Cycloaddition Reactions of A Heterocyclic Nitrone

by

Hasan Ali Saleh Al-Muallem

A Thesis Presented to the

FACULTY OF THE COLLEGE OF GRADUATE STUDIES

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
Requirements for the Degree of

MASTER OF SCIENCE

In

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June, 1992

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Cycloaddition reactions of a heterocyclic nitrone

Al-Muallem, Hasan Ali Saleh, M.S.

King Fahd University of Petroleum and Minerals (Saudi Arabia), 1992

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DHAHRAN 31261, SAUDI ARABIA

COLLEGE OF GRADUATE STUDIES

This thesis, written by

Hasan Ali Saleh Al-Muallem

under the direction of his Thesis Advisor and approved by his Thesis Committee, has been presented to and accepted by the Dean of the College of Graduate Studies, in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN CHEMISTRY.

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Member (Dr. H. Perzanowski)

Member (Dr. A. Al-Hamdan)

Chairman, Department of Chemistry

Dean, College of Graduate Studies

Date 22-10-92

In the name of God, Most Gracious, Most Merciful

"O my Lord! Advance me in knowledge."

To My Family

ACKNOWLEDGEMENT

Praise be to Allah, Lord of the Universe. May blessings and greetings be upon prophet Mohammed, his posterity, and his companions.

I wish to express my acknowledgement to the King Fahd University of Petroleum and Minerals for providing me the opportunity and support to carry out this work.

My deep appreciation and sincere gratefulness are due to my Major Advisor and Thesis Committee Chairman Dr. Sk. Asrof Ali, who has been a constant source of patient guidance, generous support, and encouragement throughout this study. I am also indebted to the other members of my Thesis Committee Dr. H. Perzanowski and Dr. A. J. Al-Hamdan for their review of my work and for their valuable suggestions and helpful remarks.

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My gratitude is due to the Chemistry Department; Chairman, Faculty Members, and Staff Members.

Finally, a word of appreciation should go to my family and friends for their moral support and encouragement.

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خلاصة الرسالة

اسم الطالب : حسن علي صالح المعلم

عنوان الدراسة : تفاعلات الإضافة الحلقية لنيترون حلقي غير متجانس

التخصص : الكيمياء

تاريخ الشهادة : ذوالحجة ١٤١٢ (يونيو ١٩٩٢م)

تناول هذا البحث دراسة السلوك الكيميائي الموضعي الإتجاهي "regiochemical" والسلوك الكيميائي المجسم "stereochemical" لتفاعلات الإضافة لنيترون حلقي غير متجانس (٥،٦- ثنائي هيدرو-١ ،٤-أوكسازين ٤-أوكسيد) مع عدة الكينات. وقد أعتمدت المدارات الجزيئية الأمامية في تفسير الدرجة العالية الملحوظة لتحكم الإتجاه الكيميائي الموضعي في هذه التفاعلات ، في حين تم تفسير انتقائية التجسم "stereoselectivity" بالنظر إلى العوامل الفراغية والتفاعلات المدارية الثانوية .

وفي هذه الدراسة تم تعيين ثوابت سرعة تفاعل الإضافة الحلقية للنيترون الحلقي غير المتجانس مع عدد من الألكينات بواسطة مطيافية الطنين النووي المغنطيسي للبروتون "^{1}H NMR" في درجة حرارة ٣٦° م . وقد أخذت في الاعتبار عدة عوامل لتفسير الاختلاف في سرعة تفاعلات الإضافة مثل الإجهاد الالتواني"torsional strain" ، وإجهاد انحناء زاوية الرابطة ، والعوامل الفراغية (من قبيل تنافرعدم الترابط) في حالة التحول .

وتضمنت الدراسة تحديد قيم حاجز انقلاب النيتروجين "nitrogen inversion" في نواتج تفاعلات الإضافة الحلقية للنيترون وذلك بواسطة التحليل الدقيق لشكل النطاق "band shape" لمطيافية الطنين النووي المغنطيسي للبروتون والكربون ، وكانت القيم واقعة في المدى ٦٦.٣- ٧٢.٩ كيلو جول/مول . كما أن قيمة حاجز انقلاب الكرسي "chair inversion" قد حددت أيضا بواسطة تحليل شكل النطاق لمطيافية الطنين النووي المغنطيسي للبروتون ووجد أنها تساوي ٤١.٥ كيلو جول/مول . وفيما عدا حالة واحدة فإن المتشكل الرئيس كان دائماً أحادي الجانب "cis" وكان في حالة إتزان مع المتشكل ذي الجانبين "trans isomer".

كذلك تمت دراسة ميكانيكية تفاعلات فك الحلقة بواسطة البيرأسيد "peracid" لعدة نواتج من تفاعلات الاضافة . إن اتجاه زوج الألكترونات المنفرد يحدد الاختيارية الموضعية "regioselectivity" في فك الحلقة والذي يتضمن إزالة ناشطة "kinetic" لبروتون من الأيون الوسيط نيتروكسونيوم.

وجرى في البحث أيضا تحضير عدة مركبات وسيطة "intermediates" يمكن استخدامها في تحضير نيترونات حلقية غير متجانسة .

درجة الماجستير في العلوم

جامعة الملك فهد للبترول والمعادن

الظهران ، المملكة العربية السعودية

١٤١٢ هـ - ١٩٩٢ م

THESIS ABSTRACT

Name of Student : Hasan Ali Al-Muallem

Title of Study : Cycloaddition Reactions of a Heterocyclic Nitrone

Major Field : Chemistry

Date of Degree : June, 1992

A study of the regiochemical and stereochemical behavior of the addition reaction of a heterocyclic nitrone, 5,6-dihydro-1,4-oxazine 4-oxide with a series of alkenes has been carried out. The high degree of regiochemical control in these concerted reactions has been explained in terms of frontier molecular orbital treatment. Stereoselectivity in these cycloadditions has been explained in terms of steric factors and secondary orbital interactions.

Rate constants for the cycloaddition of the heterocyclic nitrone with several alkenes have been determined at 36°C by ^1H NMR spectroscopy. Differences in the rates of cycloadditions have been explained in terms of combination of various factors such as torsional strain, bond angle bending strain, and steric factors (non-bonded repulsion) in the transition state.

The barrier to nitrogen inversion in the nitrone cycloaddition products has been determined by detailed band shape analysis of proton and carbon NMR spectra and were in the range of 66.3 to 72.9 kJ/mol. The chair inversion has been slowed, in one case to show the presence of the two forms of the *cis* isomers. The barrier to chair inversion is 41.5 kJ/mol as determined by proton NMR band shape analysis. Except in one case, the major conformational isomer is shown to be the *cis* conformer, which is in equilibrium with the minor *trans* conformer.

A mechanistic study of peracid induced ring opening of several cycloadducts has been carried out. The orientation of the nitrogen lone pair dictates the regioselectivity of the ring opening which involves an intramolecular kinetic deprotonation of a nitroxonium ion intermediate.

Synthesis of several intermediates which can lead to the synthesis of various heterocyclic nitrones has been made.

Master of Science Degree
King Fahd University of Petroleum and Minerals
Dhahran, Saudi Arabia
June, 1992

CHAPTER 1

INTRODUCTION

Among a plethora of functional groups, nitrone functionality has etched an important place in organic chemistry. The nitrone cycloaddition reactions, the best chemical template for constructing isoxazolidines, is extremely efficient in incorporating multiple stereocenters in a single step. The cycloadditions that are used in key steps for the synthesis of several interesting natural products, was made possible owing to the brilliant efforts of Huisgen,[22-24] LeBel,[25] and Tufariello[27] who explored systematically the inter- and intra-molecular 1,3-dipolar cycloaddition reactions.

The regio-, stereo-chemical, and reactivity aspects of nitrone cycloadditions involving both cyclic and acyclic nitrones have been explored in some detail. However, the progress in the study of stereochemical details has been hampered in most cases because of the difficulties associated with unambiguous assignment of adduct configurations.

The frontier orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena of 1,3-dipolar cycloadditions. According to Sustmann's classification,[73] nitrone cycloaddition is a type II process, where both HOMO(nitrone) - LUMO(alkene) and LUMO(nitrone) - HOMO(alkene) interactions contribute to the stabilization of the transition state. Both electron-rich and electron-deficient alkenes undergo addition faster than normal alkenes.

Even though the cycloadditions of several carbocyclic nitrones have been studied in detail, the reactions of the corresponding heterocyclic nitrones have been

scarcely mentioned in the literature. The addition reaction of 5,6-dihydro-1,4-oxazine 4-oxide, a heterocyclic nitrone, would incorporate a morpholine moiety in the cycloadducts. Compounds containing morpholine moiety are known to possess biological as well as useful industrial properties. Analogs of biologically active natural products containing piperidine nuclei can be prepared using the cycloaddition reaction of 5,6-dihydro-1,4-oxazine 4-oxide. The resultant products would have morpholine nuclei instead of piperidine. It would be interesting to assess the biological activity of these analogs.

In light of the importance of this heterocyclic nitrone, our objectives in this study were to undertake :

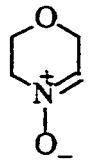
(i). a systematic study of the regio- and stereo-chemical details of the cycloaddition of the heterocyclic nitrone (I) to several mono- and di-substituted alkenes (II),

(ii). a kinetic study of the additions of the nitrone to several alkenes (II),

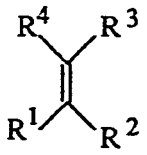
(iii). a study of nitrogen and chair-inversion in substituted perhydro-1,2-oxazolo[3,2-c][1,4]oxazines, the resultant cycloaddition products (III),

(iv). a study of the regiochemistry of the peracid induced ring opening of the isoxazolidine (III) to produce "second generation of nitrone (IV) and (V)" which would be subjected to a second cycloaddition reaction,

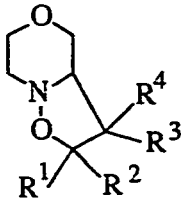
(v). a synthesis of other heterocyclic nitrones of the type (VI) which could be used in the synthesis of an important intermediate in synthesis of β-lactam antibiotics.



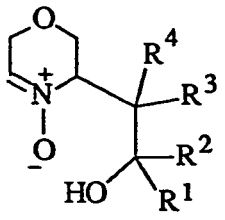
(I)



(II)



(III)



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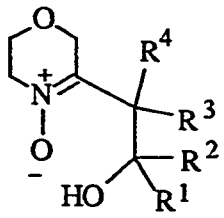

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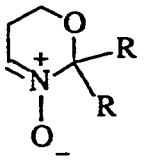
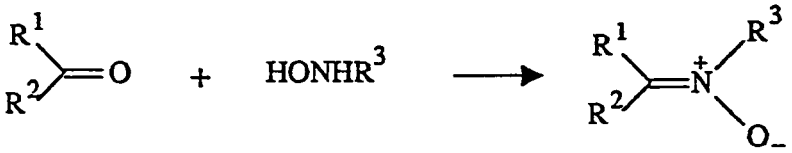


(VI)

CHAPTER 2

THE CHEMISTRY OF NITRONES

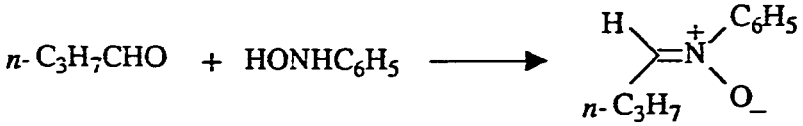
The condensation of carbonyl compounds (1), aldehydes and ketones with primary hydroxylamines (2) gives azomethine oxides (3). Early researchers coined the term "nitrones"[1], which is a contraction of the words "nitrogen" and "ketone", to describe the newly discovered functionality (3). This was done in an effort to emphasize the similarity between the newly discovered nitrone moiety and the versatile chemistry of the carbonyl compounds. For example, nitrones, like carbonyl compounds, are capable of undergoing reaction with various types of carbanions.[2-4]



(1) (2) (3)

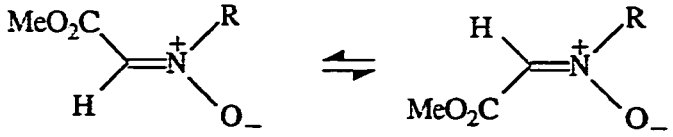
2.1 Preparation of the Nitrone

Preparation of nitrones has been reviewed in detail.[5-7] An excellent method of preparation of nitrone is the condensation of primary hydroxylamine with an aldehyde or ketone. *n*-Butyraldehyde (5) and N-phenylhydroxylamine (6) afford the Z isomer of the aldonitrone N-phenyl-C-(*n*-propyl) nitrone (7). However,



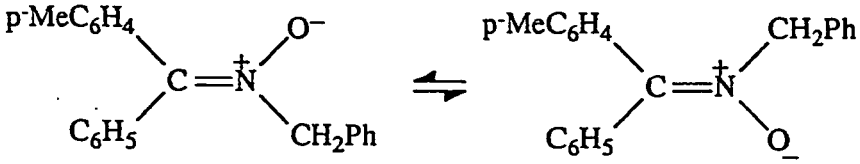
(5) (6) (Z) (7)

nitrones (8) having α-methoxycarbonyl group have been found to exist to a considerable extent in the E configuration.[8]



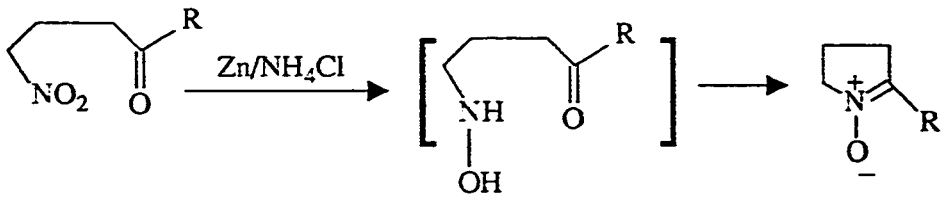
(E) (8) (Z) (8)

The energy of activation, E_a, for the isomerization of the ketonitrone (9a) into (9b) has been determined to be 33.6 kcal/mole.[9] Aldonitrones also exhibit a similar barrier to interconversion of (E) and (Z) isomers.[10]



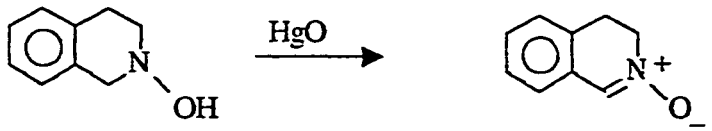
(9a) (9b)

Cyclic nitrones (12) are obtained by intramolecular condensation of hydroxylamine (11) produced by reduction of γ-nitroketones (10).



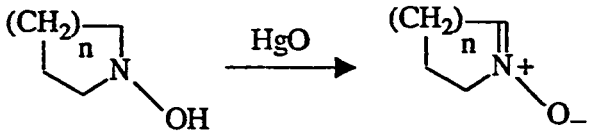
(10) **(11)** **(12)**

The conversion of secondary hydroxylamines to cyclic nitrones has been achieved by a variety of oxidants, the most notable being yellow mercuric oxide.[11]



(13) **(14)**

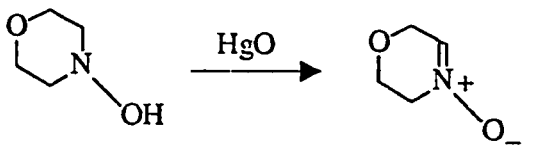
Cyclic nitrones **(14)**-**(17)** are similarly prepared by oxidation of the corresponding hydroxylamines with yellow mercuric oxide. Facile preparation of these cyclic



(15) **n = 1**

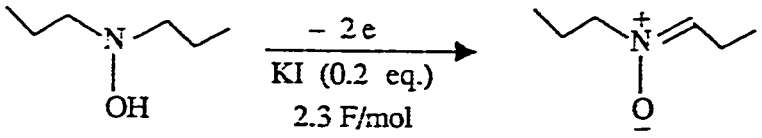
(16) **n = 2**

(17) **n = 3**



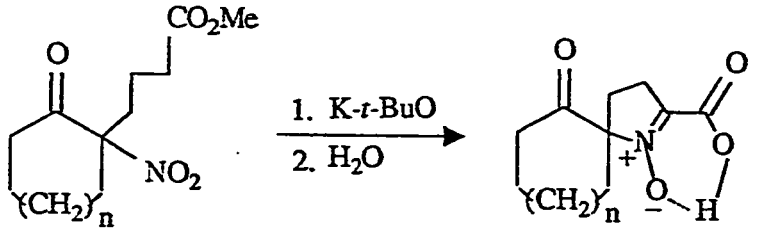
(18) **(19)**

nitrones and also acyclic nitrones (21) has been achieved by electrochemical oxidation of N-hydroxyl secondary amines (e.g. 18) using halogen as a mediator.[12]



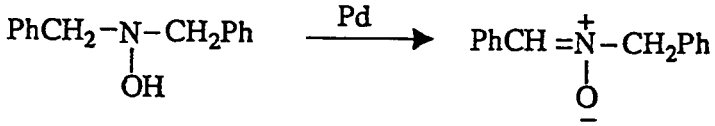
(20) (21)

Formation of nitrones (23) from tertiary nitroalkenes (22) in the presence of K-*t*-BuO has been achieved.[13]



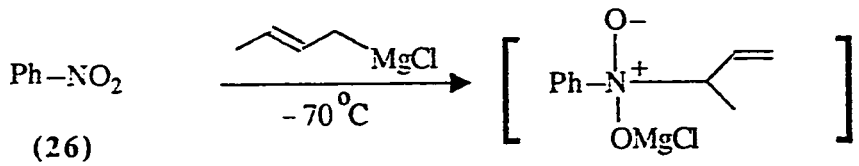
(22) (23)

Palladium catalyzed reactions of secondary hydroxylamines (both cyclic and acyclic) give the corresponding nitrones with high efficiencies.[14] Reaction of aryl



(24) (25)

and alkyl nitro compounds (26) with 2-butenyl magnesium chloride afford a new class of nitrones (27).[15] Regioselective synthesis of substituted cyclic nitrones



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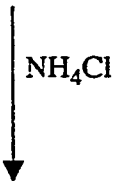
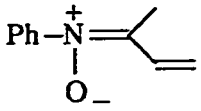
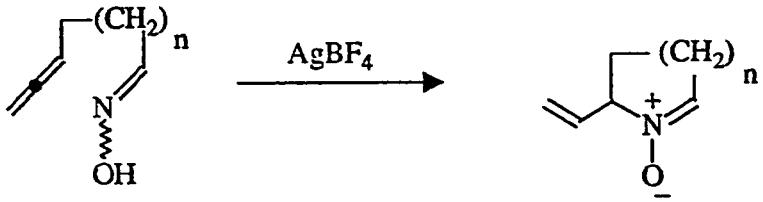




(27)

(29) is achieved by electrophile-mediated cyclizations of allenic oximes (28).[16] C-3, -4, -5, and -6-alkenyl oximes (e.g. 30) react with electron deficient alkenes at

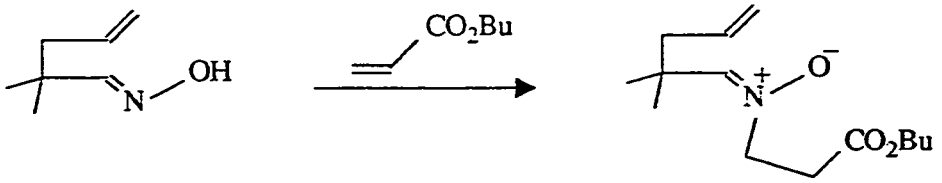


(28)

(29)

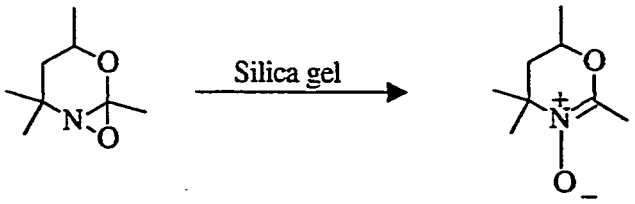
a, n = 1
b, n = 2

the nitrogen atom via Michael addition to give the corresponding C-alkenyl nitrones (31).[17]

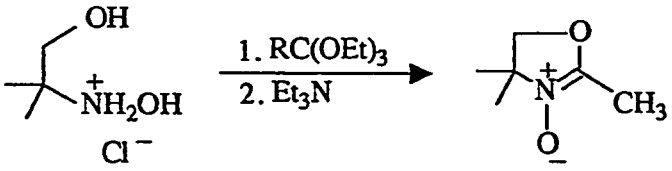


(30) (31)

Heterocyclic nitrone (33) is prepared in excellent yield by isomerization of oxaziridine (32) on silica gel.[18] Condensation of hydroxylamino alcohol (34) with triethyl orthoacetate gives the five-membered heterocyclic nitrone (35).[19]

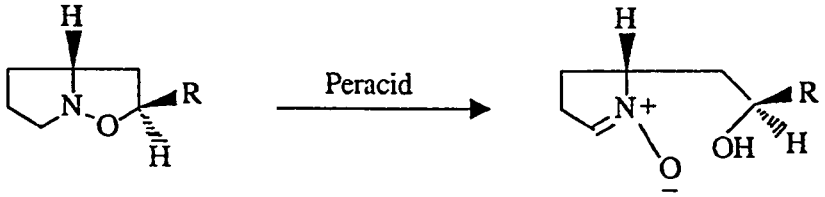


(32) (33)



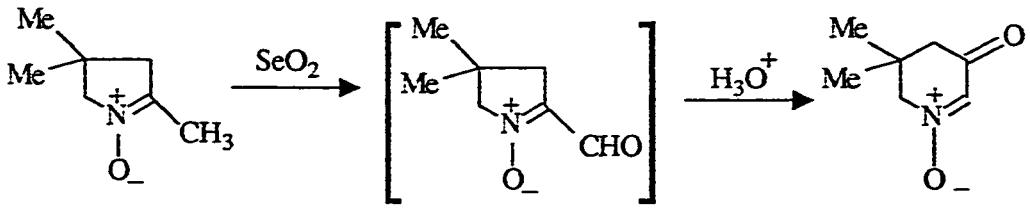
(34) (35)

Peracid induced oxidation of isoxazolidines[19] (36) gives the nitrone (37) regiospecifically. The 3-oxo derivatives of cyclic nitrones (40) and (41) are

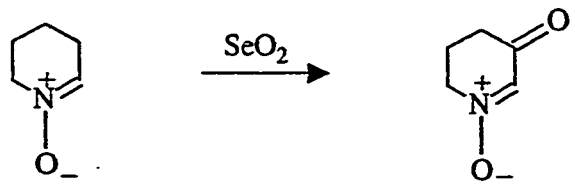


(36) (37)

prepared[20] by selenium oxide oxidation of the corresponding nitrones (38) and (16), respectively.



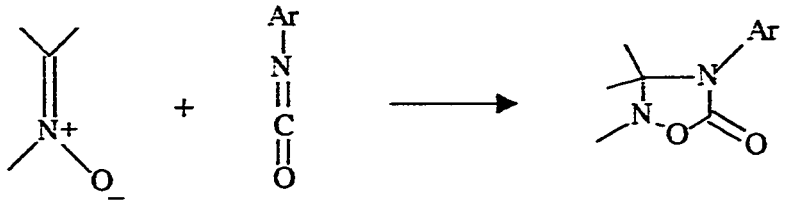
(38) (39) (40)



(16) (41)

2.2 1,3-Dipolar Cycloaddition Reactions

Although there are some similarities in the chemistry of "nitrone" and "ketone", they differ in an important area of cycloaddition chemistry. The nitrone functionality serves as 4π addends in cycloaddition reactions with an array of dipolarophiles. The earliest description of a nitrone cycloaddition, reported by Beckmann in 1890, involves the addition reaction of an aryl isocyanate (43) with a nitrone to give the cycloadduct (44).[21] However, it is only in the 1960s through

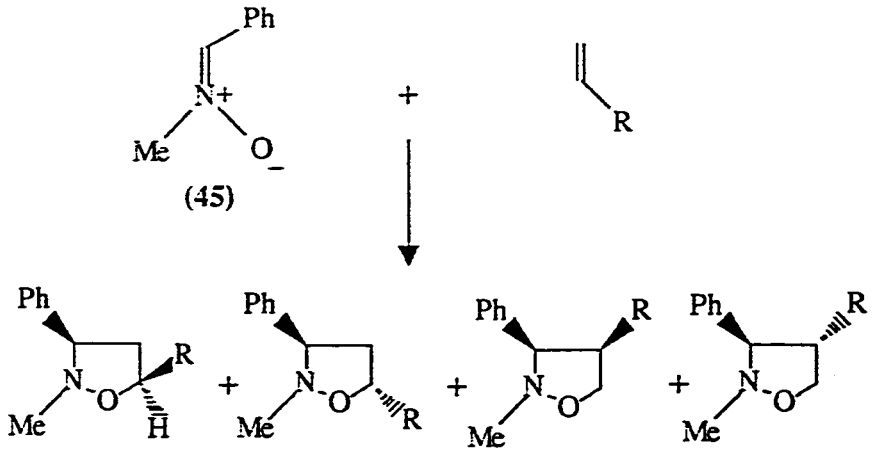


(42) (43) (44)

the pioneering work of Huisgen, nitrone functionality has etched an important place in organic chemistry.[22-24] Brilliant efforts of LeBel[25] led to an understanding of intramolecular nitrone cycloadditions. Since the pioneering applications by Tufariello[26] in the synthesis of natural products, both inter- and intramolecular additions involving nitrones and alkenes have culminated in the synthesis of several interesting alkaloidal and non-alkaloidal natural products.[27,28]

2.2.1 Nitrone Cycloaddition with Monosubstituted Alkenes

Nitrones undergo addition onto mono-substituted normal, electron-rich and aryl alkenes to give adduct regiospecifically with the oxygen terminal of the nitrone attaching itself to the more substituted end of the alkene. However, with electron-



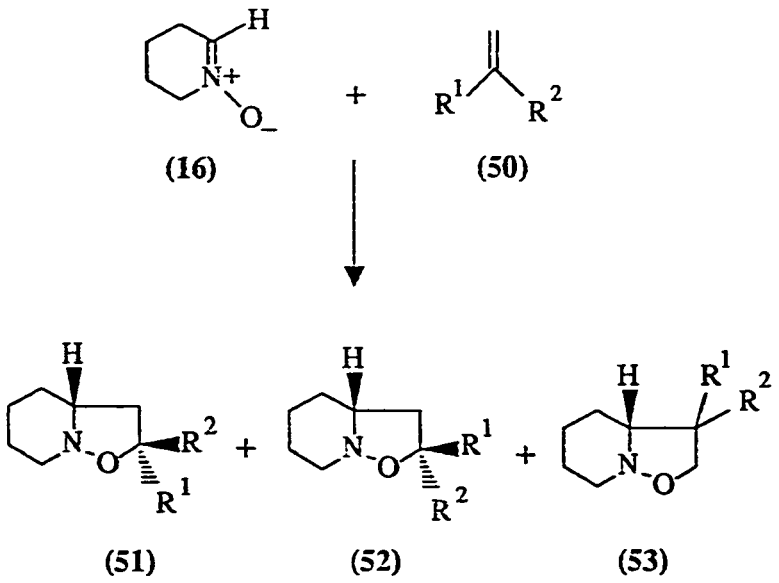
(46) (47) (48) (49)

a, R = Ph	67	33	0	0
b, R = CO_2Me	77	4	15	4
c, R = NO_2	0	0	67	33

deficient alkene methyl acrylate, a mixture of regioisomers **(46b)**, **(47b)** and **(48b)**, **(49b)** is obtained. A complete reversal of regioselection is observed in the addition reaction of the nitrone **(45)** with strongly deactivated alkene nitroethylene to give a mixture of the adducts **(48c)** and **(49c)**.[30]

2.2.2 Nitrone Cycloaddition with 1,1-Disubstituted Alkenes

The stereochemical details of nitrone cycloaddition reaction with 1,1-disubstituted alkenes **(50)** have been reported.[31] While the addition reactions of α-methyl styrene **(50a)** onto the nitrone **(16)** are found to be regioselective, the



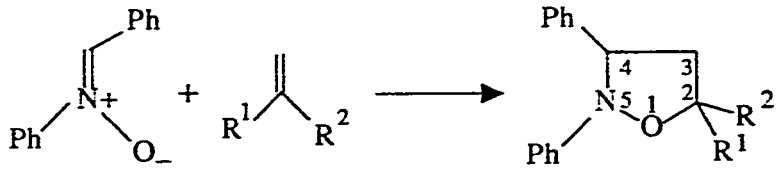
(16) (50)

(51) (52) (53)

a, $R^1 = Ph$, $R^2 = CH_3$	58	42	0
b, $R^1 = CHO$, $R^2 = CH_3$	100	~0	0
c, $R^1 = R^2 = CO_2Me$	0	0	100

corresponding cycloaddition of methacrylaldehyde (**50b**) gives the adduct (**51b**) both regio- and stereo-specifically. For steric reasons and favourable secondary orbital interactions, the smaller aldehyde group is assumed to have *endo* orientation in (**51b**). Complete reversal in regioselection is observed[32] in the addition reaction of dimethyl methylene malonate (**50c**) to give the sole adduct (**53c**).

The acyclic nitrone (**54**) undergoes regiospecific reaction with electron-rich ketene acetal (**50d**) to give the adduct (**55**).[33] The reaction of 1-*tert*-butylthio-1-cyanoethylene (**50e**),[34] 1-acetamido acrylate (**50f**)[35] and the enamine (**50g**)[36] with the nitrone (**54**) afford the 2,2-disubstituted adducts (**55**) regiospecifically in each case.



(54) (50) (55)

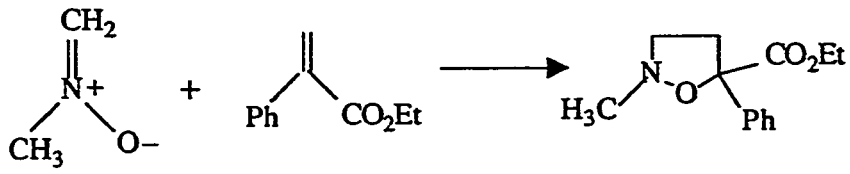
d, $R^1 = R^2 = OEt$

e, $R^1 = CN$; $R^2 = S\text{-}t\text{-}Bu$

f, $R^1 = NHCOCH_3$; $R^2 = CO_2Et$

g, R^1 =  , $R^2 = Ph$

Same pattern of addition is observed in the addition reaction of the N-methylnitrone (**56**) with 1-phenylacrylate (**50h**). The oxygen terminal of the nitrone functionality attaches itself to the substituted end of the alkene to give the adduct (**57**).[37]

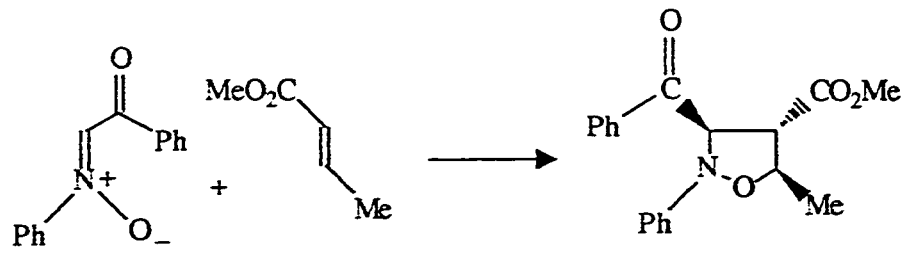


(56) (50h) (57)

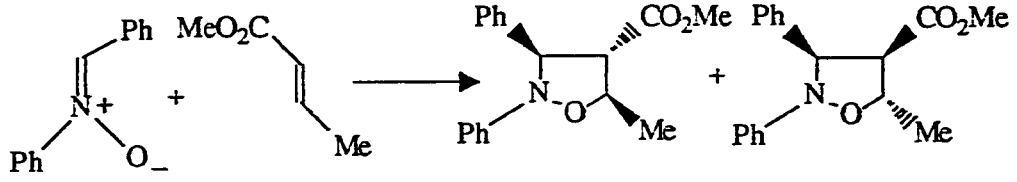
2.2.3 Nitrone Cycloaddition with 1,2-Disubstituted Alkenes

A range of stereo- and regio-selectivities has been observed in the addition reaction of nitrones and *trans*-1,2-disubstituted alkenes. While the C-benzoyl-N-phenyl nitrone (**58**) with methyl crotonate affords the adduct (**59**) exclusively, the

C,N-diphenyl nitrone (**54**) gives a mixture of adducts (**60**) and (**61**) in a ratio of 87 : 13, respectively.[38]

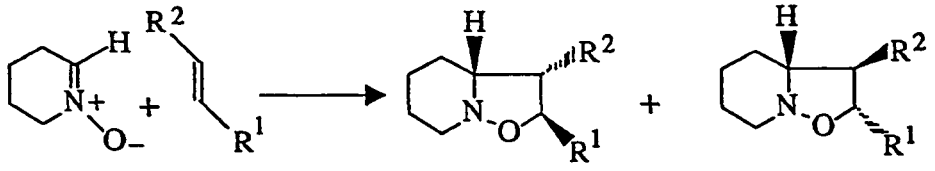


(**58**) (**59**)



(**54**) (**60**) (**61**)

The results of cycloaddition of cyclic nitrone (**16**) with crotonaldehyde and cinnamaldehyde have been shown to be both regio- and stereo-selective to give the adducts (**62a**) and (**62b**), respectively. The addition reaction of methyl cinnamate



(**16**) (**62**) (**63**)

a, $R^1 = CH_3$; $R^2 = CHO$

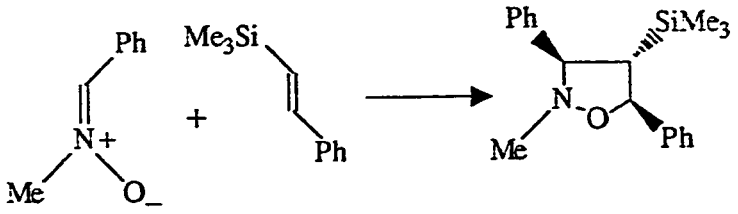
b, $R^1 = Ph$; $R^2 = CHO$

c, $R^1 = Ph$; $R^2 = CO_2Me$

d, $R^1 = R^2 = CO_2Me$

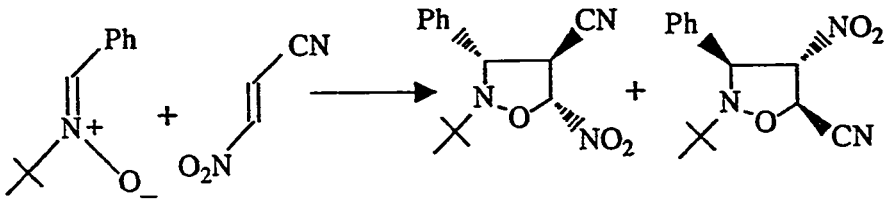
and dimethyl fumarate, however, give a mixture of adducts (62c), (63c) (87 : 13) and (62d), (63d) (60 : 40), respectively.[31]

In a recent study, the regiochemical effect of allyl silicon or oxygen atom in nitrone cycloaddition has been studied.[39] The nitrone (45) on reaction with aryl vinyl silane (65) gives (66) regiospecifically.

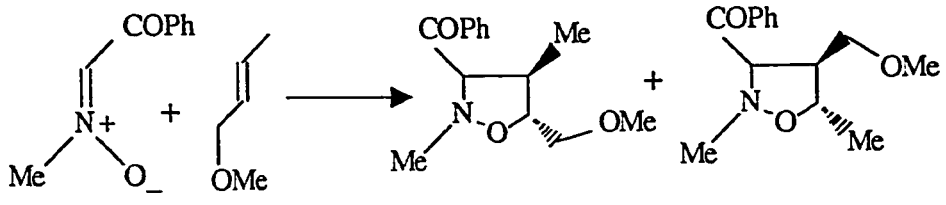


(45) (65) (66)

The regiochemical aspects of the reaction of nitrones with alkenes bearing electron-deficient substituents at both ends (68)[30] and normal substituents at both ends (72)[40] have been studied and in each case a mixture of regioisomers

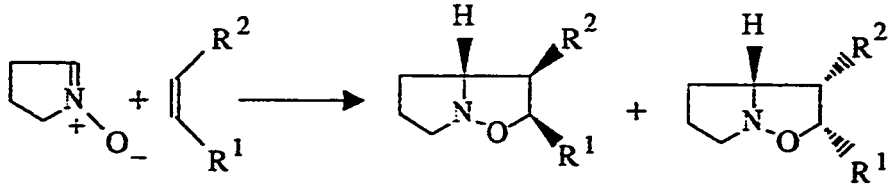


(67) (68) (69) (70)



(71) (72) (73) (74)

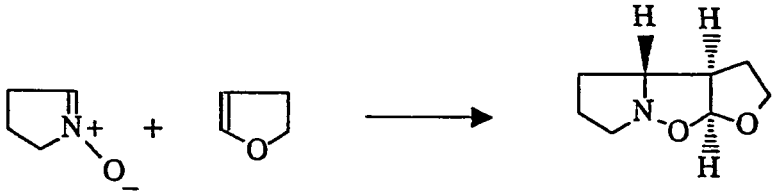
is obtained. The cycloaddition reactions of nitrones with an array of *cis*-1,2-disubstituted alkenes have been studied.[41,42] The results of the cycloadditions of cyclic nitrone with dimethyl maleate, maleic anhydride and vinylene carbonate is given below. Unlike the Diels-Alder reactions, the *exo* mode of attack is favoured in most cases. Thus the steric factors overwhelm the favourable secondary orbital interaction in deciding the stereochemical outcome of these addition reactions.



(15) **(75)** **(76)**

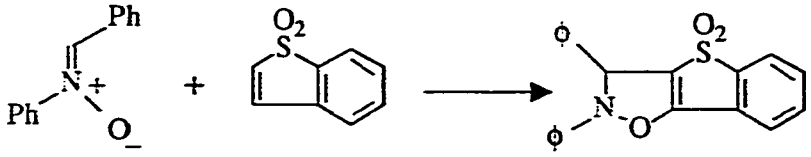
a, $R^1 = R^2 = CN$	23	:	67
b, $R^1 = R^2 = CO_2Me$	87	:	17
c, $R^1, R^2 =$ -CO-O-CO-	67	:	30
d, $R^1, R^2 =$ -O-CO-O-	74	:	26

Addition of the nitrone **(15)** to 2,3-dihydrofuran **(77)** gives the tricyclic compound **(78)** regioselectively. The oxygen terminal of the nitrone functionality



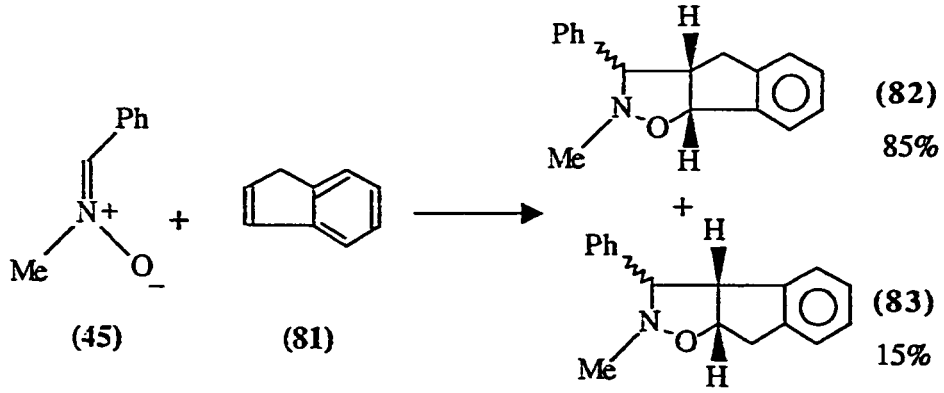
(15) **(77)** **(78)**

thus favours attachment to the end of the alkene bearing the oxygen atom.[43] If the heteroatom in the alkene is electron-withdrawing as in **(79)**, the reaction with C,N-diphenyl nitrone **(54)** yields the regioisomeric adduct **(80)**.[44] However, when



(54) (79) (80)

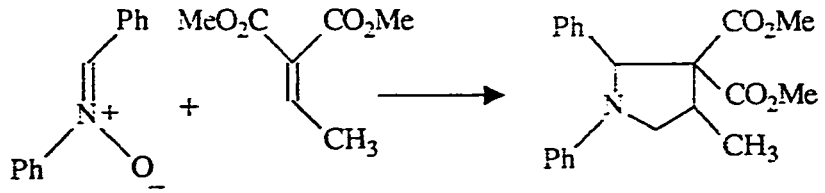
the dipolarophile does not posses a strongly activating or deactivating substituent, a loss of regiochemical control is observed. Thus addition[45] of the nitrone (45) onto (81) affords a mixture of adducts (82) and (83) in a respective ratio of 85 : 15.



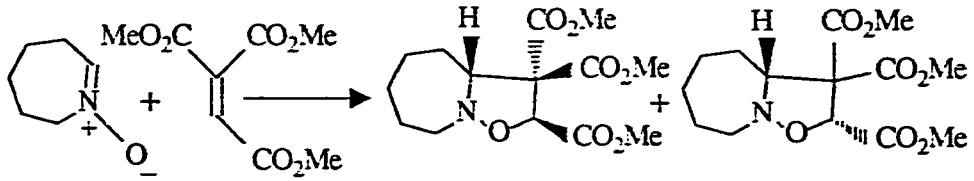
(45) (81) (82) 85% (83) 15%

2.2.4 Nitrone Cycloaddition with Trisubstituted Alkenes

Regio- and stereochemical details of nitrone cycloaddition reaction with trisubstituted alkenes have been studied. Thus, C,N-diphenyl nitrone (54) adds to the alkene (84) to give the sole regiomer (85).[46] The carbon terminal of the nitrone attaches itself to the olefinic end bearing the electron-withdrawing substituents. Likewise, the cyclic nitrone (17) on addition to tricarbomethoxy ethylene (86) leads to the mixture of adducts (87) and (88) regiospecifically.[47]



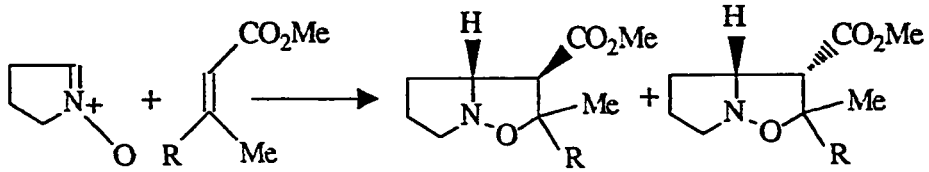
(54) (84) (85)



(17) (86) (87) : (88)

64 : 36

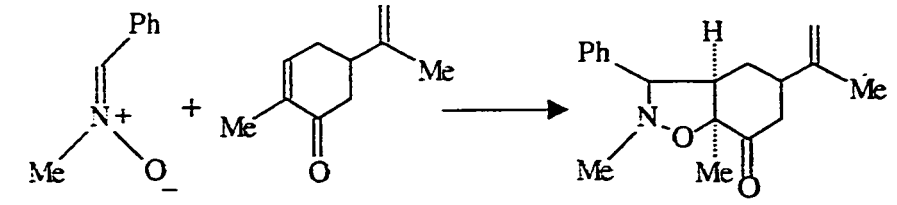
However, regioselection is reversed in the addition reaction of nitrone with trisubstituted alkenes of the type (89),[48] (92),[49] and (94).[50] In each case oxygen



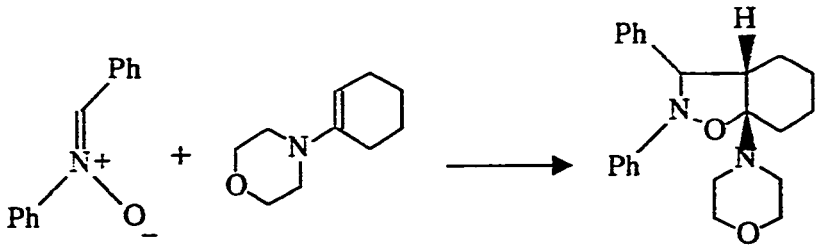
(15) (89) (90) (91)

a, R = Me	50	:	50
b, R = CO_2Me	100	:	0

terminal of the nitrone is attached to the more substituted end of the alkenes.



