NITRILE OXIDE CYCLOADDITION CHEMISTRY

A Thesis

Submitted Towards the

Degree of

Doctor of Philosophy

by

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CONTENTS

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Finally, many thanks to the staff and students in the Organic Chemistry area for their friendship and for providing an enjoyable working environment. Particular mention must be made of my research group, past and present members of Lab 5 and my close friends not associated with the Chemistry Department.

STATEMENT

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give my consent to this copy of my thesis, when deposited in the University Library, being available for loan or photocopying.

Christine Merrîcc Hughes (B.Sc. Hons).

22nd March, 1995.

PUBLICATIONS

Some of the work described in this thesis has been reported in the following publications:

1. Cycloaddition Reactions of Nitrile Oxides with Alkenes.
   Easton, C. J.; Hughes, C. M.; Savage, G. P.; Simpson, G. W.; *Adv. Heterocycl. Chem.* **60**, 261 (1994) (See Appendix 1).

2. Reversal of Regiochemistry in the Synthesis of Isoxazoles by Nitrile Oxide Cycloadditions.
   Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Savage, G. P.; Simpson, G. W.; Lubin, C. E.; *Tet. Lett.* **35**(21), 3589 (1994) (See Appendix 11).

3. Crystal Structure of 7-(2,6-dichlorophenyl)-8-aza-9-oxa-[4.3.0]-bicyclonona-1,7-diene-2-one.
   Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Savage, G. P.; Simpson, G. W.; *Z. Krist.*, (1994), submitted.

4. Crystal Structure of 9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonona-1,8-diene-2-one.
   Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Savage, G. P.; Simpson, G. W.; *Z. Krist.* **209**, 767 (1994).

5. Yeast-catalysed Reductive Ring-opening of Isoxazoles.
   Easton, C. J.; Hughes, C. M.; Kirby, K.; Savage, G. P.; Simpson, G. W.; Tiekink, E. R. T.; *J. Chem. Soc. Chem. Commun.*, 2035 (1994) (See Appendix 12).

6. Crystal Structure of α-amino-α-(2,6-dichlorophenyl)-cyclohexa-2,6-

dione.

Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Savage, G. P.; Simpson, G. W.; *Z. Krist.*, (1994), submitted.

7. Reduction of Nitrogen-Oxygen Single Bonds."Preparative Biotransformations (Whole Cells and Isolated Enzymes in Organic Synthesis)" Wiley (1994), submitted.
Easton, C. J.; Hughes, C. M.; Savage, G. P.; Simpson, G. W.

8. The Development of Crop Protection Chemicals *via* Nitrile Oxide Chemistry. Presented at: 14th National Conference, RACI, Organic Chemistry National Division, Wollongong, 3-8 July, 1994.
Hughes, C. M.

9. Aryl Nitrile Oxide Cycloaddition Reactions in the Presence of Bakers Yeast and β-Cyclodextrins.
Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Savage, G. P.; Simpson, G. W.; *Tet. Lett.* **36**(4), 629 (1995) (See Appendix 13).

ABSTRACT

Cycloaddition reactions of cyclohex-2-enone, 5,6-dihydro-2*H*-pyran-2-one and 2,3-dihydro-4*H*-pyran-4-one with 2,6-dichlorobenzonitrile oxide were investigated. The reactions of cyclohex-2-enone and 5,6-dihydro-2*H*-pyran-2-one each gave only that regioisomeric bicyclic isoxazoline with the configuration predicted by consideration of the electronic effects exerted on the double bond by the carbonyl group. 2,3-Dihydro-4*H*-pyran-4-one reacted with 2,6-dichlorobenzonitrile oxide regiospecifically, due to the electronic effects of both the carbonyl group at one terminus of the double bond and the alkoxy substituent at the other terminus; however the intermediate isoxazoline underwent ring-opening to yield 5-(2,6-dichlorophenyl)-4-(3-hydroxypropionyl)-1-aza-2-oxacyclopenta-3,5-diene directly.

The bicyclic isoxazolines derived from the cycloadditions of cyclohex-2-enone and 5,6-dihydro-2*H*-pyran-2-one with 2,6-dichlorobenzonitrile oxide were oxidised to the corresponding isoxazoles through the use of γ-activated manganese dioxide and nickel peroxide. It was also established that the former bicyclic isoxazole could be synthesised through a one-pot cycloaddition-elimination sequence using either 3-bromocyclohex-2-enone or 3-chlorocyclohex-2-enone. The regioselectivity of cycloaddition reactions is determined by the substitution pattern around the double bond of the alkene, with the oxygen of the nitrile oxide becoming attached to the more substituted terminus of trisubstituted double bond. To change the regiochemistry of the cycloaddition reaction, the site of halogenation required to be changed, therefore giving the regioisomeric isoxazole. Thus the bicyclic isoxazoles regioisomeric to those obtained from the oxidation of the isoxazolines were

obtained by the cycloaddition of 2-bromocyclohex-2-enone and 3-bromo-5,6-dihydro-2*H*-pyran-2-one.

Relative rate studies on the cycloaddition of the cycloalkenones and their halogenated analogues were conducted and it was confirmed that the reactivity of the dipolarophile decreases as the substitution around the carbon-carbon double bond increases.

The reductive N-O bond cleavage of the bicyclic isoxazoles, 9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonona-1,8-dien-2-one and 9-(2,6-dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonona-1,8-dien-2-one, to form the corresponding β-enamino ketones was achieved using palladium on carbon. Analysis of the ring-opened compounds in solution showed they were each in their imine form, however X-ray crystallographic analysis showed that in the crystalline state, each compound adopted the enamine form.

The ring-opening of the isoxazoles was also achieved using yeast. A variety of yeasts and conditions were tested and it was established that baker's yeast was the most effective in achieving reductive cleavage of the N-O bond of isoxazoles. The generality of this novel reductive ring-cleavage was investigated and it was established that the ring cleavage was only observed for bicyclic isoxazoles with carbonyl substituents attached to the C-4 position of the isoxazole ring. Following this, a mechanism for the ring-opening reaction was developed.

Finally, the cycloadditions between various nitrile oxides and ethyl cinnamate and 4-vinylpyridine in the presence of baker's yeast and β-cyclodextrin were explored. Contrary to literature reports, it was found that baker's yeast had little or no effect on any of these cycloadditions. β-Cyclodextrin was found to entrain some of the isoxazoline products formed from the cycloadditions of nitrile oxides with ethyl cinnamate but has no effect

on the regiochemical outcome of these cycloaddition reactions. β-Cyclodextrin was found to have no noticeable effect on the stereochemical outcome of the cycloaddition reactions between 2,6-dichlorobenzonitrile oxide and mesitonitrile oxide with 4-vinylpyridine.

INTRODUCTION

The worldwide agricultural industry requires reliable crop protection and progress in the productivity of modern agricultural systems is unthinkable without plant protection measures. In the 1970's the demand for agrochemicals was strong and there were about twenty-two companies with a major presence in the world agrochemical market. During the 1980's the industry was hit by both government actions to reduce food surpluses in developing countries and by lower commodity prices. New stringent regulations meant that the cost of research and development increased and companies were induced to spend a growing proportion of their research and development budget on supporting existing products. The number of companies involved in agrochemicals also declined.[1]

Now in the 1990's there are fewer technical opportunities and many major products are off-patent. This has created a much more competitive environment. The research and development costs are enormous and it may take seven years from filing a patent to first sale, and a further fifteen years before costs are recovered. However, the total world market for agrochemicals is approximately $US25,000 million, and herbicides account for 45% of this (Figure 1), making research and development a worthwhile exercise.[1]

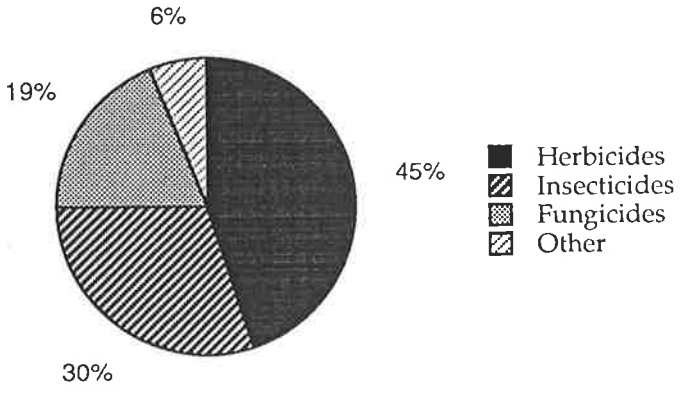


Figure 1: World Agrochemical Sales by Category (total $US25,000M).[1]

The major regions for the sale of agrochemicals are the United States of America, Western Europe and the Far East; they account for 80% of the total world sales (Figure 2).[1] Comparatively, the Australian agricultural industry is small and accounts for 1.2% of the total world sales (approximately $300M per annum).[2] Given this, an Australian company wishing to succeed in the agrochemical industry must ultimately target the lucrative international markets as well as the local market.

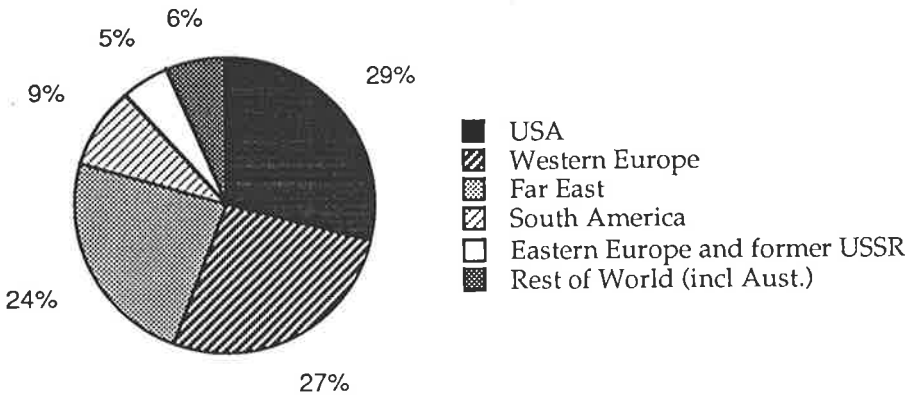
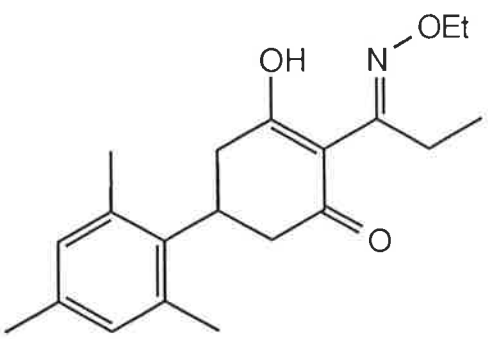


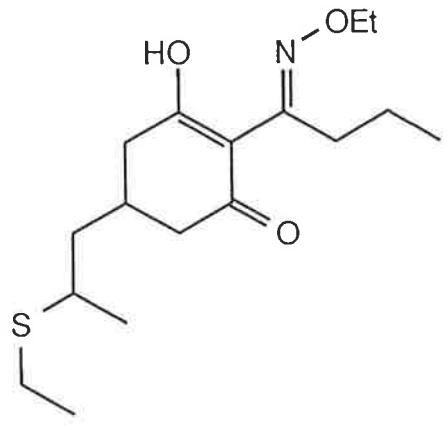
Figure 2: Sales by Regions.[1]

Very few agrochemicals have their origins in Australia, and, until the mid 1980's, herbicides were totally imported from Europe or the United States. The Commonwealth Scientific and Industrial Research Organisation (CSIRO), through the joint venture company Dunlena Pty. Ltd. (CSIRO, Division of Chemicals and Polymers, in partnership with Du Pont (Australia) Ltd. and Australian Industrial Development Corporation Ltd.), is one of the few institutions that are aiming to develop and manufacture, in Australia, agricultural chemicals for sale in this international market (the top 25 agrochemical companies have their bases in Europe, the United States of America or Japan).

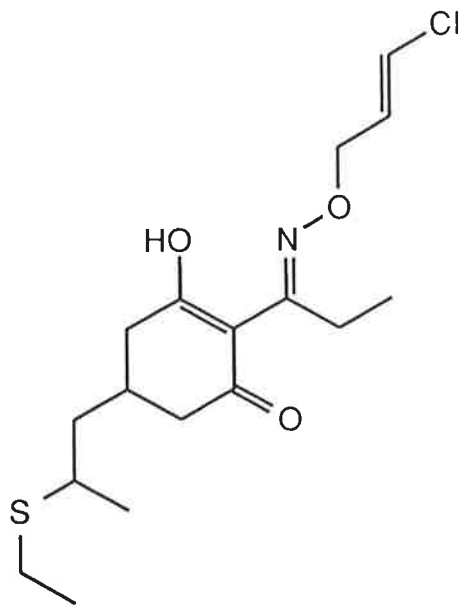
In the early 1980's an ICI research group in Melbourne, Australia, discovered and developed a new herbicide for use in wheat and barley. This new product has now been marketed in Australia and overseas under the trade name GRASP [ICIA604 (II)] (**1**).[2] This herbicide created much interest within the agricultural chemical industry as GRASP (**1**) was found to be of low acute toxicity to birds, fish, bees and earthworms, and also non-mutagenic in an array of tests and non-teratogenic in the rabbit and the rat.[2] As well as its rapid breakdown in soil and crops, other advantageous features of GRASP (**1**) compared to other available herbicides are that: it has a rate of application of 150g/ha;[3] it is able to be applied from early to late growth stages (that is post-emergence activity); and it controls a wide variety of both grass and broad-leaf weeds.[3,4] The mode of action of GRASP (**1**) and its structurally related analogues (*e.g.*, sethoxydim (**2**), clethodim (**3**) and alloxydim (**4**) is *via* acetyl-CoA carboxylase inhibition,[5,6] the enzyme that catalyses the committing step in fatty acid biosynthesis).



(1)



(2)



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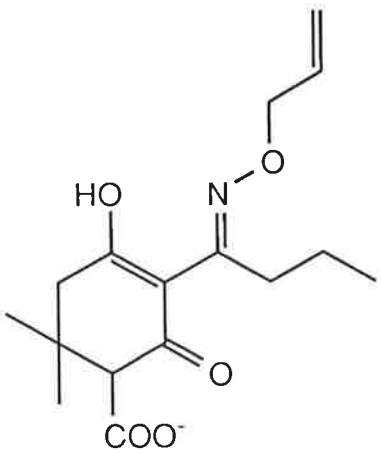
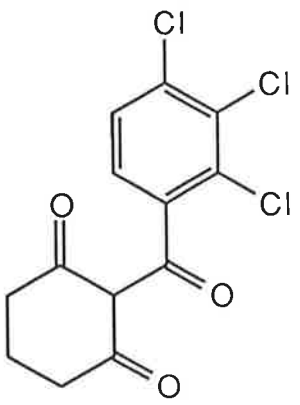


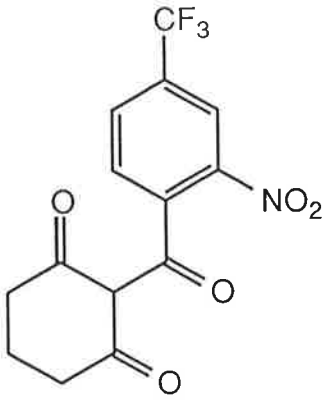
(4)

Structurally related to GRASP (**1**) are the bleacher herbicides, for example, ICIA-0051 (previously SC-0051) (**5**). As with GRASP (**1**), this class of herbicides displays both pre- and post-emergence activity against both grasses and broad-leaf weeds; however their mode of action is believed to be *via* inhibition of chlorophyll or carotenoid synthesis as bleaching of the leaves is a consequence of their application.[4] There is also some inhibition of protein synthesis at high concentrations. An advantage of these herbicides is that their rate of application is very low with activity being observed at an application rate of 11.21g/ha.[7]

The bleacher herbicides tend to show high mammalian activity; consequently not many appear in the market. However, this activity is also being explored in terms of their potential as pharmaceuticals; for example, a triketone that shows promise as a pharmaceutical is 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC) (**6**).[8]



(5)

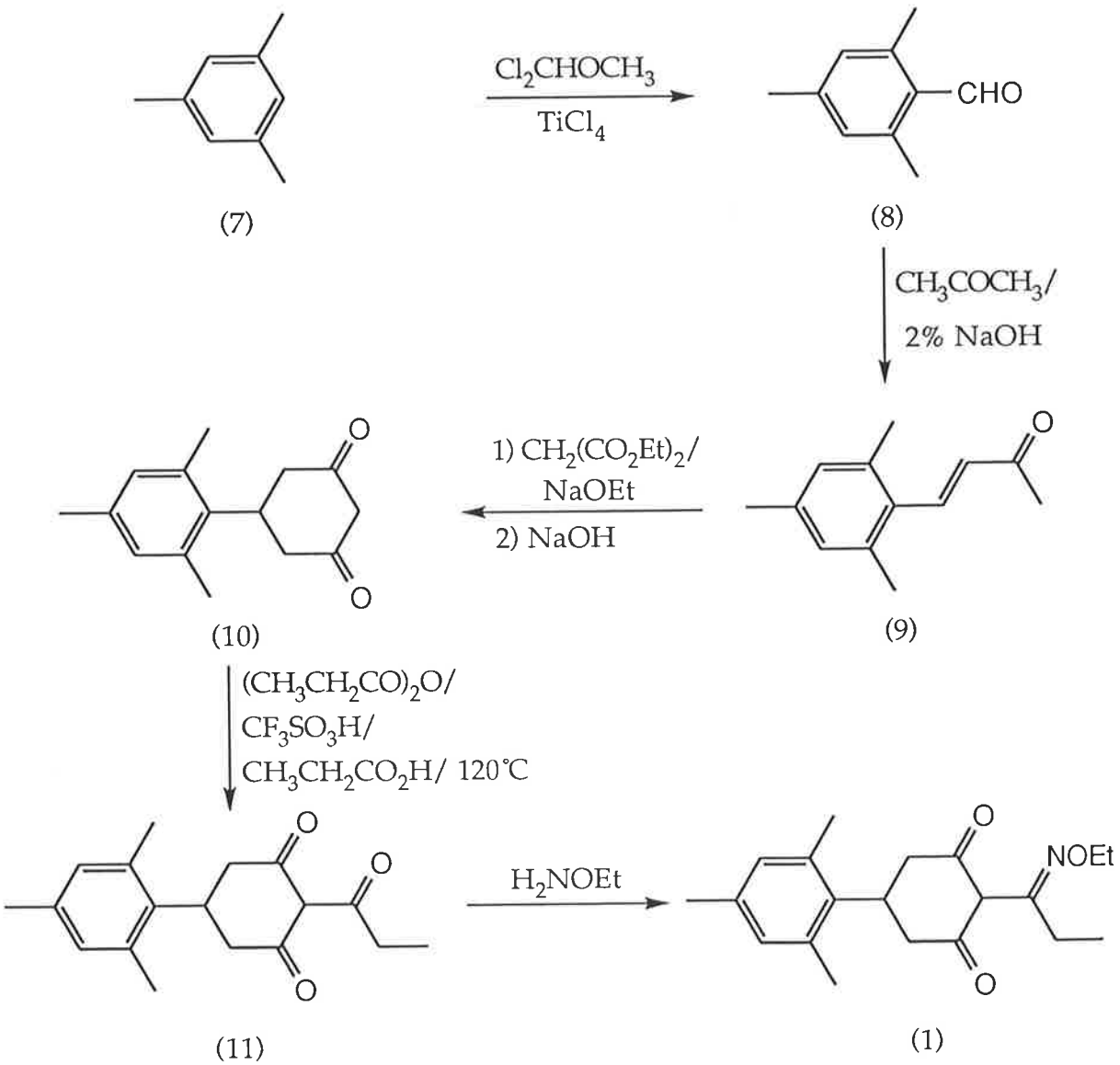


(6)

NTBC (**6**) has shown potential as a treatment for hereditary tyrosinaemia type I. Hereditary tyrosinaemia type I is a disease that generally results in death from hepatic failure during the first year of life or from primary cancer in the cirrhotic liver, usually in the first two decades. The biochemical defect is believed to be a deficiency of the enzyme fumarylacetoacetase which catalyses the degradation of fumarylacetoacetate to fumarate and acetoacetate in the biochemical pathway of tyrosine degradation. Recently NTBC (**6**) has been shown to be a potent inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase which catalyses a preceding reaction in the tyrosine degradation pathway; thus by inhibiting 4-hydroxyphenylpyruvate dioxygenase, the amount of fumarylacetoacetate formed is decreased and consequently the effects of a deficiency in fumarylacetoacetase has less impact. It is now believed that treatment with NTBC (**6**) may offer an alternative to liver transplantation in this otherwise fatal disease.[8]

The industrial synthesis of GRASP (**1**) is a five step synthesis (Scheme 1) with an overall yield of 44%.[2] The first step in the synthesis is formylation of 1,3,5-trimethylbenzene (**7**) to give the adduct (**8**), followed by an aldol

condensation to give the α,β-unsaturated ketone (**9**) and a cyclisation to give the 1,3-diketone (**10**). Subsequent acylation gives the triketone (**11**) with the exocyclic carbonyl formed then being converted to give the *N*-ethoxyimine (**1**).[2]



Scheme 1

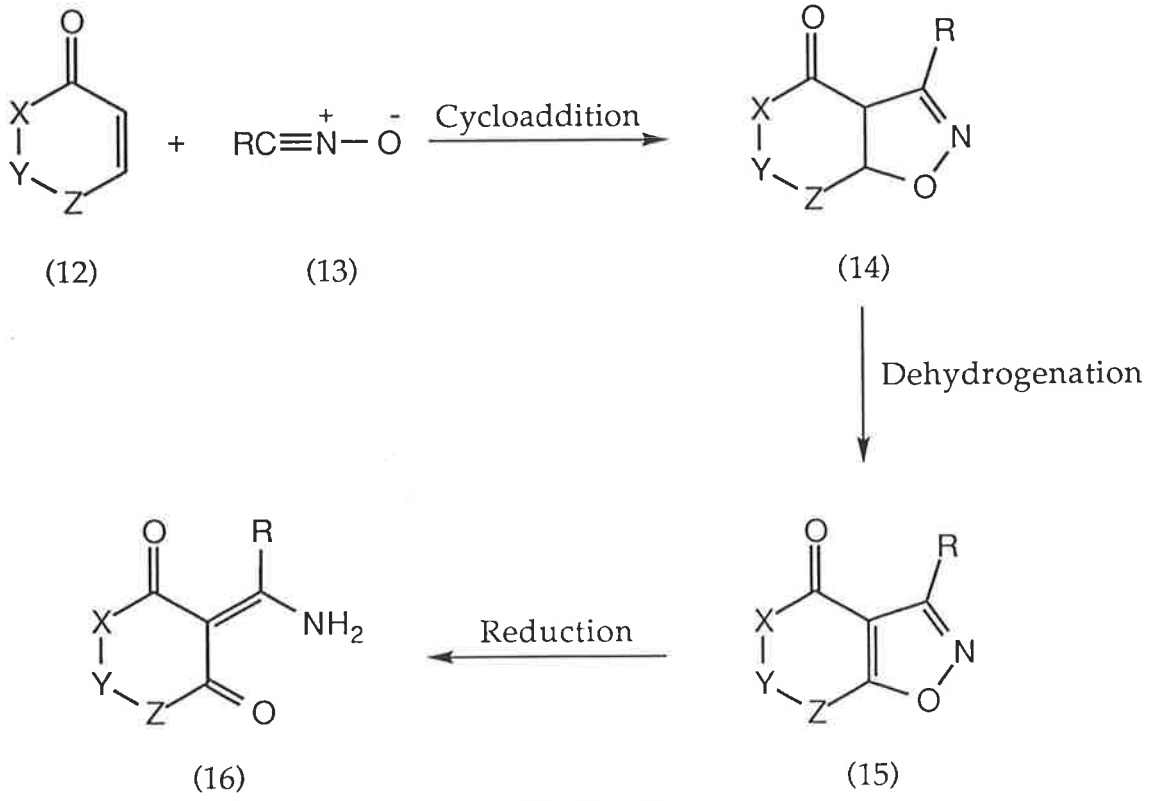
This synthetic strategy is somewhat restrictive to the type of analogue

that can be made. This method requires an aldehyde moiety with a bulky, unreactive group attached, as the initial building block for the synthesis. Thus analogues made *via* this method would be restricted to having a tail of this type. Secondly, the manner in which the cyclohexanedione ring is synthesised makes the substitution of heteroatoms into the ring system and variation of the ring size very difficult. Thus, to achieve the flexibility required to obtain these forms of structural analogues, a new synthetic pathway was required.

Due to the ongoing market success of GRASP (**1**) and the aforementioned inflexibility associated with its industrial synthesis, the crop protection group in CSIRO's Division of Chemicals and Polymers undertook a pilot project in which they chose to make structural variations of GRASP (**1**) around the β-enamino ketone portion. It was also believed that the approaches used to make analogues of GRASP (**1**) could provide a convenient route for the synthesis of analogues of the bleacher herbicides by hydrolysis of the β-enamino ketone.

The initial aim of the work presented here was to work with the CSIRO, Division of Chemicals and Polymers in exploring nitrile oxide cycloaddition chemistry with a view to its possible application to the synthesis of GRASP (**1**) and bleacher herbicide analogues. After conducting an extensive literature review on the cycloaddition of nitrile oxides to carbon-carbon double bonds (Appendix 1), it was believed that if the bicyclic isoxazoles (**15**) could be made, then it would be possible to ring-open these compounds to form the β-enamino ketones (**16**). It should be noted that it is common to refer to the GRASP-type herbicides as cyclohexanediones although they are often drawn as their imine or enamine tautomers. Isoxazoles are generally synthesised *via* the cycloaddition of nitrile oxides to alkynes, however cyclic alkynes are not readily available, thus the pathway proposed for the synthesis of the cyclohexanediones (**16**) was as shown in Scheme 2.

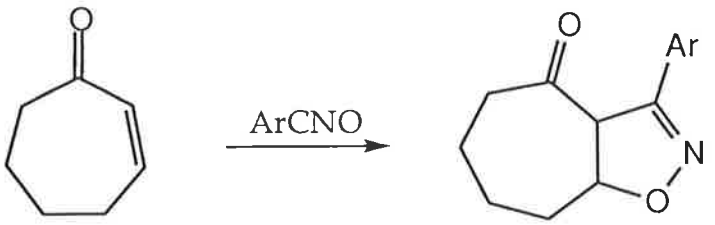
The first step in the synthetic pathway was the 1,3-dipolar cycloaddition of a cyclohexenone (**12**) to a nitrile oxide (**13**). This synthetic strategy would make variation in the ring size possible. For example, the cycloadditions of various aryl nitrile oxides to cyclopent-2-enone,[9] cyclohex-2-enone,[9] and cyclohept-2-enone (**17**) (Scheme 3)[9] make it possible to vary the ring size bearing the 1,3-diketone moiety.



(12) (13) (14) (15) (16)

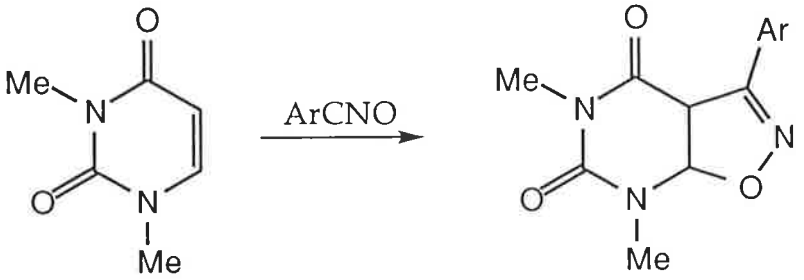
Scheme 2

There have also been examples in the literature of cycloaddition reactions to heterocycles,[10-14] for instance the cycloaddition of uracil (**18**) to aryl nitrile oxides (Scheme 4).[14] Thus it was envisaged that it would be possible to incorporate heteroatoms into the cycloalkenone system giving heteroatom substitution in the final product.



(17)

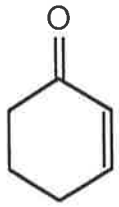
Scheme 3



(18)

Scheme 4

It was decided to use two compounds which are heterocyclic analogues of the cyclohexenone (**19**); 5,6-dihydro-2*H*-pyran-2-one (**21**) and 2,3-dihydro-4*H*-pyran-4-one (**23**). The former compound has been made *via* the condensation of 3-butenoic acid (**20**) with paraformaldehyde under strongly acidic conditions (Scheme 5).[15,16] A quick and efficient synthesis of the latter compound (**23**) was published by Danishefsky and Webb[17] in which Danishefsky's diene (1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene) (**22**) was condensed with paraformaldehyde in the presence of zinc chloride to give the dihydropyranone (**23**) in 55% yield (Scheme 6).



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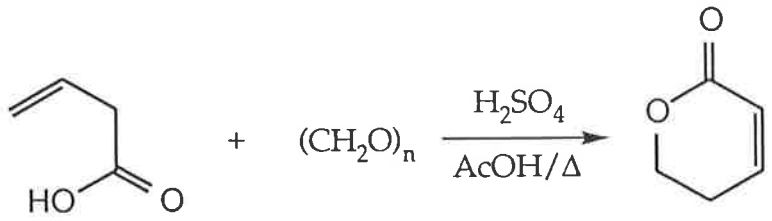
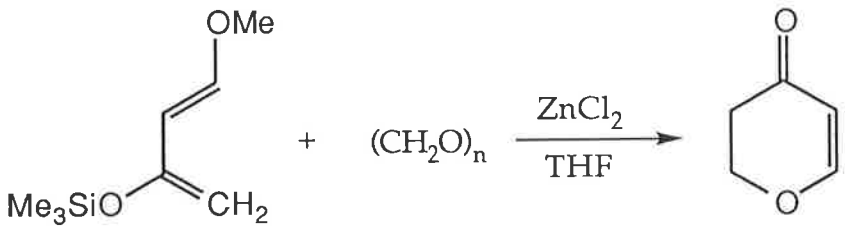


(20) (21)

Scheme 5

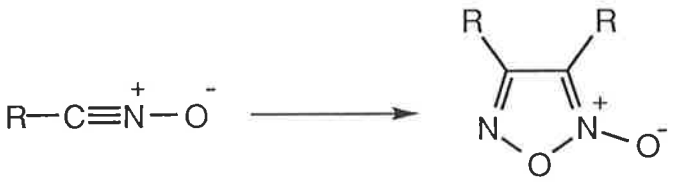


(22) (23)

Scheme 6

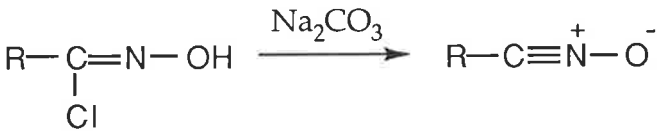
There are several methods for the synthesis of nitrile oxides reported in the literature (Appendix 1). Nitrile oxides readily self-condense to form the nitrile oxide dimers, the furoxans (**24**) (Scheme 7). To overcome this problem the nitrile oxide is often generated *in situ*.[18] The two most commonly used methods of *in situ* nitrile oxide generation are *via* the dehydrohalogenation of hydroximinoyl halides (**25**) using a base (Scheme 8),[19] or by the dehydration of primary nitroalkanes (**26**) using phenyl isocyanate in the presence of a catalytic

amount of triethylamine (Scheme 9). This latter method is frequently referred to as the Mukaiyama method.[20]



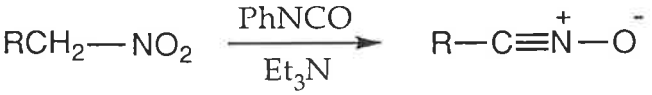
(24)

Scheme 7



(25)

Scheme 8

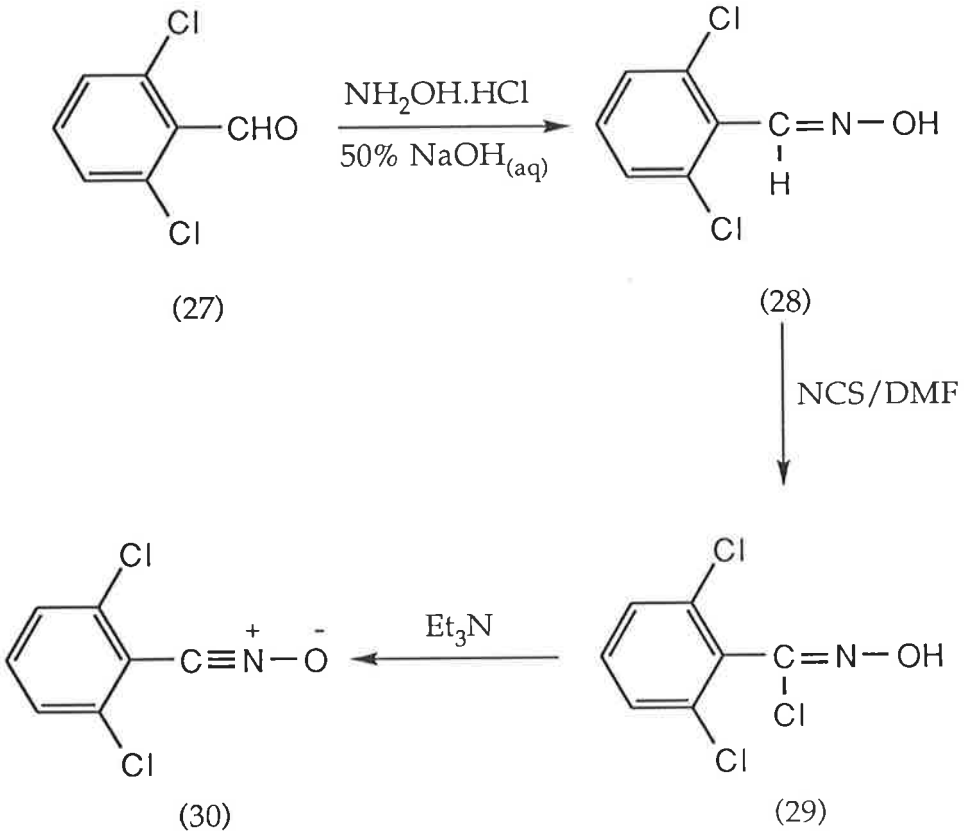


(26)

Scheme 9

The cycloaddition reactions presented in this thesis were performed using aryl nitrile oxides as they are relatively inert to dimerisation in comparison to alkyl nitrile oxides.[21] However, even amongst aryl nitrile oxides there is quite a variation in reactivity. Of the most commonly used nitrile oxides (due to ease of synthesis) the most reactive is benzonitrile oxide, followed by mesitonitrile oxide, and more stable are 2,6-dichlorobenzonitrile oxide and 2,4,6-trimethoxybenzonitrile oxide.[21] The less reactive the nitrile oxide, the fewer side-products obtained. With this in mind, it was decided to

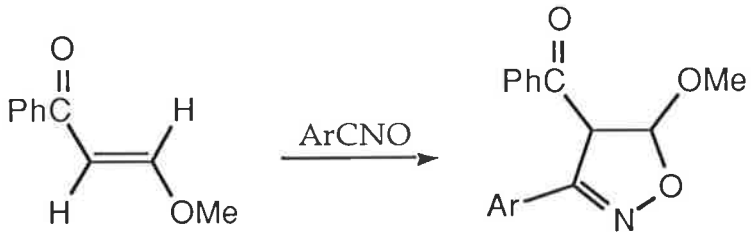
use 2,6-dichlorobenzonitrile oxide (**30**) for this section of work, synthesised *in situ* from the corresponding hydroximinoyl chloride (**29**).[22] The aldoxime precursor (**28**) can be generated from the corresponding aldehyde (**27**) (Scheme 10).[22]



Scheme 10

The orientation of the 1,3-dipolar cycloaddition reaction has been reviewed (Appendix 1). Regiochemistry is governed by steric and electronic effects, and although steric considerations almost exclusively predominate over electronic effects, a mixture of regioisomers is usually obtained with unsymmetrical 1,2-disubstituted alkenes. Then, the predominant regioisomer formed will be that which is favoured electronically; for example, carbonyl substituents are known to direct the oxygen of the nitrile oxide such that they

are at the 4-position of the cycloadducts[12,13,23-29] and alkoxy substituents tend to orientate the cycloadditions such that they are at the 5-position in the cycloadducts.[11] The cyclohexenone (**19**), 5,6-dihydro-2*H*-pyran-2-one (**21**) and 2,3-dihydro-4*H*-pyran-4-one (**23**) have the directing effect of the carbonyl group; thus the major products would be expected to have the orientation as indicated in Scheme 2. Further, 2,3-dihydro-4*H*-pyran-4-one (**23**) has the additional directing effect of the oxygen in the olefin ring system (that is, an alkoxy group attached to the double bond) that would be expected to direct the cycloaddition with high regioselectivity, similar to the regioselective cycloaddition of nitrile oxides to the 1,2-disubstituted olefin (**31**) (Scheme 11).[30]

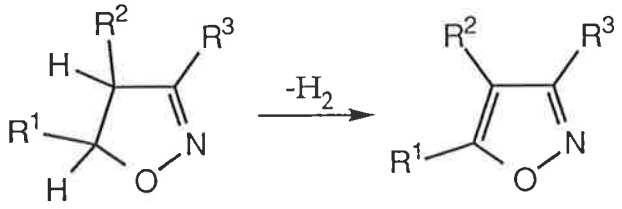


(31)

Scheme 11

Dehydrogenation of isoxazolines (Scheme 12) has been carried out by numerous methods (Appendix 1) including the use of Chloranil®,[31,32] 2,3-dichloro-5,6-dicyanobenzoquinone[33] and γ-activated manganese dioxide (γ-MnO_2).[34-36] The former two reagents are commercially available. Activated manganese dioxide can be prepared by several methods giving products of various activities. Generally, the order of activity is considered to be γ-MnO_2 > active (or β-) MnO_2 > α-MnO_2. The prefix denotes differences in the crystalline lattices of the various forms. γ-MnO_2 is prepared by stirring potassium

permanganate with manganese sulphate (Scheme 13), with the γ-MnO_2 forming as a precipitate which is subsequently filtered off.[37]



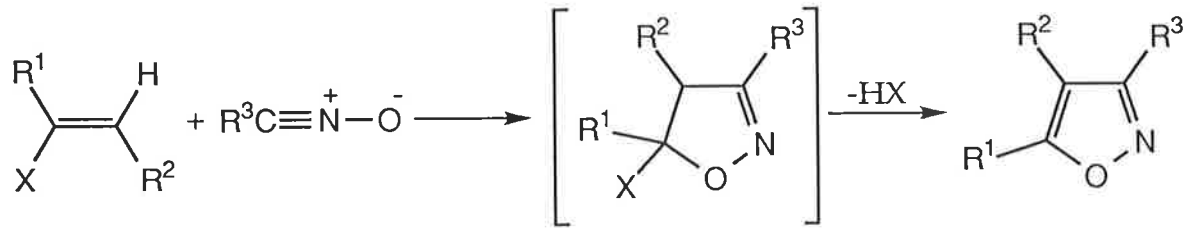
Scheme 12

$$MnSO_4 + 2KMnO_4 \longrightarrow \gamma\text{-}MnO_2\downarrow + KHSO_4 + KHMnO_4 + H_2MnO_4$$
$$+ 2H_2O$$

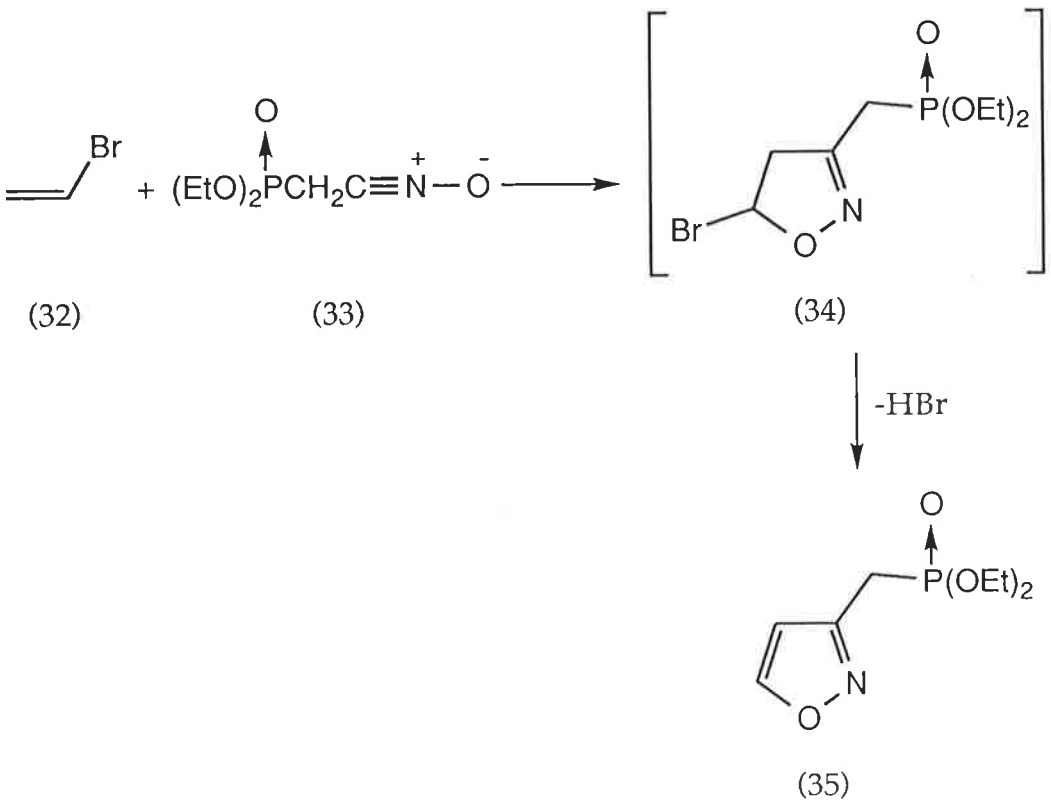
Scheme 13

An alternative method of synthesis of isoxazoles has been to construct the corresponding isoxazoline with a leaving group suitable for subsequent elimination (Scheme 14) (Appendix 1); for example the cycloaddition of vinyl bromide (**32**) to the nitrile oxide (**33**) proceeded directly to the isoxazole (**35**), presumably by the elimination of hydrogen bromide from the isoxazoline (**34**) (Scheme 15).[38] By analogy, it was anticipated in the present work that ring-fused isoxazoles could be obtained by placing an appropriate leaving group on one of the termini of the double bond of the cyclohexenone (Scheme 16). The regiochemistry of cycloaddition for the reaction of unsymmetrical olefins is governed almost entirely by steric effects, with the oxygen of the nitrile oxide becoming attached to the more hindered end of the double bond (Appendix 1).

