The synthesis and reactions of alkenyl -isoxazoles and -isoazolines

Jaki Tout

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I saw beyond the blackboard and the bare wall,
Beyond the abstract, confining symbols
A rough and simple cliff, ascending in steep tiers
To fade in mist-bound mystery.

I travelled time and space to feel again
The grip of vibram soles on weathered rock,
The trustful uplift of the body
On holds made safe by balance
Held in fingertip subjection;
I heard rope-rustle on the shelving slabs,
Friends' laughter and the headstrong wind;
I smelt the dew-damp heather, and
The gentle scent of turf and moss;
I saw the elemental rock,
Flecked with colour, scarped and wrinkled.
Cheerfully give way to skill;
Sudden sunshine on the crags,
And other ranges, distant-blue,
Guarding shadowed valleys;
I tasted joy, more wholesome sweet
Than pleasure and not cloying.

I knew the freedom of fellowship
Knit with stronger bonds than nylon.

I offered humble thanks, and quietly
Came back to the Lecture Room.

Martin Berry
Declaration

I declare that this thesis has been composed by myself and that it describes my own work except where specifically stated in the text. The work was carried out from October 1989 to January 1993 at the University of Edinburgh under the supervision of Dr R.M. Paton.
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I would like express my gratitude to Dr Mike Paton, my project supervisor, for his constant support, advice and encouragement.

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Post Graduate Lectures

The following lectures were attended during 1989-1992:
Departmental seminars, three years attendance.
Free radicals (Dr I. Gosney), 5 lectures.
Medicinal chemistry (Prof. R. Baker and Dr P. Leeson, MSD), 10 lectures.
Polymer chemistry (Dr R. M. Paton), 5 lectures.
Modern synthetic methods in organic chemistry (Dr G. Tennant), 5 lectures.
Reactive intermediates (Dr J. T. Sharp), 5 lectures.
Pharmacology of Zoladex (Dr Furr), 5 lectures.
Departmental German course (1990).
Abstract

Four vinyl-isoxazoles and -2-isoxazolines have been synthesised as potential monomers for polymerisation studies. 5-Phenyl-3-vinylisoxazole was prepared in 38% overall yield by a sequence involving cycloaddition of ethoxycarbonylfornonitrile oxide to phenylacetylene and then reduction of the resulting 3-carbethoxyisoxazole to the aldehyde using di-isobutyaluminium hydride. In the final stage Wittig olefination of the formyl-isoxazole afforded the target compound. 5-Phenyl-3-vinylisoxazole (17%) and 5-phenyl-3-vinyl-2-isoxazoline (26%) were synthesised similarly from ethyl propiolate & benzohydroximoyl chloride, and styrene & ethyl chlorooximidoacetate, respectively. 3-Phenyl-5-vinyl-2-isoxazoline (84%) was obtained in one step by cycloaddition of benzonitrile oxide to butadiene.

An alternative and more direct approach to 3-vinylisoxazolines has been developed based on the cycloaddition reactions of acrylonitrile oxide (ANO), an α,β-unsaturated nitrile oxide. ANO was generated, under modified Mukaiyama conditions, by the dehydration of 1-nitropropene with phenyl isocyanate in the presence of catalytic quantities of triethylamine. ANO was trapped by a variety of olefinic dipolarophiles as its 1,3-dipolar cycloadducts in yields ranging from 17% to 71%. Under similar conditions phenylacetylene reacted in low yield (12%). The series of α,β-unsaturated nitrile oxides was extended to include methacrylonitrile oxide and but-2-enonitrile oxide.

The dipolarophilic reactivity series was determined by competition experiments. Six dipolarophiles were investigated: styrene, α-methylstyrene, methyl acrylate, methyl vinyl ketone and three substituted styrenes (p-OMe, p-Cl and m-NO2). 13C and 1H NMR spectroscopy were used to identify the products and determine the adduct ratio. The results indicated methyl acrylate to be the most reactive dipolarophile. The 1,1-disubstitution in α-methylstyrene effectively lowered its reactivity due to steric effects.

Nitrile oxide chemistry was also utilised to prepare 3-vinylisoxazole. Cycloaddition of ANO to norbornadiene afforded a mixture of exo and endo 1:1 adducts and subsequent thermolysis under FVP conditions resulted in retro Diels-Alder fragmentation to furnish the desired product. The synthesis of 3-phenylisoxazole from benzonitrile oxide and norbornadiene was chosen as a model to optimise reaction conditions.

Preliminary polymerisation experiments were conducted using 5-phenyl-3-vinylisoxazole. Using free radical conditions it underwent facile homopolymerisation and copolymerisation with styrene, methyl methacrylate and vinyl
acetate. The corresponding vinylisoxazolines failed to polymerise under similar conditions. However, heterocycles prepared from benzonitrile oxide and m- and p-divinylbenzene did polymerise thus incorporating isoxazolines as pendant groups. The structures of the polymers were determined by elemental analysis, $^{13}$C NMR spectroscopy and mass spectrometry and selected samples were also analysed by gel permeation chromatography.
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1. INTRODUCTION

1.1 Foreword

This thesis is concerned with the synthesis of alkenyl isoxazoles and isoxazolines suitable for subsequent polymerisation. The alkenyl heterocycles were prepared using nitrile oxide cycloaddition chemistry. 1,3-Dipolar cycloaddition reactions have been studied extensively for the construction of 5-membered heterocycles but, in contrast, there has been limited application in polymer chemistry.

The field of 1,3-dipolar cycloaddition chemistry is too large to be reviewed comprehensively in the introduction section. There is, in any case, an excellent monograph on the subject edited by Padwa entitled "1,3-Dipolar Cycloaddition Chemistry". However, as nitrile oxides are central to this thesis the salient features of their chemistry are discussed. A fuller account is available in Grundmann and Grünanger's text "The Nitrile Oxides" and Torssell's "Nitrile oxides, Nitrones and Nitronates in Organic Synthesis".

There is no current published review on 1,3-dipoles in polymer chemistry and thus the introduction includes a detailed account. In this section four topics are covered: the synthesis of polyisoxazoles and poly(-2-isoxazolines); the modification of polymers via 1,3-dipolar cycloaddition; the generation and reactions of polymers containing 1,3-dipole precursors; and finally an account of vinyl-isoxazoles and 2-isoxazolines as potential monomers.
1.2 1,3-Dipoles

The category of compounds known as 1,3-dipoles was first classified by Huisgen\(^4\) in 1958. They are defined as a species which can be represented by zwitterionic octet structures and undergoes 1,3-cycloadditions to a multiple bond system, the dipolarophile. The role of dipolarophile can be filled by virtually any double or triple bond.

A feature shared by all 1,3-dipoles is an allyl anion type π system, that is four electrons in three parallel atomic π orbitals. In contrast to the allyl anion, where the middle carbon atom is free of formal charge, 1,3-dipoles contain an onium centre \(b\) whose charge compensates the negative charge distributed in the two all-octet structure over the termini \(a\) and \(c\). Thus the overall system can be regarded as a heteroallyl anion, which bears no net charge. Whereas the terminal centres of the allyl anion are always nucleophilic, those of the 1,3-dipoles are both nucleophilic and electrophilic. This ambivalence of the 1,3-dipole is illustrated by the sextet structures, and it is the key to understanding the reactivity (Scheme 1);

![Scheme 1](image)

The 1,3-dipole may or may not contain an additional π bond in the plane perpendicular to the allyl anion molecular orbital. The occurrence of this extra π bond makes 1,3-dipoles of the propargyl-allenyl type linear; 1,3-dipoles of the allyl type are bent and do not contain an orthogonal π bond. This simplified representation of 1,3-dipoles is shown in Scheme 2.
Table 1 lists some of the more common 1,3-dipoles with their octet structures.

1.2.1 1,3-Dipolar cycloaddition reactions

A 1,3-dipolar cycloaddition reaction is the coupling of a 1,3-dipole with a multiple bond system, the dipolarophile, to form a 5-membered heterocyclic ring (Scheme 3). There are certain characteristic features of the 1,3-dipolar cycloadditions irrespective of the structures of the reactants. In each case the reaction proceeds via a two plane complex (Figure 1) in which the reactants interact through their π-orbitals in a π₄s + π₂s process. The formal charges are lost in the [3+2 → 5] cycloaddition.
Table 1  Examples of typical 1,3-dipoles

Propargyl-Allenyl Type

<table>
<thead>
<tr>
<th>Nitrilium Betaines</th>
<th>Diazonium Betaines</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC(\equiv N)—CR(_2)</td>
<td>N(\equiv N)—CR(_2)</td>
</tr>
<tr>
<td>RC(\equiv N)—NR</td>
<td>N(\equiv N)—NR</td>
</tr>
<tr>
<td>RC(\equiv N)—O</td>
<td>N(\equiv N)—O</td>
</tr>
<tr>
<td>RC(\equiv N)—S</td>
<td></td>
</tr>
</tbody>
</table>

Allyl Type

<table>
<thead>
<tr>
<th>R(_2)C(\equiv NR)—CR(_2)</th>
<th>R(_2)C(\equiv O)—CR(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azomethine Ylides</td>
<td>Carbonyl Ylides</td>
</tr>
<tr>
<td>R(_2)C(\equiv NR)—NR</td>
<td>R(_2)C(\equiv O)—NR</td>
</tr>
<tr>
<td>Azomethine Imines</td>
<td>Carbonyl Imines</td>
</tr>
<tr>
<td>R(_2)C(\equiv NR)—O</td>
<td>R(_2)C(\equiv O)—O</td>
</tr>
<tr>
<td>Nitrones</td>
<td>Carbonyl Oxides</td>
</tr>
<tr>
<td>R(_2)N(\equiv NR)—NR</td>
<td>RN(\equiv O)—NR</td>
</tr>
<tr>
<td>Azimines</td>
<td>Nitrosimines</td>
</tr>
<tr>
<td>RN(\equiv NR)—O</td>
<td>RN(\equiv O)—O</td>
</tr>
<tr>
<td>Azoxy Compounds</td>
<td>Nitrosoxides</td>
</tr>
<tr>
<td>O(\equiv NR)—O</td>
<td>O(\equiv O)—O</td>
</tr>
<tr>
<td>Nitro Compounds</td>
<td>Ozone</td>
</tr>
</tbody>
</table>
Cycloaddition can occur with a variety of multiple bond systems: alkenes, alkynes, activated carbonyls, thiocarbonyls, aldimines and ketimines, nitriles and various other unsaturated systems. Thus there is vast scope\textsuperscript{1,2,5} for the preparation of 5-membered heterocycles, many of which are accessible only with difficulty by other means. The synthetic scope is illustrated using a nitrile oxide as the 1,3-dipole in Scheme 4.

**Scheme 4**

\[
\text{Reagents: } \begin{align*}
    a & : \text{CH}_2=\text{CHR}', \\
    b & : \text{RC}=\text{P}, \\
    c & : \Delta/\text{hv}, \\
    d & : \text{RC}=\text{CR}', \\
    e & : \text{R}'\text{R}''\text{C}=\text{O}, \\
    f & : \text{R}'\text{R}''\text{C}=\text{S}, \\
    g & : \text{R}'\text{N}=\text{CHR}'', \\
    h & : \text{R}'\text{C}=\text{N}.
\end{align*}
\]
1.2.2 Reaction mechanism

The mechanism of 1,3-dipolar cycloaddition has been the subject of much controversy over the past 30 years. There are three mechanisms to consider: the first was proposed by Huisgen and involves a one-step concerted process. (Scheme 5, path a).

The concerted mechanism has found greatest support in the literature due to its compatibility with experimental results. The evidence which favours the concerted mechanism are: the retention of configuration of the reactants, the large negative $\Delta S^\#$ values obtained experimentally and the very small effect that solvent polarity has on the rate of the cycloaddition reaction. Moreover, the 1,3-dipolar cycloaddition obeys the Woodward and Hoffmann selection rules for conservation of orbital symmetry as would be expected for a concerted process. It should be noted that, although the reactions are concerted, the formation of the two new $\sigma$-bonds is usually not perfectly synchronous. Due to the unsymmetrical nature of the reactants the formation of one bond may be more advanced than the other in the transition state.

The second hypothesis is a diradical mechanism which involves a stepwise addition of the dipole to the dipolarophile (Scheme 5, path b). The main supporter of the diradical mechanism has been Firestone, who argued that when the dipole HO and LU interaction are equally dominant this would be the favoured process. Furthermore the stepwise mechanism would also be promoted by incorporating radical stabilisers in the reactants such as allyl groups. Large steric groups that block a two-plane transition state may also disfavour the concerted reaction.

The last and least convincing hypothesis is a stepwise dipolar mechanism which proceeds via a zwitterionic intermediate (Scheme 5, path c); this is not considered likely as the effects of solvent polarity on the reaction rate are small.

The generally accepted view is that a typical 1,3-dipolar cycloaddition is a concerted symmetry-allowed [$\pi^4s + \pi^2s$] reaction.
1.2.3 Frontier molecular orbital theory

Frontier molecular orbital (FMO) theory has been used to rationalise the effect of substituents attached to the 1,3-dipole and the dipolarophile on the reactivity and regioselectivity of 1,3-dipolar cycloaddition reactions. The majority of the work in this field is due to Houk, Bastide and Sustmann. The theory states that the rate of cycloaddition is proportional to the stabilisation energy gained on formation of the transition state, and this in turn is proportional to the square of the area of overlap of the interacting FMOs and inversely proportional to the energy separation ($\Delta E$) of those orbitals. Thus, the smaller the energy gap between the interacting pair of FMOs the greater the energy of stabilisation (Figure 2).
The most elementary case is illustrated in Figure 3 which shows the interaction of the allyl anion frontier orbitals with those of ethylene; this addition is considered the prototype for 1,3-dipolar cycloadditions. The interactions of the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) of the reactants determine the energy of the bonding molecular orbitals and thus effect the rate and nature of the reaction.

The trend is for the HOMO energies to decrease as more electronegative elements are introduced into the dipolar system. The LUMOs also decrease in energy but to a lesser extent and therefore the HOMO energy can be taken as an approximate guide to the stability of the dipole. Substituents which raise dipole HOMO energies (electron-releasing and conjugating groups) and which lower dipolarophile LUMO energies (conjugating and electron-withdrawing groups) will accelerate dipole HOMO controlled reactions but slow down dipole LUMO controlled reactions. Usually, electron-deficient dipolarophiles lead to dipole HOMO
controlled reactions and electron-rich dipolarophiles to dipole LUMO controlled reactions.

Introducing heteroatoms and substituents alters the orbital coefficients, but the overall molecular symmetry is retained and thus the same selection rules apply. Comparison of the relative size of HO/LU and LU/HO interactions led Sustmann to rationalise the observed reactivities and the effect of substituents and to classify 1,3-dipolar cycloadditions into three groups, as illustrated in Figure 4.

Figure 4

1.2.4 Regioselectivity and stereoselectivity

The non-symmetrical nature of 1,3-dipoles and substituted dipolarophiles means that the magnitudes of the coefficients of each molecular orbital are not equal as is the case for the allyl anion and ethylene. Thus a knowledge of orbital coefficients and FMO energies for dipoles and dipolarophiles, many of which have been calculated, allows the dominant interaction to be determined and therefore the regioselectivity of the adduct to be predicted. The regioselectivity of the cycloaddition is often explained by the rule formulated by Fukui which states that the orientation is such that maximum orbital overlap is obtained.

Cycloaddition to monosubstituted alkenes occurs with almost complete regiospecificity, yielding the 5-substituted isoxazolines; this may be illustrated by using nitrile oxides again. (Scheme 6; styrene reacting with benzonitrile oxide). Only in a few cases have the minor 4-substituted regioisomers been isolated in small amounts. One such example involves the cycloaddition of benzonitrile oxide to methyl acrylate (Scheme 6); a mixture of the 5- and 4- substituted isoxazolines are formed in the ratio of 96.4 : 3.6. The union of the unsubstituted end of the dipolarophile with the carbon end of the dipole, where the larger HOMO and LUMO
coefficients, respectively, are located, always favours the formation of the 5-substituted heterocycles. With conjugating and electron-withdrawing substituents (as in methyl acrylate) bonding of the unsubstituted end of the dipolarophile with the oxygen end of the dipole, where the larger LUMO coefficient is located, produces the 4-substituted heterocycle. Alkynes behave similarly, and 5-substituted isoxazoles are usually obtained; alkynes with electron-withdrawing groups have a higher propensity to form 4-substituted heterocycles. Mixtures of isomers are usually obtained with 1,2-disubstituted alkenes and alkynes.

Scheme 6

\[ \text{PhC} \equiv \text{N}^+ - \text{O} \quad \text{CH}_2 \equiv \text{CHCO}_2\text{Me} \rightarrow \begin{array}{c} \text{Ph} \\ \text{N, O} \end{array} \text{Ph} \]

\[ \text{Ph} \equiv \text{CHPh} \]

\[ 100\% \]

The stereoselectivity of 1,3-dipolar cycloaddition reactions is one of the most potent arguments for a concerted mechanism (Section 1.2.2). When 1,3-dipoles combine with 1,2-disubstituted alkenes, the stereochemistry of the dipolarophile is carried through to the heterocyclic adduct (Scheme 7). This is also one of the factors which makes this type of reaction synthetically important for many dipoles.\(^1\)

Scheme 7

\[ + \quad \begin{array}{c} \text{a} \\ \text{b} \\ \text{c} \end{array} \quad + \quad \begin{array}{c} \text{R} \\ \text{R'} \end{array} \rightarrow \begin{array}{c} \text{a} \\ \text{b} \\ \text{c} \end{array} \quad + \quad \begin{array}{c} \text{a} \\ \text{b} \\ \text{c} \end{array} \]

\[ \text{R} \quad \text{R'} \]
1.3 Nitrile Oxides

1.3.1 Introduction

Nitrile oxides have an illustrious history. In 1800 Howard prepared the explosive mercury fulminate. The correct structure of fulminic acid and its salts remained unknown for a long time and was the subject of much speculation. It had to wait for nearly 100 years for its elucidation. In 1899 Ley suggested that fulminic acid was the N-oxide of formonitrile, i.e the parent compound of nitrile oxides. The vast knowledge of the chemistry of nitrile oxides acknowledges particularly the contributions by Wieland in the early 1900's, Quilico and associates in the 1940's, and Huisgen who, in the 1960's, systematized comprehensively 1,3-dipolar reactions and arrived at a better understanding of their mechanism.

Most nitrile oxides are short-lived, reactive species, structurally isomeric with isocyanates and cyanates. The majority, isolated as individuals, have been obtained as crystalline solids, although the lower homologs of the aliphatic series and benzonitrile oxide melt below room temperature. The structures of the parent member of the series, fulminic acid (1: \( R=H \)), and oxalodinitrile oxide 4 are illustrated below, both are explosive and have to be handled with care.

\[
\begin{align*}
\text{R—C} & \equiv \text{N} \equiv \text{O} & \text{R—N} & \equiv \text{C} \equiv \text{O} \\
\text{1} & & \text{2}
\end{align*}
\]

\[
\begin{align*}
\text{R—O—C} & \equiv \text{N} & \text{O}—\text{N} & \equiv \text{C} \equiv \text{C} \equiv \text{N} \equiv \text{O} \\
\text{3} & & \text{4}
\end{align*}
\]

1.3.2 Generation of nitrile oxides

There are two methods of nitrile oxide formation which find widest usage: oxidation of aldoximes via the corresponding hydroximoyl halide (RCX=NOH) and dehydration of primary nitroalkanes. A few other less generally applicable procedures have also been developed and these are briefly mentioned in Section 1.3.2.3. The principle methods for the generation of nitrile oxides are shown in Scheme 8.
Dimerisation to furoxans 5 (1,2,5-oxadiazole-2-oxides) is the characteristic nitrile oxide mode of decay in the absence of a dipolarophile. The furoxan is also frequently obtained as a by-product of cycloaddition reactions and, to minimise their formation, reaction conditions are usually structured to allow slow generation of the intermediate, thus maintaining a low concentration. Nitrile oxides are therefore usually generated in situ in the presence of the appropriate dipolarophile.

1.3.2.1 Oxidation of aldoximes

The oxidation of aldoximes is usually a two step sequence involving initial chlorination to the hydroximoyl chloride followed by dehydrochlorination (Scheme 8, route a and c). In early work chlorination was achieved by treatment of the aldoxime in an inert solvent at low temperatures with chlorine gas. This procedure, although still used, imposes limitations on the nature of the functionality which the aldoxime and ultimately the nitrile oxide can carry. For example, with this methodology the aldoxime cannot possess unsaturation, ketones and some aromatic rings.

Reagents: a; Cl₂, NOCl or NCS, b; Chloramine-T or NaOCl, c; Et₃N or Δ, d; PhNCO, Et₃N.
Several milder and more selective halogenating procedures have since been developed to widen the scope for this route; nitrosyl chloride, sodium hypochlorite and sodium hypobromite. The latter two reagents combine the halogenation and dehydrohalogenation steps and allow sensitive functionality such as double bonds to survive intact.

N-Bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) have both been used to halogenate aldoximes even in the presence of alkenes and methoxylated aromatic rings. A recent development in nitrile oxide cycloaddition chemistry uses Chloramine-T to generate the dipole directly for the aldoxime; this conversion is thought to proceed by chlorination of the oxime followed by base catalysed dehydrochlorination. Lead tetraacetate has been used for the direct conversion of syn-aldoximes to nitrile oxides.

Bases which have been employed for the dehydrochlorination step include sodium carbonate or sodium hydroxide in a two phase system. However, these have now been largely superseded by triethylamine which is usually added slowly and diluted in an organic solvent.

Thermolysis of hydroximoyl halides in an inert solvent has also been used to generate nitrile oxides in low steady state concentrations. This method takes advantage of the equilibrium between hydroximoyl halides and the nitrile oxide and hydrogen halides.

1.3.2.2 Dehydration of primary nitroalkanes

Another significant method involves the dehydration of primary nitro compounds with aryl isocyanates, the Muikaiyama-Hoshino method; this approach is not generally suitable for the isolation of nitrile oxides but is widely used for in situ preparation and trapping of the intermediate nitrile oxide with a suitable reagent. Incompatibility may also result with some functional groups, either in the dipole or dipolarophile, reacting with the isocyanate (e.g. OH and NH). The readily accessible primary nitroalkanes makes this a very important route.

A possible mechanism is depicted in Scheme 9. Triethylamine is only needed in catalytic amounts and starts the reaction sequence by abstracting a proton from the primary nitro compound. The resulting nitronate anion then reacts with the isocyanate to form a transitional short lived intermediate which expels carbon dioxide and aniline to form the nitrile oxide. The aniline by-product is consumed by further isocyanate to afford N,N'-diphenylurea.
1.3.2.3 Other methods of generation

An alternative, but less generally applicable, approach to nitrile oxides is that developed by Shimizu.37,38,39 Nitrile oxides bearing ethoxycarbonyl, aminocarbonyl and alkyl substituents have been generated by thermolysis of the appropriate nitroacetates in refluxing mesitylene. This method has been found to be particularly well-suited to reactions with unreactive cis-1,2-dialkyl substituted alkenes as is present in lipids.39 The proposed mechanism is shown in Scheme 10.
Furoxans, the dimers of nitrile oxides, are themselves thermally labile and have been subjected to thermolysis in refluxing solvents to provide a source of these 1,3-dipoles by cycloreversion.\textsuperscript{40,41,42} The temperature required is dependent on the nature of the substituents but is \textasciitilde{}100-250°C for thermolysis in solution and \textasciitilde{}500°C using flash vacuum pyrolysis (Scheme 11). Although the method is less generally applicable it is useful for the generation of acetonitrile oxide,\textsuperscript{43} and for difunctional nitrile oxides from bicyclic furoxans.\textsuperscript{1}

1.3.3 Cycloaddition reactions

The cycloaddition of nitrile oxides with alkenes and alkynes is a particularly important and versatile synthetic reaction and has been studied extensively.\textsuperscript{44,45} Grundmann and Grünanger\textsuperscript{46} have researched the mechanism in detail and have tabulated all the nitrile oxide cycloadducts synthesised before 1971. Cycloadditions with other unsaturated systems are addressed in Sections 1.3.3.3 and 1.3.3.4.
1.3.3.1 Cycloaddition to alkenes

The most general synthesis of 2-isoxazolines is via the 1,3-dipolar cycloaddition of nitrile oxides to alkenes. The cycloaddition, which occurs with retention of alkene stereochemistry, is slower with highly substituted compounds, while the reactivity is enhanced by conjugation. With the majority of monosubstituted alkenes the addition is almost completely regiospecific and affords 5-substituted 2-isoxazolines; however when the dipolarophile is electron deficient varying amounts of the 4-substituted 2-isoxazoline are also obtained.

Much of the current interest in nitrile oxide/isoxazoline chemistry is directed towards the functionality which is masked by the heterocyclic ring.47,48,49,50 The two most important systems which are available from these rings are γ-hydroxyamines and β-hydroxyketones from which α,β-unsaturated ketones are also accessible (Scheme 12). The isoxazoline ring may be constructed at an early stage in a synthetic pathway, the substituents modified if required, and then unmasked at an appropriate time.

\[ \text{Scheme 12} \]

β-Hydroxy ketones are generated from 2-isoxazolines by catalytic hydrogenolysis (Scheme 13). These reactions are normally carried out in an aqueous methanol mixture with either Raney nickel or palladium on activated charcoal as the hydrogenation catalyst. Boric acid51 now seems to have gained widespread acceptance as the reagent of choice for promoting hydrolysis of the β-hydroxyimine intermediate x.

The reduction of 2-isoxazolines to γ-hydroxyamines can be achieved by treatment with lithium aluminium hydride or by catalytic hydrogenation.52 This conversion, unlike β-hydroxyketone formation, involves a change in the oxidation level of the carbon skeleton, and as a consequence a new chiral centre is generated; thus a pair of diastereomeric γ-hydroxyamines results.
1.3.3.2 Cycloaddition to alkynes

Cycloaddition reactions of nitrile oxides to alkynes afford isoxazoles, the aromatic analogue of 2-isoxazolines. As mentioned earlier, triple bonds react with nitrile oxides more slowly than double bonds. However, apart from the lower reactivity, the cycloaddition of nitrile oxides to alkyne derivatives offers the same general picture as the cycloaddition to alkene compounds. Monosubstituted alkynes usually react faster than disubstituted alkynes and afford mainly the 5-substituted heterocycles. Compounds of low reactivity can be successfully led to react by preparing the 1,3-dipole \textit{in situ} in the presence of excess dipolarophile.

The isoxazole ring activates \( \alpha \)-protons to undergo aldol or Michael-type reactions\textsuperscript{53,54} which enables further functionalisation of the isoxazole ring, especially at C\textsubscript{5} where the \( \alpha \)-protons are most acidic. Selective reductive cleavage of the N-O bond in the isoxazoles leads to the unmasking of the versatile 1,3-dicarbonyl or the 1,3-iminocarbonyl systems (Scheme 14). The reduction can be effected by Na amalgam,\textsuperscript{55} sodium in alcohol,\textsuperscript{56} Grignard reagents,\textsuperscript{57} Fe(CO)\textsubscript{5} and Mo(CO)\textsubscript{6},\textsuperscript{58} electrochemistry\textsuperscript{59} and now, most frequently, by catalytic reduction over palladium, platinum or Raney nickel.
1.3.3.3 Cycloaddition with carbonyls and thiocarbonyls

Aliphatic aldehydes and ketones react with nitrile oxides to give 1,3,4-dioxazoles although a Lewis acid catalyst such as boron trifluoride-etherate must be present. More activated carbonyl compounds, such as aromatic aldehydes, undergo this reaction in the absence of catalyst.

Thiocarbonyl dipolarophiles show good reactivity towards nitrile oxides. The products, 1,4,2-oxathiazolines, undergo a thermal decomposition reaction affording isothiocyanates and the carbonyl equivalent of the dipolarophile, thus providing a method of converting thiocarbonyls to carbonyls.

1.3.3.4 Cycloaddition with imines and nitriles

Both aliphatic and aromatic imines show good reactivity towards nitrile oxides, affording high yields of 1,2,4-oxadiazolines. The nitrile group is considerably less reactive, and while aromatic, heteroaromatic and electron-deficient nitriles give reasonable yields of 1,2,4-oxadiazoles, aliphatic nitriles require activation with boron trifluoride etherate.

1.3.4 Dimerization and polymerisation

In the absence of a dipolarophile the nitrile oxides dimerize to furoxans (1,2,5-oxadiazole 2-oxides), polymerise or rearrange into isocyanates (Scheme 15). Dimerisation is the most frequently observed reaction of nitrile oxides. It occurs in both acidic and in alkaline environments and it is the normal reaction on storage.
under neutral conditions at room temperature. The resistance to dimerisation is increased by electron donating substituents.

Two mechanisms have been proposed. The formation of furoxans can be viewed as a cycloaddition to the C=N bond of the nitrile oxide. The dimerisation shows the same characteristics as other cycloaddition reactions, such as a high negative entropy of activation and a small influence of solvent on rates. On the other hand analogy with the behaviour of nitrile ylides and imines supports the 'carbene' dimerisation through a 1,2-dinitroso structure.

Macrocyclic oligomers have also been isolated in low yields in this process. Trimethylamine catalysed dimerisation leads to the formation of 1,2,4-oxadiazole 4-oxides, and pyridine directs the dimerisation to the 1,4,2,5-dioxadiazine. Fulminic acid is exceptional in that it does not give a stable furoxan; its reactions are complex and give rise to a number of trimers and tetrarers or polymers.

1.3.5 Rearrangement

Nitrile oxides undergo a photochemical or thermal rearrangement to isocyanates; the process occurs thermally between 110-140°C. The mechanism of the rearrangement is unknown. It has been established that the reaction does not proceed via separated ions or radicals because there is no sign of scrambling when a mixture of two differently labelled nitrile oxides are subjected to thermal rearrangements. It is tempting to speculate that it may occur via the sequence of Scheme 16, formation of an oxazirene which opens to the acyl nitrene, followed by the well-known migration of R to the stable isocyanate.

Scheme 16

\[
\begin{align*}
RC\equiv N^+ & \rightarrow \begin{array}{c} RC\equiv N \rightarrow \end{array} \begin{array}{c} RC\equiv N \rightarrow \end{array} RN=\overset{\text{O}}{\text{C}}\overset{\text{O}}{\text{N}} \\
& \begin{array}{c} \text{12} \end{array} & \begin{array}{c} \text{13} \end{array}
\end{align*}
\]
Scheme 15

RC=NO \xrightarrow{\text{a}} \left[ \begin{array}{c} C=NO \\ \text{R} \end{array} \right] \xrightarrow{\text{n}} \left[ \begin{array}{c} C=NO \\ \text{R} \end{array} \right] \\
R-N=C=O \xrightarrow{\text{b}} R-C=N-O \xrightarrow{\text{c}} R-C=O \\
11 \xrightarrow{\text{d}} R-N=C=O \\
R-N=C=O \xrightarrow{\text{e}} R-C=N-O \\
R-N=C=O \xrightarrow{\text{f}} R-C=N-O

a; Polymerisation, b; Oligomerisation, c; NMe₃, d; RCNO, e; NEt₃, f; Pyridine
1.3.6 1,3-Dipolar addition reactions

Nitrile oxides react with nucleophiles to form an array of hydroximic acid derivatives. The reaction with a generalised nucleophile B-H leads to a product where the nucleophilic part of the reactant has joined the carbon atom of the nitrile oxide and the oxygen bears the remaining proton, as shown below (Scheme 17). A suitable nucleophile, for example, may be ammonia or hydrogen halides. Under special conditions, nitrile oxides will also react with water, alcohols and phenols; this often requires acid or base catalysis. Most of these additions have limited synthetic interest.

\[
RC\equiv N\overset{+}{O} + B-H \rightarrow R-C\equiv N-OH
\]

Scheme 17
1.4 1,3-Dipoles in polymer chemistry

1.4.1 Introduction

Many 1,3-dipolar cycloaddition reactions are suitable for use as polymer forming reactions, since the difunctional monomers are synthesised readily and many of the dipolar additions are nearly quantitative. Stable polymer production is enhanced by the fact that certain products of the 1,3-dipolar addition are five membered aromatic heterocycles. There are three main areas of polymer chemistry where 1,3-dipoles have been employed:

(a) In the preparation of new, thermally stable polymers; for example from the reactions of bis-nitrile oxides, bis-nitrile imines or bis-azides with appropriate difunctional dipolarophiles.

(b) In the modification of polymers by the cycloaddition of a 1,3-dipole to polymers containing unsaturation. This may be done for three reasons: to alter the physical properties, to introduce reactive groups into the system or, most commonly, for cross-linking.

(c) 1,3-Dipole precursors attached onto a polymer backbone may be generated in the presence of a suitable dipolarophile. Further manipulations on the resulting polymeric material may then be possible or the polymer may be cross-linked.

Selected examples of each case will be discussed in the ensuing sections.

1.4.2 Polymer formation

The concerted 3+2 cycloaddition reaction of a 1,3-dipole to a dipolarophile has been employed as the polymer-forming reaction in the synthesis of step-growth polymers. There are essentially three 1,3-dipoles involved with this aspect of polymer chemistry; nitrile oxides, nitrile imines and azides.

1.4.2.1 Nitrile oxides

Thermally stable poly-(1,2,4-oxadiazoles), polyisoxazoles and polyisoxazolines have been produced by the reactions of bis-nitrile oxides with bis-nitriles,73 bis-acetylenes74-78 and bis-alkenes,76,77,79-84 respectively (Scheme 18). Polyfuroxans are the products formed by the dimerisation of the bis-nitrile oxides in the absence of a suitable dipolarophile.85-89

There are several examples of bis-nitrile oxides reacting with bis-alkenes reported in the literature; the difunctional nitrile oxides were generally prepared from the hydroximoyl chlorides. Heterocyclic polymers containing isoxazoline rings
have also been synthesized by the 1,3-dipolar addition of terephthalonitrile di-N-oxide to organophosphorous acid diallyl esters.\textsuperscript{83}

\textbf{Scheme 18}

\textbf{Reagents:} a; heat or triethylamine, b; N=CC_6H_4C=N, c; HC=CC_6H_4C=CH, d; no dipolarophile, e; H_2C=CHC_6H_4CH=CH_2.
Polymers containing isoxazole rings have been prepared by Overberger and Fujimoto\textsuperscript{78} by treating 1,4-diethynylbenzene with terephthalonitrile di-N-oxide in benzene. The polymer, which was stable in air below 400°C, was obtained in yields of almost 100%. These results suggested that the isoxazole ring has good thermal and oxidative stability.

Polyurethanes with isoxazoline or isoxazole linkages in the polymer chains have been prepared by the reaction of diols to isoxazoline (or isoxazole) diols with diisocyanates.\textsuperscript{83} The diols were prepared by 1,3-dipolar cycloaddition of the di-nitrile oxides with allyl or propargyl alcohol. Polyurethanes of the same structures were also prepared by 1,3-dipolar polycycloadditions of the nitrile oxides with bis(allyl or -propargyl carbamates).

Many polyfuroxans have been synthesised which are often useful for their heat resistance properties. Terephthalonitrile di-N-oxide polymerises with solvent at room temperature or in the solid state at 100°C. Interestingly, the polymer structure is dependant on the reaction conditions.\textsuperscript{90} A polyfuroxan is formed in solution at room temperature and a poly(1,2,4-oxadiazole-4-oxide) on heating in the solid state (Scheme 19).