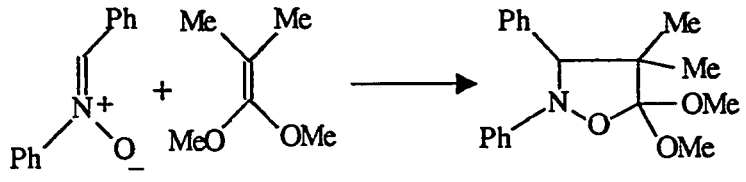
(45) (92) (93)



(54) (94) (95)

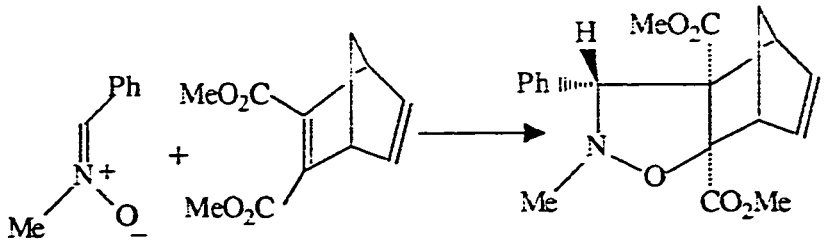
2.2.5 Nitrone Cycloaddition with Tetrasubstituted Alkenes

There are very few examples of the cycloaddition of nitrones to tetrasubstituted alkenes. The reaction of C,N-diphenyl nitrone (54) with dimethyl ketene dimethyl acetal (96) affords product (97) regiospecifically. The oxygen



(54) (96) (97)

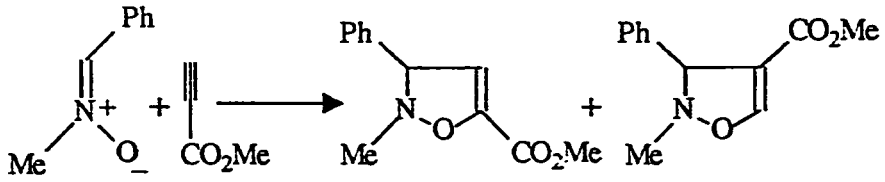
end of the nitrone, as expected, is bonded to the carbon of the alkene bearing the electron-releasing substituents.[49] The nitrone (45) reacts exclusively with tetrasubstituted olefin (98) to give product (99).[51]



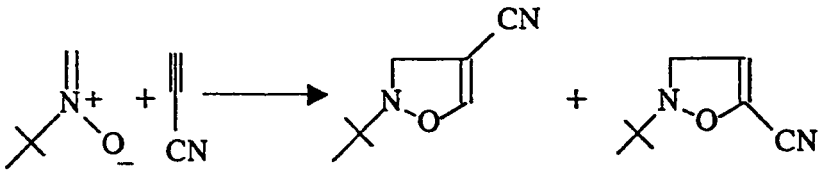
(45) (98) (99)

2.2.6 Nitrone Cycloaddition with Acetylenes

The addition reaction of the nitrone (45) with methyl propiolate (100) gives a mixture of adducts (101) and (102) in the respective ratio of 42 : 58.[52] Addition of cyanoacetylene (104) is also found to be non-regioselective.[52]

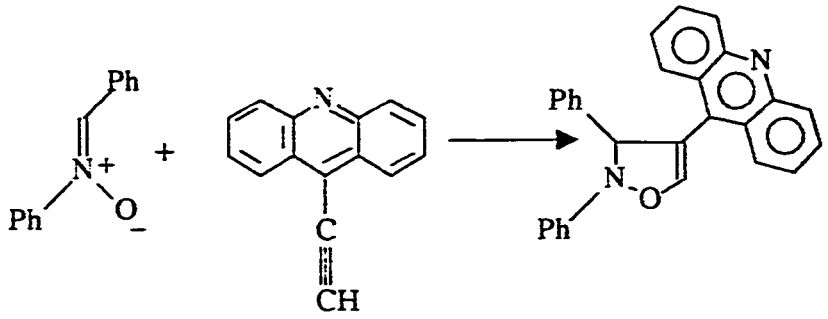


(45) (100) (101) : (102)
42 : 58



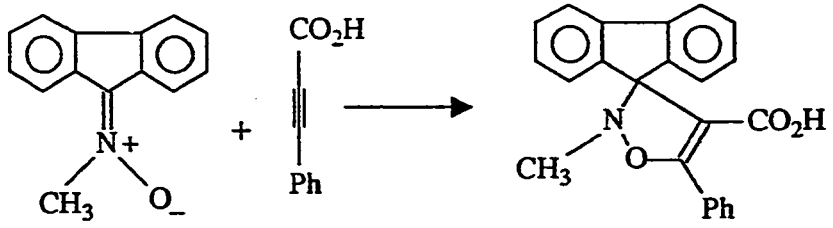
(103) (104) (105) : (106)
50 : 50

The nitrone (54) on addition to ethynylacridine (107) affords the adduct (108).[53] The reaction of phenylacetylene carboxylic acid (110) with nitrone



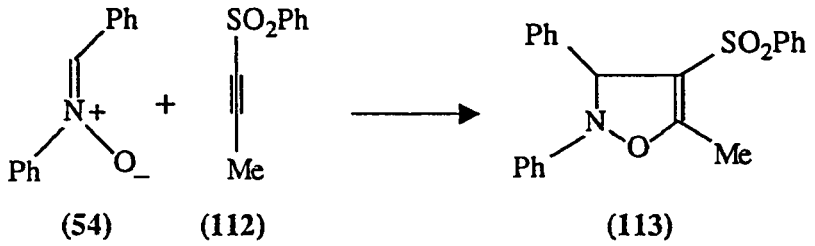
(54) (107) (108)

(109) has been explored. The addition reaction produces the isoxazoline (111)



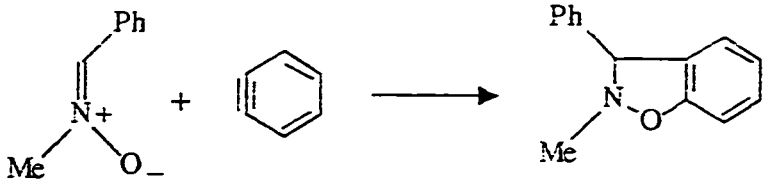
(109) (110) (111)

regiospecifically.[54] The nitrone (54) undergoes regiospecific addition to phenylsulfonyl alkyne (112) to give the adduct (113).[55] The trapping of benzyne



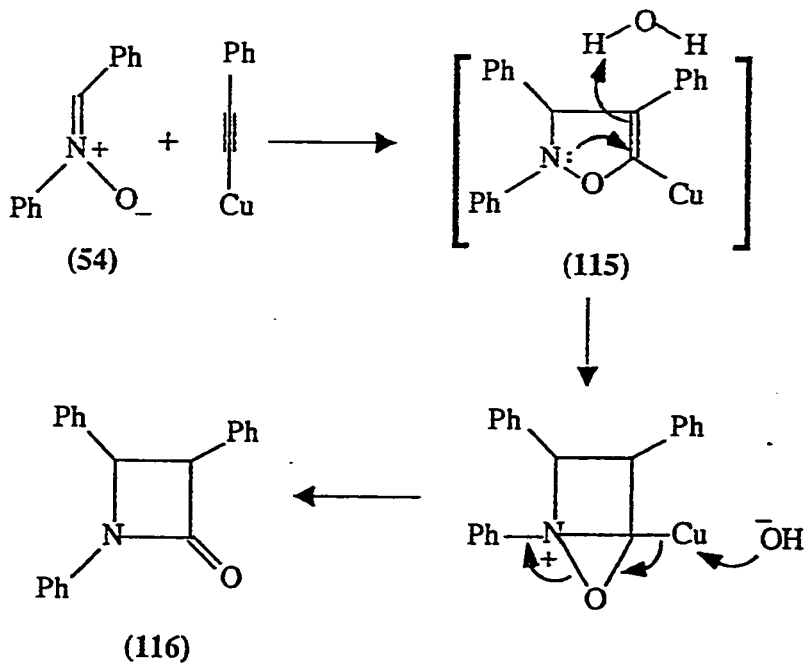
(54) (112) (113)

by the nitrone (45) has been achieved to afford the bicyclic adduct (114).[56] An



(45) (114)

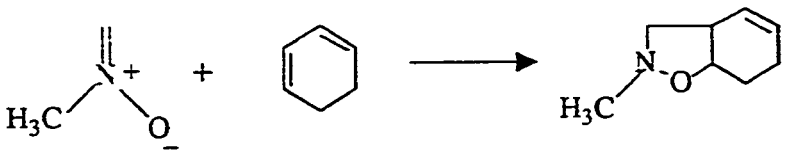
interesting reaction between the nitrone and copper acetylide yields the azetidone (116) via rearrangement of the initial adduct (115).[57]



(54) (115) (116)

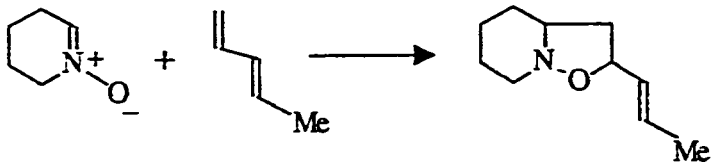
2.2.7 Nitrone Cycloaddition with Conjugated Dienes and Cumulative Multiple Bonded Systems

Even though the addition reaction of the nitrone (56) with 1,3-cyclohexadiene is capable of regiochemical complications, the mono adduct (118) is formed regioselectively with the oxygen attached to the end of the diene.[58]



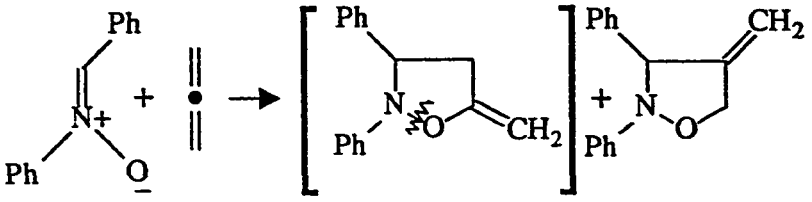
(56) (117) (118)

The addition of nitrone (**16**) onto piperylene (**119**) is found to be both site-specific and regiospecific to give the adduct (**120**).[59] Addition of nitrone (**54**) to

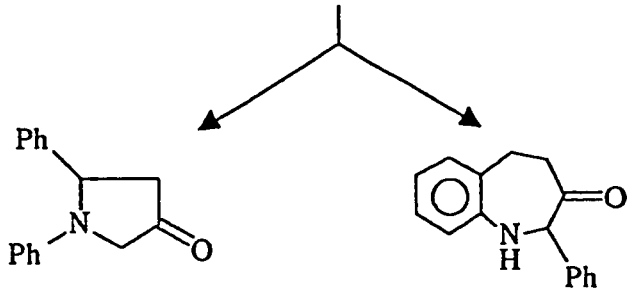


(16) (119) (120)

allene (**121**) is found to be non-regioselective to give (**122**) and (**123**). The unstable adduct (**122**) rearranges to a mixture of compounds (**124**) and (**125**) via

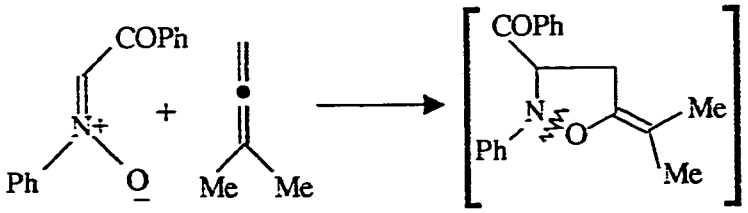


(54) (121) (122) (123)

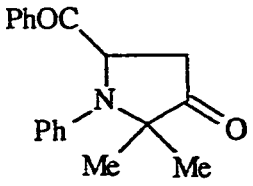


(124) (125)

N-O bond fission.[60] The reaction of 1,1-dimethylallene (**126**), however, undergoes regiospecific addition to give (**128**) via the initial adduct (**127**).[61]

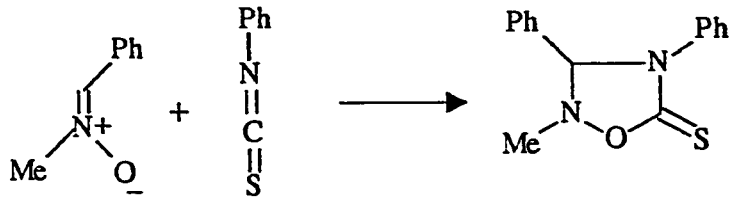


(**58**) (**126**) (**127**)



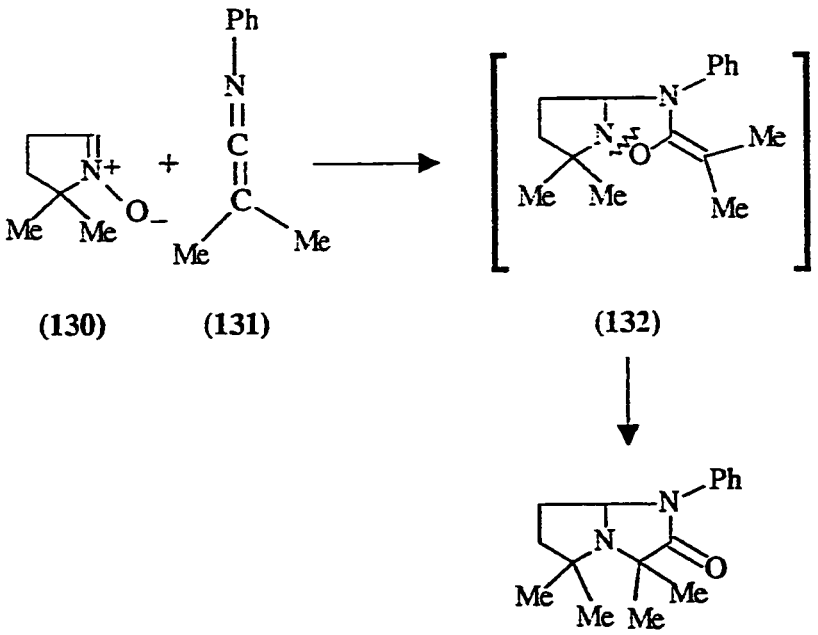
(**128**)

Cycloaddition of phenylisothiocyanate gives the adduct (**129**) regioselectively.[62]



(**45**) (**129**)

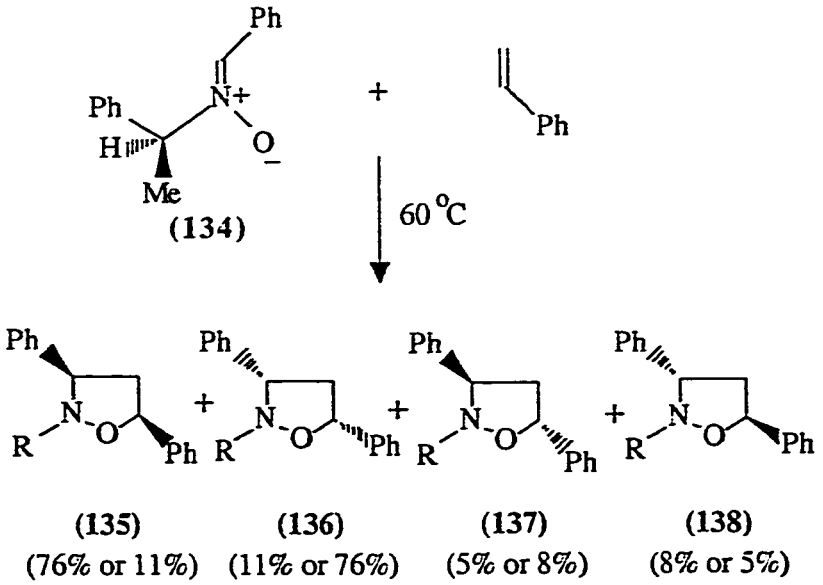
It has been shown that ketenimine (**131**) reacts with the cyclic nitrone (**130**) to give (**133**) via the initial adduct (**132**).[63]



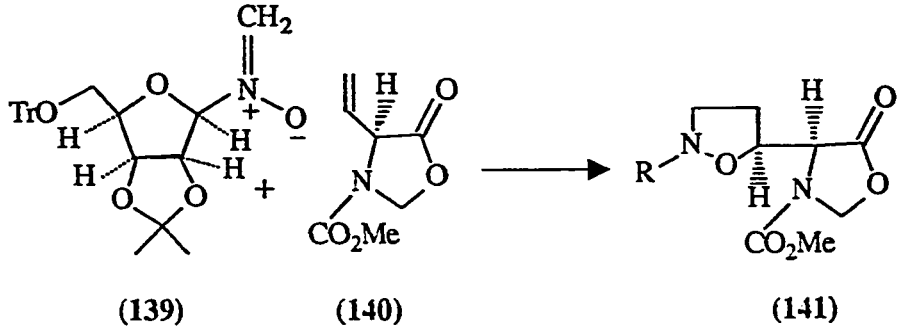
(**130**) (**131**) (**132**) (**133**)

2.2.8 Asymmetric Induction in Nitrone Cycloaddition

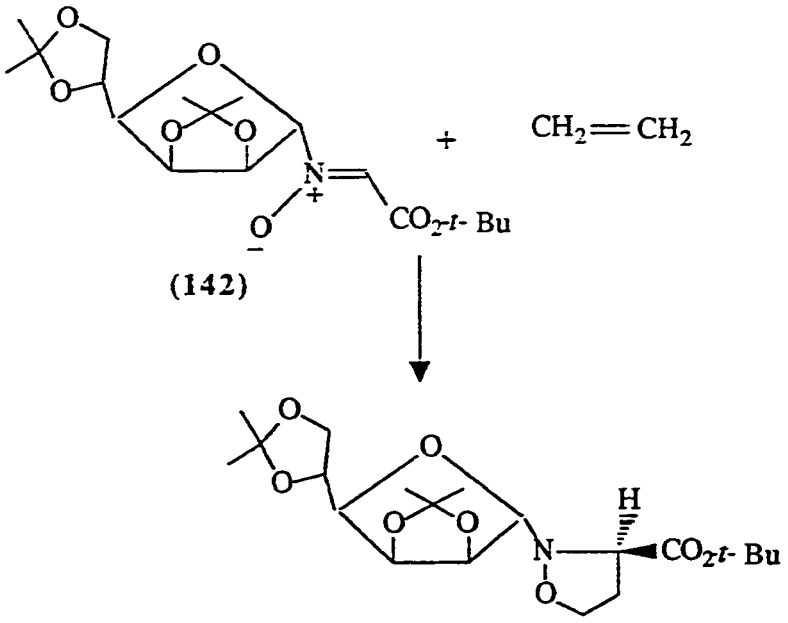
Asymmetric 1,3-dipolar cycloaddition using a chiral dipole or a dipolarophile has been reported. Thus, addition of nitrone (**134**) to styrene gives



adducts with mild asymmetric induction.[64] The chiral nitrone **(139)** with chiral alkene **(140)** affords the optically active adduct **(141)** almost as the sole product.[65]



Asymmetric induction is also observed in the addition reaction of the chiral nitrone **(142)** onto ethylene to give **(143)** which is subsequently converted to a captopril analog.[66]

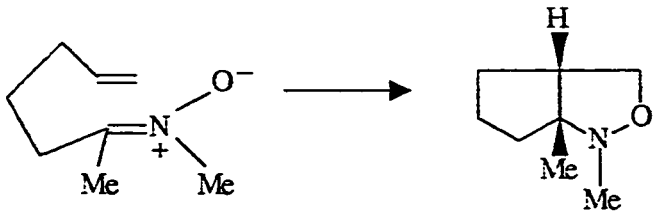


(142)

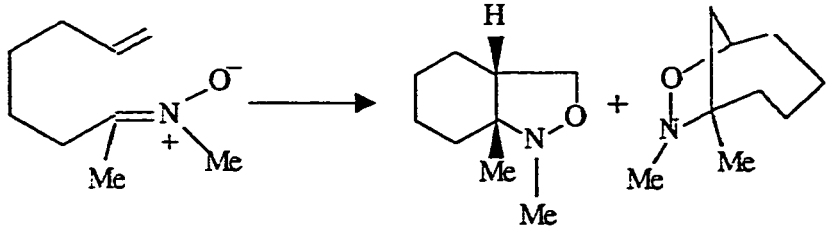
(143)

2.2.9 Intramolecular Nitrone Cycloaddition

Intramolecular nitrone cycloaddition reactions have been reviewed in detail.[6,7] Product regiochemistry in these cyclizations is markedly influenced by the number of carbon atoms between the nitrone functionality and the double bond. The general rules of regiochemistry that apply in the intermolecular version of the reaction are often reversed in the intramolecular version. While the nitrone (**144**) affords only the adduct (**145**), the homologous nitrone (**146**) gives a mixture of adducts (**147**) and (**148**) in a ratio of 2 : 1.[67]



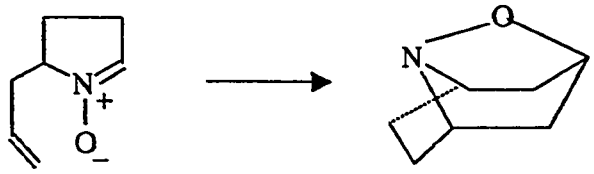
(144) (145)



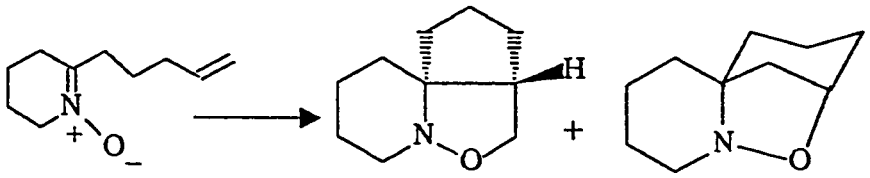
(146) (147) (148)

2 : 1

The nitrone **(149)** on thermolysis gives a single adduct **(150)**.[68] However, the nitrone **(151)** affords a mixture of regiomers **(152)** and **(153)**.[69]



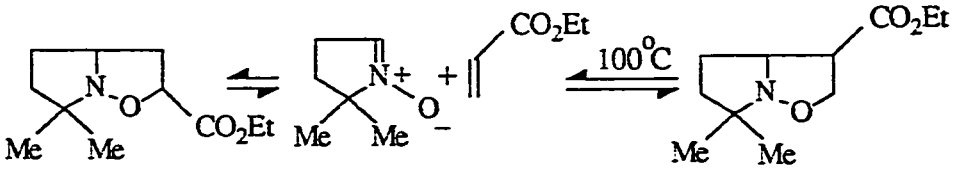
(149) **(150)**



(151) **(152)** **(153)**

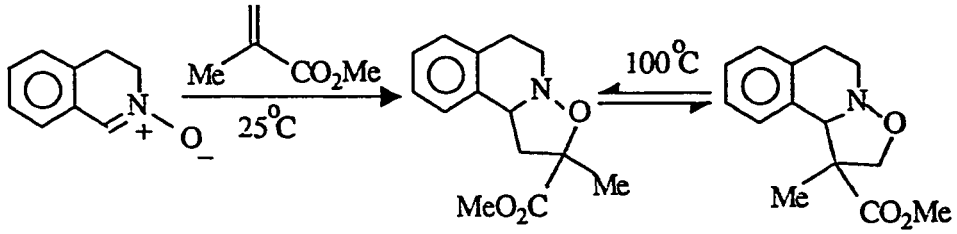
2.2.10 Cycloreversion

Isoxazolidines on heating may undergo cycloreversion to the starting nitrone and the alkene which on recombination under thermodynamic conditions may lead to the thermodynamic adduct. Thus, the kinetic adduct (**154**) on thermolysis at 100°C affords the mixture of adducts (**154**) and (**156**) in a 1 : 1 ratio.[6,70]



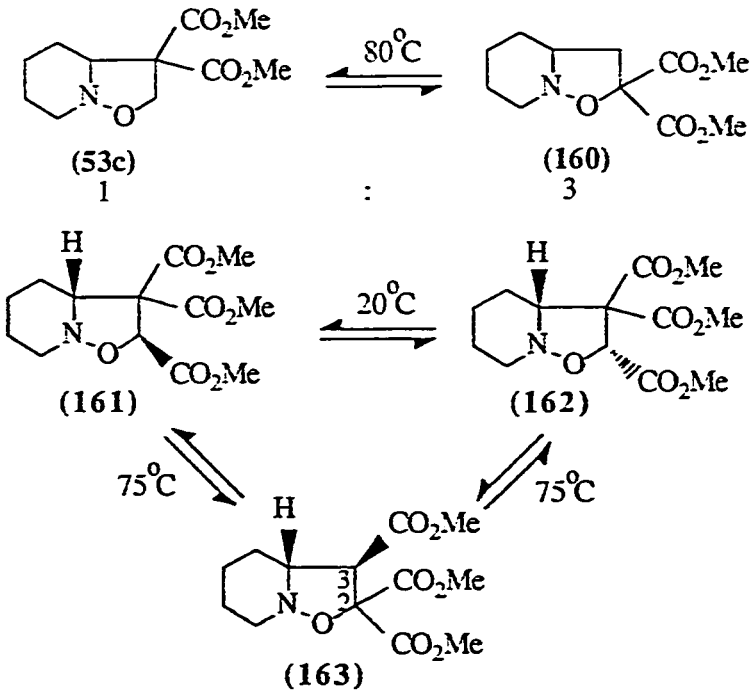
(**154**) (**155**) (**156**)

At room temperature the nitrone (**157**) on reaction with methyl methacrylate gives a mixture of (**158**) and (**159**) in a ratio of 94 : 6, which on heating (100°C) is changed to a 50 : 50 ratio.[71]



(**157**) (**158**) (**159**)

Isoxazolidines having electron-withdrawing conjugated substituents undergo cycloreversion with relative ease. Thus, the adduct (**53c**) is changed at 80°C to a mixture of (**53c**) and (**160**) in a ratio of 1 : 3, respectively.[32] The adduct (**161**) at 20°C was equilibrated to a mixture of (**161**) and (**162**) in a



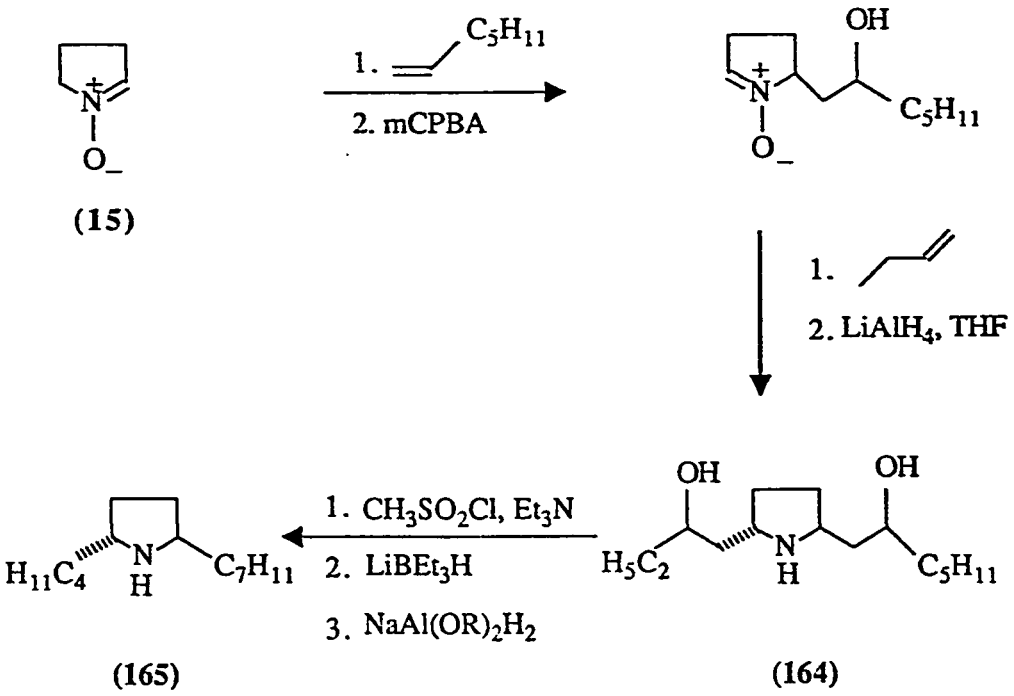
respective ratio of 70 : 30 which at 75°C is converted to the sole isomer **(163)**.[47] The results thus demonstrate that the C-3 position of the isoxazolidine has more crowded environment than C-2. Considerably more stringent conditions are required to induce cycloreversion in isoxazolidines without such activating substituents.

2.2.11 Natural Products Synthesis Based on Nitrone-Olefin Cycloaddition Reactions

Nitrone-olefin [4+2] cycloadditions offer unique advantages in the total synthesis of natural products. These 1,3-dipolar reactions[6] might be counted as one of the most useful methods for the the synthesis of five-membered heterocyclic ring systems containing one or more heteroatoms. The reactions involve the

formation of both carbon-carbon and carbon-oxygen bonds, with the singular ability to incorporate several stereochemical centers in a single step. Ring cleavage of the formed isoxazolidines furnishes intermediates suitable for conversion to traditional natural product target molecules.

Several pyrrolizidine, pyrrolidine, and piperidine alkaloids have been synthesized using nitrone-based methodology. The *Solenopsis* alkaloid (**165**) is synthesized from pyrroline-1-oxide (**15**) by double nitrone cycloaddition sequence.[87] The pyrrolidine (**164**) is obtained in a *cis : trans* ratio of 13 : 87. *Trans* selectivity is increased to 7 : 93 when replacing 1-butene by butadiene in the second cycloaddition step.

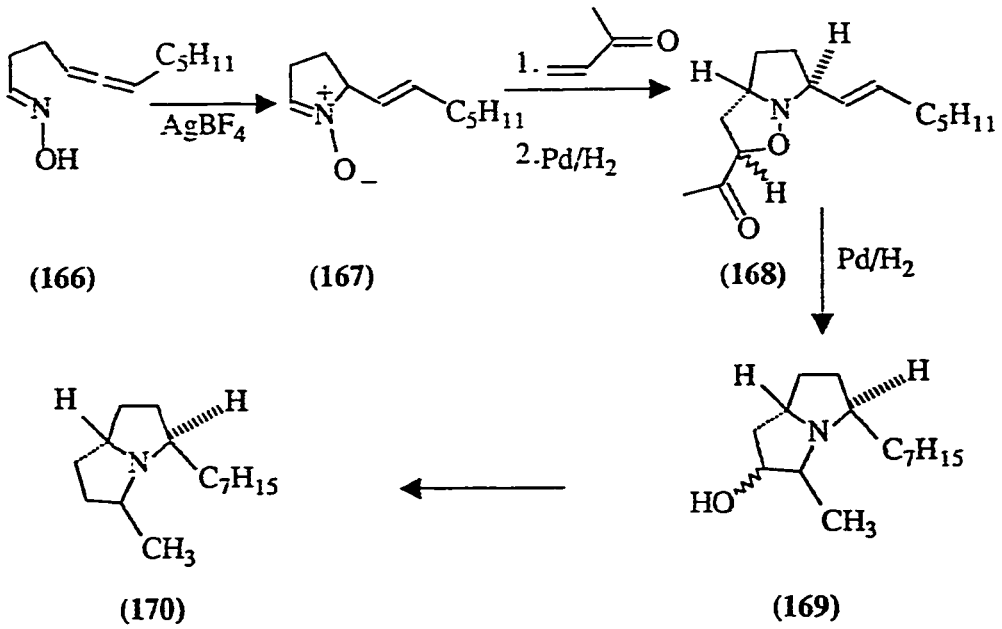


(**15**)

(**165**) (**164**)

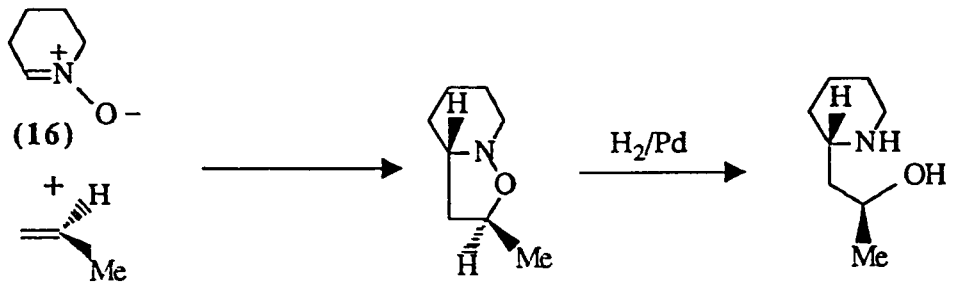
Cyclization of the allene oxime (**166**) with silver tetrafluorborate produces the nitrone (**167**). In a single step the nitrone is trapped by methyl vinyl ketone as the isoxazolidine (**168**) and then reduced to (**169**).[88] Jones oxidation,

thioketalization, and Raney-Ni desulfuration give the pyrrolizidine alkaloid **(170)**, a venom constituent from *Solenopsis* ants.



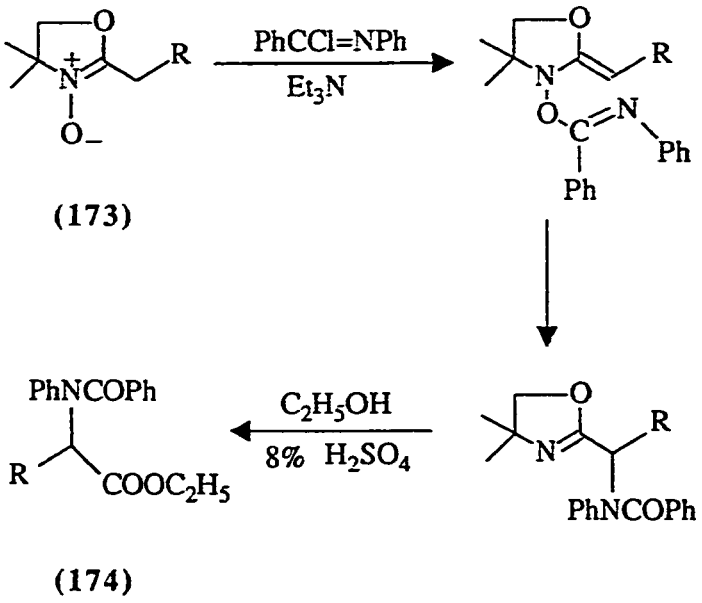
(166) **(167)** **(168)** **(169)** **(170)**

In their cycloaddition reactions, cyclic nitrones exhibit high facial selectivity (*exo* with respect to the ring, *endo* with respect to the allylanion system). Nitrone **(16)**, for instance, adds propene to give **(171)**. The latter isoxazolidine serves as a synthetic intermediate, which by hydrogenation is converted into the alkaloid sedridine **(172)**,[78] with a perfect control over the difficult 1,3-stereorelationship.



(171) **(172)**

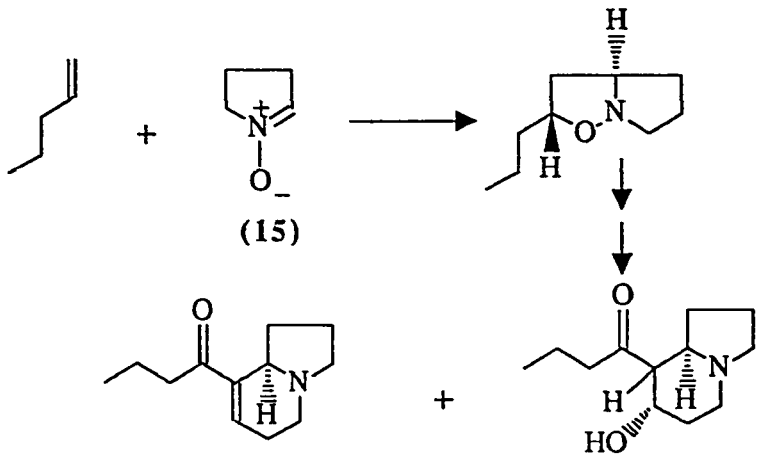
Synthesis of a number of selected amino acids has been achieved through the use of nitrone-based strategy. Acylamination of cyclic nitrones **(173)** with N-phenylbenzimidoyl chloride in the presence of triethylamine provides a route to the preparation of α-amino acids **(174)**.[89]



(173)

(174)

The synthesis of selected indolizidine alkaloids occuring in *Elaeocarpus*

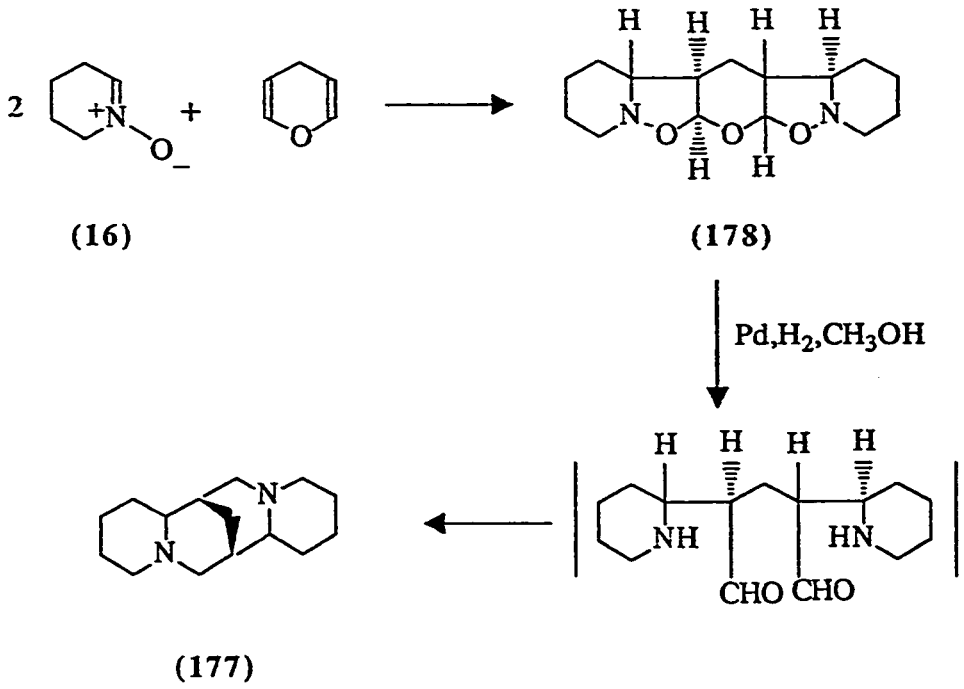


(15)

(175) **(176)**

species of the rain forests of New Guinea has been successfully achieved using nitrone methodology. (±)-Elaeokanine-A (**175**) and (±)-elaeokanine-C (**176**) are obtained from 1-pentene and 1-pyrroline-1-oxide (**15**).[90] A slightly different route toward (±)-elaeokanine-A (**175**) and -C (**176**) using nitrone cycloaddition was also reported.[91]

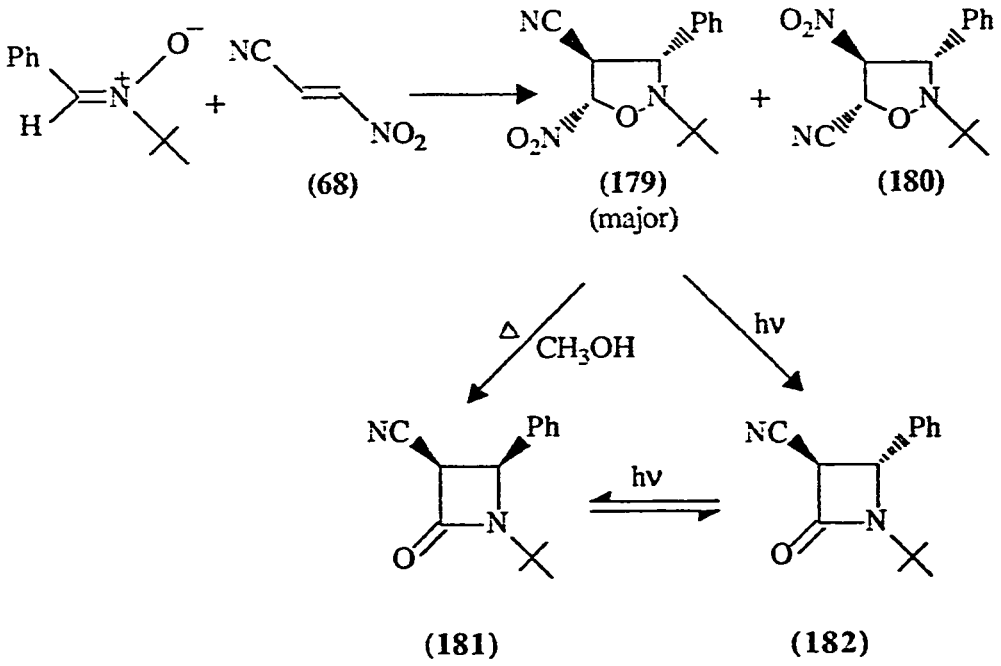
The α-isospartein (**177**), found in several species of the *Leguminosae* family has been stereoselectively synthesized through the addition of 2 moles of nitrone (**16**) onto 4H-pyran.[92] The natural product (**177**) is obtained by catalytic reduction of the adduct (**178**).