Thus, to achieve the isoxazole product with the required regiochemistry, a leaving group would need to be placed on the terminus of the double bond β to the carbonyl group.

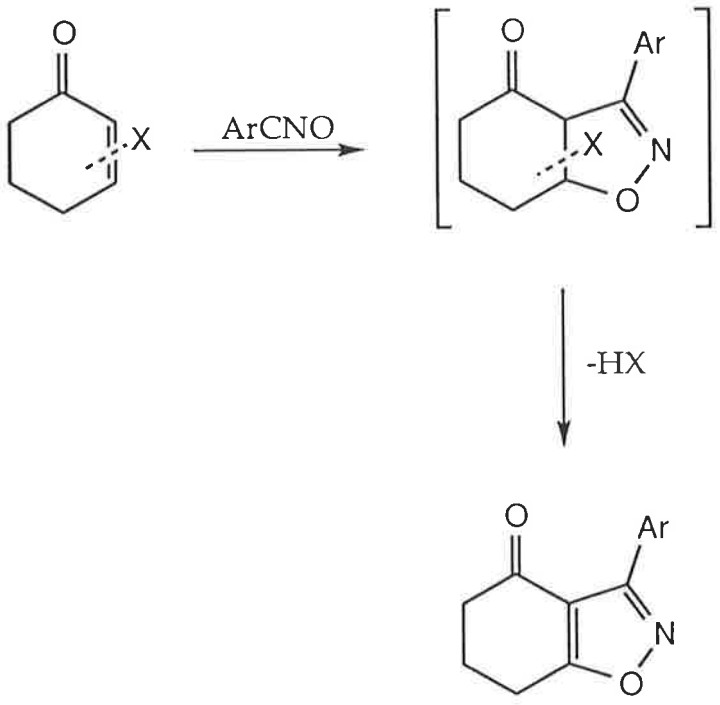


Scheme 14



(32) (33) (34) (35)

Scheme 15

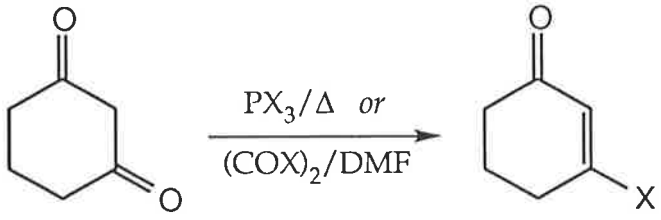


Scheme 16

The synthesis of the 3-halocyclohexenones (**37a,b**) has been reported. Crossley and Haas[39] treated 1,3-cyclohexanedione (**36**) with phosphorus trihalides (either bromide or chloride) to obtain the halocyclohexenones (**37a**) and (**37b**), respectively (Scheme 17). Alternatively, Vilsmeier reagents have been utilised with 1,3-cyclohexanedione (**36**) (Scheme 17).[40] Vilsmeier reagents are prepared from *N,N*-dimethylformamide and either oxalyl bromide or oxalyl chloride. Both reactions were reported to be quick and high yielding.

Bromination of the terminus α to the carbonyl group has also been reported. A paper by Posner *et al.* reported the use of 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**)[41] and subsequent correspondence with the authors provided a procedure for its synthesis. Initially, bromine was added across the double bond of the dihydropyran-2-one (**21**) followed by selective elimination of HBr using a hindered base, Hünig's base (diisopropylethylamine) (Scheme 18). It was anticipated that this procedure could be used to brominate the

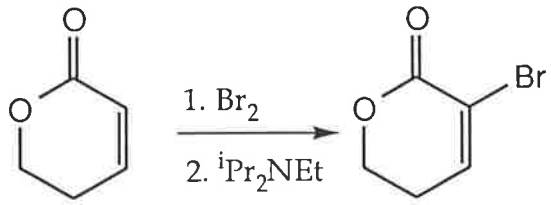
cyclohexenone (**19**) and 2,3-dihydro-*4H*-pyran-4-one (**23**) to form their corresponding brominated compounds; 2-bromocyclohex-2-enone (**39**) and 3-bromo-5,6-dihydro-*4H*-pyran-4-one (**40**).



(36) (37)

a) X = Br
b) X = Cl

Scheme 17

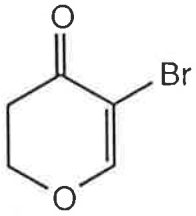


(21) (38)

Scheme 18

It was predicted that the regiochemistry of the cycloaddition of 3-bromo-5,6-dihydro-*2H*-pyran-2-one (**38**) to the nitrile oxide (**30**) would be opposite to the regiochemistry of the reactions of the 3-halocyclohexenones (**37**) to the nitrile oxide (**30**) due to cycloaddition reactions being controlled by steric considerations.

(39)

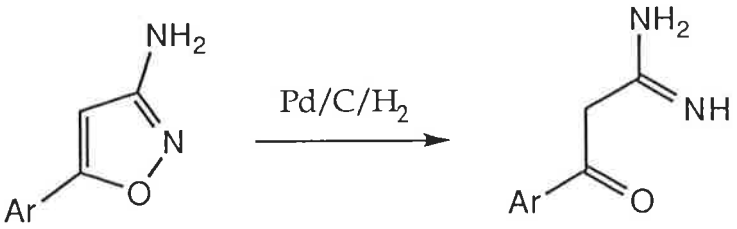


(40)

It has been well documented (Appendix 1) that the rates of 1,3-dipolar cycloaddition reactions decrease with increases in the degree of substitution of the dipolarophile, thus making the reactions susceptible to alternative pathways such as nitrile oxide dimerisation. The steric effect of a single alkyl substituent on an alkene decreases reactivity, while the rate-enhancing effect of a conjugating substituent is greater than the retarding steric effect. The steric effect becomes dominant with more highly substituted olefins. With disubstituted alkenes the reactivity is generally retarded, more so with 1,2- than 1,1-disubstitution, although the electronic effects of both substituents still affect reactivity. Trisubstituted alkenes are even less reactive and steric effects dominate. Thus it was decided that rate studies should be performed, comparing the reactivity of the dipolarophiles (**19**), (**21**) and (**23**) and their halo-substituted analogues (**37a**), (**38**), (**39**) and (**40**) to determine the degree of retardation. In this way it was aimed to establish if the halides (**37a**), (**38**), (**39**) and (**40**) could be expected to undergo cycloadditions with nitrile oxides more prone to competing dimer formation. The experiments examining the synthesis of ring-fused isoxazolines and isoxazoles, as outlined in Scheme 2, and the relative reactivities of the dipolarophiles (**19**), (**21**), (**23**), (**37a**), (**38**), (**39**) and (**40**), are discussed in Chapter 1 of the Results and Discussion of this thesis.

The interest in the synthesis of ring-fused isoxazoles is in their elaboration to β-enamino ketones. Literature concerning the elaboration of

isoxazolines and isoxazoles has been reviewed (Appendix 1). Several methods have been used in the past to achieve the ring opening of isoxazoles to β-enamino ketones but the most common is *via* metal catalysed hydrogenation;[42] for example hydrogen over palladium on carbon has been used on the isoxazole (**41**) to obtain the ~~imine~~ ketone (**42**) (Scheme 19).[43]

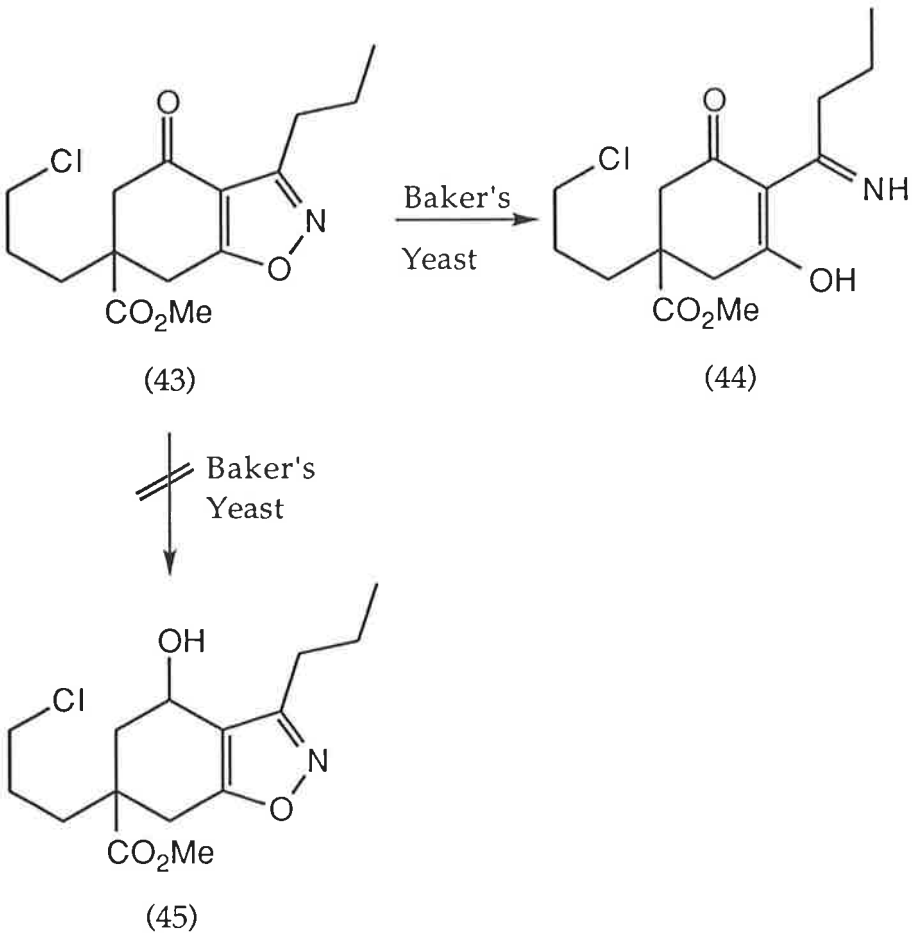


(41) (42)

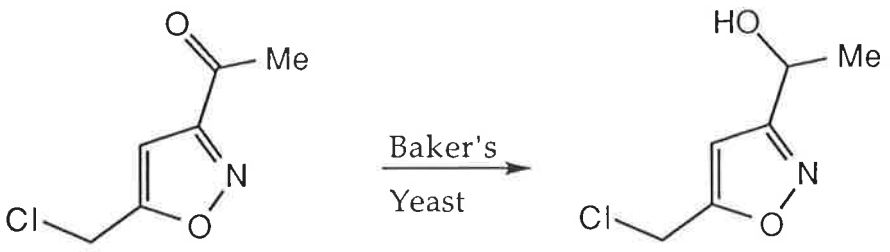
Scheme 19

During the course of other work that was being investigated in the CSIRO, Division of Chemicals and Polymers an alternative method of ring opening isoxazoles has been found.[44] Initially, attempts were being made to find a mild method of reducing the carbonyl group on the isoxazole (**43**) to form the ~~imine~~ ketone (**45**). The method involved the use of baker's yeast (sp. *Saccharomyces cerevisiae*); however on workup the alcohol (**45**) was not dectected, instead the imine (**44**) was obtained (Scheme 20). Previously, all reports in the literature on the use of baker's yeast on isoxazoles had found that the yeast did not act on the heterocyclic ring, but instead on the substituents on the ring system, such as reducing carbonyl groups to the corresponding alcohols (Schemes 21 and 22).[45,46] This property of baker's yeast has often been exploited to resolve racemic mixtures of isoxazolines and isoxazoles by selectively reducing the carbonyl group of one of the

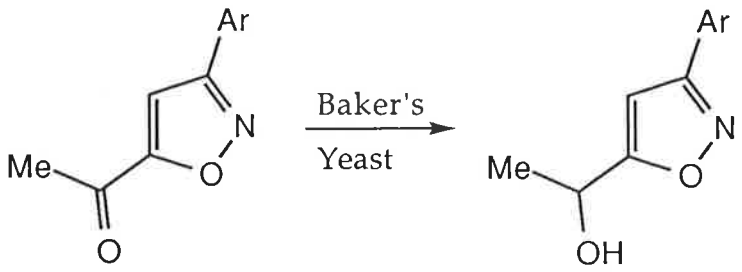
stereoisomers to yield cycloadducts that have high stereochemical purity (Scheme 23).[47] The new yeast catalysed reaction observed at CSIRO appeared to offer a viable alternative for the ring opening of isoxazoles and results of investigations to determine the generality of that process are discussed in Chapter 2 of the Results and Discussion.



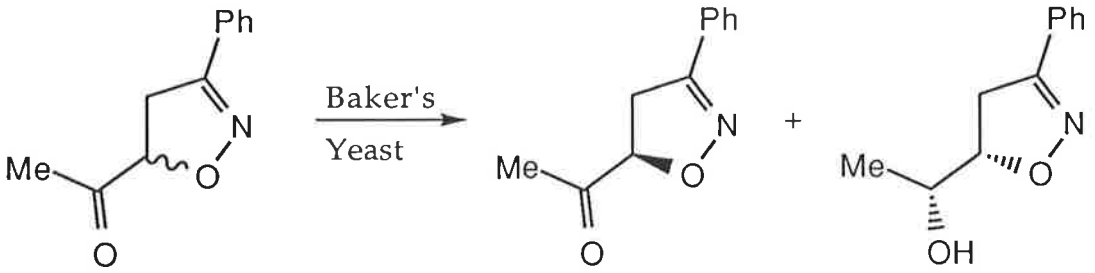
Scheme 20



Scheme 21



Scheme 22

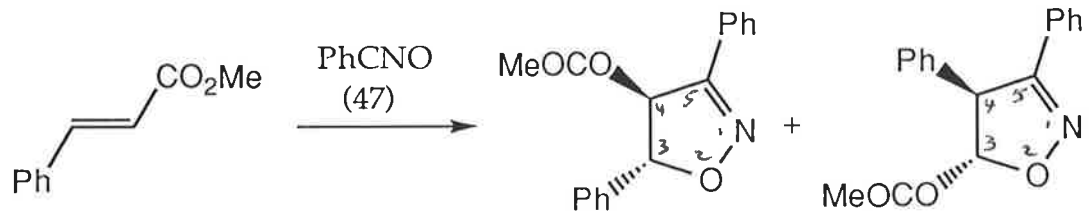


ee 99% ee 98%

Scheme 23

Control of regioselectivity has gained much attention in nitrile oxide cycloaddition chemistry (Appendix 1). There have been reports by Rama Rao *et al.* of regiocontrol in some cycloaddition reactions of nitrile oxides with cinnamates,[48,49] apparently requiring catalysis by baker's yeast, in the presence of β-cyclodextrin. As mentioned previously, regioisomeric isomers are usually obtained in the cycloaddition of 1,2-disubstituted alkenes with nitrile oxides. The reactions between nitrile oxides and cinnamates are well known, and have appeared many times in the literature.[29,50-54] About twenty years ago Christl *et al.*[50,51] reported the cycloaddition of benzonitrile oxide (**47**),

generated *in situ* with methyl cinnamate (46) (Scheme 24). The products (48) and (49) were regioisomeric and were obtained in a ratio of 70:30. These regioisomers were distinguished by the chemical shifts of the two protons on adjacent carbon atoms on the isoxazoline ring, that were observed in the ^1H nmr spectra. As predicted, the major isomer (48) was found to have the aromatic groups on the 3 and 5 positions of the isoxazoline due to both the inductive electronic effects of the ester moiety on the cinnamate and more importantly to the steric effects that the aromatic group would have on the cycloaddition reaction (Appendix 1). A coupling constant of 6 Hz was observed for the two isoxazoline ring protons attached to carbons 3 and 4. The minor isomer (49) was found to have the aromatic groups on the 4 and 5 positions and a coupling constant of 4 Hz between the C-3 and C-4 protons.

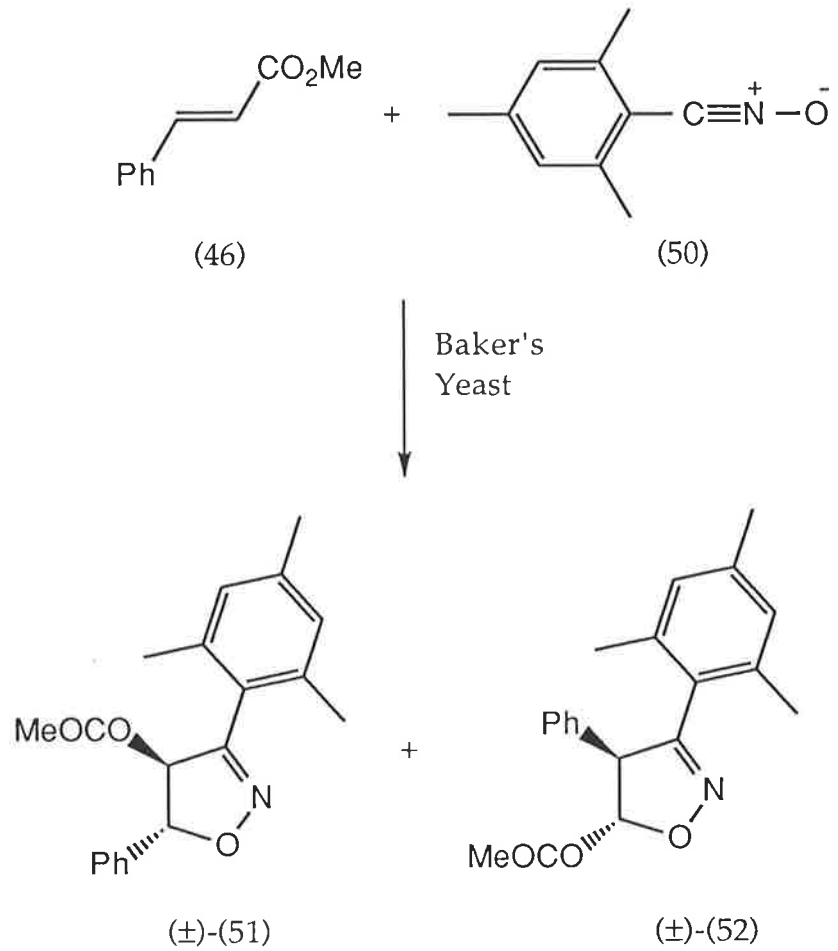


(46) (±)-(48) (±)-(49)

Scheme 24

Likewise, the cycloaddition of mesitonitrile oxide (50), formed *in situ*, with methyl cinnamate (46), gave the cycloadducts (51) and (52) in the ratio 64:36, with the major isomer (51) having the aromatic groups on the 3 and 5 positions (Scheme 25). The overall yields of these reactions were high: 89% and 93%, respectively. Thus Rama Rao *et al.'s* claim[48,49] that mesitonitrile oxide (50) would not react in aqueous media with cinnamates in the absence of

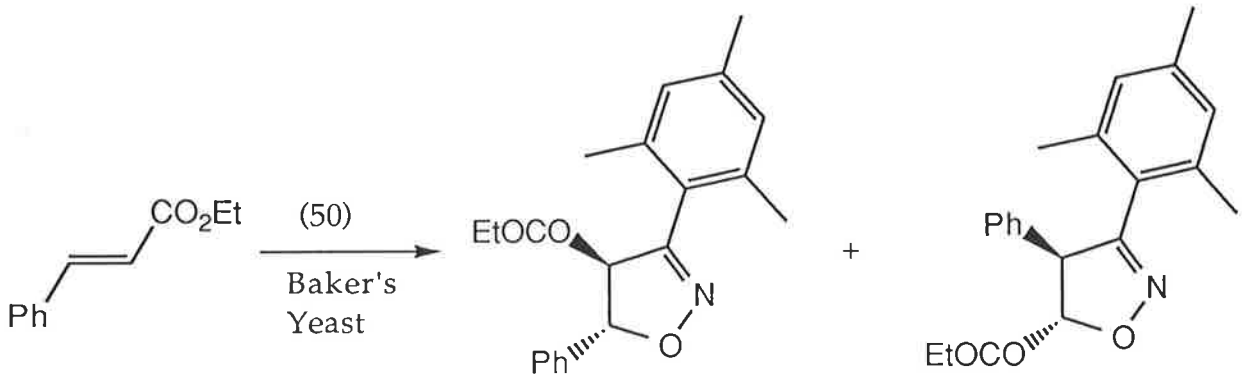
yeast was questionable.



Scheme 25

The cycloaddition of mesitonitrile oxide (**50**) with ethyl cinnamate (**53**) was reported by Rama Rao *et al.* to yield a regioisomeric mixture of the isoxazolines (**54**) and (**55**) in a ratio of 65:35, in the presence of baker's yeast (Scheme 26).[48,49] However, if β-cyclodextrin was added to the reaction mixture then, it was reported, the regioselectivity was completely reversed and only the isomer (**55**) was obtained. Rama Rao did not propose a model for the

interaction of baker's yeast and β-cyclodextrin with the nitrile oxide (**50**) and ethyl cinnamate (**53**); however he did propose a model for the interaction of the nitrile oxide (**50**) with a vinyl pyridine (Figure 3)[49] with the inference that a similar model may account for the reversal of regiochemistry in the case of the cycloaddition of the nitrile oxide (**50**) and ethyl cinnamate (**53**). It seemed that the probability of the reagents bound in such a manner, coming together in an orientation conducive to cycloaddition, would be implausible. Further, it would be expected that, if the model proposed by Rama Rao was correct, then the proportion of the cycloadduct (**54**) formed in the presence of β-cyclodextrin would be even greater due to steric considerations.



(53) (±)-(54) (±)-(55)

Scheme 26

Rama Rao *et al.* reported that the cycloaddition of 2,6-dichlorobenzonitrile oxide (**30**) with ethyl cinnamate (**53**) also required baker's yeast as a catalyst and that the reaction yielded only the regioisomer (**56**) (Scheme 27).[48,49] It was also stated that there was no noticeable change to the product formed if β-cyclodextrin was added to the reaction mixture.

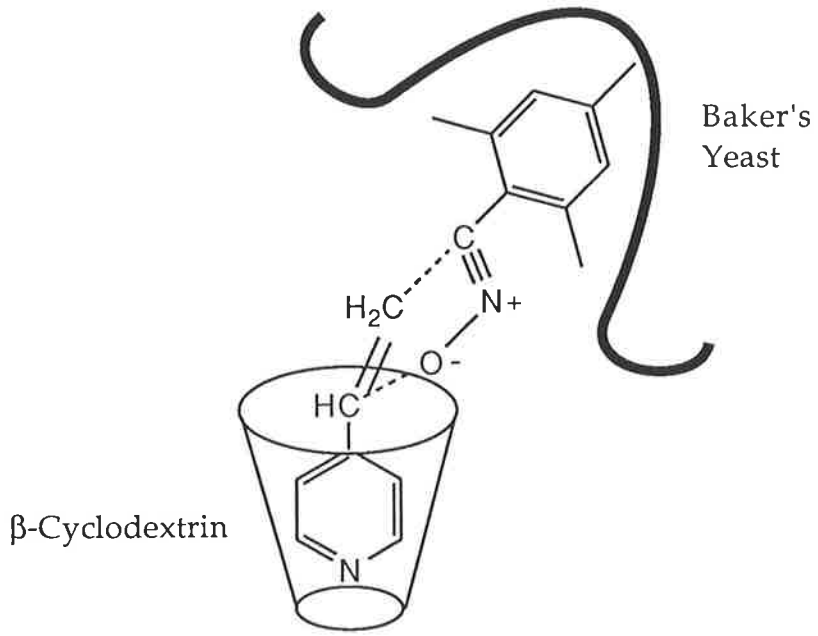
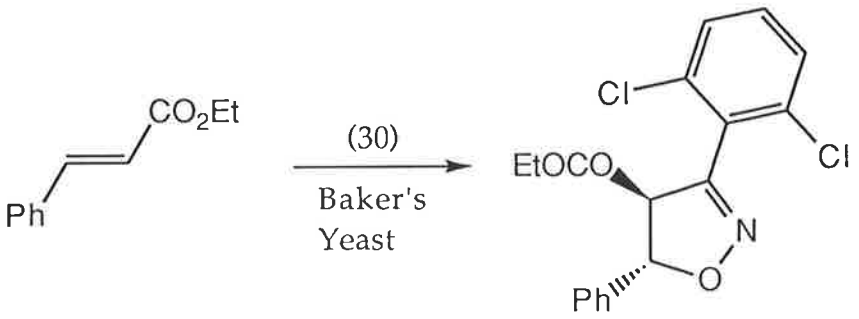


Figure 3: Proposed biocatalytic model for cycloaddition using baker's yeast and β-cyclodextrin.

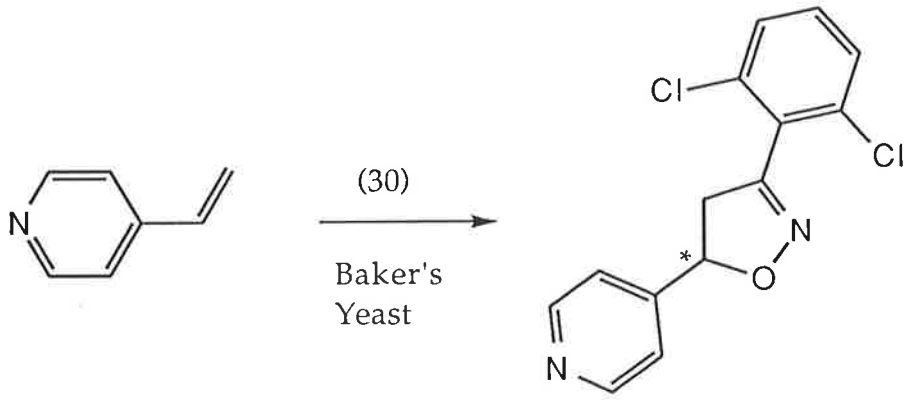


(53) (±)-(56)

Scheme 27

Curiosity about the biocatalytic model for the cycloaddition reaction between the nitrile oxide (**50**) and 4-vinylpyridine (**57**) using baker's yeast and β-cyclodextrin[49,55] ~~leads~~ led to a reexamination of this reaction. The initial experiments reported - in the absence of β-cyclodextrin - that the cycloaddition

of the nitrile oxides (30) and (50) to 4-vinylpyridine (57) (Schemes 28 and 29) gave the isoxazolines (58) and (59) in yields of 82% and 83% and with optical rotations of +66.7° and +5.1°, respectively. Again it seemed unusual that baker's yeast was required for reaction between the reactive, preformed nitrile oxides (30) and (50) and the monosubstituted olefin (57), activated to cycloaddition by virtue of the inductive electronic effect which the pyridine substituent exerts on the carbon-carbon double bond.

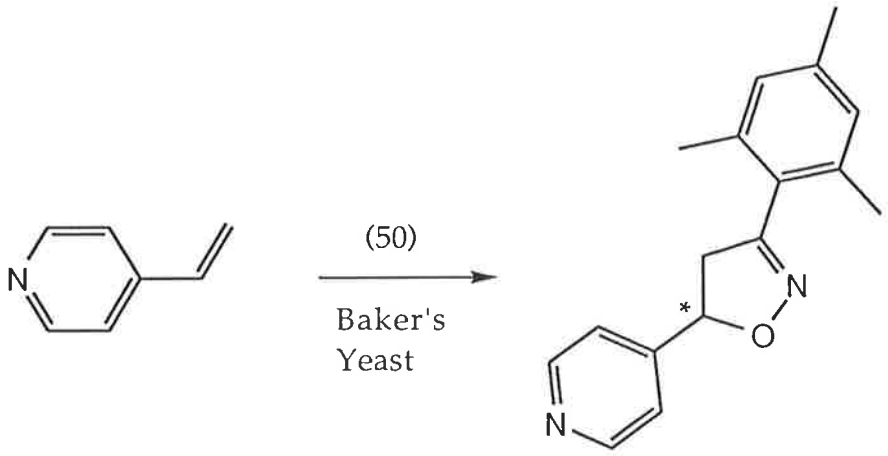


(57) (58)

Scheme 28

The reactions between the nitrile oxides (30) and (50) and 4-vinylpyridine (57) were then repeated in the presence of both baker's yeast and β-cyclodextrin The yields of the products formed were 81% and 85%, with optical rotations of +160.0° and +25.8°, respectively.[49,55]

A reexamination of the work outlined by Rama Rao *et al.* is described in Chapter 3 of the Results and Discussion.



(57) (59)

Scheme 29

CHAPTER 1

Regiocontrolled Synthesis of Ring-Fused Isoxazolines and Isoxazoles

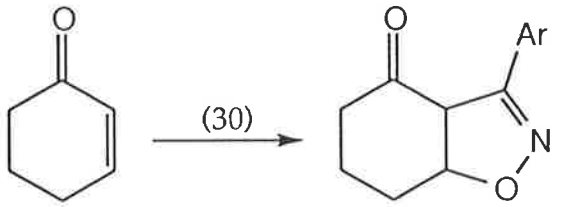
1.1 Cycloaddition of Cycloalkenes to Aryl Nitrile Oxides

In order to examine the route outlined in Scheme 2 as an approach to the synthesis of analogues of GRASP (**1**) and the bleacher herbicides, the cycloaddition reactions of the dipolarophiles (**19**), (**21**) and (**23**) with the aryl nitrile oxide (**30**) were examined. Cyclohex-2-enone (**19**) was available commercially and the two dihydropyranones (**21**) and (**23**) were synthesised as described in the Introduction. 5,6-Dihydro-2*H*-pyran-2-one (**21**) was obtained in a yield of 22%, with the reported[16] yield being 25%. The ^{1}H nmr spectrum, in deuterochloroform, was found to display a multiplet at δ 2.48, a triplet at δ 4.44 and two doublets of triplets at δ 6.03 and δ 6.97. These signals compare favourably with those reported by Nakagawa *et al.*[15] After several unsuccessful attempts to obtain a yield higher than that reported in the literature, it was decided to obtain the material commercially. 2,3-Dihydro-4*H*-pyran-4-one (**23**) was not available commercially, however following the literature procedure as outlined in Scheme 6,[17] a yield of 56%, which is slightly higher than the reported yield of 55%, was obtained for this compound. The ^{1}H nmr spectrum, in deuterochloroform, displayed triplets at δ 2.61 and δ 4.51 and doublets at δ 5.42 and δ 7.36. This pattern corresponds to that reported.[17] 2,6-Dichlorobenzohydroximinoyl chloride (**29**) was synthesised as outlined in the Introduction[22] and was obtained in an 89% yield. The ^{1}H nmr spectrum showed a multiplet at δ 7.37 corresponding to aromatic hydrogens and a singlet at δ 8.31, corresponding to the hydroxyl hydrogen. It was also possible to obtain the corresponding aldoxime (**28**) commercially, thus shortening the synthesis

by one step. The hydroximinoyl chloride (**29**) was then converted *in situ* during the cycloaddition reactions, to the nitrile oxide (**30**), by dehydrohalogenation using triethylamine.

The method for the cycloaddition of the cyclohexenone (**19**) with the nitrile oxide (**30**) involved addition of a solution of the hydroximinoyl chloride (**29**) in tetrahydrofuran to a solution of the dipolarophile (**19**) and triethylamine in tetrahydrofuran. A ^{1}H nmr spectrum of the crude product mixture showed unreacted starting materials, the dimer of the nitrile oxide (**30**) and one other compound. This was the isoxazoline (**60**) which was separated from the crude reaction mixture by chromatography on silica using light petroleum and ethyl acetate, in a ratio of 1:1, as eluant, and recrystallised from light petroleum and ethyl acetate in a yield of 40% and having a melting point of 150-151°C. The ring-fused isoxazoline (**60**) was identified using ^{1}H nmr spectroscopy and showed a multiplet resonance between δ 1.7 and δ 2.7 corresponding to the six methylene protons, a doublet at δ 4.53 corresponding to one of the bridgehead protons, a doublet of triplets at δ 5.26 corresponding to the other bridgehead proton and a multiplet at δ 7.35 attributable to the aromatic protons. The mass spectrum of the product (**60**) showed molecular ions at *m/z* 287, 285 and 283. X-ray crystallography was used to confirm the structure of the isoxazoline (**60**) (Figure 4) (Appendix 2). The cycloaddition had proceeded with the regioselectivity predicted in Scheme 30, that is, as a result of electronic effects exerted on the double bond of the cyclohexenone (**19**) by the carbonyl group.[12,13,23-27,30] The regioisomeric compound (**61**), which was anticipated to have a doublet corresponding to the hydrogen attached to C-1 at a chemical shift further upfield than that observed for the isoxazoline (**60**) due to its environment being that of a carbonyl group and alkoxy group, was not detected in the crude reaction mixture. The attainment of only one regioisomer is probably due to the relative stability of the nitrile oxide (**30**).

Reports in the literature of the cycloaddition of cyclohex-2-enone (**19**) to the more reactive benzonitrile oxide (**47**) have indicated that both the regioisomers (**62**) and (**63**) form, as shown in Scheme 31, although the regioisomer (**62**) was found to be the major product.[9]



(19) (60)

Ar = 2,6-dichlorophenyl

Scheme 30

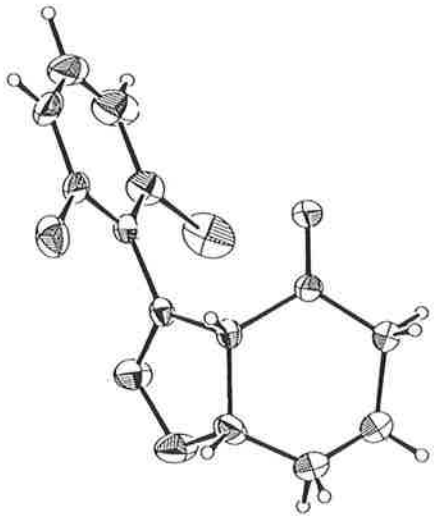
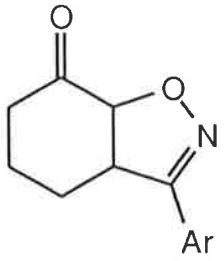
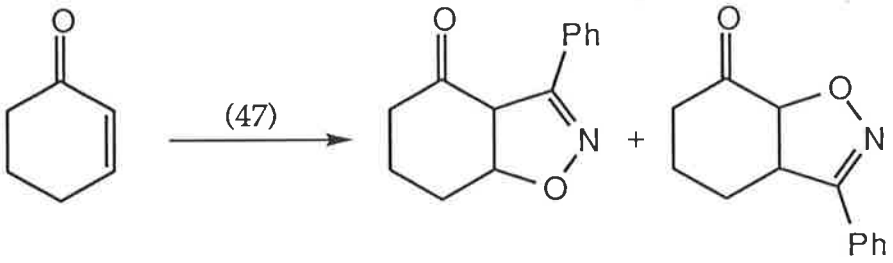


Figure 4: Molecular structure of the isoxazoline (60).



