n) The total synthesis of (+)-luciduline has also been effected in an enantioselective manner by utilizing chiral starting materials and an intramolecular cycloaddition followed by derivatization, Figure 32.(8o) There are multiple possibilities when considering the mild conditions which can be used to achieve such syntheses and the

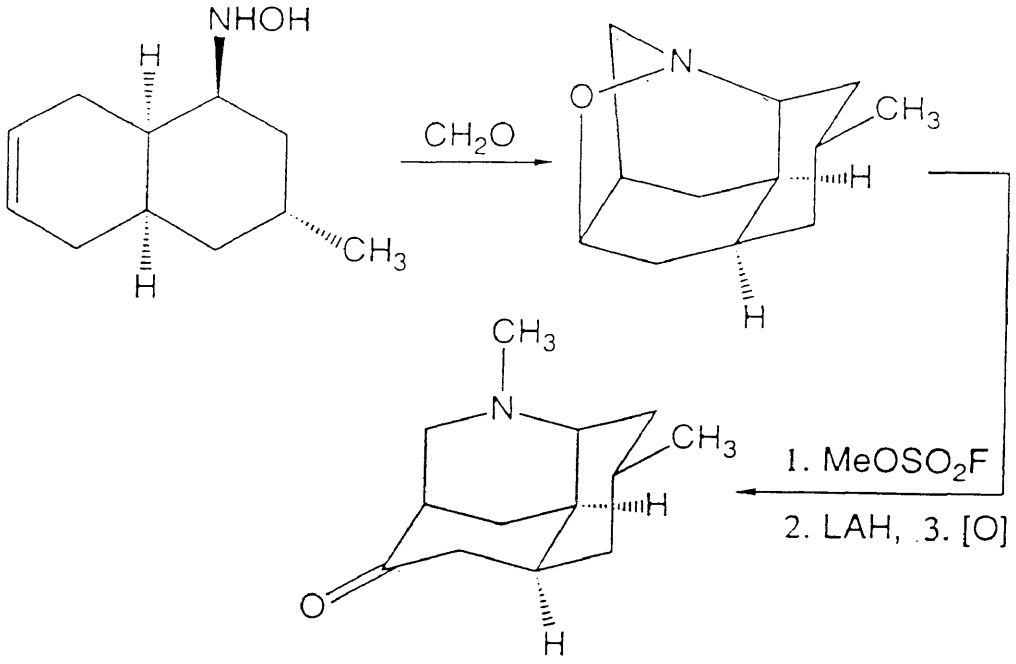
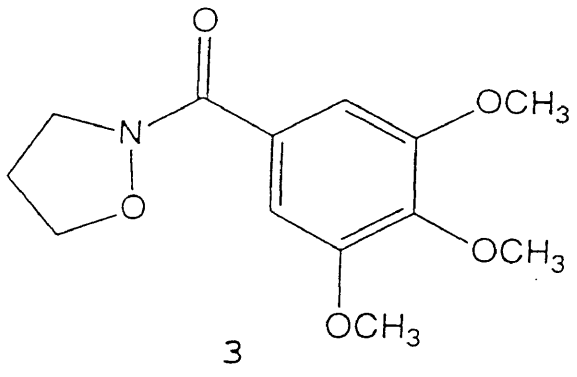


FIGURE 32

routes open by derivatization of the adducts formed.



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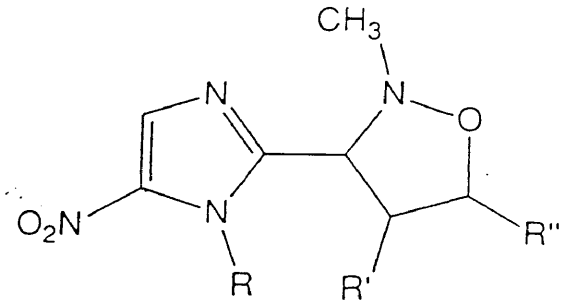

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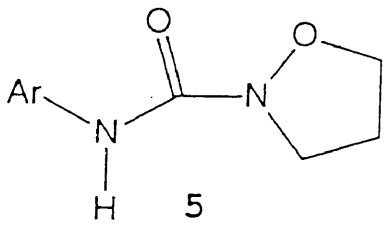


5

FIGURE 33

In addition to use in syntheses, some isoxazolidines have been found to have some fascinating applications. Figure 33 denotes several of the isoxazolidines which are known to have physiological activity. Heterocycle **3** is an N-aroylisoxazolidine which possesses central nervous depressant activity while not producing muscle relaxation.(25b) Imidazolylnitrone adducts, **4**, perform as antibacterial and antiprotozoological agents.(25c) 2-Substituted (anilinocarbonyl)isoxazolidines, heterocycle **5**, are highly effective herbicides on several varieties of weeds.(25d) Some isoxazolidinium salts are active in therapy of malignant tumors and in antibacterial operation.(25e)

Hydroboration

The other part of the investigated cycloaddition is the use of alkenyl boronate esters as dipolarophiles. These boronates are the product of a hydroboration and open many derivatization possibilities. Hydroboration includes reactions involving addition of boron-hydrogen across a carbon-carbon multiple bond. Additions of this type were found to proceed through a cyclic transition state giving syn-addition to the less hindered face of the alkene, as demonstrated in Figure 34. Alkyl boron

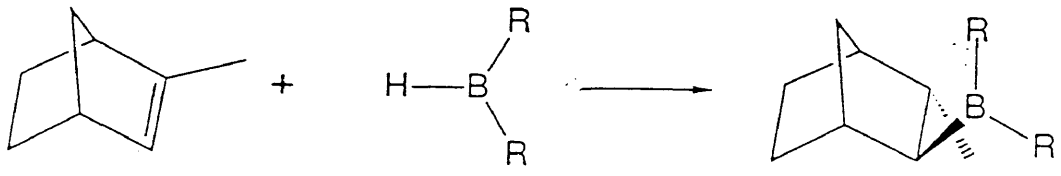


FIGURE 34

compounds are quite useful because they can be converted to a number of oxidized

products such as alcohols, carboxylic acids, aldehydes and others. These compounds are also able to add carbon containing substituents as intermediates in several rearrangment reactions.(26a)

Alkylboranes where first synthesized by Frankland by reacting dialkylzinc with triethylborate.(26b) Frankland's study also extended to addition compounds of a base with a borane reagent. Subsequent research by Alfred Stock led to the isolation of the major boranes containing only hydrogen and boron.(26c) These were first applied in organic synthesis to produce dialkoxyboranes from aldehydes or ketones which can be hydrolyzed to yield alcohols. Boranes later became commercially available through a procedure created by H. I. Schlesinger and H. C. Brown.(26d) Probably the most well known use for boranes is the hydration of alkenes in an anti-Markownikov fashion by addition of diborane followed by oxidation with hydrogen peroxide, Figure 35.(26a)

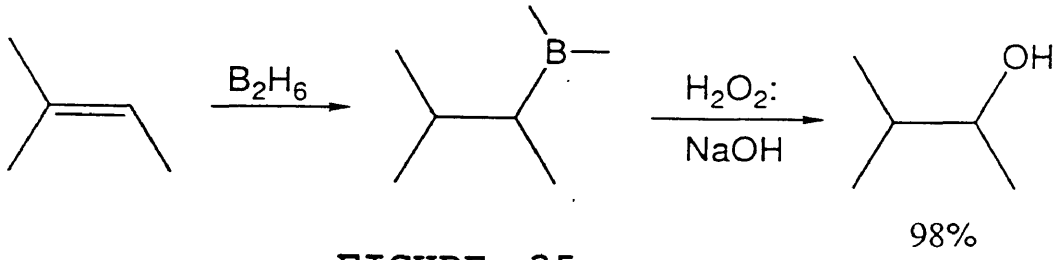


FIGURE 35

Hydroboration of alkenes with borane typically produces trialkylboranes. The extent of hydroboration can be controlled by the use of hindered alkenes. 2,3-Dimethyl-2-butene for example is only hydroborated once whereas 2-methyl-2-butene is converted to the dialkylborane, Figure 36. This method extends to include

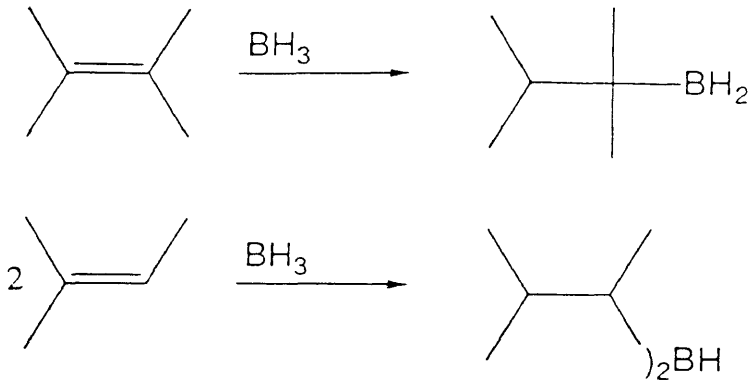


FIGURE 36

two hydroboration reactions within the same molecule to form cyclic alkylboranes. There are also several heteroboranes such as catecholborane, dibromoborane dimethylsulfide complex, bromborane dimethylsulfide and many others. The importance of most of these reagents arises from their ability to produce monoalkyl products which are easily derivatized, greater regioselectivity, or one hydroboration with alkynes.(26a)

As stated previously, the hydroboration occurs syn with respect to the double bond. Furthermore, addition results from attack on the least hindered face of the molecule and the boron adds to the least substituted end of the alkene.(26d) Borane-THF adds to 1-hexene with 94% at the terminal position and to isobutene with 99% at the unsubstituted terminus.(26e) The ratios reported refer to one alkylation event. So for the formation of a trialkylborane, the amount of minor regioisomer would be near three times that for one addition though regioselectivity does increase with each addition. These ratios are dramatically affected by the size and type of borane as mentioned previously. Borane-THF, for example, shows less site selectivity than

catecholborane.(26f)

Alkenyl boronate esters

Boronate esters are valuable for their ease of creation, general stability and ease of handling. These compounds open several pathways to other boron derivatives. The boronates are formed to possess only one alkyl substituent.

Boronates can be formed by several techniques. Most dialkoxyboranes disproportionate precluding their use for a direct approach to boronates. Catecholborane, compound **6** Figure 37, though less reactive than dialkylboranes,

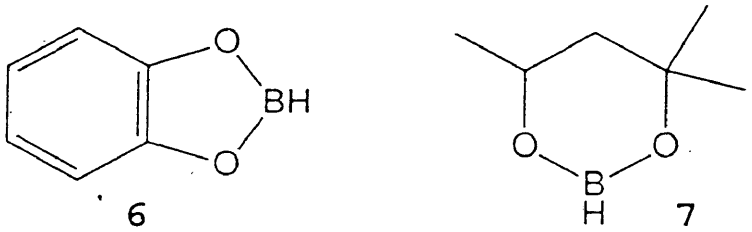


FIGURE 37

performs hydroboration in a considerably more selective manner when heated. 4,4,6-Trimethyl-1,3,2-dioxaborinane, compound **7**, reacts in a similar manner but requires higher temperatures.(26f)

A different approach to the synthesis of boronates arises from the use of dihalogenoboranes. Dichloroborane is commercially available as an etherate or as a dimethyl sulfide complex while the bromine and iodine derivatives are only available as dimethyl sulfide complexes. Dichloroborane complexes tightly to ether reducing its reactivity, however when the reaction is run in pentane in the presence of

trichloroborane to complex the ether, reactions can be productive.(26g) The dihalogenoborane-dimethyl sulfide complexes are constructed by reacting borane-dimethyl sulfide with two equivalents of trihalogenoborane-dimethyl sulfide.(26h) These reagents hydroborate alkenes and alkynes to produce the alkyldihalogenoboranes with ease.(26i) The bromine and iodine cases react rapidly at room temperature in dichloromethane without using trihaloborane to loosen the complex.(26j) These heavier halogens demonstrate interesting regioselectivity. When reacting with alkenes, the regioselectivity decreases with excess alkene and increases with shortage of the alkene relative to 9-BBN, a very selective, hindered reagent.(26k) Alkyldichloroboranes have been produced by another means through the reaction of excess trichloroborane with a trialkylborane.(26l) The above reactions bear relevance directly to the following research. As will be shown, alkenyldihalogenoboranes are readily hydrolyzed to the alkenylboronic acids. The acids can dehydrate in the presence of alcohols yielding the alkenylboronates.(26a)

Results and Discussion

The major purpose of this research was to investigate the participation of alkenylboronate esters in 1,3-dipolar cycloadditions. In their reactions with nitrones, these substrates have been shown to produce the expected boron-substituted isoxazolidines under relatively mild conditions. These cycloadducts have only been partially characterized due to many problems associated with their isolation and purification. The desire to produce boron-substituted heterocycles stems from the many known methods by which these compounds may be further transformed.