\textbf{Scheme 19}

\begin{center}
\includegraphics[width=\textwidth]{scheme19}
\end{center}
1.4.2.2 Nitrile imines

Although it has been demonstrated that the nitrile imines generated from the corresponding hydrazonyl chloride did not afford a polymer.\textsuperscript{91} Results by Stille and Gotter\textsuperscript{92,93} indicated that high molecular weight polymers could be formed from a 1,3-dipole addition to suitable dipolarophiles if the nitrile dipole was generated from a tetrazole at temperatures of about 150°C.

Thermally stable polymers containing pyrazole and triazole units in the polymer chain have been obtained through the 1,3-dipolar addition reaction of bis-nitrilimines generated from tetrazoles with diyne and dinitrile dipolarophiles. In these reactions, the nitrile imine dipole is generated from the tetrazole by the loss of nitrogen. This is illustrated in Scheme 20 for the 1,3-dipolar homopolymerisation of the ethynyltetrazole. The polymerisation of vinyltetrazole, an analogous reaction, produces a polypyrazoline.\textsuperscript{93}

\textbf{Scheme 20}

\[
\begin{array}{c}
\text{HC≡C—} \quad \text{NPh} \\
\text{N= \scriptsize{N}} \\
\text{N=N} \\
\text{HC≡C—} \quad \text{C≡N—} \quad \text{NPh} \\
\Delta \quad -\text{N}_2 \\
\text{[} \quad \text{[} \quad \text{[} \quad \text{[} \\
\text{NPh} \\
n \text{]} \quad \text{]} \quad \text{]} \quad \text{]} \\
\end{array}
\]

1.4.2.3 Azides

Analogous reactions have been carried out by Gilliams and Smets;\textsuperscript{94,95} cycloaddition of various bis-azides with bis-maleimides or bis-acetylenes gave poly-1,2,3-triazolines and triazoles respectively (Scheme 21 illustrates the synthesis of a triazole). Pyrazoline and pyrazole polymers were also prepared from diazo compounds using similar methodology.
1.4.3 Modification of polymers via 1,3-dipolar cycloaddition

1,3-Dipoles have been used for the covalent modification of polymers for three reasons: to achieve crosslinking, to attach active or reactive groups and to modify the physical properties of the polymer. The majority of reactions involve nitrile oxides; nitrones and nitrile imines are less well documented.

1.4.3.1 Nitrile oxides

Several polymers and copolymers containing unsaturation, including polybutadiene, have been cross-linked with difunctional nitrile oxides. The bis-nitrile oxides used were generated from either the corresponding bis-hydroximoyl chloride by treatment with base or by the thermolysis of bicyclic furoxans. Cycloaddition with the alkene bonds present in two different polymer chains yielded a cross-linked material; cycloaddition could also occur with pendant vinyl groups (Scheme 22).

Nitrile oxides, generated from the corresponding hydroximoyl chloride in situ, have been reported to cycloadd with the alkene double bonds of cis-1,4-polybutadiene, cis-1,4- and trans-1,4-polyisoprene, polychloroprene, unsaturated polyesters and non-stereospecific polybutadiene. The reactions are generalised in Scheme 23. The degree of modification of the polydiene depends on the initial molar excess of hydroximoyl chloride and the substituent attached to it. Using one mole of hydroximoyl chloride per double bond unit resulted up to 80% of the double bonds being modified.
### Scheme 22

\[
\text{HON} = \text{CCI} - R - \text{CCI} = \text{NOH}
\]

\[
\begin{align*}
\text{O} & \equiv \text{N} - R - \text{C} \equiv \text{N} - \text{O} \\
\text{CH} & \equiv \text{CH} \\
\text{R} & \equiv \text{polymer backbone}
\end{align*}
\]

### Scheme 23

\[
\begin{align*}
R - \text{CCI} = \text{NOH} & \xrightarrow{\Delta} R - \text{C} \equiv \text{N} - \text{O} \\
& \xrightarrow{- \text{HCl}} \left[ \text{CH}_2 - \text{CH} = \text{CR}' - \text{CH}_2 \right]_n \\
& \xrightarrow{} \left[ \text{CH}_2 - \text{CH} = \text{CR}' - \text{CH}_2 \right]_x \left[ \text{CH}_2 - \text{CH} = \text{CR}' - \text{CH}_2 \right]_y \\
\end{align*}
\]

\[
\begin{align*}
R' & = \text{CH}_3, \text{H} \\
R & = p-\text{MeOC}_6\text{H}_4, 3,4,5-(\text{MeO})_3\text{C}_6\text{H}_2, 2,4,6-(\text{MeO})_3\text{C}_6\text{H}_2, \text{MeO}_2\text{C}, \text{EtO}_2\text{C}, p-\text{MeO(CH}_2)_n\text{C}_6\text{H}_4; \ n = 2,6,7.
\end{align*}
\]
Paton et al.\textsuperscript{99} treated cis-1,4-polybutadiene (PBD) and cis-1,4-polyisoprene (PIP) with ethoxycarbonylformonitrile oxide and methoxycarbonylformonitrile oxide, generated \textit{in situ} by the thermal dehydrochlorination of the corresponding hydroximoyl chloride and examined the products by $^1$H and $^{13}$C NMR spectroscopy with the aim of obtaining definitive evidence for the structures of the products. To facilitate the interpretation of the spectra they also examined the products resulting from the reaction of the same nitrile oxides with the simple alkenes, selected as models for the unsaturation present in the PBD and PIP, respectively. For PBD the degree of modification was as high as 86%. The corresponding figure for PIP was lower (66%), an effect attributed to steric factors. $^{13}$C NMR spectroscopy confirmed the presence of both the isoxazoline rings and the pendant ethoxycarbonyl and methoxycarbonyl groups.

Transformations can be performed on the substituents, for example esters can be converted to amides.\textsuperscript{102} 1,3-Dipolar cycloadditions of nitrile oxides to polymers containing unsaturation have been used to modify their physical properties (thermal stability and elasticity).

The introduction of carboxylic acid groups into natural rubber (NR) enables the modified NR to be cross-linked by metallic bases.\textsuperscript{103} This was achieved by treatment with a bifunctional reagent containing a thiol group and a carboxylic acid or ester group, the principle being that the thiol group adds to the polyisoprene double bonds, leaving the other functional group available for subsequent cross-linking reactions.

Acrylonitrile-styrene and acrylonitrile-vinylidene chloride copolymers have been modified via 1,3-dipolar cycloaddition with 4-nitrobenzonitrile oxide.\textsuperscript{104} The nitrile groups in the copolymers were thus converted into 1,2,4-oxadiazoles. The nitrile moiety is a poorer dipolarophile than alkenes towards nitrile oxides, and the degree of modification was therefore lower; an example is illustrated in Scheme 24. The structural units in the product were identified by comparison with model oxadiazoles obtained from 4-nitrobenzonitrile oxide with isobutyronitrile.

Cycloadditions involving preformed insoluble polymer supports have been reported by Yedidia and Leznoff.\textsuperscript{105} A suspension of a 1% crosslinked divinylbenzene - styrene copolymer, containing benzyl alcohol functional groups, was treated with propiolic acid or phenylpropiolic acid to give the polymer-bound benzyl propiolate and polymer-bound benzyl phenylpropiolate. Subsequent reaction of the forementioned esters with benzonitrile oxide at 0°C yield polymer-bound benzylisoxazoles. The reaction of polymers containing terminal acetylenes with benzonitrile oxide has also been reported to occur in satisfactory yield.\textsuperscript{106}
1.4.3.2 Nitrile imines and nitrones

Nitrile imines$^{107-113}$ have been cycloadded to polymers containing unsaturation. Polymers with double bonds activated by electron-withdrawing substituents are successfully modified by the cycloaddition reaction with diphenylnitrile imine (the percentage of double bond modified was 95-100, calculated with respect to the nitrile imine)$^{107-109}$ as illustrated in Scheme 25. Modifications of non-stereospecific polybutadiene and trans-1,4-polyisoprene with diphenylnitrile imine have been reported to occur in much lower yield.$^{109}$ For example, the reaction of a nitrile imine to an unsaturated polymer (reactant ratio 2:1) resulted in 10% of the alkene double bond being modified. Natural rubber, cis-1,4-polyisoprene, does not give any cycloaddition products under similar conditions,$^{109}$ while the reaction of diphenylnitrile imine with non-stereospecific polybutadiene occurs almost entirely at the trans alkene sites.

Cis-1,4-polybutadiene has also been modified successfully with nitrones.$^{108}$ Reaction with 1 mole of precursor per 20 units in the polymer resulted typically in cycloaddition to 31% of the double bond units, corresponding to a 62% yield with respect to the nitrone.
Scheme 25

\[
\begin{align*}
\text{Ph} & \\
\text{N} & \\
\text{N} & \equiv \text{CPh} \\
\rightarrow & \\
\text{Ph} & \\
\text{N} & \\
\text{N} & \equiv \text{CPh}
\end{align*}
\]

\[
\left[\begin{array}{c}
O \\
R - \text{C} - \text{CH} = \text{CH} - \text{C}
\end{array}\right]_m
\]

\[
\rightarrow
\]

\[
\left[\begin{array}{c}
\text{R} - \text{C} - \text{CH} = \text{CH} - \text{C}
\end{array}\right]_m
\]

\[
\text{Ph} - \text{N} - \text{N} - \text{CPh}
\]

\[
\text{R} =
\]

\[
-\text{O} - \text{CH}_2 - \text{CH}_2 - \text{O} -
\]

\[
-\text{O} - \text{C}_6\text{H}_4 - \text{C}(\text{CH}_3)_2 - \text{C}_6\text{H}_4 - \text{O} -
\]

\[
-\text{O} - (\text{CH}_2)_4 - \text{O} -
\]

\[
\text{N} - \text{N}
\]

\[
\text{NH} - \text{NH}
\]

\[
-\text{O} - (\text{CH}_2)_2 - \text{C} - \text{NH} - \text{C} - \text{CH}_2 - \text{O} -
\]
1.4.4 Generation and reactions of polymer-bound 1,3-dipoles

There are few cases of a 1,3-dipole directly attached to the polymer backbone reported in the literature. The three most important examples involve nitrile imines, nitrile sulphides and azides.

The thermal decomposition of tetrazoles generates nitrile imines which are highly reactive and capable of undergoing 1,3-dipolar cycloaddition to dipolarophiles and afford excellent yields of cycloaddition products. A monomer having both styryl and tetrazoyl functional groups can be easily incorporated into polymers. The copolymer thus formed contains the tetrazole pendant groups along the polymer chain, and the thermal decomposition of these tetrazole units in a copolymer which also contains dipolarophiles provides a means for cross-linking. Stille\textsuperscript{114,115} copolymerised styryl tetrazole 14 with \textit{cis}-1,4-polyisoprene to give such a copolymer. On thermolysis nitrogen was evolved affording a nitrile imine, which underwent cycloaddition with a double bond from another polymer molecule thus creating a cross link. A general example of this process is illustrated in Scheme 26. A similar cross linking reaction has been effected by incorporation of a styryl-substituted tetrazole with an acrylonitrile polymer.\textsuperscript{92}

As the copolymerisation reactions were carried out under free radical conditions, the tetrazole rings in these styryl-substituted tetrazoles remained intact. Quantitative thermogravimetric analysis (TGA) on the copolymers, not only showed the decomposition temperatures of the tetrazole ring and of the copolymers themselves, but also indicated the amounts of nitrogen lost when the tetrazole units underwent thermal decomposition. The amounts of nitrogen evolved were also used to calculate the composition of copolymers. Thermogravimetric analysis showed that electron-withdrawing groups on the \textit{N}-phenyl group of the tetrazole ring lowered the decomposition temperature (\textasciitilde160°C), while electron donating groups raised the temperature (\textasciitilde240°C). An opposite trend was observed for substituent on the \textit{C}-phenyl group. Thus the temperature that initiates cross-linking reactions can be controlled by changing the electronic properties of the substituents on the tetrazole moieties.
The generation of polymer-bound nitrile sulphides and a study of their cycloaddition reactions has been described in detail by Paton et al.\textsuperscript{116} The nitrile sulphide precursors selected were 1,3,4-oxathiazol-2-ones, which are readily prepared from the corresponding carboxamides. A polymer bearing oxathiazolone pendant groups was prepared by polymerising the 5-isopropenyl derivative. Heating to $>100^\circ$C resulted in decarboxylation and formation of nitrile sulphides as transient intermediates and these were then trapped in the presence of a suitable dipolarophile (e.g. dimethyl acetylenedicarboxylate or ethyl propiolate). It was established that further simple manipulations could also be carried out on the resulting polymeric heterocycles. It is interesting that the same objective can also be achieved by...
polymerisation of monomers incorporating the target heterocycle. These two approaches are illustrated for methacrylonitrile sulphide in Scheme 27.

The last 1,3-dipole to be discussed, an azide, was described by Cohen et al. Poly(p-vinylbenzyl azide) was prepared by treating poly(p-vinylbenzyl chloride) with sodium azide but because of instability of this polymeric azide above 80°C, reactions with several acetylenic derivatives could not be carried to completion before cross-linking occurred. Formation of the azide was demonstrated by its characteristic reaction with acetylenedicarboxylic acid and its methyl ester, producing the corresponding 1,2,3-triazoles.

Scheme 27

Takeishi and Okawara have also reported the partial conversion of poly(vinyl chloride) to a vinyl chloride / vinyl azide copolymer and its reactions with various reagents including acetylenic derivatives. Conversion to the triazole derivative was about half complete, based on the available azide present (Scheme 28). Similarly, Vandenberg has claimed that the reaction between poly(epichlorohydrin) and sodium azide gives the corresponding polymeric azide (Scheme 29).
1.5 Vinyl-isoxazoles and -2-isoxazolines

Among polymerisations of vinyl heterocycles reported in the literature, studies involving isoxazole and isoxazoline monomers are rather seldom met.\textsuperscript{121,122} Nevertheless, macromolecules with pendant isoxazole residues could show interesting physical and chemical properties. The ring's characteristic reactivity could allow it to be transformed by suitable reagents into non-cyclic 1,3-difunctional systems.

In the ensuing sections a review of selected vinyl heterocycles will be given, indicating the method of preparation and any polymerisation details reported. For clarity vinylisoxazolines and vinylisoxazoles will be discussed separately and these will be subsectioned into 3- 4- and 5- vinyl heterocycles.
1.5.1 Vinyl-2-isoxazolines

1.5.1.1 3-Vinyl-2-isoxazolines

Baranski\textsuperscript{124} generated acrylonitrile and methacrylonitrile oxides using the Mukaiyama dehydration of primary nitroalkanes and investigated their reactions with a range of dipolarophiles. It was initially discovered that 1-nitropropene and 1-nitro-2-methylpropene reacted with phenyl isocyanate in the presence of triethylamine to give unsaturated nitrile oxides and diphenyl urea. These $\alpha,\beta$-unsaturated nitrile oxides are unstable and under the reaction conditions self-polymerised in accord with a [2+3] cycloaddition scheme to afford oligomeric isoxazolines (molecular weight $\sim 780$). However, when the nitrile oxides were generated in the presence of excess of an alkene dipolarophile, the formation of 3-vinylisoxazolines was observed (Scheme 30).

Scheme 30

\[
\text{CH}_3\text{CR} = \text{CHNO}_2 \xrightarrow{\text{PhNCO, Et}_3\text{N}} \text{CH}_2 = \text{CRC} = \text{N} - \text{O} \xrightarrow{\text{CH}_2 = \text{CHR'}} R\text{N}_x \text{O}_x
\]

$R = \text{H, Me}$

In a later publication, Baranski\textsuperscript{125} postulated that 3-nitropropene, under similar conditions, would also be capable of generating acrylonitrile oxide and forming 3-vinylisoxazolines in the presence of an alkene. This was found to be correct and a range of novel vinyl heterocycles were synthesised, the yields varying between 50\% and 86\%. As yet no polymer studies have been conducted with the 3-vinyl-2-isoxazolines.
Wade et al.\textsuperscript{126} have reported a novel route to synthesise 3-vinyl-5-phenyl-2-isoxazoline using acid catalysed nitronate cycloaddition reactions. Two routes for the preparation of 3-alkenylisoxazolines have been developed. The first approach (Scheme 31, path a) involves dehydration of a (hydroxyalkyl)isoxazoline 15 using p-toluenesulphonic acid. The second route (Scheme 31, path b) involves substitution of the sulphone group of 3-sulphonylisoxazolines 16 by vinylmagnesium bromide. The vinylisoxazoline 17 was produced in 72% yield by this method; it is a more efficient alternative to the first synthetic sequence. Simple transformations were also studied on the vinyl heterocycles. Alkenylisoxazolines have been assessed as potential Diels-Alder diene components; however preliminary studies indicate that maleic anhydride fails to react as a dienophile with 3-vinyl-5-phenylisoxazoline.

Wade\textsuperscript{127} has also researched the diastereoselective functionalisation of 3-vinyl-4,5-diphenyl-2-isoxazoline 18. This heterocycle was synthesised by the reduction of 3-benzenesulphonyl-2-isoxazoline with vinyllithium in a 55% yield as shown in Scheme 32. Compound 18 may also be obtained by the reaction with vinylmagnesium bromide or by the dehydration of the corresponding alcohol, 3-(hydroxyalkyl)-2-isoxazolines, but the yields are poor (~12-19%).

\begin{center}
\textbf{Scheme 31}
\end{center}

```
\begin{center}
\includegraphics[width=\textwidth]{scheme31}
\end{center}
```
1.5.1.2 4-Vinyl-2-isoxazolines

There are no reported examples of an isoxazoline bearing an unsubstituted vinyl moiety at the 4-position.

1.5.1.3 5-Vinyl-2-isoxazolines

In 1982 Torssell and Das\textsuperscript{128} studied the addition of nitrile oxides to butadienes and the products were utilised for further synthetic purposes. In a later publication\textsuperscript{129} 3-ethyl-5-vinyl-2-isoxazoline was synthesised by reacting butadiene with preformed trimethylsilyl ester of aci-nitropropane (30% yield). Likewise, the silyl ester of nitromethane was generated \textit{in situ} for the preparation of 3-unsubstituted 2-isoxazolines (Scheme 33). The convenient generation of nitrile oxides from hydroximoyl chlorides and triethylamine was used in other cases.

5-Vinyl-2-isoxazoline obtained from the reaction of nitromethane, triethylamine and chlorotrimethylsilane with butadiene in benzene/acetonitrile solution, is an intermediate with synthetic potential.\textsuperscript{128} Addition of various nitrile oxides, generated by the action of triethylamine on hydroximoyl chlorides, to butadiene gave a range of vinyl derivatives (yields \textit{ca} 40-80\%) (Scheme 34). They
were often contaminated with the diaddition product, resulting from reaction at both double bonds.

Jarrer et al have reported a two-step sequence to synthesise 3-(p-methylphenyl)-5-vinyl-2-isoxazoline.\textsuperscript{130} \(\text{C}_2\text{H}_5\text{O-dilithiooxime}\ x\), an oxime dianion, was initially reacted with the appropriate functionalised carbonyl compound (a nucleophilic 1,2-addition) to furnish the corresponding acyclic \(\beta\)-hydroxy-\(\gamma\)-enone oxime \(z\). The latter was cyclised with phosphorus pentoxide to afford 3-(p-methylphenyl)-5-vinylisoxazoline. The overall yield was 57%.

\[\text{Me} \begin{array}{c} \text{N} \\ \text{C} \\ \text{CH}_2\text{Li} \end{array} \quad \text{Me} \begin{array}{c} \text{N} \\ \text{C} \\ \text{CH}_2\text{CHCH}=\text{CH}_2 \end{array}\]

3-Phenyl-5-vinyl-2-isoxazoline \(19,131\) of particular interest to this thesis, and other 5-vinyl isoxazolines have been synthesised by the reaction of butadiene with various nitrile oxides.\textsuperscript{2} With respect to polymer studies, it has been reported that 3-phenyl-5-vinylisoxazoline and 3-ethoxycarbonyl-5-vinylisoxazoline undergo copolymerisation with styrene and acrylonitrile, but with extremely low conversion; homopolymerisation was unsuccessful.\textsuperscript{121}
1.5.2 Vinlylisoxazoles

1.5.2.1 3-Vinlylisoxazoles

Although the polymerisation of 3-vinyl-5-phenylisoxazole has been described by Sumimoto et al., they omitted any synthetic details and therefore a practical process for the preparation of isoxazole monomers was developed by Iwakura et al. Reaction between ethyl chloro-oximidoacetate 20 and vinyl or isopropenyl acetate 21 in the presence of triethylamine yielded 3-carboethoxyisoxazoline 22, and pyrolysis of the latter compound gave 3-carboethoxyisoxazole 23. 3-Isopropenylisoxazoles were prepared in good yield by the dehydration reaction of 3-(2-hydroxy-2-propyl)isoxazoles 24 which were provided by the Grignard reaction of 3-carboethoxyisoxazoles (Scheme 35). A number of free radical polymerisations were then investigated using monomers with one heteroatom (e.g. furan and thiophene), two heteroatoms (e.g. 3-isopropenyl-5-methylisoxazole) and three heteroatoms (e.g. 2-isopropenyl-5-methyl-1,3,4-oxadiazole); copolymerisation with styrene allowed their relative reactivities (r) to be determined.

The polymerisation of 3-vinyl-5-phenylisoxazole 25 has been reported to be a facile process under both free radical (AIBN used as initiator) and cationic conditions; it was found to be more reactive than styrene (styrene r = 0.48 ± 0.04, 3-vinyl-5-phenylisoxazole r = 0.72 ± 0.03).

It is interesting to observe that Wade, whose synthesis of 3-vinyl-5-phenylisoxazoline 17 was described earlier, also synthesised 3-vinyl-5-phenylisoxazole by dehydrogenating the corresponding isoxazoline with a 3-fold excess of tetracyanoethylene at 190°C-195°C. The yield was poor ca 16%, however it did improve slightly (33%) by using a bath temperature of 140°C; they did not succeed in driving the reaction to completion and unreacted starting material remained (47%). This reaction requires modification if it is to be a valuable synthetic proposition.
Cherton et al\textsuperscript{133} have reported a number of synthetic routes for isoxazoles bearing a long alkenyl side chain in the 3-position. The most generally applicable route involves the synthesis of 3-bromomethyl-5-isoxazole from the corresponding alcohol using phosphorus tribromide. Subsequent reaction with an appropriate Grignard reagent bearing an alkenyl group created a vinyl moiety at the 3-position.

1.5.2.2 4-Vinylisoxazoles

Bertini et al\textsuperscript{134} have reported a revised synthetic sequence to 3,5-dimethyl-4-vinylisoxazole. Extensive details of both routes are described. In both syntheses pentane-2,4-dione was converted into 1-(3,5-dimethylisoxazol-4-yl)ethanol 26 (Scheme 36). In the first procedure (path a) the dione was transformed into 3,5-dimethylisoxazole by hydroxylamine hydrochloride, then into 4-iodo-3,5-dimethylisoxazole with iodine and concentrated nitric acid, then into 3,5-dimethylisoxazol-4-ylmagnesium iodide by magnesium and ethyl bromide, and finally into the isoxazolylethanol 26 by treatment with acetaldehyde and subsequent hydrolysis; the overall yield from the dione was 31%.

In the second procedure (path b), recommended for preparative purposes, the dione was condensed with acetaldehyde to give the ethyldiene derivative, which was cyclised with hydroxylamine hydrochloride (overall yield 90%). Spontaneous
dehydration of the alcohol 26 afforded 3,5-dimethyl-4-vinylisoxazole 27, which was sufficiently pure for polymerisation experiments.

With regard to the radical polymerisation of 27, this compound spontaneously polymerises slowly at room temperature without stabilisers, or on heating. De Munno et al\textsuperscript{134} have investigated the radical polymerisation and copolymerisation of 3,5-dimethyl-4-vinylisoxazole and 5-vinylisoxazole (Section 1.5.2.3) with styrene, acrylic acid, and other comonomers which were selected on the bases of the relative reactivities to create a random distribution of heterocycle units
in the copolymer; this prevents undesired interactions when the polymers are submitted to chemical transformations.

An effective route for the synthesis of 3-phenyl-4-vinylisoxazole has been achieved by Caramella et al.\textsuperscript{135} 3-Acetoxy-2,3-dihydrothiophene-1,1-dioxide is quite a reactive dipolarophile and undergoes regioselective cycloaddition to benzonitrile oxide and mesitonitrile oxide affording a mixture of cycloadducts 28a and 28b (Scheme 37). The minor adduct 28b afforded 4-vinylisoxazoles by refluxing in toluene with 1,5-diazabicyclo[5.4.0]undec-5-ene. The course of the elimination indicates a preferred formation of the \(\beta,\gamma\)-unsaturated sulphones, conjugated with the isoxazoline C=N. Under the reaction conditions, the sulphones undergo a retrocycloaddition with the thermal extrusion of SO\(_2\).

2,4,6-Trimethyl-phenyl-4-vinylisoxazole has also been synthesised using similar methodology from thiophene dioxide-benzonitrile oxide cycloadditions and the subsequent thermal extrusion of sulphur dioxide.\textsuperscript{136}

1.5.2.3 5-Vinylisoxazole

3-Methyl-5-vinylisoxazole 29 has been reported\textsuperscript{134} as a minor product of the acetonitrile oxide addition to vinylacetylene, the addition to the double bond being predominant. Brandi\textsuperscript{132} synthesised 29 in a two-step procedure. 5-(1-Bromoethyl)-3-methylisoxazole was initially prepared in 80\% yield from 3-bromobut-1-yn-1, nitroethane, phenyl isocyanate and triethylamine in benzene. The substituted isoxazole was then added to a suspension of potassium tert-butoxide in dry benzene and the product was purified by distillation (yield 60\%). This reaction sequence is preferred as the overall yield is higher and the product easier to isolate.

The free radical polymerisation of 5-vinylisoxazole 30, synthesised by the cycloaddition of formonitrile oxide with butadiene, has been studied by De Munno et al.;\textsuperscript{123} its reactivity was compared with styrene and 3,5-dimethyl-4-vinylisoxazole. Homopolymerisation conversions vs. time indicated that 5-vinylisoxazole was more reactive than styrene. Monomer 30 revealed a polarity dependent on the nature of the copolymer, in agreement with a rather long, conjugated and poorly aromatic system characterised by high polarisability.

3-Phenyl-5-vinylisoxazole 31, a compound of interest to this thesis, has been synthesised previously\textsuperscript{137} by Kano and Adachi by refluxing 3-phenyl-5-(chloroethyl)-isoxazole in xylene in the presence of diethylamine. Compound 31 has also been used for preliminary polymerisation studies.
Scheme 37

\[
\text{ArC} &=& 
\overset{+}{\text{N}} - \overset{-}{\text{O}} + \overset{}{\text{OCOCH}_3} \\
\text{Ar} &=& \text{Ph or Mesityl}
\]

\[
\begin{align*}
\text{ArC} &=& \overset{+}{\text{N}} - \overset{-}{\text{O}} + \overset{}{\text{OCOCH}_3} \\
\text{Ar} &=& \text{Ph or Mesityl}
\end{align*}
\]
2. RESULTS AND DISCUSSION

2.1 Programme of research

Isoxazoles and their 4,5-dihydro derivatives (2-isoxazolines) have been known for many years and their chemistry examined in great detail. Less attention, however, has been paid to their role in polymer chemistry. A number of poly-isoxazoles and poly(2-isoxazolines) have been produced by the reactions of bis-nitrile oxides with bis-acetylenes and bis-alkenes, respectively, and 1,3-dipolar cycloadditions of nitrile oxides to polymers containing unsaturation have also been performed to modify their physical properties. However, polymers bearing isoxazoles and isoxazolines as pendant groups have been largely ignored.

The principle objective of the present work has been to establish procedures for the preparation of polymer-linked isoxazoles and 2-isoxazolines, and to this end four potential vinyl-isoxazole and isoxazoline monomers were selected for investigation: viz 5-phenyl-3-vinylisoxazole 25, 3-phenyl-5-vinylisoxazole 31, 5-phenyl-3-vinyl-2-isoxazoline 17 and 3-phenyl-5-vinyl-2-isoxazoline 19. A secondary aim, having developed the synthetic routes, was to investigate methods suitable for their polymerisations.

Two synthetic approaches to these compounds were adopted. The first was based largely on established chemistry of isoxazoles and isoxazolines and involved Wittig olefination of a formyl-isoxazole (or isoxazoline) prepared by reduction of the corresponding ethyl ester. The heterocyclic ring was created by nitrile oxide cycloaddition to the appropriate acetylenic or olefinic dipolarophile. This approach is illustrated retrosynthetically for isoxazole 25 in Scheme 38.
The second approach selected for investigation involved direct introduction of the vinyl group as part of the nitrile oxide component in the heterocycle ring-forming stage. This required effective methods for the generation of α,β-unsaturated nitrile oxides such as acrylonitrile oxide 32. Successful application of this method would provide a more convenient and direct route to 3-alkenyl-isoxazoles and isoxazolines (Scheme 39). As little was known about α,β-unsaturated nitrile oxides their synthesis and reactions have also been investigated.

2.2 Synthesis of vinyl-isoxazoles and 2-isoxazolines via the Wittig reaction

2.2.1 Generation of nitrile oxides

The nitrile oxides required to synthesise the target heterocycles were benzonitrile oxide and ethoxycarbonylformonitrile oxide. These are both known literature compounds and were generated in situ by dehydrochlorination of the corresponding hydroximoyl chlorides. The majority of the cycloaddition reactions were performed using triethylamine to generate the nitrile oxide; it was added slowly via a syringe pump to a chilled solution of excess dipolarophile and the hydroximoyl chloride in ether. These conditions ensured a low concentration of the
nitrile oxide, thereby reducing the formation of furoxans (1,2,5-oxadiazole-2-oxides), the competing dimerisation reaction. Triethylamine hydrochloride, the byproduct, is insoluble in ether and is easily removed by filtering through celite.

Ethyl chloro-oximidoacetate 20, the precursor to ethoxycarbonylformonitrile oxide was prepared by the nitrosation of glycine ethyl ester hydrochloride using hydrochloric acid and sodium nitrite (Scheme 40). The white crystalline product was readily storable for prolonged periods if kept in a sealed container in a refrigerator; the yield was typically 45-59%. Ethyl chloro-oximidoacetate is a highly active allergenic and therefore great care was taken during the work-up.

Scheme 40

\[
\text{EtO}_2\text{CCH}_2\text{NH}_3^+ \text{Cl}^- \xrightarrow{\text{NaNO}_2/\text{HCl}} \text{EtO}_2\text{C\text{C}Cl=NOH} \xrightarrow{\text{HCl}} \text{EtO}_2\text{C\text{C}N=O}^+
\]

To synthesise benzohydroximoyl chloride 33, benzaldoxime (prepared by methodology described by Vogel) was chlorinated in chloroform using chlorine gas; the exact quantity was essential and its addition required careful monitoring. An alternative method requires treatment of the oxime with N-chlorosuccinimide (NCS) (Scheme 41); this one-pot reaction avoids the use of chlorine and does not involve isolation of benzohydroximoyl chloride. NCS is also easy to handle and it is a comparatively clean reaction.

Scheme 41

\[
\text{PhCH=NOH} \xrightarrow{\text{NCS}, \text{pyridine}} \text{PhC\text{C}Cl=NOH} \xrightarrow{\text{NET}_3} \text{PhC=N-O}^- \xrightarrow{\text{X=Y}} \text{Ph}\begin{array}{c}X \text{O} \\ N \end{array}
\]

Dehydrochlorination may also be achieved by the thermal dissociation of the hydroximoyl chloride. This depends on the equilibrium between the hydroximoyl chloride and the nitrile oxide and HCl (Scheme 42). The cycloaddition reaction is performed under reflux in an inert solvent at 100-150°C and, as in the base-induced method, uses excess dipolarophile. The HCl gas evolved can be used to monitor the reaction.
During the course of the project, dehydrochlorination of hydroximoyl chlorides by alkali metal fluorides was reported in the literature. The reactions described involved cycloadDITION to methyl acrylate, a reactive dipolarophile, and the yields were excellent. The work-up was particularly attractive in its simplicity, the reaction being stirred at room temperature for five days, filtered through celite and washed with dichloromethane. We applied this methodology to synthesise 5-ethoxycarbonyl-3-phenylisoxazole 34 and 3-ethoxycarbonyl-5-phenylisoxazoline 35 from benzonitrile oxide or ethoxycarbonylformonitrile oxide respectively and the appropriate dipolarophile with NaF.

2.2.2 5-Phenyl-3-vinylisoxazole

3-Ethoxycarbonyl-5-phenylisoxazole, the precursor to 5-phenyl-3-vinylisoxazole, was synthesised from phenylacetylene and ethyl chloro-oximidoacetate 20. Ethoxycarbonylformonitrile oxide was generated thermally in situ by refluxing in p-xylene for ~16 hours in the presence of the dipolarophile; this method is particularly good for recalcitrant dipolarophiles. When no more HCl was detected by moist litmus paper the reaction was assumed to be complete. Concentration of the reaction mixture followed by recrystallisation of the residue from ethanol furnished the ethoxycarbonylisoxazole as a colourless, acicular solid in good yield (70%). Care was required as the byproduct, 3,4-diethoxycarbonylfuroxan, is a known strong skin irritant.

Di-isobutylaluminium hydride (DIBAL) was added to a cooled (-78°C) solution of 3-ethoxycarbonyl-5-phenylisoxazole in dry dichloromethane, thus reducing the ester and synthesising 3-formyl-5-phenylisoxazole in an 80% yield. The aldehyde was purified by dry flash chromatography; the IR spectrum revealed a characteristically strong carbonyl band at 1750 cm\(^{-1}\) and the \(^1\)H NMR spectrum contained an aldehydic peak which appeared at 10.0 p.p.m. The alcohol byproduct, formed presumably from over-reduction, was oxidised back to the desired aldehyde using pyridinium chlorochromate in excellent yield (90%).

The final stage of the synthetic sequence introduced the vinyl moiety by using classic Wittig reagents: methyltriphenylphosphonium iodide, potassium t-
butoxide in dry THF. 5-Phenyl-3-vinylisoxazole\textsuperscript{137,156} 25 was isolated as a white acicular solid (83\%) and was stored at $<0^\circ\text{C}$ to avoid degradation. The overall yield for the three step synthetic sequence was 38\%. The IR spectrum featured a strong band at 1560-1600 cm\textsuperscript{-1}, attributable to a C=N vibration; the $^1$H NMR spectrum showed three doublet of doublets, the characteristic vinyl pattern, in the 5-6 p.p.m. region. The $^{13}$C NMR spectrum was as predicted with the two quaternary peaks of C\textsubscript{3} and C\textsubscript{5} appearing at high chemical shifts due to the deshielding effects of the heteroatoms attached. (For selected NMR data see Section 2.2.7).