(61)

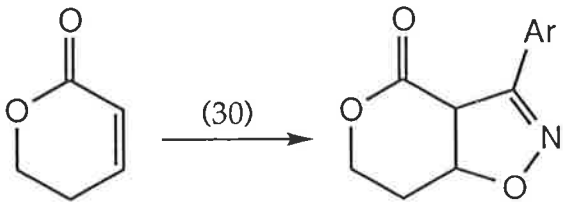


(19) (62) (63)

Scheme 31

The cycloaddition of 5,6-dihydro-2*H*-pyran-2-one (**21**) to the nitrile oxide (**30**) was carried out under the conditions stated for the cycloaddition of the cyclohexenone (**19**) and the nitrile oxide (**30**). Analysis by ^{1}H nmr of the crude product mixture again indicated that only one cycloadduct, the isoxazoline (**64**), had been formed. Isolation of the isoxazoline (**64**) from the crude product mixture by chromatography on silica, using light petroleum and ethyl acetate in a ratio of 2:3 as eluant, was followed by recrystallisation, also using light petroleum and ethyl acetate, to give the isoxazoline (**64**) in a yield of 64% and having a melting point of 159-162°C. The cycloadduct (**64**) was identified by ^{1}H nmr spectroscopy, which showed multiplet signals centred at δ 2.26 and δ 4.46 corresponding to two protons and one proton, respectively, and a doublet of

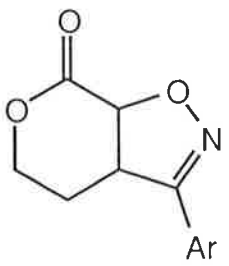
doublet of doublets at δ 4.69 corresponding to one proton. The ~~bridgehead~~ ring-junction protons gave signals of a doublet at δ 4.74 and a multiplet at δ 5.32 and the aromatic protons resonated with a multiplet between δ 7.3 and δ 7.4. The mass spectrum of the isoxazoline (**64**) showed molecular ions at *m/z* 289, 287 and 285. The chemical shift of the proton attached to C-1 of the cycloadduct (**64**) confirmed that the cycloaddition had proceeded with the expected regioselectivity, as indicated in Scheme 32, and again there appeared to be no evidence for the formation of the other regioisomer (**65**) in any of the analyses performed.



(21) (64)

Ar = 2,6-dichlorophenyl

Scheme 32

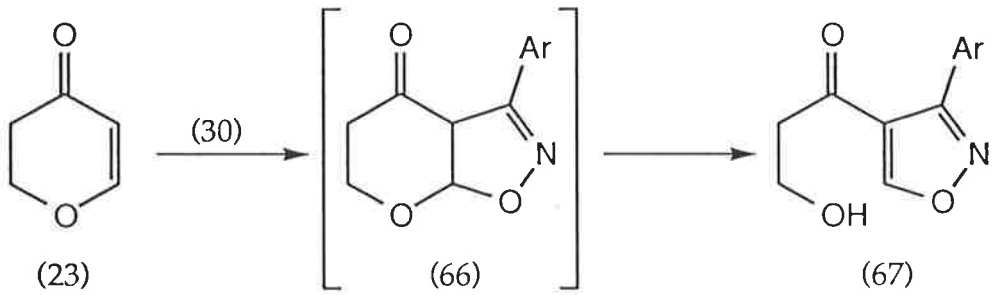


(65)

2,3-Dihydro-4*H*-pyran-4-one (**23**) reacted with 2,6-dichlorobenzonitrile

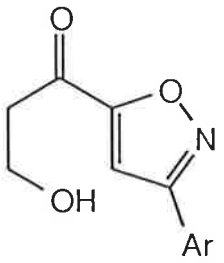
oxide (**30**) under the conditions stated for the cycloaddition of the cyclohexenone (**19**) and the nitrile oxide (**30**). ^{1}H nmr spectral analysis of the crude product mixture showed the presence of one cycloadduct, the isoxazole (**67**). The isoxazole (**67**) was isolated from the crude product mixture by chromatography on silica, using light petroleum and ethyl acetate (2:3) as eluant, and was obtained in a yield of 43% after recrystallisation from light petroleum and ethyl acetate. A melting point of 101-102°C was obtained for the recrystallised product (**67**). The ^{1}H nmr spectrum of the isoxazole (**67**) displayed a broad singlet at δ 1.87 corresponding to a hydroxyl proton, two sets of triplets at δ 2.92 and δ 3.91 each corresponding to two hydrogens, a multiplet at δ 7.38-7.48 due to the resonance of the aromatic protons and a singlet at δ 9.14 corresponding to an isoxazole methine proton. The structure of the product (**67**) was confirmed unambiguously using X-ray crystallographic analysis (Figure 5) (Appendix 3). The regiochemistry of the cycloaddition of the dipolarophile (**23**) to the nitrile oxide (**30**) had been anticipated due to the electronic effects of both the carbonyl group at one terminus of the double bond and the alkoxy substituent at the other terminus (Appendix 1) and there appeared to be no evidence for the formation of the other regioisomer (**68**) in any of the analyses performed. The isoxazoline (**66**) was the predicted product formed from the cycloaddition of the alkene (**23**) and the nitrile oxide (**30**), by analogy with the preceding two cycloaddition; reactions, however there was no trace of the signals expected for this compound in the ^{1}H nmr spectrum of the crude product, that is, two sets of doublets corresponding to protons attached the bridgehead carbons, C-1 and C-6. It is probable that the isoxazoline (**66**) formed during the course of the reaction (Scheme 33) but that the oxygen of the pyranone portion of the molecule had protonated, making it a good leaving group, and subsequently elimination occurred to give the isoxazole (**67**). On referring to the literature it was found that there had been several reports of elimination of alkoxy groups from isoxazolines to form

isoxazoles.[29,30,56,57]



Ar = 2,6-dichlorophenyl

Scheme 33



(68)

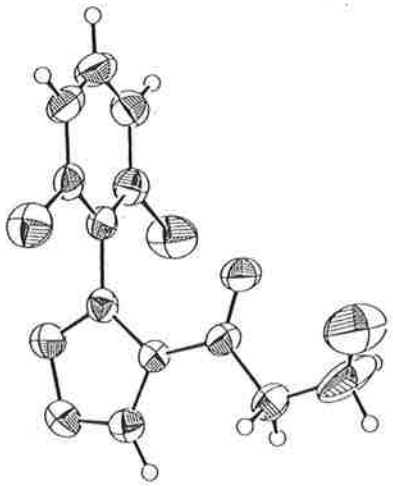


Figure 5: Molecular structure of the isoxazole (67).

The cycloaddition reactions of the dipolarophiles (**19**), (**21**) and (**23**) with the aryl nitrile oxide (**30**) proceeded with the regiochemistry anticipated in Scheme 2.

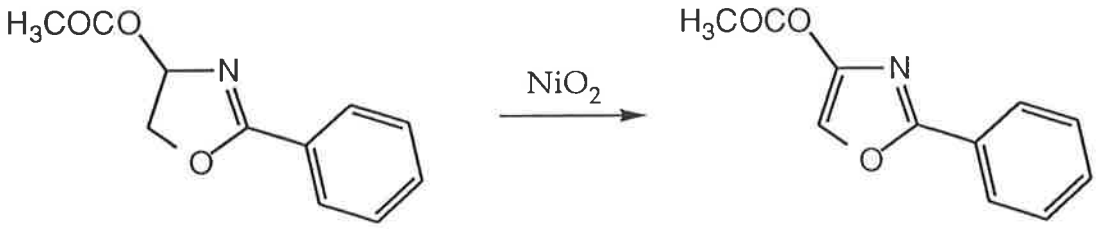
1.2 Dehydrogenation of Isoxazolines in the Formation of Isoxazoles

The next step in the synthetic route, as outlined in Scheme 2, was the dehydrogenation of isoxazolines to isoxazoles. Two of the more common oxidising agents used in the conversion of isoxazolines to isoxazoles are Chloranil®[31,32] and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[33] and initial experimentation explored the utility of these reagents in the conversion of the isoxazolines (**60**) and (**64**) to their corresponding isoxazoles (**70**) and (**71**).

The isoxazolines (**60**) and (**64**) were individually dissolved in *t*-butanol and refluxed with one mole equivalent of Chloranil® for fifteen hours. Analysis of the crude product mixtures by ^{1}H nmr spectroscopy indicated that the starting materials remained unreacted. Treatment of each of the isoxazolines (**60**) and (**64**) with two molar equivalents of DDQ, in refluxing benzene, for six hours, also yielded only starting materials on ^{1}H nmr spectral analysis of the crude product mixtures.

Due to the lack of success with the four reactions described above, it was anticipated that nickel peroxide could be used to execute the conversion of isoxazolines to isoxazoles. Previously, nickel peroxide had been reported to successfully oxidise the oxazoline (**69**) (Scheme 34).[58] Nickel peroxide (NiO_2) is generally considered to be a mild and effective oxidising agent and its synthesis is simple. The synthetic procedure for activated NiO_2 consists of combining hydrated nickel sulphate with a sodium hypochlorite and sodium hydroxide solution, which results in the formation of a black precipitate that can be

subsequently filtered and dried (Scheme 35).[59] NiO_2 was obtained in a yield of 96%.



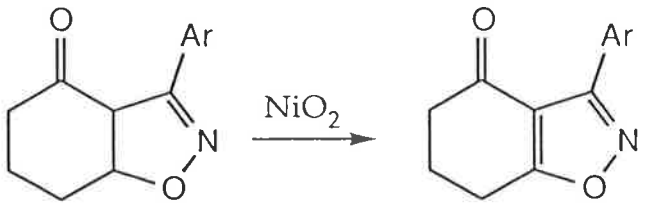
(69)

Scheme 34

$$NiSO_4.6H_2O_{(aq)} \xrightarrow[NaOH]{6\%NaClO} NiO_2\downarrow$$

Scheme 35

The isoxazoline (**60**) was refluxed in benzene with an excess of NiO_2 for two hours after which time the black suspension was removed by filtering through kenite and the solvent removed from the filtrate to yield a white crystalline solid. The product (**70**) was recrystallised from light petroleum and ethyl acetate in a yield of 65% and having a melting point of 205-207°C. The ^1H nmr spectrum of the isoxazole (**70**) displayed a pentet at δ 2.29 corresponding to two protons, triplets at δ 2.54 and δ 3.12 each corresponding to two protons and a multiplet at δ 7.40 due to aromatic protons. The mass spectrum showed molecular ion signals at *m/z* 285, 283, and 281 and X-ray crystallographic analysis was also used to confirm the structure of the isoxazole (**70**) (Figure 6) (Appendix 4).



(60) (70)

Ar = 2,6-dichlorophenyl

Scheme 36

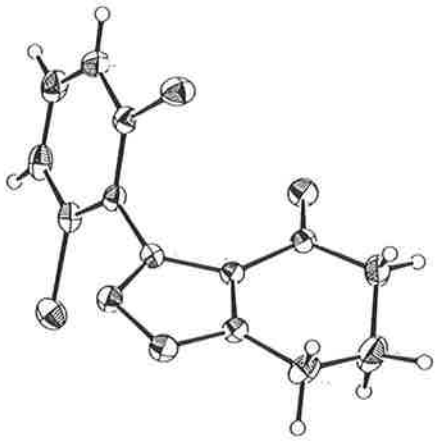
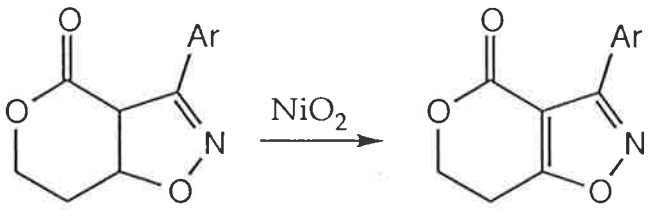


Figure 6: Molecular structure of the isoxazole (**70**).

The isoxazoline (**64**) was treated with NiO_2 under the conditions specified for the oxidation of the isoxazoline (**60**) with NiO_2. The reaction gave the one product (**71**) which was obtained in a yield of 69%, recrystallised from light petroleum/ethyl acetate, and had a melting point of 175-177°C (Scheme 37). The isoxazole (**71**) was identified using ^1H nmr spectroscopy which showed triplets at δ 3.34 and δ 4.69 each corresponding to two protons and a multiplet at δ 7.40-7.50 due to aromatic protons. The mass spectrum showed

molecular ions at *m/z* 287, 285 and 283 and the structure of the isoxazole (**71**) was confirmed by X-ray crystallographic analysis (Figure 7) (Appendix 5).



(64) (71)

Ar = 2,6-dichlorophenyl

Scheme 37

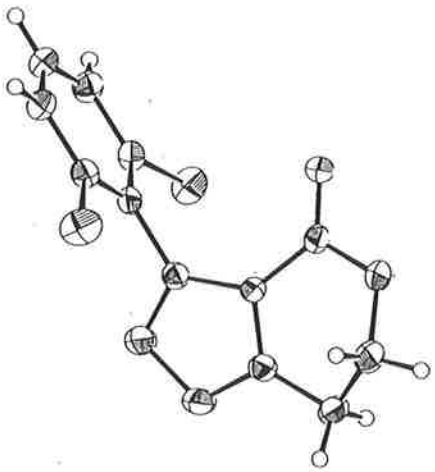


Figure 7: Molecular structure of the isoxazole (71).

The results of the transformations of the isoxazolines (**60**) and (**64**) to the isoxazoles (**70**) and (**71**) using NiO_2 compare favourably with results described below, obtained using γ-activated manganese dioxide (γ-MnO_2) to perform the same transformation. Like NiO_2, γ-MnO_2 is also considered to be a mild

oxidising agent. The synthesis of this reagent was straightforward, as described in the Introduction, and γ-MnO_2 was obtained in a quantitative yield, as a precipitate from the reaction of aqueous solutions of manganese sulphate and potassium permanganate.

The isoxazolines (**60**) and (**64**) were each refluxed for fifteen hours in benzene with an excess of γ-MnO_2. The reaction vessels were fitted with Dean-Stark apparatus, to remove water formed during the reactions, after which the reactions were worked up as described in the transformations using NiO_2. The products obtained from the reactions using γ-MnO_2 were identified as the isoxazoles (**70**) and (**71**) by comparison with the ^1H nmr spectra of the products obtained in the experiments outlined in Schemes 36 and 37, and were obtained in yields of 69% and 64%, respectively.

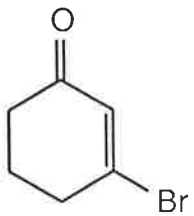
Both NiO_2 and γ-MnO_2 were simple to synthesise and there appeared to be no significant differences in the yields of the isoxazoles (**70**) and (**71**) obtained from the treatment of the corresponding isoxazolines (**60**) and (**64**) with either reagent. The NiO_2 reactions were relatively quick, that is, two hours, and only standard reflux equipment was required, whereas the γ-MnO_2 reactions required refluxing for fifteen hours with Dean-Stark apparatus (the workup procedures for both methods were the same). Thus, overall, when considering ease of synthesis, reaction time, equipment used and yields of products obtained, nickel peroxide was found to be more efficient in the conversion of the isoxazolines (**60**) and (**64**) to their corresponding isoxazoles (**70**) and (**71**).

1.3 One-pot Synthesis of Isoxazoles *via* 1,3-Dipolar Cycloaddition

As a consequence of the formation of the isoxazole (**67**) from the

reaction of 2,3-dihydro-*4H*-pyran-4-one (**23**) and 2,6-dichlorobenzonitrile oxide (**30**), it was envisaged that it could be possible to synthesis the isoxazoles (**70**) and (**71**) in one-pot reactions, as outlined in Scheme 16, using the dipolarophiles (**19**) and (**21**) with leaving groups substituted onto their carbon-carbon double bonds.

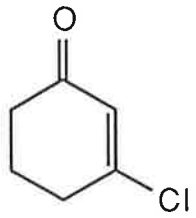
As indicated in Scheme 17, placement of a halide on the terminus of the double bond β to the carbonyl group of cyclohex-2-enone (**19**) can be achieved by two methods. The first procedure[39] involved the treatment of 1,3-cyclohexanedione (**36**) with a phosphorus trihalide at reflux for two hours followed by a standard workup. It was decided that phosphorus tribromide would be used in the reaction, with 3-bromocyclohex-2-enone (**37a**) being the product formed. The yield obtained was 65% (no yield was given in the literature for this procedure) and the ^{1}H nmr spectrum showed multiplet signals at δ 2.08, δ 2.41 and δ 2.82 each corresponding to two hydrogens and a singlet at δ 6.48 due to the hydrogen attached to C-2. Infrared analysis indicated an absorption at a frequency of 1678 cm^{-1} due to the presence of a carbonyl group.



(37a)

The alternative procedure[40] for the synthesis of the halosubstituted

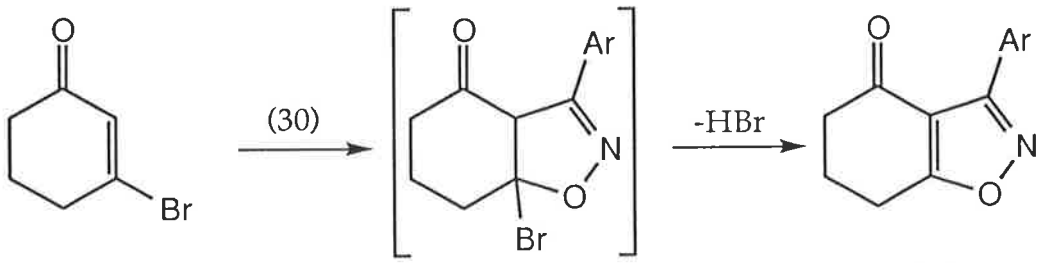
cyclohexenones (**37a**) and (**37b**) involved stirring 1,3-cyclohexanedione (**36**) in *N,N*-dimethylformamide and dichloromethane with oxalyl halides, either chloride or bromide, at 0°C. The resulting mixture was allowed to warm to room temperature over thirty minutes and then workup was conducted in the standard manner. Due to availability, the reaction was performed using oxalyl chloride and the product (**37b**) was obtained in an 85% yield, with the literature[40] yield being 93%. 3-Chlorocyclohex-2-enone (**37b**) was identified by ^{1}H nmr spectroscopy, showing multiplets at δ 2.07, δ 2.41 and δ 2.69 and a singlet at δ 6.22. Infrared analysis confirmed the presence of a carbonyl group with an absorption observed at 1680 cm^{-1}.



(37b)

The cycloaddition of 3-bromocyclohex-2-enone (**37a**) with the nitrile oxide (**30**) was perfomed under the conditions outlined for the cycloaddition of the cyclohexenone (**19**) to 2,6-dichlorobenzonitrile oxide (**30**) (see Chapter 1, **1.1**). Analysis of the crude product mixture indicated the presence of the isoxazole (**70**), unreacted starting materials and the dimer of the nitrile oxide (**30**). The product (**70**) was recrystallised directly from the crude product mixture using light petroleum and ethyl acetate and was obtained in a yield of 13%. The reaction was repeated with a reflux time of fifteen hours, instead of three hours, and the isoxazole (**70**) was obtained in a 51% yield. Formation of

the isoxazole (**70**) from this cycloaddition reaction indicated that the bromide substituent on the dipolarophile (**37a**) is a good leaving group with hydrogen bromide being spontaneously eliminated from the intermediary isoxazoline (**72**), as illustrated in Scheme 38. As discussed in the Introduction, 1,3-dipolar cycloaddition reactions are sensitive to steric effects, with all reports of cycloadditions of nitrile oxides to trisubstituted dipolarophiles occurring in such a manner that the oxygen of the nitrile oxide becomes attached to the more hindered end of the double bond. It was, therefore, not surprising that the cycloaddition of 3-bromocyclohex-2-enone (**37a**) with the nitrile oxide (**30**) yielded the isoxazole (**70**), with none of the regioisomeric isoxazole (**73**) being detected.



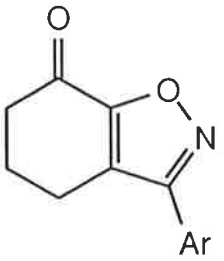
(37a) (72) (70)

Ar = 2,6-dichlorophenyl

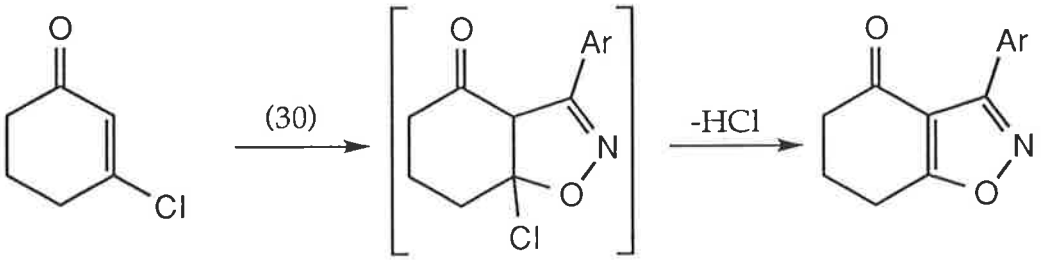
Scheme 38

Concurrently, the cycloaddition of 3-chlorocyclohex-2-enone (**37b**) with the nitrile oxide (**30**) was performed under the conditions outlined in Section 1.1 of this Chapter for the cycloaddition of the cyclohexenone (**19**) and the nitrile oxide (**30**). The isoxazole (**70**), identified by ^{1}H nmr spectroscopy, was obtained in a yield of 13%. No attempts were made to alter the reaction conditions to obtain a higher yield. Formation of the isoxazole (**70**) indicates

that a chloride substituent is also a good leaving group and that spontaneous dehydrochlorination of the isoxazoline (74) had occurred (Scheme 39).



(73)



(37b) (74) (70)

Ar = 2,6-dichlorophenyl

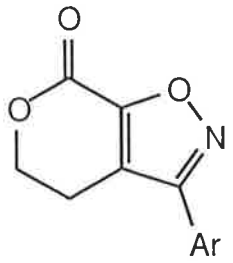
Scheme 39

The synthesis of the halosubstituted lactone (75) was also considered but it was reported[60,61] to be multi-stepped. In the light of these two factors the synthesis of the bromolactone (75) was not attempted and the most efficient synthesis of the isoxazole (71) would appear to be *via* the dehydrogenation of the corresponding isoxazoline (64) as discussed earlier (Chapter 1, **1.2**).

(75)

The cycloadditions of the dipolarophiles (**19**) and (**21**) were highly regioselective with the isoxazolines (**60**) and (**64**) being the only products obtained from the reactions; that is, there was no formation of the regioisomers (**61**) and (**65**). Therefore, as the isoxazolines (**61**) and (**65**) were not available by cycloaddition, an alternative method to dehydrogenation was required to synthesise the isoxazoles (**73**) and (**76**). It was anticipated that cyclohexenones could be constructed with halides α to the carbonyl group and thus the isoxazoles (**73**) and (**76**) could be obtained in reactions analogous to those shown in Schemes 38 and 39.

The method of synthesis of 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**), as outlined in the Introduction, was modified during the course of experimentation with the discovery that triethylamine gave a cleaner product than diisopropylethylamine and with a comparable yield. Using this modification of Posner's method,[41,62] 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**) was obtained in a crystalline form (previously it had been reported to be a liquid), in a 75% yield and having a melting point of 32-34°C. ^{1}H nmr spectrosopy was used to identify the product (**38**), with a doublet of triplets at δ 2.57 due to two hydrogens, a triplet at δ 4.49 corresponding to two hydrogens and a triplet at δ 7.27 due to one hydrogen. Mass spectrometry showed signals for the molecular ions at *m*/*z* 178 and 176.



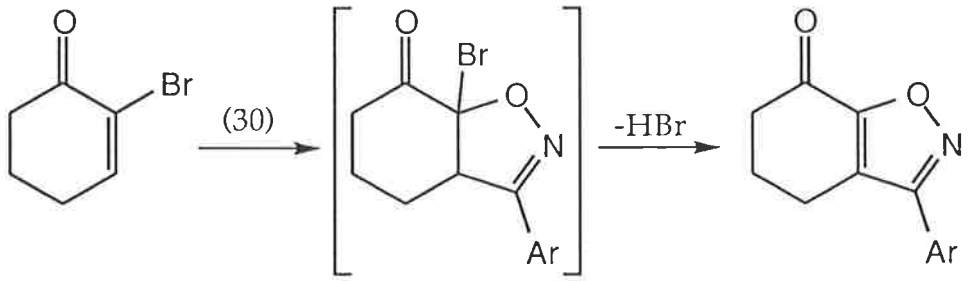
(76)

The modified procedure for the synthesis of 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**) was successfully used to brominate cyclohex-2-enone (**19**) and 2,3-dihydro-4*H*-pyran-4-one (**23**). 2-Bromocyclohex-2-enone (**39**) was obtained in a yield of 60% and had a melting point of 72-75°C. The ^{1}H nmr spectrum of 2-bromocyclohex-2-enone (**39**) displayed multiplets at δ 2.08, δ 2.45 and δ 2.64 each due to two protons and a triplet at δ 7.44 due to one proton and the mass spectrum showed molecular ions at *m/z* 176 and 174. 3-Bromo-5,6-dihydro-4*H*-pyran-4-one (**40**) was obtained in a 64% yield, having a melting point of 92-96°C, and was identified by ^{1}H nmr spectroscopy, which showed a doublet of doublets at δ 2.83 due to two protons, a triplet at δ 4.59 corresponding to two protons and a singlet at δ 7.71 due to the methine proton.

The procedure for the cycloaddition of the dipolarophile (**39**) to the nitrile oxide (**30**), a modification of the method used for the cycloadditions in Section 1.1 of this Chapter, involved addition of a solution of the hydroximinoyl chloride (**29**) in tetrahydrofuran to a solution of the dipolarophile (**39**) and triethylamine in tetrahydrofuran. A ^{1}H nmr spectrum was taken of the crude product mixture and, apart from unreacted starting materials and the dimer of the nitrile oxide (**30**), only one other compound (**73**) was detected. The crude product mixture was recrystallised from light

petroleum and ethyl acetate to give the product (**73**) in a yield of 53% and having a melting point of 108.5-110.5°C. The ring-fused isoxazole (**73**) was identified using ^{1}H nmr spectroscopy which showed a pentet resonance at δ 2.24 due to two protons, a triplet at δ 2.63 due to two protons, a triplet at δ 2.73 attributable to a further two protons and a multiplet signal at δ 7.84 due to aromatic protons. The mass spectrum of the product (**73**) showed molecular ions at *m/z* 285, 283 and 281 and X-ray crystallographic analysis was used to confirm the structure of the isoxazole (**73**) (Figure 8) (Appendix 6).

Formation of the isoxazole (**73**) from cycloaddition of 2-bromocyclohex-2-enone (**39**) and the aryl nitrile oxide (**30**) indicated that the bromo-isoxazoline (**77**) had formed as an intermediary, in an analogous reaction to those outlined in Schemes 38 and 39, which had spontaneously eliminated hydrogen bromide to give the isoxazole (**72**) (Scheme 40). The regiochemistry of the cycloaddition of 2-bromocyclohex-2-enone (**39**) and the aryl nitrile oxide (**30**) results from steric constraints imposed on the reaction by the substitution pattern around the double bond of the dipolarophile (**39**), as discussed previously.



(39) (77) (73)

Ar = 2,6-dichlorophenyl

Scheme 40

The cycloaddition of 3-bromo-5,6-dihydro-2*H*-pyran-2-one (38) to 2,6-dichlorobenzonitrile oxide (30) was conducted under the conditions described for the cycloaddition of the dipolarophile (19) to the nitrile oxide (30). Analysis of the crude product by ^{1}H nmr spectroscopy indicated the presence of the one isoxazole product (76). The isoxazole (76) was isolated from the crude product mixture by chromatography on silica, using light petroleum and ethyl acetate (3:2) as eluant, and further purified by recrystallisation to be obtained in a yield of 50%. The melting point of the isoxazole (76) was found to be 106-107°C and the ^{1}H nmr spectrum displayed triplet signals at δ 2.89 and δ 4.68 each corresponding to two protons and a multiplet at δ 7.42-7.51 due to aromatic hydrogens. Molecular ion peaks at *m/z* 285, 283 and 281 were obtained by mass spectrometry and X-ray crystallographic analysis was used to unambigously confirm the structure of the product (76) (Figure 9) (Appendix 7). Again, by analogy to the reactions outline in Schemes 38 and 39, it may be postulated that the isoxazole (76) formed by spontaneous elimination of hydrogen bromide, form the isoxazoline (78) (Scheme 41).

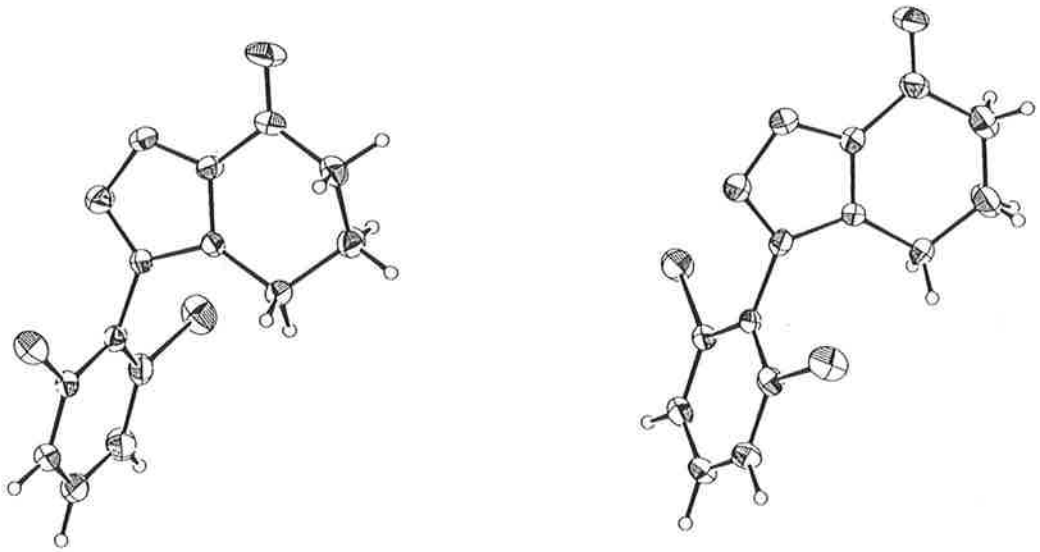
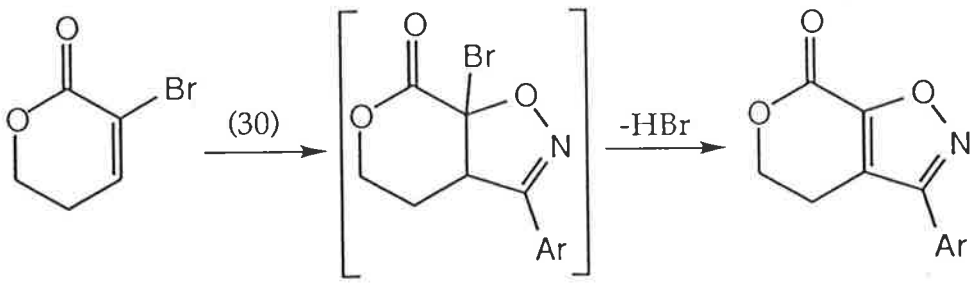


Figure 8: The two crystal structure conformations of the isoxazole (73).



(38) (78) (76)

Ar = 2,6-dichlorophenyl

Scheme 41

The cycloaddition of 3-bromo-5,6-dihydro-*4H*-pyran-4-one (**40**) to 2,6-dichlorobenzonitrile oxide (**30**) did not proceed, with only starting materials (**30**) and (**38**) and the dimer of the nitrile oxide (**30**) detectable in the ^{1}H nmr spectrum taken of the crude reaction mixture. The bromocycloalkenone (**40**) is possibly inert to cycloaddition reactions due to stabilisation by extended conjugation, as illustrated in Figure 10.

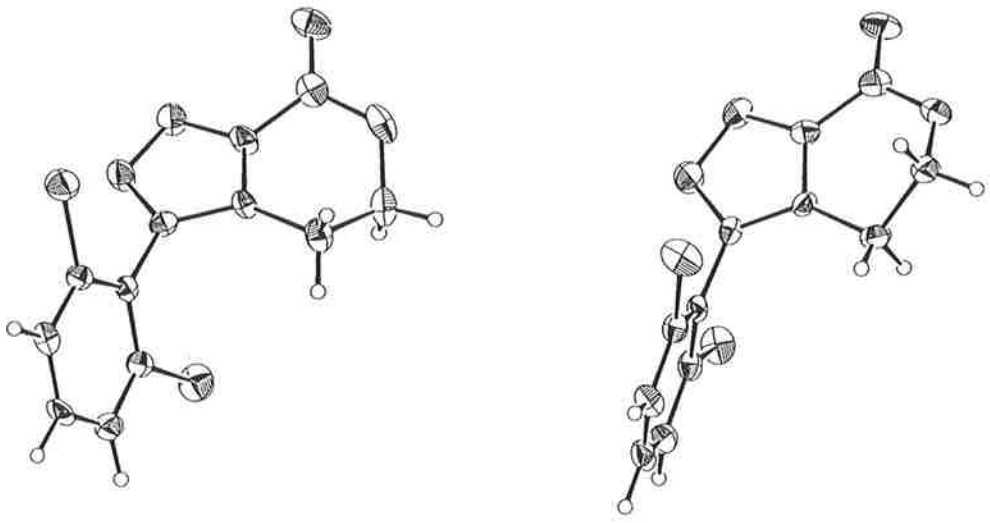
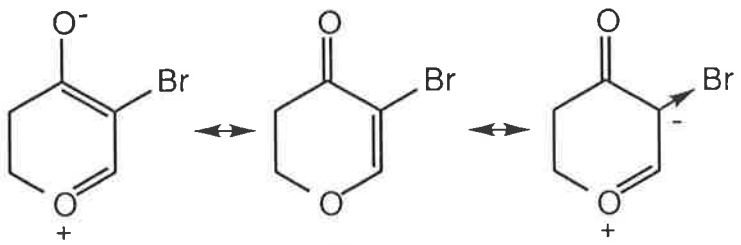


Figure 9: The two crystal structure conformations of the isoxazole (**76**).



(40)

Figure 10: Resonance contributors of 3-bromo-5,6-dihydro-4*H*-pyran-4-one (40).

The cycloaddition reactions described in this section have demonstrated that it is possible to obtain isoxazoles ina one-pot reaction from halo-substituted alkenes. The cycloadditions of the dipolarophiles (38) and (39) to the aryl nitrile oxide (30) neatly demonstrated the predomination of steric factors over electronic effects, that is, electronic effects exerted on the double bond by the carbonyl group were in direct opposition to the steric considerations due to the bromide substituent; however, only that regioisomer predicted on the basis of steric effects was formed.

1.3 Rate Studies on the Cycloaddition Reactions.

As discussed in the Introduction, the reactivity of a dipolarophile decreases as the substitution around the double bond is increased. It was envisioned that future work in nitrile oxide cycloaddition reactions could involve the use of more reactive alkyl nitrile oxides where any decrease in reactivity of the olefin would favour formation of the nitrile oxide dimer in preference to the required cycloadduct. Thus, experimentation was

undertaken to determine the relative reactivities of the dipolarophiles (**19**), (**21**), (**23**), (**37a**), (**38**), (**39**) and (**40**).

Reactions to determine the relative reactivity of the dipolarophiles (**19**), (**21**), (**23**), (**37a**), (**38**), (**39**) and (**40**) were conducted by reacting equimolar amounts of two dipolarophiles at a time with one mole equivalent of the nitrile oxide (**30**) under the conditions outlined for the cycloaddition of cyclohex-2-enone (**19**) to the nitrile oxide (**30**), in Section 1.1 of this Chapter. The crude product mixtures were analysed by ^{1}H nmr spectroscopy and the relative reactivities of the olefins were determined by comparing the quantity of each cycloadduct formed.

The first competitive experiment was performed between the cyclohexenone (**19**) and 5,6-dihydro-2*H*-pyran-2-one (**21**). The cycloadducts (**60**) and (**64**) were formed in a ratio of 43:57. As expected, the dihydropyranone (**21**) is slightly more reactive than the cyclohexenone (**19**), due to ester groups being marginally more electron withdrawing than carbonyl groups.

The competitive experiment between cyclohex-2-enone (**19**) and 2,3-dihydro-4*H*-pyran-4-one (**23**) showed that the former was the more reactive, with the cycloadducts (**60**) and (**67**) being formed in a ratio of 60:40. Extended conjugation through the ring oxygen, the double bond and the carbonyl group (Figure 11), in analogy with the brominated analogue (**40**), causes a retarding effect on the reactivity of 2,3-dihydro-4*H*-pyran-4-one (**23**).

Significantly more of the cycloadduct (**60**) than the cycloadduct (**73**) was observed on analysis of the competitive experiment between the cyclohexenone (**19**) and 2-bromocyclohex-2-enone (**39**), with the ratio of the cycloadducts being 83:17. This is consistent with other studies in the literature which have shown that trisubstituted olefins are less reactive than disubstituted olefins (Appendix 1).

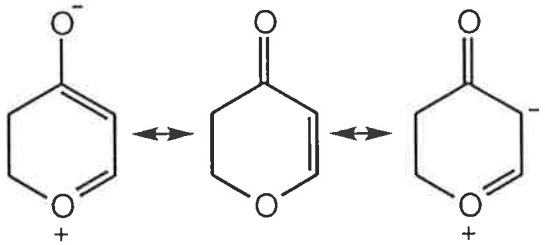


Figure 11: Resonance structures of 2,3-dihydro-*4H*-pyran-4-one (**23**).

The competitive experiment between 3-bromocyclohex-2-enone (**37a**) and 2-bromocyclohex-2-enone (**39**) demonstrated that 2-bromocyclohex-2-enone (**39**) is more reactive by approximately two-fold, with the cycloadducts (**70**) and (**73**) forming in a ratio of 34:66.