E-1-Hexenyl boronic acid

The boronate ester used was formed by a method which is generally applicable to most alkynes as seen in Figure 38. The procedure proceeds through the boronic acid formed by a hydroboration/hydrolysis sequence. The hydroboration was performed by slow addition of dibromoborane dimethyl sulfide complex, 1.0 M in dichloromethane, to a cold solution of 1-hexyne and dichloromethane.(26j) The hydroborating agent was chosen for its relatively high reactivity, high regioselectivity and ease of hydrolysis. Reaction then followed at room temperature yielding the E-1-hexenyl dibromoborane, alkene **8**. Aqueous sodium hydroxide was

then added dropwise prompting precipitation of a white solid which was E-1-hexenyl boronic acid, alkene **9**. The acid was removed from the solution by extraction with

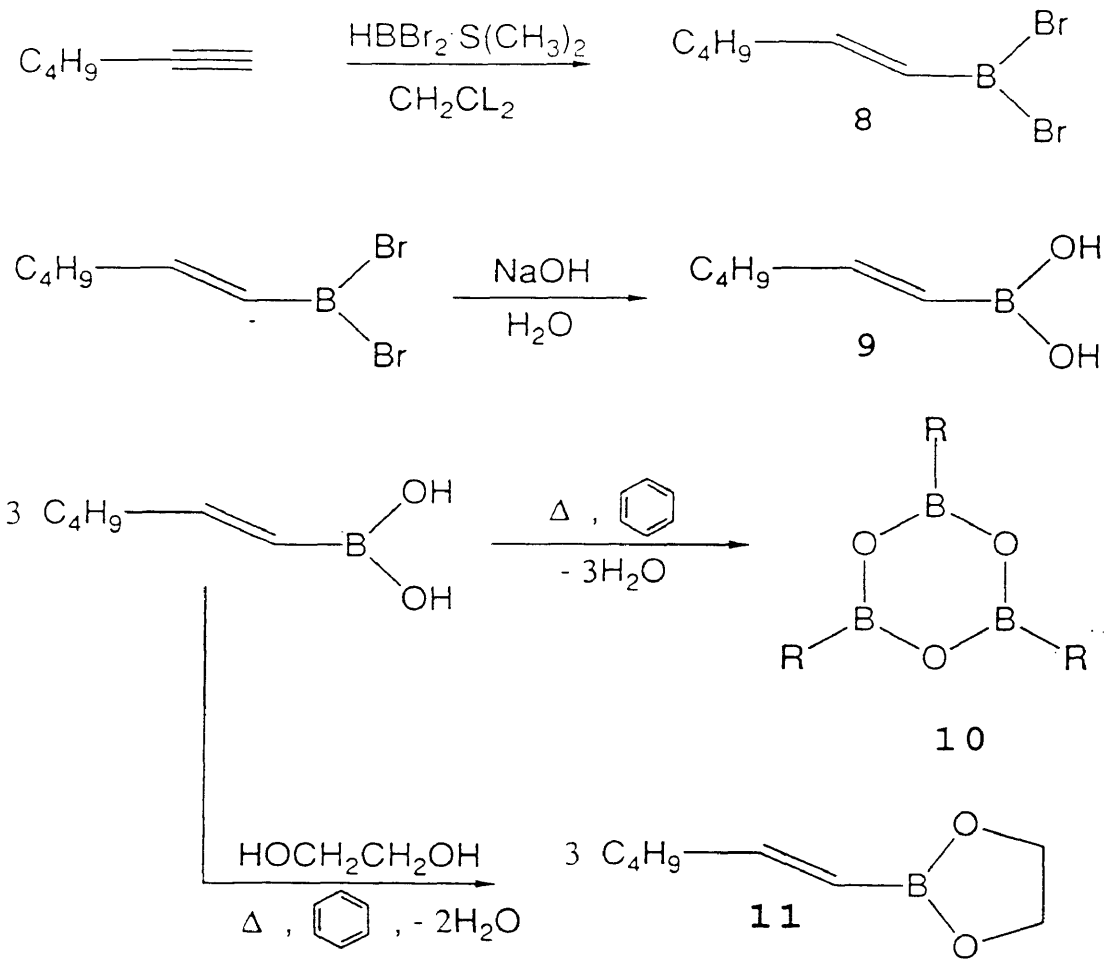


FIGURE 38

5:1 ether:dichloromethane. An off-white solid was acquired by drying the extracts with sodium sulfate preceding removal of the solvent under reduced pressure in 86% yield. This solid is a mixture of the acid and the anhydride, compound **10**. The identity of the solid was verified by proton and carbon-13 NMR, Figures 39 and 40 respectively.

FIGURE 39

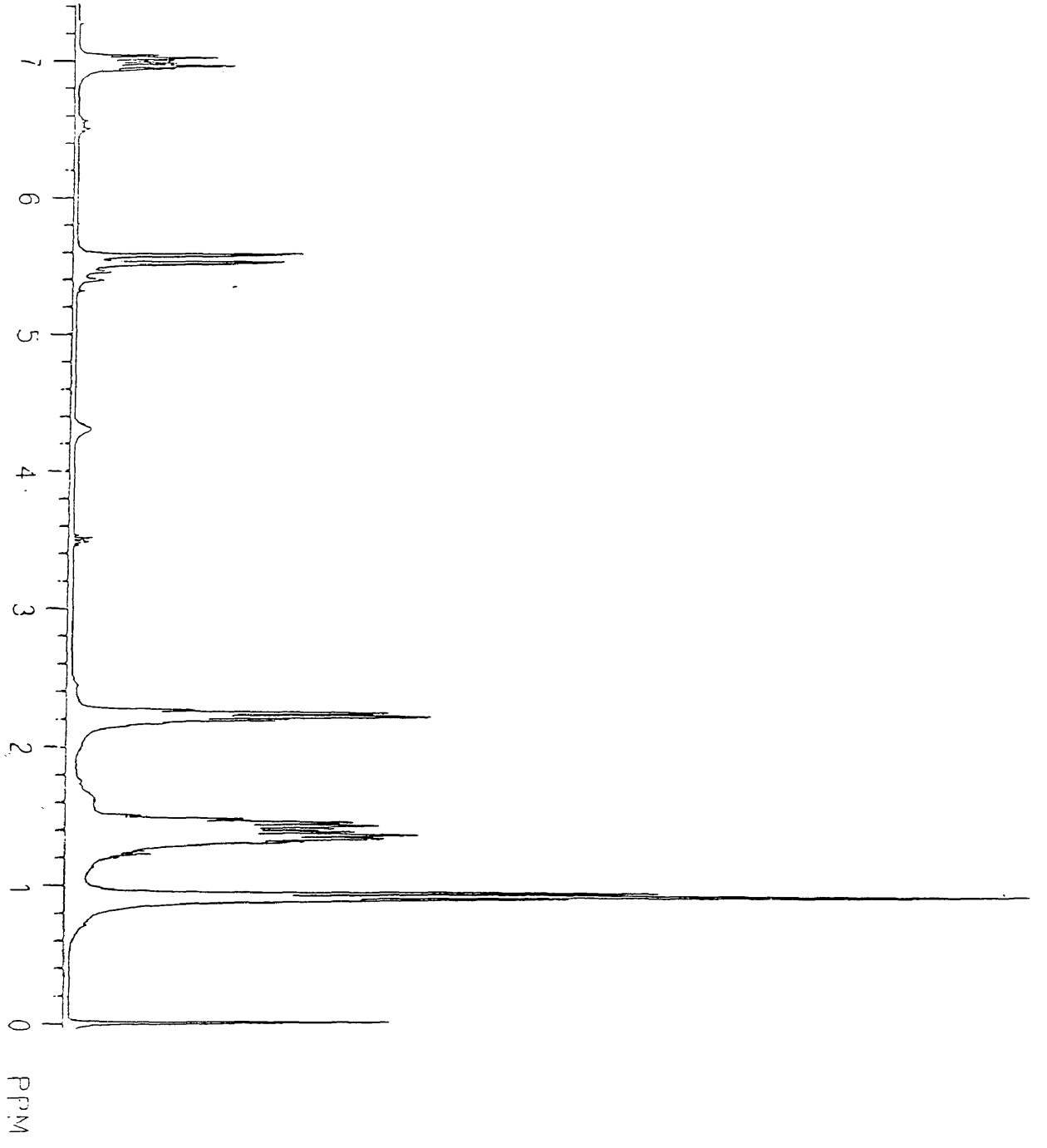
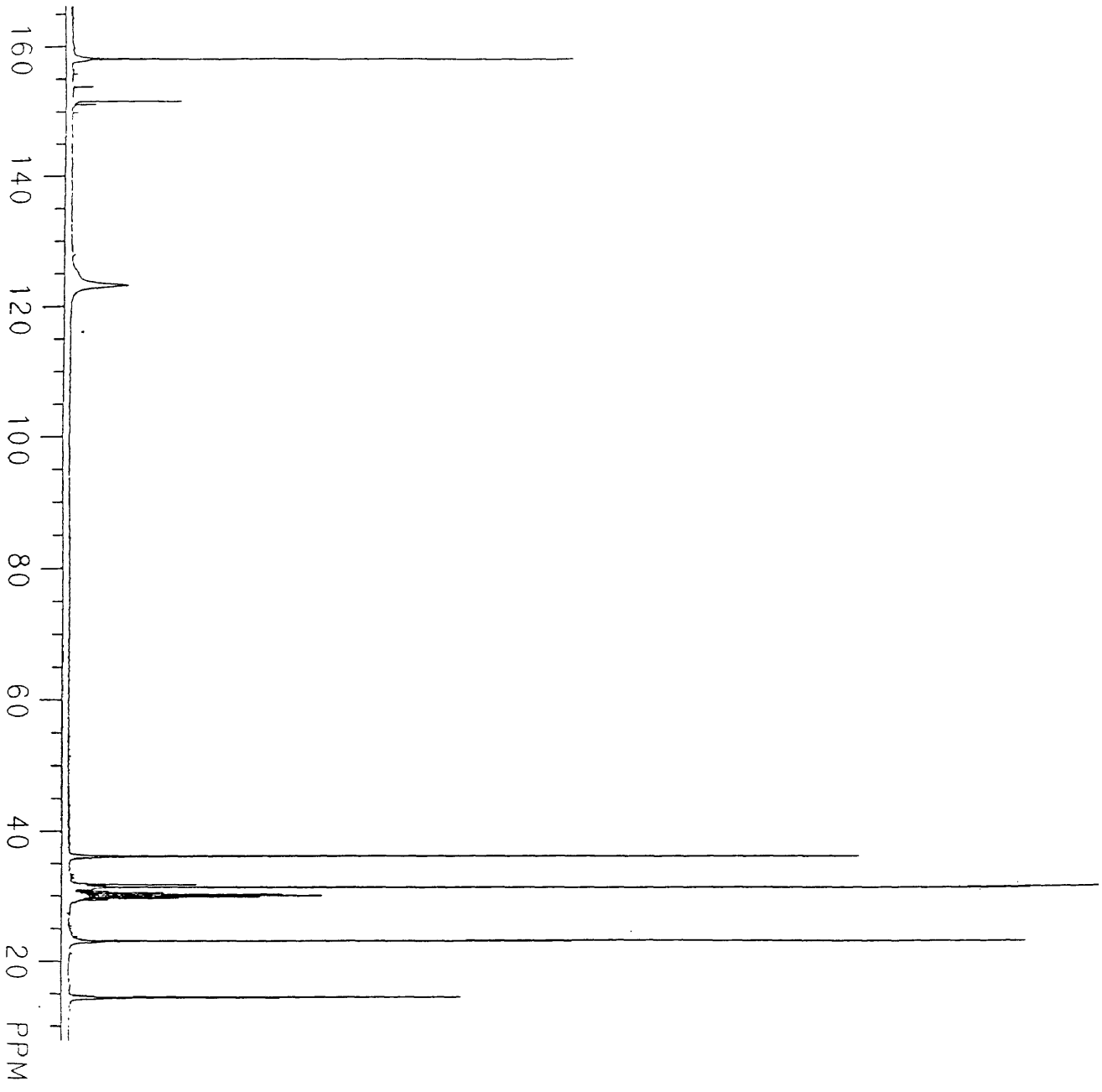


FIGURE 40



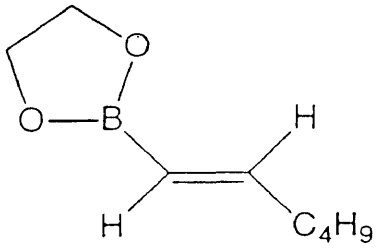
The acid/anhydride mixture can be completely converted to the trimeric anhydride by azeotropic removal of water. As expected the proton NMR shows five sets of peaks. At 0.90 ppm, the terminal methyl appears as a triplet. Next, there is a grouping of peaks between 1.29 and 1.46 ppm which integrates for four hydrogens. These peaks are the next two methylenes. At 2.19 ppm, the allylic hydrogens are seen. Finally, the two hydrogens of the alkene lie between five and seven ppm. The doublet at 5.52 ppm is the vinyl hydrogen α to boron and the doublet of triplets at 6.95 ppm is the β vinyl hydrogen. The carbon spectrum also shows six major peaks which occur in the same relative order as the proton at 14.26, 22.99, 31.18, 36.02, 123.11 and 157.96 ppm respectively.

E-B-(1-Hexenyl)-1,3-dioxaborolane

From the boronic acid or anhydride, the boronate ester can be formed by azeotropic removal of water in the presence of two alcohol functionalities. Ethylene glycol was used to produce the E-B-(1-hexenyl)-1,3-dioxaborolane, alkene **11**. The alcohol and alkyne were chosen for availability and handling ease of starting materials and dioxaborolane. Purification of the dioxaborolane was easily effected by Kugel Rohr distillation at 42° to 45°C at approximately 1.5 torr yielding a pungent colorless oil in 74 to 90% yield. The structure was confirmed by gas chromatography/mass spectrometry, ^{1}H NMR and ^{13}C NMR, Figures 41, 42 and 43.

The mass spectrum for the boronate delivers the correct molecular weight, 154. In addition, the peaks at 139, 125 and 112 result from the gradual fragmenting

FIGURE 41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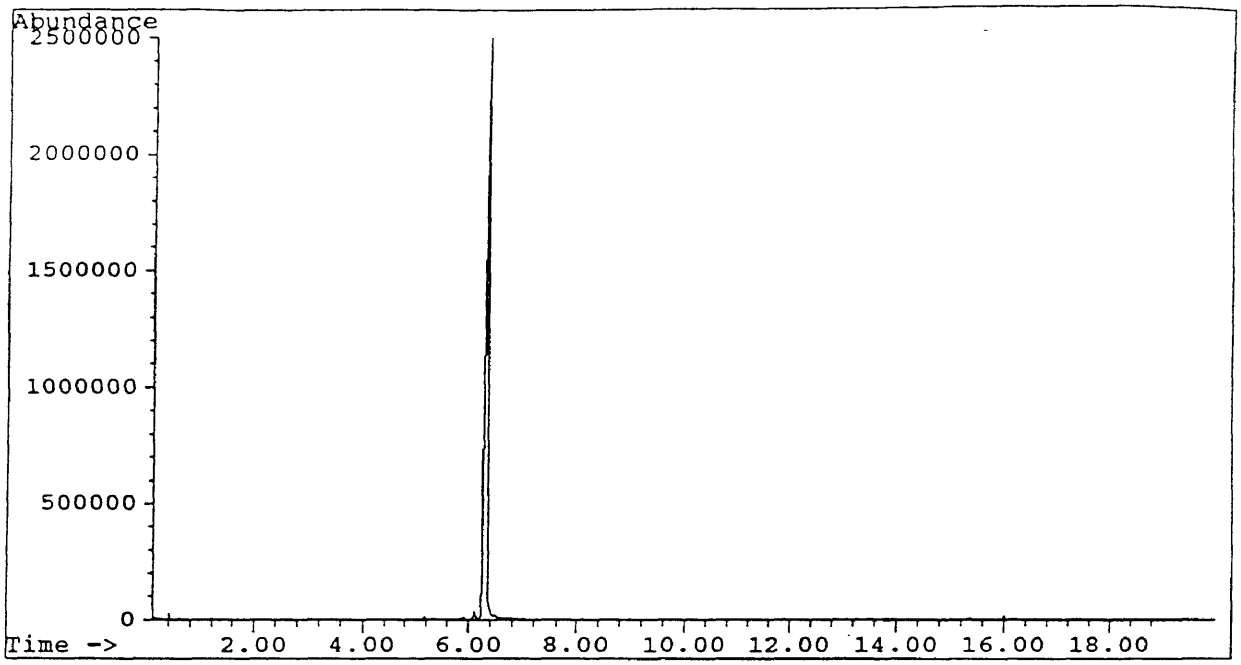
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16.00
18.00