\textbf{Scheme 43}

\begin{equation}
\text{EtO}_2\text{CCH}_2\text{NH}_3\text{Cl}^{-} \xrightarrow{a} \text{EtO}_2\text{CCl}=\text{NOH} 20 (70\%) \xrightarrow{b} \text{EtO}_2\text{C}--\text{N}--\text{O} \xrightarrow{c} \text{EtO}_2\text{CCH}_2\text{NH}_3\text{Cl}^{-} \xrightarrow{e} \text{EtO}_2\text{CCH}_2\text{NH}_3\text{Cl}^{-} \xrightarrow{d} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{f} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{g} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{h} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{i} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{j} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{k} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{l} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{m} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{n} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{o} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{p} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{q} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{r} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{s} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{t} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{u} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{v} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{w} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{x} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{y} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{z} \text{EtO}_2\text{C}=\text{NOH} \xrightarrow{\text{Reagents: a, NaNO}_2, \text{HCl, -30}^\circ\text{C}; b, \Delta; c, \text{PhC}=\text{CH}; d, \text{DIBAL, -78}^\circ\text{C}; e, \text{PCC, r.t.; f, Ph}_3\text{PCH}_3\text{I, (CH}_3)_3\text{COK, THF.}}
2.2.3 3-Phenyl-5-vinylisoxazole

The 5-vinyl heterocycle 31 was synthesised from ethyl propiolate and benzohydroximoyl chloride 33 (Scheme 44), prepared by direct chlorination of benzaldoxime using chlorine gas in a 69% yield. The nitrile oxide precursor was then reacted with ethyl propiolate, the dipolarophile, in the presence of triethylamine. In order to minimise furoxan formation, the triethylamine was diluted with a large excess of diethyl ether and dripped over six hours onto the reaction mixture, which was at 0°C for the first hour and then kept at room temperature. Examination of the reaction mixture by $^1$H NMR spectroscopy showed a regioisomeric mixture of isoxazole-4-39 (X) and -5-carboxylates 34 (Y). The isomer ratio X:Y was estimated as 1:12 by comparison of the characteristic signals for the isoxazole ring protons (9.30 p.p.m. for H$_4$ of X; 7.23 p.p.m. for H$_4$ of Y). The desired 5-carboxylate derivative was separated at this stage by crystallisation (from cyclohexane); the yield was good (60%). The product was characterised by IR, $^1$H and $^{13}$C NMR spectroscopy.

The alternative method of chlorination, described previously, requires NCS. Although avoiding the need to isolate benzohydroximoyl chloride, the yield for this reaction was lower than the two step approach using chlorine gas (31% cf 42%). Another effective route used to synthesise 5-phenyl-3-ethoxycarbonylisoxazole 34 involved replacing triethylamine with NaF (Section 2.2.1), which is thought to act as an acid captor. In this case the yield was good (69%).

The ethyl ester was treated with DIBAL at -78°C for ~50 minutes thus yielding 3-formyl-5-phenylisoxazole 40 (51%) as a white powder with a characteristically sweet smell, together with a small proportion of 5-hydroxymethyl-3-phenylisoxazole 41 (5%). The two products were easily separated by flash chromatography. The IR spectrum for the aldehyde contained a strong carbonyl band at 1715 cm$^{-1}$.

A Wittig reaction with methylene triphenylphosphorane completed the reaction sequence and, under the same conditions and using identical reagents as described in 2.2.2., furnished 3-phenyl-5-vinylisoxazole 31 as a pale yellow oil (55%). The overall yield for the three step synthetic sequence from 3-ethoxycarbonyl-5-phenylisoxazole to the target compound was 17%. The IR spectrum featured a C=N absorption at 1638 cm$^{-1}$ and the $^1$H NMR spectrum showed, in addition to the isoxazole ring H$_4$ peak at 6.48 p.p.m., the characteristic vinyl pattern, three doublets of doublets at 6.66, 6.05 and 5.55 p.p.m. It was observed that the singlet at 6.48 p.p.m., assigned to H$_4$, was broad and that vinylic...
Proton $H_A$ had an added splitting of $\sim 0.4$ Hz. This is attributed to long range coupling between the ring proton and $H_A$. (Selected NMR data are presented in Section 2.2.7).

Scheme 44

\[ \text{Reagents: } \quad \begin{align*} & \text{a, } \text{Cl}_2; \text{ b, NEt}_3; \text{ c, EtO}_2\text{CC=CH; d, Dibal, } -78^\circ \text{C; e, Ph}_3\text{PCH}_3\text{I, (CH}_3)_3\text{COK, THF.} \end{align*} \]
2.2.4 5-Phenyl-3-vinyl-2-isoxazoline

The target compound 17 was prepared from styrene and ethyl chloro-oximidoacetate 20 (Scheme 45). Triethylamine was used as base to generate the nitrile oxide and proved successful in producing a clean reaction synthesising the ester 161 35 in a satisfactory yield (62%). The cycloaddition was performed as before using an excess of the dipolarophile, styrene, to minimise the formation of the furoxan dimer. The triethylamine was added over 6 hours and the ester was isolated as a colourless oil, the last traces of impurities being removed by flash chromatography; the ester crystallised at -9°C. The product showed a typical isoxazoline ABX pattern in the ¹H NMR spectrum with the two protons (H₄a and H₅) appearing as two doublets of doublets at 3.49 and 3.05 p.p.m., respectively and H₅ as a doublet of doublets at 5.62 p.p.m.

Isoxazoline 35 was also prepared using NaF 145 (Section 2.2.1). After stirring the reactants at room temperature for six days, the resulting precipitate was filtered through celite and washed with dichloromethane. The crude product was then purified by dry flash chromatography affording 3-ethoxycarbonyl-5-phenylisoxazoline in a moderate yield of 50%.

The ester was reduced to 3-formyl-5-phenyl-2-isoxazoline 162 42 by using DIBAL at -78°C. The aldehyde was separated from traces of hydroxymethyl compound 43 by dry flash chromatography and isolated as a pale yellow oil (58%) with characteristic NMR spectrum (Section 2.2.7). The product contained an aldehydic peak at 9.9 p.p.m. in the ¹H NMR spectrum and a strong absorption at 1690 cm⁻¹ (C=O) was featured in the IR spectrum. An attempt was made to remove the very small amount of impurity causing colouration by distillation, but unfortunately the compound decomposed even at relatively low temperatures (~130 °C, 0.05 mm Hg). Using the Wittig reagents and conditions described in section 2.2.2, the aldehyde was converted to the vinyl heterocycle 17. Purification by flash chromatography furnished 5-phenyl-3-vinylisoxazoline 124, 125 as a yellow oil in a moderate yield of 58%. The overall yield for the three step synthetic sequence was 26%.

2.2.5 3-Phenyl-5-vinyl-2-isoxazoline

Although this compound could have been prepared by a sequence similar to those described earlier for compounds 25, 31 and 17 an alternative, shorter strategy was adopted based on the addition of benzonitrile oxide to 1,3-butadiene. The two routes are illustrated in Scheme 46.
The nitrile oxide was conveniently generated from benzohydroximoyl chloride and triethylamine. A solution of known volume of butadiene (one molar equivalent) in chloroform was prepared at -20°C and triethylamine was then added dropwise over 12 hours. The reaction mixture remained at 0°C throughout. Dry flash chromatography afforded 3-phenyl-5-vinylisoxazoline as a white acicular compound (45-47°C); the reaction was completely regiospecific as is generally the case for cycloadditions to monosubstituted alkenes. The yield was excellent (84%). The spectral characteristics of this compound were identical to those reported in the literature.131

Scheme 45

Reagents:  a, NaNO2, HCl, -30°C; b, NEt3; c, PhCH=CH2; d, DIBAL, -78°C; e, Ph3PCH3I, (CH3)3COK, THF.
A number of more polar components were observed on the TLC of the crude product; one is presumed to be the 2:1 products 44a and 44b (a mixture of stereoisomers) resulting from a second addition of benzonitrile oxide to the vinyl group of the initial adduct 19. These were removed by the addition of petroleum ether.

Similar diadducts have been reported previously by Torssell and Das. By analogy with their results, the major product is presumed to be compound 44a in which the relative stereochemistry of the new asymmetric centres at the 5-positions of the isoxazoline rings is meso. The preference for this product over the d,l 44b isomer can be rationalised in terms of the so called "inside alkoxy effect" proposed by Houk to explain the behaviour of nitrile oxide cycloaddition to chiral allyl ethers.

Scheme 46
2.2.6 Additional alkenyl-isoxazolines

An alternative and convenient approach to constructing polymers containing isoxazolines is to use styrene-type monomers bearing an isoxazoline substituent. It was considered that the alkenyl appendages may polymerise more readily than the 3-vinyl heterocycles. Two such compounds were selected for investigation:

(i) 5-(m-isopropenylphenyl)-5-methyl-3-phenyl-2-isoxazoline 45 (an α-methylstyrene analogue) and (ii) 3-phenyl-5-(m- & p-vinylphenyl)-2-isoxazoline 46. These were prepared from benzohydroximoyl chloride, triethylamine and the appropriate dipolarophile.

**Scheme 47**

\[
\begin{align*}
\text{PhCN}O & + \\
\end{align*}
\]

2.2.6.1 5-(m-Isopropenylphenyl)-5-methyl-3-phenyl-2-isoxazoline

Benzonitrile oxide was generated from the hydroximoyl chloride and triethylamine as previously described, and cycloadded to 1,3-diisopropenylbenzene (2.4 molar equivalents). There were two products isolated from the reaction mixture: the 1:1 adduct 45 (33% yield) was accompanied by a byproduct, a 2:1 adduct 47 (18% yield). The 1:1 product was a white crystalline solid (recrystallised from cyclohexane) and was considered a likely monomer candidate for later polymerisation studies. The $^1$H NMR spectrum showed the characteristic isoxazoline pattern; $H_{4a}$ and $H_{4b}$ absorbing at 3.57 and 3.49 p.p.m and the methyl group attached to the ring at 1.86 p.p.m. The other methyl group attached to the vinyl moiety was
seen at 2.21 p.p.m.; there were two allylic couplings of 0.7 and 1.4 Hz for Me' to H_C and H_B.

The 2:1 adduct 47, a white solid, is not suitable for polymerisation. The chemical formulae of the two novel heterocycles were verified by elemental analysis and high resolution FAB mass spectroscopy.

2.2.6.2 3-Phenyl-5-(m- & p-vinylphenyl)-2-isoxazoline

Triethylamine was added over 14 hours to a solution of benzohydroximoyl chloride and a commercially available mixture of 1,3- and 1,4-divinylbenzene which also contained 3- and 4-ethylstyrenes. Dry flash chromatography furnished three products which are described in order of elution. 3-Phenyl-5-(m- & p-ethylphenyl)-2-isoxazoline 48, an off-white solid (19%) (m.p. 40-44°C), was recrystallised from hexane. The mixture of m- & p-vinyl adducts 48 were isolated in a moderate yield (24%) (m.p. 73-76°C). The isomer ratio was determined as ~1 : 2.0 (meta : para) by comparison of the integrals for the isoxazoline ring protons H_4a and H_4b. This value is very similar to that for the mixed divinylbenzene (1 : 2.3). The \(^1\)H NMR spectrum showed the characteristic vinyl pattern, three doublets of doublets, as described for the previous heterocycles. The isoxazoline proton H_5 couples to H_4a and H_4b, as expected.

The last compound eluted was 1,3- and 1,4-bis(5-methyl-3-phenyl-2-isoxazolin-5-yl)benzene 49, another white crystalline solid (m.p. 130-135°C); the
Table 2 Selected $^{13}$C NMR spectroscopic data; ($\delta$, p.p.m.) (50 MHz; CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$R'$</th>
<th>$R''$</th>
<th>$C_3$</th>
<th>$C_4$</th>
<th>$C_5$</th>
<th>PhC</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) CO$_2$Et Ph</td>
<td>159.8*</td>
<td>99.7</td>
<td>171.5</td>
<td>126.4</td>
<td>157.0* (C=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) CH$_2$OH Ph</td>
<td>164.3*</td>
<td>98.2</td>
<td>170.1*</td>
<td>127.0</td>
<td>56.5 (CH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) CHO Ph</td>
<td>162.4*</td>
<td>96.2</td>
<td>171.9*</td>
<td>126.2</td>
<td>184.7 (C=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) CH=CH$_2$ Ph</td>
<td>162.5*</td>
<td>96.0</td>
<td>170.0*</td>
<td>127.3</td>
<td>121.2 (CH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Ph CO$_2$Et</td>
<td>160.8*</td>
<td>107.2</td>
<td>162.8*</td>
<td>127.8</td>
<td>156.7* (C=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Ph CH$_2$OH</td>
<td>162.3*</td>
<td>99.8</td>
<td>172.2*</td>
<td>128.4</td>
<td>56.0 (CH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Ph CHO</td>
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<td>106.5</td>
<td>166.2*</td>
<td>127.5</td>
<td>178.3 (C=O)</td>
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<td></td>
</tr>
<tr>
<td>(i) Ph CH=CH$_2$</td>
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<td>99.3</td>
<td>168.5*</td>
<td>128.9</td>
<td>120.4 (CH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) CO$_2$Et Ph</td>
<td>160.1</td>
<td>41.0</td>
<td>84.5</td>
<td>139.2</td>
<td>185.2 (C=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) CHO Ph</td>
<td>158.6</td>
<td>37.7</td>
<td>85.6</td>
<td>138.8</td>
<td>185.2 (C=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) CH=CH$_2$ Ph</td>
<td>156.9</td>
<td>40.9</td>
<td>82.3</td>
<td>140.5</td>
<td>122.0 (CH$_2$)</td>
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<td></td>
</tr>
<tr>
<td>(ii) Ph CH=CH$_2$</td>
<td>156.1</td>
<td>40.3</td>
<td>81.8</td>
<td>129.3</td>
<td>117.6 (CH$_2$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* alternative assignments possible

Table 3 Selected $^1$H NMR spectroscopic data; ($\delta$, p.p.m; $J$, Hz.) (80 & 200 MHz, CDCl$_3$)

| Compound | $\delta_{H_A}$ | $\delta_{H_B}$ | $\delta_{H_C}$ | $J_{AB}$ | $J_{CA}$ | $J_{CB}$ | others | $\delta_{H_{4b}}$ | $\delta_{H_{4a}}$ | $\delta_{H_5}$ | $J_{4ab}$ | $J_{4b}$ | $J_{4a5}$ | others |
|----------|---------------|---------------|---------------|---------|---------|---------|--------|--------|-----------|-----------|-----------|--------|--------|--------|--------|
| 17       | 6.73          | 5.54          | 5.41          | 11.0    | 17.7    | 1.0     | $J_{AB}$ 6.8 | 3.05    | 3.49     | 5.62     | 16.5    | 8.4     | 11.0   | -      |
| 19       | 5.32          | 5.99          | 5.91          | 10.5    | 17.0    | 1.1     |         | 3.05    | 3.47     | 5.13     | 16.6    | 8.4     | 10.5   | $J_{5A}$ 6.8 |
| 25       | 6.82          | 5.64          | 5.90          | 10.9    | 17.8    | 1.1     |          | $\delta_{H_4}$ 6.63 | -        | -        | -        | -        | -        | -      |
| 31       | 5.55          | 6.66          | 6.05          | 11.0    | 17.7    | 1.3     | $J_{AB}$ 0.9 | $\delta_{H_4}$ 6.48 | -        | -        | -        | -        | -        | -      |
yield was very low (2%). This compound is a symmetrical adduct and therefore the NMR spectrum is simplified; however splitting is seen as there are two possible diastereoisomers present.

2.2.7 Selected NMR spectroscopic data

2.2.7.1 $^{13}$C NMR spectroscopic data

$^{13}$C NMR data for the esters, aldehydes and vinyl isoxazoles (i) and 2-isoxazolines (ii) whose synthesis are described in the previous Sections, are presented in Table 2. The salient points are discussed below.

![Diagram](attachment:image.png)

The data indicate that the carbonyl carbons in the aldehydic compounds resonate at the lowest field position; they suffer the combined effects of the induced anisotropic field and a nearby electronegative element. It may also be observed that the extra $\pi$-bond present in isoxazoles is especially effective in influencing the chemical shift of the two carbons directly involved, C$_4$ and C$_5$. The C$_4$ p.p.m. values associated with the isoxazole heterocycles occur at ~100 p.p.m. whereas the isoxazoline C$_4$ is seen at ~39 p.p.m. This effect is even more pronounced for the C$_5$ values; the isoxazoles' C$_5$ peaks are ~170 p.p.m. whereas the peaks associated with the isoxazolines are typically at ~83 p.p.m.
Spectrum 1: $^1$H NMR spectrum for 5-phenyl-3-vinylisoxazoline (200 MHz, CDCl$_3$)
2.2.7.2 $^1$H NMR spectroscopic data

Selected $^1$H NMR data for the vinyl heterocycles, 25, 31, 17 and 19, are shown in Table 3. The characteristic features are discussed.

All four heterocycles have the characteristic pattern produced by the vinylic group; a doublet of doublets occurring in the 5-6 p.p.m. region. The vinyl protons vary in their order of chemical shift presumably reflecting their proximity to the more electronegative atoms. The trans coupling between $H_A$ and $H_C$ has a coupling constant of $\sim 17-18$ Hz and the cis coupling $H_A$ to $H_B$ appears to be $\sim 11$ Hz. The geminal coupling, as expected, is close to zero.

The isoxazole heterocycles have only one ring proton, $H_A$, and this appears as a singlet. Interestingly 3-phenyl-5-vinylisoxazole has a small long-range coupling of $\sim 1$ Hz between $H_A$ and $H_4$.

The isoxazoline ring protons $H_{4a}$, $H_{4b}$ and $H_5$ occur at a chemical shift of $\sim 3.4$, 3.1 and 5.4 p.p.m., respectively, each appearing as a doublet of doublets. This pattern is characteristic for 2-isoxazolines$^{124,125}$ and is illustrated in Spectrum 1 for 5-phenyl-3-vinyl-2-isoxazoline.
2.3 α,β-Unsaturated nitrile oxides

2.3.1 Introduction

The second approach to vinylisoxazoles and isoxazolines involved direct introduction of the vinyl group as part of the nitrile oxide component using an α,β-unsaturated nitrile oxide, acrylonitrile oxide (ANO) 32. This offers a shorter, more efficient route to such 3-vinyl heterocycles.

2.3.2 Acrylonitrile oxide (ANO)

The method of generation of ANO was based on a report by Baransi,124,125 who used a modified Mukaiyama procedure to successfully dehydrate 1-nitropropene and 3-nitropropene with phenyl isocyanate in the presence of catalytic amounts of triethylamine. Abstraction by base of a proton from either 1-nitropropene or 3-nitropropene results in the formation of same nitronate anion, which has three resonance structures as illustrated in Scheme 48. For the present work 1-nitropropene 50 was selected as a convenient precursor for ANO and was prepared by the condensation of acetaldehyde and nitromethane (the Henry reaction) followed by acetylation of the resulting alcohol 51. Treatment of acetate 52 with base afforded the target compound 50 (Scheme 49), a pale yellow/green oil and well-known lachrymator. The overall yield for the three stages was 24%.

**Scheme 48**
2.3.3 Cycloaddition reactions of acrylonitrile oxide (ANO)

A series of experiments were performed, at room temperature, using styrene as the dipolarophile in order to establish optimum reaction conditions. Tolylene diisocyanate (TDI) was used as an alternative dehydrating agent to phenyl isocyanate in the cycloaddition reaction of styrene to ANO, as it is known to give a relatively clean reaction. Unfortunately, in this case it gave slightly lower yields for the cycloaddition reaction (55% vs 30%). Phenyl isocyanate was therefore selected.

Varying the dipolarophile : nitropropene ratio between 1.5:1 and 5:1 established that it was advantageous for the dipolarophile to be present in a large excess. Benzene and dichloroethane were both suitable solvents; carrying out the reaction at higher temperatures (~80°C), however, dramatically decreased the yield (from 55% to 12%).

5-Phenyl-3-vinylisoxazole 25 and 5-phenyl-3-vinylisoxazoline 17 were synthesised using the optimised Mukaiyama conditions (phenyl isocyanate, triethylamine and the appropriate dipolarophile in benzene at room temperature) and the adducts were purified by dry flash chromatography. 5-Phenyl-3-vinylisoxazoline was obtained in a satisfactory yield of 55% which compares favourably to the three step synthetic sequence described earlier (Section 2.2.4) where the overall yield was 26%. In contrast for the corresponding reaction with phenylacetylene the yield of isoxazole 25 was very poor (12%), reflecting the low reactivity of this dipolarophile (~10 times less reactive than styrene165). The low yield may also be attributed to
further cycloaddition of ANO to the vinyl substituent in compound 25. It is anticipated that this vinylic group could be more reactive than the phenylacetylene itself (Scheme 50).

Scheme 50

\[
\begin{align*}
\text{CH}_2\text{=CHC} & \equiv \text{N}^{-} \quad + \\
\text{CH}_2\text{=CHCN} & \quad - \text{O} \\
\text{Ph} & \quad + \\
\end{align*}
\]

One solution to avoid this problem would be to generate 2-acetoxypropionitrile oxide 52, which can be regarded as a masked form of ANO, by dehydration of 2-acetoxy-1-nitropropene (an intermediate on the synthetic route to 1-nitropropene). Subsequent elimination of acetic acid from the cycloadduct would afford the required heterocycle (Scheme 51).

Under standard Mukaiyama conditions with styrene as dipolarophile and 2-acetoxypropionitrile as the nitrile oxide precursor, none of the expected isoxazoline 54 was formed but a 28% yield of 5-phenyl-3-vinylisoxazoline 17 was observed. It was deduced that catalytic amounts of triethylamine were removing the elements of acetic acid either from the starting material which then generates ANO, or after the nitrile oxide formation.

To establish the mechanism two additional experiments were required. In the first reaction both the dipolarophile (styrene) and phenyl isocyanate were omitted; only the triethylamine and the acetate were present. The result showed the formation of a small amount of 1-nitropropene (20% yield) which strongly favours path a. For the second experiment styrene was omitted from the reaction to see if any furoxan 53 could be detected by NMR spectroscopy and thus provide evidence for the formation of nitrile oxide 52 (path b). A large number of compounds were observed by TLC and these were subjected to dry flash chromatography. $^1$H NMR spectroscopy did not provide conclusive evidence to suggest the presence of furoxan. An IR spectrum of the reaction mixture did not contain a peak at $\sim 1600$ cm$^{-1}$, which is characteristic of a furoxan ring. The reaction conditions were the same in both experiments. It was therefore deduced that path a is the more likely mechanism.
Having established suitable conditions for generating and trapping ANO its cycloadditions with various dipolarophiles were investigated. The adducts were synthesised using Mukaiyama methodology and purification was achieved by dry flash chromatography; the yields were not optimised. The vinyl heterocycles were fully characterised by $^1$H and $^{13}$C NMR spectroscopy and mass spectrometry.

To determine their relative reactivities and to rationalise substituent effects, a series of competition experiments were also devised. Six dipolarophiles were selected on the basis of the electronic or steric nature of their substituents; $\alpha$-
Table 5 Selected $^1$H NMR spectroscopic data for the ANO adducts; ($\delta_H$, p.p.m.; $J$, Hz) (200 MHz, CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$\delta_H^B$</th>
<th>$\delta_H^C$</th>
<th>$\delta_H^A$</th>
<th>$J_{BC}$</th>
<th>$J_{BA}$</th>
<th>$J_{AC}$</th>
<th>Others</th>
<th>$\delta_H^{4b}$</th>
<th>$\delta_H^{4a}$</th>
<th>$\delta_H^5$</th>
<th>$J_{4b4a}$</th>
<th>$J_{4a5}$</th>
<th>$J_{4b5}$</th>
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</thead>
<tbody>
<tr>
<td>17</td>
<td>5.54</td>
<td>5.41</td>
<td>6.73</td>
<td>0.5</td>
<td>10.9</td>
<td>17.7</td>
<td>-</td>
<td>3.05</td>
<td>3.49</td>
<td>5.60</td>
<td>16.5</td>
<td>11.0</td>
<td>8.4</td>
</tr>
<tr>
<td>55</td>
<td>5.49</td>
<td>5.40</td>
<td>6.70</td>
<td>0.4</td>
<td>10.9</td>
<td>17.7</td>
<td>-</td>
<td>2.90</td>
<td>3.50</td>
<td>5.59</td>
<td>16.6</td>
<td>11.0</td>
<td>8.2</td>
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<tr>
<td>56</td>
<td>5.57</td>
<td>5.48</td>
<td>6.68</td>
<td>*</td>
<td>10.9</td>
<td>17.7</td>
<td>-</td>
<td>3.02</td>
<td>3.43</td>
<td>5.54</td>
<td>16.9</td>
<td>10.8</td>
<td>8.5</td>
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<td>5.57</td>
<td>5.49</td>
<td>6.71</td>
<td>*</td>
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<td>17.7</td>
<td>-</td>
<td>3.02</td>
<td>3.43</td>
<td>5.54</td>
<td>16.9</td>
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</tr>
<tr>
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<td>5.51</td>
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<td>6.68</td>
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<td>10.8</td>
<td>17.7</td>
<td>$J_{4b}0.7$</td>
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<td>-</td>
<td>16.4</td>
<td>-</td>
<td>-</td>
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<td>5.53</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
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<td>5.48</td>
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<td>-</td>
<td>16.6</td>
<td>-</td>
<td>-</td>
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</table>

*; undetected $< 0.4$ Hz

---

![Structures](https://via.placeholder.com/150)
methylstyrene, methyl acrylate, methyl vinyl ketone and three substituted styrenes; 
*p*-methoxystyrene, *p*-chlorostyrene and *m*-nitrostyrene.

Methyl methacrylate, butadiene and 1,3-diisopropenylbenzene were also 
cycloadded to ANO. The 1,3-diisopropenyl adduct is interesting as the alkenyl
appendages may polymerise more readily than the 3-vinylisoxazoline. Polymer
studies with 3-vinyl-5-vinylisoxazoline may distinguish a difference between the two
alkenyl moieties. Methyl methacrylate was investigated to observe the effect of
disubstitution by comparison with methyl acrylate.

Selected NMR data for the ANO adducts are presented in Tables 4 and 5.

**Table 4** Selected $^{13}$C NMR spectroscopic data for ANO adducts;
($\delta_c$, p.p.m.) (50 MHz; CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$C_3$</th>
<th>$C_4$</th>
<th>$C_5$</th>
<th>others</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>156.9</td>
<td>40.9</td>
<td>82.3</td>
<td>-</td>
</tr>
<tr>
<td>55</td>
<td>157.1</td>
<td>41.2</td>
<td>81.6</td>
<td>C-Cl 139.1</td>
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<tr>
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<td>157.2</td>
<td>41.3</td>
<td>81.6</td>
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<tr>
<td>57</td>
<td>157.2</td>
<td>40.7</td>
<td>82.2</td>
<td>C-O 159.3</td>
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<td>58</td>
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<td>47.5</td>
<td>84.0</td>
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<td>63</td>
<td>157.2</td>
<td>46.6</td>
<td>87.9</td>
<td>-</td>
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</table>

The $^{13}$C NMR data for ANO adducts 17 and 55-63 highlights the similarities
and differences. As expected the chemical shifts for $C_3$, which is adjacent to the
vinyl group, are very similar. On the other hand the $C_5$ values show a strong
substituent effect, varying from 77.6 p.p.m. (methoxycarbonyl) to 87.9 p.p.m. for
isoxazolines 58 and 63. The phenyl group is especially effective in influencing the
chemical shift of nearby atoms and a shift downfield (to higher $\delta$ values) is
observed; this effect is accentuated when there is also a methyl group at this 5-
position. The acetyl group, a $\pi$- acceptor, causes the largest upfield shift for $C_5$ and
$C_4$.

The $^1$H NMR spectroscopic data for the ANO adducts are shown in Table 5.
The characteristic patterns for both the vinyl and isoxazoline fragments may be
identified. The vinylic protons are relatively unaffected by changes in substitution at
the 5-position, as are the associated couplings. The chemical shift of proton H5 however is influenced strongly by the nature of the adjacent group. For example in 5-acetyl-3-vinylisoxazoline H5 is observed at 4.93 p.p.m. whereas in 5-(m-nitrophenyl)-3-vinylisoxazoline 56 it is at a much lower field, 5.72 p.p.m. A long range coupling of 0.7 Hz between HA on the 3-vinyl substituent and H4b is observed in compound 58; this is not detected in the other ANO adducts.

2.3.4 Methacrylonitrile oxide and but-2-enonitrile oxide

The series of α,β-unsaturated nitrile oxides was extended to include methacrylonitrile oxide (CH2=CMeC≡N+-O-) 64 and but-2-enonitrile oxide (CH3CH=CHC≡N+-O-) 65. The procedure used was very similar to that described in Section 2.3.2 for acrylonitrile oxide. The precursor for methacrylonitrile oxide was prepared by the condensation of acetone and nitromethane. Acetylation of the resulting alcohol and subsequent treatment with base afforded 1-nitro-2-methylpropene, in an overall yield of 20% (Scheme 50).

Scheme 50

(CH3)2C=O + CH3NO2 → a CH3C=CH2NO2 (45%) → b CH3C=CH2NO2 (80%)

Reagents: a; 10M NaOH, 5-10°C, b; H2SO4, (CH3CO)2O, 60°C, c; Na2CO3, C6H6, ∆.

The precursor to but-2-enonitrile oxide, 1-nitrobut-1-ene, was prepared from propanal and nitromethane by a three step synthetic sequence similar to that described in Section 2.3.2; an overall yield of 22% was obtained. (Scheme 51).
1-nitrobut-1-ene has a trans configuration as indicated from the $^1$H NMR spectrum which showed a large coupling constant of 13.4 Hz between the alkene protons.

Scheme 51

\[
\text{CH}_3\text{CH}_2\text{CHO} + \text{CH}_3\text{NO}_2 \xrightarrow{\text{a}} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{NO}_2 \xrightarrow{\text{b}} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{NO}_2 \xrightarrow{\text{c}} \text{CH}_3\text{CH}_2\text{CH}==\text{CHNO}_2
\]

**Reagents:** a; 10M NaOH, 5-10°C, b; H$_2$SO$_4$, (CH$_3$CO)$_2$O, 60°C, c; Na$_2$CO$_3$, C$_6$H$_6$, Δ.

2.3.5 Methacrylonitrile oxide, but-2-enonitrile oxide and propanonitrile oxide cycloaddition reactions

Methacrylonitrile oxide (MANO), but-2-enonitrile oxide (BNO) and propanonitrile oxide (PNO) were cycloadded to various dipolarophiles to form adducts 72-78. Selected $^1$H and $^{13}$C NMR spectroscopic data for those compounds are presented in Tables 6 and 7. The structures of the heterocycles, with their associated yields, are also illustrated. The MANO adducts were selected as they are good candidates for polymerisation, being structurally similar to α-methylstyrene. Although but-2-enonitrile oxide adducts bearing propenyl appendages are not suitable for polymerisation, this hitherto unknown α,β-unsaturated nitrile oxide could be compared with the ANO and MANO adducts in terms of reactivity. PNO, a saturated nitrile oxide, was included in the study comparison with the unsaturated analogues. The precursor, 1-nitropropane, is readily available.
Table 7 Selected $^1$H NMR spectroscopic data for the methacrylonitrile oxide, but-2-enonitrile oxide and propanonitrile oxide adducts ($\delta_H$, p.p.m.; $J$, Hz) (200 MHz, CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_H^a$</th>
<th>$\delta_H^b$</th>
<th>$\delta_H^c$</th>
<th>$J_{BC}$</th>
<th>$J_{CMe}$</th>
<th>$J_{BMe}$</th>
<th>$\delta_H^{4b}$</th>
<th>$\delta_H^{4a}$</th>
<th>$\delta_H^g$</th>
<th>$J_{4a4b}$</th>
<th>$J_{4a5}$</th>
<th>$J_{4b5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 (54%)</td>
<td>5.31 5.17</td>
<td>2.08</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>3.06</td>
<td>3.54</td>
<td>5.63</td>
<td>16.4</td>
<td>10.8</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>73 (20%)</td>
<td>5.34 5.30</td>
<td>2.02</td>
<td>*</td>
<td>1.2</td>
<td>1.2</td>
<td>2.86</td>
<td>3.23</td>
<td>5.18</td>
<td>16.3</td>
<td>10.6</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>74 (39%)</td>
<td>5.12 5.09</td>
<td>2.05</td>
<td>*</td>
<td>1.6</td>
<td>1.6</td>
<td>3.26</td>
<td>3.26</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>75 (53%)</td>
<td>6.20 5.97</td>
<td>1.92</td>
<td>11.7</td>
<td>1.6</td>
<td>7.2</td>
<td>3.16</td>
<td>3.63</td>
<td>5.60</td>
<td>16.6</td>
<td>10.8</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>76 (31%)</td>
<td>6.04 5.96</td>
<td>1.90</td>
<td>12.7</td>
<td>1.5</td>
<td>6.7</td>
<td>3.40</td>
<td>3.40</td>
<td>5.03</td>
<td>-</td>
<td>9.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>77 (36%)</td>
<td>2.37 1.17</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>2.88</td>
<td>3.37</td>
<td>5.53</td>
<td>16.9</td>
<td>10.7</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>78 (43%)</td>
<td>2.37 1.17</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>2.88</td>
<td>3.30</td>
<td>5.46</td>
<td>16.9</td>
<td>10.6</td>
<td>8.5</td>
<td></td>
</tr>
</tbody>
</table>

* undetected; <0.4 Hz
Table 6 Selected $^{13}$C NMR spectroscopic data

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>C$_3$</th>
<th>C$_4$</th>
<th>C$_5$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>157.8</td>
<td>42.1</td>
<td>82.5</td>
<td>-</td>
</tr>
<tr>
<td>73</td>
<td>158.3</td>
<td>39.7</td>
<td>82.3</td>
<td>-</td>
</tr>
<tr>
<td>74</td>
<td>158.1</td>
<td>47.9</td>
<td>88.3</td>
<td>-</td>
</tr>
<tr>
<td>75</td>
<td>155.5</td>
<td>45.3</td>
<td>82.1</td>
<td>-</td>
</tr>
<tr>
<td>76</td>
<td>155.1</td>
<td>40.9</td>
<td>77.6</td>
<td>C=O 170.7</td>
</tr>
<tr>
<td>77</td>
<td>159.3</td>
<td>44.9</td>
<td>81.1</td>
<td>-</td>
</tr>
<tr>
<td>78</td>
<td>159.2</td>
<td>44.8</td>
<td>81.0</td>
<td>C=O 159.3</td>
</tr>
</tbody>
</table>

The data in table 6 indicate the effect of replacing a vinyl group at the 3-position of the isoxazoline ring with either an isopropenyl or an saturated ethyl group. Unexpectedly, the C$_3$ values of the ethyl adducts are at a lower field (−159 p.p.m.) compared to the vinyl adducts (−157 p.p.m). Conversely, the propenyl appendages appear to shift the δ values for C$_3$ to a higher field (−155 p.p.m.) as predicted.

The chemical shifts of C$_5$ reflect the electronic nature of the adjacent substituent. In some cases steric factors may also be influential, for example the methyl substitution in compound 74.

Selected $^1$H NMR spectroscopic data are shown in Table 7. The MANO adducts appear to have small allylic couplings between H$_B$ (or H$_C$) and the methyl group. The geminal coupling for H$_B$ and H$_C$ is 0.8 Hz in compound 72 however this is <0.4 Hz in compounds 73 and 74 which is too small to be detected. In the propenyl adducts, compounds 75 and 76, an observed coupling of 12 Hz ($J_{AC}$) confirms the trans configuration. Compounds 77 and 78 have ethyl appendages at the 3-position which appear as a triplet and quartet at 1.17 and 2.37 p.p.m. respectively.
2.3.6 Competition experiments

2.3.6.1 Introduction

The reactivities of alkenyl dipolarophiles in cycloaddition reactions with various nitrile oxides have been reported by Battaglia et al.\textsuperscript{165} and Dondoni.\textsuperscript{166} Caramella and Grünanger have also reviewed the subject.\textsuperscript{1}

The relative dipolarophilic activities in the cycloadditions of benzonitrile oxide have been determined by Huisgen et al.\textsuperscript{167} The dipole was generated \textit{in situ} in refluxing ether (0-5°C) in the presence of a variety of olefinic and acetylenic dipolarophiles and the relative rates determined by competition experiments. A selection of the rate constants, relative to ethylene, is given in Table 8.