The competitive experiment between 5,6-dihydro-2*H*-pyran-2-one (**21**) and 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**) gave the cycloadducts (**64**) and (**76**) in a ratio of 83:17. This result is consistent with the analogous competitive experiment between cyclohex-2-enone (**19**) and 2-bromocyclohex-2-enone (**39**), which showed that species containing a trisubstituted double bond are significantly less reactive than those containing a disubstituted double bond.

Combining the results of the competitive experiments, and on the basis that the compound (**40**) is inert under these reaction conditions, it is possible to rank the relative reactivity of the olefins (**19**), (**21**), (**23**), (**37a**), (**38**), (**39**) and (**40**) towards cycloaddition with the aryl nitrile oxide (**30**), as shown in Table 1.

In conclusion, it would appear that nitrile oxide dimer formation could be a competing reaction to isoxazole formation if nitrile oxides more reactive than 2,6-dichlorobenzonitrile oxide (**30**) were used in the one-pot synthesis of isoxazoles.

Olefin	Cycloadduct	Relative Rate of Formation
(21)	(64)	12.3
(19)	(60)	9.3
(23)	(67)	6.2
(38)	(76)	2.5
(39)	(73)	1.9
(37a)	(70)	1.0
(40)	-	0

Table 1: Relative reactivities of dipolarophiles (19), (21), (23), (37a), (38), (39) and (40) towards cycloaddition with 2,6-dichlorobenzonitrile oxide (30).

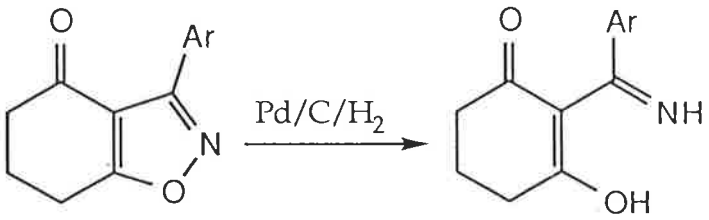
CHAPTER 2

Catalytic Ring-Opening of Isoxazoles

2.1 Hydrogenolytic Ring Cleavage of Isoxazoles

The ring opening of isoxazoles to form the corresponding β-enamino ketones was the final step in the synthesis of GRASP (**1**) analogues, as outlined in Scheme 2 in the Introduction. The cycloadduct (**70**) was treated with a catalytic amount of 5% palladium on carbon, in ethyl acetate, under hydrogen and left to stir overnight (Scheme 42). After filtering off the catalyst and removing the solvent under reduced pressure, the product (**79**) was recrystallised from light petroleum and ethyl acetate in a 98% yield and was found to decompose on heating to 229-232°C. The imine (**79**) was identified by ^{1}H nmr spectroscopy, with a singlet resonance at δ 1.92 due to the hydroxyl proton, a pentet at δ 1.97 corresponding to two protons, triplets at δ 2.43 and δ 2.64 each corresponding to two protons, a broad singlet at δ 6.06 due to the imine proton and a multiplet at δ 7.26-7.43 due to aromatic hydrogens. The mass spectrum displayed molecular ion signals at *m/z* 387, 385 and 383. X-ray crystallographic analysis of the product obtained from this experiment did not show the expected imine (**79**), but did show the tautomeric enamine (**80**) (Figure 13) (Appendix 8). Analysis of the crystal lattice indicated that the crystal asymmetric unit comprised of two molecules which have minor conformational differences. The analysis also showed that the enamine hydrogens were involved in both intermolecular and intramolecular hydrogen bonding, as shown in Figure 14. One of the conformational forms of the enamine (**80**) displayed intermolecular hydrogen bonding through a distance of 1.84 Å and intramolecular hydrogen bonding through a distance of

1.83 Å. The other conformer of the enamine (80) displayed intermolecular hydrogen bonding through a distance of 1.79 Å and intramolecular bonding through a distance of 1.84 Å. Thus the enamine (80) is a more stable tautomer in the crystalline state due to stabilisation by both the intermolecular and intramolecular hydrogen bonding. However, in a nonpolar solvent where intermolecular hydrogen bonding is negligible, that is, under conditions for ^1H nmr spectroscopy, the imine (79) tautomer is more stable due to intramolecular hydrogen bonding.



(70) (79)

Ar = 2,6-dichlorophenyl

Scheme 42

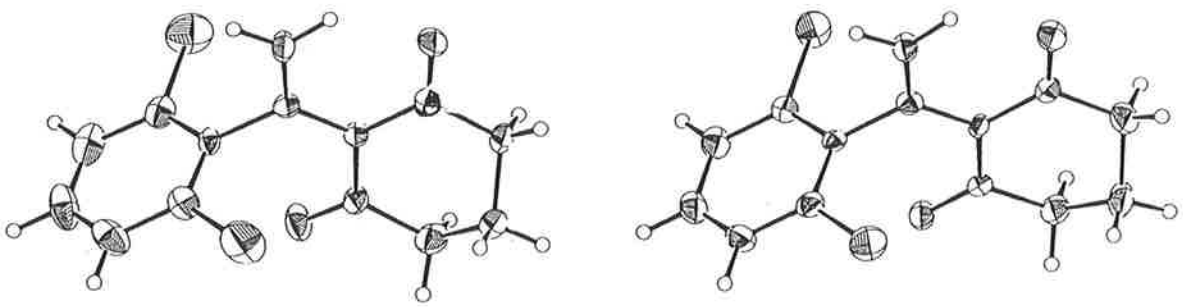
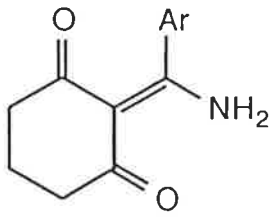


Figure 13: Molecular conformers of the enamine (80).



(80)

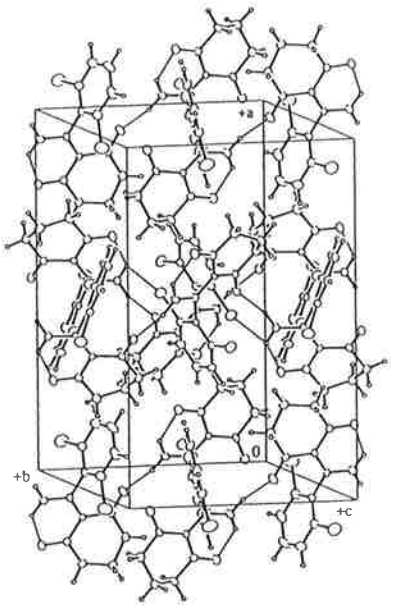
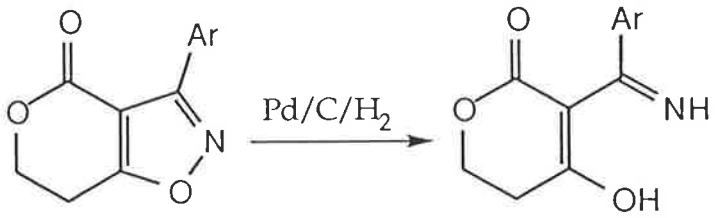


Figure 14: Intermolecular and intramolecular hydrogen bonding in the crystal lattice of the enamine (**80**).

Following the success of the ring-opening of the bicyclic isoxazole (**70**), the ring-fused isoxazole (**71**) was treated with 5% palladium on carbon, under an atmosphere of hydrogen, as described in the preceding experiment, and the ring-opened product (**81**) was obtained in a 97% yield (Scheme 43). The product (**81**) was found to decompose when heated to a temperature of 216-218°C and was identified by ^{1}H nmr spectroscopy, which displayed a singlet at δ 1.60 due to the hydroxyl hydrogen, triplets at δ 2.73 and δ 4.35 each due to two

hydrogens, a broad singlet at δ 6.34 attributed to the imine hydrogen and a multiplet at δ 7.25-7.39 due to aromatic hydrogens. The mass spectrum exhibited molecular ions at *m/z* 289, 287 and 285. In analogy with X-ray crystallographic analysis of the enamine (**80**), the X-ray crystallographic analysis of the product (**81**) indicated that the tautomeric enamine (**82**) was the energetically preferred structure in the crystalline state (Figure 15) due to both intermolecular and intramolecular hydrogen bonding (Appendix 9).



(71) (81)

Ar = 2,6-dichlorophenyl

Scheme 43

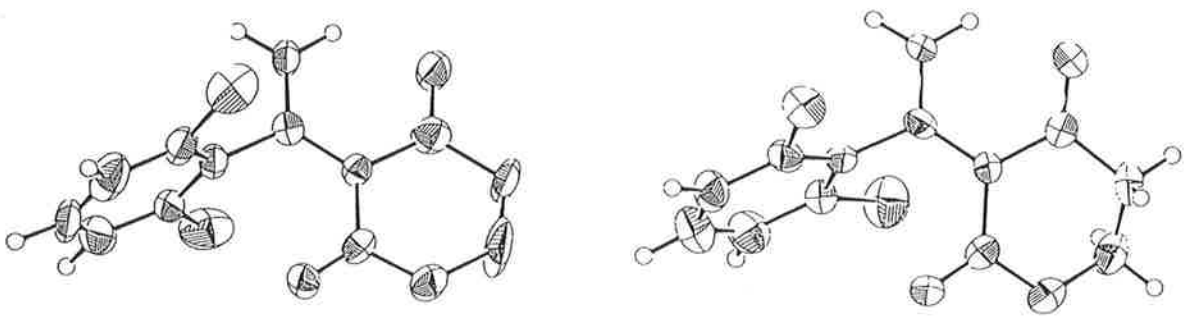
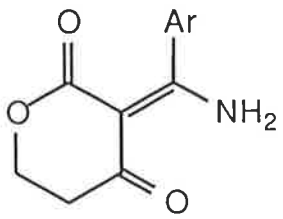


Figure 15: Molecular conformers of the enamine (**82**).

The ring-opening of the isoxazoles (**70**) and (**71**) was the final step in the

synthesis of GRASP (**1**) analogues. The synthesis of the GRASP (**1**) analogues, as outlined in Scheme 2, has been demonstrated to be a feasible alternative to the established industrial synthesis.



(82)

2.2 Ring-opening of Isoxazoles Using Baker's Yeast

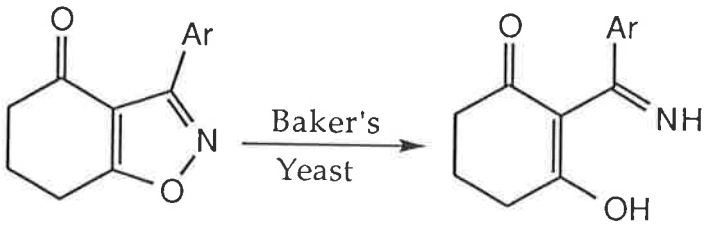
The unexpected ring-opening of the isoxazole (**43**) to form the imine (**44**), as outlined in Scheme 20 in the Introduction, was of interest as a potentially alternate method of ring-opening of the isoxazoles (**70**) and (**71**). In order to examine the generality of the ring-opening of isoxazoles by yeast, the reactions of a series of isoxazoles were investigated.

The yeasts used in all the following reactions were obtained in their dried forms and required rehydration prior to use. A typical procedure for the rehydration of a yeast involved the addition of the yeast, from a freshly opened source, to a solution of sucrose in tap water with gentle stirring. The resulting mixture was then stirred at 37°C for one hour, after which time the yeast was actively fermenting.

A reexamination of the reaction of the isoxazole (**43**) with baker's yeast was conducted to confirm the reductive cleavage of the N-O bond. The isoxazole (**43**) was added to fermenting baker's yeast (sp. *Saccharomyces*

cerevisiae), with the dry weight of the baker's yeast and the weight of the isoxazole (**43**) being in a ratio of 20:1. After twenty-four hours the baker's yeast had ceased fermenting and the mixture was filtered. The filter-cake was washed with ethyl acetate to lyse the yeast cells and dissolve any residual organic substances. The aqueous filtrate was also extracted several times with ethyl acetate. The organic solutions were combined, the solvent was removed and the components in the resulting solid were separated by chromatography on silica, with light petroleum and ethyl acetate (1:1) as eluant. ^{1}H nmr spectral analysis of the compounds isolated by chromatography showed the presence of the imine (**44**), the unreacted isoxazole (**43**) and compounds that were related to the baker's yeast, presumably released during the lysing process. The imine (**44**) was obtained in a yield of 18%; however as the isoxazole (**43**) had not been fully digested and was recovered in a yield of 73%, the corrected yield of the imine (~~78~~ 44) was calculated to be 68%. The spectral properties of the imine (**44**) were found to be identical to those previously observed.[44]

The isoxazole (**70**) was treated with fermenting baker's yeast under the same conditions used for the reaction of the isoxazole (**43**). On completion of the reaction, the components in the resulting crude mixture were separated by chromatography on silica, with light petroleum and ethyl acetate as eluant (5:3). ^{1}H nmr spectral analysis of the individual components identified the imine (**79**), the unreacted isoxazole (**70**) and compounds related to the baker's yeast. The imine (**79**) was obtained in a yield of 23% after recrystallisation from light petroleum and ethyl acetate, however the corrected yield, based on the recovered isoxazole (**70**), was 70% (Scheme 44).



(70) (79)

Ar = 2,6-dichlorophenyl

Scheme 44

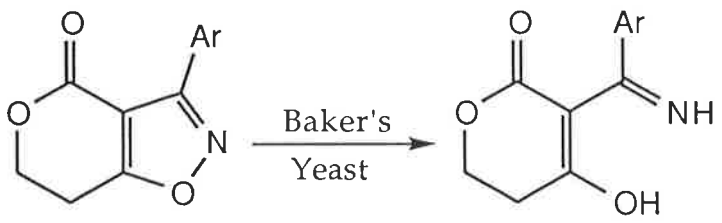
Due to the quantity of the isoxazole (**70**) recovered unchanged from the experiment above, it was postulated that the 1:20 ratio of the isoxazole (**70**) to the baker's yeast in the reaction mixture had been too high. It was anticipated that lowering the quantity of the isoxazole (**70**) added to the fermenting yeast by half, but under otherwise identical conditions, a higher percentage of the isoxazole (**70**) would be converted to the imine (**79**). Performing the reaction with the modification indicated, only 38% of the unreacted isoxazole (**70**) was recovered. The imine (**79**) was also isolated in a significantly lower yield, that is 7%, or 11% based on the recovered isoxazole (**70**). This result indicates that the imine (**79**) is digested by the baker's yeast after it forms although products from the digestion of the imine (**79**) were not detected.

As a result of the lower yield of the imine (**79**) obtained from decreasing the ratio of the isoxazole (**70**) to baker's yeast, it was speculated that the yield of the imine (**79**) may be increased by increasing the ratio of the isoxazole (**70**) to baker's yeast to 1:13. Using this modification in the treatment of the isoxazole (**70**), the imine (**79**) was isolated in a yield of 21%, with a corrected yield of 32% based on the recovery of the isoxazole (**70**). Thus the yield of the imine (**79**) was not increased.

Treating the isoxazole (**70**) with baker's yeast and shortening the reaction time to four hours - but otherwise maintaining the conditions outlined in the first experiment for the reaction of the isoxazole (**70**) with baker's yeast - gave the imine (**79**) in a yield of 19%, or 32% based on the recovery of the isoxazole (**70**). On examination of the preceeding three experiments, in which the ratio of the isoxazole (**70**) to baker's yeast and the reaction time were altered, it was established that the optimal conditions for the treatment of the isoxazole (**70**) with baker's yeast to obtain the imine (**79**), were to have the ratio of 1:20 for the isoxazole (**70**) to baker's yeast and a reaction time of twenty-four hours.

The reactions of other strains of yeast with the isoxazole (**70**) were also examined in attempts to improve the yield of the imine (**79**). The isoxazole (**70**) was treated with Munich Lager Active Dried yeast, a bottom fermenting strain of *Saccharomyces cerevisiae,* under the optimal conditions derived from the preceeding reactions. The ring-opened product (**79**) was obtained in a yield of 5%, or a corrected yield of 8% based on the recovery of the isoxazole (**70**). The top fermenting Balmoral Ale yeast (sp. *Saccharomyces cerevisiae*) was also tested, with the imine (**79**) isolated in a yield of 10%, or a corrected yield of 14% based on the recovered isoxazole (**70**).

The isoxazole (**71**) was treated with baker's yeast, in a ratio of 1:20 for the isoxazole (**71**) to baker's yeast and a reaction time of twenty-four hours. After the standard workup, the components in the resulting solid were separated by chromatography on silica, with light petroleum and ethyl acetate (5:3) as eluant, and individually analysed by ^{1}H nmr spectroscopy, with the isoxazole (**71**), the corresponding imine (**81**) and compounds related to the baker's yeast being detected. The unreacted isoxazole (**71**) was recovered in a yield of 69% and the imine (**81**) was isolated in a yield of 21%, with a corrected yield of 69%, based on the recovery of the isoxazole (**71**) (Scheme 45).

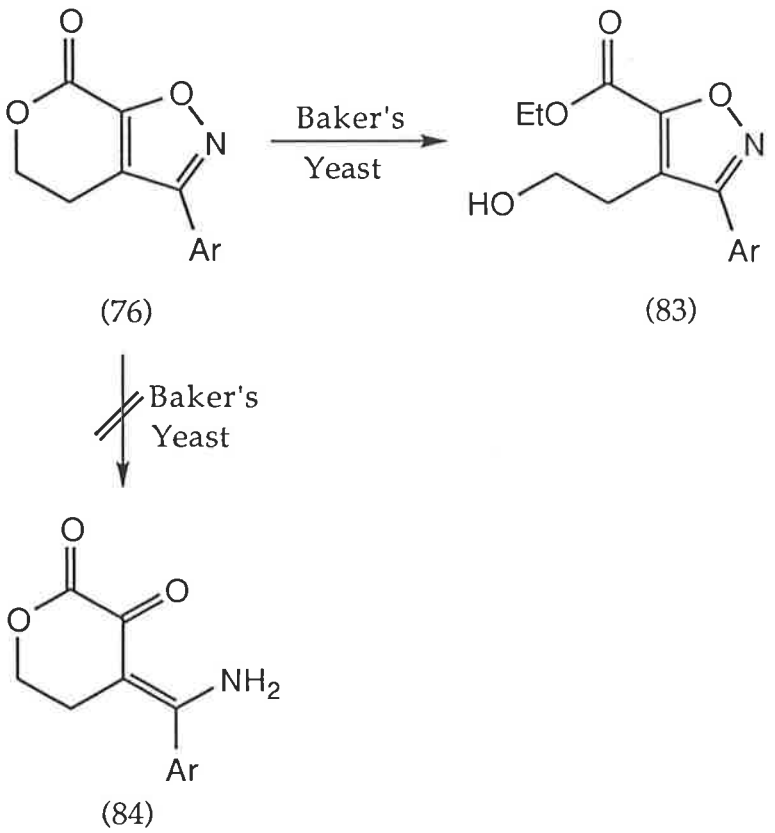


(71) (81)

Ar = 2,6-dichlorophenyl
Scheme 45

The isoxazole (**76**) was treated with baker's yeast in a ratio of 1:20, for the isoxazole (**76**) to baker's yeast, and a reaction time of twenty-four hours. After separating the components in the crude product mixture by chromatography on silica, using light petroleum and ethyl acetate (5:3) as eluant, ^{1}H nmr spectroscopy was used to identify the isoxazole (**83**), the isoxazole (**76**) and compounds related to the baker's yeast. The isoxazole (**83**) was obtained in a yield of 1% or 2% based on the recovery of the isoxazole (**76**). The ^{1}H nmr spectrum showed a triplet signal at δ 1.47 due to three protons, a singlet at δ 1.59 due to the hydroxyl proton, a triplet at δ 2.86 due to two protons, a quartet at δ 3.69 due to two protons, a quartet at δ 4.49 due to two protons and a multiplet at δ 7.44 corresponding to aromatic protons. Analysis of the isoxazole (**83**) showed molecular ions at *m/z* 333, 331 and 329 in the mass spectrum and a peak 1732 cm^{-1} due to a carbonyl group and a broad peak at 3464 cm^{-1} due to a hydroxyl group in the infrared spectrum. The enamine (**84**) was not detected. It appears that the isoxazole (**83**) is formed by hydrolysis of the lactone portion of the bicyclic isoxazole (**76**) and subsequent esterification with ethanol, a by-product of yeast fermentation (Scheme 46). There have been several reports[45,46] of baker's yeast catalysing the hydrolysis of acyclic

esters, for example the deacylation of the steroid (**85**) to give the alcohols (**86**) and (**87**) (Scheme 47);[46] however there have been no reports to date of the hydrolysis of lactones as described in Scheme 46.

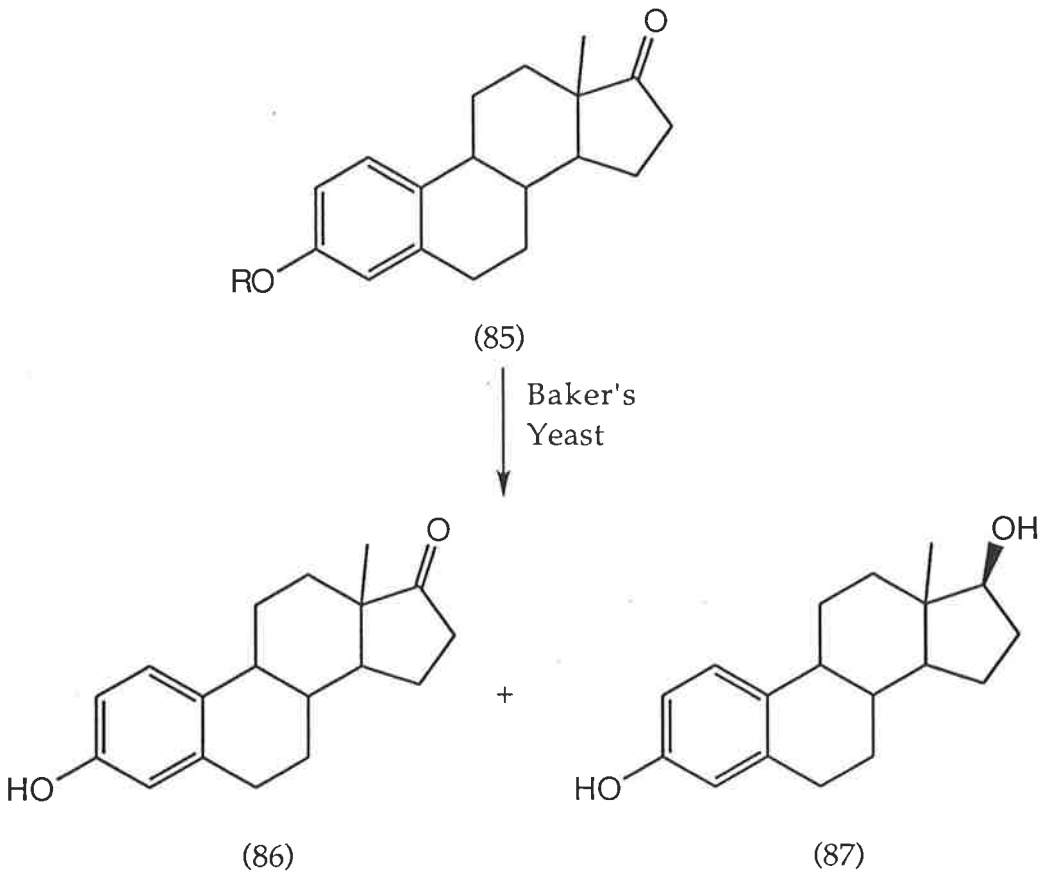


(76) (83) (84)

Ar = 2,6-dichlorophenyl

Scheme 46

The structurally related isoxazole (**73**), was found to be inert to baker's yeast and was recovered unchanged when treated with baker's yeast in a ratio of 1:20 and a reaction time of twenty-four hours.

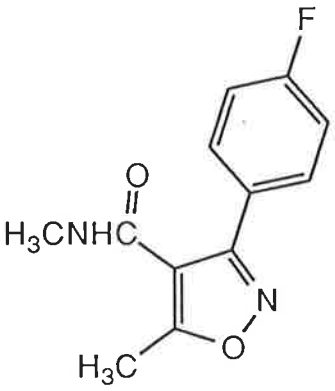


R = COAlkyl

Scheme 47

The reactions of isoxazoles that were not bicyclic with baker's yeast were also examined. A complex mixture of products, which were inseparable by chromatography on silica, was obtained as a result of treatment of the isoxazole (**67**) with baker's yeast. The commercially available isoxazoles (**88**)-(**91**) were also treated with baker's yeast, in ratios of 1:20 for the isoxazoles (**88**)-(**91**) to baker's yeast and reaction times of twenty-four hours. Purification of the product mixtures in each case, gave the unchanged isoxazoles (**88**)-(**91**), in yields ranging from 59-97%.

(88)



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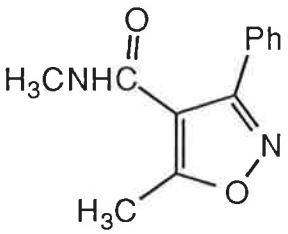

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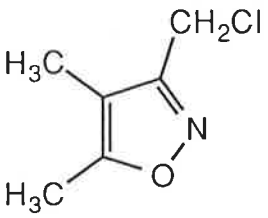
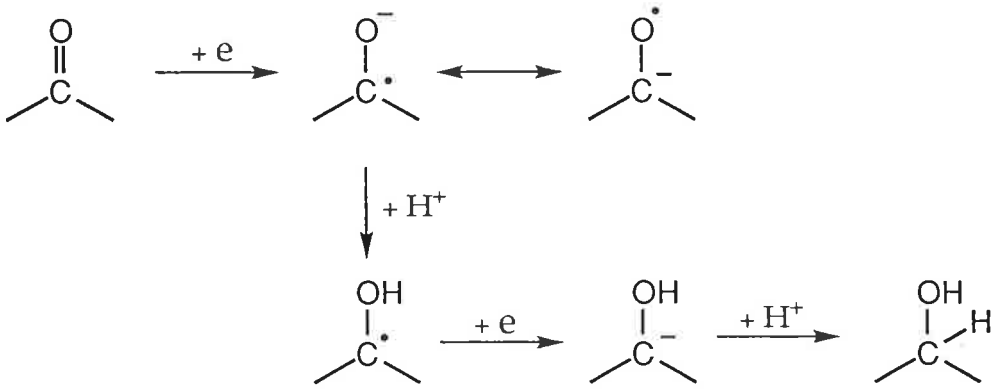


(91)

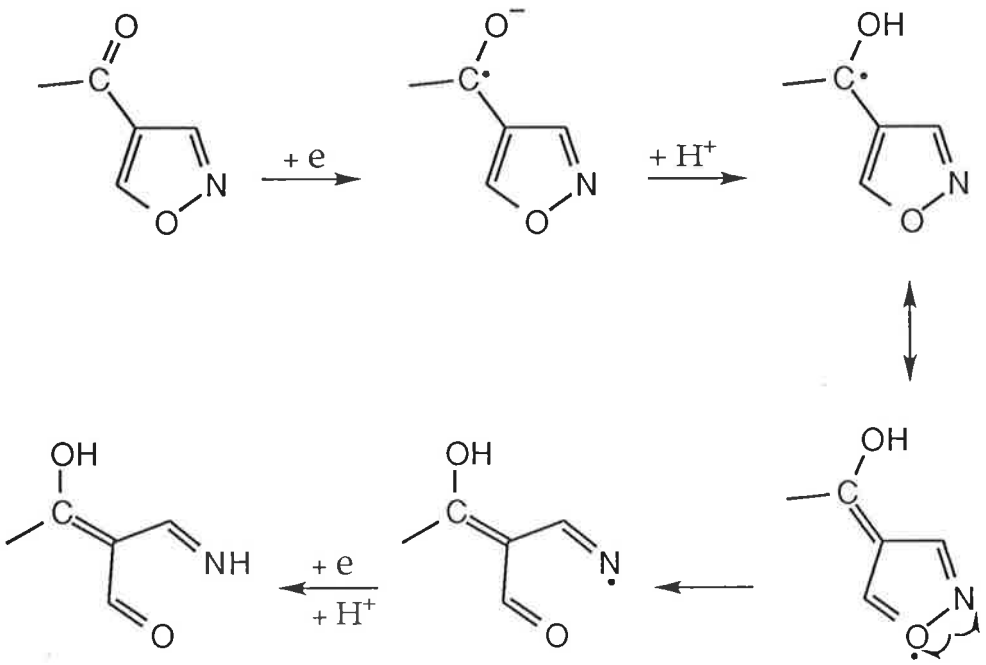
Summarising the reactions of isoxazoles with baker's yeast that have been performed, baker's yeast catalyses the N-O bond cleavage of the three bicyclic isoxazoles (**43**), (**70**) and (**71**); however N-O bond cleavage does not occur with the regioisomeric isoxazoles (**73**) and (**76**) or the monocyclic isoxazoles (**88**)-(**91**). The product that would be expected as a result of N-O bond cleavage from the reaction of the monocyclic isoxazole (**67**) with baker's yeast was not detected. The recovery of the isoxazoles (**88**)-(**91**) - unchanged after treatment with baker's yeast - indicates that an isoxazole may be required to be bicyclic to undergo N-O bond cleavage. Variations in the structures of the isoxazoles (**43**), (**70**) and (**71**) indicate that an alkyl or aryl substituent on the C-9 position, an aliphatic substituent on C-4 or a heteroatom substituted at C-3 of the bicyclic molecule can be tolerated in the N-O bond cleavage reaction.

When considering the isoxazoles (**43**), (**70**) and (**71**) which reacted with baker's yeast and the bicyclic isoxazoles (**73**) and (**76**) which did not undergo N-O bond cleavage, the most obvious difference between the two sets of molecules is the position of the carbonyl substituent, that is the isoxazoles (**43**), (**70**) and (**71**) have a carbonyl group attached to C-4 of the isoxazole ring, whereas the isoxazoles (**73**) and (**76**) have the carbonyl group attached to C-3 of the isoxazole ring. This indicates that isoxazole N-O bond cleavage is dependent on the position of the carbonyl substituent.

As outlined in Schemes 21 and 22 of the Introduction, all previous reactions of keto-isoxazoles and isoxazolines with baker's yeast reported in the literature,[45,46] have involved the reduction of ketones to alcohols. A reasonable mechanism for the yeast-catalysed reduction of ketones to alcohols is as shown in Scheme 48. It is also interesting to note that the reductions reported in the literature[45,46] involved monocyclic isoxazoles with carbonyl substituents attached to C-3 or C-5. There have been no reports involving the reactions with baker's yeast of either monocyclic or bicyclic keto-isoxazoles with carbonyl substituents on C-4. On hypothesising a mechanism for the reductive ring cleavage of a keto-isoxazole by baker's yeast, it is feasible that the keto-isoxazole undergoes electron transfer to the carbonyl substituent in analogy with the first step of the mechanism outlined in Scheme 48. It is possible that at this point the reaction is diverted from the reduction of the carbonyl as the radical ion or the protonated form is stabilised through resonance with the isoxazole ring. The delocalised radical then undergoes N-O bond homolysis followed by sequential transfer of an electron and a proton to give an imine (Scheme 49).



Scheme 48



Scheme 49

In order to examine this hypothesis, the reduction potentials for the isoxazoles (**70**), (**71**), (**73**) and (**76**) were measured.[63] It was rationalised that the isoxazoles (**70**) and (**71**) would have lower reduction potentials than the isoxazoles (**73**) and (**76**), in keeping with the mechanism proposed in Scheme

49. Accordingly, the isoxazoles (**70**) and (**71**) were found to have reduction potentials of -2.15V and -2.2V, respectively, which were relatively lower than the reduction potentials of -2.5V obtained for both the isoxazoles (**73**) and (**76**). Therefore, the ability of isoxazoles to undergo N-O bond cleavage may be predicted by measuring their reduction potentials.

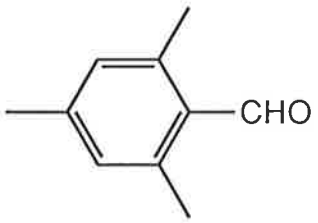
In conclusion, it is likely that the N-O bond cleavage of keto-isoxazoles by baker's yeast occurs *via* the radical mechanism outlined in Scheme 49, which is a diversion of the mechanism for the reduction of ketones to alcohols, as shown in Scheme 48. The reduction potentials measured for the isoxazoles (**70**), (**71**), (**73**) and (**76**), as discussed above, support this hypothesis.

CHAPTER 3

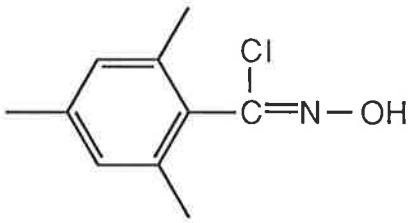
Aryl Nitrile Oxide Cycloadditions in the Presence of Baker's Yeast and β-Cyclodextrin

The cycloaddition reaction outlined in Scheme 26 and discussed in the Introduction, between ethyl cinnamate (**53**) and mesitonitrile oxide (2,4,6-trimethylnitrile oxide) (**50**) was reexamined. Mesitohydroximinoyl chloride (**93**) was synthesised from the corresponding aldehyde (**92**) in a crude yield of 23%, using the procedure outlined in Scheme 10 of the Introduction for the synthesis of 2,6-dichlorobenzohydroximinoyl chloride (**29**), having a crude melting point of 48-63°C. The yield and melting point compared reasonably well with those reported, that is 35% and 61-69°C.[22] Mesitohydroximinoyl chloride (**93**) was identified by ^{1}H nmr spectroscopy, with a singlet observed at δ 2.28 due to six hydrogens, a singlet at δ 2.41 due to three hydrogens, a singlet at δ 6.86 due to aromatic hydrogens and a singlet at δ 8.31 corresponding to the hydoxyl proton. These signals compared favourably with literature values.[22] The crude hydroximinoyl chloride (**93**) was then stirred in an ether solution, with one mole equivalent of triethylamine, to give the mesitonitrile oxide (**50**) in 93% yield. The nitrile oxide (**50**) was identified by ^{1}H nmr spectroscopy, with singlets being observed at δ 2.29 due to three hydrogens, δ 2.41 due to six hydrogens, and δ 6.89 due to aromatic hydrogens. The melting point was found to be 105-107°C which compared favourably with the literature value.[64]

All the cycloaddition reactions in this Chapter were conducted with a 1:1 mole ratio of nitrile oxide to dipolarophile and using 18.5% aqueous ethanol solution buffered to pH 7.2 unless otherwise stated.



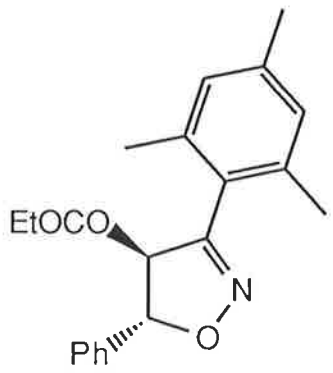
(92)



(93)

The cycloaddition reaction between mesitonitrile oxide (**50**) and ethyl cinnimate (**53**) was reexamined under the conditions specified by Rama Rao *et al.*[48,49] The two reagents were combined in buffered aqueous-ethanol to which baker's yeast was added. This mixture was then gently stirred at 37°C for twenty-four hours after which time it was extracted twice with chloroform. Analysis of the extract by ^{1}H nmr spectroscopy indicated the presence of the two cycloadducts (**54**) and (**55**) as well as the unreacted starting materials (**50**) and (**53**) and the dimer of the nitrile oxide (**50**). The isoxazolines (**54**) and (**55**) were identified by ^{1}H nmr spectroscopy and were present in a ratio of 57:43 in the crude product mixture. Chromatography of the crude product mixture on silica, with a light petroleum and ethyl acetate mixture (5:1) as eluant, was used to separate the cycloadducts (**54**) and (**55**), which were subsequently recrystallised from light petroleum, and obtained in yields of 28% and 21%, respectively. The melting points for the isoxazolines (**54**) and (**55**) were 87-89°C and 85-86°C, respectively. The ^{1}H nmr spectrum of the major regioisomer, the isoxazoline (**54**), displayed signals of a triplet at δ 0.95 corresponding to three protons, singlets at δ 2.22 and δ 2.28 corresponding to three and six protons, respectively, a multiplet at δ 4.03 due to two protons, doublets at δ 4.37 and δ 6.10 each due to one proton, a singlet at δ 6.87 due to two aromatic hydrogens and a multiplet at δ 7.33-7.47 due to the other aromatic hydrogens. The doublets observed at δ 4.37 and δ 6.10 were found to have coupling constants of 9.5 Hz (Figure 15) and corresponded to the two isoxazoline ring protons

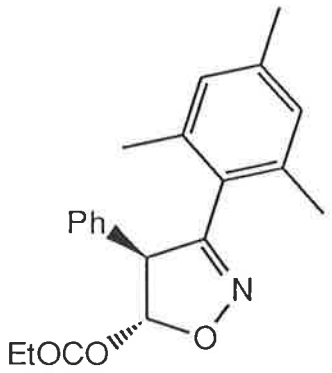
attached to C-3 and C-4. The chemical shift and coupling are consistent with a phenyl group attached to C-3 and an ester group attached to C-4.[50,51] The isoxazoline (**54**) would be expected to be the major isomer due to the electronic effect exerted on the double bond of the cinnamate (**53**) by the carbonyl group, as well as the steric repulsion in the reaction transition state between the aromatic group of the nitrile oxide (**50**) and the phenyl group of the cinnamate (**53**) (Appendix 1). This assignment of structure is also consistent with reports[50,51] of the major isomer formed in the cycloadditions of mesitonitrile oxide (**50**) and benzonitrile oxide (**47**) with methyl cinnamate (**46**) (see Schemes 24 and 25).



(±)-(54)

The ^{1}H nmr spectrum of the minor isomer, the isoxazoline (**55**), displayed a triplet at δ 1.35 due to three hydrogens, singlets at δ 1.98 and δ 2.22 due to three and six hydrogens, respectively, a quartet at δ 4.33 due to two hydrogens, doublets at δ 4.81 and δ 5.32 each corresponding to one hydrogen, a singlet at δ 6.67 due to two aromatic hydrogens and multiplets at δ 7.14-7.17 and 7.26-7.28 due to the other aromatic hydrogens. The doublets observed at δ 4.81 and δ 5.32 corresponded to the two isoxazoline ring hydrogens attached to C-3 and C-4 and had coupling constants of 4 Hz (Figure 15). The chemical shift

and coupling of these doublets are consistent with an ester moiety attached to C-3 and a phenyl group attached to C-4. The isoxazoline (55) would be expected to be the minor isomer due to unfavourable electronic and steric considerations associated with the reaction transition state of the cycloaddition of the nitrile oxide (50) and ethyl cinnamate (53) (Appendix 1).