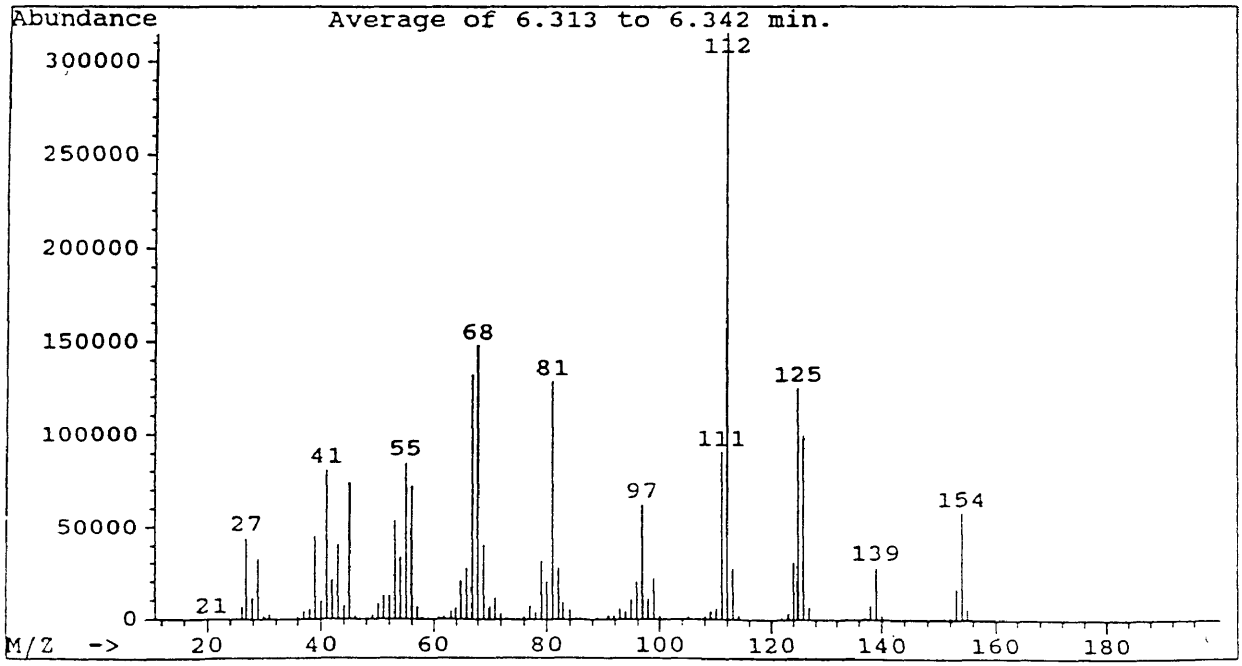

Abundance
Average of 6.313 to 6.342 min.
300000
250000
200000
150000
100000
50000
0
M/Z ->
20
40
60
80
100
120
140
160
180
21
27
41
55
68
81
97
111
112
125
139
154

FIGURE 42

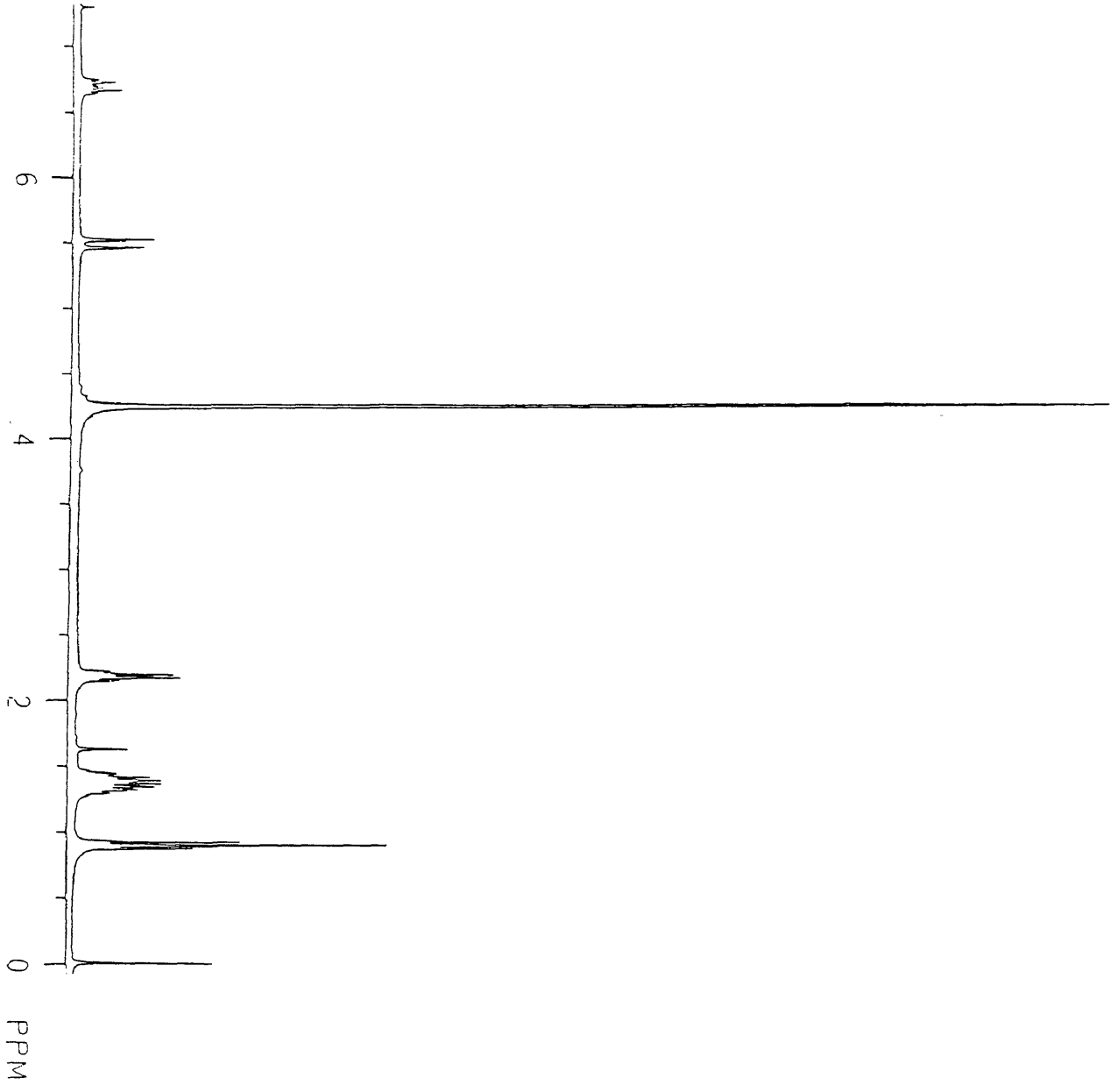
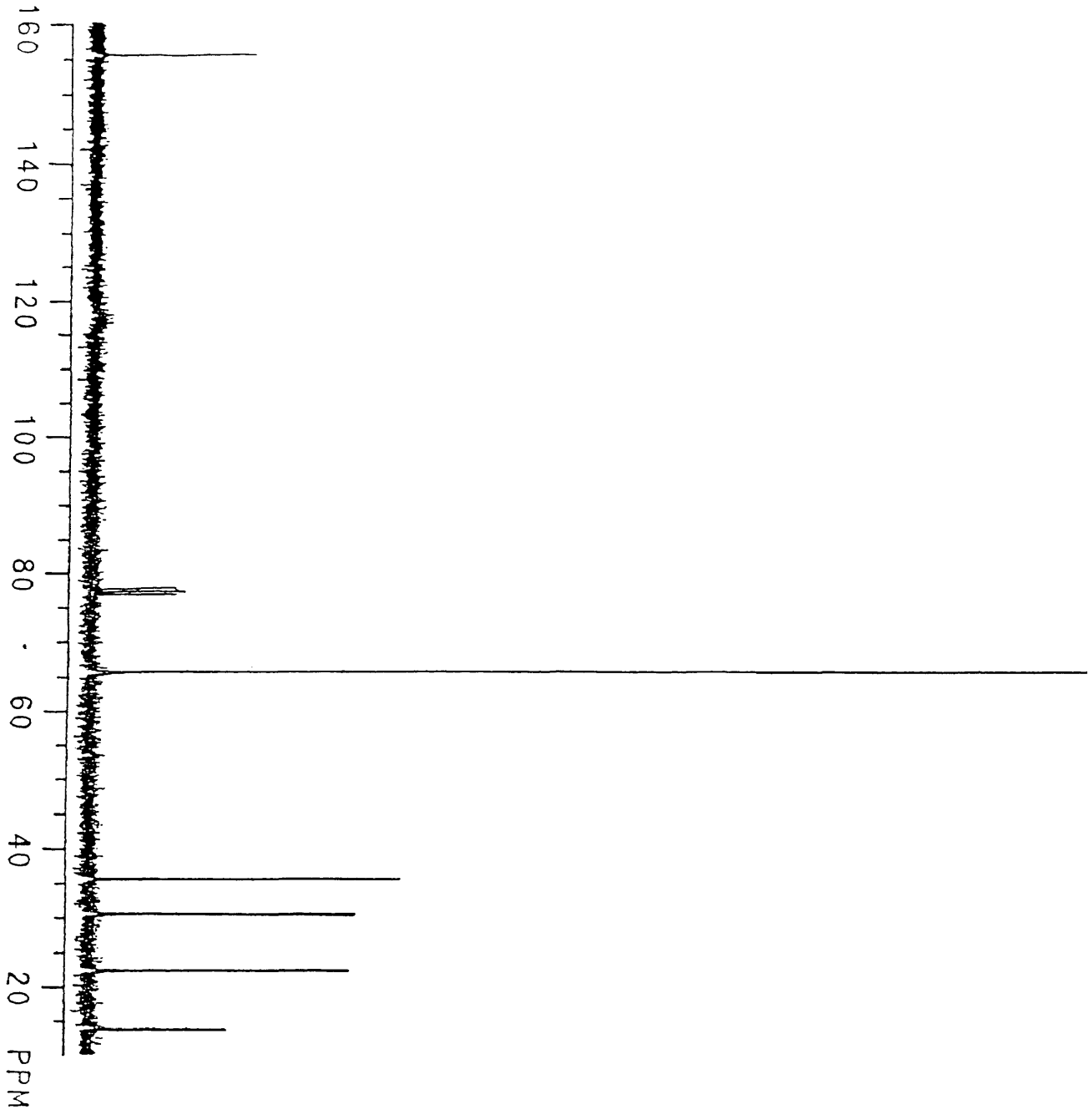


FIGURE 43



of the hydrocarbon tail. Mass 112 is the base peak because a comparably stable allyl radical cation remains upon removal of a propyl fragment in the mass spectrometer. The presence of boron is indicated by an M -1 peak for each of the peaks listed above which corresponds to the isotopic abundance of ^{10}B, 20%. The proton NMR has the same relative interpretation as the anhydride with the addition of a broad singlet at 4.2 ppm, 65.53 in the carbon NMR, which is the resonance for the methylenes of the ring. These hydrogens are indistinguishable due to rapid rotation of the boron-carbon bond. The chemical shifts in ppm from the vinyl α to the boron substituant to the methyl are as follows: ^{1}H NMR 6.65, 5.45, 2.15, 1.34 (4H), 0.90; ^{13}C NMR 155.55, 117.70, 35.63, 30.50, 22.28, 13.92.

2,3,4,5-Tetrahydropyridine-N-oxide

The nitrone chosen for this study was 2,3,4,5-tetrahydropyridine-N-oxide. The reasons for selecting the nitrone were its reactivity and production of an interesting bicyclic compound upon cycloaddition. The nitrone was produced by two methods as shown in Figure 44. The first involved yellow mercuric oxide oxidation of N-hydroxypiperidine.(15) The oxidizing agent, Hg(II)O, was produced by conversion from mercuric chloride and sodium hydroxide.(27) A solution of mercuric chloride in water at 0°C was reacted with excess sodium hydroxide through gradual addition of the base until a bright yellow/ orange color persisted, approximately 2 molar equivalents. The temperature was kept cold throughout the process to yield yellow mercuric oxide, a more reactive form, in preference over red

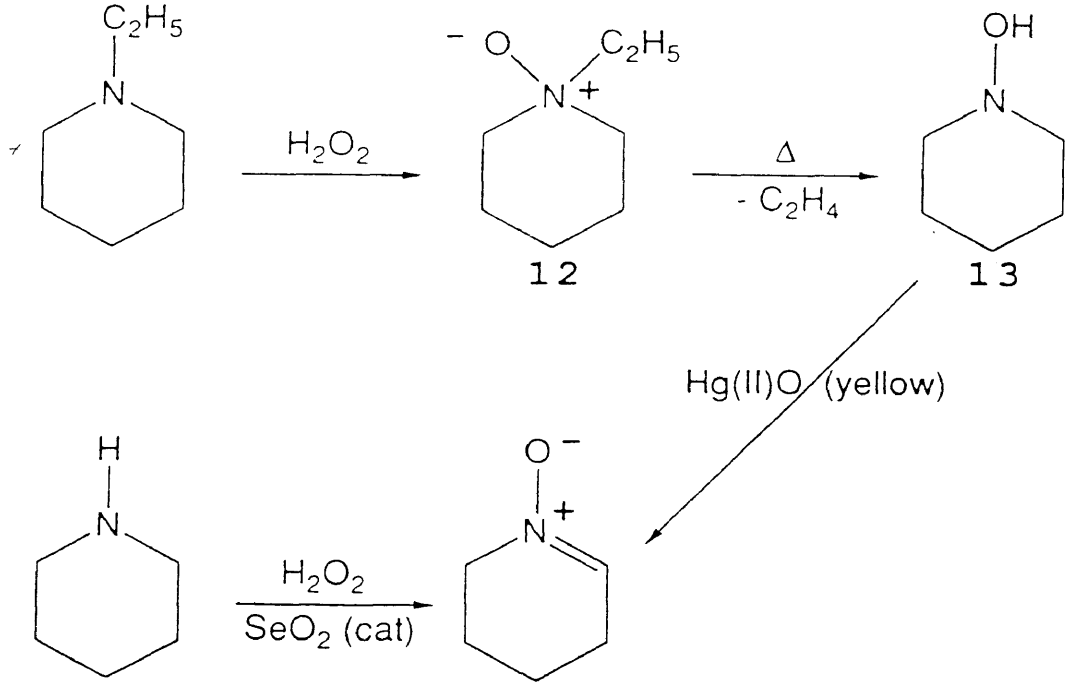


FIGURE 44

mercuric oxide. The resulting mercuric oxide was dried in an oven under high vacuum and only small amounts of heat in order to dry the solid without degradation to the red form.