<table>
<thead>
<tr>
<th>dipolarophile</th>
<th>relative rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethylene</td>
<td>1.00</td>
</tr>
<tr>
<td>styrene</td>
<td>1.15</td>
</tr>
<tr>
<td>4-nitrostyrene</td>
<td>2.34</td>
</tr>
<tr>
<td>4-methoxystyrene</td>
<td>1.70</td>
</tr>
<tr>
<td>4-chlorostyrene</td>
<td>1.55</td>
</tr>
<tr>
<td>methyl acrylate</td>
<td>8.29</td>
</tr>
<tr>
<td>methyl methacrylate</td>
<td>6.10</td>
</tr>
<tr>
<td>acetylene</td>
<td>0.40</td>
</tr>
<tr>
<td>phenylacetylene</td>
<td>0.11</td>
</tr>
<tr>
<td>methyl propiolate</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Some characteristic features appear on inspection of the data. In monosubstituted alkenes π-conjugation has a strong promoting effect whereas dissubstitution decreases the reactivity. The reactivity of alkynes is lower than that of the corresponding alkenes, showing that a gain in aromaticity in the formation of isoxazoles does not effect their rate of formation. This is consistent with an early transition state.\textsuperscript{168}

FMO calculations offer simultaneously an explanation for the relative reactivities of dipoles and dipolarophiles. Substituents in the reactants affect the HOMO - LUMO interaction in the transition state, upon which depends the activation energy, and consequently the reaction rate. Thus to rationalise reactivity
and regioselectivity in nitrile oxide 1,3-dipolar additions it is necessary to know the dipole HOMO and LUMO energy levels and molecular orbital coefficients. These have been estimated by Houk\textsuperscript{17,18} using a combination of experiment and calculation for a selection of the more common 1,3-dipoles. For example, the reported values for benzonitrile oxide gave an associated HOMO energy of -10.0 eV and a LUMO energy of -1.0 eV and formonitrile oxide has a HOMO energy of -11.0 eV and a LUMO energy of -0.5 eV.

Depending on the relative energies of the interacting frontier orbitals, the 1,3-dipolar reaction can either be controlled by the dipole HOMO and dipolarophile LUMO (Sustmann type I, Figure 4 in the Introduction Section), by the dipole LUMO and dipolarophile HOMO (Sustmann type III) or by the control of both sets of frontier orbitals (Sustmann Type II). In the former case the energy gap between the dipole HOMO and dipolarophile LUMO is the smaller and in Sustmann Type III the dipole LUMO and dipolarophile HOMO have the stronger interaction.

Most nitrile oxide additions are considered to be dipole LUMO controlled for electron-rich and conjugated dipolarophiles (Sustmann Type III). For electron-deficient dipolarophiles, dipole HOMO and LUMO control is finely balanced (Sustmann Type II) and in some cases may be dipole HOMO controlled.\textsuperscript{168} This explains why both electron-donating and electron-withdrawing substituents can accelerate a 1,3-dipolar cycloaddition.

### 2.3.6.2 Competition experiments results

The relative reactivities of a series of dipolarophiles towards acrylonitrile oxide (ANO), methacrylonitrile oxide (MANO) and propanonitrile oxide (PNO) were examined using competition experiments. The reactions were carried out using an excess of the two dipolarophiles to maintain an effectively constant concentration. The reactant ratio of dipolarophile : dipolarophile : nitro-compound was 6:6:1 and the reaction conditions were identical in each experiment.

A solution of the nitromethyl compound (1 equiv.) in chloroform was added over 16 hours (using a motorised syringe pump), at room temperature to a stirred solution of phenyl isocyanate (2.5 equivs.), triethylamine (3 drops) and the two dipolarophiles (each 6 equivs.) in chloroform. The diphenylurea byproduct was filtered off and the solvent evaporated in vacuo. Polar impurities were removed by dry flash chromatography. The resulting crude mixture of adducts was subjected to \textsuperscript{13}C and \textsuperscript{1}H NMR spectroscopy and the characteristic peaks for the two isoxazolines were identified by comparison with the authentic adducts. The \textsuperscript{13}C NMR spectra were used to determine the adduct ratio from the intensities of suitable peaks, usually
Spectrum 2: $^{13}$C NMR spectrum for the competition experiment between $\alpha$-methylstyrene and styrene showing compound 17 to be the major product (50 MHz, CDCl$_3$)

* associated carbons bracketed
C₃ and C₄ which have very similar chemical environments in the two products. A paramagnetic salt, chromium acetylacetonate (Cracac) was added to allow quantative relaxation. Comparable results were also obtained by measuring selected integrals in the proton NMR spectra.

The results, displayed in Table 9, are compared to styrene and will be rationalised and applied to FMO theory where appropriate. The procedure adopted is illustrated for a typical competition experiment, styrene vs. α-methylstyrene with ANO.

Under standard Mukaiyama conditions the two competing dipolarophiles, styrene and α-methylstyrene, were reacted with acrylonitrile oxide, generated from 1-nitropropene at room temperature. After 16 hours the reaction mixture was filtered through celite and the filtrate was subjected to a crude dry flash column to remove the base-line material. ¹³C and ¹H NMR spectroscopy were used to identify the products and to determine the adduct ratio.

The C₃ and C₄ peaks associated with 5-phenyl-3-vinylisoxazoline 17 (157.0 and 40.9 p.p.m.) and 5-methyl-5-phenyl-3-vinylisoxazoline 58 (157.2 and 46.9 p.p.m.) were identified by comparison with the authentic adducts (illustrated in Spectrum 2). The C₅ values were not considered to be as reliable as they are directly affected by variations in the adjacent substituents. Measurement of product ratio by comparison with peak heights with and without Cracac gave similar results (± 0.5%) which suggests comparable relaxation times.

The ratio of the two isoxazolines was also calculated from the proton NMR spectrum by measuring the appropriate integrals. In this case, the integral associated with the methyl group from 5-methyl-5-phenyl-3-vinylisoxazoline 58 was compared with the sum of the integrals for the ring protons H₄a and H₄b for both adducts. The ratio (58 : 17) was calculated to be 20% : 80%.

The ratios measured from the ¹H and ¹³C NMR data are the same within experimental error. The table below shows the calculated ratios.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ratio from C₃</th>
<th>ratio from C₄</th>
<th>ratio from ¹H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Phenyl-3-vinylisoxazoline 17</td>
<td>80.7%</td>
<td>80.6%</td>
<td>80%</td>
</tr>
<tr>
<td>5-Methyl-5-phenyl-3-vinylisoxazoline 58</td>
<td>19.3%</td>
<td>19.4%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Table 9 - A summary of the competition results

<table>
<thead>
<tr>
<th>Dipolarophiles selected</th>
<th>styrene vs. α-methylstyrene</th>
<th>styrene vs. methyl acrylate</th>
<th>styrene vs. p-methoxystyrene</th>
<th>styrene vs. p-chlorostyrene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrile oxide</td>
<td>ANO</td>
<td>ANO</td>
<td>ANO</td>
<td>ANO</td>
</tr>
<tr>
<td>Mixture of adducts obtained</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>ratio of adducts</td>
<td>81%</td>
<td>19%</td>
<td>28%</td>
<td>72%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dipolarophiles selected</th>
<th>styrene vs. m-nitrostyrene</th>
<th>styrene vs. methyl acrylate</th>
<th>styrene vs. p-methoxystyrene</th>
<th>methyl vinyl ketone vs. methyl acrylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrile oxide</td>
<td>ANO</td>
<td>MANO</td>
<td>PNO</td>
<td>ANO</td>
</tr>
<tr>
<td>Mixture of adducts obtained</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>ratio of adducts</td>
<td>46%</td>
<td>54%</td>
<td>12%</td>
<td>88%</td>
</tr>
</tbody>
</table>
It is concluded that α-methylstyrene is a poorer dipolarophile than styrene itself. This is consistent with previous work\textsuperscript{1} which has shown that steric effects render 1,1-disubstituted alkenes less reactive than the monosubstituted analogues.

The second pair of dipolarophiles to be examined were methyl acrylate and styrene. The appropriate peaks in the $^{13}$C NMR spectrum associated with 5-phenyl-3-vinylisoxazoline 17 and 3-methoxycarbonyl-isoxazoline 60 were identified by comparison to the authentic adducts. By measuring the C\textsubscript{3} and C\textsubscript{4} peaks a ratio of 72\% : 28\% was obtained for the two isoxazolines (compound 60 : compound 17).

The greater reactivity of methyl acrylate may be attributed to the strongly electron-withdrawing nature of the methoxycarbonyl group. This group effectively lowers the LUMO energy which decreases the HOMO dipole-LUMO dipolarophile gap (electron poor dipolarophiles favour Sustmann Type I) thus accelerating the reaction and favouring the formation of compound 60.

The next three dipolarophiles selected for the competition experiments with acrylonitrile oxide were substituted styrenes. The results (Table 10) indicate a very small difference in reactivity when the phenyl group contains a $p$-chloro or a $m$-nitro substituent; the ratios were 47\% : 53\% for styrene : $p$-chlorostyrene and 46\% : 54\% for styrene : $m$-nitro styrene. In contrast, the corresponding ratio for styrene vs $p$-methoxystyrene was 61\% : 39\%. This indicates a decrease in the reactivity of the dipolarophile reflecting the electron-donating properties of the $p$-methoxy group which raises the HOMO and LUMO energy levels (suggesting Sustmann Type II).

The associated Hammett $\sigma$-values for the substituted styrenes are compared to the relative rates in Table 10. A positive $\sigma$-value indicates an electron-withdrawing group and a negative value an electron-donating group.

The electronic effect of meta and para substituents is dampened at the reaction centres of phenyl-bearing dipolarophiles as a result of transmission across the benzene ring. The small size of the rate effect implies minute changes of MO energies; consequently a small section of the reactivity curve is involved. Notoriously small rate effects\textsuperscript{1} have been observed for the cycloaddition of nitrile oxides to substituted styrenes. Correlation of the rate data for aromatic nitrile oxides according to the Hammett equation give rise to V-shaped Hammett plots.\textsuperscript{1} Previous work by Dondoni \textit{et al}\textsuperscript{166} has shown a mild rate acceleration by both electron withdrawing and electron releasing substituents.

To identify any differences or similarities in the reactivity trends the relative rates for the cycloaddition of benzonitrile oxide (Table 8) are compared with the ANO in Table 10 for the substituted styrenes (taking styrene as unity). Surprisingly, in contrast to the BNO results ANO does not give a V-shaped Hammett plot; rather
electron-withdrawing groups accelerate the reaction and electron-donating substituents retard it.

**Table 10** Relative reactivity rates and $\sigma$-values for substituted styrenes

<table>
<thead>
<tr>
<th>dipolarophile</th>
<th>relative rates of BNO</th>
<th>relative rates of ANO</th>
<th>$\sigma$-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-nitrostyrene</td>
<td>2.04</td>
<td>-</td>
<td>0.81</td>
</tr>
<tr>
<td>3-nitrostyrene</td>
<td>-</td>
<td>1.17</td>
<td>0.71</td>
</tr>
<tr>
<td>4-chlorostyrene</td>
<td>1.48</td>
<td>1.13</td>
<td>0.24</td>
</tr>
<tr>
<td>styrene</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>4-methoxystyrene</td>
<td>1.35</td>
<td>0.63</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

The competition reaction of styrene vs. methyl acrylate with MANO was performed to investigate the effect of a methyl group attached to an $\alpha,\beta$-unsaturated nitrile oxide on the reactivity. The results indicate a slightly increased rate compared to the analogous ANO example. A methyl group is electron-donating (raising the HOMO and LUMO energy levels) and may favour Sustmann Type II behaviour.

The effect of replacing a vinyl substituent for an ethyl group in the nitrile oxide component was studied by competing styrene vs. $p$-methoxystyrene with PNO and comparing the results with the analogous ANO cycloaddition. Whereas the ethyl substituent in PNO is electron-donating, the conjugating vinyl group in ANO may be expected to raise the HOMO energy and lower the LUMO energy leading to Sustmann Type II behaviour, where the interactions are finely balanced. The ratio was 48%:52% for styrene:$p$-methoxystyrene with PNO compared to 61%:39% for the same dipolarophiles with ANO. These results suggests a shift towards Sustmann Type III for PNO.

The last competition experiment investigated the relative reactivities of methyl vinyl ketone and methyl acrylate with ANO. The percentage ratios were 63%:37% for 5-acetyl-3-vinylisoxazoline and 5-methoxycarbonyl-3-vinylisoxazoline, respectively. Although the two substituents are both electron-withdrawing it appears methyl vinyl ketone is the more reactive dipolarophile.
2.3.6.3 Molecular orbital calculations

The frontier orbital energy separations have been calculated by Houk et al.\textsuperscript{169} for various dipolarophiles with formonitrile oxide and benzonitrile oxide using the CNDO method. Although this simple treatment tends to underestimate reactivity for dipole HOMO controlled reactions, the results generally support the conclusion that electron-rich nitrile oxides react under dipole LUMO control. They also show that the presence of a conjugating phenyl group in benzonitrile oxide raises the dipole HOMO and lowers its LUMO compared with HCNO and MeCNO leading to increased reactivity. More sophisticated \textit{ab initio} calculations have been carried out on formonitrile oxide and acetonitrile oxide.\textsuperscript{170}

In order to gain a better understanding of the influence of the vinyl substituent in ANO on the frontier orbital energies, and hence the reactivity of the dipole, \textit{ab initio} SCF-MO calculations have been performed. These calculations were carried out by Dr I. Alberts using MP2 level of theory with DCP basis set.\textsuperscript{171} Four nitrile oxides were selected: formonitrile oxide, acetonitrile oxide, propanonitrile oxide (PNO) and acrylonitrile oxide (ANO); calculations have been reported\textsuperscript{17,18} previously for the first two dipoles. A summary of the data for all four nitrile oxides are given in the Appendix. The results for PNO, which bears an electron-donating group, and ANO with its conjugating vinyl substituent are of particular significance to this thesis, and the geometries and frontier orbital energies are worthy of discussion. For these calculations the CNO unit was assumed to be linear and both PNO and ANO were assigned C\textsubscript{5} symmetry.

2.3.6.3.i Geometry

The calculated optimised geometries for PNO and ANO are illustrated in Figure 7. Noteworthy features include;

(a) PNO and ANO have C-N bond lengths of ~1.19Å compared with a typical C=N bond of 1.14Å. The N-O bond length is ~1.22Å. These compare well with values for nitrile oxides determined by X-ray crystallography and microwave spectroscopy.\textsuperscript{1,2}

(b) There are significant differences in the carbon-carbon bond lengths for the two compounds. For PNO the bond joining the CNO to the adjacent carbon is 1.47Å which is typical of an sp\textsuperscript{3}-carbon to sp-carbon link. Likewise the value of 1.55Å for the CH\textsubscript{3}-CH\textsubscript{2} is as expected for an sp\textsuperscript{3}-sp\textsuperscript{3} bond. In contrast for ANO the bond joining the CNO to the vinyl group is significantly shorter (1.43Å). This observation provides clear evidence for conjugation between the vinyl and nitrile oxide moieties.
Figure 5

Optimised geometries (MP2/DZP) for nitrile oxides (bond lengths in Å).

C-N-O assumed linear
PNO staggered conformation with $C_s$ symmetry
ANO molecule assumed planar with $C_s$ symmetry
2.3.6.3.ii Frontier orbital energies and coefficients

The calculated orbital energies and molecular orbital coefficients for PNO and ANO are compared in Table 11. Of particular significance are the differences in orbital energies. Replacement of the ethyl substituent in PNO by the conjugating vinyl group in ANO raises the HOMO energy by 0.573 eV, and there is an even greater effect on the LUMO energy which is lowered by 2.703 eV. The LU-HO gap for ANO is 11.497 eV compared with 14.773 eV for PNO. A similar compression in the frontier orbital energies for benzonitrile oxide has been reported, which also contain a conjugating substituent, and is associated with augmented reactivity in cycloaddition reactions.

The substituent effect on the molecular orbital coefficient is greater for the LUMO then the HOMO, particularly for the adjacent carbon. In the LUMO the conjugating vinyl group reduces the carbon coefficient substantially (0.181 \textit{cf} 0.345) and there are also small changes for the more remote nitrogen and oxygen atoms. For the HOMO the nitrogen and oxygen coefficients are largely unchanged; however there is a small change at the carbon (-0.329 \textit{cf} -0.419).

Table 11 HO and LU $\pi$ and in-plane molecular orbital coefficients and energies for propanonitrile oxide and acrylonitrile oxide

<table>
<thead>
<tr>
<th>Nitrile oxide</th>
<th>HO ($\pi$) C</th>
<th>N</th>
<th>O</th>
<th>E (eV)</th>
<th>LU ($\pi$) C</th>
<th>N</th>
<th>O</th>
<th>E(eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNO</td>
<td>-0.419</td>
<td>-0.260</td>
<td>0.545</td>
<td>-10.227</td>
<td>0.345</td>
<td>-0.471</td>
<td>0.236</td>
<td>4.546</td>
</tr>
<tr>
<td>ANO</td>
<td>-0.329</td>
<td>-0.256</td>
<td>0.546</td>
<td>-9.654</td>
<td>0.181</td>
<td>-0.321</td>
<td>0.191</td>
<td>1.843</td>
</tr>
</tbody>
</table>

In summary the calculations confirm predictions that the vinyl group has a conjugating effect comparable with that of phenyl substituent. Acrylonitrile oxide reflects the reactivity of benzonitrile oxide more than formonitrile oxide or an alkynitrile oxide.
2.4 3-Vinylisoxazole

2.4.1 Introduction

We have sought to utilise nitrile oxide chemistry to prepare 3-vinylisoxazole 79. This previously unknown compound, which is unsubstituted at both 4- and 5-positions, would be ideally suited for polymerisation. Although formally a cycloadduct between acrylonitrile oxide and acetylene itself, direct reaction is not feasible; not only is acetylene a gas but it is also unreactive.\textsuperscript{172} Instead an indirect approach was adopted using a more reactive dipolarophile, norbornadiene, which is effectively acting as an acetylene equivalent.\textsuperscript{173} A retro Diels-Alder fragmentation would then be possible on the resulting adduct.

The method selected was based on reported syntheses\textsuperscript{174,175,176} of 5-membered heterocycles from norbornadiene with the appropriate nitrilium betaine. The synthesis of 3-phenylisoxazole from benzonitrile oxide and norbornadiene\textsuperscript{174,177} is known and thus this was chosen as a model to establish optimum reaction conditions. Product formation involves the cycloaddition-cycloreversion pathway outlined in Scheme 52. The 1,3-dipole, benzonitrile oxide, readily adds to norbornadiene yielding a mixture of cycloadducts 80 (exo) and 81 (endo). Subsequent thermolysis (>140°C) of both adducts resulted in the formation of isoxazole 82 in a retro Diels-Alder (rDA) reaction which involved the extrusion of cyclopentadiene. Parallel behaviour with acrylonitrile oxide (ANO) should afford the desired 3-vinylisoxazole via isoxazoline 83 (Scheme 53).

Scheme 52
2.4.2 The synthesis of 5-membered heterocycles via retro Diels-Alder reactions

The retro Diels-Alder (rDA) reaction is a $\pi^2s + \sigma^2s + \sigma^2s$ electrocyclic process that, as the name implies, is the reverse of the familiar Diels-Alder cycloaddition reaction.\textsuperscript{169} There are several reported cases of the products of 1,3-dipolar addition undergoing such a retrodiene reaction; a few illustrative examples are discussed. Compound 84, the adduct of diphenyl nitrilimine (generated \textit{in situ} from 85) and norbornadiene decomposes at its melting point of 135°C to give 86 (98%) along with cyclopentadiene (77%)\textsuperscript{176} (Scheme 54).

In addition to the preparation of 3-phenylisoxazole 82 described in Section 2.4.1, isoxazoline 87, the 1,3-dipolar adduct of norbornadiene and fulminic acid generated \textit{in situ} by dehydroiodination of 88, also undergoes rDA at 140-160°C to give cyclopentadiene and parent isoxazole 89 in 90% yield\textsuperscript{174} (Scheme 55).

Heating 5-phenyl-1,3,4-oxathiazol-2-one (>130°C) 91 in the presence of norbornadiene affords 3-phenylisothiazole 92, presumably via initial decarboxylation to generate benzonitrile sulphide as a transient intermediate; cycloaddition then furnishes isothiazoline 93 and subsequent elimination of cyclopentadiene in a rDA reaction (Scheme 56) affords compound 92.\textsuperscript{175}

Many rDA reactions are carried out at temperatures of 150°C or more by refluxing but unfortunately often give by-products. An alternative to solution phase thermolysis is to utilise the flash vacuum pyrolysis (FVP) technique.\textsuperscript{178} Although the temperatures involved are higher, typically 400-600°C, it is a mild method as contact times are low (10\textsuperscript{-3} - 10\textsuperscript{-1} sec); this has been used to advantage in the preparation of 3-phenylisoxazole and 3-vinylisoxazole.
The reactions of arylazides, benzonitrile oxides and diphenylnitrile imine with norbornadiene derivatives have been studied in detail by Cristina et al.179 In each case the thermally labile adducts furnished pentatomic heterocycles via Diels-Alder cycloreversions.

Scheme 54

\[
\text{PhCCI} = \text{NNHPh} \xrightarrow{\text{Et}_3\text{N}} \text{Ph}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\Delta 
\]

\[
\text{Ph} \quad \text{Ph} \\
\text{N} & \quad \text{N}
\]

\[
\begin{align*}
\text{Et}_3\text{N} & \quad \text{Et}_3\text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\text{Ph} \quad \text{Ph} \\
\text{N} & \quad \text{N}
\]

Scheme 55

\[
\text{H} - \text{C} = \text{N-OH} \xrightarrow{\text{Et}_3\text{N}} \text{N}(+O)
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\Delta 
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\text{Et}_3\text{N} \\
\text{N} & \quad \text{N}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\text{Et}_3\text{N} \\
\text{N} & \quad \text{N}
\]

\[
\text{Ph} \quad \text{Ph} \\
\text{N} & \quad \text{N}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\text{Et}_3\text{N} \\
\text{N} & \quad \text{N}
\]

\[
\text{Ph} \quad \text{Ph} \\
\text{N} & \quad \text{N}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\text{Et}_3\text{N} \\
\text{N} & \quad \text{N}
\]

\[
\text{Ph} \quad \text{Ph} \\
\text{N} & \quad \text{N}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]
Interestingly, 2-(5-norbornen-2-yl)imidazole 94 has been readily converted into 2-vinylimidazole 95 via rDA decomposition using flash vacuum pyrolysis (FVP), as depicted in Scheme 57. Previously, 2-vinylimidazoles had been obtained by lengthy reaction schemes with a low overall yield.
Figure 6 illustrating the range of possible products from the cycloaddition of benzonitrile oxide to norbornadiene.
2.4.3 Nitrile oxide cycloadditions to norbornadiene

*exo-* and *endo*-4,7-Methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole, compounds 80 and 81 (structures illustrated in Scheme 52), were constructed by the cycloaddition reaction of benzonitrile oxide, generated *in situ* by triethylamine, to norbornadiene. The crude product was subjected to dry flash chromatography affording, in addition to the desired *exo* and *endo* adducts, a fraction containing a mixture of 2:1 adducts. The *exo* and *endo* compounds were white crystalline products (m.p. *exo* 62-63°C, *endo* 61-63°C) and were identified by 1H and 13C NMR spectroscopy and mass spectrometry. Their yields were 54% and 16%, respectively. (Selected NMR data are presented in Tables 13 and 15).

The mixture of 2:1 adducts was examined by 1H NMR spectroscopy. Theoretically there are six possible 2:1 combinations (illustrated in Figure 6), however adducts 96-99 are the more thermodynamically favoured structures. Although a total of four adducts were detected only three of these were identified; *exo, endo, anti* 98, *exo, exo, syn* 97; and *exo, endo, syn* 99. Assignments were facilitated by decoupling experiments, COSY NMR spectroscopy and reference to research by Cocu *et al.*181 The *exo, exo, anti* product was not observed, possibly due to its low solubility. By measuring the appropriate integrals it was estimated that adducts 98, 97 and 99 were present in an approximate ratio of 9:9:8. The fourth compound remained elusive.

Having established conditions for the synthesis of the benzonitrile oxide adduct, *exo-* and *endo*-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole (compounds 83 and 102) were also synthesised using Mukaiyama methodology (structures illustrated in Figure 7). The ANO precursor, 1-nitropropene, was added dropwise over 18 hours at room temperature to a mixture of phenyl isocyanate, norbornadiene and triethylamine. Dry flash chromatography furnished the two isomers, in a moderate yield of 35% (*exo*) and 11% (*endo*); both compounds were fully characterised by 1H and 13C NMR spectroscopy and mass spectrometry. TLC of the reaction mixture indicated the presence of a large number of byproducts. In this case a range of 2:1 adducts were possible. Cycloaddition to the second double bond in norbornadiene would afford adducts analogous to compounds 96-101 described above for the addition of benzonitrile oxide. Furthermore a second cycloaddition of acrylonitrile oxide can take place to the 3-vinyl substitution of the first formed products (analogous to Scheme 50).

These adducts have interesting NMR features which are discussed in Section 2.4.5.4.
2.4.4 Synthesis of 3-phenylisoxazole and 3-vinylisoxazole

*exo*-4,7-Methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole 80 was refluxed in xylene (135°C) to encourage the rDA reaction. After ~ 16 hours the solvent was evaporated and the residue subjected to $^1$H NMR spectroscopy and TLC. The NMR spectrum showed no evidence of any conversion to 3-phenylisoxazole and that starting material remained. Compound 80 was then refluxed in a higher boiling point solvent, mesitylene (163°C) for 17 hours. Under these conditions 3-phenylisoxazole was formed but the proton NMR spectrum showed the presence of byproducts. Previous research by Sohár and Kövesdi\(^{177}\) suggests these other compounds may be pentacyclic isoxazolines resulting from Diels-Alder addition of cyclopentadiene to the double bond of the starting material. Purification by dry flash chromatography afforded 3-phenylisoxazole 82 as a colourless oil in good yield (75%). The product was characterised by $^1$H NMR and $^{13}$C NMR spectroscopy; the proton NMR spectrum featured a pair of doublets, one at 8.45 p.p.m. and the other at 6.66 p.p.m. which were assigned to $H_5$ and $H_4$, respectively. A coupling of 1.6 Hz typical for isoxazoles unsubstituted at both 4- and 5- positions, was observed between the two ring protons.\(^{156}\)

Thus having established the conditions under which the benzonitrile oxide-norbornadiene adduct would undergo rDA the corresponding ANO analogue was examined. Thermolysis of *exo*-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole 83 in refluxing xylene did not furnish any of the desired product. Analysis by TLC and NMR spectroscopy indicated the presence of starting material with traces of degradation products. Adduct 83 was then refluxed in mesitylene for 17 hours but again did not afford 3-vinylisoxazole; under these conditions decomposition had taken place as a vast number of unidentified components were observed on TLC. The proton NMR spectrum contained no characteristic peaks associated with the starting material, compound 83.

After the failure of simple liquid phase thermolysis to synthesise 3-vinylisoxazole, we turned to flash vacuum pyrolysis (FVP).\(^{182,183}\) FVP is a form of gas-phase thermolysis which is particularly suitable for the production and isolation of unstable reaction products. (The apparatus illustrated in Section 3.1.2.6).
Spectrum 3: $^1$H NMR spectrum for 3-vinylisoxazole (200 MHz, CDCl₃)
FVP is governed by three important principles:-

1. The contact time, the time the compound to be pyrolysed remains in the hot zone is very short - typically between $10^{-3}$ and $10^{-1}$ s.

2. The steady-state concentration of reactants and consequently products in the reaction zone is kept to a minimum.

3. Immediately after passage through the hot zone the pyrolysate is cooled to extremely low temperatures (~190°C) and thus protected from modification by subsequent reaction.

*exo*-4,7-Methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole 80, was again used as a model to establish suitable reaction conditions. FVP was carried out using a range of furnace temperatures (the pressure remained at 0.003 mm Hg) and the pyrolysate examined by $^1$H NMR spectroscopy (Table 14). At 600°C a 98% conversion to 3-phenylisoxazole was obtained but unfortunately a small amount of decomposition had occurred. When the oven temperature was lowered to 500°C the NMR spectrum of the pyrolysate indicated a trace of impurity remaining. At 400°C the reaction was extremely clean and high yielding (99%) thus a temperature of 400°C was selected as optimum for this particular reaction. In contrast, at 130°C no rDA was observed, only distillation or sublimation of the starting material occurred.

The pyrolysis of *endo* adduct 81 was also examined under FVP conditions. At both 400°C and 350°C a 99% yield of 3-vinylisoxazole was obtained. This result is consistent with previous research where the transition state for the formation and decomposition of *exo* adducts has been found to be of higher energy than that of *endo* adducts; an explanation has been provided by Woodward and Hoffmann.

An initial oven temperature of 400°C was selected for the pyrolysis of *exo*-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole, based on the results for the 3-phenyl adduct. At this temperature only partial conversion to 3-vinylisoxazole occurred, 34% of the starting material remained. On raising the temperature to 475°C a 99% yield of 3-vinylisoxazole was achieved and no traces of impurity were observed by TLC. At 140°C no fragmentation took place and only starting material was recovered. 3-Vinylisoxazole, a novel compound, was fully characterised by $^1$H and $^{13}$C NMR spectroscopy. The proton NMR spectrum (illustrated in Spectrum 3) revealed a doublet of doublets at 8.32 p.p.m. which were assigned to H$_5$ which not only couples to H$_4$ (~1.7 Hz) but also to H$_A$ from the vinyl moiety (~0.8 Hz); the latter coupling was confirmed by decoupling experiments. H$_4$ appears at 6.47 p.p.m. as a doublet with an associated coupling of 1.7 Hz.
Figure 7  Norbornadiene and norbornene cycloadducts

83 (35%)  102 (11%)

103 (21%)  104 (51%)

80 (54%)  81 (16%)
The FVP results for compounds 80 (exo), 81 (endo) and 83 (exo) are summarised in Table 14.

Table 12 FVP results

<table>
<thead>
<tr>
<th>reactant</th>
<th>furnace temperature (°C)</th>
<th>isoxazole / isoxazoline (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 (exo)</td>
<td>600</td>
<td>82 (98%)</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>500</td>
<td>82 (99%)</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>400</td>
<td>82 (99%)</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>300</td>
<td>82 (38%), 80 (62%)</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>350</td>
<td>82 (59%), 80 (41%)</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>130</td>
<td>80 (99%)*</td>
</tr>
<tr>
<td>81 (endo)</td>
<td>400</td>
<td>81 (99%)</td>
</tr>
<tr>
<td>81 (endo)</td>
<td>350</td>
<td>81 (99%)</td>
</tr>
<tr>
<td>83 (exo)</td>
<td>400</td>
<td>79 (34%), 83 (66%)</td>
</tr>
<tr>
<td>83 (exo)</td>
<td>475</td>
<td>79 (99%)</td>
</tr>
<tr>
<td>83 (exo)</td>
<td>140</td>
<td>83 (99%)*</td>
</tr>
</tbody>
</table>

* reactants distilled or sublimed

2.4.5 Norbornadiene adducts

2.4.5.1 Introduction

Although the norbornadiene adducts 80, 81, 83 and 102 were synthesised initially solely as precursors for the preparation of 3-phenylisoxazole and 3-vinylisoxazole, these adducts are also of interest with respect to reactivity and stereoselectivity. Thus a more detailed investigation was made and two additional analogues, 4,7-methano-3a,4,7,7a-tetrahydro-3-propenylbenzisoxazole 104 and 3a,7a,4,5,6,7-hexahydro-4,7-methano-3-vinylbenzisoxazole 103 were synthesised to study both the effect of substituting ANO for but-2-enonitrile oxide and of replacing norbornadiene for norbornene (structures illustrated in Figure 7).

Norbornene is a very reactive dipolarophile towards nitrile oxides; this has been attributed to strain. However, a satisfactory rationalisation in terms of deformation energies and staggering of forming bonds with respect to allylic bonds has also been provided. The olefinic C-H bonds of norbornene are bent in the endo direction by 3.4°, and only a small expenditure of energy is necessary to effect...
the 10° cis bending to reach the cycloaddition transition state geometry making deformation easy. A similar situation occurs with norbornadiene.

The high reactivity can also be attributed to the fact that the forming bonds in the exo addition are almost perfectly staggered with the bonds to the bridgehead carbons, which is highly favoured.¹⁸⁴

Interestingly, norbornene adds nitrile oxides exclusively on the exo face.¹⁸⁷ This may be attributed tentatively to the "torsional effect" and steric hindrance by the 5,6 hydrogens. In norbornadiene systems the stereospecificity is more relaxed and the cycloaddition of benzonitrile oxide to norbornadiene has been reported to afford mixtures of the exo and endo adducts in ratios of 90:10.¹⁸¹ At higher temperatures the proportion of endo attack increases.

2.4.5.2 exo-3a,7a,4,5,6,7-Hexahydro-4,7-methano-3-vinylbenzisoxazole (103)

Compound 103 was also synthesised using Mukaiyama methodology; the ANO precursor, 1-nitropropene, was added dropwise over 14 hours to a mixture of phenyl isocyanate, norbornene and triethylamine. The reaction mixture was subjected to dry flash chromatography affording the desired product compound 103 (exo) in a yield of 21% (stereospecificity discussed previously).

2.4.5.3 4,7-Methano-3a,4,7,7a-tetrahydro-3-propenylbenzisoxazole (104)

Compound 104 was synthesised under Mukaiyama conditions by the cycloaddition of but-2-enonitrile oxide, generated in situ by triethylamine, to norbornadiene. Phenyl isocyanate was used as the dehydrating agent. After 16 hours TLC indicated that all the 1-nitrobut-1-ene had been consumed. The resulting mixture was subjected to dry flash chromatography affording the exo-adduct as a pale yellow oil in a satisfactory yield of 51%; a vast number of byproducts were present in the reaction mixture and the endo adduct was not isolated.
Spectrum 4: $^1$H NMR spectrum for exo-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole (360 MHz, CDCl$_3$)
2.4.5.4 NMR spectroscopic data

Table 13 Selected $^{13}$C NMR spectroscopic data

<table>
<thead>
<tr>
<th>Compound</th>
<th>$C_3$</th>
<th>$C_{3a}$</th>
<th>$C_{7a}$</th>
<th>$C_7$</th>
<th>$C_4$</th>
<th>$C_8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>83 (exo)</td>
<td>156.8</td>
<td>55.8</td>
<td>89.3</td>
<td>49.7</td>
<td>44.6</td>
<td>42.9</td>
</tr>
<tr>
<td>102 (endo)</td>
<td>157.8</td>
<td>55.4</td>
<td>87.4</td>
<td>47.5</td>
<td>46.2</td>
<td>48.7</td>
</tr>
<tr>
<td>103 (exo)</td>
<td>157.8</td>
<td>55.3</td>
<td>87.7</td>
<td>42.6</td>
<td>38.8</td>
<td>22.3*</td>
</tr>
<tr>
<td>104 (exo)</td>
<td>155.2</td>
<td>59.6</td>
<td>88.1</td>
<td>49.6</td>
<td>44.9</td>
<td>42.7</td>
</tr>
<tr>
<td>80 (exo)</td>
<td>155.2</td>
<td>57.4</td>
<td>89.3</td>
<td>49.7</td>
<td>44.9</td>
<td>42.9</td>
</tr>
<tr>
<td>81 (endo)</td>
<td>156.4</td>
<td>57.0</td>
<td>87.3</td>
<td>47.7</td>
<td>46.7</td>
<td>48.7</td>
</tr>
</tbody>
</table>

* alternative assignment possible

The $^{13}$C NMR data in Table 15 shows the range of chemical shift values for $C_3$ (157.8-155.2 p.p.m.) $C_{3a}$ (57.4-55.3), $C_{7a}$ (89.3-87.3) $C_7$ (49.7-42.6), $C_4$ (46.7-38.8) and $C_8$ (48.7-22.3) in the norbornene and norbornadiene cycloadducts. The $C_8$ associated with the norbornene adduct 103 is at a relatively high field (~22.3 p.p.m.). The $\delta$ values for the $C_8$ carbons in the exo adducts and the endo adducts are also noticeably different, this presumably reflects the proximity to the more electronegative atoms.