(±)-(55)

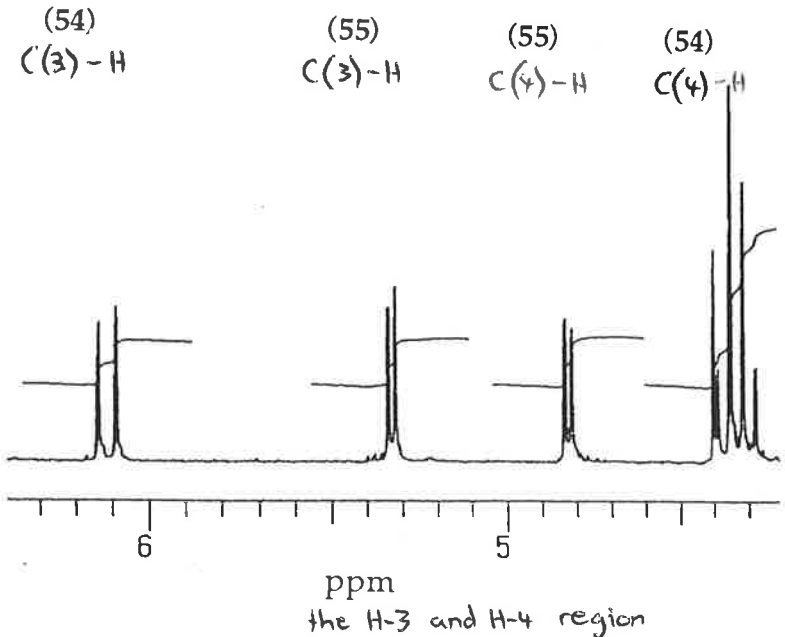


Figure 15: ^{1}H nmr spectrum of ~~C-3 and C-4~~ the H-3 and H-4 region of the isoxazolines (53) and (54) mixture in $CDCl_3$ (200MHz).

To examine the effects of β-cyclodextrin, one mole equivalent of β-cyclodextrin was added directly to a stirring mixture of ethyl cinnamate (**53**) in buffered aqueous ethanol. The nitrile oxide (**50**) and baker's yeast were added to the reaction mixure, which was then incubated, with gentle stirring for twenty-four hours. After extracting the reaction mixture twice with chloroform, ^{1}H nmr spectral analysis of the extract indicated that the isoxazolines (**54**) and (**55**) were present in a ratio of 59:41. Purification of the crude product mixture by chromatography on silica, with a mixture of light petroleum and ethyl acetate (5:1) as eluant, and subsequent recrystallisation from light petroleum gave the isoxazoline (**54**) in a yield of 29% and the minor regioisomer (**55**) in a yield of 22%.

The cycloaddition between mesitonitrile oxide (**50**) and ethyl cinnamate (**53**) was repeated in the absence of both baker's yeast and β-cyclodextrin, but under otherwise identical conditions. ^{1}H nmr spectroscopic analysis of the crude product mixture after twenty-four hours, revealed the presence of the regioisomeric isoxazolines (**54**) and (**55**) in the ratio of 61:39. The isoxazolines (**54**) and (**55**) were isolated by chromatography on silica and obtained in yields of 40% and 24%, respectively.

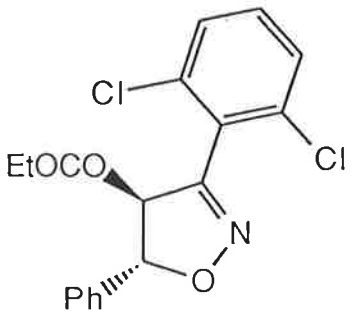
For comparison, this experiment was repeated in the presence of β-cyclodextrin, again in the absence of baker's yeast, and analysis of the crude product mixture after twenty-four hours, by ^{1}H nmr spectroscopy, showed that the isoxazolines (**54**) and (**55**) were present in a ratio of 60:40. Purification of the cycloadducts (**54**) and (**55**) using chromatography on silica gave the isoxazolines (**54**) and (**55**) in yields of 39% and 23%, respectively.

The claims of Rama Rao *et al.*[48,49] that enzymic catalysis was required for the cycloaddition between the nitrile oxide (**50**) and ethyl cinnamate (**53**) to occur in an aqueous media and that the regioselectivity of this cycloaddition

reaction could be reversed by the addition of β-cyclodextrin to the reaction mixture have been shown to be incorrect. The cycloaddition between the nitrile oxide (**50**) and ethyl cinnimate (**53**) has been shown to occur in the absence of baker's yeast and the presence of one mole equivalent of β-cyclodextrin in the reaction, whether in the presence of baker's yeast or not, has little bearing on the regioselectivity of the reaction.

In the light of the results for the cycloaddition of the nitrile oxide (**50**) with ethyl cinnamate (**53**), the cycloaddition of 2,6-dichlorobenzonitrile oxide (**30**) to ethyl cinnamate (**53**) was also reexamined. The nitrile oxide (**30**) and ethyl cinnamate (**53**) were combined in a buffered ethanol/water solution with baker's yeast. This mixture was gently stirred at 37°C for twenty-four hours and then extracted twice with chloroform. ^{1}H nmr spectral analysis of the extract indicated the presence of the two cycloadducts (**56**) and (**93**), the unreacted starting materials (**30**) and (**53**) and the dimer of the nitrile oxide (**30**). By integrating the peaks of the ^{1}H nmr spectrum obtained from the crude product mixture, the cycloadducts (**56**) and (**94**) were determined to be present in a ratio of 94:6. The components of the crude product mixture were separated by chromatography on silica, with light petroleum and ethyl acetate (5:1) as eluant, and the cycloadducts (**56**) and (**94**) were isolated in yields of 29% and 2%, respectively. The ^{1}H nmr spectrum of the major regioisomer, the isoxazoline (**56**), displayed signals of a triplet at δ 1.02 corresponding to three protons, a multiplet at δ 4.10 due to two protons, doublets at δ 4.57 and δ 6.26 each due to one proton and a multiplet at δ 7.40 due to aromatic hydrogens. The doublets observed at δ 4.10 and δ 6.26 were found to have coupling constants of 9 Hz and corresponded to the two isoxazoline ring protons attached to C-3 and C-4. X-ray crystallographic analysis was used to unequivocally assign the structure of the major isomer as being the isoxazoline (**56**) (Figure 16) (Appendix 10). The isoxazoline (**56**) was expected to

be the major isomer due to the electronic effect exerted on the double bond of the cinnamate (53) by the carbonyl group, as well as the steric repulsion in the reaction transition state between the aromatic group of the nitrile oxide (30) and the phenyl group of the cinnamate (53).



(±)-(56)

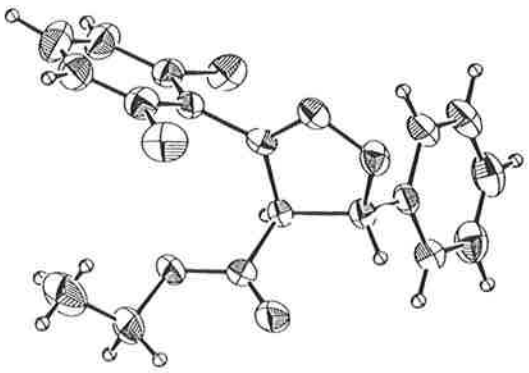
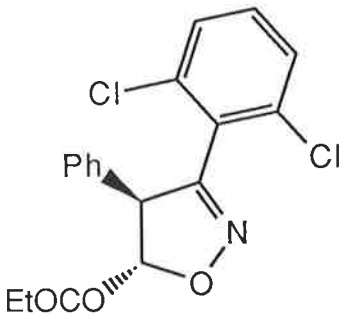


Figure 16: Molecular structure of the isoxazoline (56).

The ^{1}H nmr spectrum of the minor isomer, the isoxazoline (94), displayed a triplet at δ 1.35 due to three hydrogens, a quartet at δ 4.35 due to two

hydrogens, doublets at δ 5.24 and δ 5.27 each corresponding to one hydrogen and a multiplet at δ 7.25-7.40 due to aromatic hydrogens. The doublets observed at δ 5.24 and 5.27 corresponded to the two isoxazoline ring hydrogens attached to C-3 and C-4 and had coupling constants of 5.5 Hz. The isoxazoline (**94**) was expected to be the minor isomer due to unfavourable electronic and steric effects in the transition state of the reaction.



(±)-(94)

The cycloaddition of 2,6-dichlorobenzonitrile oxide (**30**) and ethyl cinnamate (**53**) was repeated in the presence of β-cyclodextrin and analysis of the crude product mixture after twenty-four hours, by ^{1}H nmr spectroscopy, showed that the isoxazolines (**56**) and (**94**) were present in a ratio of 97:3. Concurrently, the cycloaddition reaction between 2,6-dichlorobenzonitrile oxide (**30**) and ethyl cinnamate (**53**) was conducted in the absence of both baker's yeast and β-cyclodextrin but under otherwise identical conditions. After twenty-four hours, ^{1}H nmr spectroscopy was used to analyse the crude product mixture, with the isoxazolines (**56**) and (**94**) being detected in a ratio of 87:13. This reaction was then repeated in the absence of yeast but in the presence of β-cyclodextrin. ^{1}H nmr spectroscopic analysis of the crude product mixture revealed that β-cyclodextrin had no effect on the regiochemical

outcome of the cycloaddition reaction with the cycloadducts (**56**) and (**94**) being detected in a ratio of 87:13.

These results confirm that baker's yeast is superfluous for the cycloaddition reaction between the nitrile oxide (**30**) and ethyl cinnamate (**53**) in an aqueous medium. In comparing the ratio of the isoxazolines (**56**) and (**94**) formed in the reactions with baker's yeast with those isolated from the absence of baker's yeast, that is 94:6 and 87:13, respectively, it appeared that the baker's yeast was selectively digesting the minor isomer (**94**). This was confirmed by treating 10 mg of an 84:16 mixture of the isoxazolines (**56**) and (**94**) with baker's yeast using 18.5% aqueous ethanol solution buffered to pH 7.2. ^{1}H nmr spectral analysis of the crude product mixture indicated that the isoxazoline (**94**) had been digested as only the isoxazoline (**56**) was detected.

It is clear that the cycloadditions of the nitrile oxides (**30**) and (**50**) with ethyl cinnamate (**53**) do occur readily in the absence of baker's yeast and further, the presence of β-cyclodextrin has little effect on the regiochemical outcome of the reactions. Given these results, the basic premises of Rama Rao *et al.*,[48,49] that baker's yeast is required to catalyse the cycloaddition reactions between 2,6-dichlorobenzonitrile oxide (**30**) and mesitonitrile oxide (**50**) with ethyl cinnamate (**53**) in an aqueous medium, and that the presence of β-cyclodextrin reverses the regioselectivity of the latter cycloaddition reaction, are flawed.

Given the nature of thermodynamic equilibria between guest molecules, cyclodextrin hosts and host-guest complexes it was anticipated that the extent of complexation of the reactants by β-cyclodextrin would be greater if there was a larger ratio of β-cyclodextrin to the nitrile oxides (**30**) and (**50**) and the cinnamate (**53**) present in the reaction mixtures. Thus any effects of the cyclodextrin would be exaggerated. The cycloaddition of the aryl nitrile oxide

(**50**) (1.0 mmol) and ethyl cinnamate (**53**) (1.0 mmol) was repeated with excess β-cyclodextrin (1.5 mmol). Analysis of the crude product mixture by ^{1}H nmr spectroscopy showed that the isoxazolines (**54**) and (**55**) were present in a ratio of 46:54, suggesting that the regioselectivity of the cycloaddition reaction had in fact been altered. Encouraged by this result, a series of reactions was conducted, differing only in the ratio of β-cyclodextrin to the nitrile oxide (**50**) and ethyl cinnamate (**53**) added to the reaction mixture. As demonstrated in Table 2, the less nitrile oxide (**50**) and ethyl cinnamate (**53**) added to the reaction mixture, with respect to the amount of β-cyclodextrin, the greater the proportion of the isoxazoline (**55**) relative to its regiosiomer (**54**), detected in the crude product mixture. At a ratio of β-cyclodextrin to reactants of 96:4 (0.06 mmol each of ethyl cinnamate (**53**) and the nitrile oxide (**50**) with 1.5 mmol of β-cyclodextrin), the only cycloadduct detected by ^{1}H nmr spectroscopic analysis of the crude product mixture was the isoxazoline (**55**). An analogous result was observed in the cycloaddition of 2,6-dichlorobenzonitrile oxide (**30**) and ethyl cinnamate (**53**). The amount of the nitrile oxide (**30**) and ethyl cinnamate (**53**) in the reaction was reduced to 0.25 mmol while the amount of β-cyclodextrin added to the reaction mixture was maintained at 1.50 mmol. Analysis of the crude product mixture by ^{1}H nmr spectroscopy showed that the proportion of the isoxazoline (**93**) extracted had slightly increased with respect to the isoxazoline (**56**) extracted, such that the ratio of the two was 20:80.

Despite this observable effect, there was no evidence to suggest that the origin of the effect was during the reaction. Given the aromatic nature of the products, it was hypothesised that the effect could as likely be product complexation, that is, the β-cyclodextrin may be complexing to the major regioisomers formed in the cycloaddition reactions, thus retaining these cycloadducts in the aqueous phase during the workup of the reactions. To test this hypothesis approximately 10 mg (~0.06 mmol) of a 47:53 mixture of the

isoxazolines (**54**) and (**55**) were stirred with 1.5 mmol of β-cyclodextrin in the standard buffered ethanolic solution used in all the previous reactions. When the mixture was extracted twice with chloroform, ^{1}H nmr spectral analysis of the extract showed that the isoxazolines (**54**) and (**55**) had been isolated in the ratio 21:79. All reactions in this Chapter, up to this point, had been extracted twice with chloroform, as specified by Rama Rao *et al.*[48,49] The aqueous layer from the above experiment was extracted three times with ethyl acetate and each extract was analysed by ^{1}H nmr spectroscopy. As indicated in Table 3, the extracts were found to be sequentially enriched in the isoxazoline (**54**) until only the isoxazoline (**54**) was obtained in the final extract.

MMOLES OF REAGENTS (50)/(53)	RATIO (54):(55)
1.5	60:40
1.0	46:54
0.5	23:77
0.25	26:74
0.06	0:100

Table 2: Effect of varying the ratio of the Reagents (**50**) and (**53**) to β-cyclodextrin (1.5 mmol in each experiment) on the ratio of the cycloadducts (**54**) and (**55**).

Concurrently, 10 mg (~0.06 mmol) of a 87:13 mixture of the isoxazolines (**56**) and (**94**) were stirred with 1.5 mmol of β-cyclodextrin in the standard

buffered ethanolic solution used in all the previous reactions. When the mixture was extracted twice with chloroform, ^{1}H nmr spectral analysis of the extract showed that the isoxazolines (**54**) and (**55**) had been isolated in the ratio 80:20. Having established that the β-cyclodextrin does in fact selectively bind to the isoxazolines (**54**) and (**56**), it appears that the effect observed in the cycloadditions is entrainment of the major isomers (**54**) and (**56**) during the workup of the reactions. To test the generality of this effect, isoxazolines were synthesised containing aryl and alkyl substituents attached to C-5.

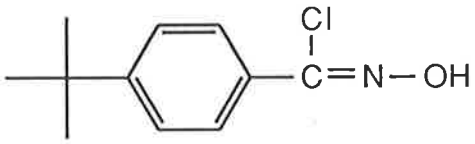
	RATIO OF ISOXAZOLINES (**54**):(**55**)
Initially	47:53
$CHCl_3$ Extraction	21:79
First Ethyl Acetate Extraction	25:75
Second Ethyl Acetate Extraction	77:33
Third Ethyl Acetate Extraction	100:0

Table 3: Effect of progressive extraction of a mixture containing the isoxazolines (**54**) and (**55**) and β-cyclodextrin.

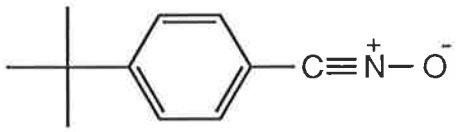
4-*t*-Butylbenzohydroximinoyl chloride (**96**) was synthesised from the corresponding aldehyde (**95**) using the procedure outlined in Scheme 10 of the Introduction for the synthesis of 2,6-dichlorobenzohydroximinoyl chloride (**29**), in a yield of 40% and with a melting point of 70-76°C. ^{1}H nmr spectroscopy was used to identify the hydroximinoyl chloride (**96**), with a singlet observed at δ 1.34 corresponding to nine hydrogens, doublets at δ 7.44

and δ 7.78 each due to two aromatic protons and a broad singlet at δ 8.38 corresponding to the hydroxyl hydrogen. Molecular ion signals were obtained at *m/z* 212 and 214 in the mass spectrum. The nitrile oxide (**97**) and the corresponding hydroximinoyl chloride (**96**) are known in the literature;[65,66] however no physical or spectral data has been reported.

(95)



(96)



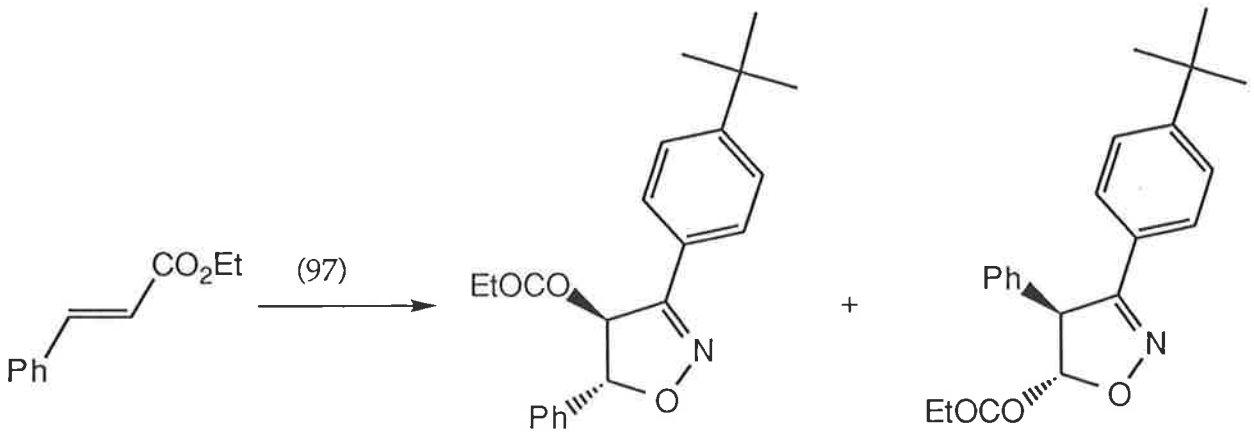
(97)

The method for the cycloaddition of ethyl cinnamate (**53**) with the nitrile oxide (**97**) involved addition of a solution of the hydroximinoyl chloride (**96**) in tetrahydrofuran to a solution of the dipolarophile (**53**) and triethylamine in tetrahydrofuran. A ^{1}H nmr spectrum of the crude product mixture showed the starting materials (**53**) and (**97**), the dimer of the nitrile oxide (**97**) and the two cycloadducts (**98**) and (**99**). The isoxazolines (**98**) and (**99**) were identified by ^{1}H nmr spectroscopy and were present in a ratio of 68:32 in the crude mixture (Scheme 50). Chromatography of the crude product mixture on silica, with light petroleum and ethyl acetate (20:1) as eluant, was used to isolate the cycloadducts (**98**) and (**99**), which were subsequently recrystallised

from light petroleum, and obtained in yields of 47% and 11%, respectively. The melting points for the isoxazolines (98) and (99) were 78-79°C and 96-97°C, respectively. The ^{1}H nmr spectrum of the major regioisomer, the isoxazoline (98), displayed signals of a triplet at δ 1.24 corresponding to three protons, a singlet at δ 1.33 corresponding to nine protons, a quartet at δ 4.25 due to two protons, doublets at δ 4.43 and δ 5.97 each due to one proton and a multiplet at δ 7.27-7.70 due to aromatic hydrogens. The doublets observed at δ 4.25 and δ 5.97 were found to have coupling constants of 6 Hz and correspond to the two isoxazoline ring protons attached to C-3 and C-4. The chemical shift and coupling of the doublets at δ 4.25 and δ 5.97 are consistent with a phenyl group attached to C-3 and an ester group attached to C-4. Mass spectrometry indicated a molecular ion at *m/z* 351. The isoxazoline (98) was expected to be the major isomer due to the electronic effect exerted on the double bond of the cinnamate (53) by the carbonyl group, as well as the steric repulsion in the reaction transition state between the aromatic group of the nitrile oxide (97) and the phenyl group of the cinnamate (53) (Appendix 1).

The ^{1}H nmr spectrum of the minor isomer, the isoxazoline (99), displayed a singlet at δ 1.27 due to nine hydrogens, a triplet at δ 1.33 due to three hydrogens, a quartet at δ 4.25 due to two hydrogens, doublets at δ 4.94 and δ 5.02 each corresponding to one hydrogen and a multiplet at δ 7.27-7.58 due to aromatic hydrogens. The doublets observed at δ 4.94 and δ 5.02 correspond to the two isoxazoline ring hydrogens attached to C-3 and C-4 and had coupling constants of 4 Hz. The chemical shift and coupling of the doublets observed at δ 4.94 and δ 5.02 are consistent with an ester moiety attached to C-3 and a phenyl group attached to C-4. Mass spectrometry indicated a molecular ion at *m/z* 351. The isoxazoline (99) was expected to be the minor isomer due to unfavourable electronic and steric considerations associated with the transition state in the cycloaddition of the nitrile oxide (97) and ethyl

cinnamate (**53**).



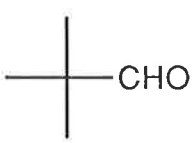
(**53**) (±)-(**98**) (±)-(**99**)

Scheme 50

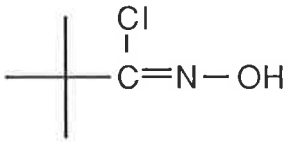
Pivalohydroximinoyl chloride (**101**) was synthesised from pivaldehyde (**100**) using the procedure outlined in Scheme 10 of the Introduction for the synthesis of 2,6-dichlorobenzohydroximinoyl chloride (**29**), in a yield of 49%. ^{1}H nmr spectroscopy was used to identify the hydroximinoyl chloride (**101**), with a singlet observed at δ 1.27 corresponding to nine hydrogens and a singlet at δ 8.50 corresponding to the hydroxyl hydrogen. Pivalohydroximinoyl chloride (**101**) is known in the literature,[67-69] however no physical or spectral data has been reported.

The method for the cycloaddition of ethyl cinnamate (**53**) with the nitrile oxide (**102**) involved addition of a solution of the hydroximinoyl chloride (**101**) in tetrahydrofuran to a solution of the cinnamate (**53**) and triethylamine in tetrahydrofuran. A ^{1}H nmr spectrum of the crude product mixture showed the unreacted starting materials (**53**) and (**102**), the dimer of the nitrile oxide (**102**) and the two cycloadducts (**103**) and (**104**). The

isoxazolines (**103**) and (**104**) were identified by ^{1}H nmr spectroscopy and were present in a ratio of 72:28 in the crude product mixture (Scheme 51). Chromatography of the crude product mixture on silica, with a light petroleum and ethyl acetate mixture (5:1) as eluant, was used to isolate the cycloadducts (**103**) and (**104**), which were subsequently recrystallised from light petroleum, and obtained in yields of 57% and 33%, respectively. The melting point for the isoxazoline (**103**) was 49°C and the isoxazoline (**104**) was obtained as a viscous oil. The ^{1}H nmr spectrum of the major regioisomer, the isoxazoline (**103**), displayed signals of a singlet at δ 1.23 corresponding to nine protons, a triplet at δ 1.33 corresponding to three protons, a doublet at δ 3.97 due to one proton, a quartet at δ 4.27 due to two protons, a doublet at δ 5.75 due to one proton and a multiplet at δ 7.27-7.38 due to aromatic hydrogens. The doublets observed at δ 3.97 and δ 5.75 were found to have coupling constants of 6.7 Hz and correspond to the two isoxazoline ring protons attached to C-3 and C-4. The chemical shift and coupling of the doublets at δ 3.97 and δ 5.75 indicated that the *t*-butyl group is attached to C-3 and the ester group attached to C-4. Mass spectrum of the isoxazoline (**103**) showed no molecular ion, but showed a fragment ion at *m/z* 102, due to the loss of the ethoxycarbonyl substituent. The isoxazoline (**103**) would be expected to be the major isomer due to the electronic effect exerted on the double bond of the cinnamate (**53**) by the carbonyl group, as well as the steric repulsion in the reaction transition state between the *t*-butyl group of the nitrile oxide (**102**) and the phenyl group of the cinnamate (**53**) (Appendix 1).



(100)



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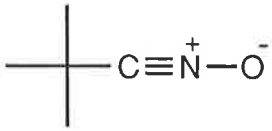
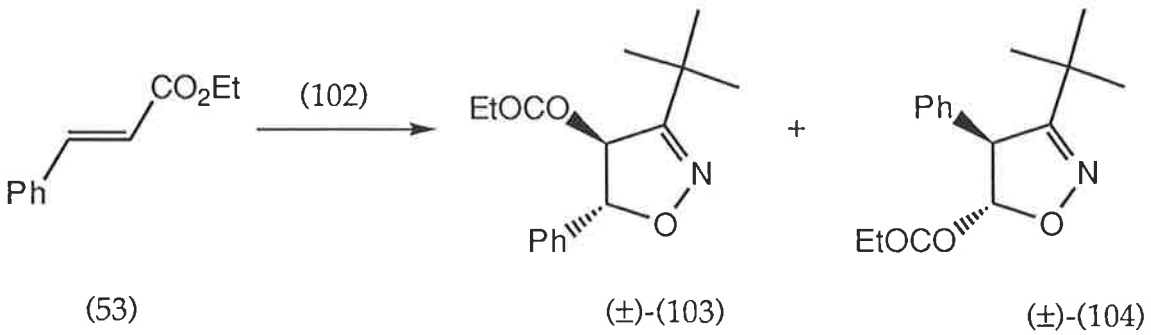


(102)

The ^{1}H nmr spectrum of the minor isomer, the isoxazoline (**104**), displayed a singlet at δ 1.08 due to nine hydrogens, a triplet at δ 1.33 due to three hydrogens, a quartet at δ 4.28 due to two hydrogens, doublets at δ 4.56 and δ 4.79 each corresponding to one hydrogen and a multiplet at δ 7.21-7.38 due to aromatic hydrogens. The doublets observed at δ 4.56 and δ 4.79 correspond to the two isoxazoline ring hydrogens attached to C-3 and C-4 and had coupling constants of 3 Hz. The chemical shift and coupling of the doublets at δ 4.56 and δ 4.79 are consistent for the ester moiety attached to C-3 and the *t*-butyl group attached to C-4. Mass spectrum of the isoxazoline (**104**) showed no molecular ion, but showed a fragment ion at *m*/*z* 102, due to the loss of the ethoxycarbonyl substituent. A molecule with this configuration would be expected to be the minor isomer due to unfavourable electronic and steric considerations associated with the reaction transition state in the cycloaddition of the nitrile oxide (**102**) to ethyl cinnamate (**53**) (Appendix 1).

Aqueous ethanolic solutions of pairs of the isoxazolines (**98**) and (**99**) and (**103**) and (**104**), synthesised from the cycloadditions of the nitrile oxides (**97**) and (**102**) with ethyl cinnamate (**53**), were then treated with β-cyclodextrin. Approximately 10 mg of a 71:29 mixture of the isoxazolines (**98**) and (**99**) were stirred for twenty-four hours with 1.5 mmol of β-cyclodextrin in 32.5 ml of the standard buffered ethanolic solution. Although the mixtures probably equilibrate very quickly, the extended time was chosen to mimic the

cycloaddition reaction conditions. The mixture was extracted twice with chloroform and ^{1}H nmr spectral analysis of the extract showed that the ratio of the isoxazoline (**98**) to the regioisomer (**99**) had been altered to 37:63. Concurrently, 10 mg of a 48:52 mixture of the isoxazolines (**103**) and (**104**) was stirred for twenty-four hours with 1.5 mmol of β-cyclodextrin in 32.5 ml of the standard buffered ethanolic solution. The mixture was extracted twice with chloroform and ^{1}H nmr spectral analysis of the extract showed that the ratio of the isoxazoline (**103**) to the regioisomer (**104**) had not been altered.



(53) (±)-(103) (±)-(104)

Scheme 51

The results of the treatment of the four regioisomeric sets of isoxazolines (**54**) and (**55**), (**56**) and (**94**), (**98**) and (**99**) and (**103**) and (**104**) with β-cyclodextrin, are summarised in Table 4. These results confirm that the effect β-cyclodextrin has on the isoxazolines is entrainment, and further, this effect varies with the substituent on C-5 not the substituent on C-3 of the isoxazolines (**54**), (**56**), (**98**) and (**103**) (Figure 17). It may be rationalised that β-cyclodextrin complexes less readily to the regioisomeric isoxazolines (**55**), (**94**) and (**99**) due to steric crowding around the aryl substituents (Figure 18).

Isoxazolines	Initial Ratio	Ratio After Extraction from β-Cyclodextrin Solution
(54)/(55)	47:53	21:79
(56)/(94)	87:13	80:20
(98)/(99)	71:29	37:63
(103)/(104)	48:52	48:52

Table 4: Effect of β-cyclodextrin on regioisomeric mixtures of isoxazolines.

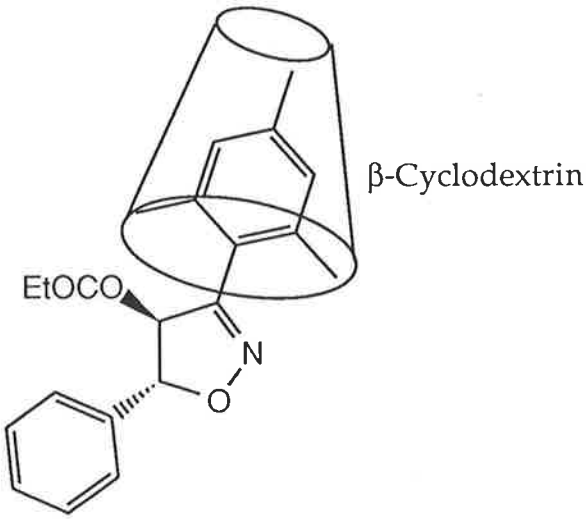


Figure 17: Inclusion complex of the mesityl group of the isoxazoline (**54**) with β-cyclodextrin.

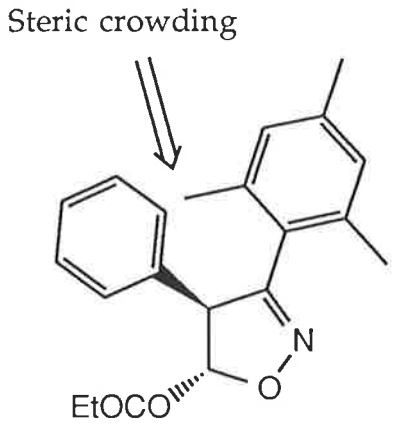


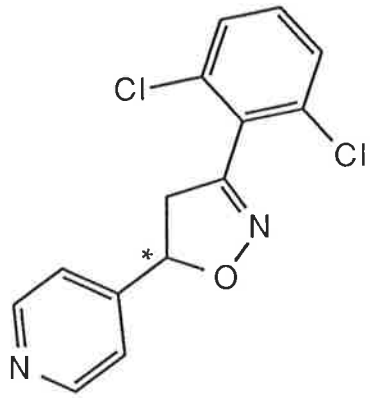
Figure 18: Steric crowding around the isoxazoline (**55**), due to the proximity of the two aromatic groups.

The experiments discussed in this Chapter to this point have been concerned with claims of Rama Rao *et al.*[48,49] concerning the regiochemical outcome of cycloaddition reactions between the aryl nitrile oxides (**30**) and (**50**) and ethyl cinnamate (**53**) in the presence of baker's yeast and β-cyclodextrin. Having reexamined those claims and found them to be flawed, other claims made by Rama Rao *et al.* [49,55] concerning the stereochemical outcome of cycloaddition reactions between 4-vinylpyridine (**57**) and the nitrile oxides (**30**) and (**50**) in the presence of baker's yeast and β-cyclodextrin, as discussed in the Introduction (see Schemes 28 and 29), were also reexamined.

All the cycloaddition reactions in this Section were conducted with a 1:1 mole ratio of the nitrile oxides (**30**) and (**50**) to 4-vinylpyridine (**57**), using 18.5% aqueous ethanol solution buffered to pH 7.2.

The cycloaddition of 2,6-dichlorobenzonitrile oxide (**30**) and 4-vinylpyridine (**57**) was examined in the absence of baker's yeast. The two reagents were combined in buffered aqueous-ethanol and gently stirred at 37°C for twenty-four hours and the mixture extracted twice with chloroform. Analysis of the extract by ^{1}H nmr spectroscopy indicated the presence of the

one cycloadduct (**58**), the unreacted starting materials (**30**) and (**57**) and the dimer of the nitrile oxide (**30**). On purification of the crude product mixture by chromatography on silica, with a light petroleum and ethyl acetate mixture (1:3) as eluant, the cycloadduct (**58**) was obtained in a yield of 29%. The isoxazoline (**58**) was identified by ^{1}H nmr spectroscopy, with signals of three doublets of doublets at δ 3.21, δ 3.83 and δ 5.82 each corresponding to one proton, a multiplet at δ 7.26-7.41 due to five hydrogens and a broad signal at δ 8.65 due to two protons. Analysis of the isoxazoline (**58**) using polarimetry indicated an optical rotation of zero. This reaction confirms that baker's yeast is not required for the cycloaddition reaction between the nitrile oxide (**30**) and 4-vinylpyridine (**57**).



(58)

The cycloaddition reaction was then repeated in the presence of one mole equivalent of β-cyclodextrin. On completion of the experiment, the isoxazoline (**58**) was obtained in a yield of 15%, and the optical rotation was found to be zero.

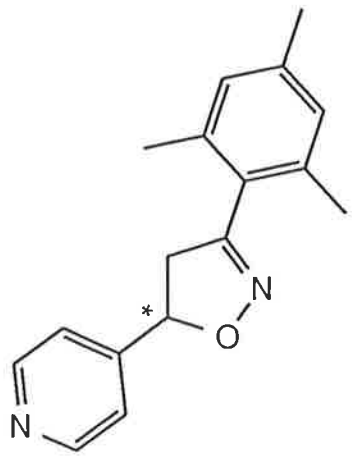
Although it had been established that baker's yeast was unnecessary for

the cycloaddition between the nitrile oxide (30) and 4-vinylpyridine (57) it seemed possible that the baker's yeast could have been selectively digesting one of the enantiomers formed in the cycloaddition, giving rise to the enantioselectivity reported by Rama Rao *et al.*[49,55] Therefore, the cycloaddition of the nitrile oxide (30) and 4-vinylpyridine (57) was repeated in the presence of baker's yeast. The isoxazoline (58) was recovered in a yield of 18% and analysis by polarimetry indicated an optical rotation of zero.

The three preceding experiments establish that baker's yeast is not required for the cycloaddition of the nitrile oxide (30) and 4-vinylpyridine (57). The presence of yeast and/or β-cyclodextrin does not appear to alter the optical activity of the isoxazoline (58) formed in the cycloadditions and it was calculated that an optical rotation of two degrees could have been detected. Rama Rao *et al.*[49,55] stated that the optical rotation of the isoxazoline (58) formed in the presence of baker's yeast was +66.7° and that the optical rotation of the same isoxazoline (58) formed in the presence of both baker's yeast and β-cyclodextrin was +160.0°. The results obtained from the cycloadditions of the nitrile oxide (30) to the vinyl pyridine (57), as described above, indicate that the isoxazoline (58) is obtained in a racemic form in each case.

The cycloaddition of mesitonitrile oxide (50) with 4-vinylpyridine (57) was also examined in the absence of baker's yeast. The two reagents were combined in buffered aqueous-ethanol and gently stirred at 37°C for twenty-four hours. The mixture was extracted twice with chloroform. Analysis of the extract by ^{1}H nmr spectroscopy indicated the presence of the one cycloadduct (59), unreacted starting materials (50) and (57) and the dimer of the nitrile oxide (50). On purification of the extract by chromatography on silica, with a light petroleum and ethyl acetate mixture (1:5) as eluant, the cycloadduct (59) was obtained in a yield of 51%. The isoxazoline (59) was identified by ^{1}H nmr spectroscopy, with signals of singlets at δ 2.18 and δ 2.30 corresponding to six

and three hydrogens, respectively, three doublets of doublets at δ 3.16, δ3.71 and δ 5.77 each corresponding to one proton, a singlet at δ 6.90 due to two hydrogens from the trimethylaryl substituent and two doublets at δ 7.49 and δ 8.76 each due to two protons. Analysis of the the isoxazoline (**59**) using polarimetry indicated an optical rotation of zero. The repetition of this experiment in the presence of baker's yeast and/or β-cyclodextrin, but under otherwise identical conditions, gave the isoxazoline (**59**) in each case with an optical rotation of zero. Rama Rao *et al.*[49,55] stated that the optical rotation of the isoxazoline (**59**) formed in the presence of baker's yeast was $^{+}5.1°$ and that the optical rotation of the same isoxazoline (**59**) formed in the presence of both baker's yeast and β-cyclodextrin was $^{+}25.8°$.



(59)

the work described in

The experiments undertaken in this Chapter give results that are contrary to recent reports by Rama Rao *et al.* [48,49,55] In the present work it has been established that baker's yeast is not required for the cycloaddition reactions of the nitrile oxides (**30**) and (**50**) with ethyl cinnamate (**53**) and 4-

vinylpyridine (**57**) to give the isoxazolines (**54**), (**55**), (**56**), (**58**), (**59**) and (**94**). β-Cyclodextrin has been found to alter the ratio of isomers isolated from the reactions of the cinnamate (**53**) with the nitrile oxides (**30**) and (**50**), but only at concentrations of reactants much lower than those reported.[48,49] This effect appears to be due to selective product complexation rather than selective product formation. Further, neither β-cyclodextrin nor baker's yeast have an effect on the optical activity of the isoxazolines (**58**) and (**59**) formed from the cycloadditions of the nitrile oxides (**30**) and (**50**) with 4-vinylpyridine (**57**).