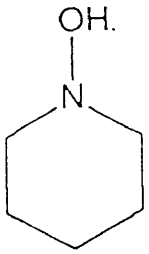
2,3,4,5-Tetrahydropyridine-N-oxide: N-hydroxypiperidine

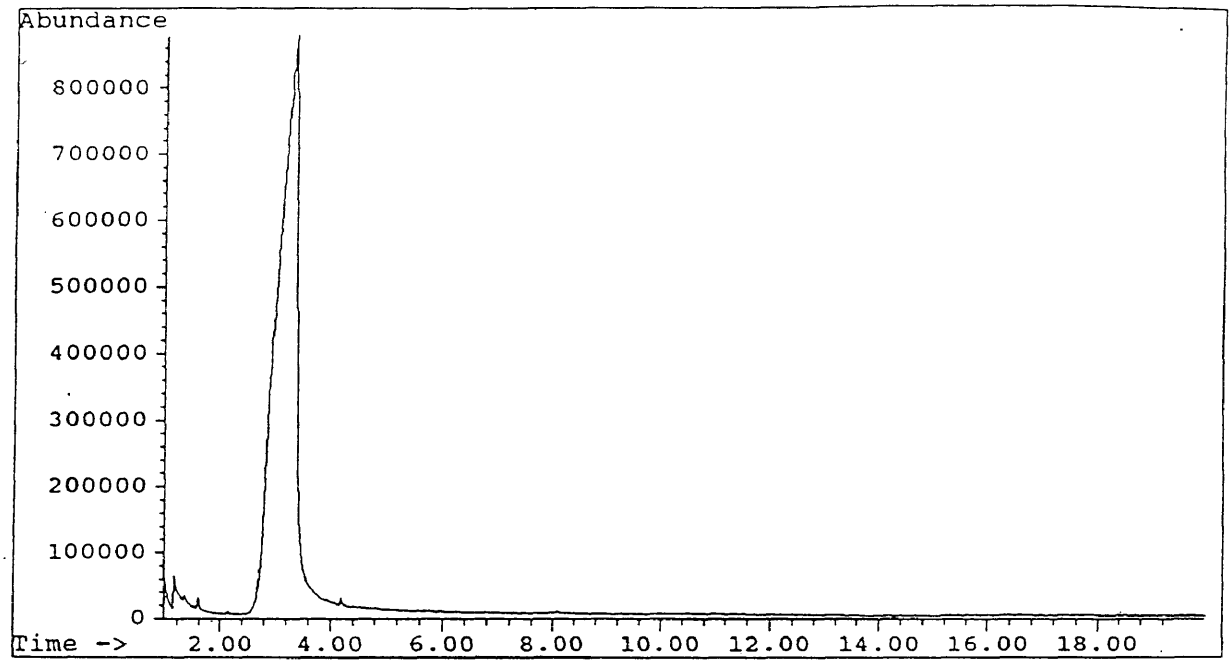
N-Hydroxypiperidine formation was accomplished by a procedure outlined by Handford *et al.*(13) N-Ethylpiperidine was first oxidized to the amine oxide, heterocycle **12**, by addition of hydrogen peroxide to an ethanol solution of the amine at 0°C followed by 3 to 5 days of stirring at room temperature. Hydrogen peroxide

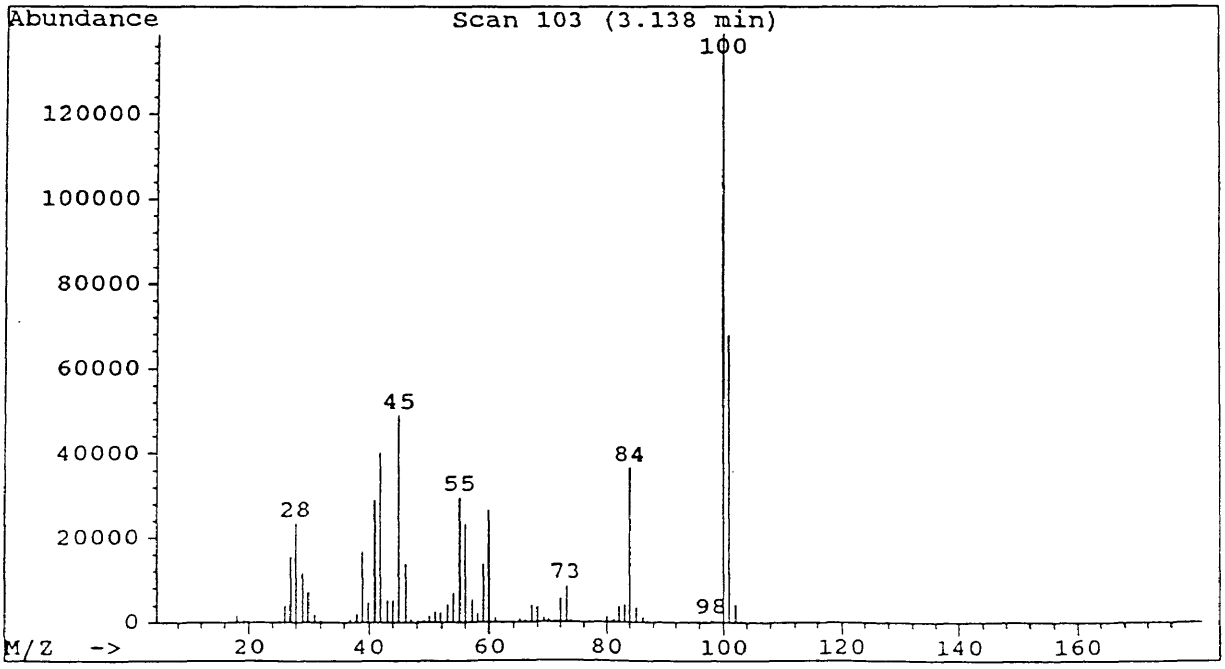
remaining after five days was consumed by slow addition of a slurry of platinum black to the mixture which had been cooled to 0°C. The platinum black was removed by filtration through Celite. The filtrate was then concentrated by distillation at 1 torr and up to 70°C. At this point, a white solid appeared which was considerably hygroscopic and often degraded quickly to a dark slush. This intermediate was heated to melting followed by reflux in order to eliminate ethylene and thus produce the N-hydroxypiperidine, heterocycle **13**. The hydroxylamine was purified by distillation at 17 torr and collected between 70° and 90°C in a receiver cooled to at least -30°C. Next, the pale yellow solid was recrystallized from ethyl acetate/hexanes to give a white smelly solid, 76% yield. The purity of the compound was verified by GC/MS, ^{1}H NMR and ^{13}C NMR.

The mass spectrum, Figure 45, indicates the correct mass, 101, with the adjacent base peak of 100 which results from loss of the hydroxyl hydrogen. Another indicative peak is the M -17 peak, mass 84, from loss of the hydroxyl. Figure 46, the proton NMR of the hydroxylamine, exhibits some unusual splittings and resonances. The peaks between 0.65 and 2.77 integrate to 1:3:2:2:2 from upfield to down. These data provide evidence for either slow interconversion between the chair conformers or slow inversion at the nitrogen on an NMR time scale. The interpretation is given in Figure 47. The ^{13}C NMR, Figure 48, shows three peaks as anticipated due to the symmetry of the molecule. The peak at 22.53 ppm represents the methylene at the four position of the heterocycle. The

FIGURE 45


OH.
N


Abundance
800000
700000
600000
500000
400000
300000
200000
100000
0
Time ->
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00


Abundance
Scan 103 (3.138 min)
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120000
100000
80000
60000
40000
20000
0
45
28
55
84
73
98
M/Z ->
20
40
60
80
100
120
140
160

FIGURE 46

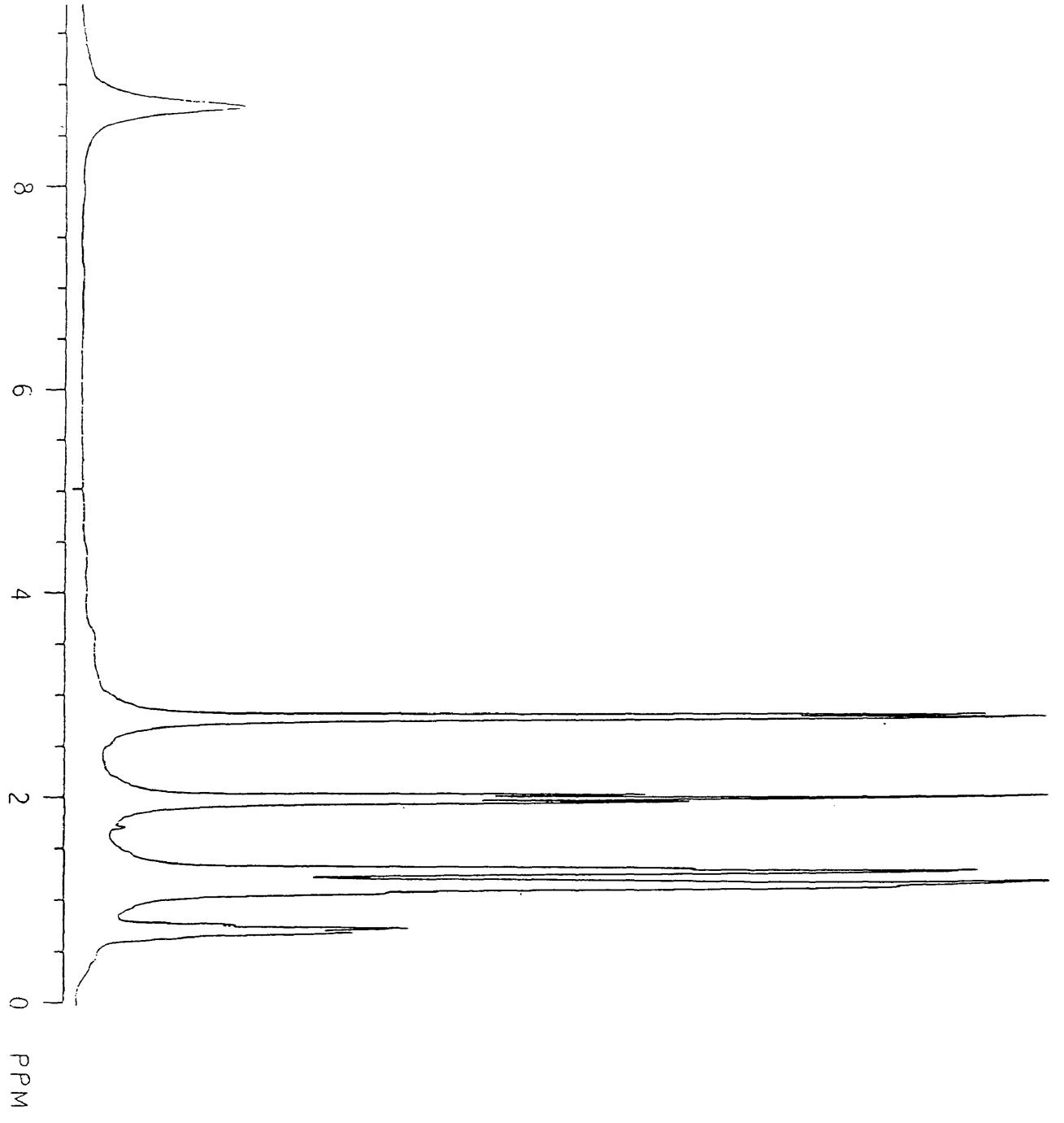
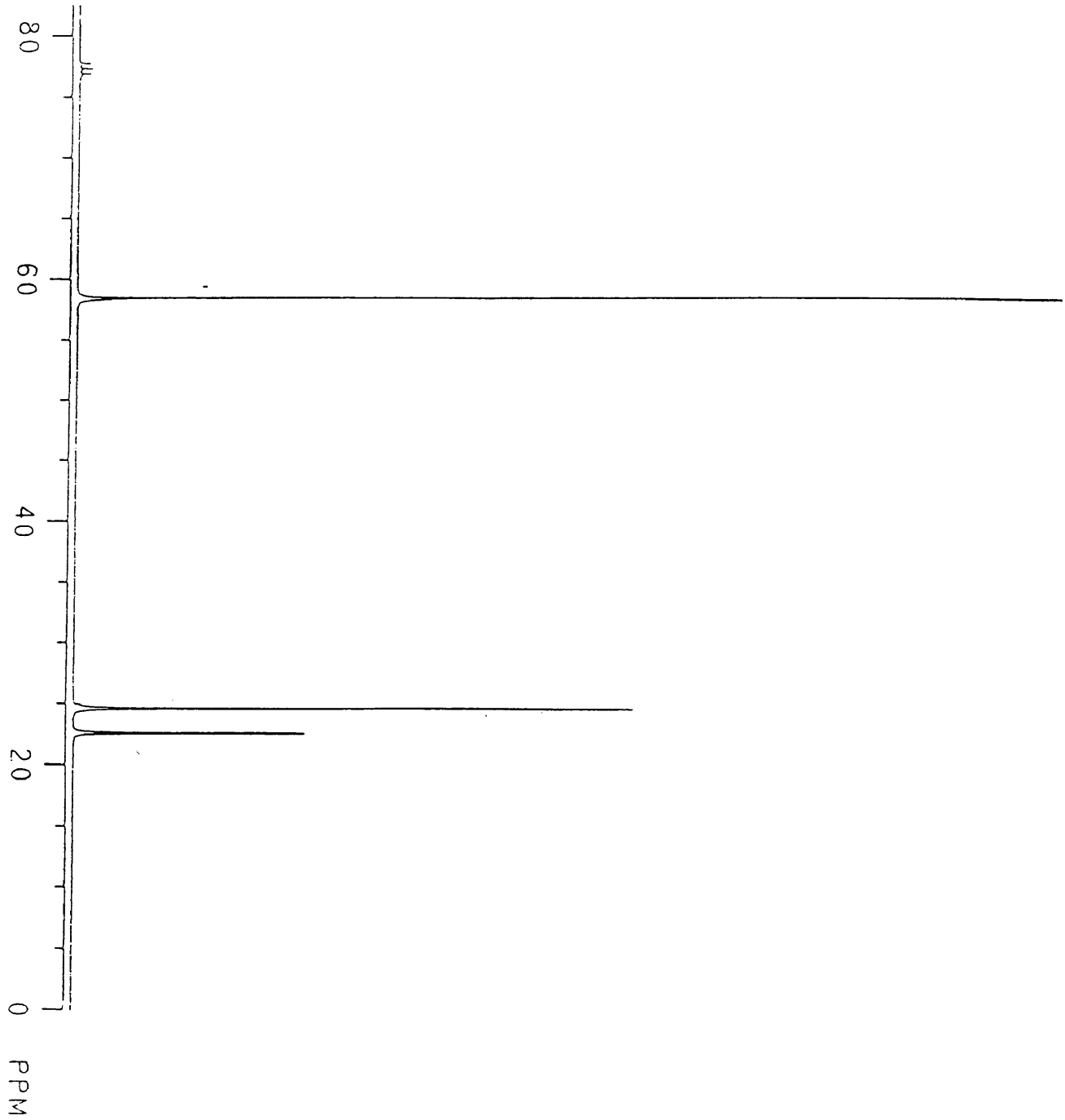
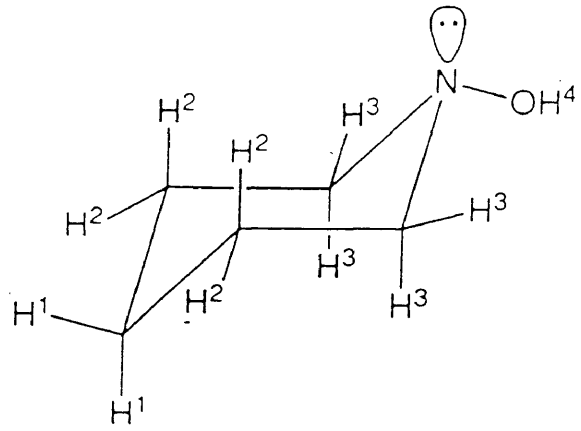