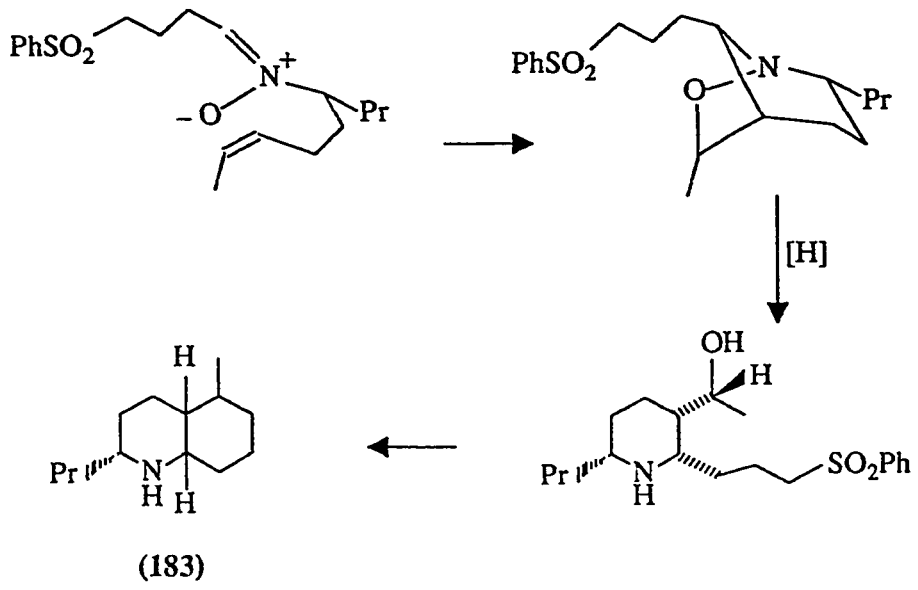
(**16**) (**178**)

(**177**)

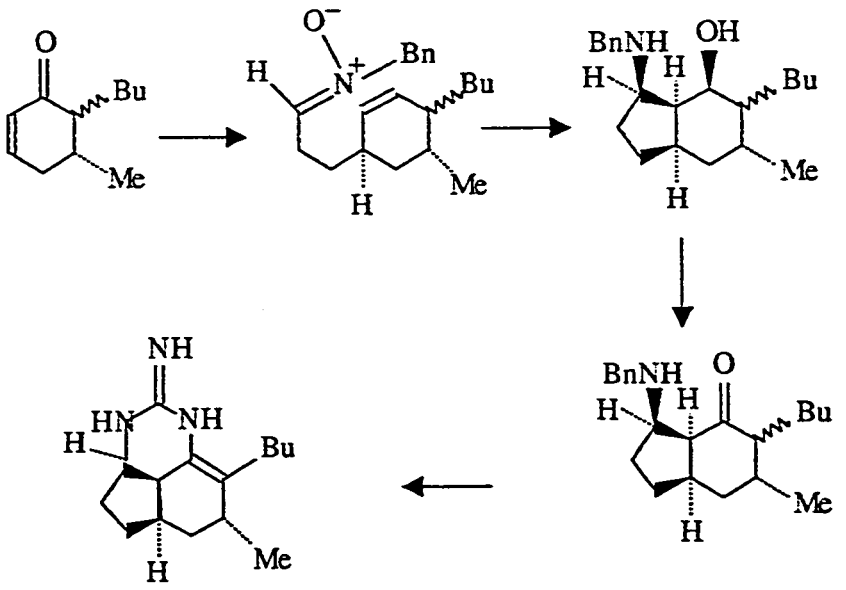
Nitrone-based strategy provides routes to β-lactams, an essential functionality to a number of potent antibiotics. Nitrones add to *trans*-1-cyano-2-nitroethylene (**68**) to give a mixture of the regioisomers (**179**) and (**180**). Both *cis*- and *trans*- β-lactams (**181**) and (**182**) can be obtained by thermally or photochemically-induced ring contraction respectively.[93,94]



The methodology of intramolecular cyclization has been used efficiently as a route to a variety of natural products. For example, it has been utilized in the synthesis of (±)-pumiliotoxin-C **(183)**, a venomous metabolite in the skin of Columbian frogs.[95]

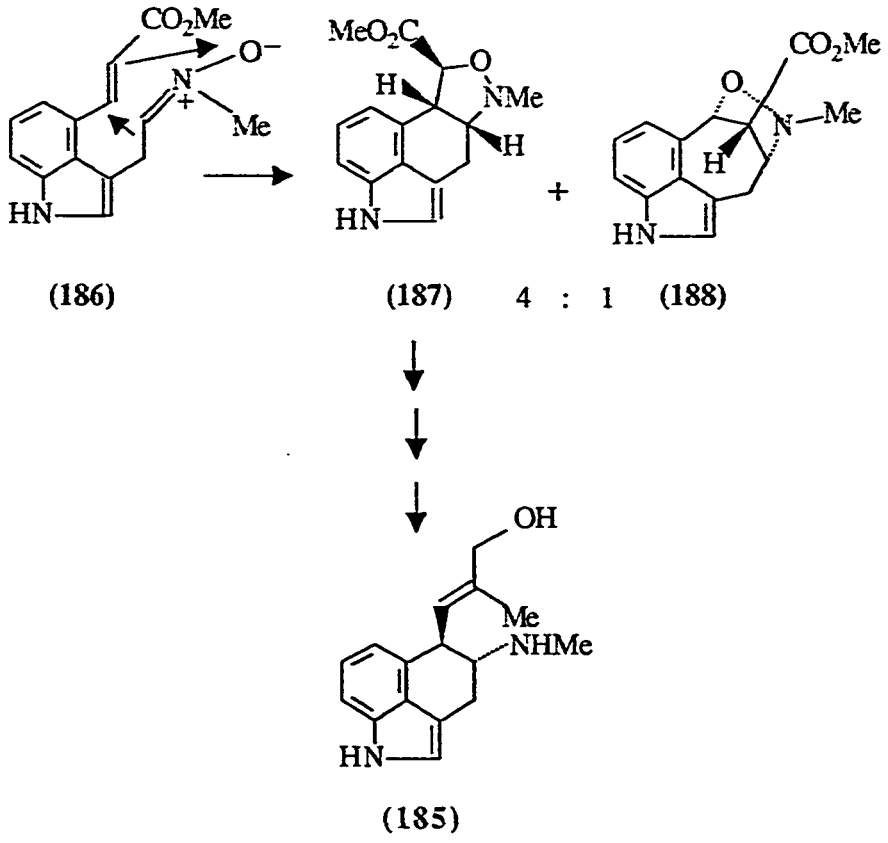


An efficient total synthesis of the antitumor antibiotic (-)-ptilocauline **(184)** was carried out by Roush.[96] A key step in the synthesis was the use of an intramolecular nitrone cyclization, which was also fruitful in the establishment of the required stereochemistry of the antibiotic.



(184)

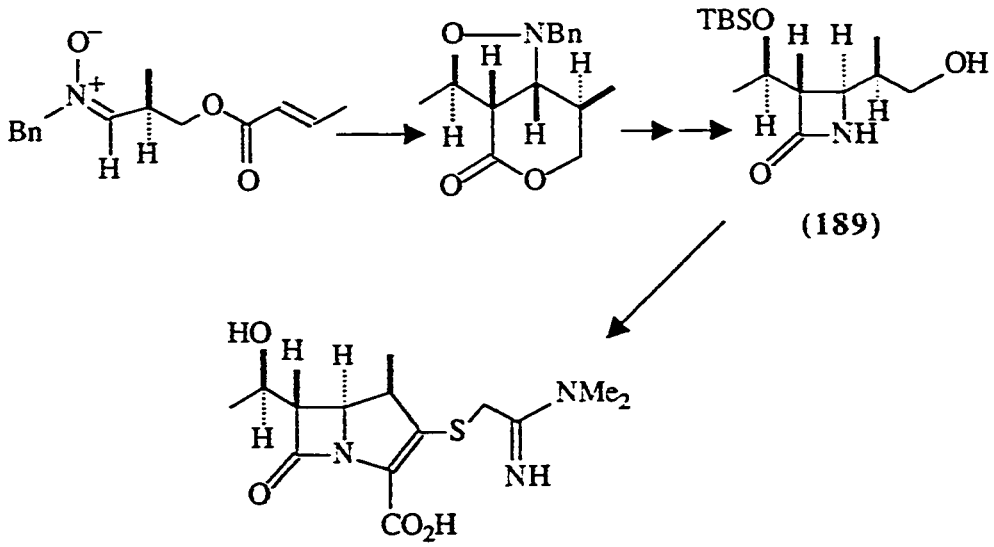
The nitrone-olefin cyclization in compound **(186)** was featured as a key step in the synthesis of the alkaloid (±)-chanoclavine **(185)**.[97]



(186) (187) 4 : 1 (188)

(185)

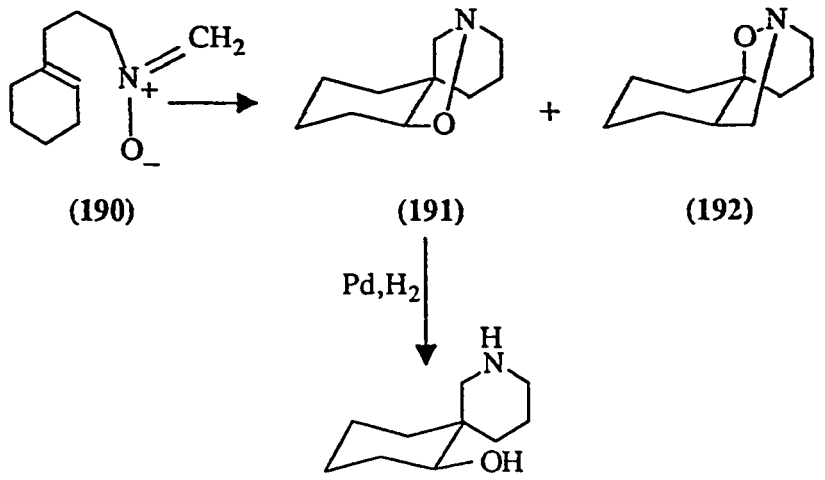
Daunamycin and related naturally occurring carbapenems possesses potent and broad-spectrum antibacterial activities. The synthesis of one of the key intermediates (**189**) of the 1β-methylcarbapenem antibiotic was investigated[98] by way of inter- and intra-molecular nitrone 1,3-dipolar cycloaddition. The following scheme shows the intramolecular cycloaddition approach.



1β-methylcarbapenem

Bn = benzyl; TBS = t-butyldimethylsilyl

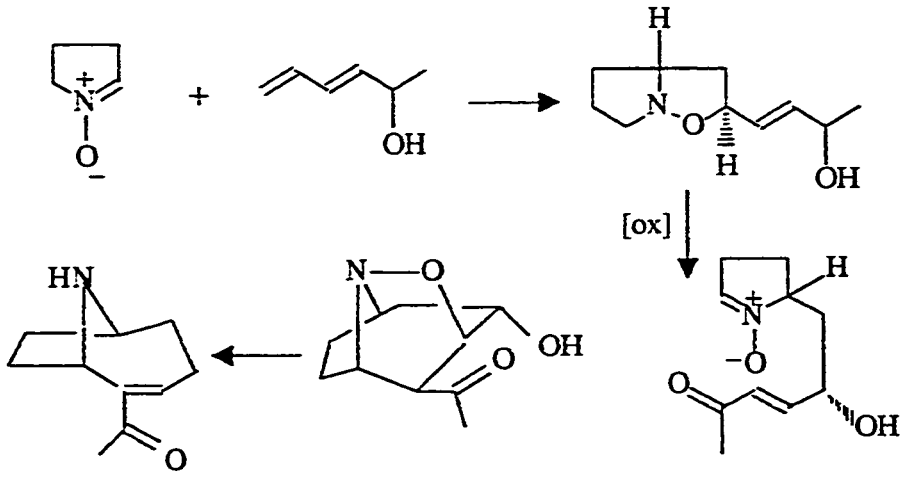
The isoxazolidine **(191)** obtained from nitrone **(190)** has been reduced to the alkaloid (±)-nitramine **(193)**,[99] which is structurally related to the electrophysiologically active histrionicotoxins, isolated from the skin of poisonous Columbian frogs.



(190) **(191)** **(192)**

(193)

Anatoxin-a (**194**) is a highly toxic alkaloid produced by the bloom-forming *cyanophyte Anabaena flos aquae.* A route[100] to this alkaloid, which is known to cause losses of cattle, employs both inter- and intramolecular cycloadditions of nitrone moieties.



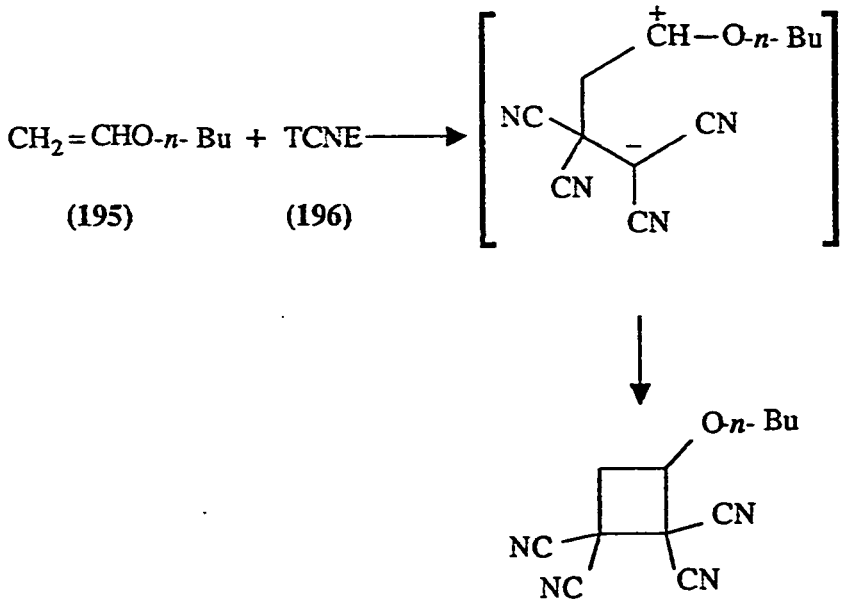
(194)

2.3 Mechanism

The frontier orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena of 1,3-dipolar cycloadditions.[23,72-77] According to Sustmann's classification,[73] the nitrone functionality is a type II dipole where both HOMO - LUMO interactions contribute to the stabilization of the transition state. Steric factors and secondary orbital interactions usually dictate the stereochemical outcome of the cycloadditions.[75,76,78]

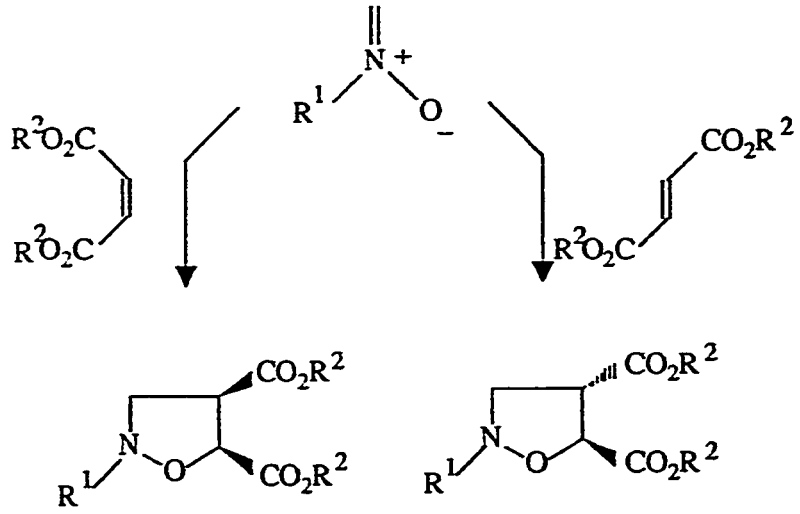
The nitrone cycloaddition reaction with alkenes is a thermally allowed $\pi^4S + \pi^2S$ process. Accumulated evidence so far indicate the concerted nature of the reaction. The low activation energy, large negative entropy of activation, and

negligible solvent effect on rate constants are some of the necessary conditions for a multicentered concerted cycloaddition reaction mechanisms.[23,79-83] The reaction of N-methyl-C-phenylnitrone (**45**) with ethylacrylate exhibits only a 2.6 fold increase on passing from dimethyl sulfoxide to toluene with dielectric constant of 48.9 and 2.4, respectively, at 25°C. The rate ratio of R(CH_3CN) / R(cyclohexane) for the addition of (**195**) to (**196**), which is known to proceed through a Zwitterionic intermediate,[84,85] is found to be 2600.



Through the application of frontier molecular orbital (FMO) theory, a coherent picture of a mechanism based on a concerted nonsynchronous process has emerged. In Type II of the cycloaddition reactions, both electron-rich and electron-deficient alkene undergo addition reaction faster than normal alkene. Kinetic data accumulated so far fit well into the U-shaped dipolarophile activity scale inherent in Type II dipolar cycloadditions.[23,86]

Because of the concerted nature of the nitrone cycloadditions, the stereochemical integrity of the alkene is maintained as described before by Tufariello[6] and Huisgen.[22]



CHAPTER 3

REGIO- AND STEREOCHEMISTRY OF CYCLOADDITION REACTIONS OF THE NITRONE (19)

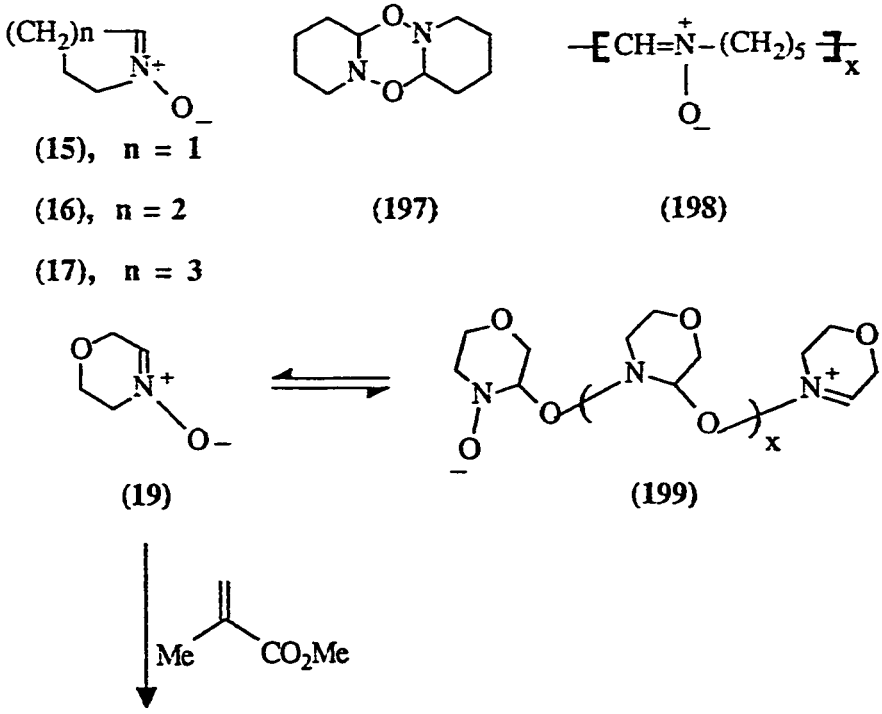
3.1 Results

3.1.1 Polymerization of the Nitrone (19)

Before proceeding with the cycloaddition reactions, behaviour of concentrated solution of the nitrone (19) was examined. Concentrated solution (1 *M*) of the nitrone (19) and its carbocyclic counterparts behave quite differently. While the nitrone (15) is stable, the nitrone (16) dimerizes to (197), and the nitrone (17) polymerizes to the polymeric nitrone (198).[107] The heterocyclic nitrone (19), on the other hand, polymerizes to (199) with a repeating skeletal -N-O-C unit (Scheme 1).[108] Reasons for this puzzling differences are not well understood.

A solution of the nitrone (19) (0.2 *M*) in dichloromethane remained stable for more than a week without any noticeable formation of the polymer (199). However, the nitrone (19), after stripping of the solvent, immediately polymerizes. A solution of the polymer (199) in deuterochloroform was found to contain the nitrone (19) (~10%). After 1 day and 7 days at 20°C, the amount of the nitrone (19) increased to 30% and 70%, respectively. A solution of the polymer and methyl methacrylate

in deuterochloroform at 20°C for 14 days afforded the cycloaddition products in almost quantitative yield *(see Experimental)*. Because of the problem associated with the polymerization, the concentration of the nitrone **(19)** was kept low and the alkenes were used in excess in the subsequent addition reactions. We did not notice any unwanted polymerization under the specified reaction conditions *(see Experimental)*.

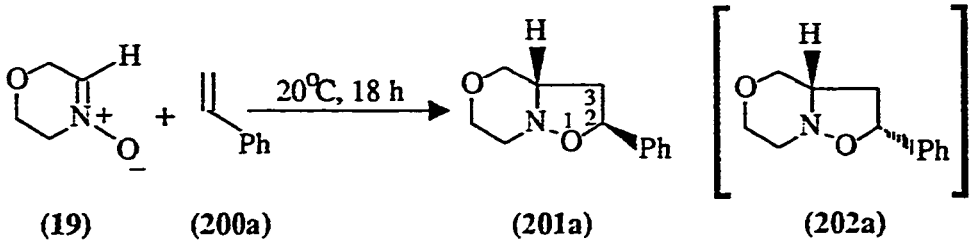


Scheme 1

3.1.2 *Addition of Styrene (200a) to Nitrone (19)*

The cycloaddition reaction of the nitrone **(19)** with styrene **(200a)**, carried out at room temperature, afforded the sole adduct **(201a)** regiospecifically and

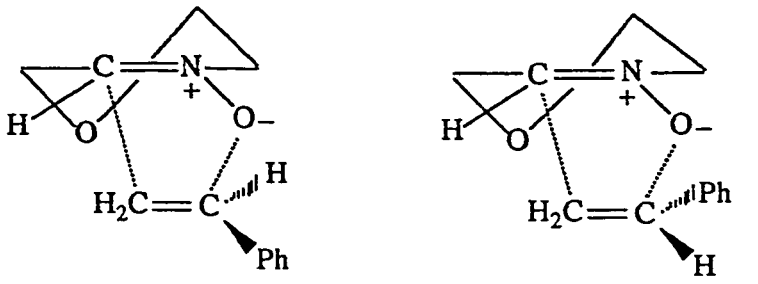
stereo-selectively. The product was purified by silica gel chromatography. NMR spectrum revealed the formation of only one adduct in 83% yield. We were unable to detect any minor isomer. The adduct was assigned the stereochemistry as depicted in **(201a)** with *exo* orientation of the phenyl substituent (Scheme 2).



(19) **(200a)** **(201a)** **(202a)**

Scheme 2

Even though the phenyl ring can stabilize the *endo* transition state by favourable secondary orbital interactions, steric encumbrance dominates the stereoselection and the *endo* product was not observed (Figure 1).

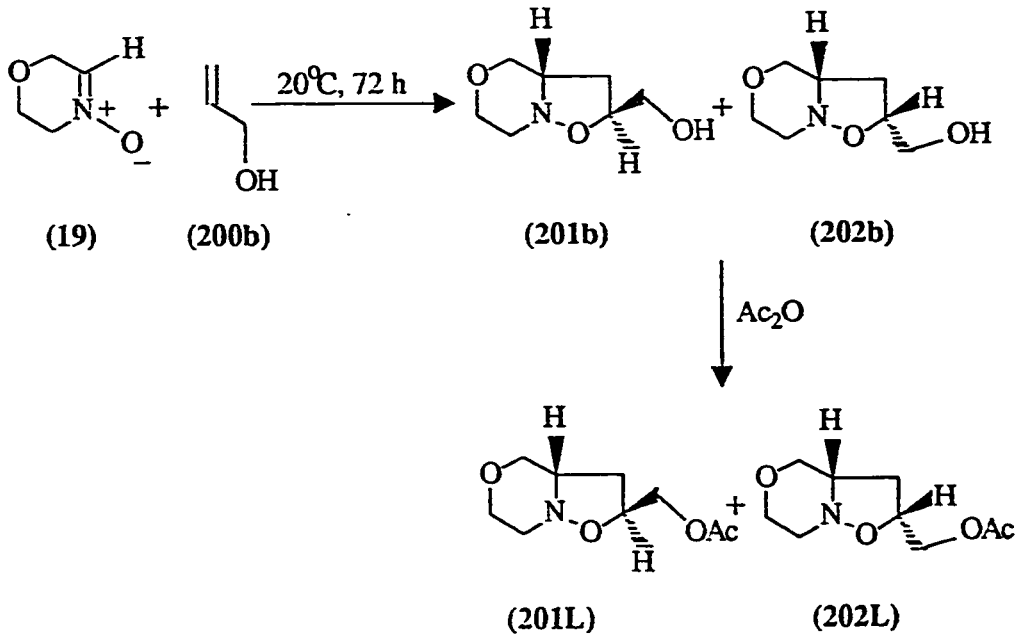


exo transition state *endo transition state*

Figure 1.

3.1.3 *Addition of Allyl Alcohol (200b) to Nitone (19)*

Allyl alcohol was allowed to react at room temperature (20°C) with the nitrone (19) as shown in Scheme 3. The overall yield of the reaction was 88%. Chromatographic purification of the crude reaction mixture provided a non-separable mixture of the two adducts (201b) and (202b) in a respective ratio of 88 : 12. The major isomer (201b) was crystallized and separated as colorless crystals. The strong absorption band at 3200 cm^{-1} in the IR spectrum revealed



Scheme 3

the presence of hydroxyl group in the two isoxazolidines (201b) and (202b). The ratio of the two isomers (201a) and (202b) was determined by converting them to the respective acetates (201L) and (202L). The ratio was estimated by the integration of the acetyl protons' singlets *(see Experimental)*. The

stereochemical outcome of this cycloaddition reaction reflects the preference for the *exo* transition state which is sterically favourable and hence gives (**201b**) as the major stereoisomer. However, the sterically disfavoured *endo* transition state leading to the formation of the minor isoxazolidine (**202b**) would enjoy the stabilizing interaction between the oxygen lone pair of the alkene (HOMO) with the nitrogen orbital of the nitrone (LUMO) (Figure 2).

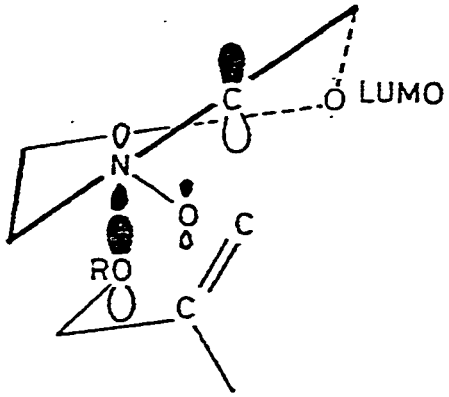


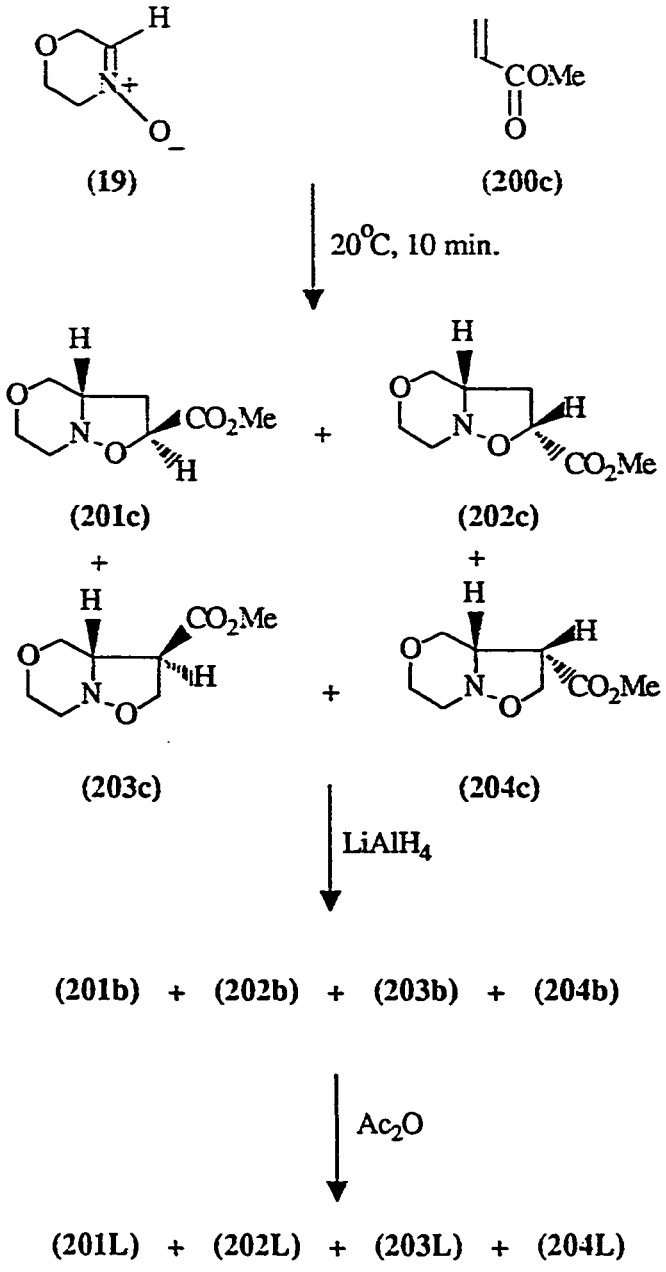
Figure 2

3.1.4 *Addition of Methyl Acrylate (200c) to Nitrone (19)*

Nitrone (**19**) cycloaddition reaction with methyl acrylate (**200c**), carried out at room temperature (20°C), afforded a non-separable mixture of four isomers (**201c**)-(**204c**) (Scheme 4). Column chromatographic purification of a portion of the crude mixture gave the purified adducts (**201c**)-(**204c**) (81% yield). The *exo* approach of methyl acrylate to the nitrone (**19**) would give the isoxazolidines (**201c**) and (**203c**), while the regioisomers (**202c**) and (**204c**) would result from the *endo* approach. Though the *endo* transition state would gain a degree of stabilization from the secondary orbital interaction, it suffers from steric encumbrance. The strong band at 1741 cm^{-1} in the IR spectrum of the purified

mixture of the adducts is an indication of the presence of ester functional groups in the adducts. The assignment of the regiochemistry of the four isomers was based on the proton NMR analysis. The ratio of the C-2 and C-3 substituted regiomers was found to be 88 : 12. The adduct with *exo* orientation was the major isomer in both pairs of the regiomers. The C-2 protons of the major adducts **(201c)** and **(202c)** showed multiplet signals at δ 4.50-4.85 with a major doublet at δ 4.80 (J 5.0, 9.0 Hz) being attributed to the *exo* adduct **(201c)**. Singlet at δ 3.78 was assigned to the methoxycarbonyl protons. Minor signals at δ 4.0-4.5 were attributed to the C-2 protons of the minor regiomers **(203c)** and **(204c)**.

Upon reduction of a portion of the crude mixture of the cycloadducts **(201c)-(204c)** with lithium aluminium hydride, the alcohols **(201b)-(204b)** were obtained. On acetylation with acetic anhydride, the later adducts gave the acetates **(201L)-(204L)**. The ratio of the acetates, hence that of the methyl acrylate adducts was estimated by the integration of the acetyl protons' singlets *(see Experimental)*. The approximate ratio of the isomers **(201c)-(204c)** was found to be 80 : 8 : 7 : 5, respectively.

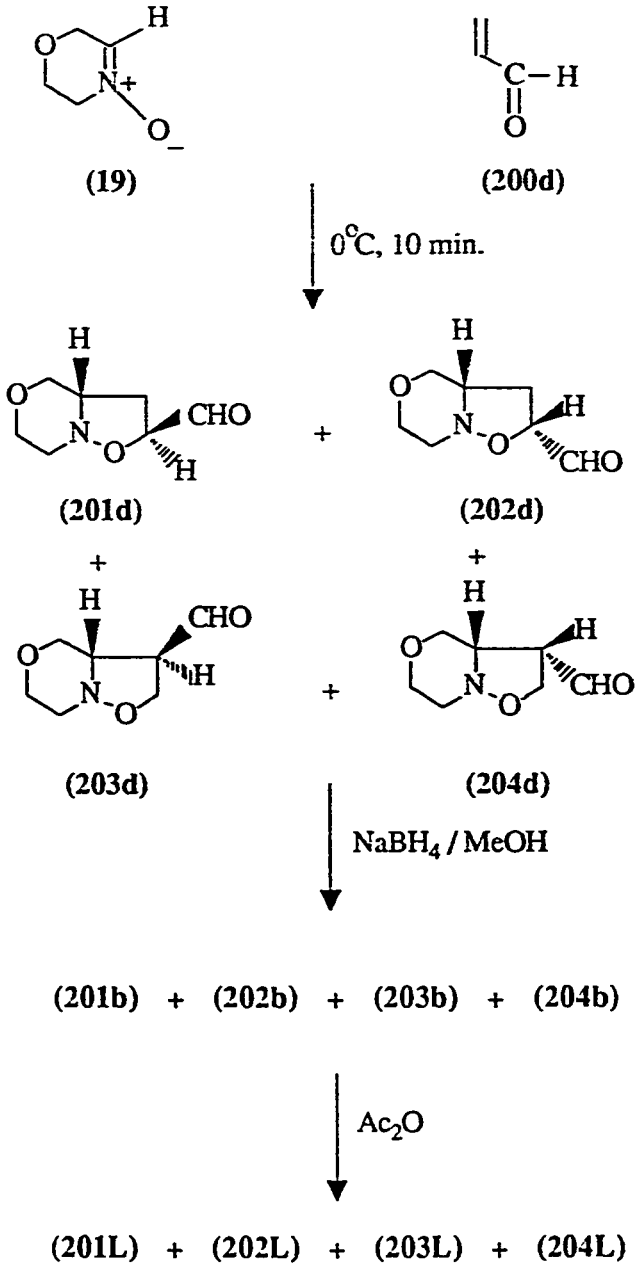

(19)
(200c)
20°C, 10 min.
(201c)
(202c)
(203c)
(204c)
LiAlH4
(201b) + (202b) + (203b) + (204b)
Ac2O
(201L) + (202L) + (203L) + (204L)

Scheme 4

3.1.5 *Addition of Acrylaldehyde (200d) to Nitrone (19)*

The cycloaddition reaction of the nitrone (**19**) with acrylaldehyde (**200d**) at 0°C afforded a mixture of four isomers (**201d**)-(**204d**) (Scheme 5). The crude mixture of the adducts (**201d**)-(**204d**), because of their labile nature, was immediately reduced with sodium borohydride in a methanolic solution to give a mixture of the alcohols (**201b**)-(**204b**) which was then chromatographically purified using ethyl acetate as the eluant (67% yield in two steps).

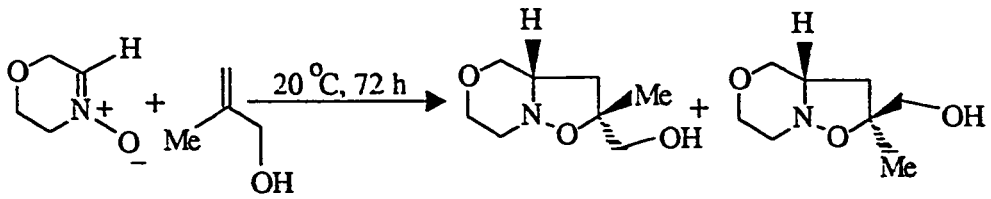
A portion of the isomers (**201b**)-(**204b**) was converted into the acetates (**201L**)-(**204L**) by treating with acetic anhydride. The IR spectrum of (**201L**)-(**204L**) had strong absorption at 1740 cm^{-1} due to the acetyl groups. The proton NMR spectrum of the isoxazolidines (**201L**), (**202L**), (**203L**), (**204L**) showed acetyl protons' singlets at δ 2.11, 2.13, 2.06, and 2.08, respectively. The ratio of the adducts (**201L**)-(**204L**), hence that of (**201d**)-(**204d**) was approximated by integration of these singlets, and was found to be 48 : 29 : 12 : 11, respectively. The acetates obtained from the allyl alcohol adducts (**201b**) and (**202b**) revealed the presence of the major and minor singlets at δ 2.11 and 2.13 respectively. By analogy,[31,32] the major adduct was assigned the stereochemistry as depicted in (**201b**) with *exo* hydroxymethyl substituent. While methyl acrylate (**200c**) gave the C-2 *endo* oriented adduct (**202c**) in 8% of the total isolated yield, the corresponding yield for the adduct (**202d**) from the addition of acrylaldehyde (**200d**) was found to be 29%. The aldehyde group, being smaller than methoxycarbonyl group, prefers to be in the *endo* orientation and thus an increased amount of the *endo* oriented C-2 and C-3 regiomers were obtained in the former case. This experimental findings confirm the assignment of the stereochemistry.


(19)
(200d)
0°C, 10 min.
(201d)
(202d)
(203d)
(204d)
NaBH4 / MeOH
(201b) + (202b) + (203b) + (204b)
Ac2O
(201L) + (202L) + (203L) + (204L)

Scheme 5

3.1.6 *Addition of Methylallyl Alcohol (200e) to Nitrone (19)*

Methylallyl alcohol (**200e**) underwent cycloaddition reaction with the nitrone (**19**) at 20°C. Chromatographic purification of the crude reaction mixture using 1 : 1 hexane-ethyl acetate mixture as eluant afforded a non-separable mixture of the isoxazolidines (**201e**) and (**202e**) (Scheme 6). Bands at 3329 and 3238 cm^{-1} in the IR spectrum are indications of hydroxyl functionality in the adducts. The ^1H NMR spectrum showed two methyl singlets; a major at δ 1.25 assigned to (**201e**), and a minor at δ 1.40 assigned to (**202e**). Integration of the C-2 methyl singlets gave a ratio of 91 : 9 of the adducts (**201e**) and (**202e**), respectively. Noticeably in this reaction, the major isomer (**201e**), has the *endo* orientation of the bulkier substituent -CH_2OH. We believe that the transition state with *endo* CH_2OH is stabilized due to the favourable interaction between the orbital of the nitrogen LUMO of the nitrone with the oxygen lone pair of the alkene *(see Figure 2)*. Stereochemistry of the adduct (**201e**) was correlated to methyl methacrylate adduct (**201f**) by chemical conversion *(see the subsequent section)*. Stereochemistry of the major adduct is based on precedent literature.[31]

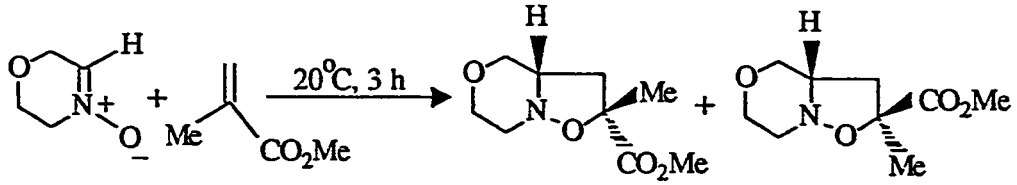


(**19**) (**200e**) (**201e**) (**202e**)

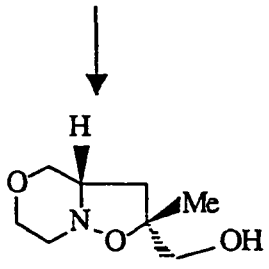
Scheme 6

3.1.7 *Addition of Methyl Methacrylate (200f) to Nitrone (19)*

Chromatographic purification (eluant 1 : 1 hexane-ethyl acetate) of the crude reaction mixture resulting from the addition of methyl methacrylate (**200f**) to the nitrone (**19**), at room temperature, afforded a non-separable mixture of isomers (**201f**) and (**202f**) (Scheme 7). A yield of 86% was recovered from this regiospecific cycloaddition reaction. The absorption band at 1730 cm^{-1} in the IR spectrum is a clear indication of the presence of an ester functional group. The ratio of (**201f**) and (**202f**) was determined to be 95 : 5, respectively by integration of the methyl singlets *(see Experimental)*. The regiospecific and highly stereoselective formation of the isomer (**201f**), with *endo* approach of CO_2Me is attributed to the favourable secondary orbital interaction by CO_2Me group. The major adduct (**201f**) was converted into the alcohol (**201e**) by reduction with lithium aluminium hydride.



(19) **(200f)** **(201f)** **(202f)**

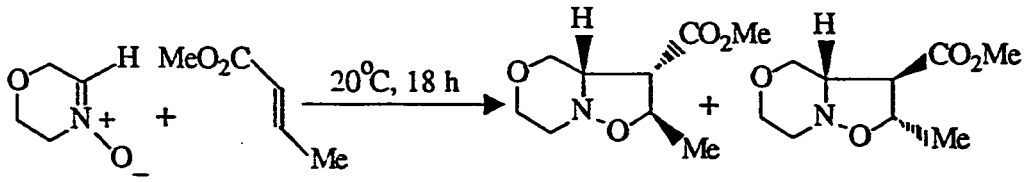


(201e)

Scheme 7

3.1.8 *Addition of Methyl Crotonate (200g) to Nitrone (19)*

The room-temperature reaction of nitrone (**19**) with methyl crotonate (**200g**) proceeded regiospecifically (Scheme 8). Chromatographic purification of the crude reaction product using ethyl acetate as eluant gave a non-separable mixture of the isoxazolidines (**201g**) and (**202g**) in a total yield of 84%. The major adduct is assigned the stereochemistry as depicted in (**201g**). Studies of the stereochemistry of nitrone-crotonate cycloadditions have amply demonstrated a significant tendency of the methoxycarbonyl group to manifest secondary orbital interactions.[109,110] The absorption band at 1734 cm^{-1} in the IR spectrum revealed the presence of ester functional group in the adducts. The protons of the C-2 methyl group of the major (**201g**) and the minor (**202g**) isomer appeared at δ 1.36 and δ 1.50, respectively in the NMR spectrum. The respective ratio was determined to be 96 : 4.



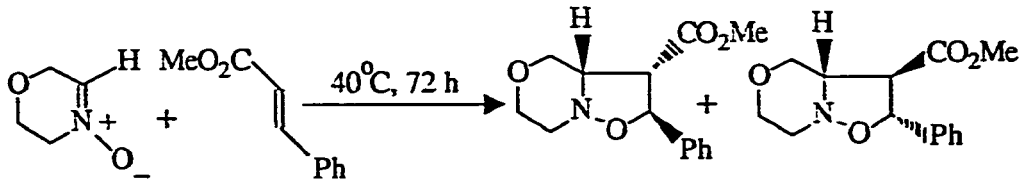
(19) **(200g)** **(201g)** **(202g)**

Scheme 8

3.1.9 *Addition of Methyl Cinnamate (200h) to Nitrone (19)*

The product afforded by the addition of *trans*-methyl cinnamate (**200h**) onto the nitrone (**19**) at 40°C was chromatographically purified with 1 : 1 dichloromethane-ethyl acetate mixture as eluant. The reaction yielded 86% of the

adducts (**201h**) and (**202h**) (Scheme 9). The major isoxazolidine was assigned the configuration as depicted in (**201h**) because of the significant tendency of the carbomethoxy group to be *endo* oriented, due to the favourable secondary orbital interaction.[109,110] The absorption at 1734 cm^{-1} in the IR spectrum is due to the ester functional group. The ^1H NMR spectrum also revealed the presence of two singlets at δ 3.78 and δ 3.81, which were assigned to the methoxycarbonyl protons of the major and minor isomer, respectively. Based on the peak hight of the methoxycarbonyl protons, the ratio of (**201h**) and (**202h**) was determined to be 94 : 6, respectively.