When considering the entrainment of the isoxazolines (**54**), (**56**) and (**98**) in the β-cyclodextrin, it is envisaged that selective complexation by β-cyclodextrin has potential as a tool for the separation of regioisomeric mixtures of isoxazolines with aryl substituents. For example, chromatography on a β-cyclodextrin column could offer an alternative to chromatography on silica in cases where it is difficult to separate regioisomeric mixtures using the latter method.

CONCLUSION

The work in this thesis has shown that it is possible to synthesise analogues of GRASP (**1**) and the bleacher herbicides utilising nitrile oxide cycloaddition chemistry. The synthetic strategy, as described in Scheme 2, is illustrated by the regioselective cycloaddition of the nitrile oxide (**30**) to the cycloalkenones (**19**), (**21**) and (**23**).

Nickel peroxide was found to be a new and rapid oxidising agent for the production isoxazoles from isoxazolines described above.

It was shown to be possible to synthesise isoxazoles directly using one-pot cycloaddition-elimination reactions. This was achieved by the cycloaddition of nitrile oxides to halo-substituted cycloalkenones. It was determined that the regioselectivity of these cycloaddition reactions is controlled by steric factors, and the regioselectivity of the reactions was reversed by altering the site of halogenation.

The final step in the synthesis of analogues of GRASP (**1**) and the bleacher herbicide involved the ring opening of bicyclic isoxazoles to form the corresponding imines. This was achieved by two methods; by catalytic hydrogenation over palladium on carbon and by using baker's yeast. The novel reductive N-O bond cleavage of isoxazoles by baker's yeast was explored and mechanism was proposed for this reaction.

Finally, the effects of baker's yeast and β-cyclodextrin on the cycloaddition of various nitrile oxides with ethyl cinnamate and 4-vinylpyridine were reexamined. Contrary to literature reports, these reactions do not require baker's yeast to proceed and β-cyclodextrin was found to have

little or no effect on either the regiochemical or stereochemical outcome of these reactions. However, at concentrations much lower than those reported in the literature, selective entrainment of isoxazolines by β-cyclodextrin was observed.

EXPERIMENTAL

GENERAL

Melting points were determined on a Kofler hot-stage under a Reichert microscope and are uncorrected.

Elemental analyses ~~were carried out by~~ were performed by the Chemical and Microanalytical Service Pty. Ltd., Melbourne, Australia.

Analytical thin layer chromatography (tlc) was performed using Merck Kieselgel $60F_{254}$ silica on aluminium backed plates. Flash chromatography refers to nitrogen-pressure driven rapid chromatography using Merck Kieselgel 60 (230-400 mesh ASTM) silica.

Infrared spectra were recorded on an Hitachi 270-30 spectrophotometer using the 1603 cm^{-1} band of polystyrene as a reference.

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on either a Bruker ACP-300 operating at 300 MHz or Varian Gemini-200 spectrometer operating at 200MHz. Chemical shifts are quoted as δ in parts per million downfield from the internal standard. Multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

Electron impact mass spectra were recorded with an AEI MS-30 double focussing mass spectrometer operating at 70 eV. Fast atom bombardment (FAB) mass spectra were recorded on a vacuum Generators ZAB 2HF mass spectrometer.

All solvents were distilled prior to use. Anhydrous diethyl ether and

tetrahydrofuran were obtained by distillation from sodium benzophenone ketyl. Drying and other purification of organic solvents and reagents were performed using standard laboratory procedures.[70]

The buffer used was potassium dihydrogen phosphate-disodium hydrogen phosphate made to a concentration of 0.5 M and having pH 7.2.

5,6-DIHYDRO-2*H*-PYRAN-2-ONE (21)

A mixture of 3-butenoic acid (**20**) (1.00 g, 12 mmol), paraformaldehyde (0.71 g), concentrated sulphuric acid (0.07 ml) and glacial acetic acid (2.91 ml) was refluxed gently for 3h then cooled to room temperature at which point sodium acetate (0.38 g, 4.6 mmol) was added with stirring. The acetic acid was removed under reduced pressure. Water was added to the reaction mixture which was subsequently immersed in an ice bath. Sodium hydroxide solution (1M) was added and the resulting mixture was extracted four times with dichloromethane. The combined organic extracts were washed with ammonium chloride solution, dried (magnesium sulphate) and the solvent was removed under reduced pressure to yield a yellow oil. The crude product was distilled to yield 5,6-dihydro-2*H*-pyran-2-one (**21**) as a colourless oil (0.26 g, 22%). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.48 [2H, m, C5-H_2], 4.44 [2H, t, J = 6 Hz, C6-H_2], 6.03 [1H, dt, J = 2 Hz, J = 10 Hz, C3-H], 6.97 [1H, dt, J = 4 Hz, J = 10 Hz, C4-H]. The ^{1}H nmr spectral data is consistent with literature values.[15,16]

2,3-DIHYDRO-4*H*-PYRAN-4-ONE (23)

To a solution of 1-methoxy-3-((trimethylsilyl)oxy)buta-1,3-diene (**22**) (2.17 g, 12.6 mmol) in tetrahydrofuran (50 ml) were added zinc chloride (1.71 g,

12.5 mmol) and paraformaldehyde (4.00 g). The resulting mixture was heated at reflux for 3h. Ice-cold saturated sodium bicarbonate solution was then added and the resulting mixture was extracted three times with ether. The combined organic layers were washed once with water, dried (magnesium sulphate) and the solvent was removed under reduced pressure. The resulting yellow oil was then distilled under reduced pressure to yield 2,3-dihydro-4*H*-pyran-4-one (**23**) as a colourless liquid (0.99 g, 56%), b.p. 67°C/15 mm Hg (lit.[17] 64°C/15 mm Hg). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.61 [2H, t, J = 7 Hz, C2-H_2], 4.51 [2H, t, J = 7 Hz, C3-H_2], 5.42 [1H, d, J = 6 Hz, C6-H], 7.36 [1H, d, J = 6 Hz, C5-H]. The ^{1}H nmr spectral data is consistent with literature values.[17]

2,6-DICHLOROBENZALDOXIME (28)

To 2,6-dichlorobenzaldehyde (**27**) (1.00 g, 5.7 mmol) in water (1.5 ml), ethanol (2 ml) and ice (2.5 ml) was added hydroxylamine hydrochloride (0.34 g, 6.5 mmol). To this mixture was added 50% sodium hydroxide solution (1.43 ml) with stirring. The mixture was stirred for 1.5h, washed with ether to remove any neutral impurities, acidified with concentrated hydrochloric acid solution and extracted twice with ether. The combined extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure. The resulting white solid was recrystallised from aqueous ethanol to yield 2,6-dichlorobenzaldoxime (**28**) as small, white, needle-like crystals (0.68 g, 61%), m.p. 148.8-149.3°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 7.2-7.4 [3H, m, aromatic hydrogens], 8.39 [1H, bs, Ar-CH=NO<u>H</u>], 8.80 [1H, s, Ar-C<u>H</u>=NOH]. I.r. (nujol): 3288, 2852, 1582, 1562, 772 cm^{-1}.

2,6-DICHLOROBENZOHYDROXIMINOYL CHLORIDE (29)

To a stirred solution of 2,6-dichlorobenzaldoxime (**28**) (5.00 g, 26.3 mmol) in *N*,*N*-dimethylformamide (22 ml) was added *N*-chlorosuccinimide (3.51 g, 26.3 mmol). The initial *N*-chlorosuccinimide addition resulted in a slight temperature decrease after which the reaction became exothermic but was kept between 25-35°C. After the cessation of the exothermic reaction the mixture was poured into ice/water (100 ml) and extracted twice with ether. The combined organic fractions were washed three times with water and dried (magnesium sulphate) and the solvent was removed under reduced pressure to yield a white solid. The crude product was recrystallised from ether/light petroleum to give 2,6-dichlorobenzohydroximinoyl chloride (**29**) as large, rectangular, colourless crystals (5.25 g, 89%), m.p. 91-92°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 7.37 [3H, m, aromatic hydrogens], 8.31 [1H, s, Ar-C(Cl)=NO<u>H</u>].

9-(2,6-DICHLOROPHENYL)-8-AZA-7-OXA-[4.3.0]-BICYCLONON]-8-EN-2-ONE (60)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (1.17g, 5.2 mmol) in dry tetrahydrofuran (4.25 ml) was added dropwise to a stirring solution of cyclohex-2-enone (**19**) (0.50g, 5.2 mmol) and triethylamine (0.80 ml, 5.72 mmol) in dry tetrahydrofuran (8.5 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the resulting residue taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and was concentrated under reduced pressure to give a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 1:1) and recrystallised from ethyl acetate/light petroleum to yield the isoxazoline (**60**) as large, rhomboid, colourless crystals

(0.59 g, 40%), m.p. 150-151°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.7-2.7 [6H, m, C3-H_2, C4-H_2 and C5-H_2], 4.53 [1H, d, J = 11 Hz, C1-H], 5.26 [1H, dt, J = 4.5 Hz, J =11 Hz, C6-H], 7.3-7.4 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 287, 285, 283 (4, 17, 24; M^+); 255 (9); 240 (19); 230 (23); 214 (100; M^+-C_3H_3NO); 185 (29; M^+-$C_5H_6O_2$). *Anal. Calcd.* for $C_{13}H_{11}Cl_2NO_2$: C, 54.95; H, 3.90; N, 4.93. Found: C, 55.13; H, 3.98; N, 4.89%. The structure was confirmed through X-ray crystallographic analysis (Appendix 2).

9-(2,6-DICHLOROPHENYL)-8-AZA-3,7-DIOXA-[4.3.0]-BICYCLONON-8-EN-2-ONE (64)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (1.14 g, 5.1 mmol) in dry tetrahydrofuran (7.7 ml) was added dropwise to a stirring solution of 5,6-dihydro-2*H*-pyran-2-one (**21**) (0.50 g, 5.1 mmol) and triethylamine (0.57 g, 5.61 mmol) in dry tetrahydrofuran (15.3 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue was taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. The crude product mixture was then purified by flash chromatography (ethyl acetate/light petroleum, 2:3) and recrystallised from ethyl acetate/light petroleum to yield the isoxazoline (**64**) as small, white, needle-like crystals (0.94 g, 64%), m.p. 159-162°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.26 [2H, m, C5-H_2], 4.46 [1H, m, C4-H], 4.69 [1H, ddd, J = 3 Hz, J = 11 Hz, J = 11 Hz, C4-H], 4.74 [1H, d, J = 11 Hz, C1-H], 5.32 [1H, m, C6-H], 7.3-7.4 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 289, 287, 285 (3, 9, 14; M^+); 250 (58; M^+-Cl); 212 (100; M^+-$COOC_2H_2$). *Anal. Calcd.* for $C_{12}H_9Cl_2NO_3$: C, 50.37; H, 3.17; N, 4.90. Found: C, 50.69; H, 3.17; N, 4.87%.

5-(2,6-DICHLOROPHENYL)-4-(3-HYDROXYPROPIONYL)-1-AZA-2-OXA-CYCLOPENTA-3,5-DIENE (67)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.46 g, 2.05 mmol) in dry tetrahydrofuran (2 ml) was added dropwise to a stirring solution of 2,3-dihydro-4*H*-pyran-4-one (**23**) (0.100 g, 1.02 mmol) and triethylamine (0.32 ml, 2.28 mmol) in dry tetrahydrofuran (4 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give the isoxazole (**67**) as a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 2:3) and recrystallised from ethyl acetate/light petroleum to yield the isoxazole (**67**) as a white crystalline solid (0.124 g, 43%), m.p. 101-102.5°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.87 [1H, bs, OH], 2.92 [2H, t, J = 5 Hz, CH_2CO], 3.91 [2H, t, J = 5 Hz, CH_2OH], 7.38-7.48 [3H, m, aromatic hydrogens], 9.14 [1H, s, C5-H]. *Anal. Calcd.* for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.18; H, 3.19; N, 4.84%. The structure was confirmed through X-ray crystallographic analysis (Appendix 3).

NICKEL PEROXIDE

A mixture of 6% sodium hypochlorite solution (18.50 ml, 14.9 mmol) and sodium hydroxide (2.60 g, 65 mmol) was added dropwise to nickel sulphate hexahydrate (8.00 g, 30 mmol) dissolved in water (18.5 ml) and the mixture was allowed to stir at room temperature for 0.5h. The resulting black precipitate was collected by vacuum filtration and washed with water. The filter cake was transferred to a round bottomed flask, benzene (50 ml) was added and any remaining water removed by azeotrope. The solvent was

removed to give a black solid which was then placed in a desiccator under reduced pressure and powered after 24h and again after 48h to give nickel peroxide (2.53 g, 93%).

γ-ACTIVATED MANGANESE DIOXIDE

To a solution of manganese sulphate (6.29 g, 37.2 mmol) in water (120 ml) at 60°C was added, with stirring, a solution of potassium permanganate (4.38 g, 27.7 mmol) in water (83 ml). The brown suspension was stirred at 60°C for 1h, filtered and the precipitate was washed with water to remove sulphate. The precipitate was dried to a constant weight at 65°C to yield γ-activated manganese dioxide as a dark brown amorphous powder (4.98 g, 100%).

3-BROMOCYCLOHEX-2-ENONE (37a)

A solution of 1,3-cyclohexanedione (**36**) (5.00 g, 45 mmol) in chloroform (20 ml) was added to phosphorous tribromide (1.4 ml, 15 mmol). This mixture was then heated to reflux for 2h. The product was poured into ice-cold water, extracted with ether and the organic layer was washed with sodium hydroxide solution, water and then dried (magnesium sulphate). The solvent was removed under reduced pressure to yield 3-bromocyclohex-2-enone (**37a**) as a pale yellow liquid (4.16 g, 53%). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.08 [2H, m, C5-H_2], 2.41 [2H, m, C6-H_2], 2.82 [2H, m, C4-H_2], 6.48 [1H, s, C2-H]. I.r. (neat): 1678, 1608 cm^{-1}.

3-CHLOROCYCLOHEX-2-ENONE (37b)

A mixture of 1,3-cyclohexanedione (**36**) (1.00 g, 8.93 mmol), *N,N*-dimethylformamide (0.90 ml, 12 mmol) and dichloromethane (25 ml) was cooled to 0°C and oxalyl chloride (0.93 ml, 11 mmol) was added over 5 min with stirring. The reaction mixture was allowed to warm to room temperature while stirring for 30 min and then it was poured into ether (40 ml) and water (100 ml). The organic layer was separated, dried (magnesium sulphate), and the solvent was removed under reduced pressure to yield 3-chlorocyclohex-2-enone (**37b**) as a bright orange liquid (0.99 g, 85%). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.07 [2H, m, C5-H_2], 2.41 [2H, m, C6-H_2], 2.69 [2H, m, C4-H_2], 6.22 [1H, s, C2-H]. I.r. (neat): 1680, 1608 cm^{-1}.

9-(2,6-DICHLOROPHENYL)-8-AZA-7-OXA-[4.3.0]-BICYCLONONA-1,8-DIEN-2-ONE (70)

*Method 1: Synthesised by the Dehydrogenation of 9-(2,6-Dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-8-en-2-one (**60**) with Nickel Peroxide.*

To a round bottomed flask, fitted with a reflux condenser, the isoxazoline (**60**) (0.10 g, 0.36 mmol), nickel peroxide (1.00 g) and benzene (10 ml) were added and the mixture was refluxed for 1h. The resulting mixture was filtered through kenite and the solvent was removed under reduced pressure to yield the isoxazole (**70**) as a white solid (0.44 g, 65%), m.p. 205-207°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.29 [2H, p, J = 6 Hz, C4-H_2], 2.54 [2H, t, J = 6 Hz, C5-H_2], 3.12 [2H, t, J = 6 Hz, C3-H_2], 7.40 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 285, 283, 281 (1; M^+), 249, 247, 245 (4, 35, 100; M^+-HCl). *Anal. Calcd.* for $C_{13}H_9Cl_2NO_2$: C, 55.34; H, 3.22; N, 4.97. Found: C, 55.36; H, 3.21; N, 5.20%. The structure was confirmed through X-ray crystallographic

analysis (Appendix 4).

Method 2: Synthesised by the Dehydrogenation of 9-(2,6-Dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-8-en-2-one (60) with γ-Activated Manganese Dioxide.

The isoxazoline (**60**) (0.10 g, 0.35 mmol) in benzene (10 ml) was heated to reflux for 15h with γ-activated manganese dioxide (0.50 g). Water that formed during the reaction was removed *via* a Dean-Stark apparatus. The resulting mixture was filtered through kenite and the solvent was removed under reduced pressure. The product (**70**) was recrystallised (ethyl acetate/light petroleum) (0.07 g, 69%). The physical and spectral data of this sample were identical to those of the sample (**70**) obtained as described above.

Method 3: Synthesised by Cycloaddition of 3-Bromocyclohex-2-enone (37a).

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (1.00 g, 4.5 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirring solution of 3-bromocyclohex-2-enone (**37a**) (1.56 g, 8.9 mmol) and triethylamine (0.68 ml, 4.9 mmol) in dry tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 1h and heated to reflux over night. The mixture was then concentrated under reduced pressure and the residue taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a solid which was recrystallised from ethyl acetate/light petroleum to yield the isoxazole (**70**) as colourless, cubic crystals (0.65 g, 51%). The physical and spectral data of this sample were identical to those of the sample (**70**) obtained as described above.

*Method 4: Synthesised by Cycloaddition of 3-Chlorocyclohex-2-enone (**37b**).*

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.86g, 3.8 mmol) in dry tetrahydrofuran (4.00 ml) was added dropwise to a stirring solution of 3-chlorocyclohex-2-enone (**37b**) (0.50 g, 3.83 mmol) and triethylamine (0.59 ml, 4.2 mmol) in dry tetrahydrofuran (8.00 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue was taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 2:3) and the product recrystallised from ethyl acetate/light petroleum to yield the isoxazole (**70**) as colourless, cubic crystals (0.14 g, 13%). The physical and spectral data of this sample were identical to those of the sample (**70**) obtained as described above.

9-(2,6-DICHLOROPHENYL)-8-AZA-3,7-DIOXA-[4.3.0]-BICYCLONONA-1,8-DIEN-2-ONE (71)

*Method 1: Synthesised by Dehydrogenation of 9-(2,6-Dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonon-8-en-2-one (**64**) with Nickel Peroxide.*

To a round bottomed flask, fitted with a reflux condenser, the isoxazoline (**64**) (0.10 g, 0.350 mmol), nickel peroxide (1.00 g) and benzene (10 ml) were added and the mixture was refluxed for 1h at which point more nickel peroxide was added (0.50 g, 5.5 mmol) and the mixture was left to reflux for a further 1h. The resulting mixture was then filtered through kenite and the solvent was removed under reduced pressure to yield the isoxazole (**71**) as a white solid (0.07 g, 69%), m.p. 175-177°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm):

3.34 [2H, t, J = 6, C5-H_2], 4.69 [2H, t, J = 6, C4-H_2], 7.40-7.50 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 287, 285, 283 (2, 4; M^+); 250, 248 (38, 100; M^+-Cl); 212, 210 (53, 79). *Anal. Calcd.* for $C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93. Found: C, 50.72; H, 2.42; N, 4.90%. The structure was confirmed through X-ray crystallographic analysis (Appendix 5).

Method 2 Synthesised by Dehydrogenation of 9-(2,6-Dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonon-8-en-2-one (64) with γ-Activated Manganese Dioxide.

The isoxazoline (**64**) (0.10 g, 0.35 mmol) in benzene (10 ml) was heated to reflux for 15h with γ-activated manganese dioxide (0.50 g). Water that formed during the reaction was removed *via* a Dean-Stark apparatus. The resulting mixture was filtered through kenite and the solvent was removed under reduced pressure. The product (**71**) was recrystallised (ethyl acetate/light petroleum) (0.06 g, 64%). The physical and spectral data of this sample were identical to those of the sample (**71**) obtained as described above.

3-BROMO-5,6-DIHYDRO-2*H*-PYRAN-2-ONE (38)

A solution of bromine (1.60 g, 10 mmol) in dichloromethane (10 ml) was added over 10 min to a stirred solution of 5,6-dihydro-2*H*-pyran-2-one (**21**) (0.98 g, 10 mmol) in dichloromethane (35 ml). This mixture was stirred for 2h after which triethylamine (1.4 ml, 10 mmol) was added over 5 min. After a further 3h the reaction was poured into water (40 ml) and the organic layer separated. The aqueous fraction was extracted twice with dichloromethane. The combined organic layers were dried (magnesium sulphate) and concentrated. The crude product (**38**) was purified by flash chromatography

(ether/light petroleum; 33:77 200 ml, 1:1 200 ml, and finally neat ether) and recrystallised from ether/light petroleum to yield 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**) as white, crystalline platelets (1.77 g, 75%), m.p. 32-34°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.57 [2H, dt, J = 4.5 Hz, J = 6 Hz, C5-H_2], 4.49 [2H, t, J = 6 Hz, C6-H_2], 7.27 [1H, t, J = 4.5 Hz, C4-H]. Mass spectrum *m/z* (rel. intensity): 178, 176 (33, 33; M^+); ~~146 (~~79; M^+-CO); ~~116 (~~23; M^+-C_2O_2); 53 (50; C_4H_5); 39 (100; $C_3H_3^+$).

2-BROMOCYCLOHEX-2-ENONE (39)

A solution of bromine (1.60 g, 10 mmol) in dichloromethane (10 ml) was added over 10 min to a stirred solution of cyclohex-2-enone (**19**) (0.96 g, 10 mmol) in dichloromethane (35 ml). This mixture was stirred for 2h after which triethylamine (1.40 ml, 10 mmol) was added over 5 min. After a further 3h the reaction mixture was poured into water (40 ml) and the organic layer was separated. The aqueous fraction was extracted twice with dichloromethane. The combined organic layers were dried (magnesium sulphate) and concentrated. The crude product was a solid which showed no starting material by thin layer chromatography thus it was recryatallized from aqueous ethanol to yield 2-bromocyclohex-2-enone (**39**) as large colourless platelets (1.06 g, 60%), m.p. 72-75°C . ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.08 [2H, m, C5-H_2], 2.45 [2H, m, C4-H_2], 2.64 [2H, m, C6-H_2], 7.44 [1H, t, J = 4.5 Hz, C3-H]. Mass spectrum *m/z* (rel. intensity): 176, 174 (48, 50; M^+); ~~147 (~~61; M^+-CO); ~~133 (~~15); ~~118 (23); 133 (15);~~ 67 (100; C_5H_7); 39 (70; $C_3H_3^+$).

3-BROMO-5,6-DIHYDRO-4*H*-PYRAN-4-ONE (40)

A solution of bromine (0.73 g, 4.5 mmol) in dichloromethane (5 ml) was

added over 10 min to a stirred solution of 2,3-dihydro-4*H*-pyran-4-one (**23**) (0.20 g, 2.05 mmol) in dichloromethane (17 ml). This mixture was stirred for 2h after which triethylamine (0.63 ml, 0.45 mmol) was added over 5 min. After a further 3h the reaction mixture was poured into water (20 ml) and the organic layer was separated. The aqueous fraction was extracted twice with dichloromethane. The combined organic layers were dried (magnesium sulphate) and concentrated. The crude product was purified by flash chromatography (ethyl acetate/light petroleum; 2:3) and recrystallised from ether/light petroleum to yield 3-bromo-5,6-dihydro-4*H*-pyran-4-one (**40**) as pale yellow, needle like crystals (0.23 g, 64%), m.p. 92-96°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.83 [2H, t, J = 6.5 Hz, C5-H_2], 4.59 [2H, t, J = 6.5 Hz, C6-H_2], 7.71 [1H, s, C2-H]. Mass spectrum *m/z* (rel. intensity): 178, 176 (100, 100; M^+); 150, 148 (99,99; M^+-CO).

7-(2,6-DICHLOROPHENYL)-8-AZA-9-OXA-[4.3.0]-BICYCLONONA-1,7-DIEN-2-ONE (73)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.26 g, 1.14 mmol) in dry tetrahydrofuran (2.00 ml) was added dropwise to a stirring solution of 2-bromocyclohex-2-enone (**39**) (0.20 g, 1.14 mmol) and triethylamine (0.17 ml, 1.25 mmol) in dry tetrahydrofuran (4.00 ml). The mixture was stirred at room temperature for 3h and heated to reflux for 1h. The mixture was then concentrated under reduced pressure and the residue was taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. This was then recrystallised from ethyl acetate/light petroleum to yield the isoxazole (**73**) as pale orange crystals (0.17 g, 53%), m.p. 108.5-110.5°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.24 [2H, p, J = 6, Hz, C4-H_2],

2.63 [2H, t, J = 6 Hz, C5-H_2], 2.73 [2H, t, J = 6Hz, C3-H_2], 7.84 [3H, m, aromatic hydrogens]. Mass spectrum m/z (rel. intensity): 285, 283, 281 (8, 37, 53; M^+); 251 (72; M^+-NO); 246 (47; M^+-Cl); 197 (100; M^+-C_5H_8O). *Anal. Calcd.* for $C_{13}H_9Cl_2NO_2$: C, 55.34; H, 3.22; N, 4.97. Found: C, 54.96; H, 3.25; N, 4.97%. The structure was confirmed through X-ray crystallographic analysis (Appendix 6).

7-(2,6-DICHLOROPHENYL)-8-AZA-3,9-DIOXA-[4.3.0]-BICYCLONONA-1,7-DIEN-2-ONE (76)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.79g, 3.5 mmol) in dry tetrahydrofuran (4.0 ml) was added dropwise to a stirring solution of 3-bromo-5,6-dihydro2*H*-pyran-2-one (**38**) (0.43 g, 2.4 mmol) and triethylamine (0.27, 2.7 mmol) in dry tetrahydrofuran (8.0 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue was taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 2:3) and recrystallised from ethyl acetate/light petroleum to yield the isoxazole (**76**) as large, rectangular, colourless crystals (0.34 g, 50%), m.p. 106-107°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.89 [2H, t, J = 6 Hz, C5-H_2], 4.68 [2H, t, J = 6 Hz, C4-H_2], 7.42-7.51 [3H, m, aromatic hydrogens]. Mass spectrum m/z (rel. intensity): 288, 285, 283 (3, 14, 21; M^+); 248 (23; M^+-Cl); 211 (100); 197 (33; M^+-$C_4H_6O_2$). *Anal. Calcd.* for $C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93. Found: C, 50.86; H, 2.49; N, 4.93%. The structure was confirmed through X-ray crystallographic analysis (Appendix 7).

COMPETITIVE STUDIES

RELATIVE RATES OF CYCLOADDITION OF 2-CYCLOHEXENE-1-ONE (19) AND 5,6-DIHYDRO-2*H* -PYRAN-2-ONE (21)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.23 g, 1.0 mmol) in dry tetrahydrofuran (1.5 ml) was added dropwise to a stirring solution of 2-cyclohexene-1-one (**19**) (0.10 g, 1.0 mmol), 5,6-dihydro-2*H*-pyran-2-one (**21**) (0.10 g, 1.0 mmol) and triethylamine (0.16 ml, 0.65 mmol) in dry tetrahydrofuran (3.00 ml). The mixture was stirred at room temperature for 1h and then refluxed for 15h. The mixture was then concentrated under reduced pressure and the crude product was analysed by ^{1}H nmr spectroscopy. The cycloadducts (**60**) and (**64**) present in a ratio of 43:57 in both the first and second runs, giving an average ratio of 43:57. This ratio was used in the calculation of the relative reactivities of the dipolarophiles (**19**) and (**21**).

RELATIVE RATES OF CYCLOADDITION OF CYCLOHEX-2-ENONE (19) AND 2,3-DIHYDRO-4*H* -PYRAN-4-ONE (23)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.23 g, 1.0 mmol) in dry tetrahydrofuran (1.5 ml) was added dropwise to a stirring solution of cyclohex-2-enone (**19**) (0.10 g, 1.0 mmol), 2,3-dihydro-4*H*-pyran-4-one (**23**) (0.10 g, 1.0 mmol) and triethylamine (0.16 ml, 0.65 mmol) in dry tetrahydrofuran (3.00 ml). The mixture was stirred at room temperature for 1h and then refluxed for 15h. The mixture was then concentrated under reduced pressure and the crude product was then analysed by ^{1}H nmr spectroscopy. The cycloadducts (**60**) and (**67**) present in a ratio of 60:40 in both the first and second runs, giving an average ratio of 60:40. This ratio was used in the calculation of the relative reactivities of the dipolarophiles (**19**) and (**23**).

RELATIVE RATES OF CYCLOADDITION OF CYCLOHEX-2-ENONE (19) AND 2-BROMOCYCLOHEX-2-ENONE (39)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.13 g, 0.57 mmol) in dry tetrahydrofuran (1.00 ml) was added dropwise to a stirring solution of 2-cyclohexene-1-one (**19**) (0.06 g, 0.57 mmol), 2-bromocyclohex-2-enone (**39**) (0.10 g, 0.57 mmol) and triethylamine (0.09 ml, 0.65 mmol) in dry tetrahydrofuran (2.00 ml). The mixture was stirred at room temperature for 1h and then heated to reflux for 15h. The mixture was then concentrated under reduced pressure and the crude product was then analysed by ^{1}H nmr spectroscopy. The cycloadducts (**60**) and (**73**) present in a ratio of 82:18 in the first run and a ratio of 84:16 in the second run, giving an average ratio of 83:17. This ratio was used in the calculation of the relative reactivities of the dipolarophiles (**19**) and (**39**).

RELATIVE RATES OF CYCLOADDITION OF 2-BROMOCYCLOHEX-2-ENEONE (39) AND 3-BROMOCYCLOHEX-2-ENONE (37a)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.38 g, 1.7 mmol) in dry tetrahydrofuran (2.00 ml) was added dropwise to a stirring solution of 2-bromocyclohex-2-enone (**39**) (0.30 g, 1.7 mmol), 3-bromocyclohex-2-enone (**37a**) (0.30 g, 1.7 mmol) and triethylamine (0.26 ml, 1.9 mmol) in dry tetrahydrofuran (4.00 ml). The mixture was stirred at room temperature for 1h and then heated to reflux for 15h. The mixture was then concentrated under reduced pressure and the crude product was then analysed by ^{1}H nmr spectroscopy. The cycloadducts (**73**) and (**70**) present in a ratio of 69:31 in the first run and a ratio of 62:38 in the second run, giving an average ratio of 66:34. This ratio was used in the calculation of the relative reactivities of the dipolarophiles (**39**) and (**37a**).

RELATIVE RATES OF CYCLOADDITION OF 5,6-DIHYDRO-2*H*-PYRAN-2-ONE (21) AND 3-BROMO-5,6-DIHYDRO-2*H* -PYRAN-2-ONE (38)

A solution of 2,6-dichlorobenzohydroximinoyl chloride (**29**) (0.63 g, 2.8 mmol) in dry tetrahydrofuran (4.25 ml) was added dropwise to a stirring solution of 5,6-dihydro-2*H*-pyran-2-one (**21**) (0.28 g, 2.8 mmol), 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**38**) (0.50 g, 2.8 mmol) and triethylamine (0.45 ml, 3.1 mmol) in dry tetrahydrofuran (8.50 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 15h. The mixture was then concentrated under reduced pressure and the crude product was then analysed by high field ^{1}H nmr spectroscopy. The cycloadducts (**64**) and (**76**) present in a ratio of 82:18 in the first run and a ratio of 83:17 in the second run, giving an average ratio of 83:17. This ratio was used in the calculation of the relative reactivities of the dipolarophiles (**21**) and (**38**).

2-[1-(2,6-DICHLOROPHENYL)-IMINOMETHYL]-3-HYDROXYCYCLOHEX-2-EN-1-ONE (79)

Method 1: Synthesised by using Palladium/Carbon/Hydrogen

The isoxazole (**70**) (0.42 g, 1.53 mmol) was dissolved in ethyl acetate (50 ml). To this solution 5% palladium on carbon (0.20 g, 0.09 mmol) was added and the resulting mixture was stirred at room temperature for 15h under an atmosphere of hydrogen. The suspension was filtered through kenite and the solvent evaporated to yield a white solid which was subsequently recrystallised from ethyl acetate/light petroleum to give the imine (**79**) as white, needle-like crystals (0.43 g, 98%), m.p. 229-232°C (decomp). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.92 [1H, bs, OH], 1.97 [2H, p, J = 6.5 Hz, C5-H_2], 2.43 [2H, t, J = 6.5 Hz,

C6-H_2], 2.65 [2H, t, J = 6.5 Hz, C4-H_2], 6.06 [1H, bs, NH], 7.26-7.43 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 287, 285, 283 (2, 4; M^+); 249, 247 (37, 100; M^+-Cl). The structure was confirmed through X-ray crystallographic analysis (Appendix 8).

Method 2: Synthesised by Treating the Isoxazole (70) with Baker's Yeast

A 2l round bottomed flask, fitted with a thermometer, was charged with sucrose (75 g), water (400 ml) and freshly opened dried yeast added in that order. The mixture was gently stirred at 37°C for 1h. The isoxazole (**70**) was added and the mixture was incubated with gentle stirring at 37°C. Kenite was added and the mixture was filtered through a large sintered glass funnel. The resulting filter-cake was washed with water (100 ml) followed by ethyl acetate (200 ml), the filtrate saturated with sodium chloride and extracted with ethyl acetate (5 x 500 ml) and the combined organic extracts were dried (magnesium sulphate). The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate/light petroleum; 3:5) and the product was recrystallised from ethyl acetate/light petroleum to give the imine (**79**) as colourless needle-like crystals. Several variations, listed below, of this procedure were tested to determine the optimal conditions for the reaction of the isoxazole (**70**) with yeast.

a) The isoxazole (**70**) (0.50 g, 1.77 mmol) was incubated for 24h with baker's yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light petroleum (0.115 g, 70% process yield, based on the isoxazole (**70**) recovered, 0.34 g).

b) The isoxazole (**70**) (0.25 g, 0.89 mmol) was incubated for 24h with baker's yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light

petroleum (0.017 g, 11% process yield, based on the isoxazole (**70**), 0.095 g).

c) The isoxazole (**70**) (0.75 g, 2.66 mmol) was incubated for 24h with baker's yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light petroleum (0.185 g, 32% process yield, based on the isoxazole (**70**) recovered, 0.23 g).

d) The isoxazole (**70**) (0.50 g, 1.77 mmol) was incubated for 4h with baker's yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light petroleum (0.095 g, 34% process yield, based on the isoxazole (**70**) recovered, 0.28 g).

e) The isoxazole (**70**) (0.50 g, 1.77 mmol) was incubated for 24h with Munich Lager yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light petroleum (0.026 g, 8% process yield, based on the isoxazole (**70**) recovered, 0.16 g).

f) The isoxazole (**70**) (0.50 g, 1.77 mmol) was incubated for 24h with Balmoral Ale yeast (10 g). The imine (**79**) was recrystallised from ethyl acetate/light petroleum (0.050 g, 14% process yield, based on the isoxazole (**70**) recovered, 0.16 g).

The spectral and physical data of the products from reactions a) - f) were identical to those obtained for the sample (**79**) as described above.

3-[1-(2,6-DICHLOROPHENYL)-IMINOMETHYL]-4-HYDROXY-5,6-DIHYDRO-2*H*-PYRAN-2-ONE (81)

Method 1: Synthesised by using Palladium/Carbon/Hydrogen

The isoxazole (**71**) (0.58 g, 2.04 mmol) was dissolved in ethyl acetate (50

ml). To this solution 5% palladium on carbon (0.20 g, 0.09 mmol) was added and the resulting mixture was stirred at room temperature for 15h under an atmosphere of hydrogen. The suspension was filtered through kenite and the solvent was evaporated to yield a white solid which was subsequently recrystallised from ethyl acetate/light petroleum to give the imine (**81**) as white, needle-like crystals (0.54 g, 93%), m.p. 216-218°C (decomp). ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.60 [1H, s, OH], 2.73 [2H, t, *J* = 6 Hz, C5-H_2], 4.35 [2H, t, *J* = 6 Hz, C6-H_2], 6.34 [1H, bs, NH], 7.25-7.39 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 289, 287, 285 (0.7, 1; M^+); 252, 250 (33, 100; M^+-Cl). The structure was confirmed through X-ray crystallographic analysis (Appendix 9).

Method 2: Synthesised by Treating the Isoxazole (71) with Baker's Yeast

A 2l round bottomed flask, fitted with a thermometer, was charged with sucrose (75 g), water (400 ml) and freshly opened dried baker's yeast (10 g) added in that order. The mixture was gently stirred at 37°C for 1h. The isoxazole (**71**) (0.50 g, 1.76 mmol) was added and the mixture was stirred for 24h. Kenite was added and the mixture was filtered through a large sintered glass funnel. The resulting filter-cake was washed with water (100 ml) followed by ethyl acetate (200 ml), the filtrate was saturated with sodium chloride and extracted with ethyl acetate (5 x 500 ml) and the combined organic extracts were dried (magnesium sulphate). The solvent was removed under reduced pressure. The resulting residue was then purified by flash chromatography (ethyl acetate/light petroleum; 3:5) and the product recrystallised from ethyl acetate/light petroleum to yield the imine (**81**) as small, yellowish prismic crystals (0.106 g, 69% process yield, based on the isoxazole (**71**) recovered, 0.345 g). The spectral and physical data of the reaction

was identical to those obtained for the sample (**81**) as described above.