The proton NMR data for the adducts bearing alkenyl moieties at the three position are shown in Table 16 (compounds 83, 102, 97 and 98). The vinyl moieties show typical trans, cis and geminal couplings of ~17.8, ~10.9 and <1 Hz, respectively. A long range coupling of ~0.6 Hz is observed between $H_A$ and $H_{3a}$.

Table 17 presents selected data for the benzonitrile oxide and acrylonitrile oxide norbornadiene / norbornene adducts. $H_{7a}$, $H_{3a}$, $H_7$ and $H_4$ all appear at similar chemical shifts. The very small coupling between the isoxazoline ring protons $H_{3a}$ and $H_4$ at the norbornadiene bridge head and also between $H_7$ and $H_{7a}$ is a clear indication of exo- geometry. A typical proton NMR spectrum for a norbornadiene adduct with exo-conformation is illustrated in Spectrum 4.
Table 14  Selected $^1$H NMR data for norbornadiene and norbornene adducts bearing alkenyl substituents
($\delta_H$, p.p.m.; $J$, Hz) (200 and 360 MHz, CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$J$</th>
<th>$J$</th>
<th>$J$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>83 (exo)</td>
<td>5.53</td>
<td>5.58</td>
<td>6.54</td>
<td>0.9</td>
<td>17.9</td>
<td>10.9</td>
<td>$J_{A3a}0.6$</td>
</tr>
<tr>
<td>102 (endo)</td>
<td>5.49</td>
<td>5.59</td>
<td>6.49</td>
<td>*</td>
<td>17.8</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>97 (exo)</td>
<td>5.42</td>
<td>5.45</td>
<td>6.47</td>
<td>0.9</td>
<td>17.8</td>
<td>10.9</td>
<td>$J_{A3a}0.7$</td>
</tr>
</tbody>
</table>

* undetected < 0.4 Hz.

Table 15  Selected $^1$H NMR data for the norbornene/norbornadiene cycloadducts
($\delta_H$, p.p.m.; $J$, Hz) (200 and 360 MHz, CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$J$</th>
<th>$J$</th>
<th>$J$</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>$\delta_H$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>83 (exo)</td>
<td>4.82</td>
<td>3.45</td>
<td>3.30</td>
<td>3.06</td>
<td>8.0</td>
<td>1.3</td>
<td>1.5</td>
<td>6.04</td>
<td>5.7</td>
<td>1.55</td>
<td>$J_{6,7}5.7$</td>
</tr>
<tr>
<td>102 (endo)</td>
<td>5.29</td>
<td>3.87</td>
<td>3.06</td>
<td>3.06</td>
<td>9.5</td>
<td>4.2</td>
<td>4.2</td>
<td>5.99</td>
<td>5.7</td>
<td>1.58</td>
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<tr>
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<td>3.13</td>
<td>2.45</td>
<td>2.45</td>
<td>8.3</td>
<td>*</td>
<td>1.6</td>
<td>1.51</td>
<td>-</td>
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<tr>
<td>104 (exo)</td>
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<td>3.46</td>
<td>3.16</td>
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<td>3.26</td>
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<td>5.92</td>
<td>6.16</td>
<td>5.8</td>
<td>1.56</td>
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</table>

* undetected < 0.4 Hz.
2.5 Polymer Studies

2.5.1 Introduction

Among polymerisations of vinyl heterocycles reported in the literature, studies involving isoxazole and isoxazoline monomers\textsuperscript{88,121} are rather seldom met. Nevertheless, macromolecules bearing pendant isoxazole (or isoxazoline) residues could show interesting physical and chemical properties owing to the polarity, basicity and coordinating power of such a ring. Besides, the ring's characteristic reactivity may allow it to be transformed by suitable reagents into non-cyclic 1,3-difunctional systems. The isoxazole nucleus could be a useful protecting group in the synthesis of polyfunctional polymers.\textsuperscript{123}

It was expected that the comparison of the polymerisation behaviour of heteroaromatic vinyl monomers would show the effect of heteroatoms on the monomer reactivity. A systematic study of polymerisation of such monomers was thus executed by Iwakura \textit{et al.}\textsuperscript{122} Isopropenyl monomers were also included in the study. Interestingly, the results indicated that monomers containing more than one heteroatom are almost always more reactive than those with just one, e.g. vinylisoxazoles are more reactive than vinylfurans or pyridines.

Radical copolymerisation studies with styrene revealed that heteroaromatic monomers are generally more reactive than styrene. The polymerisabilities of vinyl monomers have been investigated and the explanation put forward (which was based on theoretical calculations) was given in terms of the localisation energy\textsuperscript{188} or the resonance stabilisation energy\textsuperscript{189} between the attacking radical and the monomer.

Sumimoto \textit{et al.}\textsuperscript{121} have also carried some preliminary free radical polymerisations. 3-Vinyl-5-phenylisoxazole polymerised easily; however, 3-phenyl-5-vinylisoxazoline had a very low reactivity ratio and only copolymerised with acrylonitrile or styrene in a very low conversion.

Thus, in the light of this evidence, our objectives were to prepare homopolymers of 3-vinyl-5-phenylisoxazole and 5-vinyl-3-phenylisoxazole, and to examine their copolymerisation with styrene, methyl methacrylate and vinyl acetate. The facile free radical polymerisation of styrene was studied initially to establish the polymerisation technique.

A secondary objective was to carry out preliminary polymerisation experiments on selected vinylisoxazolines either involving copolymerisation with styrene or methyl methacrylate or homopolymerisation.

The polymer structure may vary when the backbone of the polymer molecule contains a carbon atom attached to four different substituents. Such polymers may
have various configurational arrangements or tacticity. Polymers with a regular arrangement are known as *tactic* polymers whereas those with a random arrangement are *atactic*. When there is a repetition of the same configuration at each progressive asymmetric carbon atom along the polymer chain the polymer is *isotactic* and if there is an alternation of configuration the polymer is *syndiotactic*. The tacticity of a polymer or copolymer may be assessed by studying the $^{13}$C NMR spectra. Normally, free radical polymerisation results in essentially atactic polymers although steric and electrostatic effects generally favour one configuration or the other and truly random polymers are rare.

In the present work, the ratio of isoxazole or isoxazoline to styrene (or methyl methacrylate or vinyl acetate) was estimated from the elemental analysis of the nitrogen content. The copolymer composition was assessed by creating calibration curves (Graphs I and II in the Experimental Section 3.12). The polymers were also characterised by $^{13}$C NMR spectroscopy (and by $^1$H NMR spectroscopy where appropriate).

Selected polymer samples were subjected to gel permeation chromatography (GPC) to determine average molecular weights and to give an indication of the molecular weight distributions. These measurements were made at BP Research and Engineering Centre, Sunbury.

GPC$^{190}$ is an analytical technique which involves injecting a dilute solution of polymer into a pumped stream of solvent flowing through a column (or columns) packed with beads of rigid, porous gel. Porous beads of highly cross-linked polystyrene are frequently used as the column packing material. As the dissolved polymer molecules pass through the column they can diffuse into the pores of the gel to an extent which depends on the size of the solute and the distribution of pore sizes in the gel. Larger molecules are eluted first. The concentration of polymer leaving the column is monitored, usually by means of a refractive index detector. The GPC curve is a plot of the detector signal, which is proportional to weight concentration of solute, versus the elution volume. Molecular weights may be determined either from the elution volume at the peak of the GPC curve ($M_{pk}$) or by numerical integration of the GPC data via a microcomputer ($M_w,M_n$).
$^{13}$C NMR spectra for the styrene and 5-phenyl-3-vinylisoxazole copolymer (Spectrum 5), polystyrene (Spectrum 6) and 5-phenyl-3-vinylisoxazole (Spectrum 7) (50 MHz, CDCl$_3$)
2.5.2 Free radical polymerisation

Styrene was selected initially as a model. The monomer was refluxed in methyl ethyl ketone (MEK) (~80°C) with azobisisobutyronitrile (ABIBN) as the initiator. 2% by weight of ABIBN to monomer was used, it was added in two batches in order to maintain the radical concentration approximately constant. The reaction was monitored by withdrawing 1 ml samples at recorded intervals. The reaction mixture was then precipitated into methanol and the product filtered, dried and weighed to establish the conversion to polymer. After nine hours polymerisation was essentially complete. Polystyrene, compound \textbf{105}, was characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy (yield 63%); the quaternary $\text{PhC}$ peak (centred at 145.4 p.p.m.) and the polymer chain 'alkane' peaks were notably broad probably due to the atactic nature of the polymer.

Poly(methyl methacrylate) \textbf{106} and poly(vinyl acetate) \textbf{107} were also prepared using the free radical polymerisation technique described above; the yields were good (82% and 91%, respectively). The homopolymers were required for analysis of the copolymers. The elemental analysis results for poly(vinyl acetate), polystyrene and poly(methylmethacrylate) indicated a small amount of nitrogen (between 0.1 and 0.2%) present; this may be due to the initiator moiety on the relatively short chain polymer.

2.5.2.1 5-Phenyl-3-vinylisoxazole and styrene copolymer (\textbf{108})

\begin{align*}
\text{CH}_2=\text{CH} & \quad \text{CH}_2=\text{CH} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \\
\text{O} & \\
\text{108}
\end{align*}

5-Phenyl-3-vinylisoxazole was successfully copolymerised with styrene (reactant ratio 1:2) under free radical conditions in moderate yield of 38%. The copolymer, a white solid with a softening point of 157-162°C, was characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy. The IR spectrum showed vibrational bands at 1616, 1573 and 1465 cm$^{-1}$ which can be attributed to the phenyl and isoxazole rings.\textsuperscript{191}

The $^{13}$C NMR spectrum of the copolymer contains peaks corresponding to both styrene and isoxazole units (as illustrated in Spectra 5 and 6). It was interesting
to observe that the styrene-derived PhC peak became considerably broader, which is attributed to it experiencing several different chemical environments. It can flanked by either two styrene units, or by two isoxazoles, or by one of each. This suggests that it is a true copolymer rather than a mixture of homopolymers. There were no olefinic peaks at 126.5 and 121.2 p.p.m. indicating the absence of any unreacted monomer.

The chemical environments of the C₃ and C₄ isoxazole carbons alter after copolymerisation with styrene. The C₃ peak was at a lower field (167.4-166.7 p.p.m.) with considerable broadening as it is no longer attached to a conjugating alkene but to the alkane polymer backbone. The C₄ peak associated with the copolymer was at ~97.8 p.p.m. and was slightly broadened; this carbon appeared at 96.0 p.p.m. in the vinylisoxazole. The C₅ peak of the isoxazole ring remained unaltered consistent with its relatively unchanged chemical environment.

The composition of the copolymer was determined by examination of the %N from the elemental analysis. The percentage incorporation of isoxazole to styrene (0.25:0.75) in the product was somewhat less than the initial reactant ratio (1:2).

The copolymer was subjected to gel permeation chromatography and the results were as follows: $M_n = 13000$, $M_w = 28800$, $M_w/M_n = 2.2$ and the $M_{pk} = 20000$, which indicates a narrow range of molecular weight distribution. Fuller details of the parameters are shown in Section 3.14 (Experimental).

2.5.2.2 5-Phenyl-3-vinylisoxazole and methyl methacrylate copolymer (109)

5-Phenyl-3-vinylisoxazole and methyl methacrylate were copolymerised (reactant ratio 1:5) using the free radical polymerisation conditions described in Section 2.5.2.; the yield was moderate at 43%. The copolymer was characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy. The IR spectrum featured a strong carbonyl band at 1727 cm⁻¹.
The $^{13}$C NMR spectrum indicates the presence of both isoxazole and methyl methacrylate units. The methyl methacrylate-derived quaternary carbon and the ester carbonyl peak were considerably broader compared with those of poly(methyl methacrylate) similar to that observed in the styrene copolymer which can be attributed to the various combinations of flanking groups. There were no olefinic peaks at 126.5 and 121.2 p.p.m., an indication that the monomer, 5-phenyl-3-vinylisoxazole, was not present. This spectrum thus provides convincing evidence for the incorporation of isoxazole rings.

The chemical shifts of both C$_3$ and C$_4$ of the isoxazole ring altered after copolymerisation with methyl methacrylate. The changes in chemical shift for the ring carbons were broadly similar to that described earlier for the corresponding styrene compound. The C$_3$ peak occurred at 162.5 p.p.m. in the isoxazole monomer but in the copolymer between 167.6 and 167.3 p.p.m. and were relatively broad. The C$_4$ peak also showed notable broadening and a change in chemical shift of ~2 p.p.m. from 96.0 to 98.4 p.p.m. The C$_5$ remained relatively unchanged.

The composition of the copolymer was assessed by examination of the %N from elemental analysis. The percentage incorporation of isoxazole to methyl methacrylate in the product (33%:67%) was determined by application of the calibration curve (Graph II, Section 3.11) and is significantly less than the the reacting ratio (1:5). This result indicates that the radicals centered on both methyl methacrylate and the isoxazole units show a preference for reaction with an isoxazole unit.

The GPC results on the copolymer are as follows: $M_n = 10000$, $M_w = 15300$ ($M_w/M_n = 1.5$) and $M_{pk} = 13000$). The $M_w/M_n$ value indicates an excellent molecular weight distribution.

2.5.2.3 5-Phenyl-3-vinylisoxazole and vinyl acetate copolymer (110)
A 1:1 mixture of 5-phenyl-3-vinylisoxazole with vinyl acetate was polymerised using the free radical procedure to give a 62% yield of copolymer. The product, a white solid with a softening point of 137-142°C, was characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy.

The elemental analysis indicated a high percentage of nitrogen (7.5%) in the copolymer corresponding to a 85:15 ratio of isoxazole to vinyl acetate units. It is concluded that the radicals centered on vinyl acetate and isoxazole units show a marked preference for reaction with an isoxazole unit.

Vinyl acetate is ~50 times less reactive as styrene towards the styrene radical,\textsuperscript{192} this may account for its very low incorporation of vinyl acetate in the copolymer. Since the copolymer consists of predominantly isoxazole units and the vinyl acetate-derived peaks are very weak, the $^{13}$C NMR spectrum appears to be very similar to that of the 5-phenyl-3-vinylisoxazole homopolymer. The C$_3$ peak is considerably broader, as observed for the other copolymers, and the chemical shifts for C$_4$ and C$_5$ remain relatively unchanged.

The IR spectrum showed a strong carbonyl band at 1733 cm$^{-1}$ and other vibrational bands at 1451, 1573 and 1614 cm$^{-1}$ attributable to the isoxazole rings.\textsuperscript{191}

### 2.5.2.4 5-Phenyl-3-vinylisoxazole homopolymer (111)

![Structure of 5-phenyl-3-vinylisoxazole homopolymer](image)

The polymerisation was performed under free radical conditions as described in Section 3.11. The homopolymer was obtained as a white powder in moderate yield (53%) and characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy.

The $^{13}$C NMR spectrum contained peaks corresponding to isoxazole units and there were no olefinic peaks present indicating the absence of any unreacted monomer. The C$_3$ peak of the isoxazole ring in the homopolymer appeared at a lower field (~168 p.p.m.) compared to the monomer (162 p.p.m) and showed notable broadening. The C$_4$ and C$_5$ peaks appeared at very similar chemical shifts before and
after polymerisation. The polymer was subjected to GPC analysis which revealed the molecular mass distribution ($M_n = 4000, M_w = 15100, M_w/M_n = 3.8$) and an Mpk of 7000.

2.5.2.4 Copolymerisation of 3-phenyl-5-($m$- and $p$-vinylphenyl)-2-isoxazoline with styrene and methyl methacrylate

3-Phenyl-5-($m$- and $p$-vinylphenyl)-2-isoxazoline was copolymerised with styrene (reactant ratio 1:3), under the free radical polymerisation conditions described in Section 2.5.3. The copolymer (compound 112), a white powder, was isolated in a satisfactory yield of 57% and the product was characterised by elemental analysis, IR and $^{13}$C NMR spectroscopy. The $^{13}$C spectroscopic data showed very small changes in the chemical shifts for $C_3$ and $C_4$ peaks with slight broadening; no olefinic peaks were observed at 136 and 114 p.p.m. The styrene-derived PhC peak had become considerably broader, which may be attributed to it experiencing several different chemical environments. It can be flanked by either two styrene units, or by two isoxazolines, or by one of each. The composition of the
copolymern was determined by examination of the %N from the elemental analysis. The ratio of isoxazoline to styrene units was determined using a calibration curve (analogous to Graphs I and II) and was found to be 33%:67% (isoxazoline:styrene).

The copolymerisation of 3-phenyl-5-\((m-\) and \(p-\) vinylphenyl)-2-isoxazoline with methyl methacrylate (reactant ratio 1:3) was achieved under the free radical polymerisation conditions described previously. The copolymer (compound 113) was formed in a 52% yield and characterised by elemental analysis, IR and \(^{13}\)C NMR spectroscopy. The IR spectrum featured a strong band at 1728 cm\(^{-1}\).

The \(^{13}\)C NMR spectrum confirmed the presence of both isoxazoline and methyl methacrylate units. The methyl methacrylate-derived quaternary carbon became broader compared to the poly(methyl methacrylate) sample suggesting a random copolymer.

The composition of the copolymer was determined by examination of the %N from the elemental analysis. The ratio of isoxazoline to methyl methacrylate units in the product (-33%:67%) was somewhat greater than the reactant ratio (1:3).

2.5.2.2 Miscellaneous polymerisation experiments

The homopolymerisation of 3-phenyl-5-vinyl-2-isoxazoline was attempted under free radical conditions, as described previously. No precipitate was observed and NMR spectroscopy confirmed the presence of unreacted isoxazoline; recrystallisation of the residue from cyclohexane afforded analytically pure 3-phenyl-5-vinyl-2-isoxazoline. Sumimoto \textit{et al}.\(^{121}\) have also attempted to polymerise the aforementioned heterocycle with little success. Presumably radical delocalisation is hindered by the presence of only one \(\pi\)-bond in the isoxazoline ring. A free radical polymerisation was also carried out using 3-phenyl-5-vinyl-2-isoxazoline with vinyl acetate as comonomer. The \(^{13}\)C NMR spectrum of the resulting white solid showed the polymeric material to be solely poly(vinyl acetate). The isomeric 5-phenyl-3-vinyl-2-isoxazoline, did not copolymerise with methyl methacrylate under free radical conditions.
2.5.3 Cationic polymerisation

It was considered that the alkenyl appendages in 5-(m-isopropenylphenyl)-5-methyl-3-phenyl-2-isoxazoline 45, an α-methylstyrene analogue, might be susceptible to cationic polymerisation as electron-releasing substituents assist in the formation of carbocations. The experimental procedure for the cationic polymerisation was based on a report by Sumi et al., and α-methylstyrene was selected as a suitable monomer to optimise the reaction conditions.

Freshly distilled α-methylstyrene and toluene (washed and dried) were introduced into a sealed reaction vessel and brought to the polymerisation temperature (-78°C). The catalyst, distilled BF₃.O(C₂H₅)₂, was added via a syringe. After ~90 minutes the polymer was isolated from the reaction mixture by reducing to half the volume and then precipitated (using methanol) to form a colourless gel (42%) which was washed and dried *in vacuo* at 40°C (15 mmHg). The polymer was characterised by IR, ¹H and ¹³C NMR spectroscopy. The proton NMR spectrum was similar to that previously reported. The methyl protons appeared between 0.1-0.3 p.p.m. and the CH₂ protons were at ~1.60 p.p.m.

5-(m-Isopropenyl)-5-methyl-3-phenyl-2-isoxazoline did not homopolymerise or copolymerise with α-methylstyrene under the cationic conditions described above and in both cases either partial or total degradation of the isoxazoline occurred. Attempts to copolymerise α-methylstyrene with both 3-phenyl-5-vinyl-2-isoxazoline and 5-phenyl-3-vinyl-2-isoxazoline also failed. In both cases the vinyl heterocycle was recovered intact and poly-α-methylstyrene was isolated. Under similar conditions styrene itself failed to polymerise. Attempted copolymerisation of styrene and α-methylstyrene yielded only poly-α-methylstyrene.

Finally an alternative experimental procedure for cationic polymerisation, based on a report by Hersberger et al., using aluminium trichloride as catalyst and a reaction temperature of -50°C was examined. α-Methylstyrene did not homopolymerise under these conditions.
2.6 Concluding remarks

A range of 3-vinyl-2-isoxazolines have been synthesised by the direct introduction of the vinyl group as part of the nitrile oxide component using an α,β-unsaturated nitrile oxide, acrylonitrile oxide (ANO). This approach is shorter and more efficient than the alternative synthetic sequence which involves Wittig olefination of a formylisoxazoline prepared by reduction of the corresponding ethoxycarbonyl derivatives. In contrast 5-phenyl-3-vinylisoxazole was formed in a poor yield in the cycloaddition reaction of phenylacetylene to ANO, suggesting that this method is not suitable for dipolarophiles with low reactivity.

Methacrylonitrile oxide (MANO), but-2-enonitrile oxide (BNO) and propanonitrile oxide (PNO) have been cycloadded to various dipolarophiles in satisfactory yield. The MANO adducts are good monomer candidates for future work, being structurally similar to α-methylstyrene. The construction of such polymer-bound heterocyclic systems remains largely unexplored.

5-Phenyl-3-vinylisoxazole has been successfully homopolymerised and copolymerised with styrene, methyl methacrylate and vinyl acetate. The ring opening of the pendant isoxazoles requires investigation as commercial applications exist (for example materials capable of complexing metal ions). Although the vinylisoxazolines failed to polymerise, it has been shown that polymers incorporating isoxazolines as pendant groups could be prepared from 3-phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline with styrene and methyl methacrylate.
3. EXPERIMENTAL

3.1 GENERAL

3.1.1 Glossary of terms, symbols and abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ABIBN</td>
<td>α,α'-azobisisobutyronitrile</td>
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<td>acrylonitrile oxide</td>
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<td>atm.</td>
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<td>b.p.</td>
<td>boiling point</td>
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<td>DEPT</td>
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<td>DIBAL</td>
<td>di-isobutyaluminium hydride</td>
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<td>diethyl ether</td>
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<td>highest occupied molecular orbital</td>
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<td>IR</td>
<td>infra-red</td>
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<td>coupling constant</td>
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<tr>
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<td>lowest unoccupied molecular orbital</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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3.1.2 Instrumentation

3.1.2.1 Elemental analysis
Elemental analyses were performed by Miss H.Grant and Mrs E.McDougall using a Carlo Erba elemental analyser model 1106.

3.1.2.2 Infra-red spectroscopy
IR spectra were recorded as Nujol mulls or liquid films on Perkin Elmer 781 and an SPC 3200 BIO RAD spectrophotometer (FTS-7). Polymer samples were prepared in chloroform and then evaporated on a NaCl disc to form a thin film.

3.1.2.3 Mass spectroscopy
Low resolution mass spectra were recorded on a Kratos MS902 instrument by Miss E.Stevenson. A Kratos MS50TC instrument was used for recording exact mass measurements and FAB spectra and was operated by Mr A.Taylor.

3.1.2.4 Melting points
Melting points were measured on a Gallencamp capillary tube apparatus and are uncorrected. Polymer softening points were taken on a Kofler hot-stage apparatus.

3.1.2.5 Nuclear magnetic resonance spectroscopy
$^1$H NMR spectra were recorded on Bruker WP80SY, WP200SY and WH360 instruments by Miss H.Grant, Mr J.R.A.Millar, Dr D.Reed and Dr I.Sadler. Two-dimensional and n.O.e spectra were recorded on the WH360 machine. Chemical shifts ($\delta$) are measured in parts per million using tetramethylsilane ($\delta = 0.0$) as a reference signal. Unless stated the solvent was deuterated chloroform (CDCl$_3$).
3.1.2.6 Flash vacuum pyrolysis

The apparatus used for flash vacuum pyrolysis experiments is illustrated below. The system was evacuated to $10^{-2} - 10^{-3}$ mbar by an Edwards Model ED100 high capacity oil pump and the pressure monitored between the trap and the pump. Experiments involved heating the substrate, contained in the inlet tube until it volatilised. A glass Büchi Kugelrohr oven was used for heating as it allows the sublimation to be monitored easily (for temperatures $>200^\circ$C a metal oven is used). The substrate passes through a silica tube (30 x 2.5 cm); the temperature of the tube was monitored by a platinum/(platinum 13% rhodium) thermocouple at its centre and was maintained at the required level by a Stanton Redcroft laboratory tube furnace. The estimated contact time in the hot zone is 1-10 milliseconds. The products were collected at the exit of the furnace in a trap surrounded by liquid nitrogen. The entire pyrolysate was dissolved in deuterated chloroform and examined by $^1$H NMR spectroscopy without further purification.

![Diagram of flash vacuum pyrolysis apparatus]

3.1.3 Chromatography

3.1.3.1 Thin layer chromatography

Preparative TLC was carried out on glass plates (20 cm x 20 cm) coated with a layer (0.5 mm) of Kieselgel GF254 silica containing 13% calcium sulphate and a fluorescent indicator. Analytical TLC was carried out on Merck aluminium-backed plates coated with Kieselgel GF254 (0.2 mm). Detection was achieved by UV irradiation (254 nm), iodine vapour staining or Brady's reagent staining.
3.1.3.2 Dry flash chromatography

Dry flash column chromatography was performed using a variety of sinters with different diameters filled with Kieselgel 60 or Kieselgel GF254 silica and eluted under a vacuum supplied by a water pump.

3.1.4 Solvents and reagents

All reagents were standard laboratory grade and were used as supplied unless specifically stated in the text. Solvents for general use were standard laboratory grade and used as supplied. Dry ether and benzene were analar grade solvents and dried over sodium wire. Dry dichloromethane was freshly distilled from calcium hydride. Dry THF was always freshly distilled from sodium and benzophenone. Acetic anhydride was purified by fractional distillation and stored over molecular sieve. Dry chloroform was obtained by distillation from phosphorus pentoxide and stored over molecular sieve.
3.2 Synthesis of nitrile oxide precursors

3.2.1 Benzohydroximoyl chloride (33)

Benzohydroximoyl chloride, the precursor to benzonitrile oxide, was prepared by a modified literature procedure.\textsuperscript{141}

A solution of $\alpha$-benzaldoxime (10.27 g, 10.3 mmol) in dry chloroform (250 ml) in a 500 ml three necked flask and was cooled to -10°C in a dry ice-acetone bath. Chlorine gas was passed through the solution (~3 p.s.i) until the colour changed from Oxford blue through emerald green to sunset yellow. The excess chlorine was removed by displacement with nitrogen gas and the solution evaporated to dryness. The white solid residue was recrystallised with chloroform and hexane to give the product as white prisms (9.08 g, 69% yield), m.p. 48-49°C (lit.,\textsuperscript{141} 50-51°C).

3.2.2 Ethyl chloro-oximidoacetate (20)

This was prepared from glycine ester hydrochloride according to the method of Skinner.\textsuperscript{140} Hydrochloric acid (35%, 31.8 ml) was added dropwise to a stirred, ice-cooled solution of glycine ethyl ester hydrochloride (50.0 g, 360 mmol) in water (150 ml); a solution of sodium nitrite (25.0 g, 360 mmol) in water (100 ml) was then dripped in with caution. A further portion of hydrochloric acid (31.8 ml) and aqueous sodium nitrite (25.0 g in 100 ml water) were then added with constant stirring. The resulting mixture was extracted with ether (2 x 200 ml). The combined ether layers were dried (magnesium sulphate) and the solvent evaporated \textit{in vacuo} to yield an oil, hexane was added (50 ml) with just enough ether to allow dissolution to occur, and the mixture placed in the freezer. Ethyl chloro-oximidoacetate, a white crystalline product, was removed by filtration and the filtrate concentrated to an oil which was again dissolved in the hexane/ether mixture and kept in the fridge overnight, thus affording a second crop of crystals (32.03 g, 59%), m.p. 78-79°C (lit.,\textsuperscript{140} 79-80°C).
3.3 Synthesis of isoxazole and 2-isoxazoline esters

3.3.1 3-Ethoxycarbonyl-5-phenylisoxazole (36)

A solution of phenylacetylene (25.0 g, 236 mmol) and ethyl chloro-oximidoacetate (36.7 g, 236 mmol) in xylene (200 ml) was heated under reflux for 24 hours. After cooling, the xylene was removed by rotary evaporation, and the residual red/brown oil crystallised overnight in the refrigerator. Recrystallisation from ethanol furnished 36 as a colourless, acicular solid (35.3 g, 70%), m.p. 50-51.5 °C (lit., 146, 147 52 °C and 50 °C); ν<sub>max</sub> (Nujol) 1740 cm<sup>-1</sup> (C=O); δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 7.78-7.74 (2H, m, ArH), 7.48-7.41 (3H, m, ArH), 6.89 (1H, s, H<sub>4</sub>), 4.44 (2H, q, J 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (3H, t, J 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (50 MHz, CDCl<sub>3</sub>) 171.5, 159.8 (C<sub>3</sub>, C<sub>5</sub>), 156.8 (C=O), 130.6, 128.9, 125.7 (PhCH), 126.4 (PhC), 99.7 (C<sub>4</sub>), 62.0 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); m/z (El) 217 (M+).

3.3.2 5-Ethoxycarbonyl-3-phenylisoxazole (34)

A solution of triethylamine (2.88 g, 29 mmol) in ether (25 ml) was added over 6 hours to a stirred solution of ethyl propiolate (1.83 g, 19 mmol) and benzohydroximoyl chloride (2.64 g, 17 mmol) in ether (25 ml). The temperature of the reaction mixture was kept at 0 °C for one hour and then at room temperature. The mixture was then filtered through celite and the solvent evaporated in vacuo. Examination of the reaction mixture by <sup>1</sup>H NMR spectroscopy showed a regioisomeric mixture of isoxazole-4- and -5-carboxylates (ratio ~1:11, respectively). The desired -5-carboxylate was separated by crystallisation (cyclohexane), the product was a white crystalline solid (2.01 g, 60%). m.p. 46-47 °C (lit., 157 47 °C); ν<sub>max</sub> (Nujol) 1740 cm<sup>-1</sup> (C=O); δ<sub>H</sub> (80 MHz, CDCl<sub>3</sub>) 7.85-7.78 (2H, m, ArH), 7.49-7.25 (3H, m, ArH), 7.23 (1H, s, H<sub>4</sub>), 4.46 (2H, dd, J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.42 (3H, t J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (50 MHz, CDCl<sub>3</sub>) 162.8, 160.8, 156.7, (C=O, C<sub>5</sub>, C<sub>3</sub>), 130.4, 128.9, 126.7 (PhCH), 127.8 (PhC), 107.2 (C<sub>4</sub>), 62.2 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); m/z (El) 217 (M+).

5-Ethoxycarbonyl-3-phenylisoxazole was also synthesised by two alternative experimental procedures: method (a) from benzaldoxime, using NCS & (b) from benzohydroximoyl chloride with NaF.

(a) α-Benzaldoxime (7.75 g, 50 mmol), NCS (6.7 g, 50 mmol) and pyridine (0.5 ml) in dry chloroform (100 ml) were stirred at room temperature for 30 minutes. After cooling to 0 °C, ethyl propiolate was added and triethylamine (5.00 g, 50 mmol) in chloroform (25 ml) was dripped in over 19 hours. After washing with water (2 x 50 ml), the organic layer was dried (magnesium sulphate) and the product
was purified by dry flash chromatography (hexane, then 5% ether/hexane) thus affording isoxazole 34 (5.0 g, 31%).

(b) Benzohydroximoyl chloride (1.55 g, 10 mmol), ethyl propiolate (2.94 g, 30 mmol) and sodium flouride (1.4 g) in dichloromethane (30 ml) were stirred at room temperature for five days. The reaction mixture was then filtered through celite, washed with dichloromethane (2 x 15 ml). The filtrates and washings were combined and evaporated to afford nearly pure isoxazole. Column chromatographic separation (silica gel, 70% dichloromethane/hexane) gave analytically pure isoxazole (1.50 g, 69%).

3.3.3 3-Ethoxycarbonyl-5-phenyl-2-isoxazoline (35)

A solution of triethylamine (5.25 g, 52 mmol) in ether (50 ml) was added over 6 hours to a stirred solution of styrene (9.59 g, 92 mmol) and ethyl chloro-oximidoacetate (7.0 g, 46 mmol) in ether (50 ml) at 0°C for one hour and then at room temperature. After the addition was complete stirring was continued for one hour, the reaction mixture was filtered through celite and the solvent evaporated in vacuo. Excess styrene was removed by high vacuum rotary evaporation, and the residue was purified using dry flash chromatography (hexane, then 2% ether/hexane), affording a colourless oil (6.34 g, 62%), (lit.,161 b.p. 162-163°C, 2.5 mmHg); \( \nu_{\text{max}} \) (film) 1720 (C=O), 1595 cm\(^{-1}\) (C=N); \( \delta_\text{H} \) (80 MHz, CDCl\(_3\)) 7.45-7.15 (5H, m, ArH), 5.67 (1H, dd, \( J_{54a} \) 11.3 Hz, \( J_{54b} \) 9.2 Hz, H\(_5\)), 4.25 (2H, q, \( J \) 7.1 Hz, OCH\(_2\)CH\(_3\)), 3.58 (1H, dd, \( J_{4a4b} \) 17.7 Hz, \( J_{4a5} \) 11.3 Hz, H\(_{4a}\)), 3.09 (1H, dd, \( J_{4b4a} \) 17.7 Hz, \( J_{4b5} \) 9.2 Hz, H\(_{4b}\)), 1.29 (3H, t, \( J \) 7.1 Hz, OCH\(_2\)CH\(_3\)); \( \delta_\text{C} \) (50 MHz, CDCl\(_3\)) 160.1 (C=O), 150.8 (C\(_3\)), 139.2 (PhC), 128.4, 128.2, 125.5 (PhCH), 84.5 (C\(_5\)), 61.6 (CH\(_2\)), 41.0 (C\(_4\)), 13.7 (CH\(_3\)); \( m/z \) (EI) 219 (M\(^+\)).