FIGURE 48





H^1— 0.70
and 1.09.
H^2— 1.10
and 1.25
H^3— 1.96
and 2.75
H^4— 8.76

FIGURE 47

methylenes on either side of the aforementioned methylene are represented by the next peak, 24.55 ppm. The peak further downfield, 58.34 ppm, corresponds to the methylenes nearest the nitrogen which shifts these carbons by its electron withdrawing character.

2,3,4,5-Tetrahydropyridine-N-oxide: Method A

From the hydroxylamine, the conversion to nitrone simply involved an oxidation. The hydroxylamine was stirred with 2.2 equivalents of mercuric oxide in dry chloroform for three hours. The resulting solution was filtered slowly through Celite and concentrated to yield a yellow oil, 78% return. The nitrone was stored in a freezer to reduce dimerization and typically formed a bright yellow semisoild. Depending on the purity of the sample, the nitrone was often used directly for the

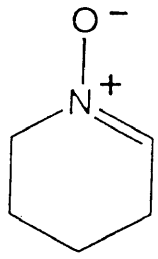
cycloaddition. One problem arising from this method was removal of mercury containing residue from the solution. Several filtering techniques and centrifugation were tried in order to fully remove these, but on standing and cooling, more would precipitate from the resultant solutions.

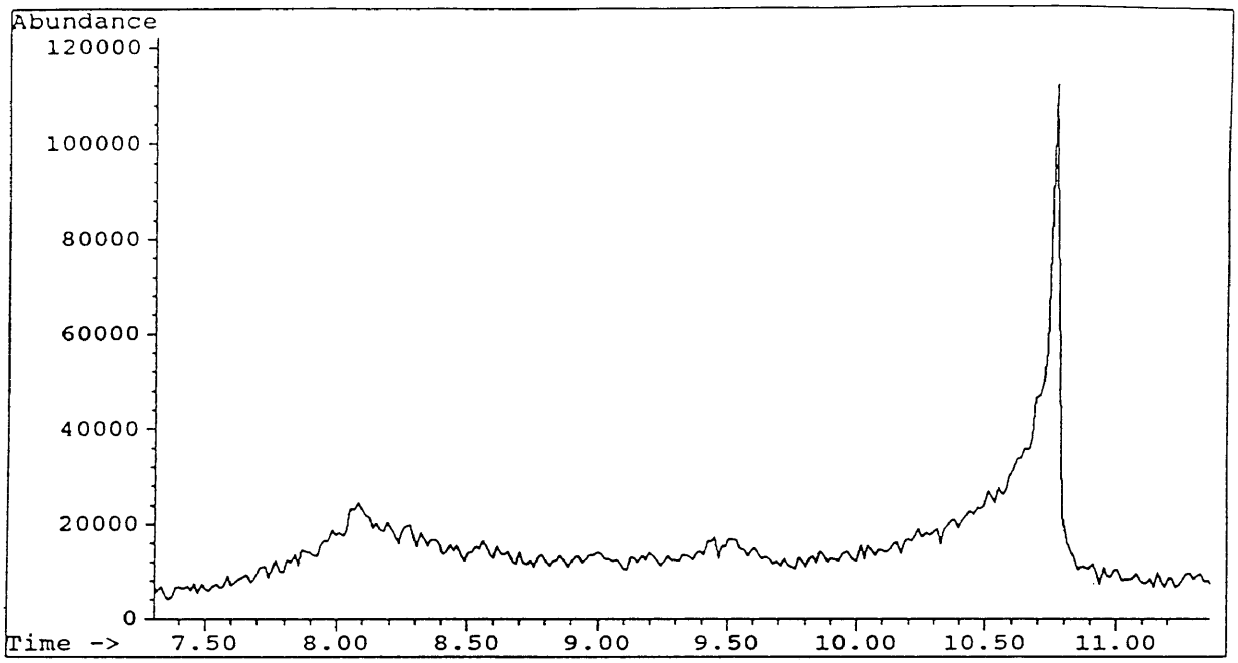
2,3,4,5-Tetrahydropyridine-N-oxide: method B

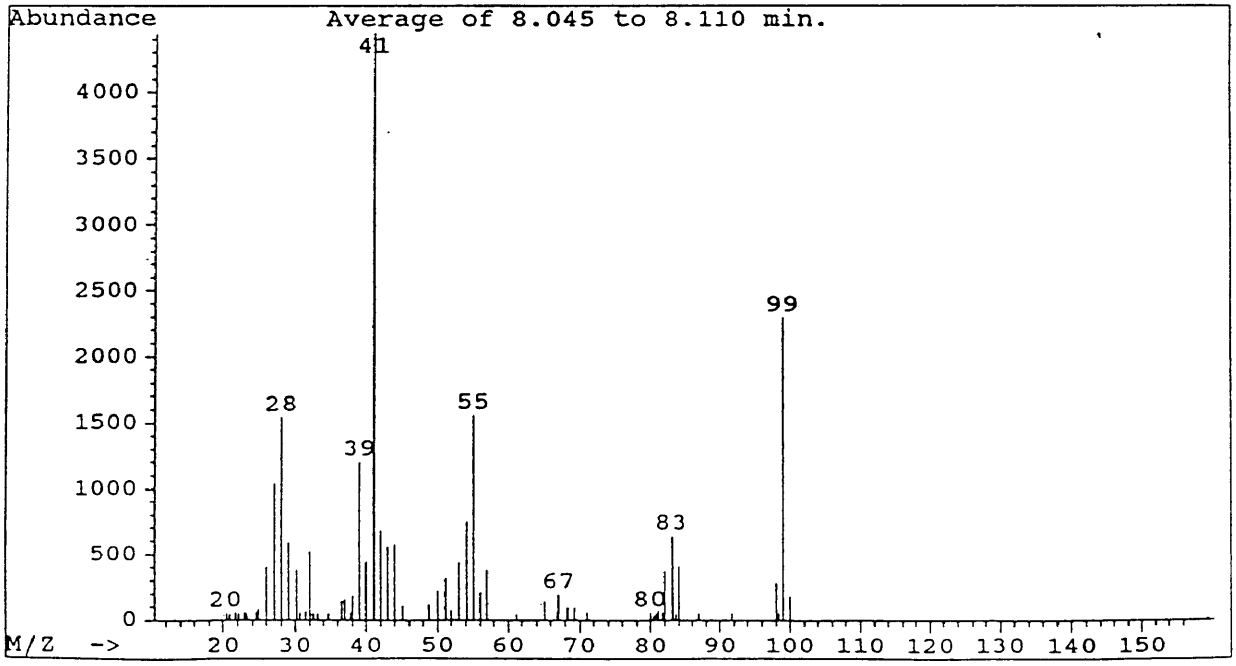
To avoid the problems of dealing with the residual mercury salts, another method was found in the literature. In the place of mercuric oxide, hydrogen peroxide was the oxidizing agent assisted by selenium dioxide catalysis.(29) Piperidine was oxidized by this technique thus foregoing the time consuming N-hydroxypiperidine preparation. To the solution of selenium dioxide (4 mol percent), piperidine and acetone was added 30% hydrogen peroxide (2 equivalents). This mixture stirred at room temperature for three hours with subsequent removal of solvent under reduced pressure and extraction into dichloromethane. Upon concentration, a yellow oil was found to contain the nitrone. GC/MS data for this reaction confirmed production of the nitrone. However, only one attempt at this method proved successful even after varying conditions.

2,3,4,5-Tetrahydropyridine-N-oxide appears in the GC/MS in two peaks. The first peak, Figure 49, shows very poor resolution and returns a mass of 99. This peak only appears in the spectrum of a cooled solution of the nitrone and corresponds to the molecular weight of the nitrone alone. The second peak, Figure 50, was typically used for routine analytical purposes to indicate the presence of the

FIGURE 49


O
N


Abundance
120000
100000
80000
60000
40000
20000
0
Time ->
7.50
8.00
8.50
9.00
9.50
10.00
10.50
11.00


Abundance
Average of 8.045 to 8.110 min.
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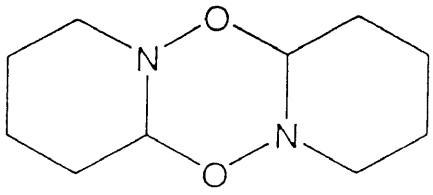
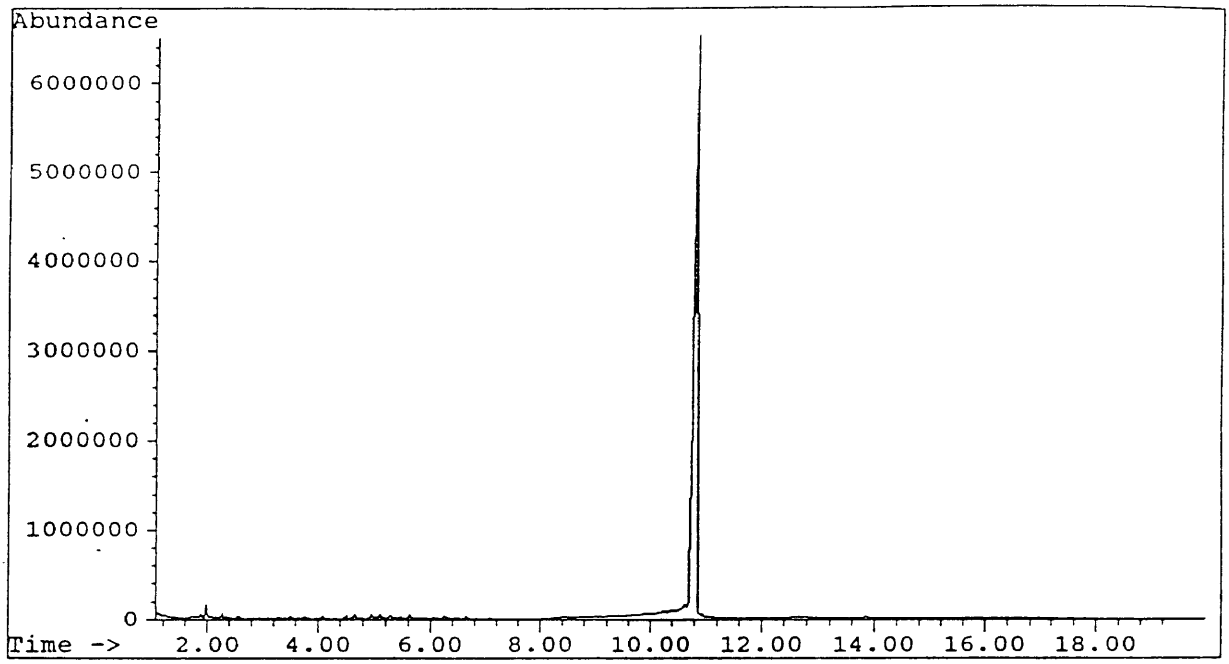
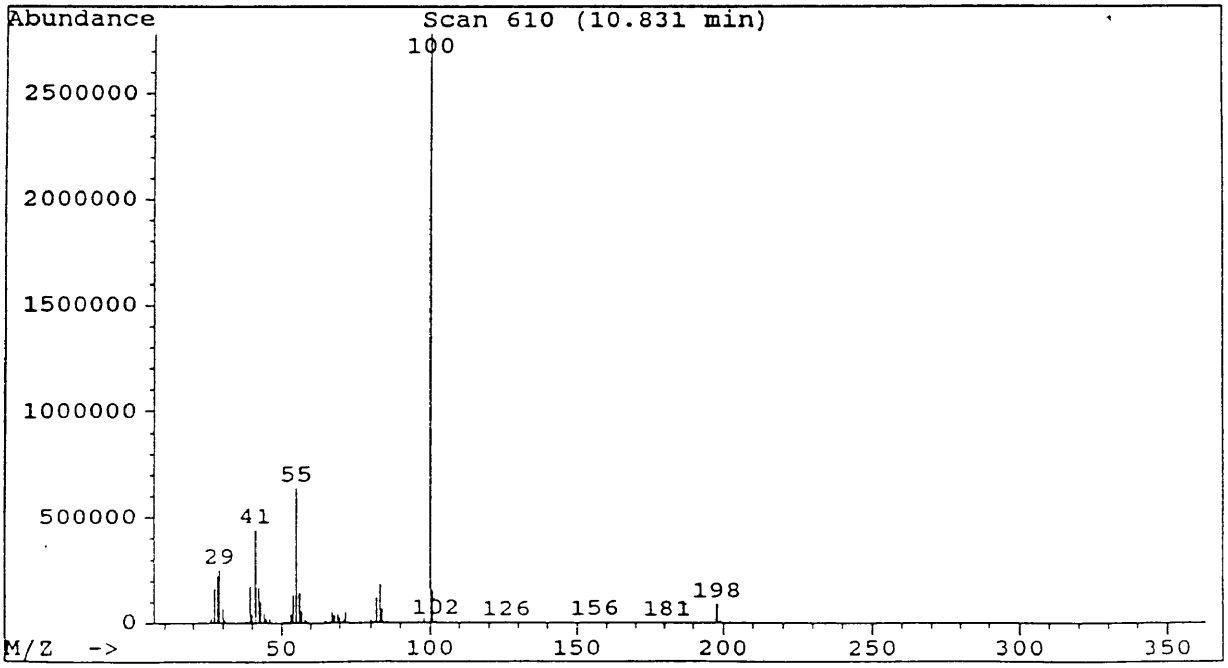
4000
3500
3000
2500
2000
1500
1000
500
0
99
28
55
39
83
67
20
80
M/Z ->
20
30
40
50
60
70
80
90
100
110
120
130
140
150