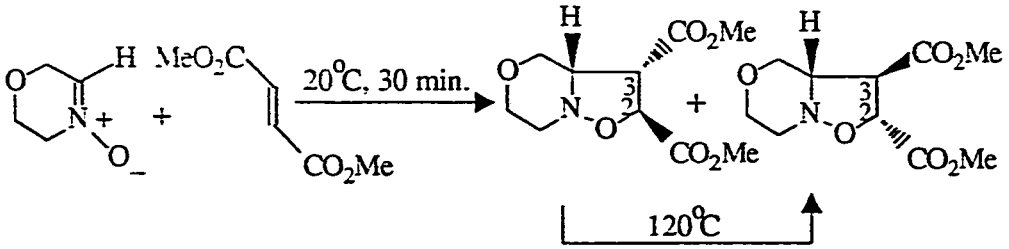


(19) **(200h)** **(201h)** **(202h)**

Scheme 9

3.1.10 *Addition of Dimethyl Fumarate (200i) to Nitrone (19)*

From the cycloaddition of dimethyl fumarate (**200i**) onto the nitrone (**19**), at room temperature (20°C), a non-separable mixture of the isoxazolidines (**201i**) and (**202i**) was obtained in 80% yield (Scheme 10). The prominent band at 1728 cm^{-1} in the IR spectrum is a clear indication of the presence of ester functional group. Proton NMR analysis enabled us to determine the ratio of the two isomers *(see Experimental)*. The ratio of (**201i**) and (**202i**) was estimated by integration of the C-2 protons, and was found to be 82 : 18, respectively. The major adduct was separated by crystallization.



(19) **(200i)** **(201i)** **(202i)**

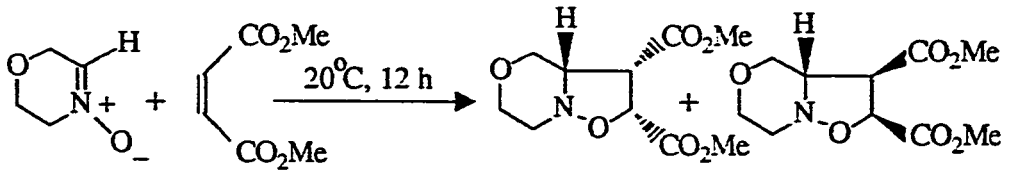
Scheme 10

The stereochemistry of the major adduct as depicted in **(201i)** is based on the result of the thermal study. The adduct **(201i)** was thermally equilibrated to the more stable product **(202i)** with *exo* oriented C-3 and *endo* oriented C-2 methoxycarbonyl groups. This is in line with the prediction that the C-2 position, with a less crowded environment than C-3, can tolerate an *endo* substituent better than C-3.[111] When the pure adduct **(201i)** was thermolyzed at 120°C in deuterobenzene, the ratio of the adducts **(201i)** and **(202i)** was found to be 15 : 85, respectively. This is an equilibrium ratio, since further heating did not change the composition.

3.1.11 *Addition of Dimethyl Maleate (200j) to Nitrone (19)*

Nitrone (19) cycloaddition onto dimethyl maleate **(200j)** was carried out at 20°C. Chromatographic purification of the product, using 1 : 1 hexane-ethyl acetate mixture as an eluant, afforded the isoxazolidines **(201j)** and **(202j)** (Scheme 11). The isolated yield was 82%. The IR spectrum exhibited absorption bands at 1761 and 1737 cm^{-1} which were attributed to the ester functional groups. Assignment of the stereochemistry of the major adduct **(202j)**, as depicted in Scheme 11, was

based on the assumption that the *exo* transition state, leading to (**202j**) would be sterically favoured.[41,42] The ratio of the isomers (**201j**) and (**202j**) was estimated by the integration of the C-2 proton signals and was found to be 4 : 96, respectively. The reasons for assignment of the *exo* structure to the major adduct (**202j**) are discussed in the following section.

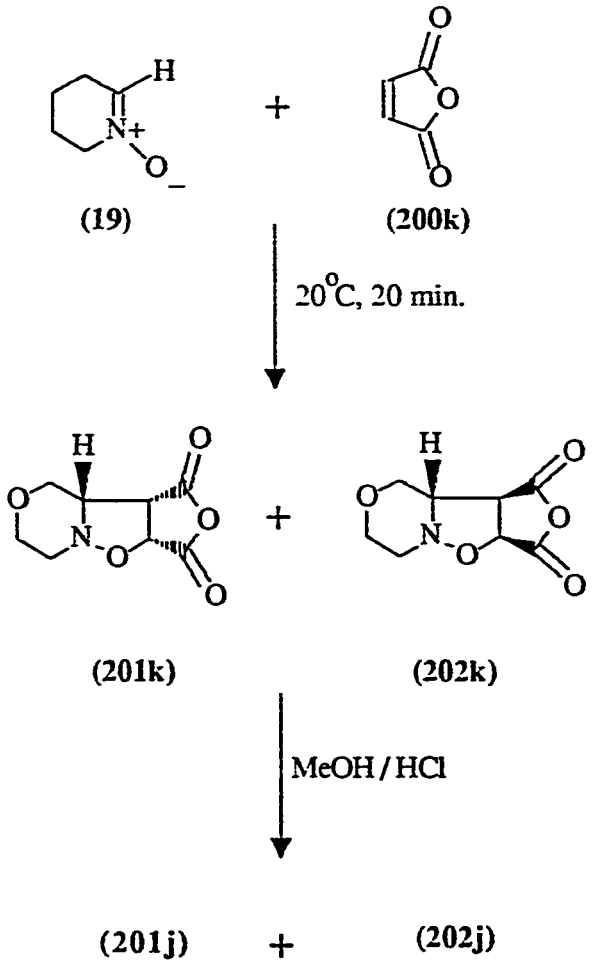


(**19**) (**200j**) (**201j**) (**202j**)

Scheme 11

3.1.12 *Addition of Maleic Anhydride (200k) to Nitrone (19)*

The cycloaddition reaction of maleic anhydride (**200k**) with nitrone (**19**) gave a mixture of adducts (**201k**) and (**202k**) in a ratio of 8 : 92 (Scheme 12). The crude reaction mixture was divided into two portions, which were then treated as follows. One portion of the crude adducts (**201k**) and (**202k**), on treatment with methanolic HCl (5 : 3, w/w), was converted into a mixture of the adducts (**201j**) and (**202j**). The major adduct (**202k**) would result from the *exo* mode of



Scheme 12

attack. We believe that the steric factor present in the *endo* transition state will overcome the favorable secondary orbital interaction. The isolated yield (based on that of the corresponding dimethyl maleate adduct) was 73%. The second portion of the crude mixture was dissolved in dichloromethane and the insoluble material was filtered off. On concentration, white crystals of the adduct **(202k)** was

obtained. The assignment of the *exo* structure to the major adducts **(202j)** or **(202k)** is based on the reasonable assumption that switching the alkene from dimethyl maleate to sterically less demanding maleic anhydride brings about an expected increase in the *endo*/*exo* ratio. Thermolysis of the pure adduct **(202j)** in deuterobenzene for 8 h at 130°C afforded the unchanged adduct. The result thus confirms the stereochemistry assigned to the more stable adduct **(202j)** or **(202k)** with the *exo*-oriented carbomethoxyl group.

3.2 Discussion

The regio- and stereo-chemical details of the nitrone (19) - alkene (200) cycloaddition along with isolated yields are reported in Table 1. Information about the reaction conditions and isolated yields of these additions are also given in the Table. The regiochemistry observed in these additions can be interpreted by the HOMO-LUMO considerations of the interacting species. In fact, for monosubstituted alkenes, the electronic nature of the substituents plays a major role in the regiochemistry of their cycloadditions to nitrones. Bulkiness of the substituent may also have some effect. The reaction of nitrone (19) with styrene reveals a marked tendency of the oxygen terminal of the nitrone to become attached regio- and stereo-selectively to the benzylic carbon to give the 2-substituted isoxazolidine (201a) as the sole adduct. This can be rationalized by the assumption that secondary orbital involvements in this case are not great enough to overcome the steric factors. Similar to styrene, allyl alcohol (200b) appears to undergo regiospecific addition to the nitrone (19) to give the adduct (201b) and (202b) in a ratio of 88 : 12.

However, the regiochemistry of the [4+2] cycloaddition reaction of nitrone (19) to monosubstituted alkenes with an electron-withdrawing substituent is more complex. For instance, the reaction of nitrone (19) with methyl acrylate (200c) and acrylaldehyde (200d), each gave rise to four adducts, diastereomeric pairs of both the 3-substituted and the 2-substituted isoxazolidines. The results discussed above are in general agreement with frontier orbital treatment of the nitrone 1,3-dipolar cycloaddition[72-76] (Figure 3). In the case of normal alkenes both HOMO(nitrone)-LUMO(alkene) and LUMO(nitrone)-HOMO(alkene) interactions prefer the formation of 2-substituted regiomers by uniting the larger terminal

TABLE 1 : Regio- and Stereo-chemistry of Cycloadditions of the Nitrone (19) with Alkenes (200) in Dichloromethane.

Alkene (200)	Temperature (°C)	Reaction time (h)	% Composition of adducts (201)	(202)	(203)	(204)	Isolated yield
a, Styrene	20	18	100	0	0	0	83
b, Allyl alcohol	20	72	88	12	0	0	88
c, Methyl acrylate	20	0.17	80	8	7	5	81
d, Acrylaldehyde	0	0.17	48	29	12	11	67
e, Methylallyl alcohol	20	72	91	9	0	0	82
f, Methyl methacrylate	20	3	95	5	0	0	86
g, Methyl crotonate	20	18	96	4	0	0	84
h, Methyl cinnamate	40	3	94	6	0	0	86
i, Dimethyl fumarate	20	0.5	82	18	-	-	80
j, Dimethyl maleate	20	0.2	4	96	-	-	82
k, Maleic anhydride	20	0.3	8	92	-	-	73[a]

[a]Isolated yield of the corresponding dimethyl maleate adduct.

coefficients in the transition state (Figure 3). As the ionization potential and electron affinity of the alkene increase (i.e. as the HOMO-LUMO levels decrease in energy) there is an increasing tendency towards the production of a regioisomeric mixture of products. For instance, with methyl acrylate or acrylaldehyde, nitrone **(19)** gave both 2- and 3-substituted isoxazolidines. The LUMO(nitrone)-HOMO(methyl acrylate) interaction dictates the formation of a 2-substituted isoxazolidine with the other HOMO-LUMO interaction favouring the formation of the 3-substituted regiomer.

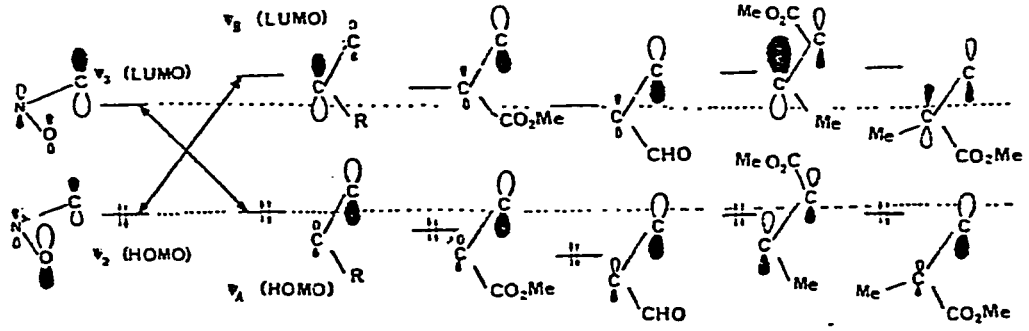
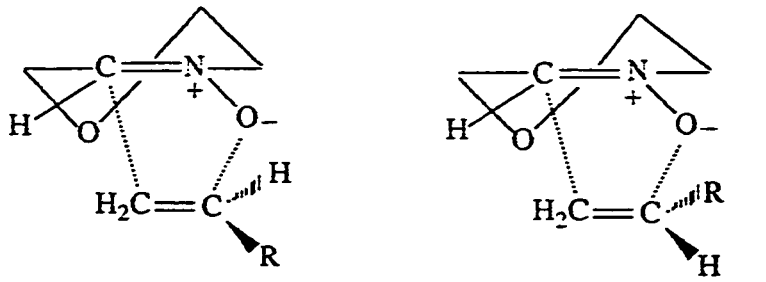


Figure 3 : A qualitative representation of the energies and orbital coefficients of nitrone and alkenes.

In all of the four alkenes **(200a)-(200d)**, the configuration of the major 2-substituted stereoisomer is assumed to have the *exo* orientation of the C-2 substituent obtained via the favorable *exo* mode of attack. For 3-substituted adducts, the major isomers were assigned the stereochemistry as depicted in **(203c)** (in case of methyl acrylate) and **(203d)** (in case of acrylaldehyde). This observation demonstrates that in these cycloadditions the favorable secondary orbital interaction benefited from the *endo* transition state is not sufficient to

override the steric compression associated with the interaction of the substituent R in the incoming dipolarophile and the appropriate ring hydrogens of the nitrone (Figure 4). The influence of steric factors appears to dominate in these cases.



exo transition state *endo transition state*

(200a), R = Ph

(200b), R = CH_2OH

(200c), R = CO_2Me

(200d), R = CHO

Figure 4

There seem to be an excellent correlation between increased production of the 3-substituted regioisomers with increasing strength of the electron-withdrawing power of the substituents. While nitrone **(19)** reacts with styrene and allyl alcohol to yield 100% of the C-2 product. The C-3 substituted product is obtained 12% with methyl acrylate, the amount of adduct increases to 23% with the relatively stronger electron-withdrawing substituent, the aldehyde.

In our study, both methylallyl alcohol and methyl methacrylate gave 2-substituted cycloadducts regiospecifically as would be predicted by the frontier orbital theory. In case of methylallyl alcohol, this can be rationalized since both Me and CH_2OH substituents have a similar effect on the frontier orbital coefficients at

both carbons in the alkene with substituted end of alkene having smaller orbital coefficient in HOMO and larger coefficient in LUMO. Thus both HOMO-LUMO interactions favour the formation of C-2 disubstituted adducts by maximum overlap of the orbitals. While the substituents methyl and methoxycarbonyl have similar effects on the size of the HOMO coefficients of the alkene, the LUMO orbitals are affected in the opposing directions. Thus, the LUMO coefficients on both carbon atoms are nearly the same. Thence, the regio-chemical outcome is determined by nitrone(LUMO) - alkene(HOMO) interaction, which favours the transition state leading to the 2-disubstituted regioisomer.

The stereochemistry, as depicted in **(201f)** for the major adduct in the methyl methacrylate **(200f)** addition is based on analogy.[32] It can be confidently assumed that the carbomethoxy group, for its ability to manifest secondary orbital interaction, would be *endo* oriented in the major isomer **(201f)**. Stereochemistry of the methylallyl alcohol adduct **(201e)** was correlated to methyl methacrylate adduct **(201f)** by chemical conversion.

The selectivity of symmetrical 1,2-disubstituted alkenes in nitrone cycloaddition is obviously uncomplicated by regiochemical considerations, as in the combination of nitrone **(19)** with dimethyl fumarate **(200i)**, dimethyl maleate **(200j)**, and maleic anhydride **(200k)**. Additionally, an important feature of the [4+2] reaction of nitrones with olefins symmetrically substituted with electron-withdrawing substituents has been established,[6,22] namely the retention of configurational relationship of the attached substituents. This stereospecificity was important in the development of the concept of a concerted cycloaddition process.

However, the substitution patterns of unsymmetrical 1,2-disubstituted olefins would play a role in regioselection in the reactions with nitrones. In practice, however, addition reactions of this class of olefins proceed with an exceptional degree of regio- and stereo-selectivity. Thus, the cycloadditions of

nitrone (**19**) to methyl crotonate (**200g**) and methyl cinnamate (**200h**) produced only regioisomers (**201g**, **202g**) and (**201h**, **202h**) respectively, in which the more potent electron-withdrawing carbomethoxy substituent occupied the C-3 position. This tendency is well accommodated by the FMO treatment.[6] The stereochemistry as depicted in (**201**) for the major adduct in the crotonate (**200g**) and cinnamate (**200h**) addition reactions is based on analogy.[48] Transition state, leading to these major products, is stabilized by favorable secondary orbital interactions involving *endo* oriented methoxycarbonyl group (Figure 5).

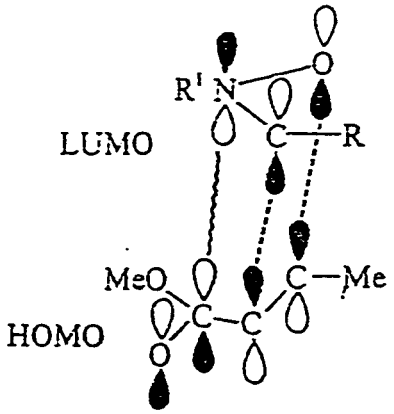


Figure 5 : Depiction of Favorable Secondary Orbital Interaction in Nitrone Cycloaddition.

In comparison to its carbocyclic counterpart (**16**), the heterocyclic nitrone (**19**) was found to be more stereoselective. For instance, while the ratio of the cycloadducts (**201i**)/(**202i**) was found to be 4.6 : 1, the corresponding ratio of the nitrone (**16**) dimethyl fumarate adducts was 1.5 : 1.[31] The presence of the heteroatom oxygen in the ring skeleton, presumably, diminishes the steric crowding at the carbon terminal of the nitrone functional group thus making this end more tolerant to an *endo* oriented substituent at the transition state.

Recently, the role of secondary orbital interactions as major *endo* orienting factors are repeatedly being questioned.[42] In one such report[74] it has even been concluded that secondary orbital overlap involving the orbitals of the nitrogen atom of a nitrone and maleonitrile gives rise to a destabilization of the *endo* transition state with respect to the *exo* form. Closed-shell repulsions. persumably, outweigh the favorable occupied-unoccupied interactions. For nitrone cycloaddition reaction, nitrone(HOMO)-maleic anhydride(LUMO) energy gap is much smaller than that of the other HOMO-LUMO combination. In fact, nitrone(LUMO)-maleic anhydride(HOMO) interaction could be considered negligible. It is our view that the nitrogen atom in the nitrone(HOMO) has a node or near node thus rendering it almost ineffective in any secondary orbital interaction involving the LUMO of the dipolarophile. The scenario is different in normal Diels-Alder reactions where favorable secondary orbital interaction overwhelmingly favours the *endo* mode of attack. The addition reactions of the nitrone **(19)** with dimethyl maleate **(200j)** or maleic anhydride **(200k)** represent examples of the highest *exo* selectivity found among cycloadditions involving these two *cis*-disubstituted alkenes with unsubstituted cyclic nitrones.[31,32,47,48] An *exo*/*endo* ratio of 92:8 *(see Table 1)* in the nitrone **(19)**-maleic anhydride **(200k)** addition reaction clearly demonstrates the prevalence of the steric encumbrance, closed-shell repulsions over the *endo* orienting factors such as electrostatic attractions and favorable secondary orbital interactions. In other words, steric encumbrance overrides the favorable secondary orbital interaction inherent in the *endo* mode of attack.

CHAPTER 4

KINETICS OF CYCLOADDITION REACTIONS

Results and Discussion

The nitrone-olefin cycloaddition is a second order reaction; first order with respect to each component of the reaction system. Determination of the second order rate constants k_2 for the cycloadditions of nitrone **(19)** onto several mono- and disubstituted alkenes in deuterated chloroform has been achieved at 36°C using ^{1}H NMR spectroscopy. All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors. The nitrone, alkenes, and cycloadducts were all stable under the mild reaction conditions.

Cycloadditions were monitored by proton NMR by following the change in the intensity of the ^{1}H NMR signals of 2-H of nitrone and α-H of alkene. The ^{1}H NMR ($CDCl_3$) signals of the 2-H and of the 3-H protons of the nitrone **(19)** appeared at δ 7.15 and 4.42, respectively. The signals of the olefinic protons of the alkenes were centered around δ_H values as follows : allyl alcohol, 5.15, 5.36, 5.95; methyl acrylate, 5.85, 6.18, 6.38; methyl methacrylate, 5.56, 6.10; methyl crotonate, 5.87, 6.90; dimethyl fumarate, 6.88; and dimethyl maleate, 6.25. These signals and in most cases C-2 H of the cycloadducts were free of overlapping signals. Therefore, the ratio of the concentrations of the nitrone and alkene were frequently determined during the kinetic runs by integrating the ^{1}H NMR signals of the olefinic protons of the nitrone and the alkene. The second-order rate constants were then determined by linear regression analysis of the data, and were

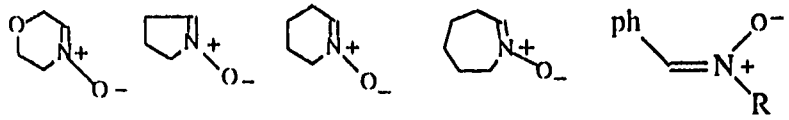
reproducible within 5-10%. The additions were followed upto 40-90% chemical conversion.

Kinetic results obtained for the cycloaddition of the nitrone **(19)** with different alkenes in $CDCl_3$ at 36°C are represented in Table 2. Kinetic measurements of k_2 for other nitrones **(15)**-**(17)**, **(45)**, and **(54)** with the same alkenes are also tabulated for the purpose of comparison. The ratio of rate constants at 36°C of nitrone **(19)** to those of the nitrones **(15)**-**(17)** is also presented in the Table. In order to avoid any possible polymerization, the concentration of the nitrone **(19)** was kept low and the alkene was used in excess. We did not notice any unwanted polymerization under the specified reaction conditions. The nitrone **(19)** was found to be more reactive than the nitrones **(15)**-**(17)**, **(45)**, and **(54)** towards all the alkenes studied *(see Table 2)*. For instance, the rate ratio for the addition reaction of the nitrones **(19)**, **(15)**, **(16)**, and **(17)** with methyl acrylate in deutereochloroform at 36°C was found to be 39 : 1 : 5.5 : 7.3, respectively.[101]

The methyl acrylate was found to be 5 times as reactive as methyl methacrylate (Table 2). This observation can be related to the steric retardation established by the introduction of the methyl group. It is also apparent that *trans*-1,2-disubstituted alkenes are more reactive than their *cis* counterparts. Hence, *trans*-dimethyl fumarate is 23 times more reactive than its *cis* isomer **(200j)**. This trend is also observed in the rate of the addition of acyclic nitrones.[102] This phenomena has been ascribed[5] to the increased steric compression between *cis* substituents in the transition state resulting from a hybridization change at carbon from sp^2 to sp^3 during the course of the reaction.

According to Sustmann's classification[73] (Figure 6), the cycloaddition reaction of nitrone onto alkene is Type II. In this type, the HOMO and LUMO energies in dipole and dipolarophile are similar, and hence, both HOMO(nitrone)-

Table 2. Rate Constants (k_2) for the Cycloaddition Reactions at 36 °C in Deutereochloroform.



(19) (15) (16) (17) (45), R = Me
(54), R = Ph

Alkene	k_2 X 10^5 l mol^{-1} s^{-1}					k_2(19) : k_2(15) : k_2(16) : k_2(17)
Allyl alcohol	37.6	-	1.82	-	-	20.7 : - : 1 : -
Methyl acrylate	2,400	62.0	340	453	-	38.7 : 1 : 5.5 : 7.3
Methyl methacrylate	453	23.4	105	407	-	19.4 : 1 : 4.5 : 17.4
Methyl crotonate	34.9	1.85	22.6	16.6	55.4[a]	18.9 : 1 : 12.2 : 9.0
Dimethyl fumarate	13,900	178	3,370	5,260	72.5[b]	78.1 : 1 : 18.9 : 29.6
Dimethyl maleate	605	13.8	209	152	24.7[b]	43.8 : 1 : 15.1 : 11.0

[a](54), 100 °C, toluene.
[b](45), 85 °C, toluene.

LUMO(alkene) and LUMO(nitrone)-HOMO(alkene) interactions contribute effectively to the stabilization of the transition state, and therefore may be important in determining reactivity and regiochemistry. The interaction that dominates in

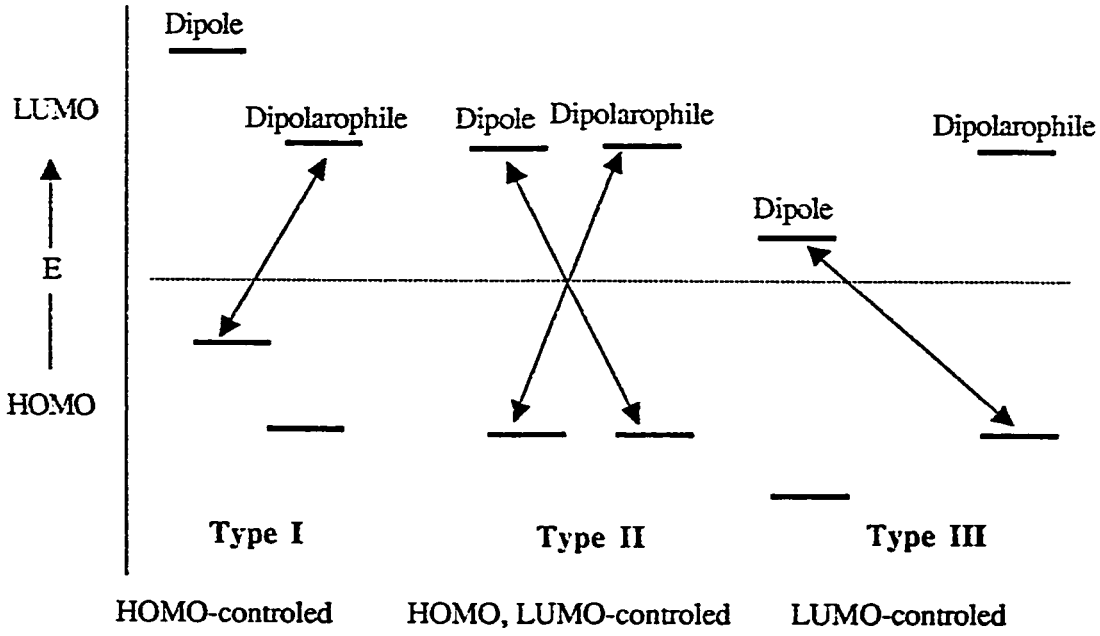


Figure 6 : Frontier molecular orbital classification[23,73] of cycloaddition reactions.

a particular case will depend on the nature of both the dipole and the dipolarophile. Figure 7 gives a representation of energies of HOMO and LUMO of the nitrone and alkenes. Both electron-deficient and electron-rich, because of smaller energy gap, would undergo additions faster than normal alkenes. As seen from Figure 7, the LUMO(dipole) - HOMO(dipolarophile) interaction dominates in the case of electron-rich alkenes, and the alternative HOMO(dipole)- LUMO(dipolarophile) interaction is dominant for very electron-poor dipolarophiles.

The explanation of the differences in reactivity and regiochemistry observed in the cycloaddition of nitrone (19) with the alkenes listed in Table 2 requires the consideration of HOMO-LUMO energy gap, orbital coefficients, substituents, steric effects and other factors. The Perturbation Molecular Orbital theory of the frontier orbital interaction offers a remarkably successful qualitative explanation of both reactivity and regiochemistry phenomena associated with the nitrone-olefin [4+2] - dipolar cycloadditons.

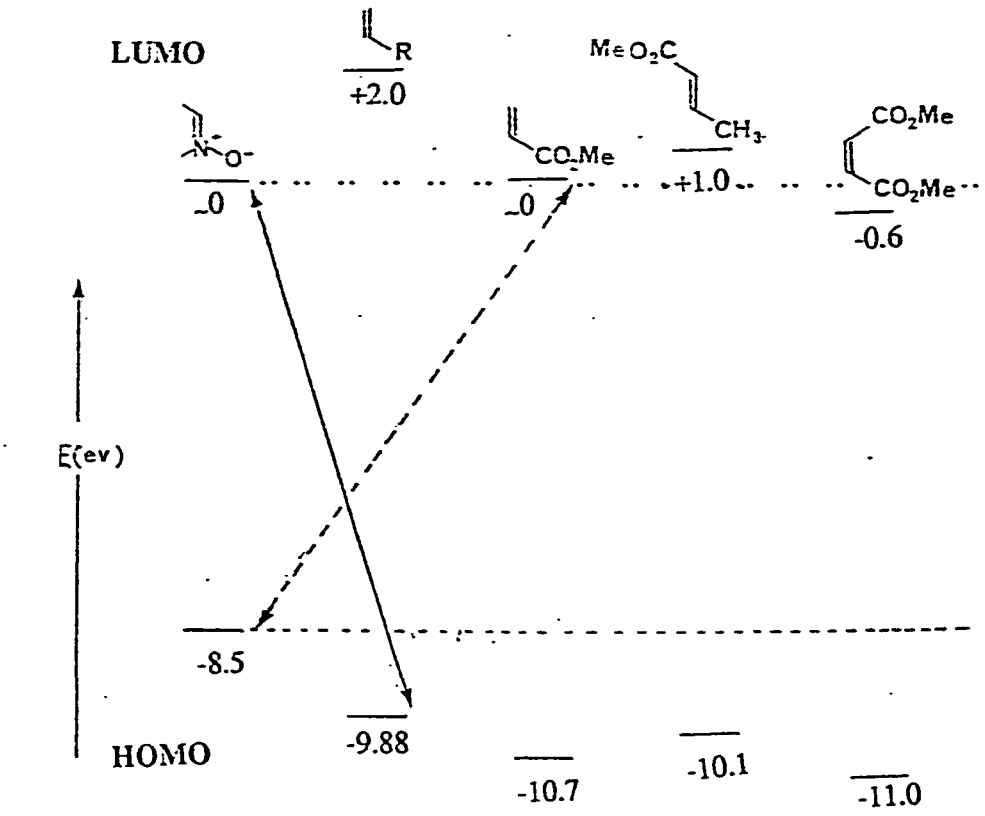
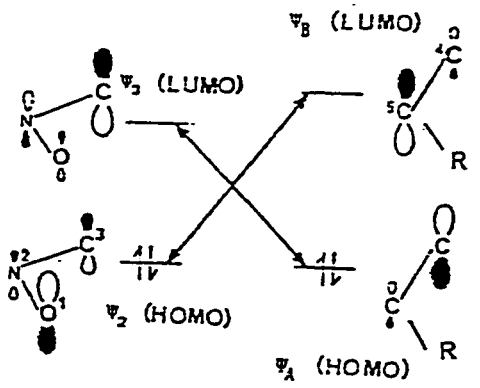


Figure 7 : Depiction of energy of frontier molecular orbital in nitrone-alkene cycloadditions.[6]

A qualitative explanation can be put forward using the crude equation (1) obtained by applying MO perturbation theory to the frontier orbital interactions

(Figure 8). The interaction or stabilization energy, ΔE, of the transition state is determined by orbital coefficients (c and c' of HOMO and LUMO, respectively), resonance integral (β), and HOMO-LUMO energy gaps. The perturbation equation (1) has been simplified and used by other workers by assuming that the numerators of the two terms are equal and the substituent changes the HOMO-LUMO energies of the alkene by same amount. One can see that switching from allyl alcohol to methyl acrylate approximately lowers the orbital energies by an equal amount. Then a loss in the second term (due to an increase LUMO(nitrone) - HOMO(alkene) energy gap) will be more than compensated by a gain in the first term. Thus an increased ΔE accelerates the addition reaction of methyl acrylate compared to that of allyl alcohol.



$$\Delta E = \frac{2\left(c_1 c_5 \beta_{O-C_5} + c_2 c_4 \beta_{C_3-C_4}\right)^2}{E_{\Psi_2} - E_{\Psi_B}} + \frac{2\left(c_1' c_5 \beta_{O-C_5} + c_3' c_4 \beta_{C_3-C_4}\right)^2}{E_{\Psi_A} - E_{\Psi_3}} \qquad (1)$$

Figure 8

FMO theory simply states that the orbitals that overlap best and are closest in energy will interact the most. That is, the larger the overlap, the greater the interaction (Figure 9). Also the more proximate the orbitals are in energy, the more

extensive the interaction. The theory considers only the energy changes arising from interactions from the highest occupied molecular orbital (HOMO) of one of the reactants and the lowest unoccupied molecular orbital (LUMO) of the other, and vice versa. Interactions of extra frontier orbitals, closed-shell repulsions, and coulombic terms are totally ignored in the FMO approximation.[103]

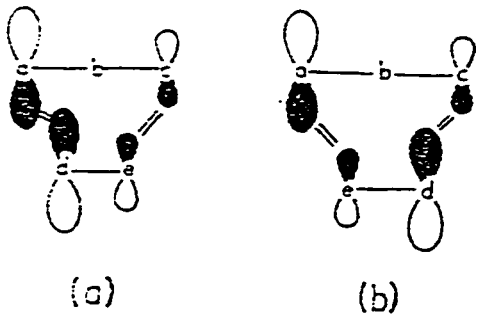


Figure 9 : Depiction of greater stabilization of transition state **(a)** than **(b)** due to different sizes of orbitals

According to second-order perturbation theory, the HOMO-LUMO interaction process will stabilize the bonding orbital (HOMO) and destabilize the antibonding orbital (LUMO). When a filled (HOMO) orbital interacts with a vacant (LUMO) orbital, both electrons will enter the orbital of lower energy,[73] and hence, the interaction will stabilize the system as a whole. The extra stabilization of the transition state by the decreased HOMO(nitrone)-LUMO(dimethyl fumarate) energy gap makes the nitrone **(19)** react faster with dimethyl fumarate than with the other alkenes *(see Table 2)*.

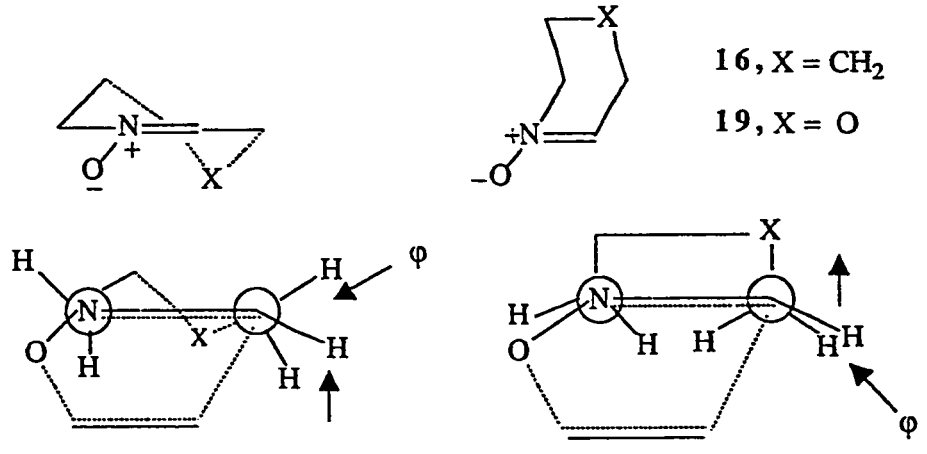
As is evident from Table 2 that cyclic nitrones invariably react faster than the acyclic nitrones. This is attributed to the fact that the cyclic nitrones exist in the E-form because of geometric constraints, and the acyclic nitrones remain in the more

stable Z-form. The cyclic nitrones (**19**), (**16**), and (**17**) are found to be more reactive than their five-membered counterpart (**15**). Perturbation Molecular Orbital theory accounts only for a fraction of activation energy. Some constraints (or its relief) present in the reaction products must be introduced to give a better picture of the transition state. The angular strain present in nitrone (**15**) is more than offset by the greater eclipsing strain (peculiar to cyclopentane systems) introduced in the transition state due to a change in hybridization from sp^2 to sp^3. The absence of similar destabilizing strains in the transition states makes (**19**), (**16**) and (**17**) more reactive than (**15**). Steric factors (non-bonded repulsions) are expected to be unfavorable in the transition state leading to the 5-5 ring system in comparison to 6-5 and 7-5 systems.

In order to understand the differences in the reactivity among the nitrones (**19**), (**16**) and (**17**), factors such as torsional strain, bond-angle bending strain and steric factors in the transition state must be considered, and also one has to take a closer look at the type of conformational isomer that takes part in cycloaddition reactions. However, the reactivity may depend on the type of conformational isomer that takes part in the addition reactions. Differences in the rates of cycloaddition of the cyclic nitrones may be due to a combination of various factors such as torsional strains, bond angle bending strain, and steric factors (non-bonded repulsions) in the transition state.[104] Like cycloalkenes,[104] the cyclic nitrones (**19**), (**16**), and (**17**) are expected to adopt the most stable flattened chair (or half-chair) conformation (Scheme 13). A minor portion of the boat form is expected to be in equilibrium with the chair form. The difference in energy between the half-chair and the half-boat conformations of cyclohexene has been approximated to be 2.7 kcal/mol.[105] The cyclic nitrone (**16**), like cyclohexene, should have similar energy difference between the two conformers. It is anticipated that the presence of the heteroatom oxygen[105] in the ring skeleton of the nitrone (**19**) would make the

energy difference between its chair and boat form smaller than the corresponding energy difference for its carbocyclic counterpart (**16**). Thus, the proportion of the boat form for the nitrone (**19**) should be considerably higher than that for the nitrone (**16**).

It may be argued that the nitrones (**19**) and (**16**) may not react via the chair form alone, active participation by the corresponding boat form, especially in the addition of the nitrone (**19**), is also expected. The torsional angle φ is about 40° and 15° (almost eclipsed) in the chair and boat form, respectively.[106] While the torsional strain in the chair form is expected to increase as the angle φ decreases in the transition state, the transition state for the addition of the boat form acquires a decreased torsional strain as the angle φ widens. Presumably, the nitrone (**19**) undergoes cycloaddition mainly via its boat form as it is associated with a high torsional strain which will be relieved as the reaction proceeds to the transition state. This may account, in part, the greater reactivity of the heterocyclic nitrone (**19**).



Chair Transition State *Boat Transition State*

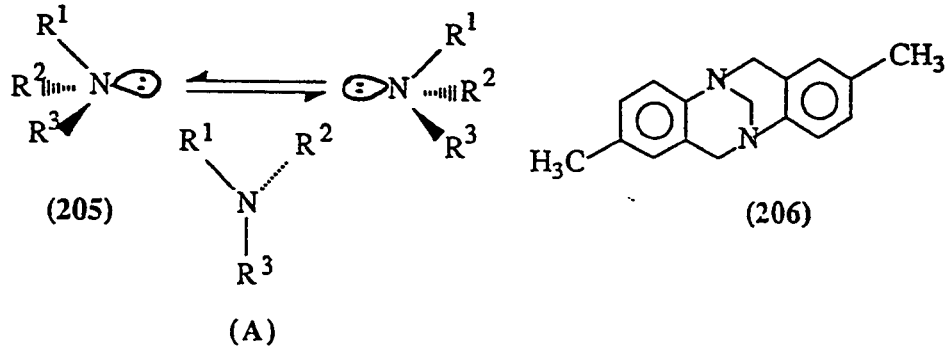
Scheme 13

CHAPTER 5

NITROGEN INVERSION

5.1 Introduction

Secondary or tertiary amine (205) having three different groups attached to nitrogen is expected to be chiral and thus resolvable (Scheme 14). Many attempts to resolve such compounds were unsuccessful because of rapid interconversion between the enantiomers. This pyramidal inversion (also called umbrella effect) happens via the planar transition state (A); the unshared pair oscillate from one side of the $R^1R^2R^3$ plane to the other.[112] Geometric constraints, however, do not permit nitrogen inversion in amines where the nitrogen atom occupies a bridgehead, such as compound (206).