Isoxazoline 35 was also prepared using NaF, as described above in method (b) for isoxazole 34. Ethyl chloro-oximinoacetate (1.52 g, 10 mmol), styrene (3.12 g, 30 mmol) and sodium fluoride (1.4 g) in dichloromethane (30 ml) were stirred for 6 days. The desired ester was purified as before (2.19 g, 50%).
3.4 Synthesis of isoxazole and 2-isoxazoline aldehydes

3.4.1 3-Formyl-5-phenylisoxazole (37)

DIBAL (1M in hexanes, 30 ml, 30 mmol) was added to a stirred, cooled (-78 °C) solution of 3-ethoxycarbonyl-5-phenylisoxazole 36 (2.21 g, 10 mmol) in dry dichloromethane (33 ml), under a nitrogen atmosphere at such a rate that the temperature did not exceed -65 °C (ca. 30 min). After stirring for a further 50 minutes, methanol (5 ml) was carefully added, followed by water (200 ml) and 1% aqueous HCl (10 ml). The product was extracted into dichloromethane (200 ml) and the combined organic portions dried over magnesium sulphate and the solvent evaporated in vacuo. The residue was subjected to dry flash chromatography (10% ether/hexane, then EtOAc) and yielded in order of elution:

(i) 3-formyl-5-phenylisoxazole 37 as a white powder (1.40 g, 80%), m.p. 54-56 °C (lit., 151 61 °C); \( \nu_{\text{max}} \) (Nujol) 1715 cm\(^{-1}\) (C=O); \( \delta_{\text{H}} \) (80 MHz, CDCl\(_3\)) 10.56 (1H, s, CHO), 7.85-7.71 (2H, m, ArH), 7.55-7.39 (3H, m, ArH), 6.85 (1H, s, H\(_4\)); \( \delta_{\text{C}} \) (50 MHz, CDCl\(_3\)) 184.7 (CHO), 171.9, 162.4 (C\(_3\), C\(_5\)), 130.8, 129.0, 125.8 (PhCH), 126.2 (PhC), 96.2 (C\(_4\)); \( m/z \) (EI) 173 (M\(^+\)).

(ii) 3-hydroxymethyl-5-phenylisoxazole 38, a white crystalline solid, (0.25 g, 14%), m.p. 100-102 °C (lit., 152 100-102 °C); \( \nu_{\text{max}} \) (Nujol) 3320 cm\(^{-1}\) (OH); \( \delta_{\text{H}} \) (80 MHz, CDCl\(_3\)) 7.74-7.64 (2H, m, ArH), 7.44-7.36 (3H, m, ArH), 6.55 (1H, s, H\(_4\)), 4.76 (2H, s, CH\(_2\)OH), 3.23 (1H, s, OH); \( \delta_{\text{C}} \) (50 MHz, CDCl\(_3\)) 170.1, 164.2 (C\(_3\), C\(_5\)), 130.0, 128.8, 125.6 (PhCH), 127.0 (PhC), 98.2 (C\(_4\)), 56.5 (CH\(_2\)OH); \( m/z \) (EI) 175 (M\(^+\)).

The hydroxymethyl derivative 38, was oxidised to aldehyde 37 with pyridinium chlorochromate (PCC).\(^{153,154}\) A solution of 3-hydroxymethyl-5-phenylisoxazole (0.5 g, 2.8 mmol) in dry dichloromethane (8 ml) was added rapidly to a suspension of PCC (1.84 g, 8.6 mmol) in dichloromethane (80 ml). After stirring for 13 hours, TLC indicated no aldehyde present. The reaction mixture was diluted with 5 volumes of dry ether. The solvent was decanted off and the black residue washed with dry ether (3 x 20 ml). The combined extracts were filtered through a pad of Florasil and the solvent evaporated in vacuo. Dry flash chromatography (25% ether/hexane, then 50% ether/hexane) afforded the aldehyde (0.44 g, 90%).
3.4.2 5-Formyl-3-phenylisoxazole (40)

5-Ethoxycarbonyl-3-phenylisoxazole 34 (0.5 g, 2.3 mmol) in dry dichloromethane (15 ml) was treated with DIBAL (7 ml, 6.9 mmol) as described above for isoxazole 37. The product mixture was subjected to dry flash chromatography (hexane then 8% ether/hexane followed by 15% ether/hexane) yielding in order of elution:

(i) 5-formyl-3-phenylisoxazole 40 as a white powder (0.21 g, 51%) (from cyclohexane), m.p. 74-75°C (lit.,158,159 75-76°C); νmax (Nujol) 1750 cm⁻¹ (C=O); δH (200 MHz, CDCl₃) 10.0 (1H, s, CHO), 7.88-7.76 (2H, m, ArH), 7.52-7.46 (3H, m, ArH), 7.28 (1H, s, H₄); δC (50 MHz, CDCl₃) 178.3 (CHO), 166.2, 163.0 (C₅, C₃), 130.7, 129.9, 129.1, 126.8 (PhCH), 127.5 (PhC), 106.5 (C₄).

(ii) 5-hydroxymethyl-3-phenylisoxazole 41 as white powder (0.02 g, 5%), m.p. 52°C (lit.,160 52°C); νmax (Nujol) 3340 cm⁻¹ (OH); δH (200 MHz, CDCl₃) 7.73-7.43 (2H, m, ArH), 7.41-7.38 (3H, m, ArH), 6.51 (1H, s, H₄), 4.74 (2H, s, CH₂), 4.05 (1H, s, OH); δC (50 MHz, CDCl₃) 172.2, 162.3 (C₅, C₃), 129.9, 128.7, 126.6 (PhCH), 128.4 (PhC), 99.8 (C₄), 56.0 (CH₂).

3.4.3 3-Formyl-5-phenyl-2-isoxazoline (42)

3-Ethoxycarbonyl-5-phenyl-2-isoxazoline 35 (4.99 g, 22 mmol) in dry dichloromethane (70 ml) was treated with DIBAL (66 ml, 66 mmol) as described previously for isoxazole 37. The crude product was subjected to dry flash chromatography (hexane, then 3% ether/hexane), to afford 3-formyl-5-phenyl-2-isoxazoline 42 as a pale orange oil (2.85 g, 71%), (lit.,162 90-100°C, 0.025 mmHg.); νmax, (Nujol) 1690 cm⁻¹ (C=O); δH (80 MHz, CDCl₃) 9.95 (1H, s, CHO), 7.24-7.36 (5H, m, ArH), 5.86 (1H, dd, J₅₄a 11.3 Hz, J₅₄b 9.1 Hz, H₅), 3.53 (1H, dd, J₄₅a 11.3 Hz, J₄₅₄₄b 17.6 Hz, H₄₄a) 3.07 (1H, dd, J₄₅b 9.1 Hz, J₄₅₄₄b 17.6 Hz, H₄₄b); δC (50 MHz, CDCl₃) 185.2 (CHO), 158.6 (C₃), 138.8 (PhC), 128.6, 128.5, 125.6 (PhCH), 85.6 (C₅), 37.7 (C₄). A trace of 3-hydroxymethyl-5-phenyl-2-isoxazoline was also obtained.
3.5 Synthesis of alkenyl-isoxazoles and 2-isoxazolines

3.5.1 5-Phenyl-3-vinylisoxazole (25)

All glassware was thoroughly dried in an oven (120°C) for 12 hours. Methyltriphenyolphosphonium iodide (2.34 g, 5.8 mmol) was placed in a nitrogen purged flask and dry THF (15 ml) was added. Potassium t-butoxide (0.96 g, 8.7 mmol) in THF (7 ml) was added and the resulting bright yellow solution was stirred for 10 minutes. A solution of 3-formyl-5-phenylisoxazole (0.45 g, 2.6 mmol) in THF (7 ml) was dripped into the reaction mixture and this was stirred at room temperature for 3 hours. Water (15 ml) was then added to terminate the reaction and the product extracted into chloroform (3 x 50 ml). The combined organic layers were dried (magnesium sulphate) and the solvent evaporated in vacuo. The brown crystalline residue was subjected to dry flash chromatography (hexane, then 10% ether/hexane), affording the product as white crystals (0.38 g, 83%); m.p. 44-46°C (from cyclohexane) (lit.,137,156 b.p. 76°C, 50 mmHg). νmax (Nujol) 1640 cm⁻¹ (C= C); δH (80 MHz, CDCl3) 7.74-7.79 (2H, m, ArH), 7.39-7.51 (3H, m, ArH), 6.82 (1H, dd, JAC 17.8 Hz, JAB 10.9 Hz, Ha), 6.63 (1H, s, H4), 5.90 (1H, dd, JCA 17.8 Hz, JCB 1.1 Hz, Hc), 5.64 (1H, dd, JBA 10.9 Hz, JBC 1.1 Hz, Hb); δC (50 Mz, CDCl3) 170.0 (C5), 162.5 (C3), 130.0, 126.0, 127.5 (PhCH, C₅A), 127.3 (PhC), 121.2 (C₆B), 96.0 (C₄); m/z (EI) 171 (M⁺).

Isoxazole 25 was also synthesised using the Mukaiyama methodology (Section 3.5.8).

3.5.2 3-Phenyl-5-vinylisoxazole (31)

Methyltriphenyolphosphonium iodide (2.34 g, 5.8 mmol) in dry THF (15 ml) was placed in a dry nitrogen-purged flask, potassium t-butoxide (0.96 g, 8.7 mmol) in THF (15 ml) was added and the resulting yellow solution stirred for 15 minutes. 5-Formyl-3-phenylisoxazole (0.45 g, 2.6 mmol) was dissolved in THF (7 ml) and dripped into the reaction mixture and the reaction worked up as described for isoxazole 25. Dry flash chromatography (hexane, then 8% ether/hexane) afforded 3-phenyl-5-vinylisoxazole as a pale yellow oil (0.24 g, 55%), (lit.,137 b.p. 95-97°C);
\[ \nu_{\text{max}} \text{ (Nujol)} \ 1638 \text{ cm}^{-1} (C=C); \delta_H \ (80 \text{ MHz, CDCl}_3) \ 7.71-7.49 \ (5H, m, ArH), 6.66 \ (1H, dd, J_{BC} 1.3 \text{ Hz, } J_{BA} 11.0 \text{ Hz, } H_B), 6.48 \ (1H, s, H_4), 6.05 \ (1H, dd, J_{CA} 17.7 \text{ Hz, } J_{CB} 1.3 \text{ Hz, } H_C), 5.55 \ (1H, ddd, J_{AC} 17.7 \text{ Hz, } J_{AB} 11.0 \text{ Hz, } J_{A4} <0.4 \text{ Hz, } H_A); \delta_C \ (50 \text{ MHz, CDCl}_3) \ 168.5 \ (C_5), 162.4 \ (C_3), 132.5, 130.5, 122.1 \ (\text{PhCH, } C_A), 128.9 \ (\text{PhC}), 120.4 \ (C_B), 99.3 \ (C_4); m/z (EI) 171 (M^+). \]

3.5.3 5-Phenyl-3-vinyl-2-isoxazoline (40)

Methyltriphenylphosphonium iodide (3.55 g, 8.8 mmol) in dry THF (25 ml) was placed in a dry nitrogen-purged flask and potassium t-butoxide (1.48 g, 13.3 mmol) in THF (12 ml) was added; the resulting bright yellow solution was stirred for 15 minutes. 3-Formyl-5-phenyl-2-isoxazoline (0.70 g, 4 mmol) was dissolved in THF (12 ml) and dripped into the reaction mixture and the reaction worked up as described for isoxazole 25. The brown residue was subjected to dry flash chromatography (hexane then 10% ether/hexane), affording the vinyl heterocycle 40 as a yellow oil (0.40 g, 58%) (lit.,\textsuperscript{124,125} 140-142°C, 5-6 mmHg). \[ \nu_{\text{max}} \text{ (Nujol)} \ 1630 \text{ cm}^{-1} (C=C); \delta_H \ (200 \text{ MHz, CDCl}_3) \ 7.34 \ (5H, m, ArH), 6.74 \ (1H, dd, J_{AB} 10.9 \text{ Hz, } J_{AC} 17.7 \text{ Hz, } H_z, H_A), 5.62 \ (1H, dd, J_{5HB} 8.4 \text{ Hz, } J_{5Ha} 11.0 \text{ Hz, } H_5), 5.54 \ (1H, dd, J_{BA} 10.9 \text{ Hz, } J_{BC} 0.5 \text{ Hz, } H_B), 5.41 \ (1H, dd, J_{CB} 0.5 \text{ Hz, } J_{CA} 17.7 \text{ Hz, } H_C), 3.49 \ (1H, dd, J_{4a4b} 16.5, J_{4a5} 11.0 \text{ Hz, } H_{4a}), 3.05 \ (1H, dd, J_{4b4a} 16.5 \text{ Hz, } J_{4b5} 8.4 \text{ Hz, } H_{4b}); \delta_C \ (50 \text{ MHz, CDCl}_3) \ 156.9 \ (C_3), 140.5 \ (\text{PhC}), 128.4, 127.3, 125.5 \ (\text{PhCH, } C_A), 122.0 \ (C_B), 82.3 \ (C_5), 40.9 \ (C_4); m/z (EI) 174 (M^+). \]

5-Phenyl-3-vinyl-2-isoxazoline was also synthesised via the Mukaiyama method (Section 3.5.7).
3.5.4 3-Phenyl-5-vinyl-2-isoxazoline (19)

Triethylamine (4.05 g, 40 mmol) in chloroform (10 ml) was added dropwise, over 6 hours, to a mixture of butadiene (10 ml, 40 mmol) and benzohydroximoyl chloride (6.2 g, 40 mmol) in chloroform (30 ml) at -20°C. The reaction mixture was stirred at 0°C for a further 6 hours. After washing with water (100 ml), the yellow solution was dried (magnesium sulphate) and the solvent evaporated in vacuo. The residue was subjected to dry flash chromatography (hexane, then 9% ether/hexane), affording the product as acicular white crystals (5.83 g, 84%) m.p. 45-47°C (lit., 131 45-47°C). \( \nu_{\text{max}} \) (Nujol) 1634 cm\(^{-1} \) (C=C); \( \delta_H \) (200 MHz, CDCl\(_3\)) 7.57-7.39 (5H, m, ArH), 5.93 (1H, ddd, \( J_{AC} \) 17.0 Hz, \( J_{AB} \) 10.2 Hz, \( J_{A5} \) 6.8 Hz, HA), 5.38 (1H, dd, \( J_{CB} \) 1.1 Hz, \( J_{CA} \) 17.0 Hz, HC), 5.25 (1H, dd, \( J_{BA} \) 10.2 Hz, \( J_{BC} \) 1.1 Hz, HB), 5.13 (1H, dddd, \( J_{54b} \) 8.4 Hz, \( J_{54a} \) 10.5 Hz, \( J_{5A} \) 6.8 Hz, \( J_{5B} \) 1.0 Hz, H5), 3.47 (1H, dd, \( J_{4a5} \) 10.5 Hz, \( J_{4a4b} \) 16.6 Hz, Ha4), 3.05 (1H, dd, \( J_{4b4a} \) 16.6 Hz, \( J_{4b5} \) 8.4 Hz, H4b); \( \delta_C \) (50MHz, CDCl\(_3\)) 156.1 (C3), 135.8, 130.7, 126.4 (PhCH, CA), 129.3 (PhC), 117.6 (CB), 81.7 (C5), 40.3 (C4); \( m/z \) (EI) 174 (M\(^+\)).

3.5.5 5-(m-Isopropenylphenyl)-5-methyl-3-phenyl-2-isoxazoline (45)

A solution of triethylamine (1.44 g, 14.5 mmol) in ether (20 ml) was added over 16 hours to 1,3-diisopropenylbenzene (1.32 g, 23.8 mmol) and benzohydroximoyl chloride (1.32 g, 8.5 mmol) in ether (25 ml) at 0°C for 1 hour, then at room temperature. The reaction mixture was then filtered through celite, the solvent evaporated in vacuo and the product purified by dry flash chromatography (hexane, then 4% ether/hexane, then 8% ether/hexane) to afford in order of elution:

(a) 5-(m-isopropenylphenyl)-5-methyl-3-phenyl-2-isoxazoline 45 as a white crystalline solid (0.77 g, 33%), m.p. 61-62°C (from cyclohexane) (Found: C, 82.1; H, 6.9; N, 4.9%. C\(_{19}\)H\(_{19}\)NO requires C, 82.3; H, 6.8; N, 5.1%); (Found: \( m/z \) 278.154 49. C\(_{19}\)H\(_{20}\)NO requires \( M \), 278.154 48); \( \delta_H \) (360 MHz, CDCl\(_3\)) 7.72-7.69 (3H, m, ArH), 7.46-7.37 (6H, m, ArH), 5.46, 5.16 (2H, dd, \( J_{BMe} \) \( J_{CMe} \) 0.7 Hz, 1.4 Hz, HC,
HB). 3.57 (1H, d, J4a4b16.6 Hz, H4a), 3.49 (1H, d, J4b4a16.6 Hz, H4b), 2.21 (3H, dd, JMe'B, Me'C1.4 Hz, 0.7 Hz, HMe'), 1.86 (3H, s, HMe); δC (50 MHz, CDCl3) 155.8 (C3), 145.2 (PhC), 129.0, 128.3, 128.1, 126.2, 124.2, 123.5, 121.4 (PhCH), 112.6 (C_B), 87.7 (C5), 48.2 (C4), 27.9 (Me), 21.5 (Me'); m/z (FAB) 278 (M+1).

(b) 1,3-bis-(5-methyl-3-phenyl-2-isoxazolin-5-yl)benzene 47 (0.87 g, 18%), m.p. 118-120°C; (Found: C, 78.7; H, 6.2; N, 6.9%. C26H24N2O2 requires C, 78.8; H, 6.1; N, 7.1%); (Found: m/z 397.189 8. C26H25N2O2 requires 397.191 59.), δH (360 MHz, CDCl3) 7.47-7.42 (7H, m, ArH), 7.25-7.13 (7H, m, ArH), 3.32 (4H, m, H4a, H4b, H4a, H4b); 1.57, 1.59 (6H, d, HMe'Me'); δC (50 MHz, CDCl3) 155.7 (C3), 145.3 (PhC), 129.3, 128.6, 123.2, 120.3 (PhCH), 87.5 (C5), 47.9 (C4), 27.7 (Me, Me'); m/z (FAB) 397 (M+1).

3.5.6 3-Phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline (46)

A solution of triethylamine (1.44 g, 14.5 mmol) in ether (20 ml) was added over 14 hours to a solution of 1,3- and 1,4-divinylbenzene (3.87 g, 29 mmol), (composition of dipolarophile: 38.7% 1,3-divinylbenzene, 10.5% 1,4-divinylbenzene, 32.9% 3-ethylystryene, 10.5% 4-ethylstyrrene; supplied by Aldrich), and benzohydroximoyl chloride (1.36 g, 8.5 mmol) in ether (30 ml) at 0°C for 1 hour then at room temperature. The reaction mixture was filtered through celite and the filtrate concentrated. The product was purified by dry flash chromatography (hexane, then 6% ether/hexane) to afford in order of elution:

(a) 5-(m- and p-ethylphenyl)-3-phenyl-2-isoxazoline 48 as an off-white crystalline solid (0.46 g, 19%), m.p. 40-44°C (from hexane); (Found: C, 82.3; H, 6.4; N, 5.5% C18H17NO requires C, 82.1; H, 6.5; N, 5.3%); (Found: m/z 264.138 85. C18H18NO requires M, 264.138 83); m/z (FAB) 264 (M+1). NMR data is given for the m-isomer- the major component. δH (200 MHz, CDCl3) 7.71-7.22 (9H, m, ArH), 5.27 (1H, dd, J5a5b10.9 Hz, J5b5a8.4 Hz, H5), 3.75 (1H, dd, J4a510.9 Hz, J4a4b16.6 Hz, H4a), 3.34 (1H, dd, J4b58.4 Hz, J4b4a16.6 Hz, H4b), 2.65 (2H, q, JAB7.5 Hz,
(b) 3-phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline 46 as a white solid (0.53 g, 24%), m.p. 73-76°C; (Found: C, 81.3; H, 6.5; N, 5.3% \text{C}_{18}H_{15}NO \text{ requires C, 82.1; H, 6.5; N, 5.3%}); (Found: m/z 262.334 34. \text{C}_{18}H_{16}NO \text{ requires } M, 262.334 34); m/z (FAB) 262 (M⁺+1). NMR data given for the m-isomer (major isomer); δ_H (200 MHz, CDCl₃) 7.74-7.26 (5H, m, ArH), 6.71 (1H, dd, J_{AB}10.9 Hz, J_{AC}17.6 Hz, H_A), 5.79 (1H, dd, J_{BA}10.9 Hz, J_{BC}0.9 Hz, H_B), 5.74 (1H, dd, J_{CA}17.6, J_{CB}0.9 Hz, H_C), 5.27 (1H, ddd, J_{5a}10.9 Hz, J_{5b}8.4 Hz, H_5), 3.76 (1H, dd, J_{4a4b}16.6 Hz, J_{4a5}10.9 Hz, H_4a), 3.34 (1H, dd, J_{4b4a}16.6 Hz, J_{4b5}8.4 Hz, H_4b); δ_C (50 MHz, CDCl₃) 155.9 (C₃), 140.2, 137.4 (PhC), 129.3, 137.4 (PhC'), 126.5, 125.5, 125.0, 123.0 (PhCH), 136.1 (CA), 114.1 (CB), 82.6 (C₅), 42.5 (C₄). By measuring the integrals for the ring protons, H₄a and H₄b, for the two isomers the ratio m-isomer : p-isomer was estimated to be ~ 4:1. H₄a for the p-isomer appeared at 3.78 p.p.m. and H₄b at 3.33 p.p.m (J_{4a4b}16.6 Hz); the other peaks were obscured by the major adduct.

(c) 1,3- and 1,4-bis(5-methyl-3-phenyl-2-isoxazolin-5-yl)benzene 49 as a white crystalline solid (0.08 g, 2%), m.p. 130-135°C, (Found: C, 77.6; H, 5.8; N, 6.8; \text{C}_{24}H_{20}N₂O₂ \text{ requires C, 78.0; H, 5.4; N, 7.3%}); (Found: m/z 369.447 18. \text{C}_{24}H_{21}N₂O₂ \text{ requires } M, 369.447 17.); m/z (FAB) 369 (M⁺+1). The NMR data is for the major isomer (m-isomer). δ_H (200 MHz, CDCl₃) 7.72-7.35 (10H, m, PhCH), 5.73 (1H, dd, J_{5a}10.9 Hz, J_{5b}8.5 Hz, H_5), 3.77 (1H, dd, J_{4a4b}16.7 Hz, J_{4a5}10.9 Hz, H_4a), 3.34 (1H, dd, J_{4b4a}16.7 Hz, J_{4b5}8.5 Hz, H_4b); δ_C (50 MHz, CDCl₃) 156.0 (C₃), 141.5, 141.4 (PhC), 130.0, 129.3, 123.2 (PhCH), 82.2 (C₅), 43.0 (C₄).

General procedure for Mukaiyama methodology

The following heterocycles were synthesised by applying the Mukaiyama method. A solution of the nitromethyl compound (1 equiv.) in benzene was added over 12 hours (using a motorised syringe pump), at room temperature, to a stirred solution of phenyl isocyanate (2.5 equivs.), triethylamine (3 drops) and the appropriate dipolarophile (5-6 equivs.) in benzene. Diphenylurea was filtered off and the solvent evaporated in vacuo. The residue was purified using dry flash chromatography.
Preparation of 1-nitropropene

The required alcohol was prepared according to the method of Sprang and Degering.\textsuperscript{195} Aqueous sodium hydroxide (100 ml, 10 M) was added slowly over a period of 40 minutes to a cold mixture of freshly distilled acetaldehyde (55.9 ml, 1 mole) and nitromethane (53.8 ml, 1 mole). The reaction mixture was stirred mechanically in a one litre, three-necked round bottom flask for 1 hour after all the alkali had been added and the temperature was maintained between 5-10\textdegree C. Cold acetic acid (500 ml, 2M) was then added to neutralise the reaction which was then finally saturated with NaCl. The product was taken up in ether and dried (magnesium sulphate). Ether, unreacted aldehyde and nitromethane were removed by distillation under reduced pressure using a cardice/acetone bath. The remaining residue was purified by Kugelrohr distillation (70\textdegree C, 0.75 mmHg) affording 1-nitropropan-2-ol as a colourless oil (59 g, 56%); \( \delta_H \) (80 MHz, CDCl\textsubscript{3}) 4.39-4.28 (3H, m, H\textsubscript{BC}), 3.56 (1H, s, OH), 1.17 (3H, d, \( J_{6.3} \) Hz, H\textsubscript{A}); \( \delta_C \) (50 MHz, CDCl\textsubscript{3}) 81.2 (C\textsubscript{C}), 64.6 (C\textsubscript{B}), 19.2 (C\textsubscript{A}).

2-Acetoxy-1-nitropropane was prepared from the 1-nitropropan-2-ol (5 g, 48 mmol) by treatment at 60\textdegree C with acetic anhydride (6.37 g, 62 mmol) in the presence of concentrated sulphuric acid (15 drops). Half of the necessary anhydride was added rapidly to the stirred alcohol followed by the balance at such a rate that the temperature remained around 60\textdegree C. After an additional two hours, acetic acid and excess acetic anhydride were removed by Kugelrohr distillation (50\textdegree C, 0.75 mmHg). The product distilled over as a colourless oil (77\textdegree C, 0.75 mmHg) (6.00 g, 93%); \( \delta_H \) (80 MHz, CDCl\textsubscript{3}) 5.42-5.51 (1H, m, H\textsubscript{B}), 4.44-4.49 (2H, m, H\textsubscript{C}), 2.00 (3H, s, H\textsubscript{Me}), 1.30 (3H, d, \( J_{6.6} \) Hz, H\textsubscript{A}); \( \delta_C \) (50 MHz, CDCl\textsubscript{3}) 169.8 (C=O), 78.0 (C\textsubscript{C}), 66.5 (C\textsubscript{B}), 20.6 (CH\textsubscript{3}), 16.8 (C\textsubscript{A}).

The nitroalkyl acetate (5.09 g, 37.7 mmol) and anhydrous sodium carbonate (3.99 g, 37.7 mmol) were heated under reflux in benzene (60 ml) in an apparatus provided with a Dean-Stark water trap until no more acetic acid collected. After removal of sodium acetate and sodium carbonate by filtration, the benzene solution was concentrated and the residue Kugelrohr distilled (18\textdegree C, 0.75 mmHg) to afford 1-nitropropene 50 as a pale green oil (1.5 g, 46%), (lit.,\textsuperscript{196} pale green oil, b.p. 52.0-52.3\textdegree C). \( \delta_H \) (80 MHz, CDCl\textsubscript{3}) 7.19 (1H, dd, \( J_{9.3} \) Hz, J\textsubscript{AB} 6.4 Hz, H\textsubscript{A}), 6.94 (1H, dm, J\textsubscript{CB} 13.4 Hz, J\textsubscript{CA} 0.9 Hz, H\textsubscript{C}), 1.75 (3H, dd, J\textsubscript{AB} 6.6 Hz, J\textsubscript{AC} 0.9 Hz, H\textsubscript{a}); \( \delta_C \) (50 MHz, CDCl\textsubscript{3}) 139.9 (C\textsubscript{B}), 138.1 (C\textsubscript{C}), 13.2 (C\textsubscript{A}).

\[
\begin{align*}
\text{CH}_3\text{CH} &= \text{CHNO}_2 \\
\text{A} & \quad \text{B} & \quad \text{C}
\end{align*}
\]
3.5.7 5-Phenyl-3-vinyl-2-isoxazoline (17)

A solution of 1-nitropropene (0.5 g, 5.7 mmol) in benzene (10 ml) was added dropwise over 12 hours to a stirred mixture of phenyl isocyanate (1.57 g, 13.2 mmol), styrene (3.12 g, 30 mmol) and triethylamine (3 drops) in benzene (20 ml), as described in the general procedure above. Dry flash chromatography (hexane, then 10% ether/hexane) furnished isoxazoline 17 (0.54 g, 55%), which was identical to that prepared previously (section 3.5.3).

5-Phenyl-3-vinyl-2-isoxazoline was also synthesised from 1-nitropropene using tolylene diisocyanate (TDI) as the dehydrating agent. 1-Nitropropene (0.5 g, 5.7 mmol) in dichloroethane (20 ml) was added dropwise over 14 hours to TDI (1.24 g, 7.1 mmol), styrene (0.89 g, 8.5 mmol) and triethylamine (0.15 g, 1.5 mmol) in dichloroethane (10 ml). After the reaction was complete chloroform (10 ml) and diaminoethane (0.15 g) were added to facilitate the work-up. The reaction mixture was filtered through celite and washed thoroughly with ether and chloroform. The filtrate was concentrated and the product purified by dry flash chromatography (hexane, then 15% ether/hexane) (0.29 g, 30%); see Section 3.5.3 for NMR data.

3.5.8 5-Phenyl-3-vinylisoxazole (25)

1-Nitropropene (0.5 g, 5.7 mmol) in dichloromethane (20 ml) was added dropwise over 18 hours to TDI (1.25 g, 7.2 mmol), phenylacetylene (0.87 g, 8.5 mmol) and triethylamine (0.15 g, 1.5 mmol) in dichloroethane (10 ml). The procedure was continued as described in section 3.5.1. Dry flash chromatography (hexane, then 8% ether/hexane) furnished isoxazole 25 (0.12 g, 12%); see Section 3.5.1. for NMR data.

3.5.9 5-(p-Chlorophenyl)-3-vinyl-2-isoxazoline (55)

A solution of 1-nitropropene (0.5 g, 5.7 mmol) in benzene (10 ml) was added over 18 hours to phenyl isocyanate (1.57 g, 13.2 mmol), p-chlorostyrene (4.16 g, 30 mmol) and triethylamine (3 drops) in benzene (20 ml), as described in the general procedure. The orange/brown residue was subjected to dry flash chromatography (hexane, then 7% ether/hexane), which afforded 5-(p-chlorophenyl)-3-vinyl-2-isoxazoline as a yellow oil (0.36 g, 30%), (Found: m/z 208.053 4. C_{11}H_{11}Cl_{35}NO requires M, 208.052 91); δ_H (200 MHz, CDCl_3) 7.39-7.13 (5H, m, ArH), 6.70 (1H, dd, J_{AB} 10.9 Hz, J_{AC} 17.7 Hz, H_A), 5.59 (1H, dd, J_{54a} 11.0 Hz, J_{54b} 8.3 Hz, H_5), 5.49 (1H, dd, J_{BA} 10.9 Hz, J_{BC} 0.4 Hz, H_B), 5.40 (1H, dd, J_{CB} 0.4 Hz, J_{CA} 17.7 Hz, H_C),
3.50 (1H, dd, J_{4a}4b16.6 Hz, J_{4a}511.0 Hz, H_{4a}), 2.90 (1H, dd, J_{4b}4a16.6 Hz, J_{4b}58.3 Hz, H_{4b}); δ\text{C} (50 MHz, CDCl\textsubscript{3}) 157.1 (C\textsubscript{3}), 139.1 (C-Cl), 133.9 (PhC), 128.7, 127.3, 126.4, (PhCH, C\textsubscript{A}), 122.5 (C\textsubscript{B}), 81.6 (C\textsubscript{5}), 41.2 (C\textsubscript{4}); m/z (FAB) 208 (M\textsuperscript{+}+1).

3.5.10 5-(m-Nitrophenyl)-3-vinyl-2-isoxazoline (56)

1-Nitropropene (0.25 g, 2.9 mmol) in chloroform (10 ml) was added over 16 hours to a solution of phenyl isocyanate (0.79 g, 6.6 mmol), m-nitrostyrene (1.28 g, 8.7 mmol) and triethylamine (3 drops), as described in the general procedure. The resulting residue was purified by flash chromatography (hexane, then 6% ether/hexane) which afforded 5-(m-nitrophenyl)-3-vinyl-2-isoxazoline as an orange oil (0.21 g, 34%). (Found: m/z 219.076 96. \text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_3 requires M, 219.076 95); δ\text{H} (200 MHz, CDCl\textsubscript{3}) 8.24-8.21 (2H, m, ArH), 7.75-7.63 (2H, m, ArH), 6.68 (1H, dd, J_{AB}10.9 Hz, J_{AC}17.7 Hz, H_{A}), 5.72 (1H, dd, J_{5a}4b11.1 Hz, J_{5b}4a7.8 Hz, H_{5}), 5.57 (1H, dd, J_{BA}10.9 Hz, H_{B}), 5.48 (1H, d, J_{CA}17.7 Hz, H_{C}), 3.61 (1H, dd, J_{4a}4b16.6 Hz, J_{4a}511.1 Hz, H_{4a}), 3.05 (1H, dd, J_{4b}4a16.6 Hz, J_{4b}57.8 Hz, H_{4b}); δ\text{C} (50 MHz, CDCl\textsubscript{3}) 156.9 (C\textsubscript{3}), 148.3 (C-NO\textsubscript{2}), 142.9 (PhC), 132.7, 123.5, 122.2, 122.5 (C\textsubscript{B}, PhCH), 120.6 (C\textsubscript{A}), 80.9 (C\textsubscript{5}), 41.3 (C\textsubscript{4}).

3.5.11 5-(p-Methoxyphenyl)-3-vinyl-2-isoxazoline (57)

1-Nitropropene (0.3 g, 3.4 mmol) in chloroform (10 ml) was added over 18 hours to a solution of phenyl isocyanate (1.27 g, 10.7 mmol), p-methoxystyrene (3.09 g, 23 mmol) and triethylamine (3 drops) in chloroform (20 ml), as described in the general procedure. The residue was purified by dry flash chromatography (hexane, then 8% ether/hexane) which afforded 5-(p-methoxyphenyl)-3-vinyl-2-isoxazoline as a yellow/orange oil (0.38 g, 54%). (Found: m/z 205.110 26. \text{C}_{12}\text{H}_{14}\text{NO}_2 requires M, 205.110 27); δ\text{H} (80 MHz, CDCl\textsubscript{3}) 7.37-7.20 (2H, m, ArH), 6.92-6.81 (2H, m, ArH), 6.71 (1H, dd, J_{AC}17.7 Hz, J_{AB}10.9 Hz, H_{A}), 5.57 (1H, d, J_{BA}10.9 Hz, H_{B}), 5.54 (1H, dd, J_{5a}4b10.8 Hz, J_{4b}58.5 Hz, H_{5}), 5.49 (1H, d, J_{CA}17.7 Hz, H_{C}) 3.77 (1H, s, OCH\textsubscript{3}), 3.43 (1H, dd, J_{4a}4b16.9 Hz, J_{4a}510.8 Hz, H_{4a}) 3.02 (1H, dd, J_{4b}4a16.9 Hz, J_{4b}58.5 Hz, H_{4b}); δ\text{C} (50 MHz, CDCl\textsubscript{3}) 159.3 (COCH\textsubscript{3}), 157.2 (C\textsubscript{3}), 132.3 (PhCH), 126.6, 113.8 (PhCH\textsubscript{2}), 127.1 (C\textsubscript{A}), 121.9 (C\textsubscript{B}), 82.2 (C\textsubscript{5}), 40.7 (C\textsubscript{4}), 54.9 (CH\textsubscript{3}); m/z (FAB) 205 (M\textsuperscript{+}+1).