FIGURE 50


O
N
N
O


Abundance
6000000
5000000
4000000
3000000
2000000
1000000
0
Time ->
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00


Abundance
Scan 610 (10.831 min)
100
2500000
2000000
1500000
1000000
55
500000
41
29
198
102
126
156
181
0
M/Z ->
50
100
150
200
250
300
350

nitrone. With mass 198, this peak represents the dimer of the nitrone which occurs upon standing at room temperature or heating. Since the percentage of dimer increased on heating and the elution of the nitrone itself was quite broad, the dimer GC peak was often the only peak of the two present. The ^{1}H NMR and ^{13}C NMR, Figures 51 and 52, also reveal that the nitrone is in fact formed. The most indicative peak of the proton spectrum is the triplet at 7.11 ppm. This peak represents the vinyl hydrogen. The hydrogens α to the nitrogen opposite the vinyl hydrogen appear at 3.71 ppm. The other three methylenes are not as far downfeild, 2.36, 1.91 and 1.65 ppm. As anticipated, the five groups of peaks, 17.44, 22.83, 25.58, 57.94, and 97.83 ppm, the vinyl carbon. The dimer was purified by flash chromatography on Baker Silica gel (40 μ). The NMR spectra are contained in Figures 53 and 54. The ^{13}C spectrum has five peaks as expected where each signal corresponds to two carbons of the symmetrical dimer. The carbons at the site of the bond fromation appear at 95.38 ppm. The methylenes adjacent to the nitrogens are shifted to 52.10 ppm while the remaining methylenes are at 21.91, 24.04 and 28.10 depending mostly on their distance from the heteroatoms. In the proton, the signals at 3.92 are hydrogens near the ring juncture. The hydrogens on the other carbon adjacent to the nitrogen appear as two peaks at 2.19 and 2.85 ppm. The other hydrogens are seen between 0.90 and 1.50 ppm.