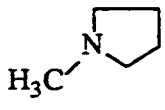


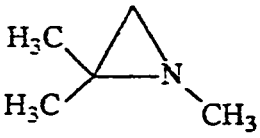
Scheme 14

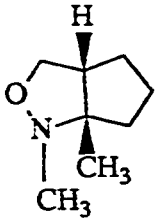
The rate of inversion varies over a considerable range depending on the nature of the substituents attached to nitrogen. In ammonia, primary, and secondary amines, the rates of inversion are too fast to be seen by NMR. For NH_3

there are 2 x 10^{11} inversions every second and this rapid inversion in gas phase has been attributed to the tunneling.[113] The inversion is less rapid in substituted ammonias.[114]

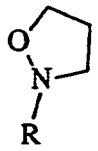
	H_3N	H_3CNH_2	NF_3
	(207)	**(208)**	**(209)**
Inversion barrier (kJ/mol)	24	20	209

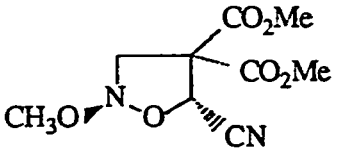






	(210)	**(211)**	**(212)**
Inversion barrier (kJ/mol)	29	44	57





(213) **(214)**

a, R = CH_3; b, R = [$CH(CH_3)_2$]

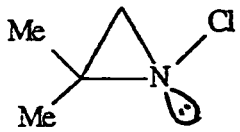
Inversion barrier (kJ/mol)	65	62	126

Scheme 15

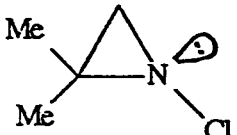
Nitrogen inversion barriers for several amines have been listed in Scheme 15. Nitrogen trifluoride[115] has much higher inversion barrier than than that of ammonia or methylamine.[116] While N-methylpyrrolidine (**210**) has an inversion barrier of 29 kJ/mol,[117] the N-methylisoxazolidine (**213**), in contrast, has a considerable higher barrier of 65 kJ/mol.[118] Inversion barrier increases considerably when the nitrogen is a part of 3-membered ring such as 1,2,2-

trimethylaziridine (211).[117] Among the cyclic amine listed in the Scheme 15, the isoxazolidine (214), with two heteroatoms attached to nitrogen has the highest inversion barrier and therefore the compound (214) and its invertomer has been separated successfully.[119]

The effect of various types of substituents and ring size has been explained in molecular orbital terms.[120,121] A π donor or an electronegative substituent strongly favours the pyramidal structure over the planar and thus inversion barrier is raised. In the three-membered ring, the nitrogen inversion occurs very slowly. The bond angles at nitrogen in the planar transition state deviate greatly from the normal bond angles. The combined effects of small ring size and heteroatom substituents are amply demonstrated in N-chloro-2,2-dimethylaziridine (215) and (216). The *cis*- and *trans*- isomers have been separated successfully and they have been shown to have nonequivalent substituents at room temperature and even at 120°C.[122]

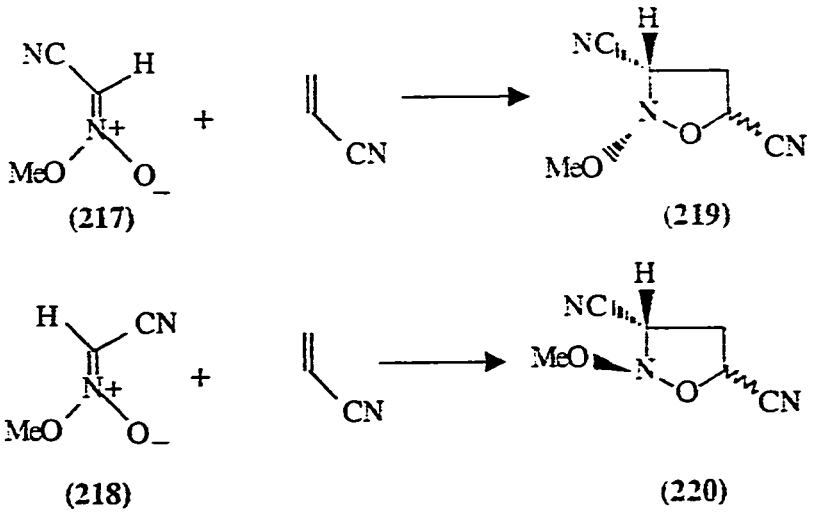


(215)



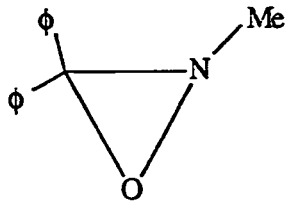
(216)

If two heteroatoms are present, even the three-membered ring is no longer necessary. Thus, cycloaddition of nitronic ester (217) and (218) with acrylonitrile, under kinetic control, gave the adduct (219) and (220), respectively (Scheme 16). Under the experimental conditions the adduct (219)



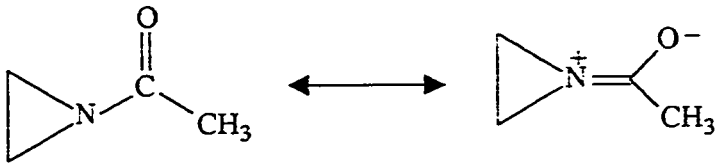
Scheme 16

does not interconvert to its nitrogen invertomer (220).[123,124] Both enantiomers of the oxaziridine (221), which is optically active solely because of an asymmetric nitrogen atom, have been prepared.[125]

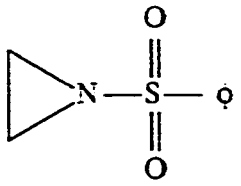


(221)

A π acceptor substituent strongly favours the planar geometry and lowers the inversion barrier. Thus, no temperature dependence in NMR spectra is noted for the compound (222) which prefers the planar geometry.[126] Another aziridine (223) with a π acceptor substituent has been found to have a relatively low inversion barrier of 42 kJ/mol.[127]



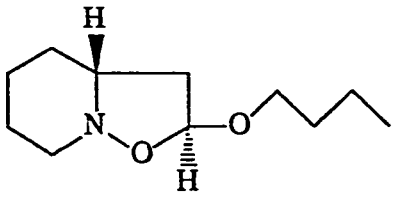
(222)



(223)

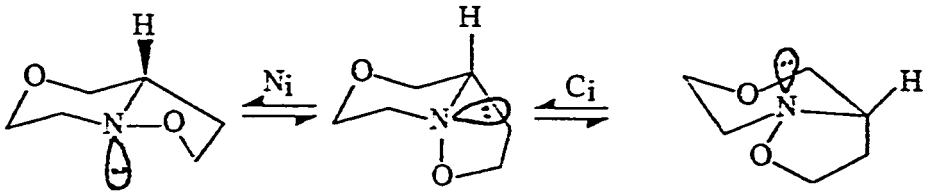
Scheme 17

Nitrogen inversion barrier in the isoxazolidine **(224)**, a nitrone cycloaddition product, is large enough to be observable by dynamic nuclear magnetic resonance spectroscopy. The isoxazolidine **(224)** interchanges between the invertomers at a rate of ca. 10 s^{-1} at 30°C.[128]



(224)

The addition products of nitrone **(19)** with alkene **(200)** can, in principle, exist in three different conformations, the *trans* conformer **(A)** and the *cis* pair **(B)** and **(C)** (Scheme 18). While the *cis* pair is in rapid equilibrium by chair inversion (C_i), one of the *cis* conformers, **(B)**, is converted into the *trans* conformer by a relatively slow nitrogen inversion process (N_i). The study[136] on

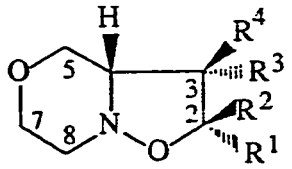


(A) (B) (C)

Scheme 18

the cycloaddition products of nitrone (16), which lacks an oxygen atom in the ring skeleton of the six-membered ring, indicated the overwhelming preference for the *trans* conformer. The orientation of the lone pair of electrons on nitrogen holds the key for the selection of regiochemical course in the peracid induced ring opening of nitrone (16) cycloaddition products to generate a second generation of nitrones[137] *(see Chapter 6)*. Conformational analysis of the cycloadducts (201) is of both theoretical and practical importance. Hence, we undertook a systematic study to determine the *cis* $\rightleftharpoons$ *trans* equilibrium constant (K) and nitrogen inversion barrier for several cycloadducts (201) by NMR spectroscopy. The compounds studied are shown in Table 3.

TABLE 3 : Cycloadducts Studied for Conformational Analysis.



Isoxazolidine	R^1	R^2	R^3	R^4
(201a)	H	Ph	H	H
(201b)	H	CH_2OH	H	H
(202b)	CH_2OH	H	H	H
(201e)	CH_2OH	CH_3	H	H
(201f)	CO_2CH_3	CH3	H	H
(201g)	H	CH_3	CO_2CH_3	H
(201h)	H	Ph	CO_2CH_3	H
(201i)	H	CO_2CH_3	CO_2CH_3	H
(202j)	H	CO_2CH_3	H	CO_2CH_3
(201L)	H	CH_2OCOCH_3	H	H
(201m)	CH_2OCOCH_3	CH_3	H	H

5.2 Results and Discussion

The ^{13}C NMR spectra of all compounds investigated, except **(201b)**, showed broad peaks slightly above ambient temperature. On lowering the temperature, the spectral lines sharpened and showed the presence of two distinct isomers. The ^{13}C NMR chemical shifts of compounds **(201)** were assigned on the basis of the data[136] on isoxazolidines obtained from nitrone **(16)** reactions, general chemical shift arguments and consideration of substituent effects, and are given in Table 4.

The ^{13}C chemical shifts of C-2, C-3, C-4, and C-8 of isomers of **(201)** are similar to those of the isomers obtained with nitrone **(16)** with corresponding substituents. However, the major isomer in case of nitrone **(19)** adducts showed similar chemical shifts to those of the minor isomer of nitrone **(16)** adducts, and the minor isomer of nitrone **(19)** adducts showed similar chemical shifts to those of the major isomer of nitrone **(16)** adducts. The major isomer of nitrone **(16)** adducts was shown to be the *trans* isomer from X-ray diffraction[47] and chemical shift data. So it follows that the major isomer of **(201)** should have the *cis* conformation **(B)** and **(C)**, whereas the minor isomer should have the *trans* conformation **(A)**. This assignment is further supported by low temperature ^{1}H NMR studies *(see section 5.2.2)*. The chemical shifts are given in Table 4.

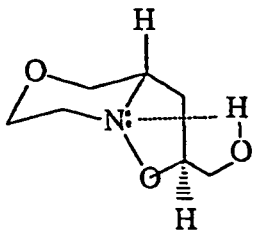
In any one compound, we studied, the carbons of the *cis* isomer are more shielded than the corresponding carbons of the *trans* isomer, excepting the C-2 which is less shielded in the *cis* isomer. The axial oxygen substituent of the morpholine ring in the *cis* conformer **(B)** will have *γ-gauche* interactions with C-5 and C-7, whereas the axial $-CH_2-$ substituent of the *cis* conformer **(C)** will have *γ-gauche* interaction with C-8, leading to shielding. This provides further evidence that the major isomer is indeed the *cis* pair.

TABLE 4 : ^{13}C NMR Chemical Shifts[a] of Adducts (201).

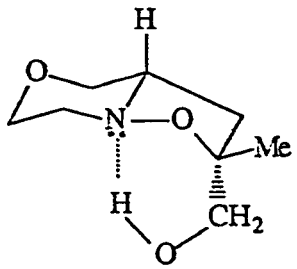
Compound		C-2	C-3	C-4	C-5	C-7	C-8	Other[b]
(201a)	*cis*	78.36	37.30	59.62	65.00	64.87	49.56	^{i}142.01 ^{o}128.16 ^{p}127.34 ^{m}125.98
	trans	77.32	38.60	64.90	69.67	69.52	55.42	^{i}140.53 ^{o}127.56 ^{p}127.34 ^{m}126.48
(201b)		77.95	30.23	59.84	65.21	64.77	49.67	CH_2- 63.78
(202b)	*cis*	79.95	31.58	58.40	65.33	64.89	57.03	CH_2- 65.23
	trans	76.24	32.06	63.90	69.91	65.23	55.53	
(201e)	*cis*	84.27	37.16	58.60	68.32	64.07	51.10	Me - 24.32 CH_2 - 69.65
	trans	80.46	38.36	64.99	69.60	65.57	55.48	Me - 22.42
(201f)	*cis*	80.76	52.64	63.25	64.76	63.79	49.33	^{i}139.64 ^{o}128.53 ^{p}128.11 ^{m}126.41 CO-172.56 OMe- 56.38
	trans	79.97	55.78	65.04	68.16	67.06	52.29	^{i}138.48 ^{o}128.38 ^{p}128.11 ^{m}126.41 CO-170.93
(201g)	*cis*	76.68	52.42	60.90	62.86	62.86	49.80	CO - 170.04, 170.68; Me 52.81
	trans	76.10	56.15	64.62	68.32	65.21	51.75	CO - 169.70, 16.51; Me 52.63
(201h)	*cis*	75.28	52.47	62.67	64.90	63.84	49.08	CO-173.16 Me-19.70 MeO - 54.23
	trans	74.73	55.66	64.80	68.03	66.62	52.11	CO-171.32 Me-19.12
(201l)	*cis*	74.65	31.45	59.15	65.70	65.09	49.78	CO - 170.75 CH_2 - 64.57
	trans	73.35	33.95	65.10	69.60	69.52	55.68	CH_3 - 20.70
(201m)	*cis*	82.00	37.94	64.15	68.76	64.88	51.02	Me-24.79 CO - 170.90 CH_2 - 65.16
	trans	78.41	40.12	64.67	69.86	69.09	55.51	Me-24.84 CH_3 - 24.65

a, in ppm relative to internal TMS at -25 °C.
b, i, o, p, m, refers to ipso, ortho, para, meta carbons of the phenyl group.

Where we observe only one isomer throughout the temperature range -50°C to +50°C as in the (**201b**), the ring carbon shifts match those of the *cis* (major) isomer. So we conclude that (**201b**) exists in the *cis* conformation almost 100 percent, since the *cis* conformation is generally preferred over the *trans* in these systems. The additional stability rendered by the intramolecular N:···H-O hydrogen bonding, possible only in the *cis* conformation of (**201b**), completely precludes the presence of any *trans* conformer for this compound. Importance of the intramolecular H-bonding is further demonstrated in the methyl allyl alcohol adduct (**201e**), where the major isomer is found to be the *trans* isomer from the chemical shift data. The intramolecular H-bonding in (**201e**) is possible only in the *trans* conformation and hence this conformer predominates. The corresponding compound of (**201e**) in the isoxazolidine series of nitrone (**16**), exists in solution exclusively as the *trans* conformer, whereas the corresponding compound of (**201b**) in the series of nitrone (**16**) adducts, showed the presence of two isomers. While the adduct (**201b**) remains exclusively in the *cis* form because of the stabilizing N:···H-O bonding, the corresponding acetyl derivative (**201L**) does not



(**201b**)



(**201e**)

enjoy such stabilization, as such the *trans* form of (**201L**) exists to some extent. Changing the methyl allyl alcohol adduct (**201e**) to its acetyl derivative (**201m**), results in the *cis/trans* ratio changing from 18 : 82 to 50 : 50. The N:···H-O bonding which is possible only in the *trans* form of (**201e**) allows this adduct to be

the predominant conformer. All these evidences support the fact that the *cis* conformation of all adducts (**201**), with the exception of (**201e**), are thermodynamically more stable than the *trans* conformation, whereas in the adducts of nitrone (**16**), the opposite is true.

5.2.1 Nitrogen Inversion

^{13}C NMR spectra show well separated signals for the two isomers; the *trans* conformer and the *cis* pair down to -50°C. Integration of relevant peaks gives the population trends in these systems. In the ^{1}H NMR spectrum, the C-2 proton shows distinct peaks for the two isomers at low temperatures. Equilibrium constants for the *cis* $\rightleftharpoons$ *trans* isomerization were calculated from the integration of ^{1}H NMR and ^{13}C NMR peaks and the values are reported along with the corresponding ΔG^{o} values at 298 K in Table 5.

To measure the barrier to nitrogen inversion, the coalescence temperature method could not be used as the populations for the two exchanging sites are widely different. Hence, a complete band-shape analysis, corresponding to a non-coupled two-site exchange with unequal populations was employed. The C-2 protons offered convenient signals to study the band shapes with variable temperatures, as these signals are away from any overlapping signals and show only first order couplings. The methyl methacrylate adduct (**201f**) does not have C-2 protons, however, the methyl protons at C-2 were singlets and the band shape of these were used in the analysis. The methyl allyl alcohol adduct (**201e**) also does not have protons at C-2 and there were no well separated methyl proton signals for the two isomers. In order to overcome this difficulty, the band shape of the ring carbon resonances of (**201e**) were utilized. For this purpose three ring

carbon signals were used at each temperature and the rate constants obtained are an average of three calculated values.

Obtaining accurate exchange rate constants by fitting NMR band shape is well known to be fraught with difficulties, and considerable errors in thermodynamic parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ if Eyring plots are used.[138] In fact many of the errors are systematic in nature, and those resulting for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are often mutually compensatory so that $\Delta G^{\neq}$ is better defined near the coalescence temperature. Although $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were obtained, we put little significance on them for reasons stated above, and are not reported herein. The $\Delta G^{\neq}$ values calculated for +25°C (near coalescence temperature) are reported in Table 5. (In making use of Eyring plots, it was assumed that the transmission coefficient was unity).

The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines.[139] A high inversion barrier of 65.3 kJ/mol has been reported[140] for $\overline{CH_2CH_2CH_2ON}(Me)$ in deuterochloroform. For the adducts of nitrone **(16)**,[136] the nitrogen inversion barriers are in the range of 65.2 to 69.0 kJ/mol. The nitrogen inversion barriers determined in this study are in the range of 66.3 to 72.9 kJ/mol. The data indicate a slight increase in barrier in going from nitrone **(16)** adducts to nitrone **(19)** adducts. The structural change of introducing an oxygen atom in the six-membered ring may lead to an increase in barrier. The similarity in the range of values further confirms that we are indeed measuring the nitrogen inversion barrier rather than the chair inversion barrier, as the morpholine ring inversion barrier is much lower than that of piperidine.[141]

TABLE 5 : Free Energies of Activation for Nitrogen Inversion, Equilibrium Constants, and Standard Free Energy Changes for *cis* $\rightleftharpoons$ *trans* Isomerization of the Studied Cycloadducts at 298 K in $CDCl_3$

Adduct	$\Delta G^{\neq}$ (kJ/mol)	*cis*	:	*trans*	K	ΔG^{o}(kJ/mol)
(201a)	68.6	80	:	20	0.25	+3.4
(201b)	_	100	:	0	0.0	_
(201e)	66.3	18	:	18	4.5	-3.8
(201f)	69.5	90	:	10	0.11	+5.4
(201g)	66.4	65	:	35	0.53	+1.5
(201h)	66.6	65	:	35	0.53	+1.5
(201i)	70.2	83	:	17	0.20	+3.9
(202j)	72.9	90	:	10	0.11	+5.4
(201L)	ND[a]	90	:	10	0.11	+5.4
(201m)	ND[a]	50	:	50	1.0	0.0

[a]ND : Not Determined.

5.2.2 *Chair Inversion*

The efforts[136] to slow down the chair inversion in the series of adducts of nitrone (**16**) had been unsuccessful even at temperature down to -110°C. This is also true for all compounds studied here except for dimethyl fumarate adduct (**201i**). The major isomer signals of (**201i**) started to broaden as the temperature was taken below -60°C. Further lowering of the temperature resulted in further broadening of the signal and then reappeared as two sets of peaks of unequal intensity corresponding to the two *cis* isomers. The signals of the *trans* isomer remained sharp throughout the low temperature range (Figure 10). The two *cis* isomers were in a ratio 1.6 : 1 at -95°C in CD_2Cl_2 whereas in toluene-d8 at -95°C the ratio was 4.2 : 1.

Detailed band shape analysis of C-2 proton signals of the two *cis* isomers was carried out over a temperature range of -80°C to -30°C. Using the Eyring's plot, free energy of activation for the ring inversion from the major *cis* isomer to the minor *cis* isomer was calculated to be 42.7 kJ/mol at -60°C. If we assume the chair inversion goes through an intermediate twist-boat form, then a transmission coefficient of 1/2 should be used in the Eyring equation. If we use a coefficient of 1/2, then the $\Delta G^{\neq}$ has a value of 41.5 kJ/mol at -60°C. The chair inversion barrier for morpholine has been determined[141] from coalescence temperature (-70°C) to be 41.2 kJ/mol. This further proves that the lower barrier is for the chair inversion and the higher barrier is for the nitrogen inversion.

In most systems studied here and in the isoxazolidine series of nitrone (**16**), chair inversion could not be slowed down in the temperatures accessible in the NMR probe with common solvents. This may be due to the chemical shifts of the two *cis* isomers being not sufficiently far apart and/or the amount of one of the *cis* isomers is exceedingly small.

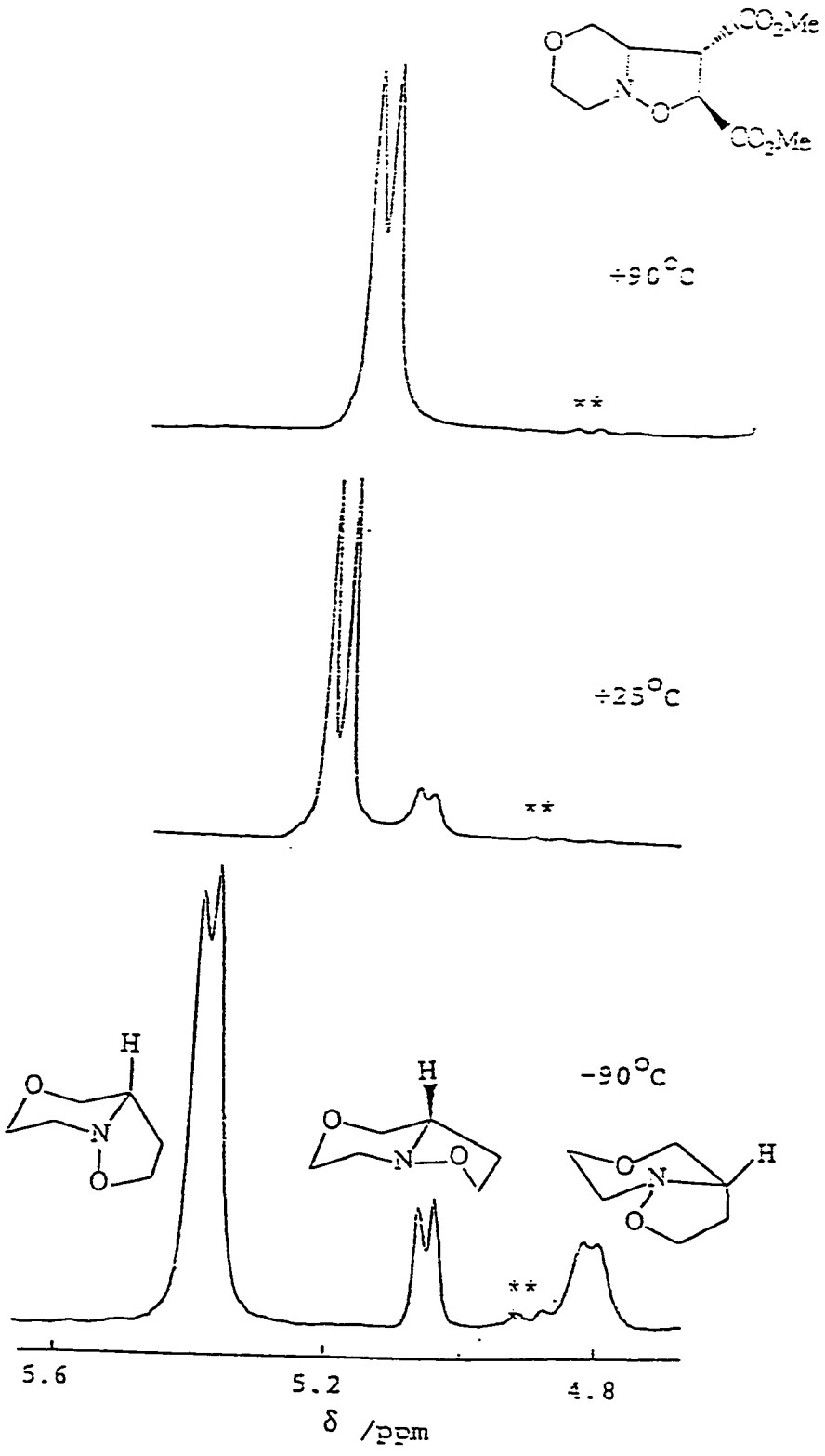


Figure 10 : C-2 H signals of dimethyl fumarate adduct (**201i**) in toluene-d_8 at three different temperatures. At -90°C, all three isomers show distinct peaks; at +25°C, averaged *cis* isomers and the *trans* isomer; at +90°C, all three isomers are averaged out. * denotes peaks due to impurities.

Since the rate of nitrogen inversion is relatively slow at -100°C, we carried out a study at this temperature using crystals of the styrene adduct (**201a**), to investigate the nature of the conformation in the solid state. To a pre-cooled sample (-150°C) of CD_2Cl_2 in an NMR tube, a few crystals of (**201a**) were added. The NMR tube was then quickly transfered to the probe maintained at -95°C, and the spectra recorded at intervals of two minutes. Upto about 10 minutes, spectra showed the presence of only one isomer, a broad quartet at δ 5.46 corresponding to the major (*cis*) isomer, with no peaks at δ 5.04 for the minor isomer. After 10 minutes, the sample was warmed to room temperature and then returned to -95°C in the probe. The spectrum recorded showed clearly the presence of the minor isomer (~20%) (Figure 11). This experiment shows clearly that the styrene adduct (**201a**) crystallizes solely in the *cis* conformation and at -95°C, the rate of interconversion to *trans* is extremely slow due to high nitrogen inversion barrier. Since only one quartet was evident around δ 5.46 for the 2-H, it is possible that only one form of the *cis* isomers is present for (**201a**) or the other form is found only in trace amounts. This may also explain the inability to slow the chair inversion in many of the compounds studied here. We feel that the major of the two *cis* isomers has the conformation (**B**), as an oxygen substituent is better tolerated in the axial position than an alkyl substituent.

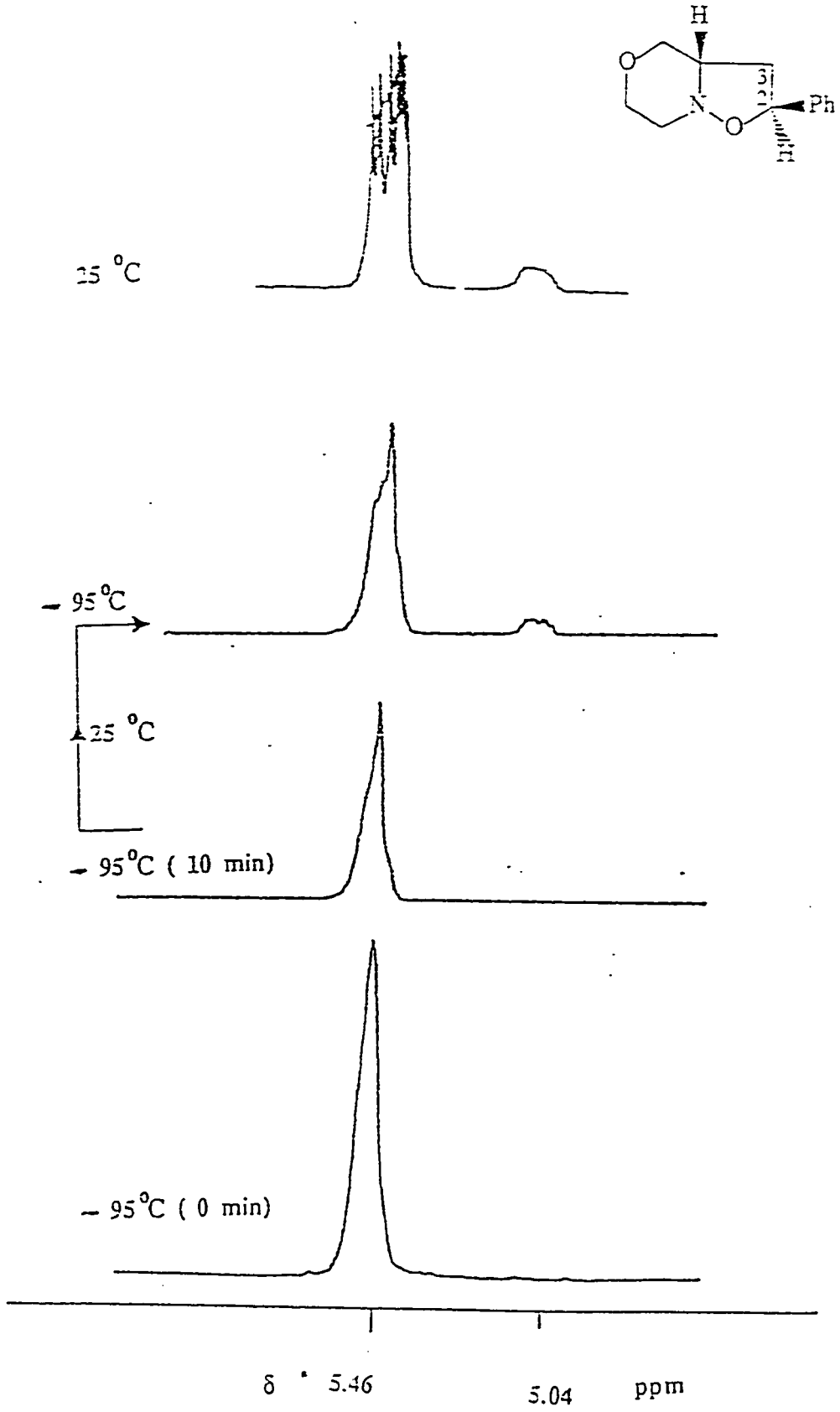


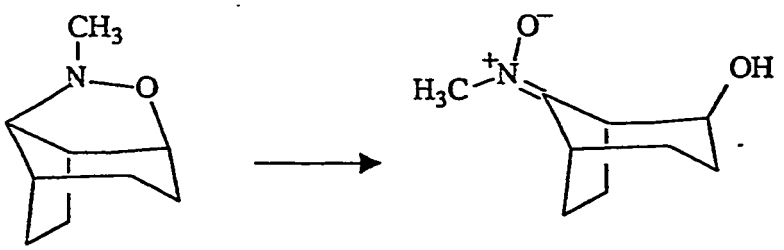
Figure 11 : Investigation of the nature of the conformation in the solid state of the styrene adduct (201a) by ^{1}H NMR at low temperature.

CHAPTER 6

PERACID INDUCED RING OPENING OF THE ISOXAZOLIDINE

6.1 Introduction

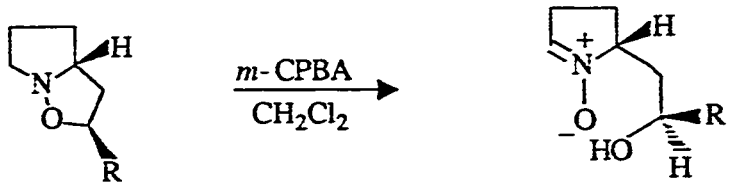
Nitrones generated by peracid induced ring opening of isoxazolidines marked the beginning of the utilization of second generation of nitrones.[19,129,130] For example, isoxazolidine (225) upon treatment with peracetic acid gave nitrone



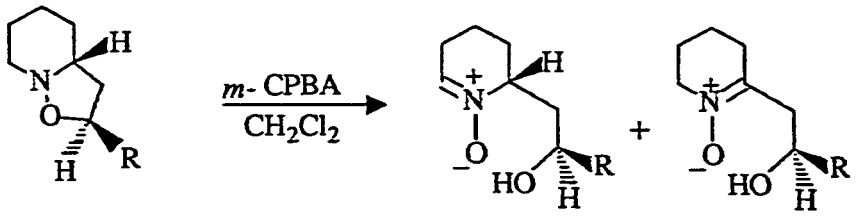
(225) (226)

(226). While the cycloadduct (36) upon treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane afforded the less substituted nitrone (37) as the sole product,[19] the corresponding 6-5 ring fused adduct (227a) gave the mixture of less substituted (228a) and more substituted nitrone (229a) in a respective ratio of 35 : 65.[131,132] However, the adduct (230) afforded the more substituted nitrone (231) regiospecifically.[132] Similar regiospecificity favouring the formation of less substituted nitrone has been reported for the 5-5 system having various

substituents. The newly generated nitrones have been exploited in the synthesis of several natural products using a second cycloaddition reaction.[19,87,133]



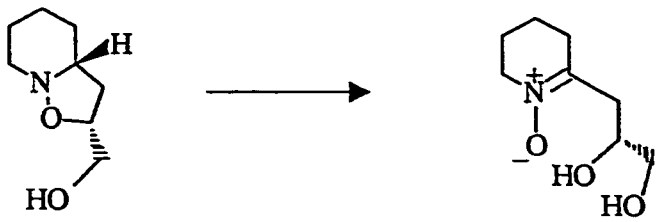
(36) (37)



(227) (228) (229)

a, 35 : 65

b, 27 : 73



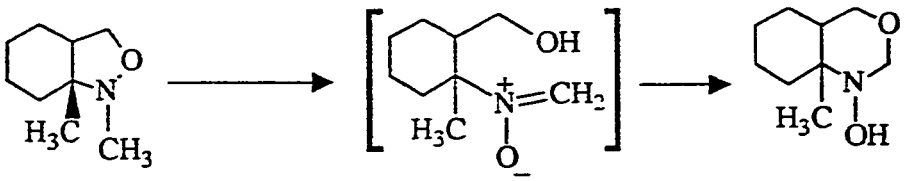
(230) (231)

a, R = Ph

b, R = CH_2OH

The progress in the application of the second generation nitrones in 6-5 series is hampered by the lack of regioselectivity observed in the ring opening reaction.[131,134,135] Formation of the more substituted nitrone is found to be

favoured in the 6-5 series. In another series of ring opening reaction of the adduct (**232**) obtained by intramolecular cycloaddition reaction, the N-hydroxy compound (**233b**) (via the nitrone (**233a**)) is obtained in excellent yields.[129,130]



(**232**) (**233a**) (**233b**)

In order to understand this difference in regiochemical behavior in the peracid induced ring opening of the isoxazolidines, we undertook a study of the ring opening of several cycloadducts (**201**) described in earlier sections. The finding of our study sheds further light on the mechanistic aspects of this ring opening reaction.

6.2 Results and Discussion

Regiochemistry of the *m*-chloroperbenzoic acid ring opening of the cycloadducts (**201**) in different solvents are included in Table 6. For the purpose of comparison, the data for ring opening reactions[132] of the adducts (**36**) and (**227**) (obtained from the corresponding carbocyclic nitrones (**15**) and (**16**), respectively) are also incorporated in the Table.

As is evident from Table 6, the isoxazolidine (**36**) with 5-5 fused ring system, upon treatment with *m*-CPBA in dichloromethane, affords the less substituted nitrone (**37**) as the sole product. However, in acetic acid solvent, the more substituted nitrone (**234**) becomes the exclusive product.

Quite interestingly, the adduct (**227**) with a 6-5 fused ring system, gave a mixture of nitrones (**228**) and (**229**) both in dichloromethane and acetic acid. In each case, the more substituted nitrone (**229**) becomes the predominant product.

In our study, the regiochemical analysis of the peracid induced ring opening of the adduct (**201a**) was hampered due to some unexpected complication. While the more substituted nitrone (**237a**) is stable, the less substituted nitrone (**235a**) is in equilibrium with the bridged bicyclic hydroxylamine (**236a**) by tautomerization (Scheme 19). The ^{1}H NMR spectra of the crude reaction mixture revealed the presence of three double doublets at δ 5.10, 5.85, and 5.18, assigned to the benzylic protons of (**235a**), (**236a**), and (**237a**), respectively. The alcohol proton of (**236a**) appeared at δ 4.67. Efforts to separate the bridged tautomer (**236a**) from the nitrones (**235a**) and (**237a**) by rapid silica gel chromatography were unsuccessful. Although there is a wide difference in R_f values of (**236a**) and (**235a**), a nonseparable mixture of (**235a**) and (**236a**) are eluted. Persumably the tautomerization happens during evaporation of eluted solvents. Similar tautomerization has been observed in some acyclic nitrone

TABLE 6 : Regiochemistry of the *m*-Chloroperbenzoic Acid Induced Ring Opening of the Cycloadducts (201) in Different Solvents.

Solvent	Adduct	% Composition of 5-membered Nitrone		% Composition of 6-membered Nitrone		% Composition of Heterocyclic nitrone	
		L. S.[a] (37)	M. S.[b] (234)	L. S. (228)	M. S. (229)	L. S. (235 + 236)	M. S. (237)
CH_2Cl_2	a, R = Ph	100	0	35	65	79	21
HOAc	a, R = Ph	0	100	35	65	35	65
CH_2Cl_2	b, R = CH_2OH	100	0	27	73	90	~10
HOAc	b, R = CH_2OH	~0	100	18	82	25	75

[a]L. S. denotes Less Substituted,

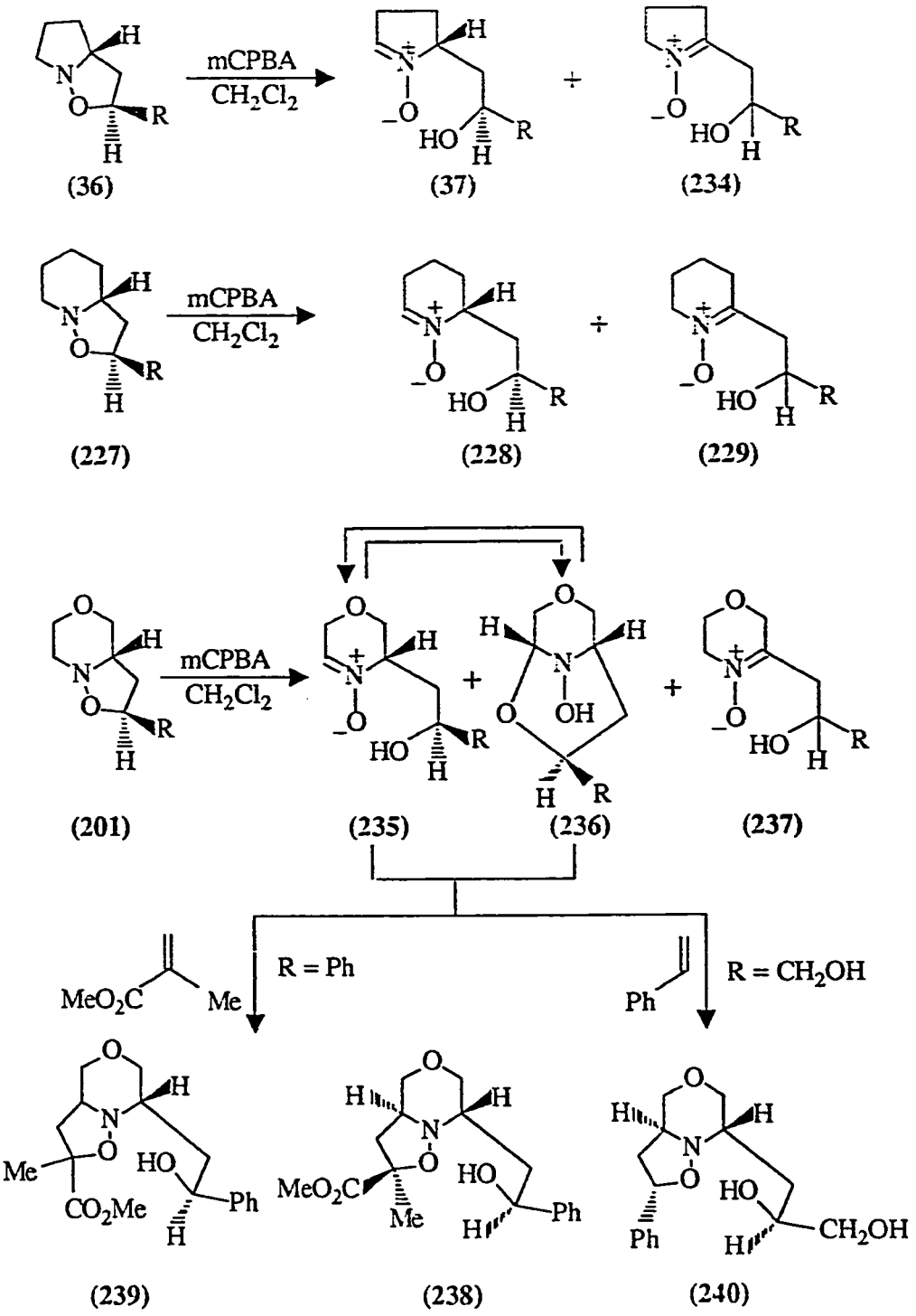
[b]M. S. denotes More Substituted.

systems.[129,130] The ratio of the isomers (**235a** + **236a**) and (**237a**) are approximated using integration of the benzylic protons. The ratio of the tautomers (**235a**) and (**236a**) was found to be 18 : 82, respectively.

To get around the problem associated with the tautomerization, we treated a crude mixture of (**235a**), (**236a**), and (**237a**) with excess methyl methacrylate (**200f**) at 50°C for 24 h. The proton NMR spectrum of the reaction mixture revealed the absence of either nitrone (**235a**) or the bridged tautomer (**236a**). Instead, the spectrum revealed the presence of the adducts (**238**) and (**239**) along with the unreacted more substituted nitrone (**237a**) which were then separated by silica gel chromatography. Precedent literature[87,131] and the present work revealed that the more substituted nitrone remained unreactive under this mild experimental conditions.

Likewise, the crude reaction mixture containing (**235b**), (**236b**), and (**237b**), obtained by peracid treatment of the allyl alcohol adduct (**201b**), was repeated with excess styrene at 50°C for 24 h. The NMR spectrum revealed the presence of the single adduct (**240**) and the unreacted more substituted nitrone (**237b**) *(see Experimental section)*. We were able to assess the ratio of nitrones from the isolated yields of the adducts. The results are included in Table 6.

The behavior of the adducts (**201**) differs from that of the isoxazolidine (**227**). While in dichloromethane the less substituted nitrone is formed regioselectively, the more substituted nitrone (**237**) becomes the predominant isomer in acetic acid solvent.