3.5.12 5-Methyl-5-phenyl-3-vinyl-2-isoxazoline (58)

1-Nitropropene (0.65 g, 7.4 mmol) in benzene (10 ml) was added over 28 hours to phenyl isocyanate (2.36 g, 19.7 mmol), α-methylstyrene (5.36 g, 45 mmol) and triethylamine (4 drops), as described in the general procedure. Dry flash
chromatography (hexane, then 4% ether/hexane) afforded 5-methyl-5-phenyl-3-vinyl-2-isoxazoline as a pale yellow oil (0.13 g, 28%). (Found: \( m/z \) 188.108 1. \( \text{C}_{12}\text{H}_{14}\text{NO} \) requires \( M, 188.107 \) 53) \( \delta_H \) (200 MHz, CDC\( \text{Cl}_3 \) 7.64-7.27 (5H, m, ArH), 6.68 (1H, ddd, \( J_{AB}10.9 \) Hz, \( J_{AC}17.7 \) Hz, \( J_{A4b}0.7 \) Hz, \( H_A \)), 5.51 (1H, d \( J_{BA}10.9 \) Hz, \( H_B \)), 5.40 (1H, dd, \( J_{CA}17.7 \) Hz, \( J_{CB}0.8 \) Hz, \( H_C \)), 3.28 (1H, d, \( J_{4a4b}16.4 \) Hz, \( H_{4a} \)), 3.19 (1H, d, \( J_{4a4b}16.4 \) Hz, \( H_{4b} \)), 1.74 (1H, s, CH\( _3 \)); \( \delta_C \) (50 MHz, CDC\( \text{Cl}_3 \) 157.2 (C\( _3 \)), 145.1 (PhC), 128.3, 127.2, 127.1, 124.4 (PhCH, C\( _A \)), 121.6 (C\( _B \)), 87.9 (C\( _5 \)), 46.7 (C\( _4 \)), 28.0 (CH\( _3 \)); \( m/z \) (FAB) 188 (M\(^{+}\)+1).

3.5.13 5-Acetyl-3-vinyl-2-isoxazoline (59)

1-Nitropropene (0.4 g, 4.6 mmol) in chloroform (10 ml) was added over 16 hours to a solution of phenyl isocyanate (1.27 g, 10.7 mmol), methyl vinyl ketone (1.61 g, 23 mmol) and triethylamine (3 drops), as described previously. Dry flash chromatography (hexane, then 5% ether/hexane) furnished 5-acetyl-3-vinyl-2-isoxazoline 59 as a colourless oil (0.19 g, 30%), (Found: \( m/z \) 139.155 3. \( \text{C}_7\text{H}_9\text{NO}_2 \) requires \( M, 139.155 \) 28); \( \delta_H \) (200 MHz, CDC\( \text{Cl}_3 \) 6.67 (1H, dd, \( J_{AB}10.9 \) Hz, \( J_{AC}17.7 \) Hz, \( H_A \)), 5.62 (1H, d, \( J_{BA}10.9 \) Hz, \( H_B \)), 5.53 (1H, d, \( J_{CA}17.7 \) Hz, \( H_C \)), 4.93 (1H, dd, \( J_{5a4b}6.7 \) Hz, \( J_{5a}11.5 \) Hz, \( H_5 \)), 3.34 (1H, dd, \( J_{4a4b}17.2 \) Hz, \( J_{4a5}11.5 \) Hz, \( H_{4a} \)), 3.19 (1H, dd, \( J_{4a4b}17.2 \) Hz, \( J_{4b5}6.7 \) Hz, \( H_{4b} \)), 2.31 (3H, s, COCH\( _3 \)); \( \delta_C \) (50 MHz, CDC\( \text{Cl}_3 \) 159.4 (C=O), 157.4 (C\( _3 \)), 125.6 (C\( _A \)), 123.2 (C\( _B \)), 84.0 (C\( _5 \)), 47.5 (C\( _4 \)), 18.1 (CH\( _3 \)); \( m/z \) (FAB) 139 (M\(^{+}\)).

3.5.14 5-Methoxycarbonyl-3-vinyl-2-isoxazoline (60)

1-Nitropropene (0.5 g, 5.7 mmol) in benzene (10 ml) was added over 13 hours to a solution of phenyl isocyanate (1.57 g, 13.2 mmol), methyl acrylate (2.58 g, 30 mmol) and triethylamine (3 drops) in benzene (20 ml), as described in the general procedure. Dry flash chromatography furnished 5-methoxycarbonyl-3-vinyl-2-isoxazoline as yellow oil (0.27 g, 30%)(lit.,\(^{124,125} \) m.p.55-56°C). \( \nu_{\text{max}} \) 1760, 1115 cm\(^{-1} \) (C=O, CO); \( \delta_H \) (80 MHz, CDC\( \text{Cl}_3 \) 6.50 (1H, dd, \( J_{AB}10.9 \) Hz, \( J_{AC}17.7 \) Hz, \( H_A \)), 5.48 (1H, d, \( J_{BA}10.9 \) Hz, \( H_B \)), 5.38 (1H, d, \( J_{CA}17.7 \) Hz, \( H_C \)), 4.94 (1H, dd, \( J_{5a4b}9.1 \) Hz, \( J_{5a}9.1 \) Hz, \( H_5 \)), 3.63 (1H, s, CO\( _2\text{CH}_3 \)), 3.24 (2H, d, \( J_{4b5}9.1 \) Hz, \( J_{4a5}9.1 \) Hz, \( H_{4a,4b} \)); \( \delta_C \) (50 MHz, CDC\( \text{Cl}_3 \) 170.2 (CO\( _2\text{Me} \)), 156.8 (C\( _3 \)), 125.5 (C\( _B \)), 123.2 (C\( _A \)), 77.6 (C\( _5 \)), 52.5 (CH\( _3 \)), 36.9 (C\( _4 \)); \( m/z \) (FAB) 205 (M\(^{+}\)+1).
3.5.15 5-Methoxycarbonyl-5-methyl-3-vinyl-2-isoxazoline (61)

1-Nitropropene (0.5 g, 5.7 mmol) in chloroform (10 ml) was added over 18 hours to a stirred mixture of phenyl isocyanate (1.57 g, 13.2 mmol), methyl methacrylate (6.61 g, 66 mmol), and triethylamine (3 drops) in chloroform (20 ml), as described previously. Dry flash chromatography (hexane, then 4% and 6% ether/hexane) afforded 5-methoxycarbonyl-5-methyl-3-vinyl-2-isoxazoline as a yellow oil (0.75 g, 71%), (Found: m/z 170.081 70. C_{8}H_{12}NO_{3} requires M, 170.081 71); δ_{H} (200 MHz, CDCl_{3}) 6.54 (1H, dd, J_{AB}10.9 Hz, J_{AC}17.7 Hz, H_{A}), 5.50 (1H, d, J_{BA}10.9 Hz, H_{B}), 5.39 (1H, d, J_{CA}17.7 Hz, H_{C}), 3.69 (3H, s, H_{Me}), 3.52 (1H, d, J_{4a4b}16.9 Hz, H_{4a}), 2.88 (1H, d, J_{4b4a}16.9 Hz, H_{4b}), 1.56 (3H, s, H_{Me}); δ_{C} (50 MHz, CDCl_{3}) 170.6 (CO_{2}CH_{3}), 155.9 (C_{3}), 124.5 (C_{A}), 121.8 (C_{B}), 85.6 (C_{5}), 52.8 (CO_{2}CH_{3}), 43.1 (C_{4}), 23.8 (CH_{3}); m/z (FAB) 170 (M^{+}+1).

3.5.16 3,5-divinyl-2-isoxazoline (62)

A solution of butadiene (1.86 g, 2.9 ml, 34 mmol) in chloroform (10 ml) was prepared using a cardice/acetone bath. 1-Nitropropene (0.3 g, 3.4 mmol) in chloroform (10 ml) was added over 14 hours to a solution of phenyl isocyanate (0.95 g, 7.9 mmol), butadiene and triethylamine (3 drops) in chloroform (20 ml). The reaction mixture was stirred at room temperature for 17 hours, as described in the general Mukaiyama procedure. 3,5-divinyl-2-isoxazoline was purified by dry flash chromatography (hexane, then 6% ether/hexane) and was isolated as a yellow oil (0.085 g, 20%), (Found: m/z 123.068 40. C_{7}H_{9}NO requires M, 123.068 41); δ_{H} (200 MHz, CDCl_{3}) 6.67 (1H, dd, J_{AB}10.8 Hz, J_{AC}17.7 Hz, H_{A}), 5.89 (1H, ddd, J_{A5}6.9 Hz, J_{AB}10.2 Hz, J_{AC}17.0 Hz, H_{A'}), 5.55 (1H, d, J_{BA}10.8 Hz, H_{B}), 5.48 (1H, d, J_{CA}17.6 Hz, H_{C}), 5.38 (1H, d, J_{CA'}17.0 Hz, H_{C'}), 5.25 (1H, dd, J_{B'A}10.2 Hz, J_{BC}1.0 Hz, H_{B'}), 5.03 (1H, ddd, J_{5A'}6.9 Hz, J_{5a4a}10.6 Hz, J_{5a4b}8.5 Hz, H_{5}), 3.32 (1H, dd, J_{4a5}10.6 Hz, J_{4a4b}16.5 Hz, H_{4a}), 2.83 (1H, dd, J_{4b4a}16.5 Hz, J_{4b5}8.5 Hz, H_{4b}); δ_{C} (50 MHz, CDCl_{3}) 157.4 (C_{3}), 135.8 (C_{A'}), 126.8 (C_{A}), 121.9, 117.8 (C_{B}, C_{B'}), 81.9 (C_{5}), 38.5 (C_{4}); m/z (FAB) 123 (M^{+}).
3.5.17 5-Methyl-5-(m-isopropenylphenyl)-3-vinyl-2-isoxazoline (63)

1-Nitropropene (0.75 g, 8.6 mmol) in benzene (10 ml) was added over 17 hours to a solution of phenyl isocyanate (2.35 g, 19.7 mmol), 1,3-diisopropenylbenzene and triethylamine (3 drops) in benzene (20 ml), as described in the general procedure. The orange/brown residue was subjected to dry flash chromatography (hexane, then 7% ether/hexane) thus affording 5-methyl-5-(m-isopropenylphenyl)-3-vinyl-2-isoxazoline as a yellow oil (0.36 g, 17%), (Found: m/z 239.319 89. C16H17NO requires M, 239.319 99); δ_H (80MHz, CDCl3) 7.54-7.53 (1H, m, ArH), 7.43-7.30 (3H, m, ArH), 6.67 (1H, dd, J_AB 10.9 Hz, J_AC 17.7 Hz, H_A), 5.51 (1H, d, J_BA 11.0 Hz, H_B), 5.40 (1H, d, J_CA 17.7 Hz, H_C), 5.37 (1H, s, H_C'), 5.09 (1H, dm, J_B'Me' 1.2 Hz, H_Me'), 3.26 (1H, d, J_CA 16.4 Hz, H_A), 3.19 (1H, d, J_CA 16.4 Hz, H_A), 2.15 (3H, d, J_CA 1.2 Hz, H_Me), 1.74 (3H, s, H_Me); δ_C (50 MHz, CDCl3) 157.5 (C3), 145.2, 142.9 (Ph_C, C_A'), 129.9, 128.3, 127.1, 124.9, 125.5, 121.6 (Ph_CH, C_A), 121.5 (C_B), 112.7 (C_B') 87.9 (C5), 46.6 (C4), 27.3, 21.6 (C_Me'C_Me'); m/z (FAB) 239 (M⁺).

3.6 Synthesis of 3-propenyl-2-isoxazolines

Preparation of 1-nitrobut-1-ene

1-Nitrobutan-2-ol was prepared according to the method of Sprang and Degering, as described for 1-nitropropan-2-ol. Aqueous sodium hydroxide (100 ml, 10 M) was added over 40 minutes to a cold mixture of freshly distilled propionaldehyde (71.7 ml, 1 mole) and nitromethane (53.8 ml, 1 mole). After 45 minutes a white gelatinous precipitate resulted which was then neutralised (acetic acid, 500 ml, 2M) and saturated with NaCl. After extracting into ether and drying (magnesium sulphate), unreacted aldehyde and nitromethane were removed by distillation. The product was purified by kugelrohr distillation (50°C, 0.3 mmHg)
and was a colourless oil (54 g, 45%), m.p. ~10°C; δ\(_\text{H}\) (80 MHz, CDCl\(_3\)) 5.45 (1H, dm, \(J_{\text{CD,CD}}\) 4.8 Hz, H\(_\text{C}\)), 4.45 (2H, dm, \(J_{\text{DC,DC}}\) 4.8 Hz, H\(_\text{D}\)), 1.97 (2H, s, H\(_B\)), 1.20 (3H, t, \(J_{\text{CH-CH}}\) 6.4 Hz, H\(_A\)); δ\(_\text{C}\) (50 MHz, CDCl\(_3\)) 79.8 (C\(_\text{D}\)), 69.5 (C\(_\text{C}\)), 26.1 (C\(_B\)), 8.6 (C\(_A\)).

1-Nitrobutan-1-ol (20.0 g, 168 mmol), acetic anhydride (25.0 g, 245 mmol) and concentrated sulphuric acid (15 drops) were stirred at 60°C, half the acetic anhydride was added rapidly and then dropwise. After 2 hours, acetic acid and excess acetic anhydride were removed by distillation (42°C, 0.5 mmHg). 2-Acetoxy-1-nitrobutane distilled over as a colourless oil (24.0 g, 87%); δ\(_\text{H}\) (80 MHz, CDCl\(_3\)) 5.45 (1H, dd, \(J_{\text{CB}} J_{\text{CD}}\) 3.4 Hz, H\(_\text{C}\)), 4.45 (2H, dm, \(J_{\text{DC,DC}}\) 3.4 Hz, H\(_\text{D}\)), 3.00 (1H, s, OH), 1.97 (2H, s, H\(_B\)), 1.20 (3H, t, \(J_{\text{CH-CH}}\) 6.4 Hz, H\(_A\)); δ\(_\text{C}\) (50 MHz, CDCl\(_3\)) 169.9 (C=O), 76.9 (C\(_\text{D}\)), 70.9 (C\(_\text{C}\)), 24.5 (C\(_B\)), 20.6 (CH\(_3\)).

2-Acetoxy-1-nitrobutane (10.0 g, 76 mmol) and anhydrous sodium carbonate (8.0 g, 76 mmol) were heated under reflux in benzene (60 ml) in an apparatus provided with a Dean-Stark water trap until no more acetic acid collected. After removal of sodium acetate and sodium carbonate by filtration, the benzene solution was concentrated and the residue kugelrohr distilled (30°C, 0.75 mmHg) to afford 1-nitrobut-1-ene 71 (4.4 g, 58%) (lit., b.p. 55°C, 12 mmHg; δ\(_\text{H}\) (80 MHz, CDCl\(_3\)) 7.31 (1H, dd, \(J_{\text{A,C}}\) 13.4 Hz, J\(_{\text{DB}}\) 1.6 Hz, H\(_\text{D}\)), 6.96 (1H, dd, \(J_{\text{CD,CD}}\) 13.4 Hz, J\(_{\text{CB}}\) 6.7 Hz, H\(_\text{C}\)), 2.30 (2H, ddd, J\(_{\text{BD}}\) 1.6 Hz, J\(_{\text{BC}}\) 6.7 Hz, J\(_{\text{BA}}\) 7.4 Hz, H\(_\text{B}\)), 1.12 (3H, t, J\(_{\text{AB}}\) 7.4 Hz, H\(_A\)); δ\(_\text{C}\) (50 MHz, CDCl\(_3\)) 143.6 (C\(_\text{D}\)), 138.5 (C\(_\text{C}\)), 21.3 (C\(_B\)), 11.2 (C\(_A\)).

\[
\text{CH}_3\text{CH}_2\text{CH}==\text{CHNO}_2
\]

A B C D

3.6.1 5-Phenyl-3-propenyl-2-isoxazoline (75)

1-Nitrobut-1-ene (0.41 g, 3.9 mmol) in benzene (15 ml) was added over 12 hours to a solution of phenyl isocyanate (1.09 g, 9.1 mmol), styrene (2.15 g, 21 mmol) and triethylamine (3 drops) in chloroform (20 ml), as described previously. The brown residue was subjected to dry flash chromatography (hexane, then 8% ether/hexane), affording 5-phenyl-3-propenyl-2-isoxazoline as a yellow oil (0.39 g, 53%). (Found: m/z 188.107 52. C\(_{12}\)H\(_{13}\)NO requires M, 188.107 52); δ\(_\text{H}\) (200 MHz, CDCl\(_3\)) 7.41-7.29 (5H, m, H), 6.20 (1H, dd, J\(_{\text{AC}}\) 11.7 Hz, J\(_{\text{AM}}\) 1.6 Hz, H\(_\text{A}\)), 5.97 (1H, dd, J\(_{\text{CA}}\) 11.7 Hz, J\(_{\text{CM}}\) 7.2 Hz, H\(_\text{C}\)), 5.60 (1H, dd, J\(_{\text{CD}}\) 8.3 Hz, J\(_{\text{CB}}\) 10.9 Hz, H\(_\text{B}\)), 3.63 (1H, dd, J\(_{\text{CB}}\) 16.6 Hz, J\(_{\text{CA}}\) 10.9 Hz, H\(_\text{A}\)), 3.16 (1H, dd, J\(_{\text{CD}}\) 16.6 Hz, J\(_{\text{CB}}\) 8.3 Hz, H\(_\text{B}\)), 1.92 (3H, dd, J\(_{\text{CM}}\) 1.6 Hz, J\(_{\text{MC}}\) 7.2 Hz, H\(_\text{M}\)); δ\(_\text{C}\) (50 MHz, CDCl\(_3\)) 155.5 (C\(_3\)), 133.5, 132.1, 128.6, 125.7, (PhCH, C\(_B\)), 127.9 (PhC), 119.3 (C\(_A\)), 82.1 (C\(_5\)), 45.3 (C\(_4\)), 15.4 (CH\(_3\)); m/z (FAB) 188 (M\(^{+}\)1).
3.6.2 5-Methoxycarbonyl-3-propenyl-2-isoxazoline (76)

1-Nitrobut-1-ene (0.5 g, 4.9 mmol) in benzene (20 ml) was added over 11 hours to a solution of phenyl isocyanate (1.57 g, 13.2 mmol), methyl acrylate (2.57 g, 29.8 mmol) and triethylamine (3 drops) in chloroform (20 ml), as described previously. Dry flash chromatography was used for purification (hexane, then 6% ether/hexane, then 8% ether/hexane) furnishing 5-methoxycarbonyl-3-propenyl-2-isoxazoline (0.26 g, 31%). (Found: m/z 169.1818. C$_8$H$_{11}$NO$_3$ requires M, 169.18177); $\delta$H ($360$ MHz, CDCl$_3$) 6.04 (1H, dd, $J_{\text{AC}}$12.7 Hz, $J_{\text{AMe}}$1.5 Hz, H$_A$), 5.96 (1H, dd, $J_{\text{CA}}$12.7 Hz, $J_{\text{CMe}}$6.7 Hz, H$_C$), 5.03 (1H, t, $J_{\text{54a}}$9.0 Hz, $J_{\text{54b}}$9.0 Hz, H$_5$), 3.40 (2H, d, $J_{\text{4a}}$9.0 Hz, $J_{\text{4b}}$9.0 Hz, H$_{4a}$, H$_{4b}$), 1.90 (3H, dd, $J_{\text{MeC}}$6.7 Hz, $J_{\text{MeA}}$1.5 Hz, H$_{\text{Me}}$), 3.78 (3H, s, H$_{\text{Me}}$); $\delta$C (50 MHz, CDCl$_3$) 170.7 (C=O), 155.1 (C$_3$), 134.8 (C$_A$), 117.5 (C$_B$), 77.6 (C$_S$), 52.6 (CH$_3$), 40.9 (C$_4$), 15.5 (CH$_3$); m/z (FAB) 169 (M$^+$).

3.7 Synthesis of 3-isopropenyl-2-isoxazolines

Preparation of 1-nitro-2-methylpropene

1-Nitro-2-methylpropan-2-ol was prepared according to the method of Sprang and Degering, as described for 1-nitropropan-2-ol. Aqueous sodium hydroxide (100 ml, 10 M) was added over 40 minutes to a cold mixture of freshly distilled acetone (74.0 ml, 1 mole) and nitromethane (53.8 ml, 1 mole). After an hour an off-white precipitate resulted which was then neutralised (acetic acid, 500 ml, 2M) and saturated with sodium chloride. The product was extracted into ether and dried (magnesium sulphate) and any unreacted acetone and nitromethane were removed by distillation. The desired alcohol, a colourless oil, was purified by distillation (b.p. 40-50°C, 0.75 mmHg) (58 g, 55%); $\delta$H (80 MHz, CDCl$_3$) 4.35 (2H, s, H$_C$), 3.10 (1H, s, OH), 1.27 (6H, s, H$_A$.H$_B$); $\delta$C (50 MHz, CDCl$_3$) 84.7 (C$_C$), 69.3 (C$_B'$), 26.2 (C$_A$, C$_B$). 2-Acetoxy-2-methyl-1-nitropropane was prepared from 1-nitro-2-methylpropan-2-ol (5 g, 31 mmol) by treatment at 60°C with acetic anhydride (6.37 g, 62 mmol) in the presence of concentrated sulphuric acid (10 drops), half of the acetic anhydride was added rapidly and then dropwise. After 4 hours, acetic acid and excess acetic anhydride were removed by distillation. The product distilled over as a colourless oil (60°C, 0.5 mmHg) (5.71 g, 83%); $\delta$H (80 MHz, CDCl$_3$) 4.74 (2H, s, H$_C$), 1.92 (3H, s, Me$'$), 1.45 (6H, s, H$_{\text{BA}}$); $\delta$C (50 MHz, CDCl$_3$) 176.6 (C=O), 170.2 (C-O), 81.6 (C$_C$), 24.2, 21.5 (C$_A$, C$_B$, CH$_3$).
The nitroalkyl acetate (3.0 g, 18 mmol) and anhydrous sodium carbonate (1.91 g, 11 mmol) was heated under reflux in benzene (30 ml) in an apparatus provided with a Dean-Stark water trap until no more acetic acid collected. After removal of sodium acetate and sodium carbonate by filtration, the crude mixture was distilled which afforded 1-nitro-2-methylpropene 68 as a pale green oil (b.p. 35-40 °C, 0.75 mmHg) (0.98 g, 53%); δ_H (80 MHz, CDCl_3) 6.85 (2H, t, J_CA1.3 Hz, H_C), 2.13 (3H, d, J_AC1.3 Hz, H_A), 1.83 (3H, d, J_MeC1.3 Hz, H_Me); δ_C (50 Mz, CDCl_3) 149.8 (C_B), 134.5 (C_C), 23.4, 19.2 (C_A, CH_3).

\[
\text{CH}_3
\]

CH_3C==CHNO_2

A  B  C

3.7.1 3-Isopropenyl-5-phenyl-2-isoxazoline (72)

1-Nitro-2-methylpropene (0.5 g, 4.9 mmol) in benzene (10 ml) was added dropwise over 13 hours to phenyl isocyanate (1.14 g, 11 mmol), styrene (2.71 g, 26 mmol) and triethylamine (3 drops) in benzene (20 ml). The work-up was as described in the general procedure. The orange/brown residue was subjected to dry flash chromatography (hexane, then 8% ether/hexane), affording 3-isopropenyl-5-phenyl-2-isoxazoline as an orange oil (0.50 g, 54%) (lit., 124-125 °C; δ_H (200 MHz, CDCl_3) 7.33-7.30 (5H, m, ArH), 5.63 (1H, dd, J_54a10.8 Hz, J_54b8.6 Hz, H_5), 5.31 (1H, t, J_BCB0.8 Hz, H_B), 5.17 (1H, t, J_CB0.8 Hz, H_C), 3.54 (1H, dd, J_4a4b16.4 Hz, J_4a510.8 Hz, H_4a), 3.06 (1H, dd, J_4b4a16.4 Hz, J_4b58.6 Hz, H_4b), 2.08 (3H, dd, J_MeC, J_Meb0.8 Hz, H_Me); δ_C (50 MHz, CDCl_3) 157.8 (C_3), 140.6 (C_A), 135.1 (PhC), 128.3, 127.8, 125.5 (PhCH), 119.3 (C_B), 82.5 (C_5), 42.1 (C_4), 18.7 (CH_3); m/z (FAB) 188 (M^+1).

3.7.2 3-Isopropenyl-5-vinyl-2-isoxazoline (73)

1-Nitro-2-methylpropene (0.38 g, 3.4 mmol) in benzene (10 ml) was added dropwise over 14 hours to phenyl isocyanate (0.94 g, 7.8 mmol), butadiene (0.93 g, 17 mmol) (condensed by cardice/acetone) and triethylamine (3 drops) in benzene (15 ml); as described in the general procedure. Dry flash chromatography furnished 3-isopropenyl-5-vinyl-2-isoxazoline as a yellow oil (0.091 g, 20%), (Found: m/z 137.084 07. C_8H_10NO requires M, 137.084 06); δ_H (200 MHz, CDCl_3) 5.88 (1H, dd, J_B'A'10.2 Hz, J_B'C'0.8 Hz, H_B'), 5.34 (1H, d, J_B'Me1.2 Hz, H_B), 5.30 (1H, d, J_CMe1.2 Hz, H_C), 5.18 (1H, ddm, J_54a10.6 Hz, J_54b8.5 Hz, H_5), 5.02 (1H, ddm, J_A'C'17.5 Hz, J_A'B'9.5 Hz, H_A'), 3.23 (1H, dd, J_4a4b16.3 Hz, J_4a510.6 Hz, H_4a), 2.86 (1H, dd,
$J_{4b4a}^{16.3}$ Hz, $J_{4b5}^{8.5}$ Hz, H$_{4b}$), 2.02 (3H, s, CH$_3$); 8C (50 MHz, CDCl$_3$) 158.3 (C$_3$), 135.9 (C$_A$), 135.5 (C$_A$), 119.3 (C$_B$), 117.6 (C$_B$), 82.3 (C$_3$), 39.7 (C$_4$), 18.8 (CH$_3$); 

$m/z$ (FAB) 137 (M$^+$).

3.7.3 3-Isopropenyl-5-(m-isopropenylphenyl)-5-methyl-2-isoxazoline (74)

1-Nitro-2-methylpropene (0.25 g, 2.47 mmol) in benzene (10 ml) was added dropwise over 12 hours to phenyl isocyanate (0.78 g, 6.6 mmol), 1,3-diisopropenylbenzene (2.37 g, 15 mmol) and triethylamine (3 drops) in benzene (15 ml), as described in the general procedure. The crude reaction mixture was subjected to dry flash chromatography, furnishing 3-isopropenyl-5-(m-isopropenylphenyl)-5-methyl-2-isoxazoline as an orange oil (0.24 g, 39%) (Found: $m/z$ 254.355 07. C$_{17}$H$_{20}$N$_0$ requires $M$, 254.355 05); $\delta$$_H$ (200 MHz, CDCl$_3$) 7.54-7.50 (1H, m, ArH), 7.35-7.24 (3H, m, ArH), 5.27, 5.36 (2H, dm, $J_{BC}^{0.8}$ Hz, $J_{B'Me}^{J_{C'Me}^{1.4}}$ Hz, H$_B$, H$_C$), 5.12, 5.09 (2H, dd, $J_{BC}^{0.9}$ Hz, $J_{B'Me}^{J_{C'Me}^{1.6}}$ Hz, H$_B$, H$_C$), 3.26 (2H, s, H$_{4a}$, H$_{4b}$), 2.15, (3H, d, $J_{Me'B}^{1.4}$ Hz, Me$'$), 2.05 (3H, t, $J_{Me'B}^{J_{Me'C}^{1.6}}$ Hz, H$_{Me}$), 1.73 (3H, s, Me$''$); 8C (50 MHz, CDCl$_3$) 158.1 (C$_3$), 145.5 (PhC), 129.4, 124.5, 121.1, 121.0 9 (PhCH), 121.6 (C$_B$), 112.8 (C$_B$), 88.3 (C$_5$), 47.9 (C$_4$), 28.4, 21.4, 18.7 (C$_A$, C$_A$', CH$_3$); $m/z$ (FAB) 254 (M$^{++}$).

3.8 Synthesis of 3-ethyl-2-isoxazolines

3.8.1 3-Ethyl-5-phenyl-2-isoxazoline (77)

1-Nitropropane (0.25 g, 2.8 mmol) in toluene (20 ml) was added dropwise over 13 hours to phenyl isocyanate (0.78 g, 6.6 mmol), styrene (1.78 g, 17 mmol) and triethylamine (3 drops) in toluene (20 ml); as described previously in the general procedure. Dry flash chromatography (hexane, then 8% ether/hexane) furnished 3-
ethyl-5-phenyl-2-isoxazoline as white crystalline solid (0.18 g, 36%), m.p. 52-53°C (Found: \(m/z\) 176.107 54. \(\text{C}_{11}\text{H}_{14}\text{NO}\) requires \(M, 176.107 53\)); \(\delta_H\) (200 MHz, CDCl\(_3\)) 7.38-7.27 (5H, m, ArH), 5.53 (1H, dd, \(J_{5A/4}8.2\) Hz, \(J_{5B/4}10.7\) Hz, \(H_5\)), 3.37 (1H, ddd, \(J_{4A/5}10.7\) Hz, \(J_{4A/4b}16.9\) Hz, \(J_{4A/4a}0.9\) Hz, \(H_{4A}\)), 2.88 (1H, ddd, \(J_{4B/5}8.2\) Hz, \(J_{4B/4a}16.9\) Hz, \(J_{4B/4b}0.9\) Hz, \(H_{4B}\)), 2.37 (2H, qd, \(J_{AB}7.5\) Hz, \(J_{A4a/4b}0.9\) Hz, \(H_A\)), 1.17 (3H, t, \(J_{BA}7.5\) Hz, \(H_B\)); \(\delta_C\) (50 MHz, CDCl\(_3\)) 159.3 (C\(_3\)), 128.7 (PhC), 128.4, 127.8, 125.5 (PhCH), 81.1 (C\(_5\)), 44.9 (C\(_4\)), 21.1 (C\(_B\)), 10.7 (C\(_A\)); \(m/z\) (FAB) 176 (\(M^+\)+1).

3.8.2 3-Ethyl-5-(\(p\)-methoxyphenyl)-2-isoxazoline (78)

1-Nitropropane (0.25 g, 2.8 mmol) in toluene (20 ml) was added dropwise over 16 hours to phenyl isocyanate (0.78 g, 6.6 mmol), \(p\)-methoxystyrene (2.28 g, 17 mmol) and triethylamine (3 drops) in toluene (20 ml); as described in the general procedure. Dry flash chromatography (hexane, then 9% ether/hexane) afforded 3-ethyl-5-(\(p\)-methoxyphenyl)-2-isoxazoline as a yellow oil (0.25, 43%), (Found: \(m/z\) 206.118 9. \(\text{C}_{12}\text{H}_{14}\text{NO}_2\) requires \(M, 206.118 10\)); \(\delta_H\) (200 MHz, CDCl\(_3\)) 7.07-7.69 (4H, m, ArH), 5.46 (1H, dd, \(J_{5A/4}10.6\) Hz, \(J_{5B/4}8.5\) Hz, \(H_5\)), 3.77 (3H, s, Me'), 3.30 (1H, ddd, \(J_{4A/5}10.6\) Hz, \(J_{4A/4b}16.9\) Hz, \(J_{4A/4a}0.04\) Hz, \(H_{4A}\)), 2.88 (1H, ddd, \(J_{4B/5}8.5\) Hz, \(J_{4B/4a}16.9\) Hz, \(J_{4B/4b}0.9\) Hz, \(H_{4B}\)), 2.37 (2H, q, \(J_{AB}7.5\) Hz, \(H_A\)), 1.17 (3H, t, \(J_{BA}7.5\) Hz, \(H_B\)); \(\delta_C\) (50 MHz, CDCl\(_3\)) 159.3 (C=O), 132.9 (PhC), 127.1, 113.9 (PhCH), 81.0 (C\(_5\)), 55.1 (CH\(_3\)C=O), 44.8 (C\(_4\)), 21.1 (C\(_B\)), 10.7 (Me'); \(m/z\) (FAB) 206 (\(M^+\)).

3.9 Synthesis of norbornadiene and norbornene adducts

3.9.1 exo-3a,7a,4,5,6,7-Hexahydro-4,7-methano-3-vinylbenzisoxazole (97)

1-Nitropropene (0.5 g, 5.7 mmol) in benzene (10 ml) was added dropwise over 14 hours to a solution of phenyl isocyanate (1.57 g, 13.2 mmol), norbornene (2.82 g, 30 mmol) and triethylamine (3 drops) in benzene (20 ml). The work up was as described in the general Mukaiyama procedure. Dry flash chromatography (hexane, then 5% ether/hexane) afforded exo-3a,7a,4,5,6,7-hexahydro-4,7-methano-3-vinylbenzisoxazole as a yellow oil (0.94 g, 21%); (Found: \(m/z\) 164.107 6. \(\text{C}_{10}\text{H}_{14}\text{NO}\) requires \(M, 164.107 0\)); \(\delta_H\) (200 MHz, CDCl\(_3\)) 6.47 (1H, ddd, \(J_{AB}10.9\) Hz, \(J_{AC}17.8\) Hz, \(J_{A3a/3A}0.7\) Hz, \(H_A\)), 5.45 (1H, dd, \(J_{CB}0.9\) Hz, \(J_{CA}17.8\) Hz, \(H_C\)), 5.42 (1H, dd, \(J_{BC}0.9\) Hz, \(J_{BA}10.9\) Hz, \(H_B\)), 4.43 (1H, d, \(J_{7a/3a}8.3\) Hz, \(H_{7a}\)), 3.13 (1H, dd, \(J_{3a/7a}8.3\) Hz, \(J_{3a/4}1.6\) Hz, \(H_{3a}\)), 2.45 (2H, s, \(H_4, H_7\)), 1.51 (6H, m, \(H_5, H_6, H_8\)); \(\delta_C\) (50 MHz,
3.9.2 4,7-Methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazoles (83 & 102)

1-Nitropropene in benzene (15 ml) was added dropwise over 18 hours to phenyl isocyanate (1.57 g, 13.2 mmol), norbornadiene (2.76 g, 30 mmol) and triethylamine (3 drops) in benzene, as described in the general Mukaiyama procedure. The residue was subjected to dry flash chromatography (hexane, then 5% ether/hexane) and yielded in order of elution:

(a) exo-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole 83 as a pale yellow oil (0.93 g, 35%), (Found: m/z 162.091 89. C_{10}H_{12}NO requires M, 162.091 88); \(\delta_H\) (360 MHz, CDCl_{3}) 6.54 (1H, ddd, \(J_{AB}10.9\) Hz, \(J_{AC}17.9\) Hz, \(J_{AA}0.6\) Hz, \(H_A\)), 6.29 (1H, dd, \(J_{66.55.7}\) Hz, \(J_{673.0}\) Hz, \(H_6\)), 6.04 (1H, ddd, \(J_{565.8}\) Hz, \(J_{543.2}\) Hz, \(J_{570.5}\) Hz, \(H_5\)), 5.58 (1H, dd, \(J_{CB}0.9\) Hz, \(J_{CA}17.9\) Hz, \(H_C\)), 5.53 (1H, dd, \(J_{BC}0.9\) Hz, \(J_{BA}10.9\) Hz, \(H_B\)), 4.82 (1H, d, \(J_{7a3a8.0}\) Hz, \(H_{7a}\)), 3.45 (1H, dd, \(J_{3a7a8.0}\) Hz, \(J_{3a41.5}\) Hz, \(H_{3a}\)), 3.30, 3.06 (2H, bd, \(J_{43a1.5}\) Hz, \(J_{760.8}\) Hz, \(H_4, H_7\)), 1.55 (2H, s, \(H_8\)); \(\delta_C\) (50 MHz, CDCl_{3}) 156.8 (C_{3}), 139.9 (C_{A}), 134.9, 126.3 (C_{5}, C_{6}), 121.1 (C_{B}), 89.3 (C_{7a}), 55.8 (C_{3a}), 49.7 (C_{7}), 44.6 (C_{4}), 42.9 (C_{8}); m/z (FAB) 162 (M^{+}+1).
(b) endo-4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole 102 as a yellow oil (0.09 g, 11%). (Found: m/z 162.091 89. C_{10}H_{12}NO requires M, 162.091 88); δ H (200 MHz, CDCl₃) 6.49 (1H, dd, J_{AB}10.8 Hz, J_{AC}17.8 Hz, H_A), 6.11 (1H, dd, J_{6,5}5.7 Hz, J_{6,7}2.9 Hz, H_6), 5.99 (1H, J_{5,6}5.7 Hz, J_{5,4}2.9 Hz, H_5), 5.59 (1H, d, J_{CA}17.8 Hz, H_C), 5.49 (1H, J_{BA}10.8 Hz, H_B), 5.29 (1H, dd, J_{7,a}9.5 Hz, J_{7,a}7.4 Hz, H_{7,a}), 3.87 (1H, dd, J_{3,a7,a}9.5 Hz, J_{3,a}4.2 Hz, H_{3,a}), 3.06 (2H, bs, H_4, H_7), 1.58 (2H, s, H_8); δ C (50 MHz, CDCl₃) 157.8 (C_3), 140.8 (C_A), 120.8 (C_B), 129.0, 133.7 (C_5, C_6), 87.4 (C_7,a), 55.4 (C_3,a), 48.7 (C_8), 47.5 (C_7), 46.2 (C_4); m/z (FAB) 162 (M^+1).