1,3-Dipolar cycloadditions

The nitrone was reacted with two dipolarophiles, 1-decene and more

FIGURE 51

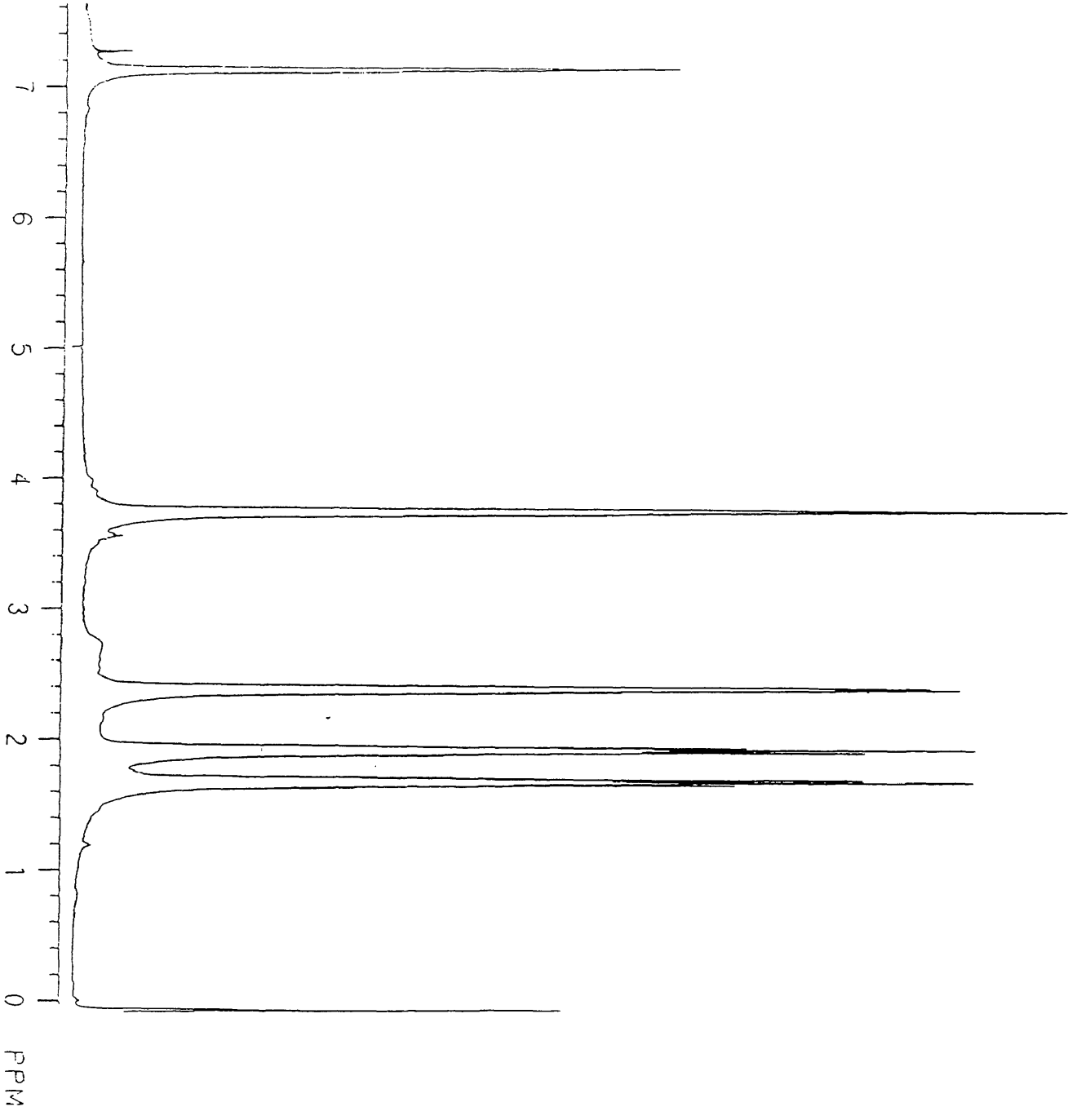


FIGURE 52

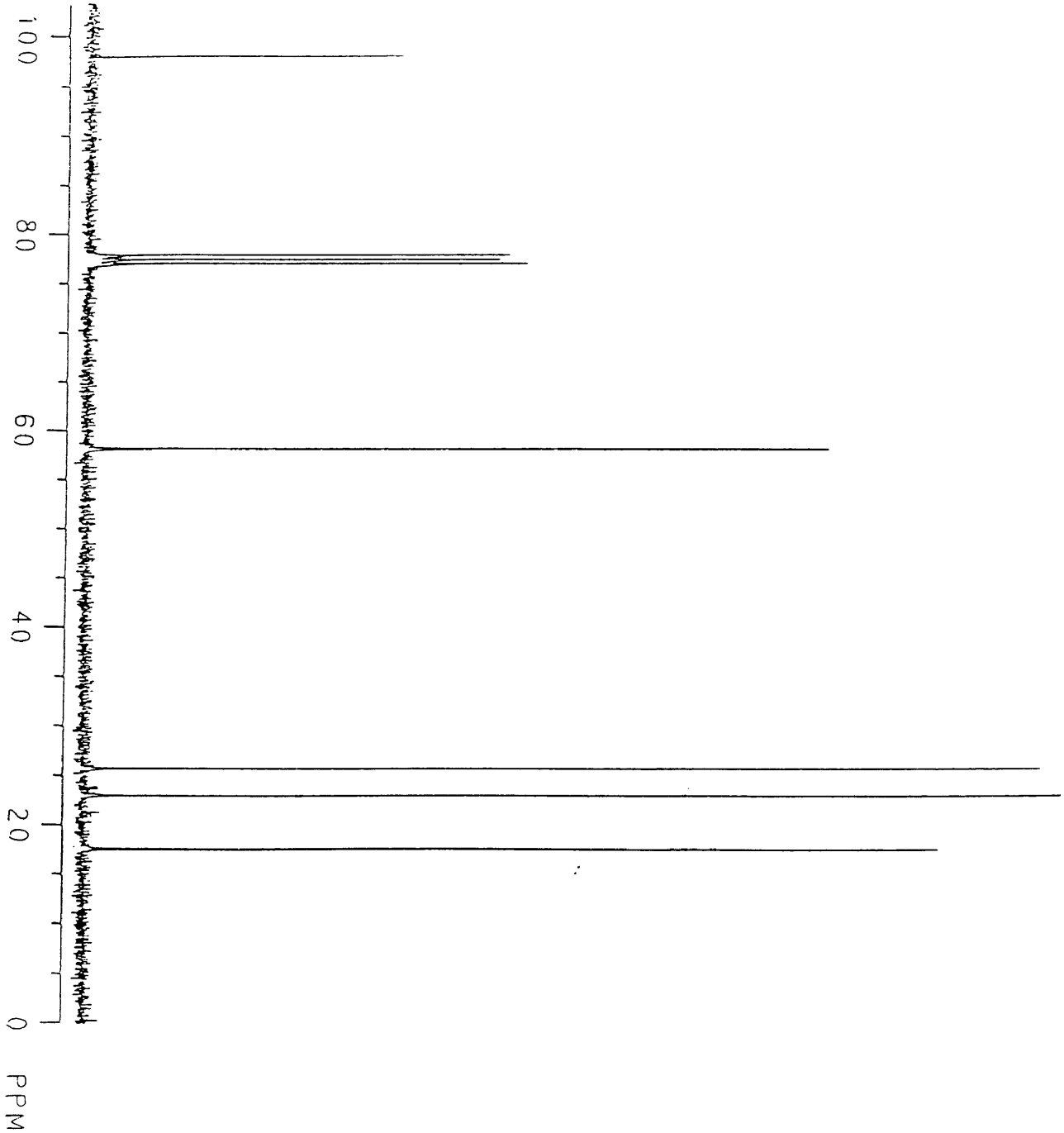


FIGURE 53

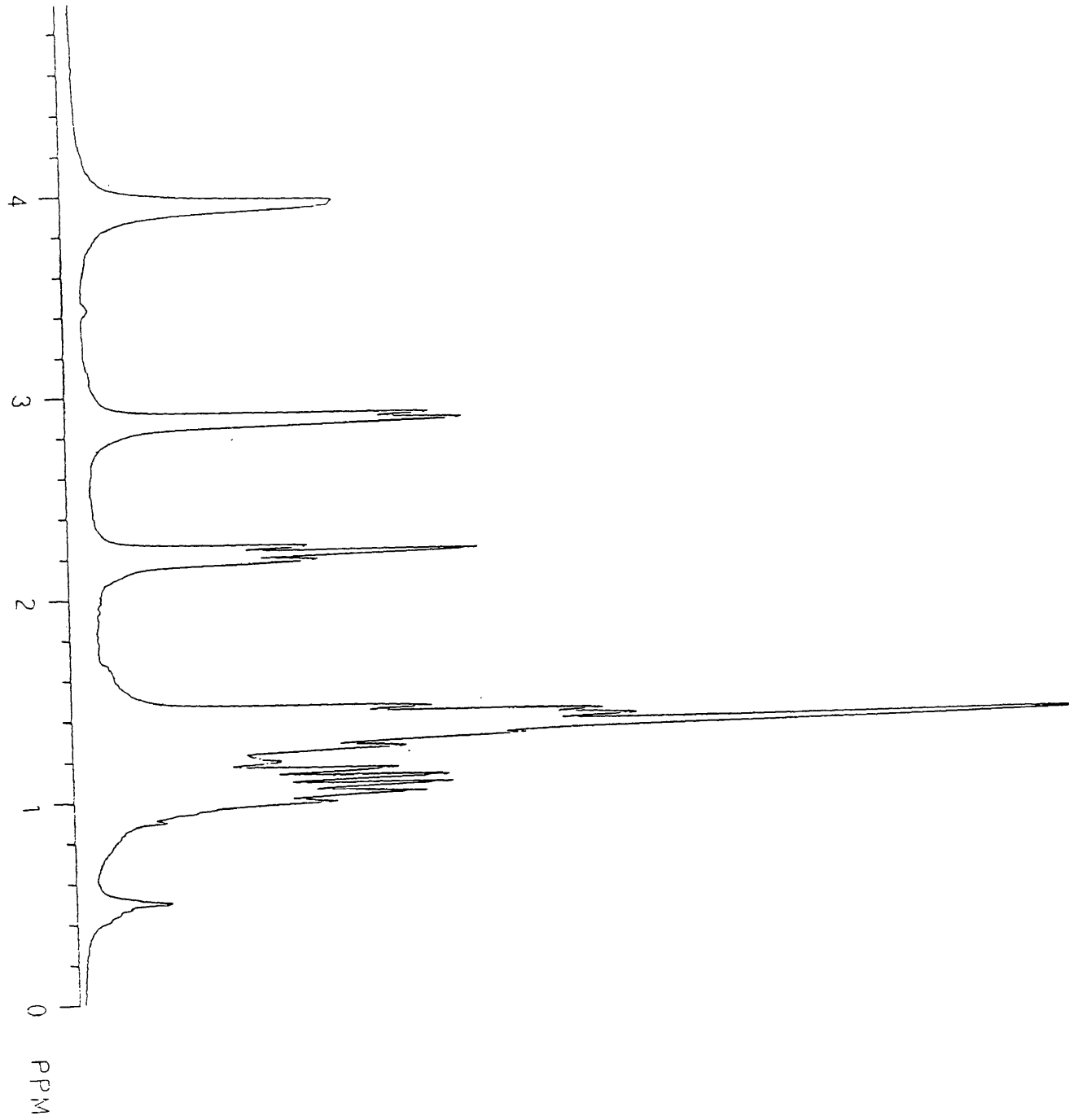
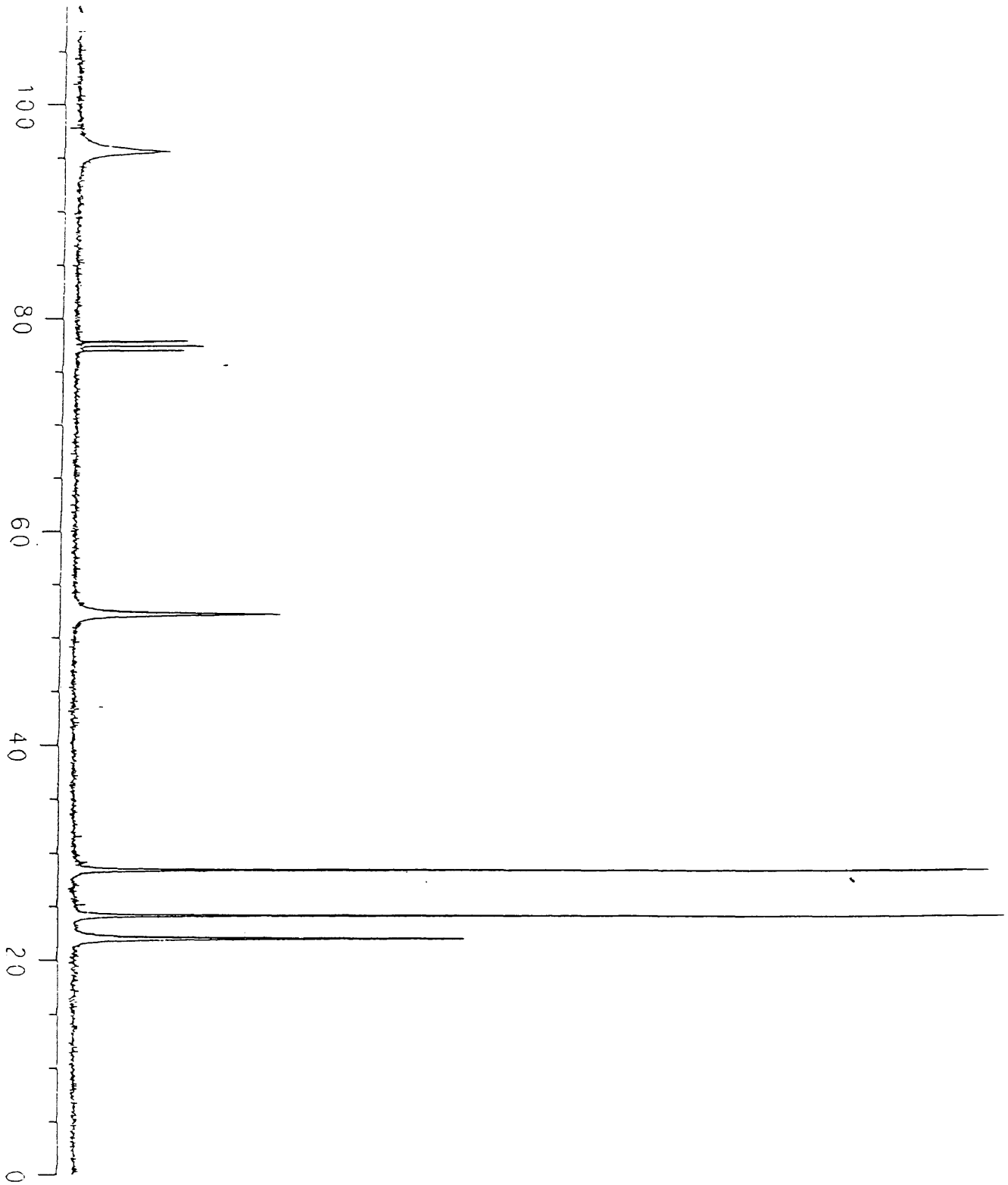


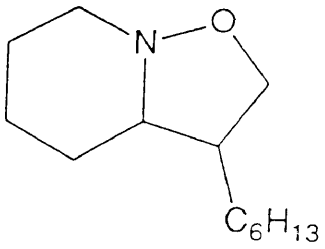
FIGURE 54

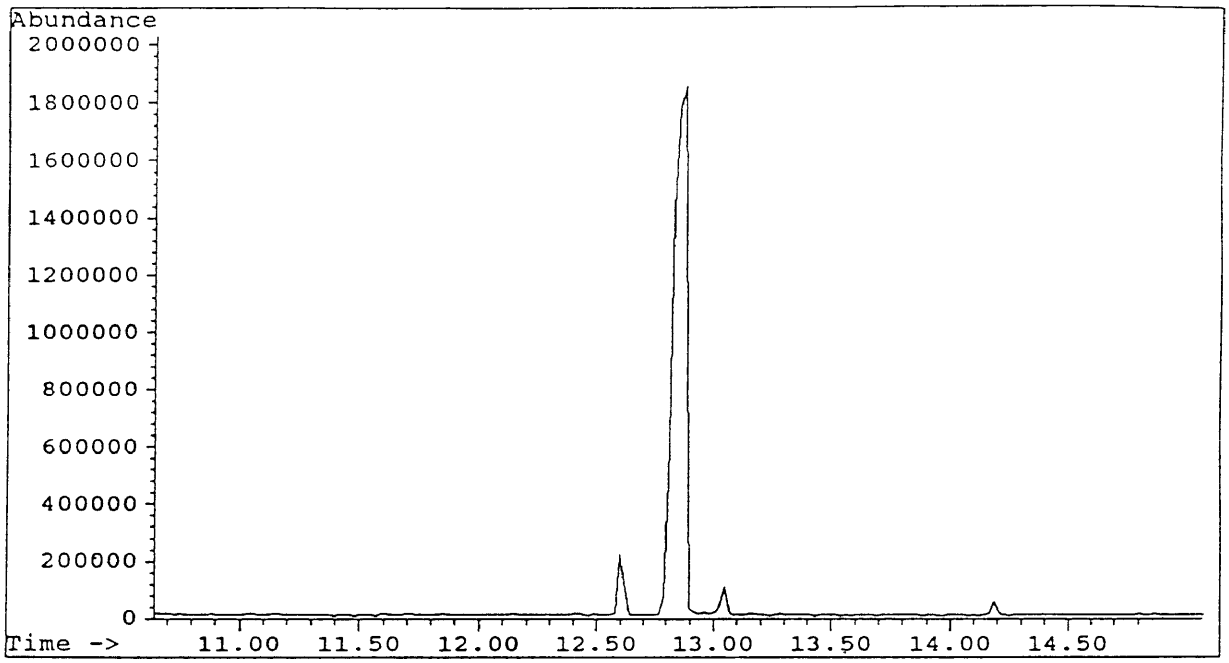


importantly, E-B-(1-hexenyl)-1,3-dioxaborolane. 1-Decene was used as a model reaction and proceeded as expected to yield cycloadducts of molecular weight of 239 by GC/MS, Figure 55. The alkenyl boronate was then tested over a variety of temperatures, 50°C, 70°C, 90°C and 110°C, and found to react best at 90°C in a sealed tube for seven hours or less. In addition, slight excess of boronate reduced the impurities as detected by the mass spectrometry. Again, the desired product was found by GC/MS, Figure 56, to have weight 253 as predicted and a base peak of 100. Figure 57 demonstrates the ^{1}H NMR for the crude boronate cycloadduct, more correctly 3-butyl-3,3a,4,5,6,7-hexahydro-2H-isoxazolo-[2,3b]-pyridine-3-(1,3-dioxaborolane). The appearance of broad singlet near four ppm, next to that of the unreacted starting dioxaborolane, indicates the presence an additional dioxaborolane.

Attempts to isolate both the decene and boronate cycloadducts proved difficult. Procedures tested include preparative gas chromatography, flash chromatography, preparatory thin layer chromatography, distillation, recrystallization and derivatization. All proved regretfully unsuccessful. The cycloadduct apparently reverts on heating, thus thwarting prep GC attempts. Strangely though, it eluted well on the capillary column of the GC/MS. The capillary column possessed a similar stationary and temperature parameters to the packed preparatory column. Even at relatively low temperatures, 70°C in a Kugel Rohr distillation, the percentage of cycloadduct decreased as ester was removed. Silica gel techniques are ineffective because the boron compounds react resulting in

FIGURE 55


N
O
C_6H_{13}


Abundance
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1600000
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1200000
1000000
800000
600000
400000
200000
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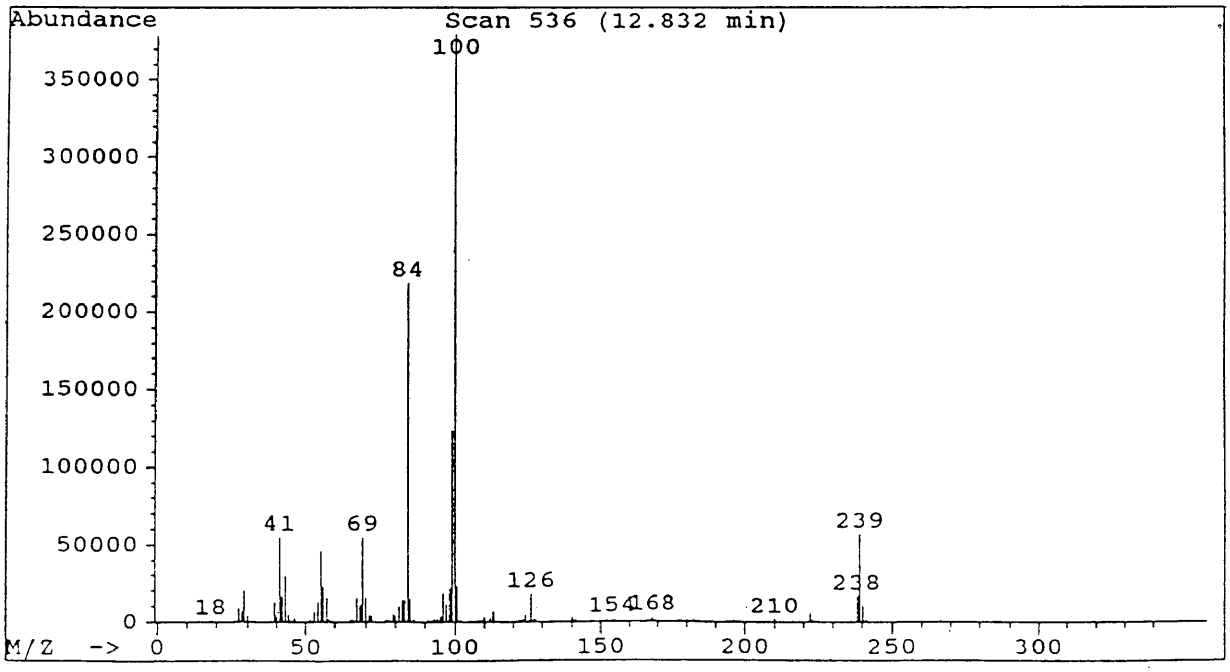
11.00
11.50
12.00
12.50
13.00
13.50
14.00
14.50


Abundance
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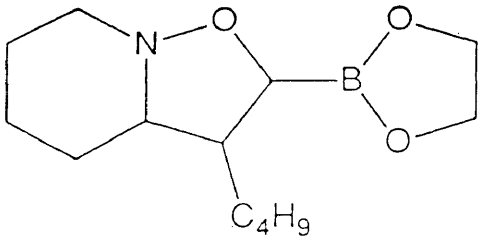
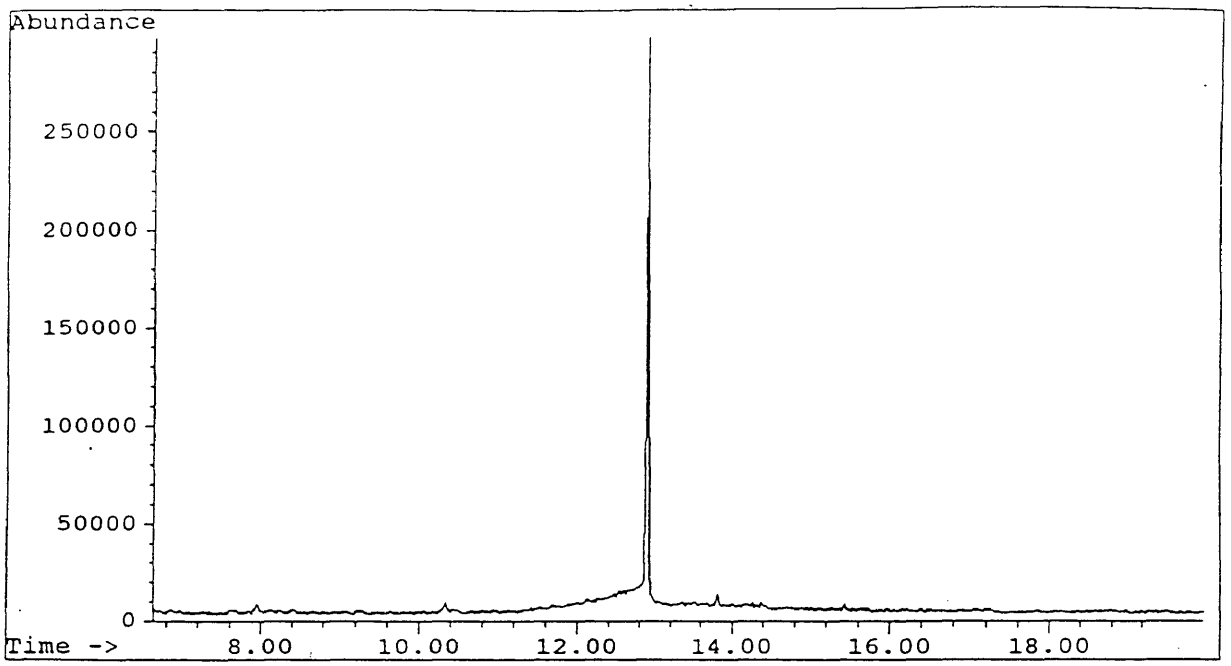
350000
300000
250000
84
200000
150000
100000
41
69
239
50000
126
238
18
154
168
210
0
M/Z ->
0
50
100
150
200
250
300