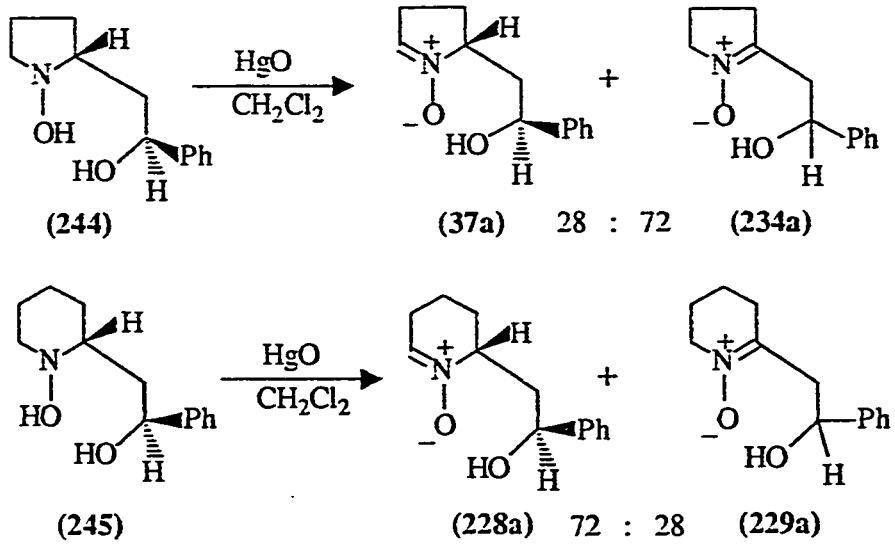


a, R = Ph

b, $R = CH_2OH$

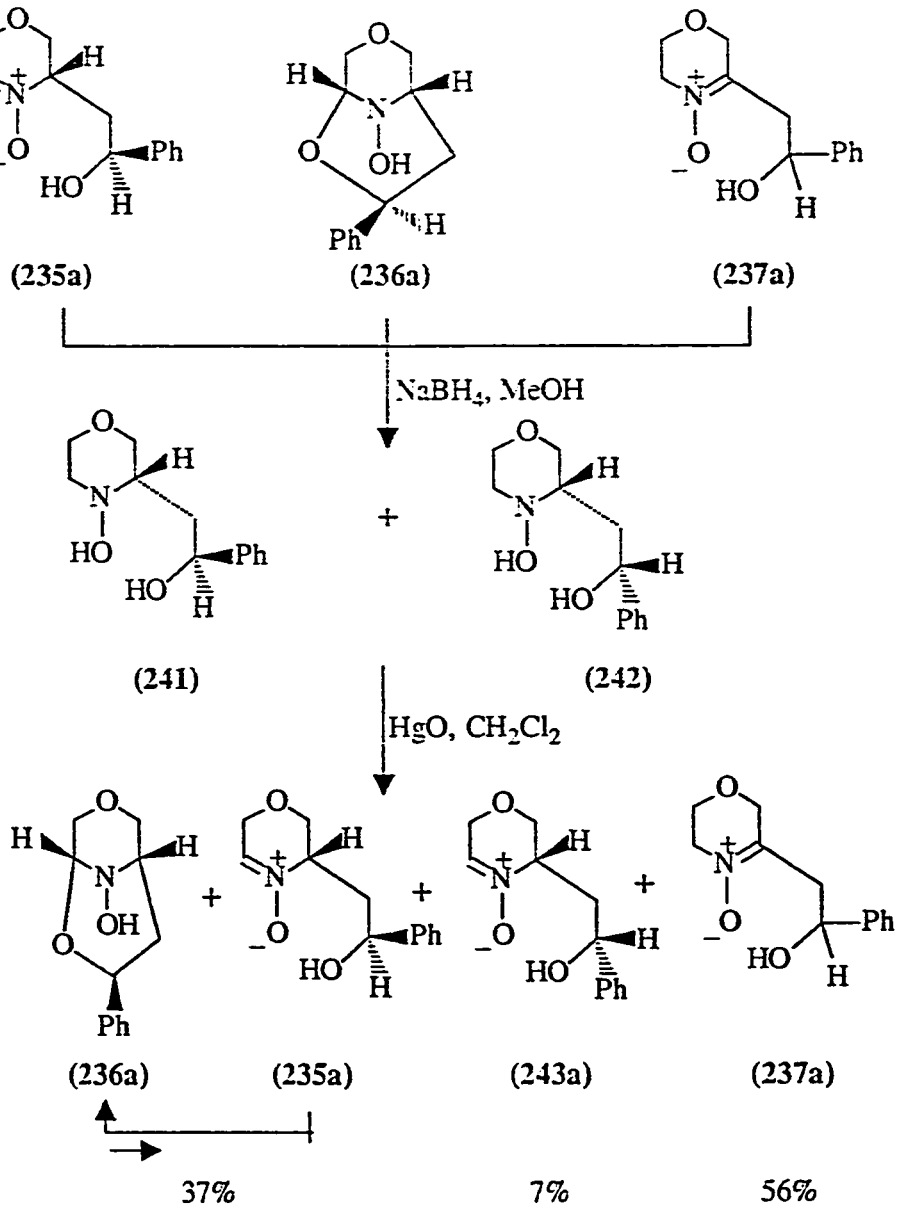
Scheme 19

It is interesting to note that the N-hydroxypyrrolidine (244) and piperidine derivative (245) upon treatment with HgO in dichloromethane afforded a mixture of nitrones in each case (Scheme 20). The mixture of nitrones (235a), (237a),



Scheme 20

and the bridged compound, obtained from peracid reaction of (201a) in methanol, (236a), on $NaBH_4$ reduction afforded a mixture of hydroxylamines (241) and (242). While (235a) and (236a) gave (241), the more substituted nitrone (237a) afforded a mixture of diasteromers (241) and (242). Mercuric oxide oxidation of a mixture of (241) and (242) in dichloromethane gave a mixture of nitrones (235a), (243a), and (237a). While (241) gives (235a) and (237a), the hydroxylamine (242) may lead to the formation of (243a) and (237a) (Scheme 21). Initially, the product mixture did not contain the tautomer (236a).

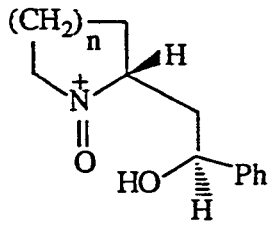


Scheme 21

However, within two hours, the NMR spectrum revealed the formation of the tautomer (236a) (5% of the total products). After 48 h, complete equilibration took place, the ratio of (235a), (236a), (243a), and (237a) was found to be 6 : 31 : 7 : 56, respectively. The benzylic proton of the additional nitrone (243a)

appeared at δ 4.93 as a dd. The ratio of the isomers was determined by integration of the benzylic protons. The ratio of less substituted ((235a) + (236a) + (243a)) and more substituted nitrone (237a) was thus found to be 44 : 56, respectively.

Although, the peracid induced ring opening of isoxazolidines was known for over three decades, yet the mechanistic pathway the reaction traverses is still a matter of speculation.[129,130] It is widely presumed that both the peracid induced ring opening and HgO oxidation involve the intermediacy of a nitrosonium ion intermediate (246) (Figure 12) which then tautomerizes to the nitrones.



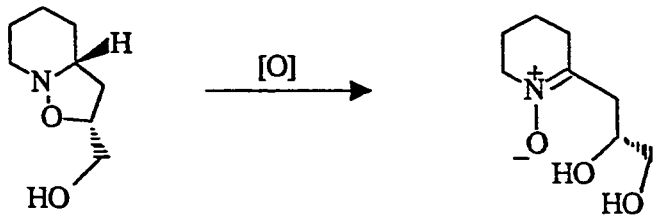
(246)

Figure 12

The difference in regiochemical behavior observed in the peracid induced ring opening of the isoxazolidines (36) and (227) and (201) seems to be puzzling. Very recently, a proposed mechanism[132] takes a closer look at the orientation of the lone pair of electrons on nitrogen which probably holds the key for a better understanding of the mechanism of peracid induced ring opening of the isoxazolidine.

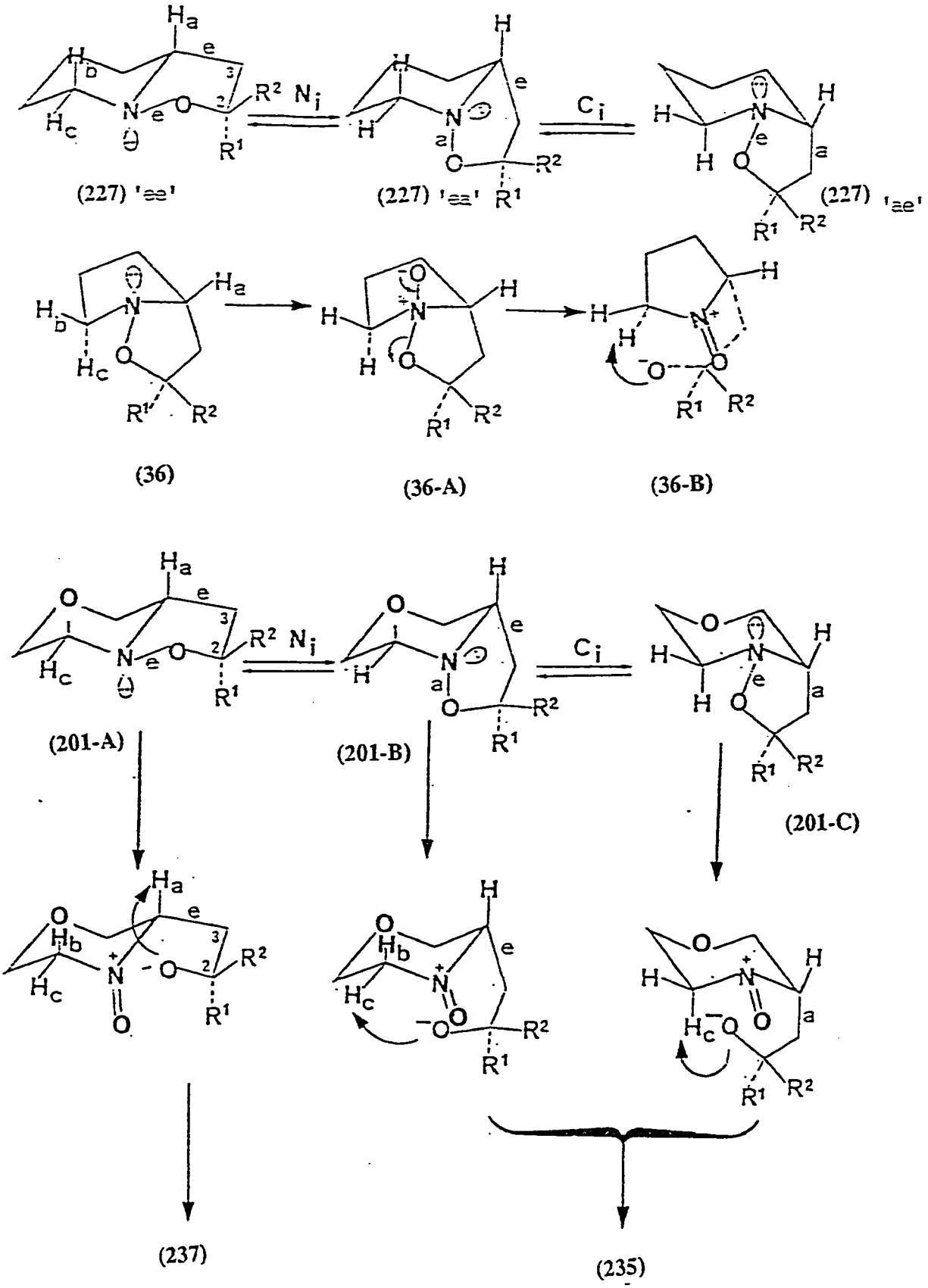
Geometric constraints do not permit nitrogen inversion in the isoxazolidine (36), which must remain *cis*-fused. However, the 6-5 system as exemplified by (227) and (201) can exist in three different conformations,[128,132] the *trans* conformer (A) ('ee') and the *cis* pair (B) ('ea') and (C) ('ae') ('a' and 'e'

represent axial and equaterial substituents on the six membered ring). While the *cis* pair are in rapid equilibrium by chair inversion (C_i), one of the conformers **(B)** is converted to the *trans* conformer (C) by a relatively slow nitrogen inversion process (N_i). While the *trans* compound (A) is the favoured conformer in the piperidine derivative **(227)**, the *cis* pair is the predominant conformer in the morpholine series **(201)**. It seems that amine oxide intermediate **(36-A)** obtained by peracid oxidation of the adduct **(36)** would be converted to the nitroxonium salt **(36-B)** in which the alkoxide ion finds H_c in its immediate vicinity. Fast kinetic deprotonation thus results in the formation of the less substituted nitrone **(37)** as the sole product. Of the corresponding amine oxide from the adducts **(201)** and **(227)** only the *cis* conformer leads to the less substituted nitrones **(235** and **228,** respectively) and the corresponding *trans* conformer leads to the more substituted nitrones **(237** and **229,** respectively) (Scheme 22). As expected, the adduct **(230)**, which exists only in its *trans* conformation, leads to the exclusive formation of the nitrone **(231)**.



(230) **(231)**

It is evident from Table 7 that the population ratio of the adducts and the regioisomeric nitrones are quite similar. The high barrier to nitrogen inversion and the activation barrier for peracid oxidation may be of comparable magnitude. In such cases, the Curtin-Hammet principle may not apply. As such the ratio of products would depend on the population ratio of the starting conformers.



Scheme 22

Interestingly, in protic solvents such as acetic acid, the more substituted nitrones are formed either regiospecifically or regioselectively *(see Table 6)*. This could be attributed to the fact that the alkoxide ion intermediate **(36-A)** is protonated fast and the acid-catalyzed tautomerization of the protonated **(36-B)** results in the exclusive formation of the thermodynamic-controlled products, the more substituted nitrone **(234)**.

TABLE 7 : Composition of conformers and regiochemistry of *m*-CPBA induced ring opening of the isoxazolidines in dichloromethane.

Isoxazolidine	% Composition of conformers[a]		% Composition of the nitrones			
	cis pair	*trans*	L. S.[b]		M. S.[c]	
(36a)	100	0	**(37a)**	100	**(234a)**	0
(36b)	100	0	**(37b)**	100	**(234a)**	0
(227a)	22	78	**(228a)**	35	**(229b)**	65
(227b)	42	58	**(228b)**	30	**(229b)**	70
(201a)	80	20	**(235a)**	80	**(237a)**	20
(201b)	100	0	**(235b)**	90	**(237b)**	~10

[a] in $CDCl_3$ at 25°C,

[b] L. S. denotes Less Substituted,

[c] M. S. denotes More Substituted.

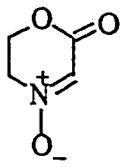
CHAPTER 7

SYNTHESIS OF SOME HETEROCYCLIC NITRONES

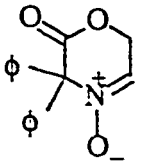
7.1 Introduction

The cyclic nitrones not only undergo addition reactions faster than their acyclic counterparts, also their cycloadditions are found to be more stereoselective. This is mainly attributed to the fact that whereas cyclic nitrones must remain in E-form, the acyclic counterpart may undergo E ⇌ Z isomerization under the reaction conditions. Such isomerizations lead to the stereochemical complication.

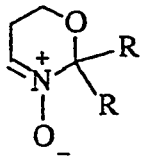
It would be interesting to design some special nitrones which would enjoy the advantages inherent in cyclic system and at the same time the cycloaddition product could be changed to open form whenever desired. Keeping this view in mind, we attempted synthesis of the following type of nitrones. For instance, the heterocyclic nitrones (249) on addition reaction with methyl crotonate would lead



(247)

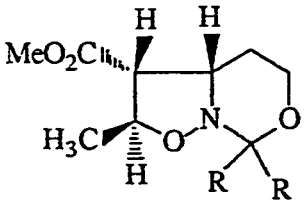


(248)

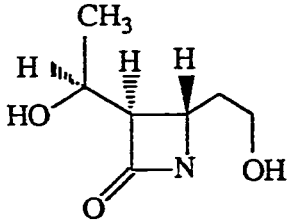


(249)

to the formation of the adduct (**250**) both regio- and stereoselectively. The adduct would then be converted into (**251**), a valuable intermediate in the synthesis of β-lactam antibiotics.[6,7]



(**250**)



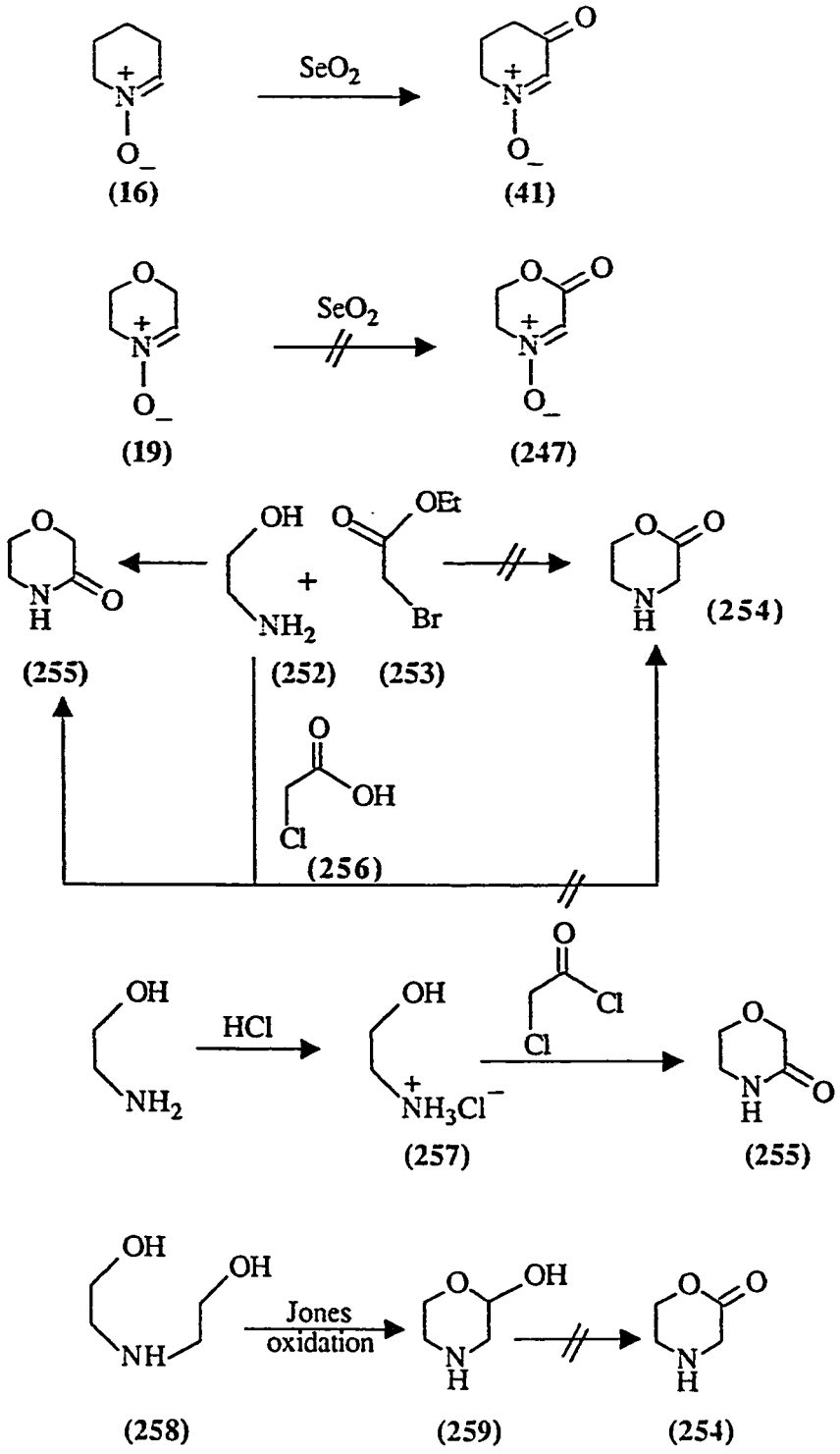
(**251**)

7.2 Results and Discussion

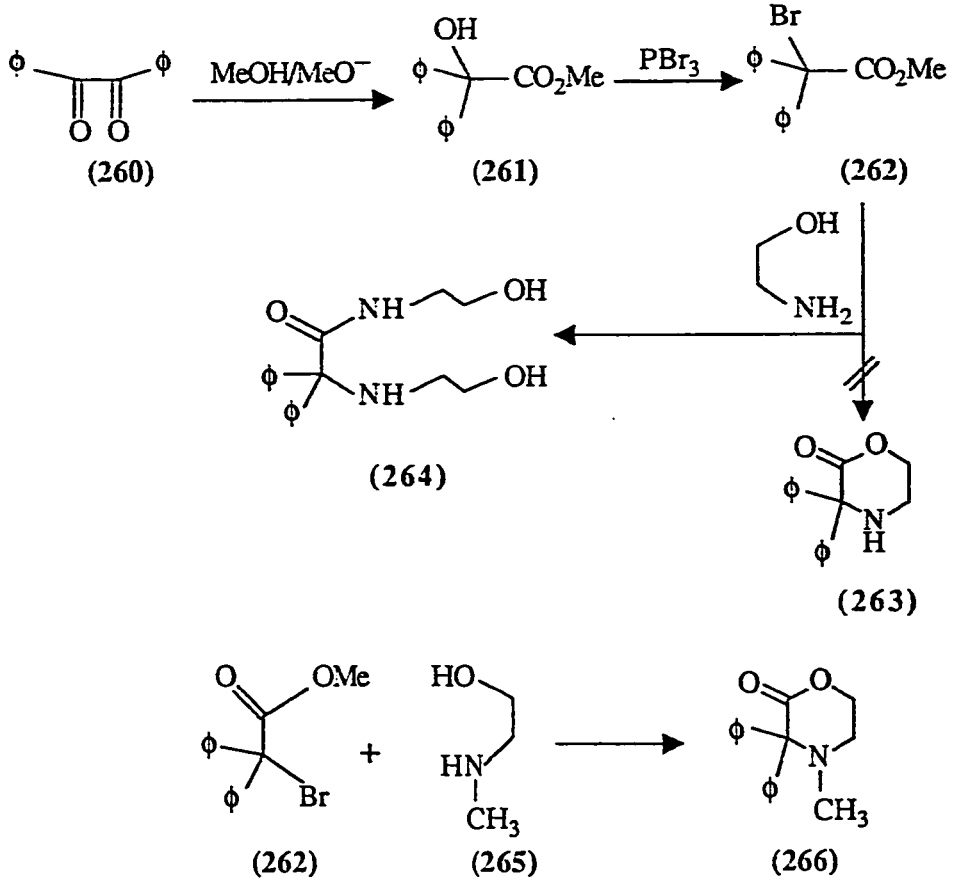
Although the ketonitrone (41) known before is synthesized from the parent nitrone (16) by SeO_2 oxidation,[20] attempted synthesis of the ketonitrone (247) by similar procedure from (19) was a complete failure. Repeated trials under different reaction conditions afforded intractable materials. Then, we attempted to synthesise 2-morpholinone (254) which would then be converted into the desired ketonitrone (247). Literature search[145,146,147] revealed that it is indeed a difficult task to synthesize 2-morpholinone (254). The percentage yield of reported procedures, varies from 1 to 4% yield.

In our attempts, ethanolamine (252) upon treatment with ethyl bromoacetate (253) afforded 3-morpholinone (255) (in low yield) instead of 2-morpholinone (254). Similar results were obtained under several experimental conditions. Mixture of ethanolamine (252), chloroacetic acid (256), and concentrated H_2SO_4 again afforded the undesired 3-morpholinone (255). Blocking the amino group as HCl salt,[148] as in (257), followed by treatment with chloroacetylchloride, met the same fate, again 3-morpholinone is obtained.

It was anticipated that diethanolamine (258) on oxidation should afford the intermediate hemiacetal (259) which should give the compound (254) on further oxidation. However, this turned out to be an unsuccessful venture.

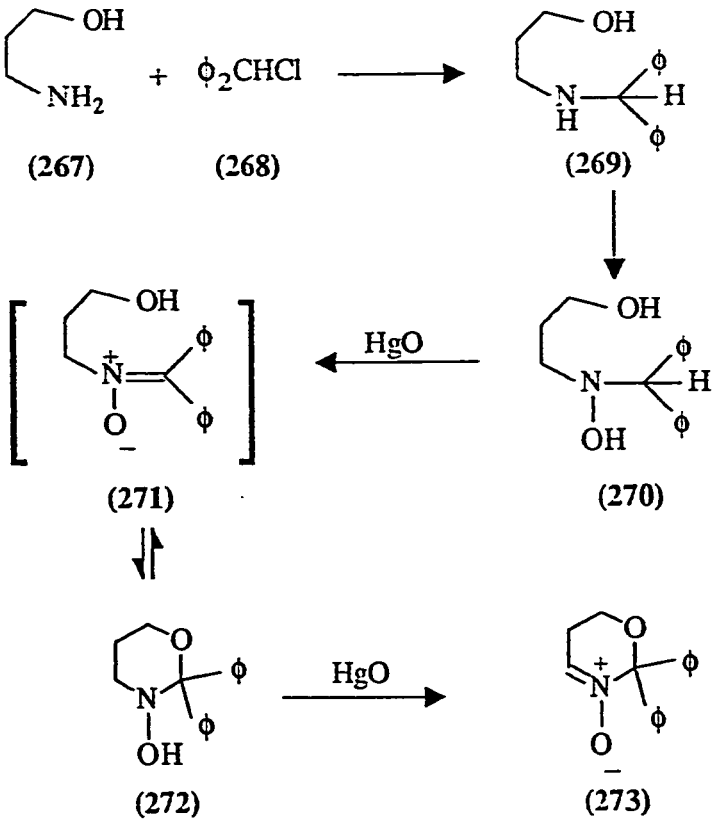

SeO2
(16)
(41)
SeO2
(19)
(247)
OH
OEt
O
O
+
NH2
Br
(254)
(255)
(252)
(253)
OH
Cl
(256)
OH
HCl
NH2
OH
+
NH3Cl−
Cl
Cl
(257)
(255)
OH
OH
NH
Jones
oxidation
(258)
(259)
(254)

Next, we focussed our attention on the synthesis of (263) which could be converted into the nitrone (248). Benzil (260) was converted to (262) via (261) by a known procedure. However, (262) upon treatment with ethanolamine under varying reaction conditions afforded (264) instead of (263). The result was puzzling, since the similar reaction of (262) with (265) affords (266) in a reasonably good yields.[149]



Finally, we synthesized the amine (269) through the reaction of (267) and (268). The secondary amine (269) on oxidation with *m*-CPBA gave the hydroxylamine (270). Finally, the stage is set for HgO oxidation of the

hydroxylamine (270) which is anticipated to give the nitrone (273). We anticipate an exciting outcome of this reaction.



CHAPTER 8

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed on a Carbo-Erba elemental analyser 1106. IR spectra were recorded on a Nicholet 5 DBX FT IR and are reported in wave numbers (cm^{-1}). The ^{1}H NMR spectra were recorded on a Brucker AC-80 NMR spectrometer operating at a proton frequency of 80.0 MHz using deutereochloroform as solvent and TMS as internal standard. A Varian XL-200 NMR spectrometer operating at a proton frequency of 200.0 MHz was also used to record ^{1}H and ^{13}C NMR spectra. Plastic TLC cards, coated with silica gel, with fluorescent indicator (Eastman, No. 6060) were used to monitor the reaction progress, and to determine appropriate solvent system for elution. Silica gel chrmatographic separations were performed with flash silica. All solvents were reagent grade. The 4-hydroxymorpholine and all the liquid alkenes were distilled before use. The nitrone (19) solution in dichloromethane was kept in the freezer in order to avoid any polymerization . The formation of the nitrone was assumed to be quantitative in the percentage yield calculations for the subsequent cycloadditions. Cycloaddition reactions were carried out under a positive pressure of nitrogen.

8.1 Cycloaddition Reactions of the Nitrone (19) with the Alkenes (200)

8.1.1 4-Hydroxymorpholine (18)

4-Hydroxymorpholine (**18**) was prepared by the oxidation of morpholine. To a stirring sample (62.79 ml, 62.73 g) of morpholine cooled in an ice bath was added 100 ml of 30% hydrogen peroxide. The addition was carried out over a period of 25 minutes maintaining the temperature of the mixture below 10°C. After complete addition of hydrogen peroxide (ca. 30 min), when the temperature exceeded 50°C, the flask was immediately immersed in the ice and H_2O. The mixture temperature continued to raise to 90°C and the reaction mixture was slowly brought to room temperature. An ample amount of anhydrous potassium carbonate was added to the mixture in order to salt out the 4-hydroxymorpholine. In a separatory funnel, the organic layer was collected, and the aqueous layer was extracted with dichloromethane (4 x 30 ml). The extracts were collected and dried over anhydrous sodium sulfate. The organic layer and extracts were evaporated on the steam bath. The product was then subjected to fractional distillation. Unreacted morpholine distilled at 65-70°C and 65 mm Hg, and the 4-hydroxymorpholine (**18**) was collected at 10 mm Hg over a boiling range of 78-100°C and was redistilled to give 19 g (b_{20} 90-93°C).

8.1.2 5,6-Dihydro-1,4-oxazine 4-oxide (19)

Preparation of the nitrone (**19**) was accomplished by the oxidation of 4-hydroxymorpholine. The oxidant, yellow mercuric oxide (40.0 g, 185 mmol) was added portion wise to a stirred solution of 4-hydroxymorpholine (**18**) (6.00 g, 58.2 mmol) in CH_2Cl_2 (200 ml) at 0°C under an N_2 atmosphere. Within minutes after HgO addition, the reaction mixture became grayish, presumably due to

liberation of Hg and formation of mercuric salts. Stirring was continued for an additional 0.5 h at 0°C. Reaction completion was checked by TLC (silica gel, ethyl acetate). Sufficient amount of magnesium sulfate anhydrous was added to the mixture after which it was filtered through a bed of MgSO4. Cold (0°C) CH_2Cl_2 was used to wash the bed and the filtrate was collected in an ice-cooled flask. The nitrone (**19**) solution in dichloromethane was kept in the freezer in order to avoid any polymerization. The formation of the nitrone was assumed to be quantitative. The percentage yield calculations for the subsequent cycloadditions were based on this assumption.

The nitrone (**19**) for the kinetic runs was prepared by HgO oxidation of 4-hydroxymorpholine (**18**) in $CDCl_3$ at 0°C. δ_H ($CDCl_3$) : 3.6-4.10 (4H, m), 4.42 (2H, m), 7.15 (1H, m); δ_H (D_2O, DSS) : 3.85 (2H, m), 4.10 (2H, apparent t, J 6.0 Hz), 4.55 (2H, apparent q, J 2.5 Hz), 7.52 (1H, hept, J 1.5 Hz).

8.1.3 2-Phenylperhydro-1,2-oxazolo[3,2-c]oxazine (201a)

A solution of the nitrone (**19**) (5.0 mmol) and styrene (3.0 cm^3) in 25 cm^3 of dichloromethane was stirred at room temperature (20°C) for 18 h. The progress of reaction was monitored by TLC. After the completion of reaction, the solvent and excess styrene were removed by a stream of nitrogen. The crude residue was purified by silica gel column chromatography using 1 : 1 hexane-ethyl acetate mixture as the eluant to give the adduct (**201a**) (852 mg, 83%) as colorless crystals, m.p. 100-101°C (dichloromethane-hexane). (Found : C, 70.39; H, 7.48; N, 6.97. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.83%); $\upsilon_{max.}$(KBr) 2975, 2920, 2864, 1457, 1386, 1322, 1271, 1249, 1150, 1121, 1109, 1033, 963, 904, 859, 761, and 704 cm^{-1}; δ_H at 25°C : 2.13 (1H, ABMX, J 4.0, 7.0, 12.0 Hz), 2.25-4.20 (8H,m), 5.06 (0.2H, br), 5.41 (0.8H, dd, J 4.0 10.0 Hz), 7.40 (5H, m).

8.1.4 *Isomers of 2-Hydroxymethylperhydro-1,2-oxazolo [3,2c][1,4]oxazine (201b)-(202b)*

Allyl alcohol (5.0 cm^3) was added to a solution of the nitrone (19) (5.0 mmol) in 25 cm^3 of dichloromethane. The reaction mixture was stirred at room temperature (20°C) under a positive pressure of nitrogen for 72 h. Thin layer chromatography was used to monitor the reaction. Thereafter, a stream of nitrogen removed the solvent and excess allyl alcohol. Column chromatography of the crude reaction mixture over silica gel using ethyl acetate as eluant gave a non-separable mixture (700 mg, 88%) of the two isoxazolidines **(201b)** and **(202b)**. Crystallization of the chromatography product provided the major isomer **(201b)** as colorless crystals, m.p. 67-68°C (dichloromethane-ether) (Found : C, 52.70; H, 8.36; N, 9.03. $C_7H_{13}NO_3$ requires C, 52.80; H, 8.23; N, 8.80%; $\upsilon_{max.}$(KBr) 3200, 2957, 2864, 1462, 1273, 1255, 1153, 1118, 1098, 1062, and 994 cm^{-1}; δ_H at 22°C : 2.16 (1H, m), 2.42 (1H, m), 3.02 (2H, m), 3.26-4.26 (8H, m), and 4.50 (1H, m). The ratio of the cycloadducts **(201b)** and **(202b)** was determined by converting them into the corresponding acetates **(201L)** and **(202L)** (*vide infra*). Estimation of the ratio was based on the integration of the acetyl protons' signals.

8.1.5 *Isomers of Methyl Perhydro-1,2-oxazolo[3,2-c] [1,4]oxazine-2- and -3-carboxylate (201c)-(204c)*

To a stirred solution of nitrone **(19)** (5.0 mmol) in 25 cm^3 of dichloromethane, was added 3.0 cm^3 of methyl acrylate **(200c)**. Stirring continued under a positive pressure of nitrogen and at room temperature for 10 minutes. Completion of the reaction was ensured by TLC. The crude reaction mixture was freed from the solvent and excess methyl acrylate by a stream of nitrogen. A portion of the crude mixture of the cycloadducts **(201c)**-**(204c)** was

treated with lithium aluminium hydride. This reduction reaction afforded a mixture of the adducts **(201b)**-**(204b)**. On acetylation with acetic anhydride the later adducts gave the corresponding acetates **(201L)**-**(204L)**.

Another portion of the adducts was purified by column chromatography over silica gel. A mixture of 1 : 1 dichloromethane-ethyl acetate was used as the eluant. The process provided the adducts **(201c)**-**(204c)** from which the adduct **(201c)** crystalized on long standing in the freezer, m.p. 39-40°C (dichloromethane) (Found : C, 51.27; H, 7.07; N, 7.69. $C_8H_{13}NO_4$ requires C, 51.33; H, 7.00; N, 7.48%). Following data describes IR and NMR spectrum of the purified mixture of the adducts **(201c)**-**(204c)** : $\upsilon_{max.}$(neat) 2975, 2880, 1741, 1457, 1438, 1272, 1211, 1124, 1112 , and 1081 cm^{-1}; δ_H at 22°C : 2.02-2.70 (2H, m), 2.96-3.30 (2H, m), 3.36-4.02 (8H, m, including methyl singlet at δ 3.78), 4.50-4.85 (1 H, m, with a major dd at δ 4.80 (J 5.0, 9.0 Hz)). Minor signals at δ 4.0-4.50 were attributed to the C-2 protons of the minor regiomers **(203c)** and **(204c)**.

8.1.6 Isomers of Perhydro-1,2-oxazolo[3,2-c][1,4] oxazine-2- and -3-carbaldehyde (201d)-(204d)

To a solution of the nitrone **(19)** (5.0 mmol) in 25 cm^3 being stirred at 0°C, was added 1.5 cm^3 of acrylaldehyde **(200d)**. After 10 minutes, the dichloromethane was evaporated from the reaction mixture with a stream of nitrogen. Then, absolute methanol (15 cm^3) was added to the reaction flask, followed by addition of sodium borohydride (1 g, 26.4 mmol). A volume of 10 cm^3 of distilled water was added to the above mixture, which was then saturated with potassium carbonate and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and the solvent was removed by a stream of N_2. Afterward, the product was purified by column chromatography over silica gel eluted by ethyl

acetate. A sample (404.4 mg, 2.54 mmol) (67% yield in two steps) of the alcohol adducts **(201b)-(204b)** was recovered from the chromatographic purification.

A portion of the purified adducts **(201b)-(204b)** was treated with acetic anhydride over one night at room temperature. This treatment gave the acetates **(201L)-(204L)**, $\upsilon_{max.}$(KBr) 2960, 2865, 1740, 1675, 1450, 1365, 1235, 1125, 1087, 1035, 850, 788, and 727 cm^{-1}; δ_H at 22°C : 2.00 (1H, m), 2.06, 2.08, 2.11, 2.13 (3H, four singlets), 2.50 (1H, m), 3.08 (2H, m), 3.32-4.42 (7H, m), 4.62 (1H, m). The singlets at δ 2.11, 2.13, 2.06, and 2.08 were assigned to the C-2 acetyl protons of the adducts **(201L)-(204L)** respectively. The ratio of the adducts **(201L)-(204L)**, hence that of **(201d)-(204d)** was approximated by integration of these singlets, and was found to be 48 : 29 : 12 : 11, respectively.

8.1.7 Isomers of 2-Hydroxymethyl-2-methylperhydro-1,2-oxazolo[3,2-c][1,4]oxazine (201e)-(202e)

A dichloromethane solution (25 cm^3) containing the nitrone **(19)** (5.0 mmol) and methyl allyl alcohol **(200e)** (5.0 cm^3) were mixed and stirred at room temperature (20°C) for 72 h. Removal of the solvent and excess alkene was achieved by a stream of nitrogen. The crude reaction mixture was chromatographed using 1 : 1 hexane-ethyl acetate mixture as eluant to give a non-separable mixture of the adducts **(201e)** and **(202e)** (710 mg, 4.10 mmol, 82% yield) from which the major adduct **(201e)** was obtained as colorless crystals, m.p. 70-71°C (dichloromethane-hexane) (Found : C, 55.39; H, 8.88; N, 8.23. $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%); $\upsilon_{max.}$(KBr) 3329, 3238, 2972, 2930, 2884, 1471, 1461, 1448, 1386, 1272, 1135, 1064, 1031, 899, 859, 773, and 702 cm^{-1}; δ_H at 26°C : 1.25 (3H, s), 1.80-2.84 (3H, m), 3.06-4.18 (9H, m). Minor singlets at δ 1.40 was assigned to the minor isomer. The ratio of the adducts

(201e) and (202e) was determined by integration of the C-2 methyl signals, and was found to be 91 : 9.

8.1.8 *Isomers of Methyl 2-methylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine -2-carboxylate (201f)-(202f)*

To a stirred solution of the nitrone (**19**) (5.0 mmol) in 25 cm^3 of dichloromethane, was added 3.0 cm^3 of methyl methacrylate (**200f**) at 20°C. After stirring for 3 h under a N_2 atmosphere, the solvent and excess alkene were evaporated by a stream of nitrogen. Purification of the crude cycloadducts was achieved by column chromatography over silica gel using 1 : 1 hexane-ethyl acetate mixture as eluant. A non-separable mixture of the isomers (**201f**) and (**202f**) was afforded , from which the major adduct (**201f**) was obtained as colorless needles, m.p. 59-60°C (ether) (Found : C, 53.76; H, 7.72; N, 7.21. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%); $\upsilon_{max.}$(KBr) 2975, 2845, 1730, 1480, 1467, 1448, 1437, 1304, 1253, 1183, 1138, 1078, 884, and 693 cm^{-1}; δ_H at -5°C : 1.55 (0.9 x 3H, s), 1.86 (0.1 x 3H, s), 2.14 (1H, appeared. q, J 6.0 Hz), 2.48 (1H, m), 2.74-3.22 (3H, m), 3.34-4.16 (4H, m), 3.83 (3H, s). The NMR spectrum of the crude mixture revealed the C-2 methyl of the minor isomer at δ 1.62 (s). The ratio was determined to be 95 : 5.

8.1.9 *Isomers of Methyl 2-methylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine3-carboxylate (201g)-(202g)*

A solution of nitrone (**19**) (5.0 mmol) in 25 cm^3 of dichloromethane was stirred at 20°C with 3.0 cm^3 of methyl crotonate (**200g**) under N_2-atmosphere for 18 h. A stream of nitrogen into the reaction mixture removed the solvent and excess alkene. The residue was chromatographed with ethyl acetate as eluant, which gave a non-separable mixture of the adducts (**201g**) and (**202g**). The major adduct was

crystallized from the adduct mixture on standing in the freezer, m.p. 35-36°C (dichloromethane-hexane) (Found : C, 53.82; H, 7.64; N, 7.10. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%); $\upsilon_{max.}$ (KBr) 2954, 2859, 1734, 1458, 1396, 1286, 1218, 1202, 1128, 1025, 944, 847, and 728 cm^{-1}; δ_H at 20°C : 1.36 (3H, d, J 6.0 Hz), 2.50-4.24 (8H, m), the C-3 H appeared at δ 2.94 as a dd (J 6.0, 9.0 Hz), 3.76 (3H, s), 4.53 (0.35H, quint., J 6.0 Hz), 5.04 (0.65H, quint, J 6.0 Hz). The C-2 methyl of the minor isomer appeared at δ 1.50 (d, J 6.0 Hz). The ratio of the major and minor isomers was 96 : 4, respectively.

8.1.10 Isomers of Methyl 2-phenylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine3-carboxylate (201h)-(202h)

Methyl cinnamate (8.0 mmol) was added to a stirring solution of the nitrone **(19)** (5.0 mmol) in 25 cm^3 of dichloromethane. The reaction was stirred at 40°C, under a positive pressure of N_2 for a period of 72 h. The solvent and excess alkene were removed by a stream of nitrogen. Chromatography using 1 : 1 dichloromethane-ethyl acetate mixture as eluant, gave the adducts **(201h)** and **(202h)**. Crystallization afforded the major adduct **(201h)** as colorless crystals, m.p. 86-87°C (dichloromethane-hexane) (Found : C, 64.03; H, 6.61; N, 5.58. $C_{14}H_{17}NO_4$ requires C, 63.86; H, 6.51; N, 5.32%); $\upsilon_{max.}$(KBr) 2985, 2957, 2883, 2864, 1734, 1455, 1263, 1208, 1179, 1088, 987, 852, 783, and 704 cm^{-1}; δ_H at -30°C : 2.85-4.45 (8H, m), 3.78 (3H, s), 5.52 (0.35H, d, J 5.0 Hz), 6.01 (0.65H, d, J 6.5 Hz), 7.45 (5H, m). The singlet at δ 3.81 was assigned to the methoxycarbonyl protons of the minor isomer **(202h)**. The ratio of **(201h)** and **(202h)** was found to be 94 : 6, respectively.

8.1.11 *Isomers of trans-Dimethylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine-2,3-dicarboxylate (201i)-(202i)*

Dimethyl fumarate (6.0 mmol) was added to a solution of nitrone (**19**) (5.0 mmol) in 25 cm^3 of dichloromethane. The reaction mixture was stirred at room temperature (20°C) under a positive pressure of N_2. After 30 minutes, the solvent and excess alkene were removed by a stream of N_2. The non-separable mixture of adducts (**201i**) and (**202i**) was purified by silica gel chromatography using 1 : 1 hexane-ethyl acetate mixture as the eluant. The major adduct (**201i**) was separated by repeated crystallization, m.p. 69-70°C (dichloromethane-hexane) (Found : C, 49.13; H, 6.27; N, 6.01. $C_{10}H_{15}NO_6$ requires C, 48.97; H, 6.17; N, 5.71%); $\upsilon_{max.}$(KBr) 2960, 1787, 1728, 1428, 1379, 1293, 1220, 1124, 1091, 1045, and 1027 cm^{-1}; δ_H at +22°C : 2.60-4.35 (8H, m), 3.78 (3H, s), 5.06 (0.17H, d, J 5.0 Hz), 5.24 (0.83H, d, J 5.0 Hz). The C-2 H of the minor isomer (**202i**) appeared at δ 4.87 (0.25H, d, J 5.0 Hz) and δ 4.97 (0.75H, d, J 8.0 Hz). The ratio of the adducts was determined by integration of the C-2 proton signals, and found to be 82 : 18.

8.1.12 *Isomers of cis-Dimethylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine-2,3-dicarboxylate (201j)-(202j)*

A sample of 7.0 mmol of dimethyl maleate (**200j**) was added to 25 cm^3 of dichloromethane containing 5.0 mmol of nitrone (**19**). Stirring of the reaction mixture was continued at 20°C for 12 h. A stream of nitrogen, removed the solvent and excess alkene from the reaction mixture. Chromatographic purification of the product residue with 1 : 1 hexane-ethyl acetate as eluant yielded a non-separable mixture of the adducts (**201j**) and (**202j**) in 82% yield, from which the major adduct (**202j**) was obtained as colorless plates, m.p. 70-71°C (dichloromethane-hexane) (Found : C, 49.23; H, 6.28; N, 5.83. $C_{10}H_{15}NO_6$ requires C, 48.97; H,

6.17; N, 5.71%): $\upsilon_{max.}$(KBr) 3013, 2985, 2948, 2873, 2845, 1761, 1737, 1437, 1331, 1222, 1125, 1088, 982, and 860 cm^{-1}; δ_H at -50°C : 2.90 (1H, m), 3.28 (1H, m), 3.40-4.20 (6H, m), 3.76 (3H, s), 3.80 (3H, s), 4.80 (0.10H, d, J 9.5 Hz), 5.13 (0.90H, d, J 10.0 Hz). C-2 H of the minor isomer **(201j)** appeared at δ 4.84 (0.8H, d, J 9.0 Hz) and 4.92 (0.2H, d, J 10.0 Hz). The ratio of the conformers and diastereomers was determined by integration of the C-2 proton signals.