METHYL 5-(3-CHOLROPROPYL)-3-HYDROXY-2-(1-PROPYLIMINOMETHYL)-CYCLOHEX-2-EN-1-ONE-5-CARBOXYLATE (44)

A 2l round bottomed flask, fitted with a thermometer, was charged with sucrose (75 g), water (400 ml) and freshly opened dried baker's yeast (10 g) added in that order. The mixture was gently stirred at 37°C for 1h. The isoxazole (**43**) (0.50 g, 1.67 mmol) was added and the mixture was incubated with gentle stirring at 37°C for 24h. Kenite was added and the mixture was filtered through a large sintered glass funnel. The resulting filter-cake was washed with water (100 ml) followed by ethyl acetate (200 ml), the filtrate saturated with sodium chloride and extracted with ethyl acetate (5 x 500 ml) and the combined organic extracts were dried (magnesium sulphate). The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate/light petroleum; 1:1) and the product was recrystallised from ethyl acetate/light petroleum to give the imine (**44**) as colourless platelet-like crystals (0.091 g, 68% process yield, based on the isoxazole (**43**) recovered, 0.37 g). ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.02 (3H, t, $CH_2CH_2C\underline{H}_3$), 1.5-2.0 (7H, m, $CH_2C\underline{H}_2CH_3$, $C\underline{H}_2C\underline{H}_2CH_2Cl$, O<u>H</u>), 2.49 (2H, t, $C\underline{H}_2CH_2CH_3$), 2.8-3.1 (4H, m, C4-H_2, C6-H_2), 3.50 (2H, t, $C\underline{H}_2Cl$), 3.68 (3H, s, -OCOC<u>H</u>$_3$), 6.34 (1H, bs, N<u>H</u>). The ^{1}H nmr spectrum for the imine (**43**) is consistent with the spectrum obtained from CSIRO.[44]

TREATMENT OF ISOXAZOLES (67), (73), (76) AND (88)-(91) WITH BAKER'S YEAST

The isoxazoles (**67**),(**73**), (**76**) and (**88**)-(**91**) (0.50 g) were individually treated with baker's yeast (10 g) using an incubation time of 24h. The reaction of the isoxazole (**67**) gave a complex mixture of products ~~was obtained~~ which was inseparable by chromatography on silica. The reaction of the isoxazole (**73**) with baker's yeast gave only starting material (0.34 g, 67%). The crude product mixture obtained from the reaction of the isoxazole (**76**) was purified by flash chromatography (ethyl acetate/light petroleum; 3:5) and the product was recrystallised from ethyl acetate/light petroleum to yield ethyl 5-(2,6-dichlorophenyl)-4-(2-hydroxyethyl)isoxazole-3-carboxylate (**83**) as a colourless, viscous oil (8 mg, 2% process yield, based on the isoxazole (**76**) recovered, 0.135 g). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.47 [3H, t, J = 7 Hz, $C\underline{H}_3$-CH_2-], 1.59 [1H, s, -O$\underline{H}$], 2.86 [2H, t, J = 6 Hz, OH-CH_2-$C\underline{H}_2$-], 3.69 [2H, q, J = 6 Hz, OH-$C\underline{H}_2$-CH_2-], 4.49 [2H, t, J = 7 Hz, CH_3-$C\underline{H}_2$-O-], 7.44 [3H, m, aromatic hydrogens]. I.r. (neat): 3464, 2924, 1732, 1600, 1562, 1480 cm^{-1}. Mass Spectrum*m/z* (rel.intensity): 333, 332, 331 (9, 49, 73; M$^+$), 230, 228, 226 (17, 78, 100), 176, 174, 172 (13, 65, 98). HR mass spect. found M$^+$, *m/z* 329.0224; $C_{14}H_{13}{}^{35}Cl_2NO_4$ requires M$^+$, *m/z* 329.0210. The reaction of the isoxazole (**88**) with baker's yeast gave only starting material (0.30 g, 59%), as did the reactions of the isoxazole (**89**) (0.45 g, 90%), the isoxazole (**90**) (0.47 g, 97%) and the isoxazole (**91**) (0.36 g, 71%).

MESITOALDOXIME

To mesitoaldehyde (**92**) (8.00 g, 54 mmol) in water (13.5 ml), ethanol (13.5 ml) and ice (23 ml) was added hydroxylamine hydrochloride (4.13 g, 59 mmol). To this mixture was added 50% sodium hydroxide solution (10.80 ml) with stirring. The mixture was stirred for 1.5h, washed with ether to remove

any neutral impurities, acidified with concentrated hydrochloric acid solution and extracted twice with ether. The combined extracts were dried (calcium sulphate) and the solvent was removed under reduced pressure. The resulting white solid was recrystallised from aqueous ethanol to yield mesitoaldoxime as small, white, trapezoid crystals (8.81 g, 33%), m.p. 118-123°C (Lit.[22] 125-127°C). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.74 [1H, bs, CH=NOH], 2.29 [3H, s, CH_3], 2.37 [6H, s, $(CH_3)_2$], 6.86 [2H, s, aromatic hydrogens], 8.42 [1H, s, CH=NOH].

MESITOHYDROXIMINOYL CHLORIDE (93)

To a stirred solution of mesitoaldoxime (2.5 g, 15.3 mmol) in *N,N*-dimethylformamide (13 ml) was added *N*-chlorosuccinimide (2.05 g, 15.3 mmol). The initial *N*-chlorosuccinimide addition resulted in a slight temperature decrease after which the reaction became exothermic but was kept between 25-35°C using an ice bath. After the cessation of the exothermic reaction the mixture was poured into ice/water (50 ml) and washed twice with ether. The combined organic fractions were washed three times with water and dried (calcium sulphate) and the solvent was removed under reduced pressure to yield mesitohydroximinoyl chloride (**93**) as a pale yellow powder (2.11 g, 70%), m.p. 48-63°C (Lit.[22] 61-69°C). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.28 [6H, s, $(CH_3)_2$], 2.41 [3H, s, CH_3], 6.86 [2H, s, aromatic hydrogens], 8.31 [1H, s, C(Cl)=NOH]. ^{1}H nmr spectral data is consistent with the literature values.[22]

MESITOBENZONITRILE OXIDE (50)

To a solution of mesitohydroximinoyl chloride (**93**) (1.5 g, 7.6 mmol) in tetrahydrofuran (30 ml) was added triethylamine (1.16 ml, 8.4 mmol). This

mixture was stirred for 2h at room temperature and the solvent was removed under reduced pressure. The resulting solid was dissolved in chloroform and washed three times with water. The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure to yield mesitonitrile oxide (**50**) as a pale, yellow powder (1.14 g, 93%), m.p. 105-107°C (Lit.[22] 110-112°C). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 2.29 [3H, s, $C\underline{H}_3$], 2.41 [6H, s, $(C\underline{H}_3)_2$], 6.89 [2H, s, aromatic hydrogens].

(±)-ETHYL 5-(2,4,6-TRIMETHYLPHENYL)-3-PHENYL-Δ^2-ISOXAZOLINE-4-CARBOXYLATE (54)

(±)-ETHYL 5-(2,4,6-TRIMETHYLPHENYL)-4-PHENYL-Δ^2-ISOXAZOLINE-3-CARBOXYLATE (55)

The nitrile oxide (**50**) (0.242 g, 1.5 mmol) and ethyl cinnamate (**53**) (0.26 g, 1.5 mmol) were taken into a 30% ethanol solution (20 ml) and added to pH 7.2 buffer (12.5 ml). This mixture was incubated at 37°C for 30h. The mixture was saturated with sodium chloride and extracted with chloroform (2 x 20 ml). The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**54**) and (**55**) were found to be present in a ratio of 61:39. The isoxazolines (**54**) and (**55**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum. The method followed was identical to the method outlined by Rama Rao *et al.*[48,49]

Isoxazoline (54) (0.202 g, 40%), m.p. 87-89°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 0.95 [3H, t, J = 7 Hz, $C\underline{H}_3$-CH_2-], 2.22 [3H, s, $C\underline{H}_3$-Ar], 2.28 [6H, s, $(C\underline{H}_3)_2$-Ar], 4.03 [2H, m, CH_3-$C\underline{H}_2$-], 4.37 [1H, d, J = 9.5 Hz, C4-H], 6.10 [1H, d, J = 9.5 Hz,

C3-H], 7.25-7.40 [7H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 337 (100; M^+), 192 (58), 186 (67), 104 (96).

Isoxazoline (55) (0.119 g, 24%), m.p. 85-86°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.35 [3H, t, J = 7 Hz, $C\underline{H}_3$-CH_2-], 1.98 [3H, s, $C\underline{H}_3$-Ar], 2.22 [6H, s, $(C\underline{H}_3)_2$-Ar], 4.33 [2H, q, J = 7 Hz, CH_3-$C\underline{H}_2$-], 4.81 [1H, d, J = 4 Hz, C3-H], 5.32 [1H, d, J = 4 Hz, C4-H], 7.14-7.17 [2H, m, aromatic hydrogens], 7.26-7.28 [3H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 337 (7; M^+), 264 (100; M^+-$OCOCH_2CH_3$), 161 (70).

Variations of this procedure were undertaken to determine the effects of β-cyclodextrin and/or baker's yeast on the cycloaddition of the nitrile oxide (**50**) and ethyl cinnamate (**53**).

a) Baker's yeast (0.50 g) was added to the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**54**) and (**55**) were found to be present in a ratio of 57:43 (Lit.[48,49] 65:35). The isoxazolines (**54**) and (**55**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**54**) (0.14 g, 28%) and the isoxazoline (**55**) (0.110 g, 21%).

b) β-Cyclodextrin saturated 30% ethanol solution (20 ml) and β-cyclodextrin saturated pH 7.2 buffer (12.5 ml) were used in the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**54**) and (**55**) were found to be present in a ratio of 60:40. The isoxazolines (**54**) and (**55**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**54**) (0.196 g, 29%) and the

isoxazoline (**55**) (0.116 g, 23%).

c) Baker's yeast (0.50 g), β-cyclodextrin saturated 30% ethanol solution (20 ml) and β-cyclodextrin saturated pH 7.2 buffer (12.5 ml) were added to the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**54**) and (**55**) were found to be present in a ratio of 59:41 (Lit.[48,49] 0:100). The isoxazolines (**54**) and (**55**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**54**) (0.146 g, 29%) and the isoxazoline (**55**) (0.111 g, 22%).

d) To a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g, 1.5 mmol), the nitrile oxide (**50**) and ethyl cinnamate (**53**) were added in sequentially decreasing amounts, that is the nitrile oxide (**50**)/ethyl cinnamate (**53**), 1:1, (1.0 mmol, 0.50 mmol, 0.25 mmol, 0.06 mmol). These mixtures were incubated at 37°C for 30h, extracted with chloroform (2 x 20 ml). Analysis of the crude product mixtures by ^{1}H nmr spectroscopy showed that the isoxazolines (**54**) and (**55**) were present in ratios of 46:54, 23:77, 26:74 and 0:100, respectively, in the extracts.

(±)-ETHYL 5-(2,6-DICHLOROPHENYL)-3-PHENYL-Δ^2-ISOXAZOLINE-4-CARBOXYLATE (56)

(±)-ETHYL 5-(2,6-DICHLOROPHENYL)-4-PHENYL-Δ^2-ISOXAZOLINE-3-CARBOXYLATE (94)

The nitrile oxide (**30**) (0.282 g, 1.5 mmol) and ethyl cinnamate (**53**) (0.26 g, 1.5 mmol) were taken into a 30% ethanol solution (20 ml) and added to pH 7.2 buffer (12.5 ml). This mixture was incubated at 37°C for 30h. The mixture was saturated with sodium chloride and extracted with chloroform (2 x 20 ml).

The extracts were dried (magnesium sulphate) and concentrated under reduced pressure. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**56**) and (**94**) were found to be present in a ratio of 87:13. The isoxazolines (**56**) and (**94**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum. The method followed was identical to the method outlined by Rama Rao *et al.*[48,49]

Isoxazoline (**56**). (0.191 g, 35%), m.p. 88-89°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.02 [3H, t, J = 7 Hz, $C\underline{H}_3$-CH_2-], 4.10 [2H, m, CH_3-$C\underline{H}_2$-], 4.57 [1H, d, J = 9 Hz, C4-H], 6.26 [1H, d, J = 9 Hz, C3-H], 7.40 [8H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 367, 365, 363 (2, 8, 12, M^+), 192 (100), 150, 148, 146 (1, 11, 37). The structure was confirmed through X-ray crystallographic analysis (Appendix 10).

Isoxazoline (**94**). (0.027 g, 5%), m.p. 87°C. ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.35 [3H, t, J = 7 Hz, $C\underline{H}_3$-CH_2-], 4.35 [2H, q, J = 7 Hz, CH_3-$C\underline{H}_2$-], 5.24 [1H, d, J = 5.5 Hz, C3-H], 5.27 [1H, d, J = 5.5 Hz, C4-H], 7.25-7.40 [8H, m, aromatic hydrogens].

Variations of this procedure were undertaken to determine the effects of β-cyclodextrin and/or baker's yeast on the cycloaddition of the nitrile oxide (**30**) and ethyl cinnamate (**53**).

a) Baker's yeast (0.50 g) was added to the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**56**) and (**94**) were found to be present in a ratio of 94:6 (Lit.[48,49] 100:0). The isoxazolines (**56**) and (**94**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**56**) (0.158 g, 29%) and the isoxazoline (**94**) (0.011 g, 2%).

b) β-Cyclodextrin saturated 30% ethanol solution (20 ml) and β-cyclodextrin saturated pH 7.2 buffer (12.5 ml) were used in the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**56**) and (**94**) were found to be present in a ratio of 87:13. The isoxazolines (**56**) and (**94**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**56**) (0.328 g, 60%) and the isoxazoline (**94**) (0.044 g, 8%).

c) Baker's yeast (0.50 g), β-cyclodextrin saturated 30% ethanol solution (20 ml) and β-cyclodextrin saturated pH 7.2 buffer (12.5 ml) were added to the reaction mixture. The crude product mixture was analysed by ^{1}H nmr spectroscopy and the isoxazolines (**56**) and (**94**) were found to be present in a ratio of 97:3 (Lit.[48,49] 100:0). The isoxazolines (**56**) and (**94**) were separated from the crude product mixture by flash chromatography (ethyl acetate/light petroleum; 1:5), and recrystallised from light petroleum to yield the isoxazoline (**56**) (0.186 g, 34%) and the isoxazoline (**94**) (0.005 g, 1%).

d) To a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g, 1.5 mmol), the nitrile oxide (**30**) (0.47 g, 0.25 mmol) and ethyl cinnamate (**53**) (0.044 g, 0.25 mmol) were added. Analysis of the crude product mixture by ^{1}H nmr spectroscopy showed the isoxazolines (**56**) and (**94**) were present in a ratio of 80:20.

TREATMENT OF A REGIOISOMERIC MIXTURE OF ISOXAZOLINES (54) AND (55) WITH β-CYCLODEXTRIN

A 47:53 mixture of isoxazolines (**54**) and (**55**) (10 mg) was taken into a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g,

1.5 mmol). This mixture was incubated at 37°C for 30h and extracted with chloroform (2 x 20 ml) followed by ethyl acetate (3 x 20ml). The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure. Analysis by ^{1}H nmr spectroscopy of the the combined chloroform extracts showed the isoxazolines (**54**) and (**55**) present in a ratio of 21:79, the first ethyl acetate extract, 25:75, the second ethyl acetate extract, 77:33, third ethyl acetate extract,100:0.

TREATMENT OF A REGIOISOMERIC MIXTURE OF ISOXAZOLINES (56) AND (94) WITH β-CYCLODEXTRIN

A 87:13 mixture of isoxazolines (**56**) and (**94**) (10 mg) was taken into a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g, 1.5 mmol). This mixture was incubated at 37°C for 30h and extracted with chloroform (2 x 20 ml). The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure. The combined extracts were analysed by ^{1}H nmr spectroscopy which showed that the isoxazolines (**56**) and (**94**) were present in a ratio of 80:20.

TREATMENT OF A REGIOISOMERIC MIXTURE OF ISOXAZOLINES (56) AND (94) WITH BAKER'S YEAST

A 87:13 mixture of isoxazolines (**56**) and (**94**) (10 mg) was taken into a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and baker's yeast (0.50 g). This mixture was incubated at 37°C for 30h and extracted with chloroform (2 x 20 ml). The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure. The combined extracts were analysed by ^{1}H nmr spectroscopy and showed only the presence of the isoxazoline (**56**), that is

the ratio of the isoxazolines (**56**) and (**94**) was 100:0.

4-*t*-BUTYLBENZALDOXIME

To 4-*t*-butylbenzaldehyde (**95**) (19.4 g, 120 mmol) in water (27 ml), ethanol (27 ml) and ice (46 ml) was added hydroxylamine hydrochloride (9.17 g, 132 mmol). To this mixture was added 50% sodium hydroxide solution (21.60 ml) with stirring. The mixture was stirred for 1.5h, washed with ether to remove any neutral impurities, acidified with concentrated hydrochloric acid solution and extracted twice with ether. The combined extracts were dried (calcium sulphate) and the solvent was removed under reduced pressure. The resulting white solid was recrystallised from aqueous ethanol to yield 4-*t*-butylbenzaldoxime as white, needle-like crystals (10.95 g, 52%), m.p. 105-106°C. ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.32 [9H, s, ($C\underline{H}_3$)$_3$], 7.40 [2H, d, J = 6.5Hz, aromatic hydrogens], 7.52 [2H, d, J = 6.5 Hz, aromatic hydrogens], 8.14 [1H, s, C<u>H</u>=NOH], 8.48 [1H, bs, CH=NO<u>H</u>]. Mass spectrum (FAB) *m/z* (rel. intensity): 178 (100; M^++H), 154 (75), 136 (64).

4-*t*-BUTYLBENZOHYDROXIMINOYL CHLORIDE (**96**)

To a stirred solution of 4-*t*-butylbenzaldoxime (10.0 g, 56 mmol) in *N*,*N*-dimethylformamide (80 ml) was added *N*-chlorosuccinimide (7.54 g, 56 mmol). The initial *N*-chlorosuccinimide addition resulted in a slight temperature decrease after which the reaction became exothermic and the mixture was kept between 25-35°C using an ice bath. After the cessation of the exothermic reaction the mixture was poured into ice/water (150 ml) and extracted twice with ether. The combined organic fractions were washed three times with water and dried (calcium sulphate) and the solvent was removed

under reduced pressure to yield the hydroximinoyl chloride (**96**) as a yellow powder (9.16 g, 77%), m.p. 70-76°C. ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.27 [9H, s, $(C\underline{H}_3)_3$], 8.50 [1H, s, C(Cl)=NO<u>H</u>]. Mass spectrum (FAB) *m/z* (rel. intensity): 214, 212 (32, 85; M^+ + H), 163, 161 (21, 99), 56 (100).

(±)-ETHYL 5-(4-*t*-BUTYLPHENYL)-3-PHENYL-Δ^2-ISOXAZOLINE-4-CARBOXYLATE (98)

(±)-ETHYL 5-(4-*t*-BUTYLPHENYL)-4-PHENYL-Δ^2-ISOXAZOLINE-3-CARBOXYLATE (99)

A solution of 4-*t*-butylbenzohydroximinoyl chloride (**96**) (1.00g, 4.7 mmol) in dry tetrahydrofuran (15.0 ml) was added dropwise to a stirring solution of ethyl cinnamate (**53**) (0.83 g, 4.5 mmol) and triethylamine (0.72 ml, 5.2 mmol) in dry tetrahydrofuran (30.0 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue was taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 1:20) and recrystallised from ethyl acetate/light petroleum to yield the two isoxazoliness (**98**) and (**99**) in the ratio 68:32 by ^{1}H nmr (200 MHz, $CDCl_3$).

<u>Isoxazoline (98)</u> (0.78 g, 47%), m.p. 78-79°C. ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.24 [3H, t, J = 7Hz, $C\underline{H}_3CH_2$-], 1.33 [9H, s, $(CH_3)_3$-Ar-], 4.25 [2H, q, J = 7 Hz, $CH_3C\underline{H}_2$], 4.43 [1H, d, J = 6 Hz, C4-H], 5.97 [1H, d, J = 6 Hz, C3-H], 7.27-7.70 [9H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 351 (46; M^+), 336 (39, M^+-CH_3), 192 (48), 160 (36), 146 (58), 105 (100), 77 (43). HR mass spect. found

M^+, *m/z* 351.1793; $C_{22}H_{25}NO_3$ requires M^+, *m/z* 351.1834.

Isoxazoline (**99**) (0.19g, 11 %), m.p. 96-97°C. ^1H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.27 [9H, s, $(CH_3)_3$-C-], 1.33 [3H, t, *J* = 7Hz, CH_3CH_2-], 4.29 [2H, q, *J* = 7 Hz, CH_3CH_2], 4.94 [1H, d, *J* = 4 Hz, C3-H], 5.02 [1H, d, *J* = 4 Hz, C4-H], 7.27-7.58 [9H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 351 (32; M^+), 278 (100), 114 (30), 91 (44). HR mass spect. found M^+, *m/z* 351.1766; $C_{22}H_{25}NO_3$ requires M^+, *m/z* 351.1834.

PIVALDOXIME

To pivaldehyde (**100**) (1.00 g, 11.6 mmol) in water (3 ml), ethanol (3 ml) and ice (5 ml) was added hydroxylamine hydrochloride (0.89 g, 12.8 mmol). To this mixture was added 50% sodium hydroxide solution (1.2 ml) with stirring. The mixture was stirred for 1.5h, washed with ether to remove any neutral impurities, acidified with concentrated hydrochloric acid solution and extracted twice with ether. The combined extracts were dried (calcium sulphate) and the solvent was removed under reduced pressure. The resulting white solid was recrystallised from aqueous ethanol to yield pivaldoxime as a labile, pale yellow liquid (1.07 g, 91%). ^1H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.11 [9H, s, $(CH_3)_3$], 1.95 [1H, bs, CH=NOH], 4.80 [1H, s, CH=NOH]. I.r. (nujol): 3396, 2976 cm^{-1}.

PIVALOHYDROXIMINOYL CHLORIDE (101)

To a stirred solution of pivaldoxime (10.0 g, 99 mmol) in *N,N*-dimethylformamide (80 ml) was added *N*-chlorosuccinimide (13.2 g, 99 mmol). The initial *N*-chlorosuccinimide addition resulted in a slight

temperature decrease after which the reaction became exothermic and the mixture was kept between 25-35°C using an ice bath. After the cessation of the exothermic reaction the mixture was poured into ice/water (150 ml) and was extracted twice with ether. The combined organic fractions were washed three times with water and dried (calcium sulphate) and the solvent was removed under reduced pressure to yield a the hydroximinoyl chloride (**101**) as a labile, colourless liquid (7.24 g, 54%). ^{1}H nmr (300 MHz, $CDCl_3$) δ (ppm): 1.27 [9H, s, $(C\underline{H}_3)_3$], 8.50 [1H, s, C(Cl)=NO$\underline{H}$].

(±)-ETHYL 5-*t*-BUTYL-3-PHENYL-Δ^2-ISOXAZOLINE-4-CARBOXYLATE (103)

(±)-ETHYL 5-*t*-BUTYL-4-PHENYL-Δ^2-ISOXAZOLINE-3-CARBOXYLATE (104)

A solution of pivalohydroximinoyl chloride (**101**) (0.5 g, 3.7 mmol) in dry tetrahydrofuran (4.0 ml) was added dropwise to a stirring solution of ethyl cinnamate (**53**) (0.65g, 3.5 mmol) and triethylamine (0.60 ml, 4.1 mmol) in dry tetrahydrofuran (8.0 ml). The mixture was stirred at room temperature for 1h and heated to reflux for 3h. The mixture was then concentrated under reduced pressure and the residue taken up in chloroform. The solution was washed with water three times, dried (magnesium sulphate) and concentrated under reduced pressure to give a yellow crude product. This was then purified by flash chromatography (ethyl acetate/light petroleum, 1:5) from ethyl acetate/light petroleum to yield two compounds in the ratio 72:28 by ^{1}H nmr (200 MHz, $CDCl_3$). The major product (**103**) was recrystallised from ethyl acetate/light petroleum. The minor product (**104**) was obtained as a viscous oil.

Isoxazoline (**103**) (0.55 g, 57%), m.p. 49°C. ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.23 [9H, s, $(CH_3)_3$-C-], 1.33 [3H, t, J = 7 Hz, $C\underline{H}_3CH_2$-], 3.97 [1H, d, J = 6.7 Hz, C3-

H], 4.27 [2H, q, J = 7 Hz, $CH_3C\underline{H_2}$], 5.75 [1H, d, J = 6.7 Hz, C4-H], 7.27-7.38 [5H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 202 (16; M^+-$CO_2CH_2CH_3$), 192 (68), 146 (44),105 (100), 57 (74; $(CH_3)_3$). HR mass spect. found M^+-$C_3H_5O_2$, *m/z* 202.1273; $C_{16}H_{21}NO_3$-$C_3H_5O_2$ requires M^+-$C_3H_5O_2$, *m/z* 202.1319.

Isoxazoline (**104**) (0.318 g, 33%). ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 1.08 [9H, s, $(CH_3)_3$-C-], 1.33 [3H, t, J = 7 Hz, $C\underline{H_3}CH_2$-], 4.28 [2H, q, J = 7 Hz, $CH_3C\underline{H_2}$], 4.56 [1H, d, J = 3 Hz], 4.79 [1H, d, J = 3 Hz], 7.21-7.38 [5H, m, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 202 (25; M^+-$CO_2CH_2CH_3$), 57 (100; $(CH_3)_3$). HR mass spect. found M^+-$C_3H_5O_2$, *m/z* 202.1252; $C_{16}H_{21}NO_3$-$C_3H_5O_2$ requires M^+-$C_3H_5O_2$, *m/z* 202.1319.

TREATMENT OF A REGIOISOMERIC MIXTURE OF ISOXAZOLINES (98) AND (99) WITH β-CYCLODEXTRIN

A 71:29 mixture of isoxazolines (**98**) and (**99**) (10 mg) was taken into a 30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g, 1.5 mmol). This mixture was incubated at 37°C for 30h, extracted with chloroform (2 x 20 ml) and dried (magnesium sulphate). The solvent was removed under reduced pressure and analysis of the extract by ^{1}H nmr spectroscopy showed that the isoxazolines (**98**) and (**99**) were present in a ratio of 37:63.

TREATMENT OF A REGIOISOMERIC MIXTURE OF ISOXAZOLINES (103) AND (104) WITH β-CYCLODEXTRIN

A 48:52 mixture of isoxazolines (**103**) and (**104**) (10 mg) was taken into a

30% ethanol solution (20 ml), pH 7.2 buffer (12.5 ml) and β-cyclodextrin (1.70 g, 1.5 mmol). This mixture was incubated at 37°C for 30h, extracted with chloroform (2 x 20 ml) and dried (magnesium sulphate). The solvent was removed under reduced pressure and analysis of the extract by ^{1}H nmr spectroscopy showed that the ratio of the isoxazolines (**103**) and (**104**) had not altered.

5-(2,6-DICHLOROPHENYL)-3-(4-PYRIDINYL)-Δ^2-ISOXAZOLINE (58)

The nitrile oxide (**30**) (0.146 g, 0.7 mmol) and 4-vinylpyridine (**57**) (0.06 ml, 0.7 mmol) were taken into a 30% ethanol solution (10 ml) and pH 7.2 buffer (6.5 ml) was added. This mixture was incubated at 37°C for 30h. The mixture was saturated with sodium chloride and was extracted with chloroform (2 x 10 ml),. The extracts were dried (magnesium sulphate) and concentrated under reduced pressure to yield the isoxazoline (**58**) as a sticky gum (0.06 g, 29%), $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone). ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 3.21 [1H, dd, J = 7 Hz, J = 17 Hz, C4-Ha], 3.83 [1H, dd, J = 11 Hz, J = 17 Hz, C4-Hb], 5.82 [1H, dd, J = 7 Hz, J = 11 Hz, C3-H], 7.26-7.41 [5H, m, aromatic hydrogens], 8.65 [2H, bs, aromatic hydrogens]. Mass spectrum (FAB) *m/z* (rel. intensity): 297, 295, 293 (5, 26, 39; M^+ + H), 75, 73, 71 (22, 37, 58), 56, 54 (81, 100). The method followed was identical to the method outlined by Rama Rao *et al.*[49,55]

Variations of this procedure were undertaken to determine the effects of β-cyclodextrin and/or baker's yeast on the cycloaddition of the nitrile oxide (**30**) and 4-vinylpyridine (**57**).

a) The reaction was scaled up two-fold and baker's yeast (0.50 g) was added to the reaction mixture. This reaction gave the isoxazoline (**58**) (0.08 g,

18%; Lit.[49,55] 81%), $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone) (Lit.[49,55] $[\alpha]_D^{25}$ +66.7° (c, 0.1 in acetone)).

b) The reaction was scaled up two-fold and β-cyclodextrin (1.76 g) was added to the reaction mixture. This reaction gave the isoxazoline (**58**) (0.07 g, 15%, $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone).

5-(2,4,6-TRIMETHYLPHENYL)-3-(4-PYRIDINYL)-Δ^2-ISOXAZOLINE (59)

The nitrile oxide (**50**) (0.250 g, 1.55 mmol) and 4-vinylpyridine (**57**) (0.11 ml, 1.55 mmol) were taken into a 30% ethanol solution (20 ml) and pH 7.2 buffer (12.5 ml) was added. This mixture was incubated at 37°C for 30h. The mixture was saturated with sodium chloride and was extracted with chloroform (2 x 20 ml). The extracts were dried (magnesium sulphate) and the solvent was removed under reduced pressure to yield the isoxazoline (**58**) as a sticky gum (0.21 g, 51%), $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone and c, 1.0 in acetone). ^{1}H nmr (200 MHz, $CDCl_3$) δ (ppm): 2.17 [6H, s, $(C\underline{H}_3)_2$-Ar], 2.30 [3H, s, $C\underline{H}_3$-Ar], 3.16 [1H, dd, J = 7 Hz, J = 17 Hz, C4-Ha], 3.71 [1H, dd, J = 11 Hz, J = 17 Hz, C4-Hb], 5.77 [1H, dd, J = 7 Hz, J = 11 Hz, C3-H], 6.90 [2H, s, aromatic hydrogens], 7.49 [2H, d, J = 5.5 Hz, aromatic hydrogens], 8.76 [2H, d, J = 5.5 Hz, aromatic hydrogens]. Mass spectrum *m/z* (rel. intensity): 267 (25; M^+ + H), 69 (100), 55 (93). The method followed was identical to the method outlined by Rama Rao *et al.*[49,55]

Variations of this procedure were undertaken to determine the effects of β-cyclodextrin and/or baker's yeast on the cycloaddition of the nitrile oxide (**50**) and 4-vinylpyridine (**57**).

a) Baker's yeast (0.50 g) was added to the reaction mixture. This reaction gave the isoxazoline (**59**) (0.18 g, 44%; Lit.[49,55] 88%), $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone

and c, 1.0 acetone) (Lit.[49,55] $[\alpha]_D^{25}$ +5.1° (c, 0.1 in acetone)).

b) β-Cyclodextrin (1.76 g, 1.55 mmol) was added to the reaction mixture. This reaction gave the isoxazoline (**59**) (0.27 g, 66%, $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone and c, 1.0 in acetone).

c) Baker's yeast (0.50 g) and β-cyclodextrin (1.76 g, 1.55 mmol) were added to the reaction mixture. This reaction gave the isoxazoline (**59**) (0.20 g, 49%; Lit.[49,55] 89%), $[\alpha]_D^{25}$ 0° (c, 0.1 in acetone and c, 1.0 acetone) (Lit.[49,55] $[\alpha]_D^{25}$ +25.8° (c, 0.1 in acetone)).

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APPENDIX 1

Easton, C.J., Hughes, C.M., Savage, G.P. and Simpson, G.W. (1994) Cycloaddition reactions of nitrile oxides with alkenes.
Advances in Heterocyclic Chemistry, v. 60, pp. 261-327, 1994

APPENDIX 1A

Addendum to Appendix 1

Between the compilation of the review in *Advances in Heterocyclic Chemistry* and the writing of this thesis, a number of reports have appeared in the literature regarding 1,3-dipolar cycloaddition reactions between nitrile oxides and alkenes. In general these reports provide more examples of topics already discussed. In the area of nitrile oxide synthesis the use of microwave technology to dehydrochlorinate hydroximinoyl chlorides has been reported [94JCR(S)116], the synthesis of alkoxy nitrile oxides has been described [93ACS1004], organometallic complexes have been used in nitrile oxide synthesis [93BCJ2685], and nitrile oxides have been prepared from from nitrolic acids [93LA441] and nitroalkenes [94TL5517].

Further mechanistic studies using *ab initio* calculations for nitrile oxide cycloadditions [93CRV2493, 93JOC6038] have been conducted.

Reactivity of α,β-bond of a nitrogen substituted allene [93JCR(S)203] in cycloaddition reactions and chemoselectivity in cycloaddition reactions to allenes [93JCR(S)398] and diazepines [93T7001] have been reported. Rate enhancement, using metal complexed nitrile oxides [94JA2324], have also been reported in the area of olefin reactivity towards nitrile oxides.

Further examples of regioselective nitrile oxide cycloaddition to monosubstituted [93JCR(S)482, 94CC993, 94T10491, 93JHC1297, 93JA4401], 1,1-disubstituted [93H591, 93T10629, 94JCS(P1)485, 94M301, 94M553, 94T3773, 94T5561], trisubstituted [93LA1169, 94M735, 93M1201] and tetrasubstituted [94CC2185, 93JOC4524, 94CB581] alkenes have been reported.

The directing effect of acyl [93AJC1401, 93H591,94T7969, 93T8899,

94TA607, 94JHC251], alkylthiyl [94T7969], sulphinyl [93JCR(S)346] and alkoxy [93JCS(P1)75] substituents on the alkene have been described and the use of metal complexation in directing the regioselectivity of nitrile oxide cycloaddition reactions [94JA2324, 93SC1673, 93TL2529] have been used. *Ab initio* calculations of chemical interactions in the regiocontrol of the reaction of formonitrile oxide with methyl vinyl ether has also been reported [94JCS(F1)1077].

Improved stereoselectivity in nitrile oxide cycloaddition reactions have been achieved through the use of metal complexation [94CB1243, 93SC1673, 93TL2529] and chiral auxiliaries [93CL1847, 93JA7472, 93JCR(S)482, 93TL6063, 94JCS(P1)485, 93TA607]. There have also been some model calculations on the chemical interactions involved in stereoselectivity of some cycloaddition reactions [93JCS(F1)29, JCS(F1)3913, 93JOC6038].

The elaboration of isoxazolines to β-hydroxy ketones [94CC993, 94TL3163, 93S1206, 94T10491], isoxazoles [93H591, 93S1104], β-hydroxyesters [93ACS1004] and β-keto esters [93ACS1004] have also been described in the literature.

Intramolecular nitrile oxide cycloaddition chemistry remains an expanding area with many articles appearing in the literature since the compilation of the review in *Advances in Heterocyclic Chemistry* [93CL557, 93H345, 93T2005, 93JOC7320, 93TL4075, 93TL5959, 93TL4075, 94TL4197, 94CL63, 94CC449, 94M735, 94CL63, 94TL4197, 94T7543, 94SC1669, 941107].

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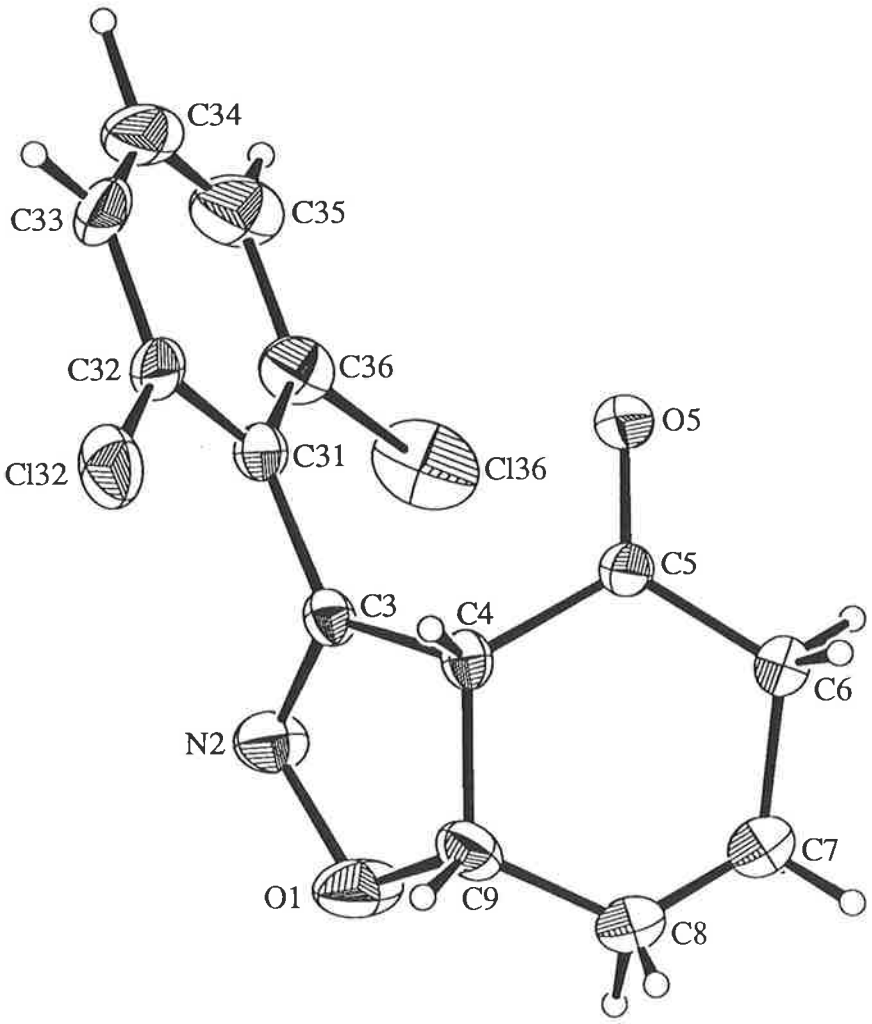
APPENDIX 2

Crystal structure of

9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-8-en-2-one (**60**)



The numbering of the atoms in this structure is consistent with the X-ray crystal data.