3.9.3 exo-4,7-Methano-3a,4,7,7a-tetrahydro-3-propenylbenzisoxazole (104)

1-Nitrobut-1-ene (0.52 g, 4.9 mmol) in benzene (15 ml) was added over 16 hours to phenyl isocyanate (1.57 g, 13.2 mmol), norbornadiene (2.76 g, 30 mmol) and triethylamine (3 drops) in benzene (20 ml). The work up was as described in the general Mukaiyama procedure. Dry flash chromatography (hexane, then 6% ether/hexane) afforded 4,7-methano-3a,4,7,7a-tetrahydro-3-propenylbenzisoxazole as a pale yellow oil (0.49 g, 51%). (Found: m/z 176.107 54. C_{11}H_{14}NO requires M, 176.107 53); δ H (200 MHz, CDCl₃) 6.23 (1H, dcl, J_{1,6}16.5 Hz, J_{6,7}3.0 Hz, H_6), 6.13 (1H, dd, J_{CA}11.5 Hz, J_{CMe}5.6 Hz, H_C), 6.02 (1H, dd, J_{AC}11.5 Hz, J_{AMe}1.3 Hz, H_A), 5.99 (1H, ddd, J_{5,6}5.8 Hz, J_{5,7,5.7} Hz, J_{5,4}3.2 Hz, H_5), 4.77 (1H, d, J_{7,a}8.1 Hz, H_{7,a}), 3.46 (1H, d, J_{3,a7,a}8.1 Hz, H_{3,a}), 3.16 (1H, t, J_{7,7,a}0.8 Hz, J_{7,7,a}3.0 Hz, H_7), 2.96 (1H, dm, J_{4,3,a}1.5 Hz, H_4), 1.93 (3H, dd, J_{MeA}1.3 Hz, J_{MeC}5.6 Hz, H_{Me}), 1.00 (2H, s, H_8); δ C (50 MHz, CDCl₃) 155.2 (C_3), 139.7 (C_A), 135.3, 133.6 (C_5, C_6), 117.4 (C_B), 88.1 (C_7,a), 59.6 (C_3,a), 49.6 (C_7), 44.9 (C_4), 42.7 (C_8), 15.9 (CH_3); m/z (FAB) 176 (M^+1).

3.9.4 4,7-Methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazoles (80 & 81)

A solution of triethylamine (0.72 g, 7.3 mmol) in ether (10 ml) was added over 15 hours to norbornadiene (1.75 g, 19 mmol) and benzoxydiximoyl chloride (0.68 g, 4.3 mmol) in ether (20 ml) at 0°C for an hour, then at room temperature. After filtering through celite, the residue was purified by dry flash chromatography (hexane, then 10% ether/hexane) affording in order of elution:
(a) exo-4,7-methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole 80 a white crystalline product (0.50 g, 54%), m.p. 62-63°C (from 40-60 petroleum ether), (lit., 181 63.5-64.5°C), δH (200 MHz, CDCl3) 7.77-7.72 (2H, m, ArH), 7.73-7.40 (3H, m, ArH), 6.34 (1H, dd, J6,55.8 Hz, J6,7 3.0 Hz, H6), 6.08 (1H, dd, J5,65.8 Hz, J5,4 3.3 Hz, H5), 4.97 (1H, dd, J7a1.3 Hz, J7a3a 8.2 Hz, H7a), 3.76 (1H, dd, J3a7a 8.2 Hz, J3a40.6 Hz, H3a), 3.26 (1H, d, J77a 1.3 Hz, H7), 3.14 (1H, d, J4,3a 0.6 Hz, H4), 1.64 (2H, s, H8); δC (50MHz, CDCl3) 155.5 (C3), 139.8, 135.2, 129.6, 128.5 (PhCH), 128.9 (PhC), 126.3, 128.5 (C5,C6), 89.2 (C7a), 57.4 (C3a), 49.7 (C7), 44.9 (C4), 42.9 (C8); m/z (FAB) 211 (M+).

(b) endo-4,7-methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole 81 a white crystalline solid, (0.15 g, 16%), m.p. 61-63°C (lit., 181 62-64°C), δH (200 MHz, CDCl3) 7.72-7.65 (2H, m, ArH), 7.41-7.34 (3H, m, ArH), 6.16 (1H, dd, J6,55.8 Hz, J6,7 3.4 Hz, H6), 5.92 (1H, dd, J5,6 5.8 Hz, J5,4 3.0 Hz, H5), 5.41 (1H, dd, J7a74.2 Hz, J7a3a 9.5 Hz, H7a), 4.13 (1H, dd, J3a7a 9.5 Hz, J3a44.0 Hz, H3a), 3.36 (2H, bs, H3a, H5), 1.56 (2H, s, H8); δC (50 MHz, CDCl3) 156.4 (C3), 134.9, 133.9, 129.6 (PhCH), 129.2 (PhC), 128.5 (C6), 126.4 (C5), 87.3 (C7a), 57.0 (C3a), 48.7* (C8), 47.7 (C7), 46.7 (C4); m/z (FAB) 211 (M+).

(c) A fraction containing a mixture of 2:1 adducts, which were examined by 1H NMR (identification was confirmed by decoupling experiments and COSY NMR), (25 mg, 1.2%); m/z (FAB) 331 (M+1). The salient peaks observed for each 2:1 adduct are indicated; δH (360 MHz, CDCl3), (i) exo, endo, anti : 5.17 (1H, dd, H5), 5.06 (1H, d, H7a), 4.09 (1H, dd, H6), 3.49 (1H, d, H3a), 3.08 (1H, d, H7), 2.97 (1H, d, H4). (ii) exo, exo, syn ; 4.77 (2H, d, H7a, H6), 3.83 (2H, d, H3a, H5), 3.09 (1H, d, H7), 1.58 (2H, s, H8), (iii) exo, endo, syn : 5.17 (1H, dd, H5), 4.47 (1H, d, H7a), 4.07 (2H, dd, H6, H3a). By measuring the appropriate integrals the three compounds identified were found to be present in the approximate ratio of 9:9:8. A trace of a fourth adduct was also obtained but unable to be identified; the exo, exo, anti adduct was not observed.
3.10 Synthesis of 3-phenylisoxazole and 3-vinylisoxazole

3.10.1 3-Phenylisoxazole (82)

3-Phenylisoxazole was synthesised from 4,7-methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole. Two methods were used;

(a) Thermolysis in solution

Compound 80 (51 mg, 0.26 mmol) was heated under reflux in xylene (15 ml) at 135°C for 16 hours. The solvent was evaporated in vacuo (0.01 mmHg, 60°C) and the residue was examined by 1H NMR spectroscopy and TLC. Starting material was recovered and there was no evidence of any conversion to 3-phenylisoxazole. The experiment was repeated using a higher boiling point solvent, mesitylene. Adduct 80 (58 mg, 0.27 mmol) was refluxed in mesitylene (15 ml) (163°C) for 17 hours, and after the solvent was removed, 1H NMR spectroscopy revealed that the characteristic isoxazole peaks at 8.45 and 6.66 p.p.m. were present, TLC confirmed no starting material remained. Dry flash chromatography (hexane, then 8% ether/hexane) furnished 3-phenylisoxazole as a colourless oil (30 mg, 75%), (lit.,174 b.p. 103-105°C, 6 mmHg); δH (200 MHz, CDCl3) 8.45 (1H, d, J5,4 1.6 Hz, H5), 7.84-7.78 (2H, m, ArH), 7.49-7.42 (3H, m, ArH), 6.66 (1H, d, J4,5 1.6 Hz, H4); δC (50 MHz, CDCl3) 161.4 (C3), 158.8 (C5), 129.9, 128.8, (PhCH), 126.8 (PhC), 102.3, (C4); m/z (FAB) 146 (M+).

(b) Flash vacuum pyrolysis (FVP)

Instrumentation details are in Section 3.1.2.6. 4,7-Methano-3a,4,7,7a-tetrahydro-3-phenylbenzisoxazole (16.0 mg, 0.08 mmol) was placed in the inlet tube. The pyrolysis parameters were as follows; furnace temperature 400°C, inlet temperature 145°C, pressure 0.003 mm Hg and sublimation time 15 minutes. The product was a colourless oil (10.8 mg, 99%). See previous section for NMR data.

3.10.2 3-Vinylisoxazole (79)

3-Vinylisoxazole was synthesised from 4,7-methano-3a,4,7,7a-tetrahydro-3-vinylbenzisoxazole 83 by two methods:

(a) Thermolysis in solution

Compound 83 (21.7 mg, 0.13 mmol) was refluxed in xylene (135°C) for 17 hours. The solvent was removed in vacuo and the residue subjected to 1H NMR
spectroscopy and TLC. The analysis showed the residue contained almost entirely starting material. The adduct 83 (19.9 mg, 0.12 mmol) was then refluxed in mesitylene (163°C) for 19 hours. TLC indicated a vast number of components and \(^1\)H NMR spectroscopy did not show any characteristic isoxazole peaks at ca 8.32 and 6.47 p.p.m.

(b) Flash vacuum pyrolysis (Section 3.1.2.6)

Compound 83 (18 mg, 0.12 mmol) was placed in the inlet tube. The pyrolysis parameters were as follows; furnace temperature 475°C, inlet temperature 145°C, pressure, 0.001 mm Hg and sublimation time 15 minutes. 3-Vinylisoxazole collected as a pale yellow oil (11.5 mg, 99%), (Found: \(m/z\) 96.044 93. \(C_5H_6NO\) requires \(M\), 96.044 94); \(\delta_H\) (200 MHz, CDCl\(_3\)) 8.32 (1H, dd, \(J_{5,A}1.7\) Hz, \(J_{5,4}0.8\) Hz, \(H_5\)), 6.82 (1H, dd, \(J_{CA}17.8\) Hz, \(J_{AB}10.9\) Hz, \(H_A\)), 6.47 (1H, d, \(J_{4,5}1.7\) Hz, \(H_4\)), 5.90 (1H, dd, \(J_{CA}17.8\) Hz, \(J_{CB}0.9\) Hz, \(H_C\)), 5.61 (1H, dd, \(J_{BC}0.9\) Hz, \(J_{BA}10.9\) Hz, \(H_B\)); \(\delta_C\) (50 MHz, CDCl\(_3\)) 160.7 (C\(_3\)), 158.2 (C\(_5\)), 124.9 (C\(_A\)), 121.5 (C\(_B\)), 101.1 (C\(_4\)); \(m/z\) (FAB) 96 (\(M^+1\)).
Graph I: Styrene and 5-phenyl-3-vinylisoxazole copolymer

Graph II: Methyl methacrylate and 5-phenyl-3-vinylisoxazole copolymer
3.11 Free radical polymerisation of styrene, methyl methacrylate and vinyl acetate

General procedure

The polymers were prepared from 30% solutions (by weight) of monomers in refluxing methyl ethyl ketone (MEK) (~80°C) with α,α'-azobisisobutyronitrile (ABIBN) as initiator. 2% ABIBN on monomer was used; 1.3% was added initially and the remaining 0.7% after 2-3 hours. Multiple additions were used to keep the radical concentration approximately constant. The reactions were terminated after approximately 9 hours, by which time polymerisation was assumed to be essentially complete.

The polymers and copolymers were purified by precipitating directly into a suitable non-solvent (hexane or methanol). The solvent/non-solvent mixture was decanted and the polymer redissolved in chloroform and reprecipitated. This procedure was repeated and the product was then filtered and dried in a vacuum oven (50°C, 12 mmHg) for 2 hours. The ratio of isoxazole or isoxazoline to styrene (or methyl methacrylate or vinyl acetate) was estimated from the elemental analysis for the nitrogen content. The composition of the copolymer was determined by calculating the percentage of nitrogen for various monomer combinations (x,y), thus creating a calibration curve (illustrated in Graphs I and II). The polymers were further characterised by $^{13}$C NMR spectroscopy (and by $^1$H NMR where appropriate).

3.11.1 Polystyrene (105)

The polymerisation was carried out as described above using styrene (5.0 g, 48 mmol) in MEK (12 ml) with ABIBN (106 mg) as initiator. The polymer was precipitated into methanol (3 x 300 ml) yielding 3.2 g (63%) of polystyrene. The time taken for polymerisation was established by monitoring the reaction by withdrawing 1 ml samples, precipitating, filtering, drying and then weighing, thus establishing the percentage conversion to polymer that had occurred. The IR spectrum was identical to the authentic sample; $\nu_{\text{max}}$ 3100, 2921, 2848, 1600, 1451 cm$^{-1}$. Softening point 150-157°C; [Found: C, 92.3; H, 7.7; N, 0.2%. (C₈H₈)n requires C, 92.3; H, 7.7; N, 0.0%]; $\delta_H$ (80 MHz, CDCl₃) 7.2-5.8 (5H, m, ArH), 2.2-0.6 (3H, m, -CH-CH₂-); $\delta_C$ (50 MHz, CDCl₃) 145.9-145.2 (PhC), 127.8, 125.5 (PhCH), 48.5-40.0 (-CH-CH₂-).
3.11.2 Poly(methyl methacrylate) (106)

The polymerisation was carried out as before using methyl methacrylate (MMA) (5.08 g, 51 mmol) in MEK (12 ml) with ABIBN (50.1 mg). The polymer was precipitated into hexane (3 x 300 ml) giving 4.18 g (82%) of poly(methyl methacrylate). The IR spectrum was identical to an authentic sample of poly(methyl methacrylate) \( \nu_{\text{max}} \) 1728 cm\(^{-1}\) (C=O), Softening point 165-175°C; [Found: C, 59.7; H, 8.3; N, 0.2%. (C\(_5\)H\(_8\)O\(_2\))\(_n\) requires C, 60.0; H, 8.0; N, 0.0%]; \( \delta_H \) (80 MHz, CDCl\(_3\)) 3.58-3.50 (3H, bs, CO\(_2\)CH\(_3\)), 2.1-1.5 (3H, bs, CH\(_3\)), 1.3-0.5 (2H, m, CH\(_2\)); \( \delta_C \) (50 MHz, CDCl\(_3\)) 178.2, 177.9, 177.6, 176.9 (C=O), 54.2, 52.5 (CH\(_2\)-CCH\(_3\)), 51.6 (CO\(_2\)CH\(_3\)), 44.3 (CH\(_2\)-CCH\(_3\)), 18.5 (CH\(_3\)).

3.11.3 Poly(vinyl acetate) (107)

The polymerisation was carried out as described in Section 3.11; vinyl acetate (3.01 g, 35 mmol) was refluxed in MEK (7 ml) with ABIBN (0.603 g). The polymer was precipitated into hexane (3 x 100 ml) giving 2.74 g (91%) of poly(vinyl acetate) as a white solid/foam. \( \nu_{\text{max}} \) 1733 cm\(^{-1}\) (C=O); [Found: C, 62.0; H, 8.1; N, 0.1%. (C\(_5\)H\(_8\)O\(_2\))\(_n\) requires C, 60.0; H, 8.0; N, 0.0%]; \( \delta_H \) (80 MHz, CDCl\(_3\)) 4.8-4.7 (1H, bs, CH\(_2\)-CH), 2.1-1.7 (3H, bs, CH\(_3\)), 1.8-1.7 (2H, bs, CH\(_2\)); \( \delta_C \) (50 MHz, CDCl\(_3\)) 169.4 (C=O), 66.8, 67.8 (CH), 40.2 (CH\(_2\)), 21.5 (CH\(_3\)).

3.12 Free radical polymerisation of vinyl-isoxazoles and isoxazolines and the preparation of their copolymers

3.12.1 Copolymerisation of styrene and 5-phenyl-3-vinylisoxazole (108)

The polymerisation was carried out as described in Section 3.11 using styrene (262 mg, 2.5 mmol) and 5-phenyl-3-vinylisoxazole (215 mg, 1.3 mmol) with ABIBN (5.0 mg) in MEK. The polymer precipitated into methanol (2 x 80 ml) as a fine white solid (182 mg, 38%). Softening point 157-162°C; \( \nu_{\text{max}} \) (film) 1616, 1573, 1465, 1026, 1217, 1260 cm\(^{-1}\) (isoxazole rings)\(^{191}\); [Found: C, 83.2; H, 7.7; N, 2.8%]; \( \delta_C \) (50 MHz, CDCl\(_3\)) 168.9 (C\(_5\)), 167.4-166.7 (C\(_3\)), 145.2 (PhC, styrene-derived), 140.4, 137.9, 129.6, 128.7 (PhC), 127.6, 126.8, 125.7 (PhCH, styrene-derived), 97.8 (C\(_4\)), 43.8, 43.0, 42.7, 41.8 (-CH-CH\(_2\)).
3.12.2 Copolymerisation of methyl methacrylate and 5-phenyl-3-vinylisoxazole (109)

The polymerisation was carried out as described previously using MMA (2.95 g, 29.5 mmol) and 5-phenyl-3-vinylisoxazole (0.70 g, 5.9 mmol) with ABIBN (76 mg). The polymer was precipitated into methanol (3 x 15 ml) yielding 1.59 g (43%) of copolymer. Softening point 128-132°C; $\nu_{\text{max}}$ (film) 1727 (C=O), 1616, 1573, 1451, 1192, 1148 cm$^{-1}$ (isoxazole ring); [Found: C, 69.0; H, 6.4; N, 3.9%]; $\delta_{C}$ (50 MHz, CDCl$_3$) 177.8, 177.3, 176.9 (C=O), 169.3, 168.9, 168.6 (C$_5$), 167.6, 167.3 (C$_3$), 129.2, 128.5, 125.4, 124.8 (PhCH), 127.0 (PhC), 98.4 (C$_4$), 54.1 (CH$_2$-CCH$_3$), 51.5 (CO$_2$CH$_3$), 44.5, 31.4 (CH$_2$-CCH$_3$, CH$_2$-CH), 18.0 (CH$_3$).

3.12.3 Copolymerisation of vinyl acetate and 5-phenyl-3-vinylisoxazole (110)

The free radical polymerisation was carried out as described before using 5-phenyl-3-vinylisoxazole (215 mg, 1.26 mmol) and vinyl acetate (215 mg, 2.5 mmol) with ABIBN (5.1 mg). The polymer was precipitated into hexane (80 ml x 2) yielding 353 mg (82%) of polymer. Softening point 137-142°C; $\nu_{\text{max}}$ (film) 1733 (C=O) 1451, 1573, 1614 cm$^{-1}$ (isoxazole ring); [Found: C, 73.7; H, 5.5; N, 7.5%]; $\delta_{C}$ (50 MHz, CDCl$_3$) 169.4 (C=O), 165.9 (C$_3$), 129.5, 128.5, 125.6 (PhCH), 127.2 (PhC), 98.1 (C$_5$), 69.8 (CH), 39.8, 39.9 (CH$_2$, C$_4$), 32.7, 31.4 (CH$_2$-CH), 21.5 (CH$_3$C=O).

3.12.4 Homopolymerisation of 5-phenyl-3-vinylisoxazole (111)

The polymerisation was carried out under free radical conditions as before using 5-phenyl-3-vinylisoxazole (0.32 g, 1.92 mmol) with ABIBN (7.0 mg). The polymer was precipitated into methanol (3 x 20 ml) yielding 0.17 g (53%) of polymer. Softening point 155-163°C; $\nu_{\text{max}}$ (film) 1440, 1590 and 1600 cm$^{-1}$ (isoxazole ring); [Found: C, 76.3; H, 5.3, N, 7.8%. (C$_{11}$H$_{11}$NO)$_n$ requires C, 77.2; H, 5.1; N, 7.9%]; $\delta_{C}$ (50 MHz, CDCl$_3$) 169.5 (C$_5$), 165.9 (C$_3$), 127.2 (PhC), 129.5, 129.2, 125.6 (PhCH), 98.1 (C$_4$), 32.7 (CH$_2$-CH).

3.12.5 Attempted homopolymerisation of 3-phenyl-5-vinyl-2-isoxazoline

The free radical polymerisation conditions were as described previously; 3-phenyl-5-vinyl-2-isoxazoline (0.32 g, 1.85 mmol) with ABIBN (7 mg) in MEK. The addition of both methanol (100 ml) and hexane (100 ml) did not result in a precipitate; however a faint cloudiness was observed with methanol. TLC and $^1$H
NMR spectroscopy confirmed the presence of unreacted isoxazoline in the mother liquor; the spectrum featured the characteristic patterns attributed to the vinyl and ring protons (see Section 3.5.4). Recrystallisation (cyclohexane) afforded pure isoxazoline (0.28g, 88%) (m.p. and mixed m.p. 45-47°C).

3.12.6 Attempted copolymerisation of 3-phenyl-5-vinyl-2-isoxazoline and vinyl acetate

The free radical polymerisation was carried out as described in Section 3.11 using 3-phenyl-5-vinylisoxazoline (216 mg, 2.6 mmol) and vinyl acetate (215 mg, 2.5 mmol) with ABIBN (51 mg). After the addition of methanol (75 ml) a white precipitate formed (150 mg, 70%). The IR spectrum of this solid was identical to the authentic poly(vinyl acetate) and the $^{13}$C NMR confirmed the absence of any isoxazoline units in the polymeric product; there were no peaks at 156.1 (C$_3$), 81.7 (C$_5$) and 40.3 (C$_4$) associated with the heterocyclic ring. The mother liquor was evaporated and the resulting white solid was subjected to TLC and $^1$H NMR spectroscopy; the spectrum was identical to that of the authentic sample of 3-phenyl-5-vinylisoxazoline. After purification by recrystallisation (cyclohexane) 200 mg of 3-phenyl-5-vinylisoxazoline was recovered (m.p. and mixed m.p. 45-47°C).

3.12.7 Attempted copolymerisation of 5-phenyl-3-vinyl-2-isoxazoline and methyl methacrylate

5-Phenyl-3-vinylisoxazoline (0.70 g, 4.1 mmol) and methyl methacrylate (2.95 g, 20 mmol) were heated under reflux with ABIBN (76 mg) in MEK. Methanol was added (3 x 200 ml) and a white precipitate resulted; the $^{13}$C NMR spectrum indicated that only methyl methacrylate had polymerised as no characteristic isoxazoline peaks were observed. Elemental analysis confirmed the result; [Found: C, 59.9; H, 8.2; N, 0.1%. (C$_5$H$_8$O$_2$)$_n$ requires C, 60.0; H, 8.0; N, 0.0%]. The isoxazoline was recovered from the mother liquor and was purified by Kugelrohr distillation (0.57 g, 81%).

3.12.8 Attempted copolymerisation of 3-phenyl-5-vinylisoxazole and styrene

The free radical polymerisation was conducted as described before; 3-phenyl-5-vinylisoxazole (41.0 mg, 0.24 mmol) and styrene (49.0 mg, 0.48 mmol) with ABIBN (3 mg) were refluxed in MEK for 10 hours. Methanol (100 ml) was added and a thick white precipitate was seen immediately. After drying, the solid was subjected to $^{13}$C NMR spectroscopy and elemental analysis; the results showed
the product was entirely polystyrene; [Found: C, 92.3; H, 7.7; N, 0.1%. (C₈H₈)ₙ requires C, 92.3; H, 7.7; N, 0.0%]; δC (50 MHz, CDCl₃) 145.8-145.0 (PhC), 127.8, 125.4, 124.9 (PhCH), 48.5-40.4 (CH-CH₂). The unreacted isoxazole was recovered from the mother liquor and purified by recrystallization (30 mg, 73%).

3.12.9 Copolymerisation of styrene and 3-phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline (112)

3-Phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline (155 mg, 0.57 mmol) and styrene (178 mg, 1.78 mmol) were copolymerised under free radical conditions using ABIBN (11.4 mg) in MEK. After refluxing for 12 hours, methanol (100 ml) was dripped slowly into the reaction mixture. A white precipitate formed which was purified by reprecipitation to furnish the copolymer (190 mg, 57%). Softening point 122-130°C; νmax (film) 1600 (C=N), 1447, 1029, 988 cm⁻¹; [Found: C, 83.2; H, 7.8; N, 2.8%]; δC (50 MHz, CDCl₃) 156.1 (C₃), 145.2 (PhC, styrene-derived), 140.4, 137.9 (2 PhC), 129.6, 128.7 (PhC'), 127.6, 127.3, 125.7 (PhCH, styrene-derived), 82.6 (C₅), 45.0, 43.0 (CH-CH₂), 41.8 (C₄).

3.12.10 Copolymerisation of methyl methacrylate and 3-phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline (113)

3-Phenyl-5-(m- and p-vinylphenyl)-2-isoxazoline (155 mg, 0.57 mmol) and methyl methacrylate (170 mg, 1.7 mmol) were heated under reflux in MEK with ABIBN (11.4 mg). After 10 hours, methanol (25 ml) was added and a white precipitate resulted (168 mg, 52%). Softening point 128-132°C; νmax (film) 1728 cm⁻¹ (C=O), 1597 (C=N), 1447, 903 cm⁻¹; [Found: C, 69.0; H, 7.4; N, 2.9%]; δC (50 MHz, CDCl₃) 177.8, 177.5, 176.9 (C₃, MMA-derived), 156.0 (C₃), 129.2, 128.5 (PhC), 82.2 (C₅), 54.2 (CH₂CCH₃), 51.4 (CO₂CH₃), MMA derived), 44.5 (CH₂CCH₃, MMA-derived), 18.0 (CH₃).

3.13 Cationic polymerisation

General procedure

The solvent, toluene, was purified by washing successively with conc. sulphuric acid, water and aqueous 10% sodium carbonate; it was then dried over calcium chloride and distilled over metallic sodium. Freshly distilled monomer and toluene were introduced into a sealed reaction vessel and brought to the polymerisation temperature (-78°C). The catalyst, distilled BF₃·O(C₂H₅)₂, was introduced with a syringe. After ca 90 minutes the polymer was isolated from the reaction mixture by reducing to half the volume and then addition of the appropriate
precipitating solvent (methanol or hexane). The product was washed and dried in vacuo at 40°C (15 mm Hg).

3.13.1 Poly-α-methylstyrene (114)

Distilled BF₃·O(C₂H₅)₂ (0.09 ml) in toluene (0.5 ml) was added to a solution of α-methylstyrene (5 ml) in toluene (50 ml) at -78°C. After 95 minutes methanol was added (120 ml) and a colourless gel formed, which was washed and dried (1.73 g, 42%); \( \nu_{\text{max}} \) (film) 1495 cm\(^{-1} \); \( \delta_H \) (80 MHz, CDCl₃) 7.37-7.02 (PhCH), 1.70-1.53 (CH₂), 0.1-0.3 (CH₃); \( \delta_C \) (50 MHz, CDCl₃) 149.7 (PhC), 128.9, 128.1, 127.3, 126.7, 125.4, 124.8 (PhCH), 60.8 (CH₂), 43.1 (CH₂CCH₃), 23.7 (CH₃).

3.13.2 Attempted copolymerisation of α-methylstyrene and 5-(m-isopropenyl)-5-methyl-3-phenyl-2-isoxazoline

BF₃·O(C₂H₅)₂ (0.09 ml) in toluene (0.5 ml) was added to a solution of the isoxazoline (0.5 g, 1.3 mmol) and α-methylstyrene (1.0 g, 8.39 mmol) in toluene (20 ml). After 90 minutes methanol (100 ml) was added and a yellow gel (501 mg) resulted. \( ^{13} \text{C} \) NMR spectroscopy showed that only poly-α-methylstyrene was present. The mother liquor was analysed by \( ^1 \text{H} \) NMR spectroscopy and TLC which showed that the isoxazoline had degraded.

3.13.3 Attempted homopolymerisation of 5-(m-isopropenyl)-5-methyl-3-phenyl-2-isoxazoline

The cationic polymerisation was carried out as described in the general procedure. BF₃·O(C₂H₅)₂ (0.09 ml) in toluene (0.5 ml) was added to a solution of the isoxazoline (500 mg, 1.3 mmol) in toluene (10 ml). After 90 minutes cold methanol (150 ml) was added but the precipitate formed was extremely fine and could not be isolated. The TLC and \( ^1 \text{H} \) NMR spectrum of the mixture indicated the presence, not only of unreacted isoxazoline, but also several other components due to partial degradation.

3.13.4 Attempted polymerisation of styrene

The polymerisation conditions were as described previously for α-methylstyrene. Distilled BF₃·O(C₂H₅)₂ (0.09 ml) in toluene (0.5 ml) was added to a solution of styrene (5 ml) in toluene (50 ml) at -78°C. After 95 minutes methanol was added (120 ml) but no precipitate was observed. Hexane (120 ml) was added but
again no precipitate resulted. $^1$H NMR spectroscopy indicated the presence of unreacted styrene.

3.13.5 Attempted copolymerisation of styrene and $\alpha$-methylstyrene

Distilled BF$_3.0$(C$_2$H$_5$)$_2$ (0.09 ml) in toluene (0.5 ml) was added to a solution of styrene (2.5 ml) and $\alpha$-methylstyrene (2.5 ml) in toluene (50 ml) at -78°C. After 95 minutes methanol was added (120 ml) and a white precipitate formed, The IR spectrum of the product was superimposable on that of the authentic sample of poly-$\alpha$-methylstyrene. Unreacted styrene was recovered from the mother liquor.

3.13.6 Attempted copolymerisation of 3-phenyl-5-vinyl-2-isoxazoline and $\alpha$-methylstyrene

The cationic polymerisation was carried out as before; BF$_3.0$(C$_2$H$_5$)$_2$ (0.2 ml) in toluene (10 ml) was added to a solution of the isoxazoline (1.04 g, 6.0 mmol) and $\alpha$-methylstyrene (2.01 g, 17.0 mmol) in toluene (20 ml). Methanol (175 ml) was added after 110 minutes and a white precipitate formed which was subjected to elemental analysis and $^{13}$C NMR. The results indicated the polymer was composed of entirely $\alpha$-methylstyrene; the isoxazoline remained intact in the mother liquor. The heterocycle was recovered (800 mg, 77%) and recrystallised (cyclohexane) m.p. and mixed m.p. 45-47°C.

3.13.7 Attempted copolymerisation of 5-phenyl-3-vinyl-2-isoxazoline and $\alpha$-methylstyrene

BF$_3.0$(C$_2$H$_5$)$_2$ (0.09 ml) in toluene (2 ml) was added to a solution of the isoxazoline (300 g, 17.0 mmol) and $\alpha$-methylstyrene (350 mg, 2.9 mmol) in toluene (15 ml) at -78°C, as described in the general cationic polymerisation procedure. Only $\alpha$-methylstyrene polymerised successfully as indicated by the IR and $^{13}$C spectra of the product. The isoxazoline (258 mg) was recovered from the mother liquor; the $^1$H NMR spectrum was identical to that of the authentic sample.
3.14 Gel permeation chromatography

Gel permeation chromatography (GPC) measurements were conducted by Dr Peter James (Environmental and Chemical Analysis Group) at BP Research Centre, Sunbury. A selection of polymer samples were submitted in order to determine their average molecular weights and to give an indication of the molecular weight distributions. The parameters used are indicated below. The technique is briefly discussed in Section 2.5.1.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mn</th>
<th>Mw</th>
<th>Mw/Mn</th>
<th>Mpk</th>
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<tbody>
<tr>
<td>A</td>
<td>4000</td>
<td>15100</td>
<td>3.8</td>
<td>7000</td>
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<tr>
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<td>28800</td>
<td>2.2</td>
<td>20000</td>
</tr>
<tr>
<td>C</td>
<td>3800</td>
<td>12500</td>
<td>3.3</td>
<td>32000, 3000</td>
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<tr>
<td>D</td>
<td>10000</td>
<td>15300</td>
<td>1.5</td>
<td>13000</td>
</tr>
<tr>
<td>E</td>
<td>17000</td>
<td>31700</td>
<td>1.9</td>
<td>34000</td>
</tr>
</tbody>
</table>

A; 5-Phenyl-3-vinylisoxazole homopolymer
B; Copolymer of 5-phenyl-3-vinylisoxazole and styrene
C; Polystyrene
D; Copolymer of 5-phenyl-3-vinylisoxazole and methyl methacrylate
E; Poly(methyl methacrylate)

Experimental conditions:
**Solvent:** THF, 1 ml/minute flow rate.
**Columns:** μ-styrage 104.103.500.100Å pore size.
**Detector:** refractive index.
**Samples:** approx 0.2% w/v in THF; 200μl polymer solution injected onto the GPC columns.
**Calibration:** Polystyrene standards; polystyrene equivalent molecular weights are reported.
<table>
<thead>
<tr>
<th></th>
<th>NHO (in-plane)</th>
<th>HO ((\pi))</th>
<th>LU ((\pi))</th>
<th>NLU (in-plane)</th>
<th>Total Charges</th>
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<tr>
<td></td>
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<td>(C_N)</td>
<td>(C_O)</td>
<td>(\varepsilon) (eV)</td>
<td>(C_C)</td>
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<td>0.256</td>
<td>-0.546</td>
<td>-10.546</td>
<td>-0.329</td>
</tr>
</tbody>
</table>

\(^a\) Calculations performed at MP2 level of theory with DZP basis set (W.J. Hehre, L. Radom, P.v.R. Schleyer and J.A. Pople "Ab Initio M.O. Theory", Wiley, New York, 1986). \(^b\) \(C_{rev}\): NHO, HO = \(\pi_x, \pi_y\); LU, NLU = \(\pi_y, \pi_x^*\). \(^c\) \(C_5\): HO, LU lie in plane \((\sigma_{yz})\) containing one hydrogen; NHO, NLU lie in plane perpendicular to \(\sigma_{yz}\). \(^d\) \(C_{2v}\): HO, LU lie perpendicular to molecular plane; NHO, NLU in molecular plane.
References

46. Ref 2, p 86.


142. K. Thestrup-Pedersen, Marselisborg Hospital, quoted by Torrsell in ref. 3, p.74.


Ref. 1, p. 291.


Unpublished observations by I. Alberts.

Ref 1. p. 92.


192. Ref 190, p. 223.