8.1.13 Reaction of the Nitrone (19) with Maleic Anhydride (200k)

To a stirred solution composed of nitrone **(19)** (5.0 mmol) dissolved in 25 cm^3 of dichloromethane, was added 4.0 mmol of maleic anhydride **(200k)**. The reaction was performed in moisture-free condition under positive pressure of N_2. Stirring was continued for 20 minutes. The crude reaction mixture was divided into two portions. One portion was stirred with methanolic HCl (5 : 3, w/w) (5 cm^3). After 12 hours of stirring at 20°C, the volume of the reaction mixture was reduced to 5 cm^3 by removal of the solvent with a N_2-stream. Ten cm^3 of H_2O was added to the reaction flask, and the mixture was extracted (2 x 20 cm^3) with 1 : 1 hexane-ethyl acetate mixture. The aqueous layer was then saturated with K_2CO_3 and extracted with CH_2Cl_2 (3 x 20 cm^3). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed by a stream of N_2 to give a mixture of adducts **(201j)** and **(202j)**, in the ratio of 8 : 92. The second portion of the crude mixture was dissolved in dichloromethane and the insoluble material was filtered off. On concentration, white crystals of the adduct **(202k)** were obtained, m.p, 137-139°C, $\upsilon_{max.}$(KBr) 2983, 2956, 2909, 2891, 2848, 1866, 1787, 1461, 1424, 1261, 1235, 1220, 1193, 1110, 1055, and 1013 cm^{-1}; δ_H at 35°C (80 MHz) : 3.25-4.10 (8H, m) and 5.05 (1H, d, J 8.0 Hz). We were unable to obtain a satisfactory elemental analysis for the adduct **(202k)**, persumably due to its hygroscopic nature.

8.1.14 Isomers of 2-Acetoxymethylperhydro-1,2-oxazolo [3,2-c][1,4]oxazine (201L)-(202L)

A sample (160 mg, 1.0 mmol) of the crude mixture of isoxazolidines (**201b**) and (**202b**) was heated in acetic anhydride (2 ml) at 60°C for 12 h. After removal of excess acetic anhydride, the residue was purified by silica gel chromatography using 1 : 1 ethyl acetate-hexane mixture as the eluant. This gave the acetates (**201L**)-(**202L**) (181 mg, 90% yield) as colorless liquid (Found : C, 53.54; H, 7.40; N, 6.85. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%); $\upsilon_{max.}$(neat) 2975, 2920, 2864, 1741, 1453, 1371, 1237, 1124, 1045, 974, and 849 cm^{-1}; δ_H ($CDCl_3$ at 35°C) : 1.85 (2H, m), 2.11 (3H, s), 2.80-4.00 (7H, m), 4.15 (2H, m), and 4.60 (1H, m). A minor singlet appeared at δ 2.13 (3H, s). The ratio of the two singlets at δ 2.11 and 2.13 was found to be 88 : 12.

8.1.15 Isomers of 2-Acetoxymethyl-2-methylperhydro-1,2-oxazolo[3,2-c][1,4]oxazine (201m)-(202m)

The isoxazolidines (**201e**)-(**202e**) were acetylated by heating a sample (137 mg, 1.0 mmol) of the reaction mixture of (**201e**)-(**202e**) in acetic anhydride (2 ml) at 60°C for 12 h. After the elapse time, excess acetic anhydride was removed and the residue was chromatographed using 1 : 1 ethyl acetate-hexane mixture as eluant to give the corresponding acetates (**201m**)-(**202m**) (194 mg, 90% yield) as colorless liquid (Found : C, 55.65; H, 7.83; N, 6.37. $C_{10}H_{17}NO_4$ requires C, 55.80; H, 7.96; N, 6.51%); $\upsilon_{max.}$(neat) 2995, 2883, 1743, 1456, 1374, 1238, 1089, 1043, 902, and 851 cm^{-1}; δ_H ($CDCL_3$ at 35°C) : 1.32 (3H, s), 1.88 (2H, m), 2.10 (3H, s), and 3.05-4.25 (9H, m).

8.1.16 Thermal Equilibration of the Cyclodducts (201i) and (202j)

A solution of the adduct (**201i**) (60 mg) and dimethyl fumarate (**200i**) (6 mg) in hexadeuterated benzene (0.7 cm^3) in a sealed NMR tube was heated at 120°C for 5 h. The ratio of the adducts (**201i**) and (**202i**) was found to be 15 : 85. Further heating did not change the adduct ratio. Similar thermolysis of the pure adduct (**202j**) (65 mg) in presence of dimethyl maleate (**200j**) (10 mg) in C_6D_6 for 8 h at 130°C afforded the unchanged adduct (**202j**). Careful analysis of the NMR spectra revealed the absence of the minor isomer (**201j**).

8.1.17 Polymer of the Nitrone (19)

Polymer of the nitrone (**19**) was prepared as described in the literature[108] with slight modification. Solvent dichloromethane was removed by gently blowing nitrogen into a solution of the nitrone. The residual gum was triturated with ether to give the polymer (**199**) as white powder, m.p. 145-165°C (decomp.) (lit.[108] m.p. 156-165°C). Unlike earlier report,[108] the polymer was found to be readily soluble in deutereochloroform; δ_H 2.50-4.40 (6H, broad signals), 4.65 (1H, broad signals). The polymer solution also contained minor amount of the nitrone (**19**) (~ 10 %) as revealed in the NMR spectrum.

A solution of the polymer (200 mg), as prepared above, in potassium carbonate-washed chloroform (4 cm^3) was treated with methyl acrylate (100 mg) to trap the nitrone (**19**). After 10 min, the mixture was added dropwise to ether (50 cm^3). The NMR spectrum of the resulting white polymer (140 mg), again revealed the presence of the monomer (**19**) (~5%), thus, indicating the equilibration between the mono- and poly-meric forms.

8.1.18 Reaction of the Polymer with Methyl Methacrylate

A solution of the polymer **(199)** (30 mg) in potassium carbonate-washed $CDCl_3$ (0.7 cm^3) revealed the presence of the poly- and mono-mer in a respective ratio of 90 : 10 . After 1 day and 7 days at 20°C, the corresponding ratios were changed to 70 : 30 and 30 : 70, respectively. A solution of the polymer (30 mg) and methyl methacrylate **(200f)** (65 mg) in $CDCl_3$ (0.7 cm^3) at 20°C for 14 days afforded the cycloadducts **(201f)** and **(202f)** in almost quantitative yield.

8.2 Kinetics of Cycloaddition Reactions

The ^1H NMR technique was used in the kinetic study of the cycloadditions of nitrone (**19**) onto several alkenes. The NMR spectra for the kinetic runs were recorded on a Brucker AC-80 spectrometer operating at a proton frequency of 80.0 MHz and in the pulse Fourier transform mode.

A known mass of the investigated alkene was placed in an NMR tube purged with N_2. A suitable volume of the nitrone solution was transfered to a vial and completely freed from CH_2Cl_2 by blowing N_2 at 0°C and the residue was then dissolved in $CDCl_3$. The nitrone in $CDCl_3$ was then transfered to the NMR tube and sealed immediately. The mixture was thoroughly mixed and quickly scanned by the NMR spectrometer. The NMR tube was kept at 36 ± 0.5°C throughout the kinetic measurements. The initial concentration of the nitrone was determined by NMR integration and using the known concentration of the alkene. Concentration of the nitrone (**19**) was kept low to avoid polymerization. The ratio of the concentrations of the nitrone, alkene, and cycloadducts was determined at various time intervals by integration of the signals due to 2-H of the nitrone and the olefinic protons of the alkene. In cases of overlap of signals due to 2-H nitrone and alkene, other proton signals of the nitrone and cycloadducts were used to determine the concentration ratio of the reactants. Measurements were continued upto 40-90% chemical conversion of the alkene. The second-order rate constants k_2 were determined by means of the least-mean squares analysis of the data, and was reproducible within 5-10%.

8.2.1 *Addition of the Nitrone (19) to Allyl Alcohol (200b)*

The initial concentration of allyl alcohol = (a) = 0.658 *M*, and that of the nitrone = (b) = 0.177 *M*. The values of ln [(a - x) /(b - x)] at various times were as follows : 0 min, 1.32; 14 min, 1.48; 45 min, 1.79; 102 min, 2.43; 182 min, 3.29; 202 min, 3.51. The linear regression analysis of this data gives the following : Correlation Coefficient = 1.00; Slope = 0.0109 min^{-1}; Intercept = 1.32; k_2 = 37.6 x 10^{-5} l mol^{-1} s^{-1}.

8.2.2 *Addition of the Nitrone (19) to Methyl Acrylate (200c)*

The initial concentration of methyl acrylate (a) was equal to that of the nitrone (b) = 0.0931 *M*. The values of 1/[C], where [C] = [nitrone] = [methyl acrylate], at various times were as follows : 0 min, 10.7; 1 min, 12.1; 2.58 min, 15.5; 4.58 min, 16.1; 6.58 min, 23.4; 10.83 min, 24.8; 20.08 min, 40.3; 36.18 min, 63.2. The linear regression analysis of this data gives the following : Correlation Coefficient = 0.997; Slope = 1.44 min^{-1}; Intercept = 11.0; k_2 = 2,400 x 10^{-5} l mol^{-1} s^{-1}.

8.2.3 *Addition of the Nitrone (19) to Methyl Methacrylate (200f)*

The initial concentration of the nitrone = (a) = 0.0943 *M*, and that of methyl methacrylate = (b) = 0.0757 *M*. The values of ln [(a - x) /(b - x)] at various times were as follows : 0 min, 0.220; 3.50 min, 0.232; 10.67 min, 0.264; 25.50 min, 0.366; 59.83 min, 0.539; 95.67 min, 0.693. The linear regression analysis of this data gives the following : Correlation Coefficient = 0.998; Slope = 0.00506 min^{-1}; Intercept = 0.221; k_2 = 453 x 10^{-5} l mol^{-1} s^{-1}.

8.2.4 *Addition of the Nitrone (19) to Methyl Crotonate (200g)*

The initial concentration of methyl crotonate = (a) = 0.285 *M*, and that of the nitrone = (b) = 0.180 *M*. The values of ln [(a - x) /(b - x)] at various times were as follows : 0 min, 0.482; 45 min, 0.633; 78 min, 0.717; 137 min, 0.810; 198 min, 0.982; 330 min, 1.22. The linear regression analysis of this data gives the following : Correlation Coefficient = 0.995; Slope = 0.00220 min^{-1}; Intercept = 0.520; $k_2 = 34.9 \times 10^{-5}$ l mol^{-1} s^{-1}.

8.2.5 *Addition of the Nitrone (19) to Dimethyl Fumarate (200i)*

The initial concentration of dimethyl fumarate = (a) = 0.0453 *M*, and that of the nitrone = (b) = 0.0151 *M*. The values of ln [(a - x) /(b - x)] at various times were as follows : 0 min, 1.10; 0.97 min, 1.43; 2.13 min, 1.61; 3.63 min, 1.99; 6.13 min, 2.50; 7.63 min, 3.15. The linear regression analysis of this data gives the following : Correlation Coefficient = 0.992; Slope = 0.251 min^{-1}; Intercept = 1.10; $k_2 = 13{,}900 \times 10^{-5}$ l mol^{-1} s^{-1}.

8.2.6 *Addition of the Nitrone (19) to Dimethyl Maleate (200j)*

The initial concentration of dimethyl maleate (a) was equal to that of the nitrone (b) = 0.0675 *M*. The values of 1/[C], where [C] = [nitrone] = [dimethyl maleate], at various times were as follows : 0 min, 14.8; 1 min, 15.5; 2.50 min, 15.8; 4.25 min, 16.4; 7.00 min, 17.4; 17.0 min, 21.8; 34.83 min, 27.5; 38.08 min, 29.4; 81.67 min, 44.39. The linear regression analysis of this data gives the following : Correlation Coefficient = 0.999; Slope = 0.363 min^{-1}; Intercept = 15.0; $k_2 = 605 \times 10^{-5}$ l mol^{-1} s^{-1}.

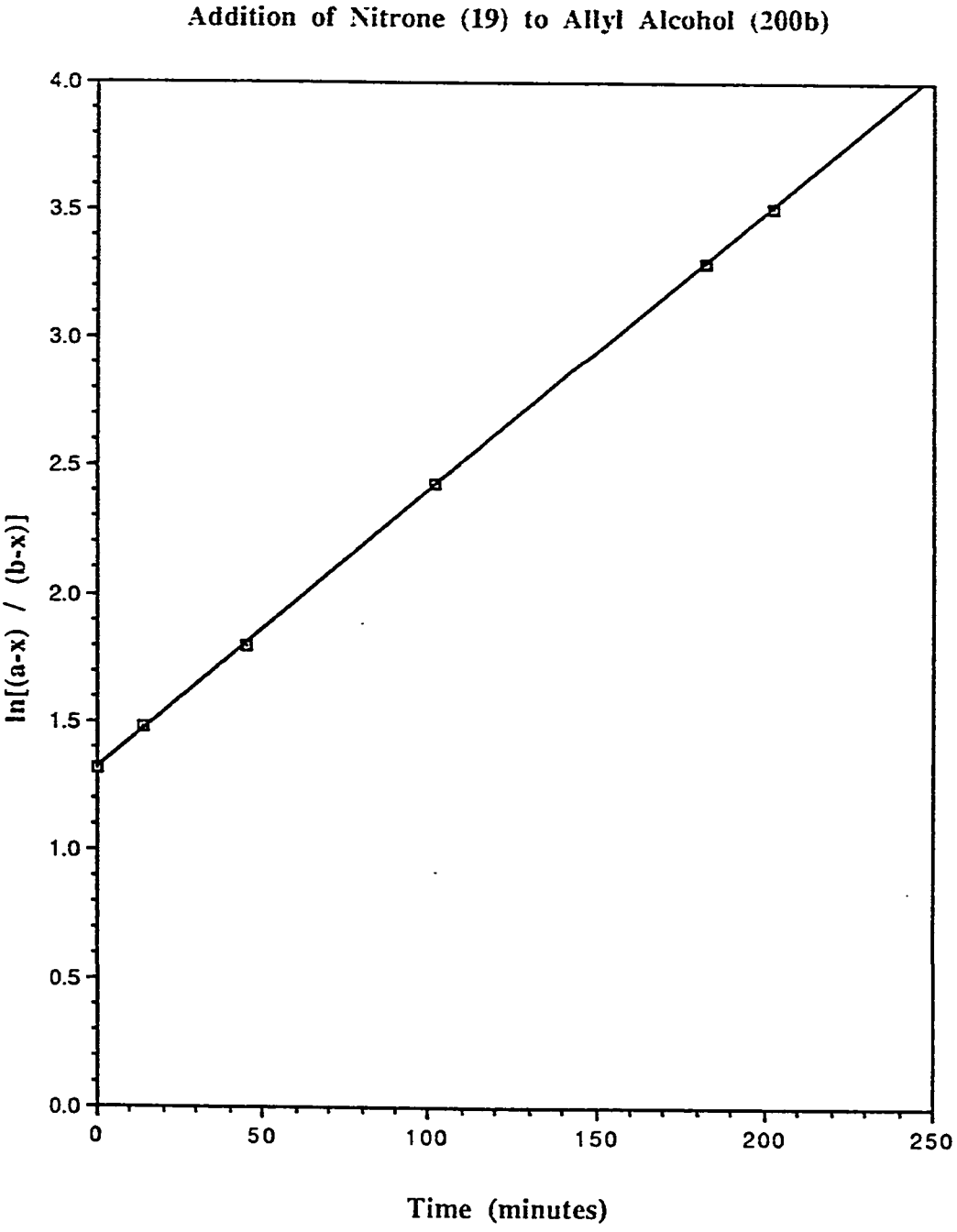

Addition of Nitrone (19) to Allyl Alcohol (200b)
ln[(a-x) / (b-x)]
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
50
100
150
200
250
Time (minutes)

Figure 13

Addition of Nitrone (19) to Methyl Acrylate (200c)

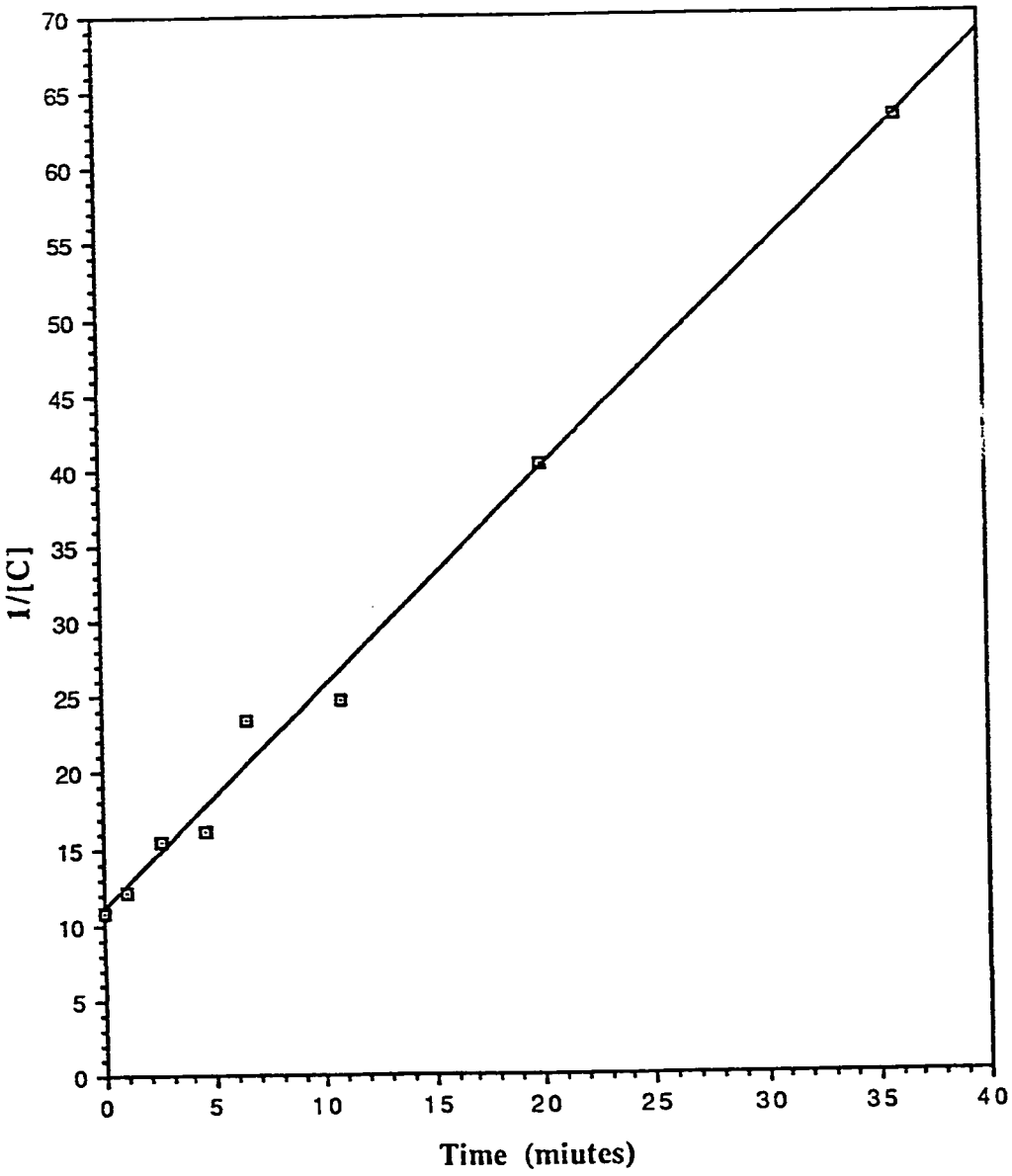


Figure 14

Addition of Nitrone (19) to Methyl Methacrylate (200f)

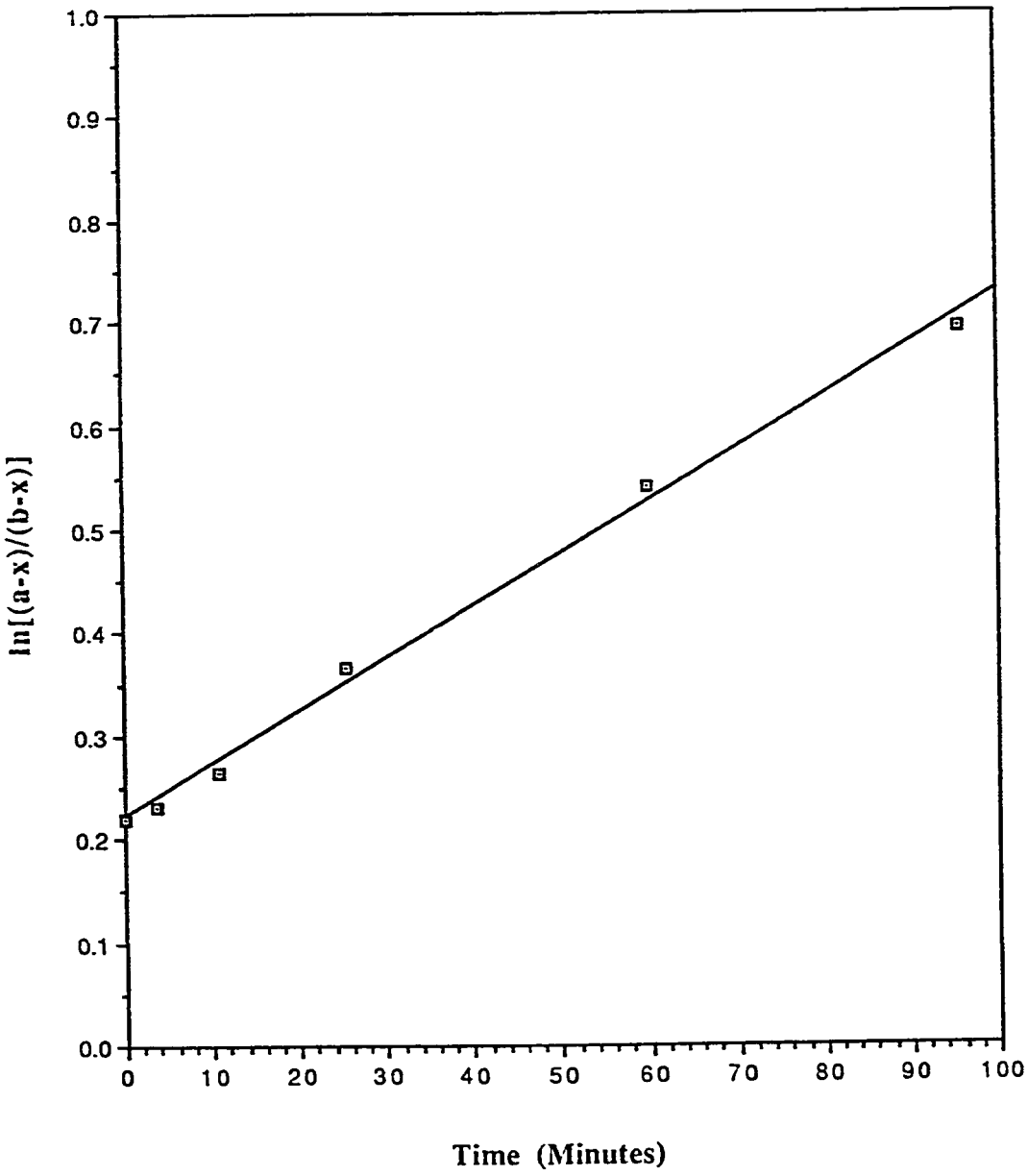


Figure 15

Addition of Nitrone (19) to Methyl Crotonate (200g)

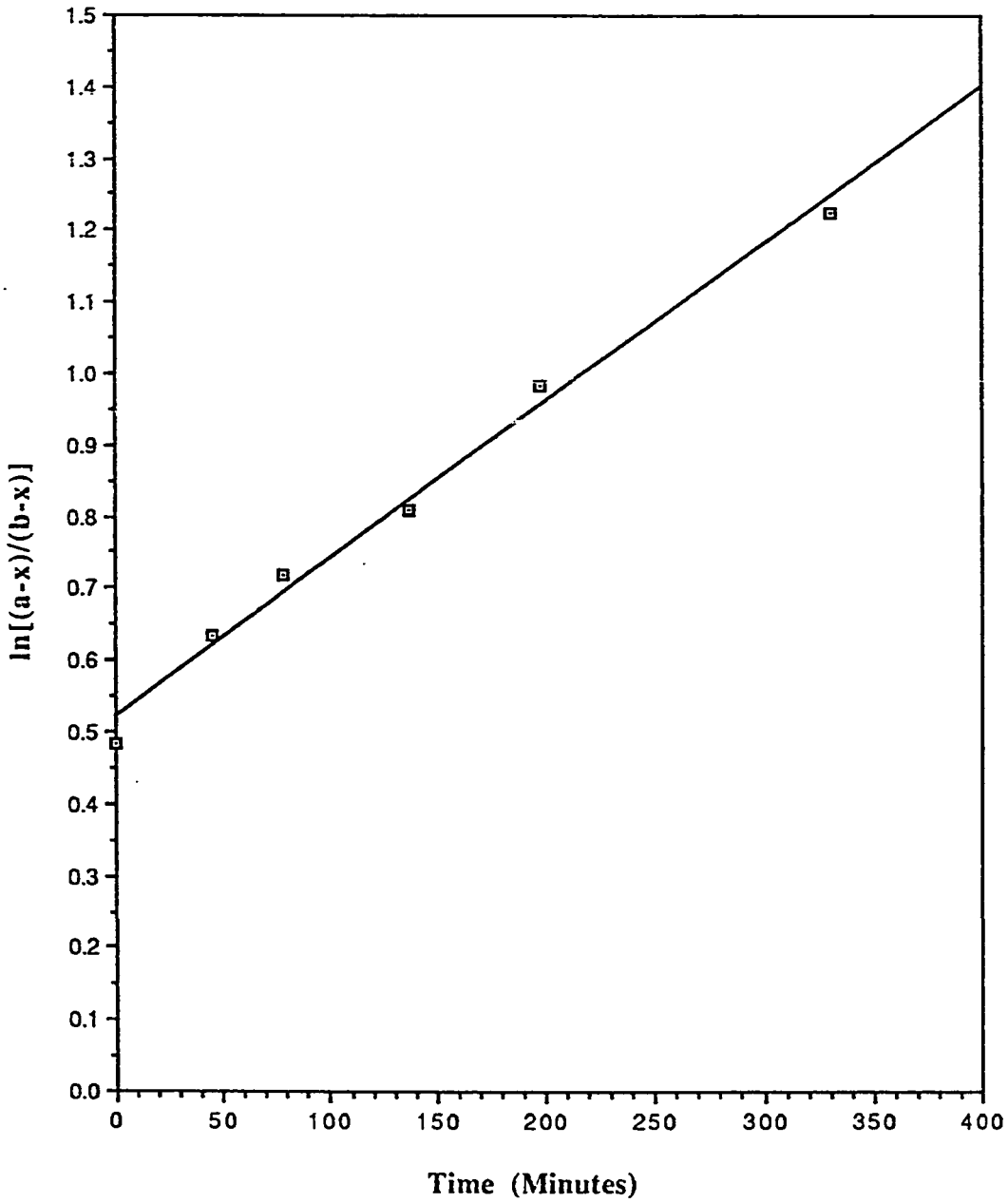


Figure 16

Addition of Nitrone (19) to Dimethyl Fumarate (200i)

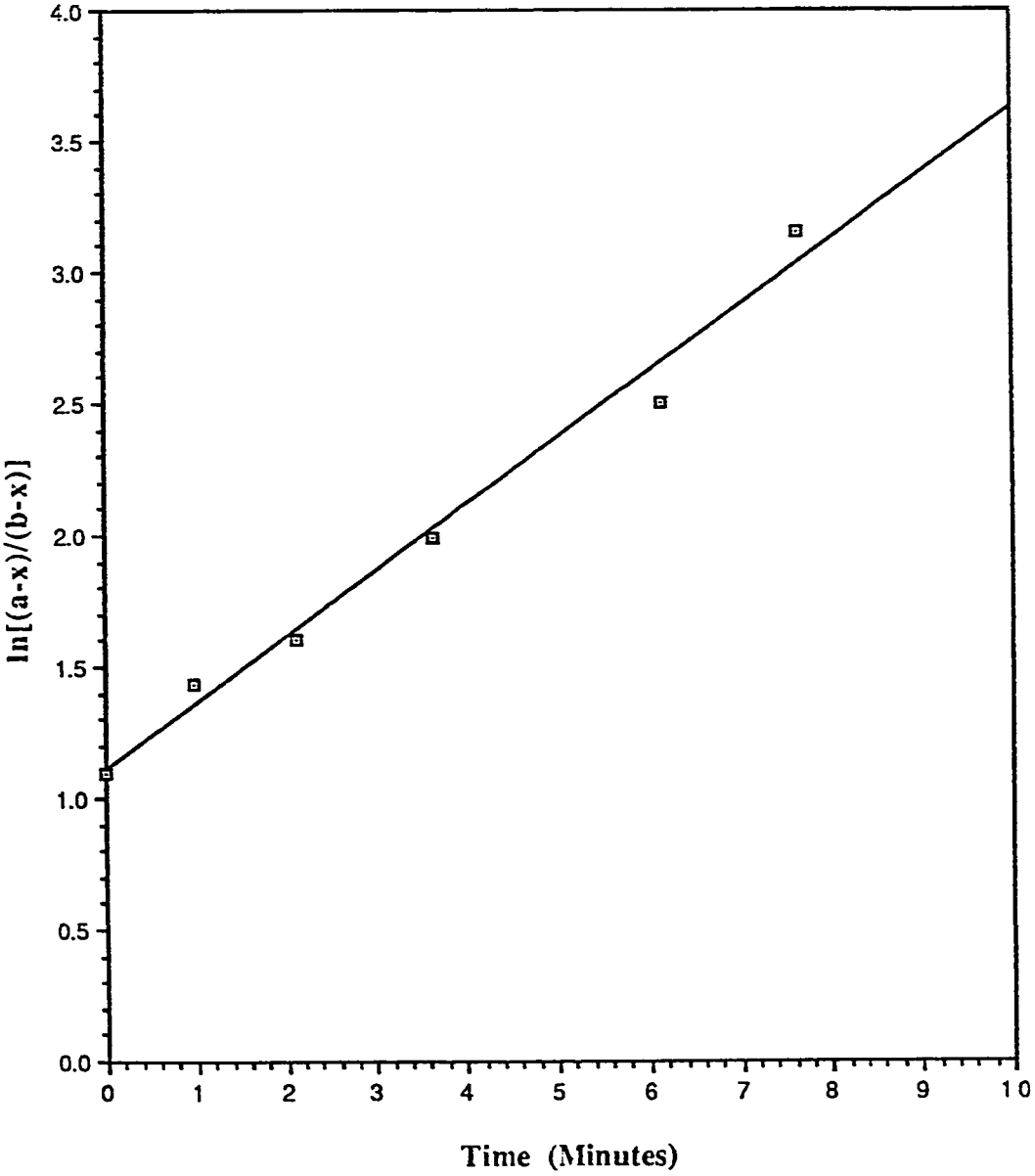


Figure 17

Addition of Nitrone (19) to Dimethyl Maleate (200j)

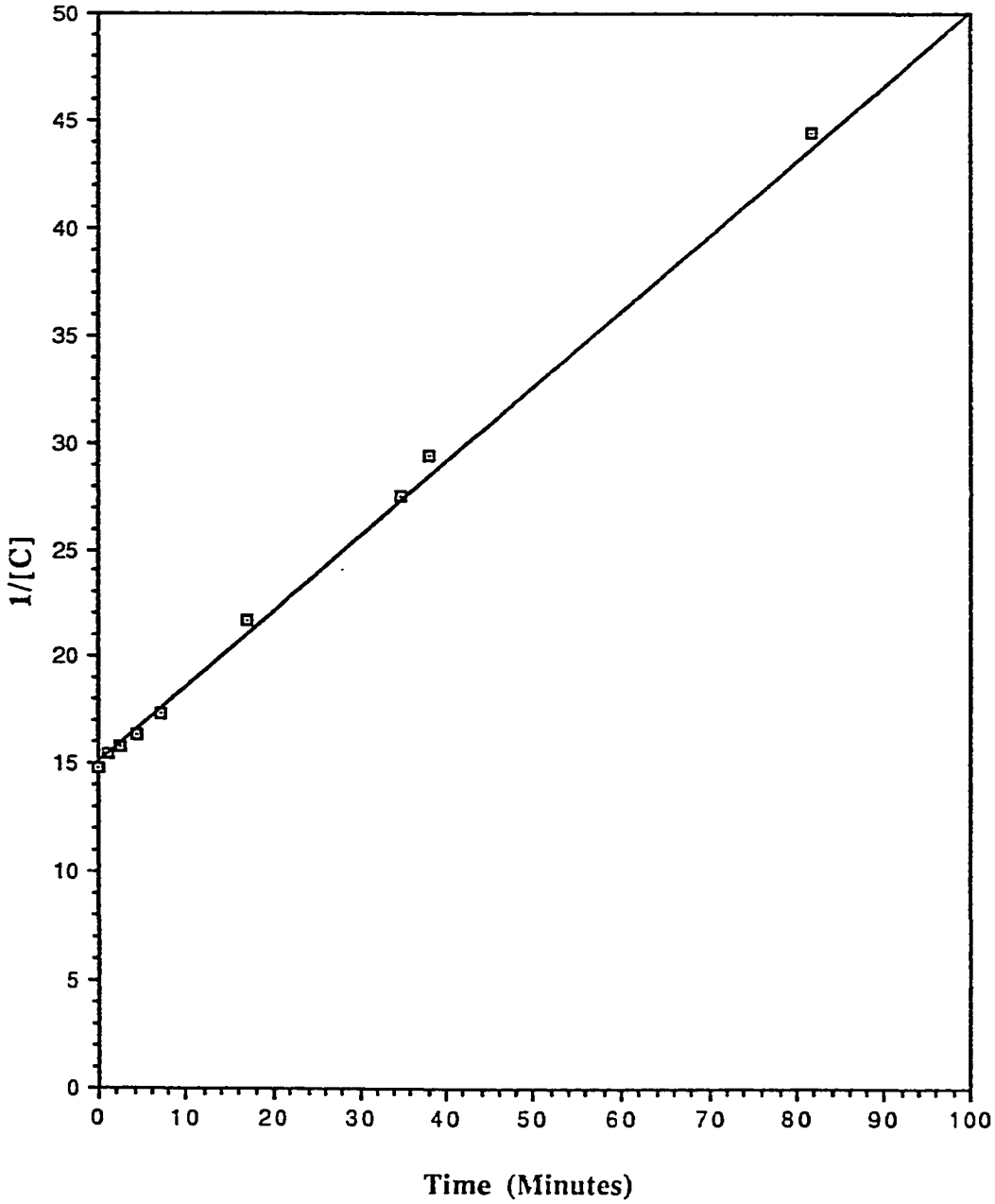


Figure 18

8.3 Conformational Analysis of Substituted Perhydro-1,2-oxazolo[3,2-c][1,4]oxazines

The variable temperature ^{13}C NMR spectra were recorded on a Varian XL-200 NMR spectrometer, operating in the Fourier transform mode, with digital resolution of 0.31 Hz at 50.3 MHz. The investigated oxazines (**201**) were studied as 50 mg/ml solution in $CDCl_3$ with TMS as internal standard. The spectra were obtained in the usual way with wide band proton decoupling and off-resonance decoupling to determine multiplicities of signals. Temperature control was achieved using the XL-200 temperature controller and calibrated using standard chemical shifts of methanol and glycol for low and high temperatures respectively. The temperatures were accurate to ±0.5°C. ^1H NMR spectra were recorded at 200.05 MHz on the same instrument.

Simulations of exchange-affected ^{13}C NMR spectra were carried out using a computer program,[142] corresponding to a two non-coupled sites exchange with unequal populations. At least three ring carbon resonances were utilized at each temperature, and matching of simulated and experimental spectra was carried out by eye (by superposing calculated spectra over the experimental spectra). The rate constant obtained at each temperature was an average of three calculated values. Simulation of exchange-affected ^1H NMR spectra were carried out by modifying the library two-site exchange program used above. The first-order coupling of the protons is simply assumed as giving overlapping two-site exchanges with same population ratio and equal rates of exchange. The intensity at each point is calculated applying the Hahn, Maxwell,[143] and McConnell (HMM) equation[144] for two-site exchange, for each of the overlapping cases, which are displaced from one another by certain frequencies corresponding to the coupling constant, and then the

intensities were summed to give the band shape at that point. For cases of coupling to 2 and 3 equivalent protons, appropriate intensity ratios were also taken into account. Samples of experimental and calculated spectra done for determination of nitrogen inversion barrier of the studied adducts **(201)** are shown in Figures 19-24. Figure 25 shows the experimental and simulated spectra of the C-2 H signals of dimethyl fumarate adduct **(201i)** done for determination of barrier to chair inversion.