FIGURE 56


N
O
O
B
O
C_4H_9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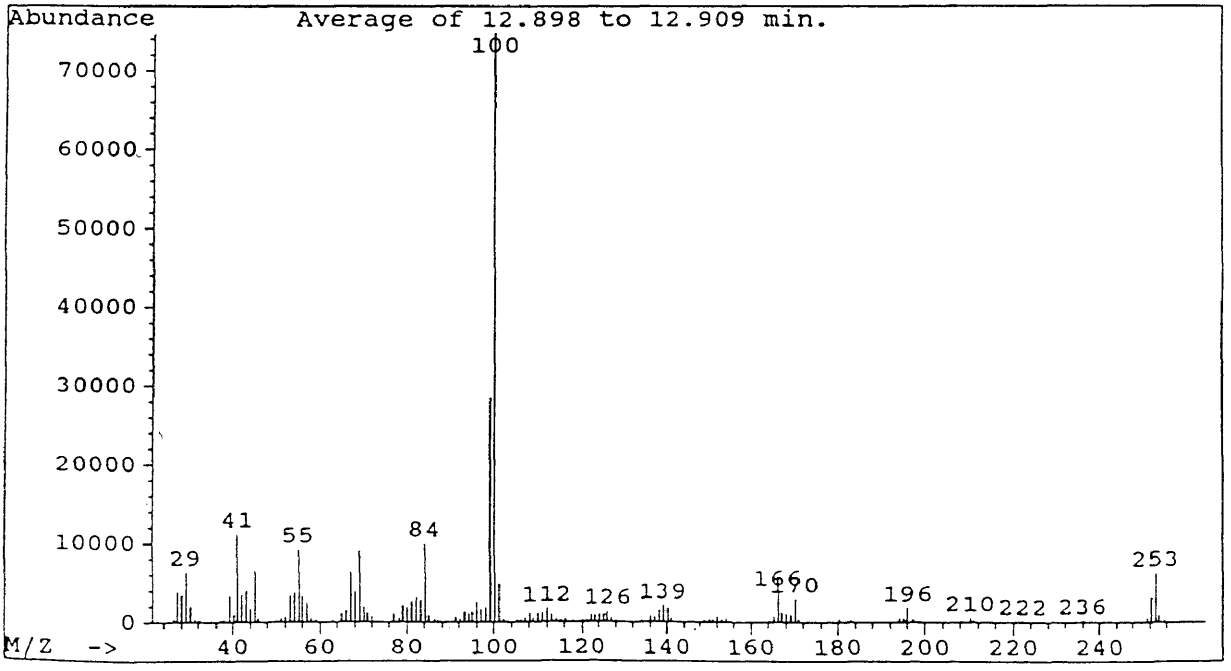
16.00
18.00


Abundance
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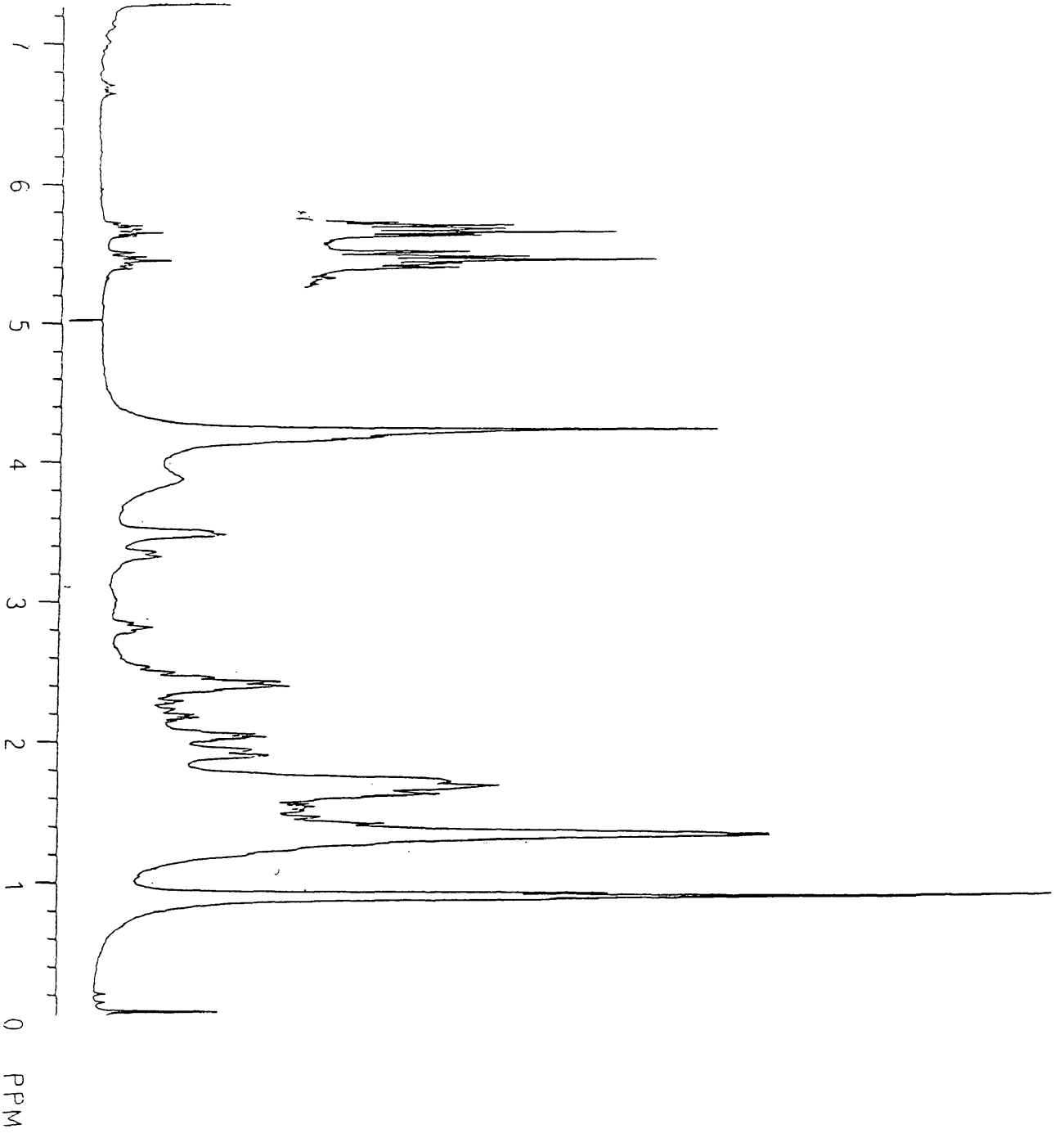
60000
50000
40000
30000
20000
10000
0
29
41
55
84
112
126
139
166
190
196
210
222
236
253
M/Z ->
40
60
80
100
120
140
160
180
200
220
240

FIGURE 57



poor elution. Possibilities for future attempts are reverse phase chromatography and separation after some derivatization technique.

The data listed above indicate that the expected cycloadduct is present. Thus, the initial attempt to construct a boron-substituted heterocycle was successful. Further research should be conducted to examine the reactions of a variety nitrones and alkenylboronate esters and a means of purifying these compounds.

Experimental

All reactions were conducted under an atmosphere of nitrogen and stirred magnetically unless otherwise noted. Reagents were obtained from commercial suppliers. NMR spectra were acquired on a General Electric QE-300 NMR spectrometer, proton at 300 MHz and carbon at 75 MHz. Samples for NMR were dissolved in $CDCl_3$. Chemical shifts are expressed in ppm downfield from tetramethylsilane followed by multiplicities (s,singlet; d,doublet; t,triplet; q,quartet; m,multiplet) and number of hydrogens. Mass spectra were obtained on a Hewlett-Packard 5971a mass selective detector coupled to a HP5890 Series II gas chromatograph, OV-1 capillary column (0.20 mm diameter, 0.33 μm film thickness). Temperature programming for these chromatographs was as follows: 60°C, 2 min: 11°C/min to 140°C: 17°C/min to 250: 250°C, 4 min.

E-1-Hexenyl boronic acid. To a dry 1 L three-neck round bottom flask containing CH_2Cl_2 (100 ml) and 1-hexyne (20 ml, 0.2 mol) near 0°C, $HBBr_2{\cdot}S(CH_3)_2$ in CH_2Cl_2 (200 ml, 1.0 M, 0.2 mol) was added slowly via syringe. After addition, the mixture warmed to room temperature and stirred for 3 hours. The flask was again cooled to 0°C followed by slow addition of a solution of NaOH (147 ml, 3 M,

0.44 mol) through an addition funnel, stirring for 1 hour. The solution was extracted three times with 250 ml 5:1 diethyl ether/CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated affording a white solid, the boronic acid (19 g, 86%). ^{1}H NMR δ 0.90 (t,3H), 1.33 (m,4H), 2.18 (m,2H), 5.42 (d,1H), 6.53 (dt,1H). ^{13}C NMR ($(CH_3)_2SO$) δ 14.26, 22.92, 31.18, 123.11, 151.43.

E-B-(1-Hexenyl)-1,3-dioxaborolane. E-1-Hexenyl boronic acid (19g, 0.15 mol) was placed in a 1000 ml round bottom flask with benzene (750 ml) and ethylene glycol (9.2 g, 0.15 mol). Benzene and water were azetropically removed until the distillate was clear and the total volume was one third of the original. The remainder of the solvent was then removed under reduced pressure leaving a yellow oil. The ester was purified to a colorless oil by Kugel Rohr distillation and collected from 42° to 45°C at 1.5 torr (20 g, 87%). ^{1}H NMR δ 0.87 (t,3H), 1.34 (m,4H), 2.15 (m,2H), 4.21 (bs,4H), 5.45 (d,1H), 6.65 (dt,1H). ^{13}C NMR δ 13.92, 22.28, 30.50, 35.63, 65.53, 117.70, 155.55. MS *m/z*(%) 154.1 (18), 125.0 (40), 112.0 (100), 81.0 (41), 68.0 (46).

Mercuric oxide. Mercuric chloride (150 g, 0.552 mol) in water was cooled to 0°C and stirred mechanically. Approximately 2 equivalents NaOH were added slowly enough to maintain the low temperature as a 3M solution ($\sim$360 ml) until the solution turned bright orange. The suspension was then filtered, and the water was removed from the powder in a vacuum oven at 1.5 torr, 45°C yielding bright orange mercuric oxide (105 g, 88%).

N-Hydroxypiperidine. Hydrogen peroxide (30%, 340 ml) was added through an addition funnel over 4 hours to a 1000 ml three-neck round bottom cooled to near 0°C containing 1-ethylpiperidine (137 ml, 1.0 mol) and ethanol (100 ml). This mixture then stirred at room temperature for 3 to 5 days. After which, the solution was cooled to 0°C, and a slurry of platinum black (0.125g) in water was very slowly added via an addition funnel followed by stirring for 4 hours. The solvents were removed by distillation at 1 torr and up to 70°C. The resultant white solid was heated to melting and eventually reflux through a wide bore condenser for 15 minutes gently, 30 minutes moderately and 30 minutes vigorously. A dark oil was distilled through a 15 cm path using a nitrogen line to attain a pressure of 17 torr on a vacuum pump. A pale yellow solid was collected between 70° and 90°C in a receiver in a bath of acetonitrile cooled by liquid nitrogen to near -35°C. The solid was recrystallized from ethyl acetate by adding hexanes till cloudy before cooling. The white solid collected was verified to be N-hydroxypiperidine (82g, 81%). ^{1}H NMR δ 0.70 (m,1H), 1.11 (m,3H), 1.25 (bd,2H), 1.96 (t,2H), 2.75 (bd,2H), 8.76 (vbs,1H). ^{13}C NMR δ 22.53, 24.55, 58.34. MS *m/z*(%) 101 (49), 100 (100), 84 (27) 60 (19).

2,3,4,5-Tetrahydropyridine-N-oxide. Method A. Mercuric oxide (20 g, 0.092 mol) was placed in 110 ml chloroform. N-Hydroxypiperidine (4.0 g, 0.040 mol) was added after the suspension turned from orange to gray/green. After 3 hours, the solution was allowed to settle and was filtered through Celite. The

solvent was removed from the filtrate under reduced pressure to yeild a yellow oil (3.1 g, 78%). ^{1}H NMR δ 1.65 (m,2H), 1.91 (m,2H), 2.36 (m,2H), 3.71 (dt,2H). ^{13}C NMR δ 17.44, 22.83, 25.58, 57.94, 97.83. MS *m/z*(%) 99 (51), 83 (16), 55 (38). [dimer: ^{1}H NMR δ 1.05 (m,4H), 1.35 (m,8H), 2.19 (bt,2H), 2.85 (bd,2H), 3.92 (vbd,2H). ^{13}C NMR δ 21.91, 24.04, 28.30, 52.10, 95.38. MS *m/z*(%) 198 (3), 100 (100), 83 (6), 55(20)]

Method B. Piperidine (4.2 g, 0.049 mol) in acetone (110 ml) was cooled to 0°C. Hydrogen peroxide (30%, 0.109 mol) was added, followed quickly by addition of selenium dioxide (0.219 g, 0.0020 mol) in acetone. The solution was maintained at 0°C for 15 minutes and at room temperature for 3 hours. The solution was prepared for extraction by adding 200 ml water and CH_2Cl_2 until two layers formed. The mixture was extracted with three 300 ml portions of CH_2Cl_2. The organic layer was dried with Na_2SO_4 and was evaporated under reduced pressure.

3-Octyl-3,3a,4,5,6,7-hexahydro-2H-isoxazolo-[2,3b]-pyridine. Nitrone from method A (3.8 g, 0.038 mol), the alkene, 1-decene (4.7 g, 0.042 mol) and benzene (5 ml) in a sealed tube were heated at 90°C for 5 hours. The benzene was removed under reduced pressure. A yield of 68% was determined by using tetradecane as an internal standard. MS *m/z*(%) 239 (19), 100 (100), 99 (32), 84 (57), 69 (13), 55 (12).

3-Butyl-3,3a,4,5,6,7-hexahydro-2H-isoxazolo-[2,3b]-pyridine-3-(1,3-dioxaborolane). 2,3,4,5-Tetrahydropyridine-N-oxide (3.8 g, 0.038 mol), E-B-(1-

hexenyl)-1,3-dioxaborolane and benzene (5 ml) were placed in a sealed tube. The tube was subsequently heated at 90°C for five hours. The yield was determined to be 55% by gas chromatography with tetradecane as an internal standard. MS *m/z*(%) 253 (8), 100 (100), 99 (38), 84 (13), 69 (12), 55(12).

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