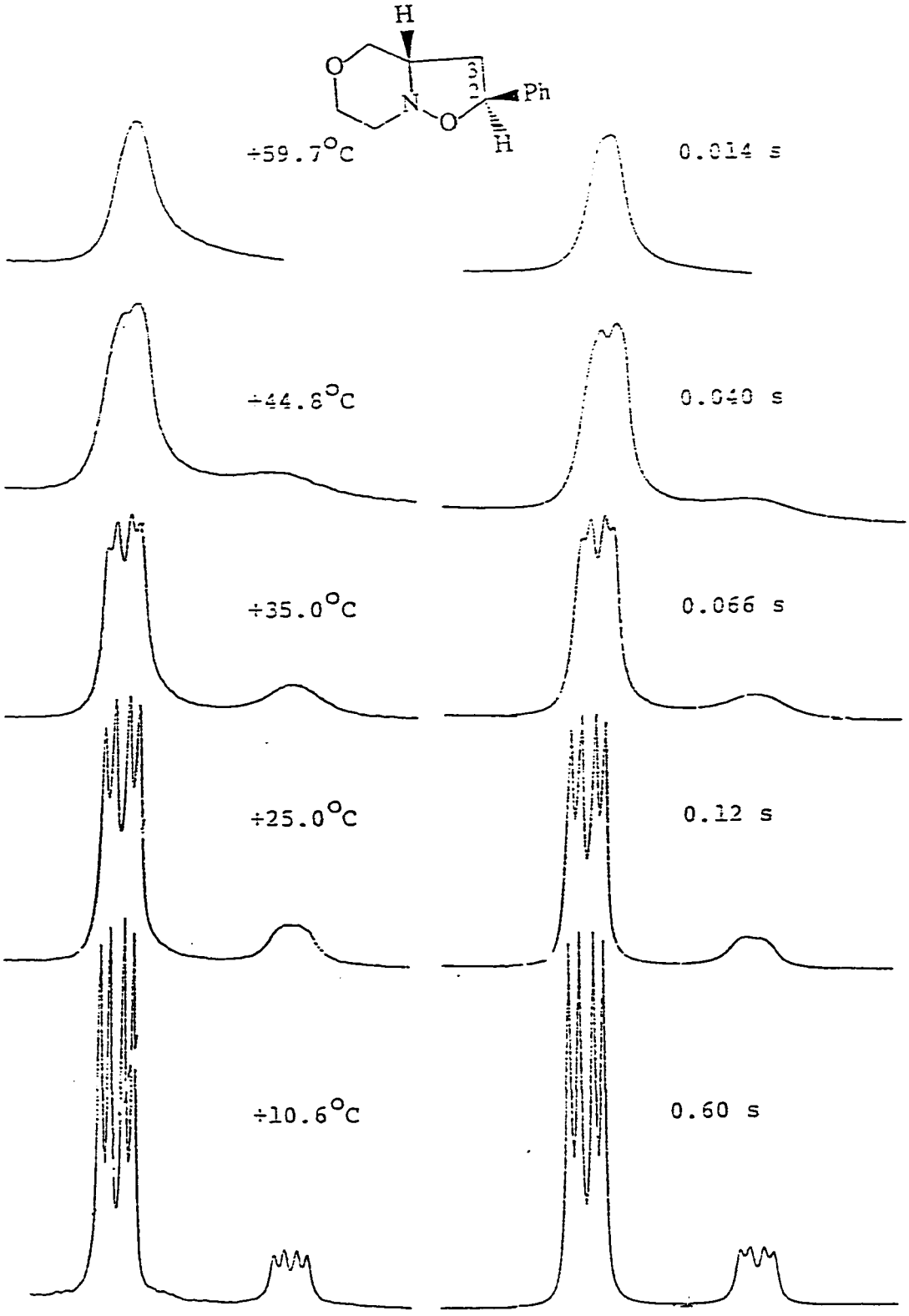


Figure 19 : Experimental and calculated band shapes of the C-2 H signals of styrene adduct (**201a**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

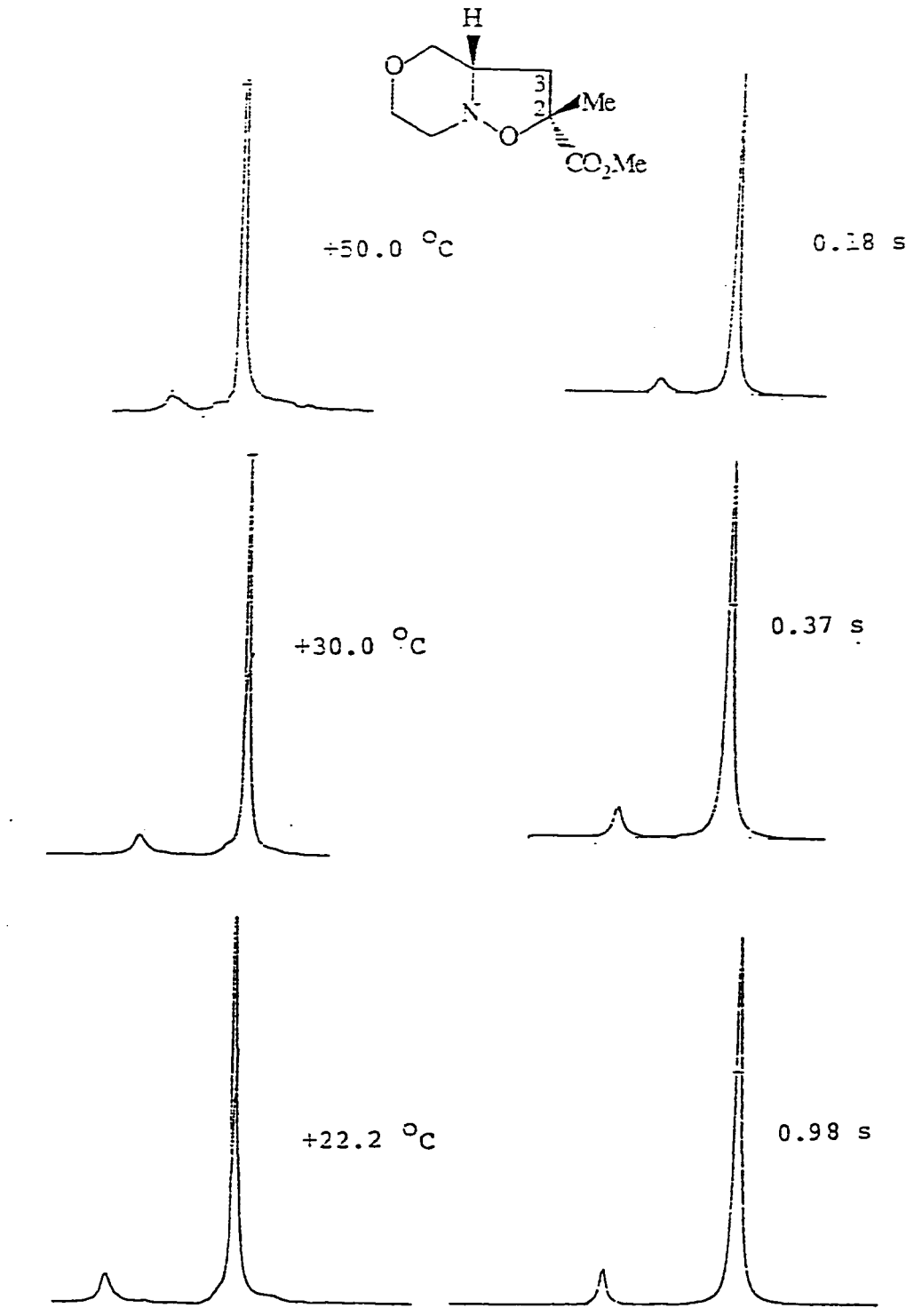


Figure 20 : Experimental and calculated band shapes of the signals of methyl protons of methyl methacrylate adduct (**201f**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

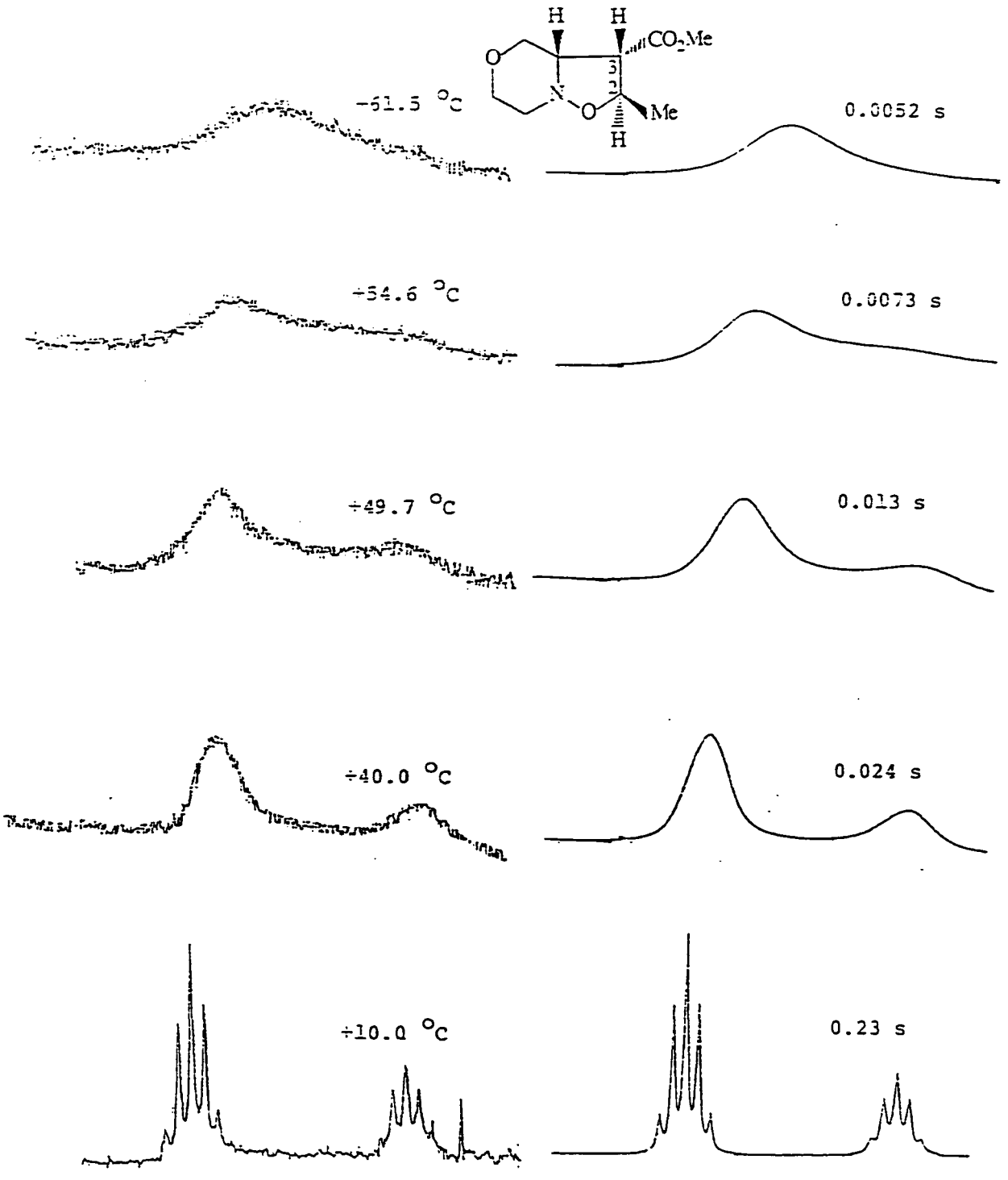


Figure 21 : Experimental and calculated band shapes of the C-2 H signals of methyl crotonate adduct (**201g**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

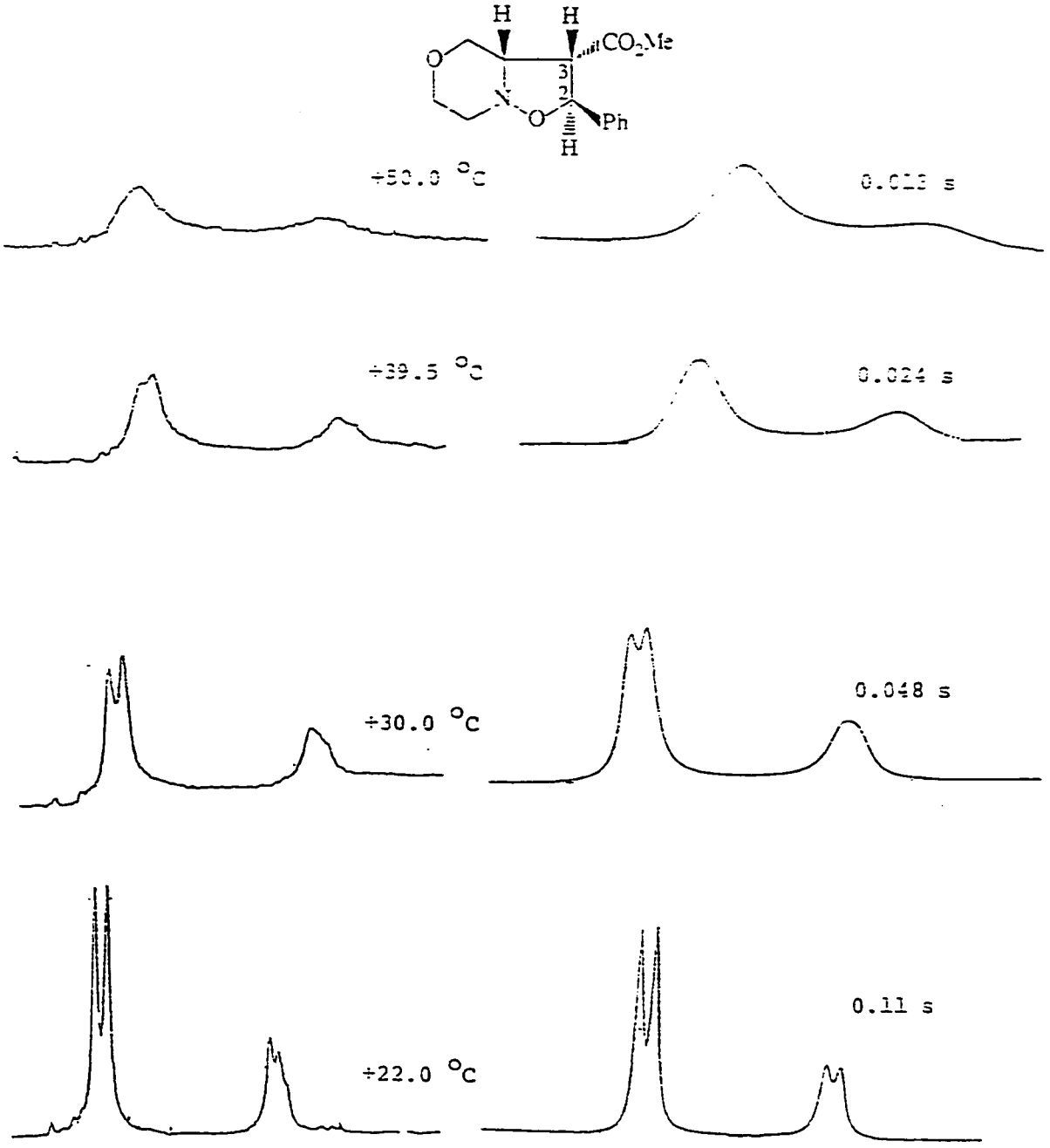


Figure 22 : Experimental and calculated band shapes of the C-2 H signals of methyl cinnamate adduct (**201h**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

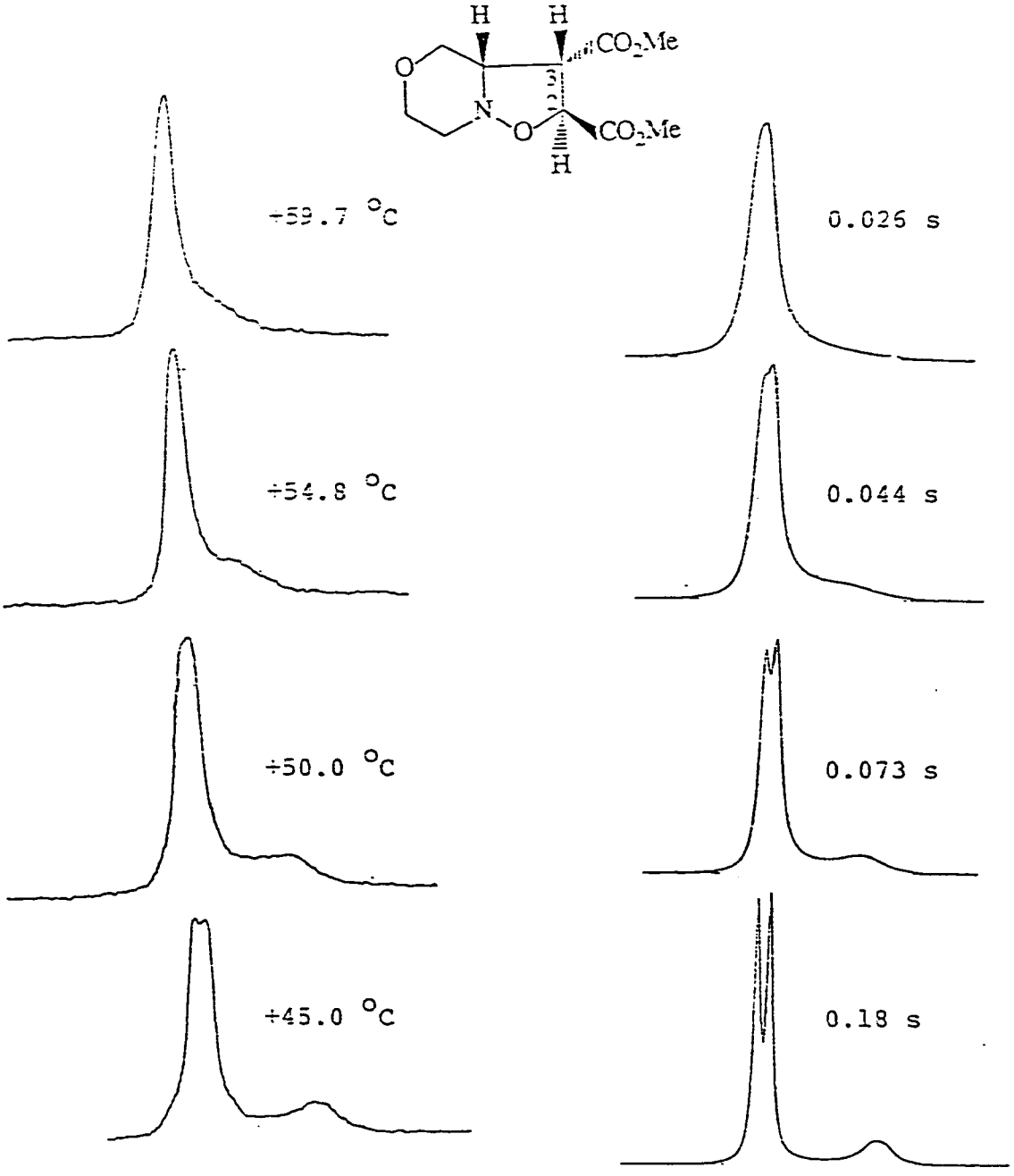


Figure 23 : Experimental and calculated band shapes of the C-2 H signals of dimethyl fumarate adduct (**201i**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

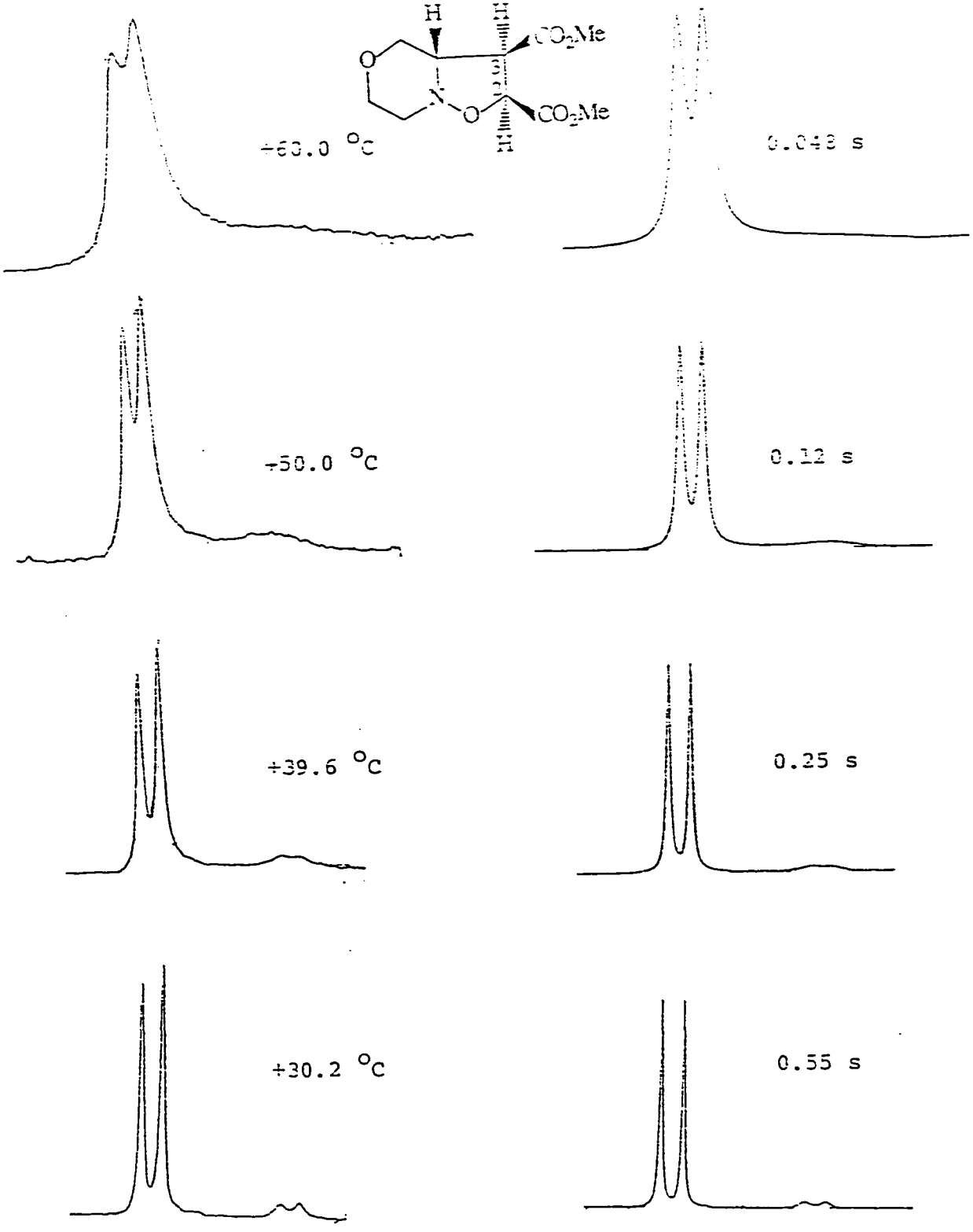


Figure 24 : Experimental and calculated band shapes of the C-2 H signals of dimethyl maleate adduct (**202j**) at different temperatures. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the calculated spectra.

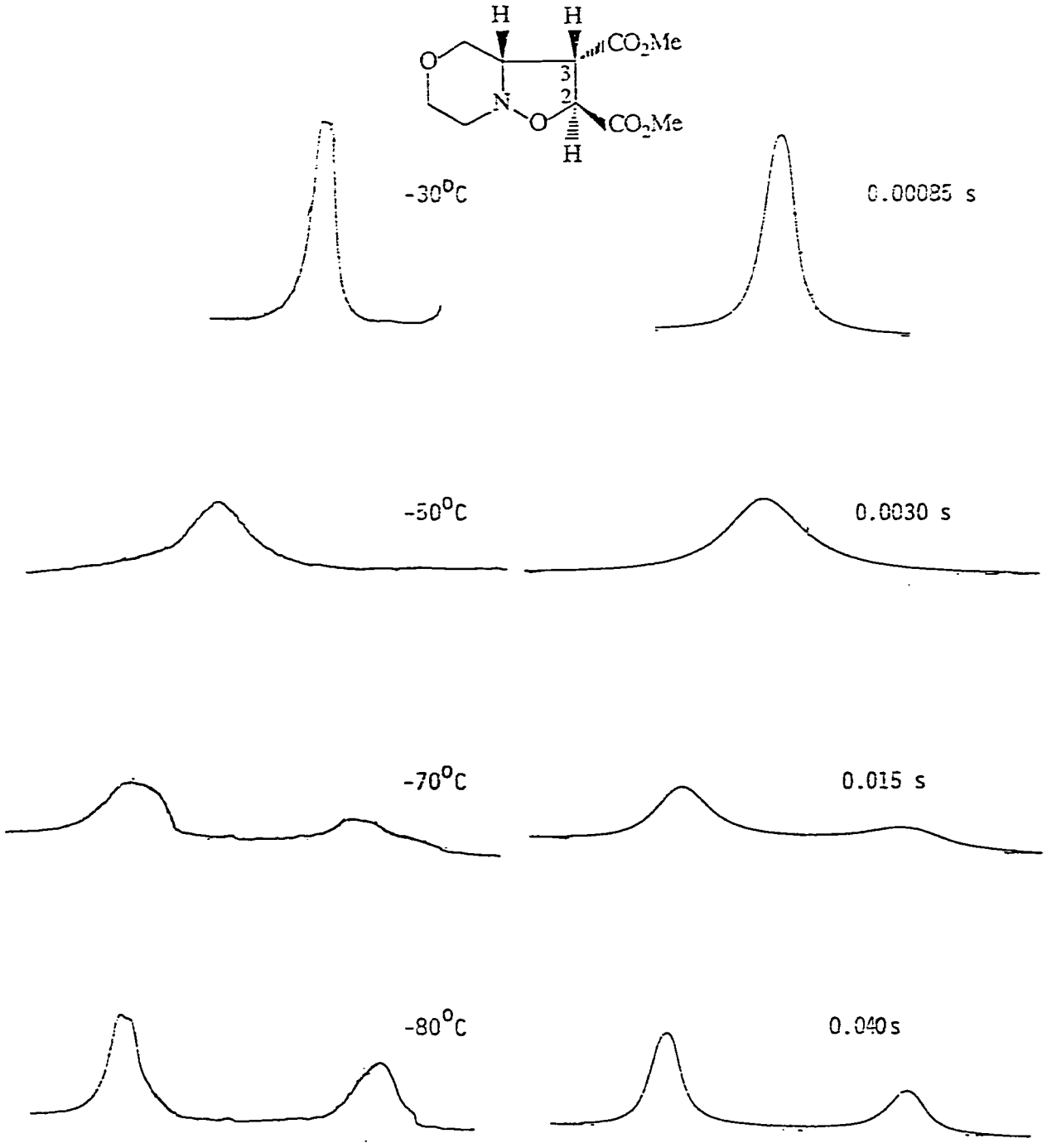


Figure 25 : Experimental and simulated spectra of the C-2 H signals of dimethyl fumarate adduct (**201i**) done for determination of barrier to chair inversion. The temperatures and the corresponding lifetimes of the major specie are indicated respectively on the experimental and the simulated spectra.

8.4 Peracid Induced Ring Opening of the Isoxazolidine

8.4.1 Reaction of the Styrene Adduct (201a) with *m*-CPBA and Cycloaddition Reaction of the Resulting Nitrones with Methyl Methacrylate

8.4.1.1 Ring Opening Reaction in CH_2Cl_2

To a cold (-10°C) solution of the styrene adduct (**201a**) (403 mg, 1.97 mmol) in CH_2Cl_2 (30 ml) was added *m*-CPBA (90% purity, 2.17 mmol). The reaction mixture was stirred at -10°C under N_2 for 30 minutes. The organic layer was washed with 5% $NaHCO_3$ solution (3 x 15 ml). The combined aqueous layer was extracted with dichloromethane (3 x 30 ml). The combined organic layer was dried (Na_2SO_4) and evaporated to give a mixture of (**235a**), (**236a**), and (**237a**) in a respective ratio of 14 : 65 : 21 as determined by the integration of the benzylic protons which appeared at δ 5.10, 5.85 and 5.18, respectively. (In a separate experiment, efforts to separate the bridged hydroxylamine (**236a**) by silica gel chromatography using ethyl acetate as the eluant were unsuccessful. A mixture of the tautomers (**235a**) and (**236a**) were obtained due to equilibration. Extensive decomposition occurred during chromatography).

To the above mixture of nitrones (obtained in almost quantitative yield) in CH_2Cl_2 (10 ml), was added methyl methacrylate (**200f**) (1 ml) and six drops of acetic acid. (It was persumed that the presence of acid would increase the rate of conversion of the bridged hydroxylamine (**236a**) to the less substituted nitrone

(235a)). The reaction mixture was heated at 50°C in a closed vessel for 24 h. After removal of the solvent and excess alkene, the crude reaction mixture was chromatographed. Elution with ethyl acetate afforded the adduct (238) as white crystals (396 mg, 62.8%); $\upsilon_{max.}$ (KBr) 3356, 3063, 3033, 2977, 2964, 2943, 2920, 2910, 1749, 1463, 1450, 1438, 1287, 1259, 1241, 1220, 1136, 1118, 1091, 1023, 1004, 912, 856, 768, 748, 738, and 796 cm^{-1}; δ_H at 20°C : 1.73 (2H, m), 1.57 (3H, s), 2.14 (1H, dd, J 6.0, 12.0 Hz), 2.90 (1H, t, J 12.0 Hz), 3.00-4.15 (7H, m), 3.80 (3H, s), 5.15 (1H, t, J 7.0 Hz), and 7.30 (5H, m). Continued elution afforded a mixture of diastereomers (239) (58 mg, 9.2%) as a colorless oil. The proton NMR spectra revealed the presence of the following major signals : 1.50 (3H, s), 3.75 (3H, s), 4.95 (1H, m). This was not analyzed further.

Finally, the more substituted nitrone (237a) was eluted with a 5 : 1 ethyl acetate-methanol mixture to give colorless crystals (25 mg, 6%); $\upsilon_{max.}$ (KBr) 3239, 2938, 2881, 2350, 2313, 1634, 1479, 1456, 1438, 1334, 1250, 1170, 1160, 1132, 1107, 1049, 1004, 884, 766, 744, 708, and 624 cm^{-1}; δ_H at 20°C : 2.63 (1H, dd, J 7.5, 14.0 Hz), 3.10 (1H, dd, J 3.5, 14.0 Hz), 3.50-4.33 (6H, m), 5.18 (1H, dd, J 3.5, 7.5 Hz), 6.05 (1H, br), and 7.30 (5H, m).

8.4.1.2 *Ring Opening Reaction in Acetic Acid*

To a solution of the styrene adduct (201a) (453 mg, 2.21 mmol) in acetic acid (8 ml), was added the *m*-CPBA (2.43 mmol). The reaction mixture was stirred at 20°C for 1 h. After removal of acetic acid by a stream of nitrogen, dichloromethane (10 ml) and methyl methacrylate (4 ml) were added to the residue. After heating the reaction mixture at 50°C in a closed vessel for 24 h, solvent and excess methyl methacrylate were removed. The residual mixture was taken up in

CH_2Cl_2 (30 ml) and washed with 5% $NaHCO_3$ solution (3 x 15 ml) to remove *m*-chloroperbenzoic acid. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give the crude adducts **(238)**, **(239)**, and the unreacted nitrone **(237a)**. The mixture was separated by chromatography as described above (under ***(8.4.1.1)***) to give the isomers **(238)**, **(239)** (37%) and **(237a)** (48%). (In a separate experiment, the ring opening reaction was run in acetic acid and the nitrone mixture **(235a)**, **(236a)**, and **(237a)** was isolated following procedure in the previous *m*-CPBA reaction in CH_2Cl_2 solvent. As before, the integration of the benzylic proton signals gave the composition of the nitrone mixture *(see Table 6)*).

8.4.2 Reduction of the Nitrone Mixture (235a), (236a), (237a) with Sodium Borohydride and Mercury(II) Oxide Oxidation of the Resulting Hydroxylamines (241) and (242)

8.4.2.1 Preparation of the Nitrone Mixture and Reduction with $NaBH_4$

To a solution of the adduct **(201a)** (205 mg, 1.0 mmol) in methanol (15 ml) was added *m*-CPBA (1.10 mmol) at 0°C. After stirring the reaction mixture at 0°C for 30 minutes, excess sodium borohydride (200 mg, 5.3 mmol) was added. Stirring was continued at 20°C for 1 h. After removal of methanol by a stream of N_2, the residual mixture was taken up in 25 ml of 10% HCl solution. The acid layer was washed with ether (3 x 15 ml) to remove *m*-CPBA. The aqueous layer

was saturated with anhydrous K_2CO_3 and extracted with CH_2Cl_2 (3 x 25 ml). The organic layer was dried (Na_2SO_4) and evaporated. The resultant residue was purified by chromatography using ether as the eluant to give a non-separable mixture of hydroxylamines **(241)** and (242) as white solid (190 mg, 85%), m.p. 124-126°C; $\upsilon_{max.}$ (KBr) 3275, 2900, 2840, 1490, 1445, 1415, 1100, 1045, 977, 933, 838, 760, and 695 cm^{-1};.δ_H at 20°C (80 MHz) : 1.53-2.38 (2H, m), 2.55-4.16 (7H, m), 4.57-5.09 (3H, br), 4.98 (1H, dd, J 4.0, 8.0 Hz), 7.12-7.48 (5H, m).

8.4.2.2 Mercury(II) Oxide Oxidation of the Hydroxylamines Mixture (241) and (242)

To a solution of the hydroxylamines **(241)** and **(242)** (50 mg) in dichloromethane (3 ml) at 0°C, was added excess yellow mercury(II) oxide (250 mg). The reaction mixture was stirred for 30 minutes during which the yellow mercury(II) oxide turned to grayish precipitate. Filtering the reaction mixture through a small bed of $MgSO_4$ and evaporation of the resultant solution afforded the mixture of nitrones **(235a)**, **(243a)**, and **(237a)** (47 mg) as a colorless liquid. Initially, the proton NMR spectrum failed to reveal the presence of the tautomer **(236a)**. However, the tautomer was present to the extent of approximate 5% after 2 h. After 48 h, complete equilibration took place and it accounted for 31% of the total yield. The benzylic protons of **(235a)**, **(236a)**, **(237a)**, and **(243a)** appeared, respectively, at δ 5.10 (J 4.0, 8.0 Hz), 5.85 (J 4.0, 12.0 Hz), 4.93 (J 3.0, 10.0 Hz), and 5.10 (J 4.0, 8.0 Hz). The integration of these signals revealed the presence of the isomers **(235a)**, **(236a)**, **(237a)**, and **(243a)** in a respective ratio of 6 : 31 : 56 : 7.

8.4.3 Reaction of the Allyl Alcohol Adduct (201b) with *m*-CPBA and Cycloaddition Reaction of the Resulting Nitrones (235b, 236b, 237b) with Styrene

8.4.3.1 Ring Opening in CH_2Cl_2

To a solution of the adduct **(201b)** (392 mg, 2.46 mmol) in CH_2Cl_2 (30 ml) at -10 °C, was added *m*-CPBA (535 mg, 3.10 mmol). The reaction was over within 30 minutes at -10°C as indicated by TLC (ethyl acetate). However, the resulting nitrone mixture **(235b), (236b), (237b)** was not soluble in CH_2Cl_2 due to its very polar nature. It deposited on the walls of the flask. Addition of methanol (5 ml) made the reaction mixture homogeneous. To this was added styrene (5 ml) and the reaction mixture was heated at 50°C in a closed vessel for 24 h. After removal of the solvents and excess styrene, the crude residue was taken up in water (10 ml) and washed with CH_2Cl_2 (4 x 20 ml). The unreacted more substituted nitrone **(237b)** remained in the aqueous layer and the organic layer contained the adduct **(240)** and *m*-CPBA.

Organic Layer : The organic layer was stripped of the solvent and the residue was taken up in 20 ml of 10% HCl solution. The aqueous acid layer was washed with ether (3 x 20 ml) to remove the *m*-CPBA. The aqueous layer was made basic and saturated with anhydrous K_2CO_3. Extraction with CH_2Cl_2 (3 x 20 ml) followed by drying (Na_2SO_4) and removal of the solvent afforded the clean adduct **(240)** as a faint liquid (450 mg, 64.5%).

Aqueous Layer : The water was removed under vacuum to give a clean yellow residue which contained the nitrone (**237b**) along with several minor products.

8.4.3.2 *Ring Opening in Acetic Acid*

Oxidation of the adduct (**201b**) was carried out in acetic acid with *m*-CPBA using the procedure described for the similar reaction of the adduct (**201a**). Acetic acid was removed with a gentle stream of nitrogen and the residual mixture was reacted with styrene. The remaining procedure is same as described above under *(8.4.3.1)*. The adduct (**240**) was obtained in 24% yield.

Aqueous Layer : As described above under *(8.4.3.1)*, the aqueous layer afforded the unreacted nitrone (**237b**).

8.5 Synthesis of Some Heterocyclic Nitrones

8.5.1 2-Oxo-5,6-dihydro-1,4-oxazine 4-oxide (247)

To a freshly prepared nitrone (**19**) (10 mmol) in methanol, was added SeO_2 (1.24 g, 11.2 mmol). The reaction mixture was stirred at room temperature for 48 h. (In a separate experiment, oxidation of the nitrone (**19**) with SeO_2 was carried out in methanol under reflux (80°C)). Reaction progress was monitored by frequent checking of TLC (silica gel, ethyl acetate-methanol). After the elapsed time, the red-brown mixture was mixed with silica gel and chromatographed using ethyl acetate as eluant. In the two experiments, TLC (silica gel, ethyl acetate) revealed formation of several products with no well defined TLC spots. We could not identify the products from NMR spectroscopy.

8.5.2 2-Morpholinone (254)

We attempted to synthesize 2-morpholinone (**254**) which would then be converted into the desired ketonitrone (**247**). Ethyl bromoacetate (**253**) (8.02 g, 48.0 mmol) was mixed with 5.86 g (96.0 mmol) of ethanolamine (**252**) . The reaction was exothermic. After 30 hours at room temperature, the highly sticky yellowish reaction mixture was washed with 7 ml of a saturated solution of K_2CO_3, and extracted with CH_2Cl_2 (6 x 20 ml). The organic layer was dried (Na_2SO_4) and evaporated. The reaction afforded 3-morpholinone (**255**) in low yield (189 mg, 4%), δ_H at 20°C (80 MHz) : 2.97 (1H, broad singlet), 3.48 (2H, t), 3.72 (2H, triplet of doublets), and 4.07 (2H, s).

Similar results were obtained under various experimental conditions. In a second experiment, ethyl bromoacetate (6.07 g, 36.3 mmol) was added dropwise to precooled (0.0°C) ethanolamine (4.83 g, 79.0 mmol). The addition was carried

out over a period of 2.3 h maintaining the temperature below 30°C. Similar work up as above afforded (255) in 6.8% yield. Same procedure was repeated with ethanolamine and ethyl bromoacetate in a respective mmol ratio of 4 : 1. However, the reaction mixture was kept in refrigerator at 2-5°C for 5 days. To the sticky mixture which was insoluble in ether, water was added , and then extracted with CH_2Cl_2. Again, NMR spectra indicated formation of (255).

In a fourth trial, 2.30 g, (37.7 mmol) of ethanolamine was added to 5.8 ml of cold concentrated sulfuric acid (0.0°C). To this highly viscous acidic mixture, was added ethyl bromoacetate (5.90 g, 35.3 mmol). The reaction mixture was then brought to room temperature and stirred overnight. After the elapsed time, the mixture was added to a K_2CO_3-ice mixture, and filtered. Extraction of the filtrate with CH_2Cl_2 afforded 421.7 mg (11.8%) of (255).

To a solution of ethanolamine (2.15 g, 35.2 mmol) in concentrated H_2SO_4 (5.6 ml) at 0.0°C, was added 3.38 g (35.7 mmol) of monochloroacetic acid (256). After stirring the reaction mixture overnight at room temperature, it was added to ice-K_2CO_3 mixture. The aqueous solution was then extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated with a stream of N_2 to give (255) (272.5 mg, 7.65% yield).

The amino group of ethanolamine (252) was blocked as HCl salt. Dry HCl was bubbled under dry condition into a solution of ethanolamine (1.72 g, 28.2 mmol) in dry CH_2Cl_2 (30 ml). To the prepared salt (257), was added 3.20 g (28.3 mmol) of chloroacetylchloride under N_2. The reaction mixture was kept over a week stirring at 45°C under N_2. After removal of the solvent by a stream of N_2, the white solid residue was made basic with a solution of 10% K_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. NMR spectroscopy showed that the isolated product was 3-morpholinone (255).

Jones reagent (16.6 mmol) was dropwise added to a solution of 651 mg (6.20 mmol) of diethanolamine (**258**) in acetone (5 ml). After stirring for 40 min at room temperature, the reaction mixture was extracted with CH_2Cl_2 (4 x 30 ml). The organic layer was evaporated by a stream of nitrogen. It was anticipated that diethanolamine (**258**) on oxidation should afford the intermediate hemiacetal (**259**) which should give the compound (**254**) on further oxidation. However, NMR spectrum of the reaction product (148 mg) was very complicated.

8.5.3 Methyl benzilate (261)

Benzil (**260**) was converted into methyl benzilate (**261**) by two methods. In one method, benzilic acid was first prepared via addition of benzil (50.0 g, 237.8 mmol) in portions to a solution of KOH (1.41 mol) in 100 ml distilled H_2O. The mixture was stirred at 86-92°C for 8.5 h, during which additional 90 ml of distilled water was added. After the elapsed time, the mixture was diluted with 450 ml distilled water and kept in refrigerator overnight. Thereafter, the unreacted benzil (15.8 g) was removed by filtration. The filtrate was made acidic with 150 ml of diluted H_2SO_4 ($3H_2O$: $1H_2SO_4$). Then, the benzilic acid was filtered off, washed with H_2O and dried (44 g, m.p. 149-152°C). From the recently prepared benzilic acid, 5.001 g (21.91 mmol) was dissolved in methanol (50 ml) and cooled in ice bath. To this solution, 40 ml of concentrated H_2SO_4 was added in small portions while maintaining the low temperature. The mixture became pink and was stirred at room temperature for 1 day. After the elapsed time, the pink solution was slowly damped into ice (350 ml) and extracted with ether. The organic layer was then washed with 10% $NaHCO_3$ and dried. Crystallization from hexane-ether afforded methyl benzilate (**261**), m.p. 70-72°C, δ_H at 20°C : 3.17 (3H, s), 3.88 (1H, s), and 7.20-7.50 (10H, m).

In a second experiment, methyl benzilate (**261**) was prepared through rearrangement of benzil and sodium methoxide in methanol solution. Benzil (50 g, 237.8 mmol) was added to a freshly prepared sodium methoxide (470 mmol) in 1000 ml of methanol (dried by distillation from magnesium methoxide). The reaction mixture was refluxed for 2 h and then stirred at room temperature for one night under dry conditions. After the elapsed time, solvent was removed with a stream of nitrogen. Ice was then added to the purple residue, and the solid product was filtered off and washed with H_2O. After several recrystallization, white needle crystals of (**261**) were separated (15.7 g), m.p. 71-73°C (CH_2Cl_2-hexane); δ_H at 22.6°C (200 MHz) : 3.88 (3H, s), 4.25 (1H, s), and 7.32-7.58 (10H, m).

8.5.4 Methyl α-bromo-α,α–diphenylacetate (262)

Methyl benzilate (15.662 g, 64.65 mmol) prepared above was dissolved completely in 100 ml of dry benzene. To this ester solution, was added phosphorous tribromide (35.4 g, 131 mmol). After being stirred and refluxed for 8 hours under moisture-free condition, the reaction mixture was left to stand over night at room temperature. Then, the mixture was poured into 350 ml of ice and the benzene layer was separated and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The product isolated (**262**) was then crystallized from hexane (12.5 g), m.p. 37-39°C, δ_H at 20°C (80 MHz) : 3.82 (3H, s), and 7.23-7.48 (10H, m).

8.5.5 2-Oxo-3,3-diphenylmorpholine (263)

In attempts to synthesize (**263**), methyl α-bromo-α,α-diphenylacetate (**262**) (4.38 g, 14.4 mmol) was added in small portions to 3.51 g (57.4 mmol) of ethanolamine and was stirred while maintaining the room temperature. The mixture

was then cautiously warmed up to 40°C until the solution was complete and then was maintained at 2-4°C for 3 days. The crystals formed were filtered and washed with cold methanol. These crystals were then dissolved in water and extracted with CH_2Cl_2. The aqueous layer was made basic with $NaHCO_3$ and then extracted with CH_2Cl_2. Evaporation of the organic layer afforded (**264**) which was soluble in acetone but insoluble in H_2O or cold CH_2Cl_2, m.p. 142-144°C (methanol-H_2O); $\upsilon_{max.}$ (KBr) 3320, 3272, 2922, 2875, 1645. 1519, 1493, 1488, 1455, 1444, 1376, 1345, 1319, 1304, 1225, 1127, 1068, 1052, 949, 920, 888, 833, 778, 724, and 703 cm^{-1}; δ_H at 20°C (80 MHz) : 1.38-1.85 (2H, br), 2.33 (4H, t), 3.43 (2H, m), 3.65 (4H, m), and 7.10-7.52 (10H, m).

A portion of (**264**) (205 mg) in 20 ml of dry benzene was refluxed for 4 h (95°C). TLC experiments did not indicate any progress. Therefore, 6 drops of concentrated H_2SO_4 were added and the reaction mixture was further refluxed for 3.5 h. Then 150 ml of ice was added to the reaction mixture and neutralized with 10% $NaHCO_3$ solution. Again, TLC test of the dried organic layer (Na_2SO_4) did not indicate any progress of the reaction.

Another portion of (**264**) (205 mg) was dissolved in 6 ml of methanolic HCl (1 : 1). After 48 hours of standing at room temperature, the reaction mixture was made basic with 30 ml of 10% K_2CO_3 solution, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated with a stream of N_2. The NMR spectrum revealed mostly the presence of unreacted materials along with other unidentified products.

A third portion of (**264**) (101 mg) was added to 1 ml of concentrated H_2SO_4 and stirred at room temperature for 24 h. After the elapsed time, the reaction mixture was mixed with ice, neutralized with 10% $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4). Also here the NMR

spectrum revealed mostly the presence of unreacted materials along with other unidentified products.

8.5.6 N-(Diphenylmethyl)-N-hydroxy-3-amino-1-propanol (270)

Chlorodiphenylmethane (**268**) (4 g, 20 mmol) was stirred with 3-amino-1-propanol (**267**) (15.0 g, 200 mmol) for 3.5 h at room temperature and for 15 min at 50°C. The reaction mixture was kept in refrigerator over 2 days. Then, the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, neutralized with Na_2CO_3, dried (Na_2SO_4), and evaporated. Fractional distillation of the product afforded (**269**) at 160°C and 0.10 millibar (2.77 g, 57% yield), δ_H at 20°C (80 MHz) : 1.72 (2H, quint, J4.5 Hz), 2.8 (2H, t, J4.5 Hz), 3.0 (2H, b), 3.75 (2H, t, J4.5 Hz), 4.80 (1H, s), and 7.1-7.5 (10H, m). *m*-Chloroperbenzoic acid (645 mg, 3.75 mmol) was added in portions to a solution of (**269**) (241 mg, 1 mmol) in 23 ml of CH_2Cl_2 at 0.0°C. TLC was used to monitor the reaction progress. After 50 minutes of stirring, the reaction mixture was washed with a saturated solution of $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Chromatographic purification of the product residue with 1 : 1 hexane-ethyl acetate as eluant afforded (**270**) in 80% yield, m.p 132-133°C, $\upsilon_{max.}$ (KBr) 3250, 2847, 1595, 1490, 1448, 1420, 1365, 1295, 1060, 1028, 963, 920, 812, 745, and 700 cm^{-1}; δ_H at 20°C : 1.45-2.08 (2H, m), 2.63-2.90 (2H, m), 3.23-4.10 (3H, m), 4.73 (1H, d), 6.20 (1H, s), and 6.83-7.60 (10H, m).

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