Bond distances (Å) for

9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-8-en-2-one (60)

atom	atom	distance	atom	atom	distance
Cl(32)	C(32)	1.709(9)	C(5)	C(6)	1.457(9)
Cl(36)	C(36)	1.728(9)	C(6)	C(7)	1.45(1)
O(1)	N(2)	1.393(7)	C(7)	C(8)	1.25(1)
O(1)	C(9)	1.410(8)	C(8)	C(9)	1.43(1)
O(5)	C(5)	1.186(7)	C(31)	C(32)	1.389(9)
N(2)	C(3)	1.246(7)	C(31)	C(36)	1.348(9)
C(3)	C(4)	1.479(8)	C(32)	C(33)	1.34(1)
C(3)	C(31)	1.451(9)	C(33)	C(34)	1.32(2)
C(4)	C(5)	1.499(9)	C(34)	C(35)	1.36(2)
C(4)	C(9)	1.505(9)	C(35)	C(36)	1.37(1)

Bond angles (deg.) for

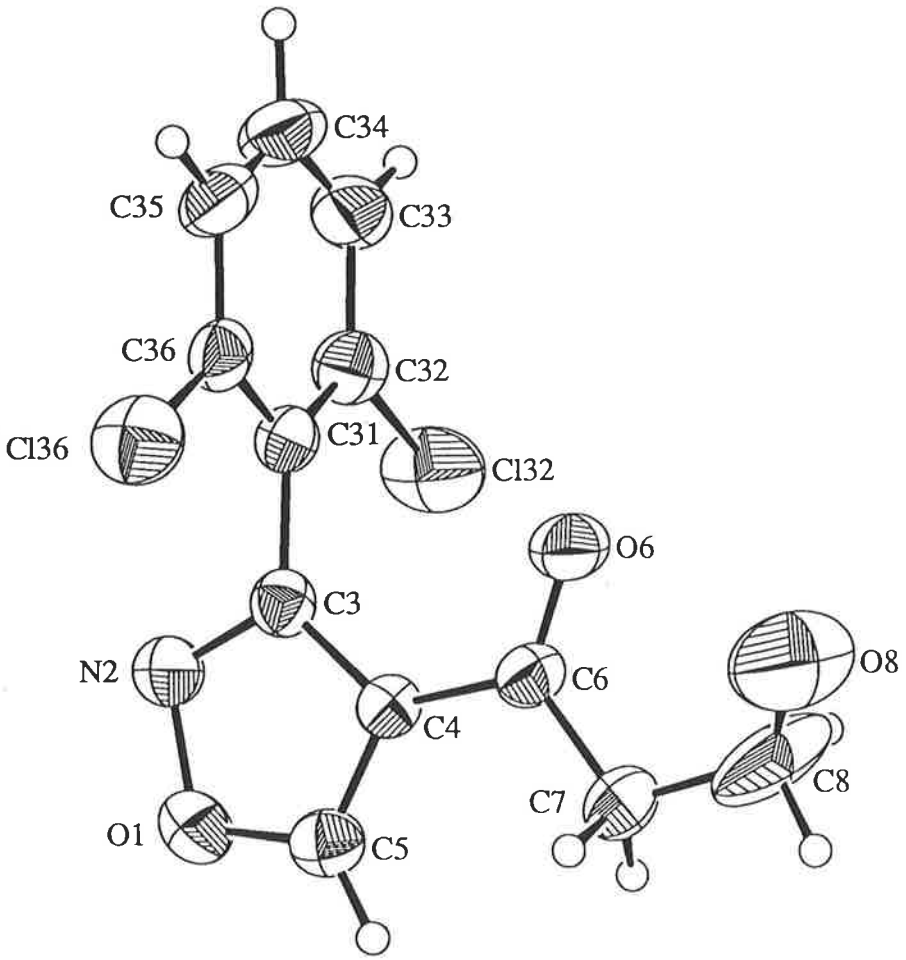
9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-8-en-2-one (60)

atom	atom	atom	angle	atom	atom	atom	angle
N(2)	O(1)	C(9)	110.1(5)	O(1)	C(9)	C(8)	111.0(9)
O(1)	N(2)	C(3)	109.6(6)	C(4)	C(9)	C(8)	115.0(7)
N(2)	C(3)	C(4)	113.7(6)	C(3)	C(31)	C(32)	121.1(7)
N(2)	C(3)	C(31)	119.1(6)	C(3)	C(31)	C(36)	122.0(7)
C(4)	C(3)	C(31)	127.2(6)	C(32)	C(31)	C(36)	116.8(7)
C(3)	C(4)	C(5)	112.9(5)	Cl(32)	C(32)	C(31)	118.7(6)
C(3)	C(4)	C(9)	101.2(5)	Cl(32)	C(32)	C(33)	119.9(9)
C(5)	C(4)	C(9)	117.1(5)	C(31)	C(32)	C(33)	121.3(9)
O(5)	C(5)	C(4)	119.2(6)	C(32)	C(33)	C(34)	120(1)
O(5)	C(5)	C(6)	121.8(7)	C(33)	C(34)	C(35)	122(1)
C(4)	C(5)	C(6)	119.0(6)	C(34)	C(35)	C(36)	117(1)
C(5)	C(6)	C(7)	114.8(7)	Cl(36)	C(36)	C(31)	119.5(7)
C(6)	C(7)	C(8)	122.5(9)	Cl(36)	C(36)	C(35)	117.9(9)
C(7)	C(8)	C(9)	126(1)	C(31)	C(36)	C(35)	122.6(9)
[illegible]	[illegible]	[illegible]	104.6(6)				

APPENDIX 3

Crystal structure of

5-(2,6-dichlorophenyl)-4-(3-hydroxypropionyl)-1-aza-2-oxa-cyclopenta-3,5-diene
(67)



Bond distances (Å) for

5-(2,6-dichlorophenyl)-4-(3-hydroxypropionyl)-1-aza-2-oxa-cyclopenta-3,5-diene (67)

atom	atom	distance	atom	atom	distance
Cl(32)	C(32)	1.714(7)	C(4)	C(6)	1.449(8)
Cl(36)	C(36)	1.713(7)	C(6)	C(7)	1.466(7)
O(1)	N(2)	1.405(6)	C(7)	C(8)	1.49(1)
O(1)	C(5)	1.321(6)	C(31)	C(32)	1.350(8)
O(6)	C(6)	1.207(6)	C(31)	C(36)	1.377(8)
O(8)	C(8)	1.208(8)	C(32)	C(33)	1.382(9)
N(2)	C(3)	1.287(6)	C(33)	C(34)	1.360(9)
C(3)	C(4)	1.411(7)	C(34)	C(35)	1.359(9)
C(3)	C(31)	1.467(8)	C(35)	C(36)	1.380(8)
C(4)	C(5)	1.342(7)			

Bond angles (deg.) for

5-(2,6-dichlorophenyl)-4-(3-hydroxypropionyl)-1-aza-2-oxa-cyclopenta-3,5-diene (67)

atom	atom	atom	angle	atom	atom	atom	angle
N(2)	O(1)	C(5)	108.3(4)	O(8)	C(8)	C(7)	122.6(9)
O(1)	N(2)	C(3)	105.8(5)	C(3)	C(31)	C(32)	121.9(7)
N(2)	C(3)	C(4)	111.5(5)	C(3)	C(31)	C(36)	119.6(7)
N(2)	C(3)	C(31)	117.8(6)	C(32)	C(31)	C(36)	118.5(6)
C(4)	C(3)	C(31)	130.7(6)	Cl(32)	C(32)	C(31)	119.4(6)
C(3)	C(4)	C(5)	104.0(6)	Cl(32)	C(32)	C(33)	118.8(7)
C(3)	C(4)	C(6)	128.6(6)	C(31)	C(32)	C(33)	121.8(7)
C(5)	C(4)	C(6)	127.4(6)	C(32)	C(33)	C(34)	118.1(7)
O(1)	C(5)	C(4)	110.4(5)	C(33)	C(34)	C(35)	122.1(7)
O(6)	C(6)	C(4)	119.9(6)	C(34)	C(35)	C(36)	118.2(7)
O(6)	C(6)	C(7)	121.2(6)	Cl(36)	C(36)	C(31)	120.6(5)
C(4)	C(6)	C(7)	118.9(5)	Cl(36)	C(36)	C(35)	118.2(6)
C(6)	C(7)	C(8)	114.3(5)	C(31)	C(36)	C(35)	121.2(7)

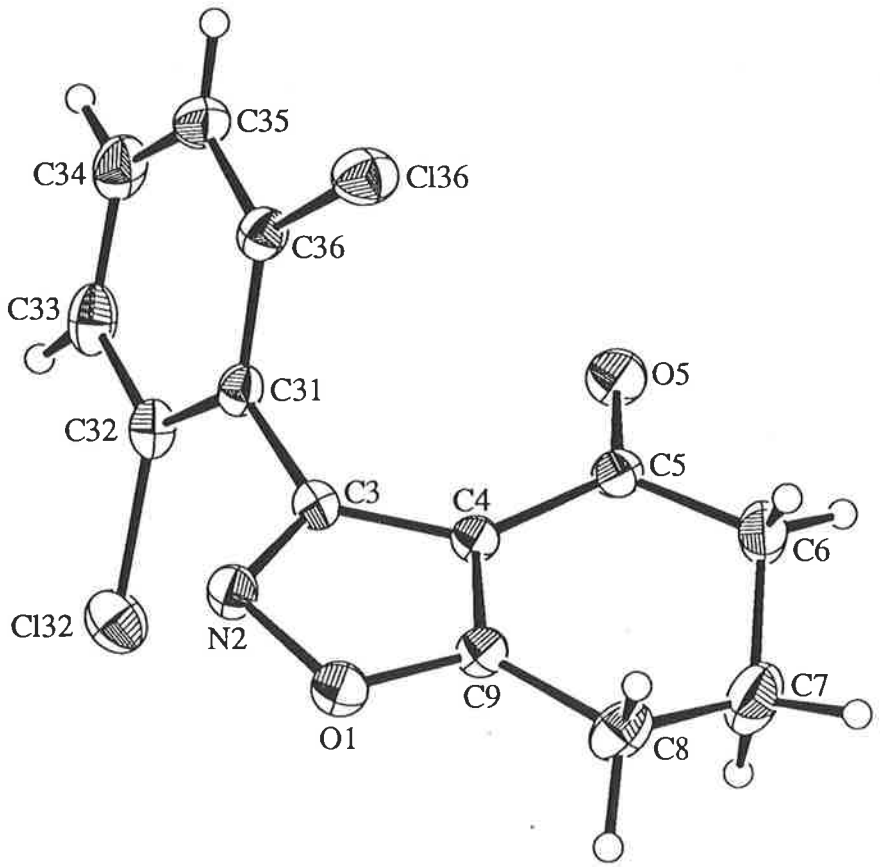
Torsion Angles (deg) for 5-(2,6-dichlorophenyl)-4-(3-hydroxypropionyl)-1-aza-2-oxa-cyclopenta-3,5-diene (67)

(1)	(2)	(3)	(4)	angle
Cl(32	C(32)	C(31)	C(3)	-2.1(8)
Cl(32	C(32)	C(31)	C(36)	179.9(4)
Cl(32	C(32)	C(33)	C(34)	178.9(5)
Cl(36	C(36)	C(31)	C(3)	1.3(8)
Cl(36	C(36)	C(31)	C(32)	179.3(5)
Cl(36	C(36)	C(35)	C(34)	-179.0(5)
O(1)	N(2)	C(3)	C(4)	0.0(7)
O(1)	N(2)	C(3)	C(31)	178.8(5)
O(1)	C(5)	C(4)	C(3)	-0.5(7)
O(1)	C(5)	C(4)	C(6)	179.9(5)
O(6)	C(6)	C(4)	C(3)	2(1)
O(6)	C(6)	C(4)	C(5)	-178.4(7)
O(6)	C(6)	C(7)	C(8)	-11(1)
O(8)	C(8)	C(7)	C(6)	52(1)
N(2)	O(1)	C(5)	C(4)	0.5(7)
N(2)	C(3)	C(4)	C(5)	0.3(7)
N(2)	C(3)	C(4)	C(6)	179.9(6)
N(2)	C(3)	C(31)	C(32)	-88.7(7)
N(2)	C(3)	C(31)	C(36)	89.3(8)
C(3)	N(2)	O(1)	C(5)	-0.3(6)
C(3)	C(4)	C(6)	C(7)	-179.5(6)
C(3)	C(31)	C(32)	C(33)	178.9(6)
C(3)	C(31)	C(36)	C(35)	-178.0(6)
C(4)	C(3)	C(31)	C(32)	89.9(9)
C(4)	C(3)	C(31)	C(36)	-92.2(8)
C(4)	C(6)	C(7)	C(8)	170.9(7)
C(5)	C(4)	C(3)	C(31)	-178.3(7)
C(5)	C(4)	C(6)	C(7)	0.1(9)
C(6)	C(4)	C(3)	C(31)	1(1)
C(31)	C(32)	C(33)	C(34)	-2(1)
C(31)	C(36)	C(35)	C(34)	0(1)
C(32)	C(31)	C(36)	C(35)	0.0(9)
C(32)	C(33)	C(34)	C(35)	2(1)
C(33)	C(32)	C(31)	C(36)	0.9(9)
C(33)	C(34)	C(35)	C(36)	-2(1)

APPENDIX 3

Crystal structure of

9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonona-1,8-dien-2-one (**70**)



The numbering of the atoms in this structure is consistent with the X-ray crystal data.

Bond distances (Å) for

9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonona-1,8-dien-2-one (70)

atom	atom	distance	atom	atom	distance
Cl(32)	C(32)	1.719(3)	C(7)	H(7a)	1.14(5)
Cl(36)	C(36)	1.714(3)	C(7)	H(7b)	1.07(4)
O(1)	N(2)	1.411(3)	C(8)	C(9)	1.459(5)
O(1)	C(9)	1.324(4)	C(8)	H(8a)	1.02(4)
O(5)	C(5)	1.207(4)	C(8)	H(8b)	0.86(4)
N(2)	C(3)	1.289(4)	C(31)	C(32)	1.370(4)
C(3)	C(4)	1.402(4)	C(31)	C(36)	1.384(4)
C(3)	C(31)	1.469(4)	C(32)	C(33)	1.369(5)
C(4)	C(5)	1.445(4)	C(33)	C(34)	1.354(6)
C(4)	C(9)	1.340(4)	C(33)	H(33)	0.95(4)
C(5)	C(6)	1.488(5)	C(34)	C(35)	1.350(5)
C(6)	C(7)	1.497(6)	C(34)	H(34)	0.84(3)
C(6)	H(6a)	0.88(4)	C(35)	C(36)	1.367(5)
C(6)	H(6b)	1.04(5)	C(35)	H(35)	0.90(3)
C(7)	C(8)	1.506(6)			

Bond angles (deg.) for

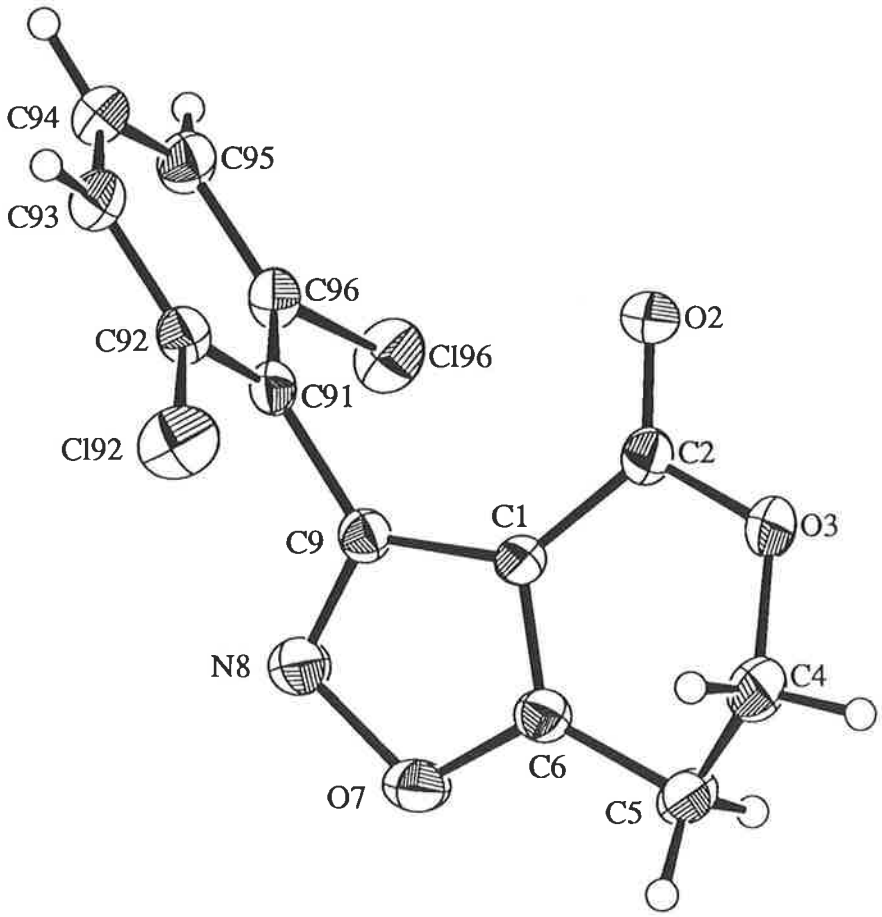
9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonona-1,8-dien-2-one (70)

atom	atom	atom	angle	atom	atom	atom	angle
N(2)	O(1)	C(9)	108.3(2)	C(7)	C(8)	H(8b)	112(3)
O(1)	N(2)	C(3)	105.3(2)	C(9)	C(8)	H(8a)	113(2)
N(2)	C(3)	C(4)	111.9(3)	C(9)	C(8)	H(8b)	104(3)
N(2)	C(3)	C(31)	119.6(3)	H(8a)	C(8)	H(8b)	110(3)
C(4)	C(3)	C(31)	128.5(3)	O(1)	C(9)	C(4)	110.2(3)
C(3)	C(4)	C(5)	134.6(3)	O(1)	C(9)	C(8)	121.9(3)
C(3)	C(4)	C(9)	104.4(3)	C(4)	C(9)	C(8)	128.0(3)
C(5)	C(4)	C(9)	121.0(3)	C(3)	C(31)	C(32)	123.1(3)
O(5)	C(5)	C(4)	122.8(3)	C(3)	C(31)	C(36)	120.1(3)
O(5)	C(5)	C(6)	123.0(3)	C(32)	C(31)	C(36)	116.8(3)
C(4)	C(5)	C(6)	114.2(3)	Cl(32)	C(32)	C(31)	119.9(3)
C(5)	C(6)	C(7)	113.9(3)	Cl(32)	C(32)	C(33)	118.3(3)
C(5)	C(6)	H(6a)	110(2)	C(31)	C(32)	C(33)	121.8(3)
C(5)	C(6)	H(6b)	118(3)	C(32)	C(33)	C(34)	119.2(4)
C(7)	C(6)	H(6a)	115(2)	C(32)	C(33)	H(33)	115(2)
C(7)	C(6)	H(6b)	90(2)	C(34)	C(33)	H(33)	125(2)
H(6a)	C(6)	H(6b)	111(3)	C(33)	C(34)	C(35)	121.3(4)
C(6)	C(7)	C(8)	113.6(4)	C(33)	C(34)	H(34)	119(3)
C(6)	C(7)	H(7a)	110(3)	C(35)	C(34)	H(34)	119(3)
C(6)	C(7)	H(7b)	103(2)	C(34)	C(35)	C(36)	119.0(4)
C(8)	C(7)	H(7a)	106(3)	C(34)	C(35)	H(35)	123(2)
C(8)	C(7)	H(7b)	105(2)	C(36)	C(35)	H(35)	117(2)
H(7a)	C(7)	H(7b)	119(3)	Cl(36)	C(36)	C(31)	119.0(3)
C(7)	C(8)	C(9)	107.9(3)	Cl(36)	C(36)	C(35)	119.1(3)
C(7)	C(8)	H(8a)	110(2)	C(31)	C(36)	C(35)	121.9(3)

APPENDIX 5

Crystal structure of

9-(2,6-dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonona-1,8-dien-2-one (**71**)



Bond distances (Å) for

9-(2,6-dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonona-1,8-dien-2-one (71)

atom	atom	distance	atom	atom	distance
Cl(92)	C(92)	1.707(2)	C(5)	C(6)	1.461(3)
Cl(96)	C(96)	1.708(3)	C(5)	H(5a)	0.94(3)
O(2)	C(2)	1.188(3)	C(5)	H(5b)	0.96(2)
O(3)	C(2)	1.338(3)	C(9)	C(91)	1.469(3)
O(3)	C(4)	1.449(3)	C(91)	C(92)	1.372(3)
O(7)	N(8)	1.426(2)	C(91)	C(96)	1.372(3)
O(7)	C(6)	1.320(3)	C(92)	C(93)	1.369(3)
N(8)	C(9)	1.289(3)	C(93)	C(94)	1.357(4)
C(1)	C(2)	1.438(3)	C(93)	H(93)	0.93(2)
C(1)	C(6)	1.330(3)	C(94)	C(95)	1.354(4)
C(1)	C(9)	1.407(3)	C(94)	H(94)	0.92(2)
C(4)	C(5)	1.491(4)	C(95)	C(96)	1.375(3)
C(4)	H(4a)	0.96(2)	C(95)	H(95)	0.93(2)
C(4)	H(4b)	1.03(3)			

Bond angles (deg.) for

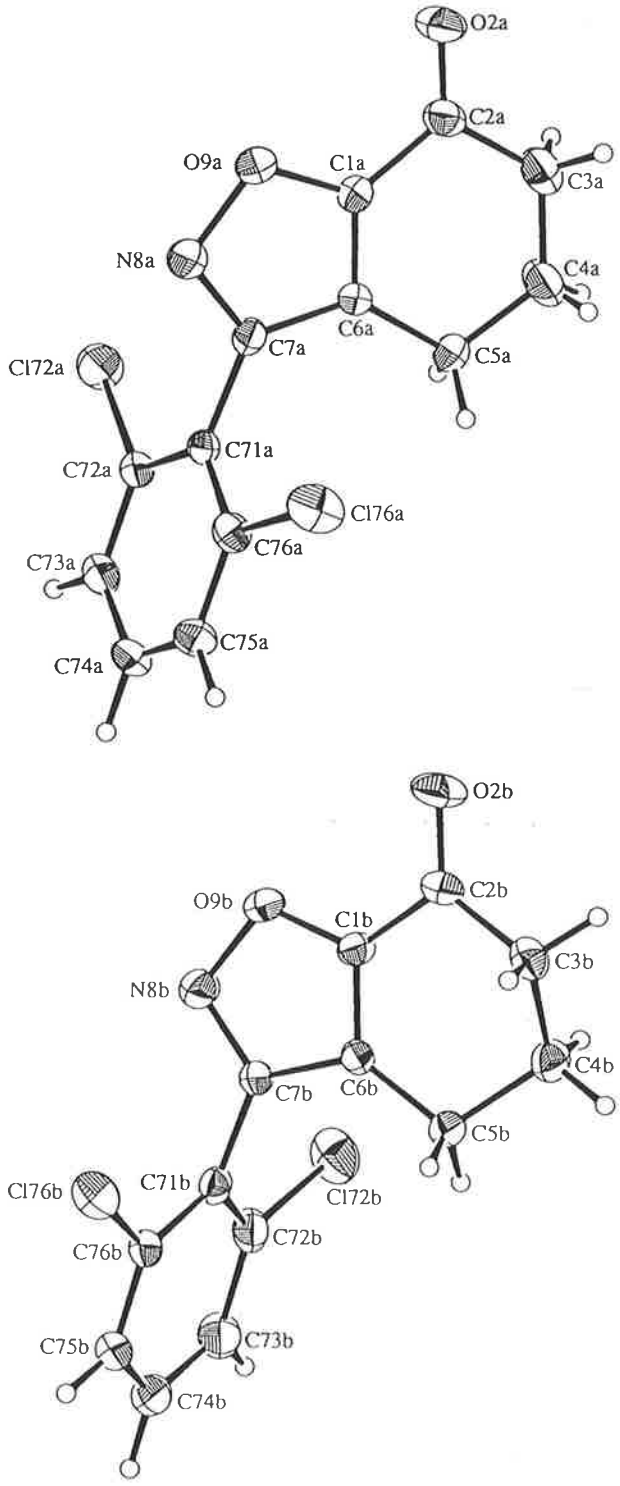
9-(2,6-dichlorophenyl)-8-aza-3,7-dioxa-[4.3.0]-bicyclonona-1,8-dien-2-one (71)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(3)	C(4)	119.1(2)	C(1)	C(6)	C(5)	123.9(2)
N(8)	O(7)	C(6)	107.9(2)	N(8)	C(9)	C(1)	111.7(2)
O(7)	N(8)	C(9)	105.0(2)	N(8)	C(9)	C(91)	119.3(2)
C(2)	C(1)	C(6)	121.3(2)	C(1)	C(9)	C(91)	129.0(2)
C(2)	C(1)	C(9)	133.7(2)	C(9)	C(91)	C(92)	120.6(2)
C(6)	C(1)	C(9)	104.6(2)	C(9)	C(91)	C(96)	121.8(2)
O(2)	C(2)	O(3)	119.5(2)	C(92)	C(91)	C(96)	117.6(2)
O(2)	C(2)	C(1)	125.5(2)	Cl(92)	C(92)	C(91)	119.6(2)
O(3)	C(2)	C(1)	114.9(2)	Cl(92)	C(92)	C(93)	118.7(2)
O(3)	C(4)	C(5)	113.2(2)	C(91)	C(92)	C(93)	121.7(2)
O(3)	C(4)	H(4a)	102(2)	C(92)	C(93)	C(94)	118.8(3)
O(3)	C(4)	H(4b)	107(1)	C(92)	C(93)	H(93)	118(1)
C(5)	C(4)	H(4a)	116(2)	C(94)	C(93)	H(93)	123(1)
C(5)	C(4)	H(4b)	111(1)	C(93)	C(94)	C(95)	121.5(3)
H(4a)	C(4)	H(4b)	107(2)	C(93)	C(94)	H(94)	120(2)
C(4)	C(5)	C(6)	105.2(2)	C(95)	C(94)	H(94)	118(2)
C(4)	C(5)	H(5a)	113(2)	C(94)	C(95)	C(96)	118.9(3)
C(4)	C(5)	H(5b)	107(2)	C(94)	C(95)	H(95)	123(1)
C(6)	C(5)	H(5a)	108(2)	C(96)	C(95)	H(95)	118(1)
C(6)	C(5)	H(5b)	111(1)	Cl(96)	C(96)	C(91)	119.3(2)
H(5a)	C(5)	H(5b)	112(2)	Cl(96)	C(96)	C(95)	119.3(2)
O(7)	C(6)	C(1)	110.7(2)	C(91)	C(96)	C(95)	121.4(2)
O(7)	C(6)	C(5)	125.4(2)				

APPENDIX 6

Crystal structures of

7-(2,6-dichlorophenyl)-8-aza-9-oxa-[4.3.0]-bicyclonona-1,7-dien-2-one (73)



Bond distances (Å) for

7-(2,6-dichlorophenyl)-8-aza-9-oxa-[4.3.0]-bicyclonona-1,7-dien-2-one (73)

atom	atom	distance
Cl(72a	C(72a)	1.710(7)
Cl(72b	C(72b)	1.708(8)
Cl(76b	C(76b)	1.716(7)
Cl(76a	C(76a)	1.712(7)
O(2a)	C(2a)	1.209(8)
O(2b)	C(2b)	1.188(7)
O(9b)	N(8b)	1.397(7)
O(9b)	C(1b)	1.329(8)
O(9a)	N(8a)	1.407(7)
O(9a)	C(1a)	1.349(8)
N(8b)	C(7b)	1.295(8)
N(8a)	C(7a)	1.301(7)
C(1a)	C(2a)	1.45(1)
C(1a)	C(6a)	1.326(8)
C(1b)	C(2b)	1.461(9)
C(1b)	C(6b)	1.326(8)
C(2a)	C(3a)	1.49(1)
C(2b)	C(3b)	1.46(1)
C(3a)	C(4a)	1.37(1)
C(3b)	C(4b)	1.491(9)

atom	atom	distance
C(4a)	C(5a)	1.42(1)
C(4b)	C(5b)	1.51(1)
C(5a)	C(6a)	1.474(9)
C(5b)	C(6b)	1.453(9)
C(6b)	C(7b)	1.422(9)
C(6a)	C(7a)	1.392(9)
C(7a)	C(71a)	1.473(9)
C(7b)	C(71b)	1.468(9)
C(71b)	C(72b)	1.37(1)
C(71b)	C(76b)	1.378(9)
C(71a)	C(72a)	1.37(1)
C(71a)	C(76a)	1.357(9)
C(72b)	C(73b)	1.39(1)
C(72a)	C(73a)	1.352(9)
C(73b)	C(74b)	1.37(1)
C(73a)	C(74a)	1.35(1)
C(74b)	C(75b)	1.36(1)
C(74a)	C(75a)	1.34(1)
C(75b)	C(76b)	1.348(9)
C(75a)	C(76a)	1.372(8)

Bond angles (deg.) for

7-(2,6-dichlorophenyl)-8-aza-9-oxa-[4.3.0]-bicyclonona-1,7-dien-2-one (73)

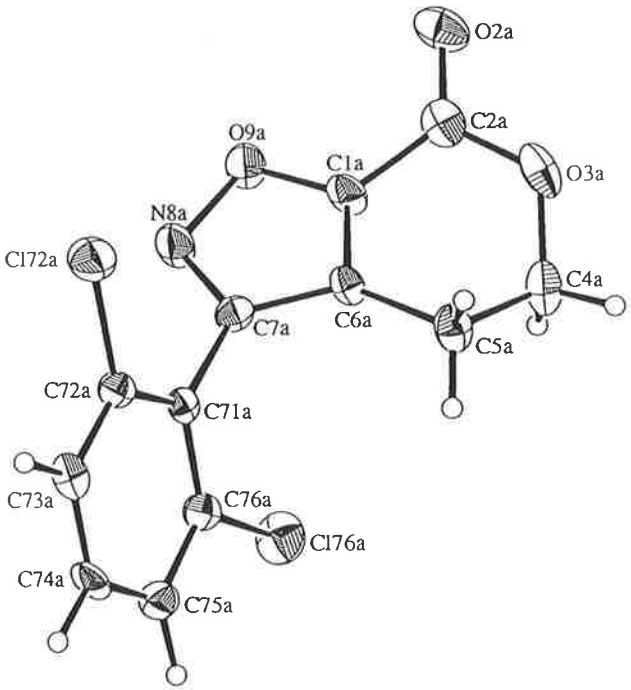
atom	atom	atom	angle	atom	atom	atom	angle
N(8b)	O(9b)	C(1b)	108.7(5)	C(1a)	C(6a)	C(7a)	105.1(6)
N(8a)	O(9a)	C(1a)	107.2(5)	C(5a)	C(6a)	C(7a)	133.0(6)
O(9b)	N(8b)	C(7b)	104.9(5)	N(8a)	C(7a)	C(6a)	111.6(6)
O(9a)	N(8a)	C(7a)	105.7(5)	N(8a)	C(7a)	C(71a)	120.7(6)
O(9a)	C(1a)	C(2a)	122.5(6)	C(6a)	C(7a)	C(71a)	127.7(6)
O(9a)	C(1a)	C(6a)	110.4(6)	N(8b)	C(7b)	C(6b)	112.1(5)
C(2a)	C(1a)	C(6a)	127.1(7)	N(8b)	C(7b)	C(71b)	121.3(6)
O(9b)	C(1b)	C(2b)	124.7(6)	C(6b)	C(7b)	C(71b)	126.6(5)
O(9b)	C(1b)	C(6b)	111.0(6)	C(7b)	C(71b)	C(72b)	120.5(7)
C(2b)	C(1b)	C(6b)	124.2(6)	C(7b)	C(71b)	C(76b)	122.3(7)
O(2a)	C(2a)	C(1a)	124.2(9)	C(72b)	C(71b)	C(76b)	117.2(7)
O(2a)	C(2a)	C(3a)	124.7(8)	C(7a)	C(71a)	C(72a)	121.9(7)
C(1a)	C(2a)	C(3a)	111.0(7)	C(7a)	C(71a)	C(76a)	120.1(7)
O(2b)	C(2b)	C(1b)	121.6(7)	C(72a)	C(71a)	C(76a)	117.9(6)
O(2b)	C(2b)	C(3b)	125.5(7)	Cl(72b	C(72b)	C(71b)	119.4(6)
C(1b)	C(2b)	C(3b)	112.9(6)	Cl(72b	C(72b)	C(73b)	119.4(7)
C(2a)	C(3a)	C(4a)	120.1(8)	C(71b)	C(72b)	C(73b)	121.2(8)
C(2b)	C(3b)	C(4b)	114.7(6)	Cl(72a	C(72a)	C(71a)	119.9(5)
C(3a)	C(4a)	C(5a)	125.5(9)	Cl(72a	C(72a)	C(73a)	119.2(6)
C(3b)	C(4b)	C(5b)	113.0(6)	C(71a)	C(72a)	C(73a)	120.9(6)
C(4a)	C(5a)	C(6a)	111.9(6)	C(72b)	C(73b)	C(74b)	118.9(8)
C(4b)	C(5b)	C(6b)	109.6(6)	C(72a)	C(73a)	C(74a)	120.1(7)
C(1b)	C(6b)	C(5b)	124.3(6)	C(73b)	C(74b)	C(75b)	120.9(8)
C(1b)	C(6b)	C(7b)	103.3(6)	C(73a)	C(74a)	C(75a)	120.4(7)
C(5b)	C(6b)	C(7b)	132.5(6)	C(74b)	C(75b)	C(76b)	119.2(8)
C(1a)	C(6a)	C(5a)	121.9(7)	C(74a)	C(75a)	C(76a)	119.4(6)

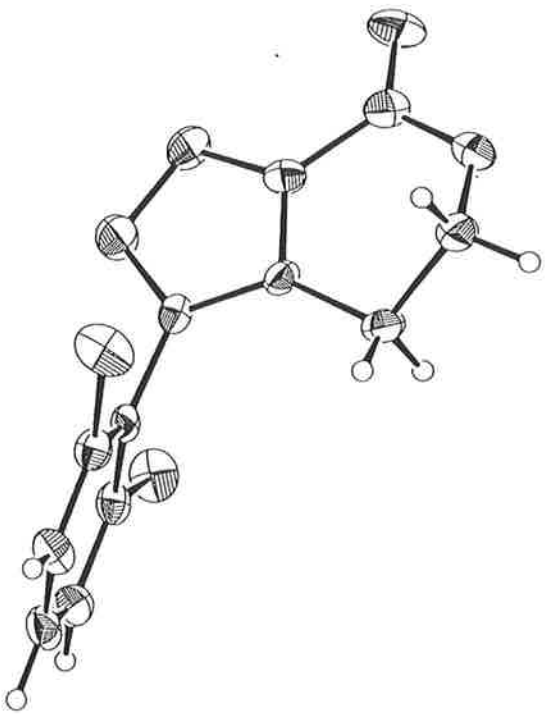
Cl(76b	C(76b)	C(71b)	119.3(5)
Cl(76b	C(76b)	C(75b)	118.0(7)
C(71b)	C(76b)	C(75b)	122.6(8)
Cl(76a	C(76a)	C(71a)	119.6(5)
Cl(76a	C(76a)	C(75a)	119.2(5)
C(71a)	C(76a)	C(75a)	121.2(6)

APPENDIX 7

Crystal structures of

7-(2,6-dichlorophenyl)-8-aza-3,9-dioxa-[4.3.0]-bicyclonona-1,7-dien-2-one (76)





Bond distances (Å) for

7-(2,6-dichlorophenyl)-8-aza-3,9-dioxa-[4.3.0]-bicyclonona-1,7-dien-2-one (**76**)

atom	atom	distance	atom	atom	distance
Cl(72b	C(72b)	1.723(8)	C(4a)	C(5a)	1.50(1)
Cl(72a	C(72a)	1.718(7)	C(4b)	C(5b)	1.51(1)
Cl(76b	C(76b)	1.709(8)	C(5a)	C(6a)	1.47(1)
Cl(76a	C(76a)	1.699(7)	C(5b)	C(6b)	1.48(1)
O(2a)	C(2a)	1.19(1)	C(6a)	C(7a)	1.40(1)
O(2b)	C(2b)	1.18(1)	C(6b)	C(7b)	1.40(1)
O(3a)	C(2a)	1.34(1)	C(7a)	C(71a)	1.46(1)
O(3a)	C(4a)	1.45(1)	C(7b)	C(71b)	1.481(9)
O(3b)	C(2b)	1.33(1)	C(71a)	C(72a)	1.374(9)
O(3b)	C(4b)	1.42(1)	C(71a)	C(76a)	1.368(9)
O(9a)	N(8a)	1.391(7)	C(71b)	C(72b)	1.37(1)
O(9a)	C(1a)	1.322(9)	C(71b)	C(76b)	1.397(9)
O(9b)	N(8b)	1.398(7)	C(72a)	C(73a)	1.37(1)
O(9b)	C(1b)	1.329(9)	C(72b)	C(73b)	1.37(1)
N(8a)	C(7a)	1.287(9)	C(73b)	C(74b)	1.35(1)
N(8b)	C(7b)	1.305(9)	C(73a)	C(74a)	1.35(1)
C(1a)	C(2a)	1.44(1)	C(74a)	C(75a)	1.37(1)
C(1a)	C(6a)	1.32(1)	C(74b)	C(75b)	1.36(1)
C(1b)	C(2b)	1.48(1)	C(75b)	C(76b)	1.36(1)
C(1b)	C(6b)	1.32(1)	C(75a)	C(76a)	1.37(1)

Bond angles (deg.) for

7-(2,6-dichlorophenyl)-8-aza-3,9-dioxa-[4.3.0]-bicyclonona-1,7-dien-2-one (76)

atom	atom	atom	angle
C(2a)	O(3a)	C(4a)	119.6(7)
C(2b)	O(3b)	C(4b)	120.6(7)
N(8a)	O(9a)	C(1a)	105.8(6)
N(8b)	O(9b)	C(1b)	108.0(6)
O(9a)	N(8a)	C(7a)	107.5(7)
O(9b)	N(8b)	C(7b)	104.7(7)
O(9a)	C(1a)	C(2a)	122.1(9)
O(9a)	C(1a)	C(6a)	112.6(8)
C(2a)	C(1a)	C(6a)	124.8(9)
O(9b)	C(1b)	C(2b)	122.9(8)
O(9b)	C(1b)	C(6b)	111.2(8)
C(2b)	C(1b)	C(6b)	125.4(9)
O(2a)	C(2a)	O(3a)	120(1)
O(2a)	C(2a)	C(1a)	127(1)
O(3a)	C(2a)	C(1a)	113.0(9)
O(2b)	C(2b)	O(3b)	121.3(9)
O(2b)	C(2b)	C(1b)	126(1)
O(3b)	C(2b)	C(1b)	112.5(8)
O(3a)	C(4a)	C(5a)	113.3(7)
O(3b)	C(4b)	C(5b)	113.0(7)
C(4a)	C(5a)	C(6a)	105.0(7)
C(4b)	C(5b)	C(6b)	107.9(7)
C(1a)	C(6a)	C(5a)	121.1(8)
C(1a)	C(6a)	C(7a)	103.5(8)
C(5a)	C(6a)	C(7a)	135.3(9)
C(1b)	C(6b)	C(5b)	119.4(8)

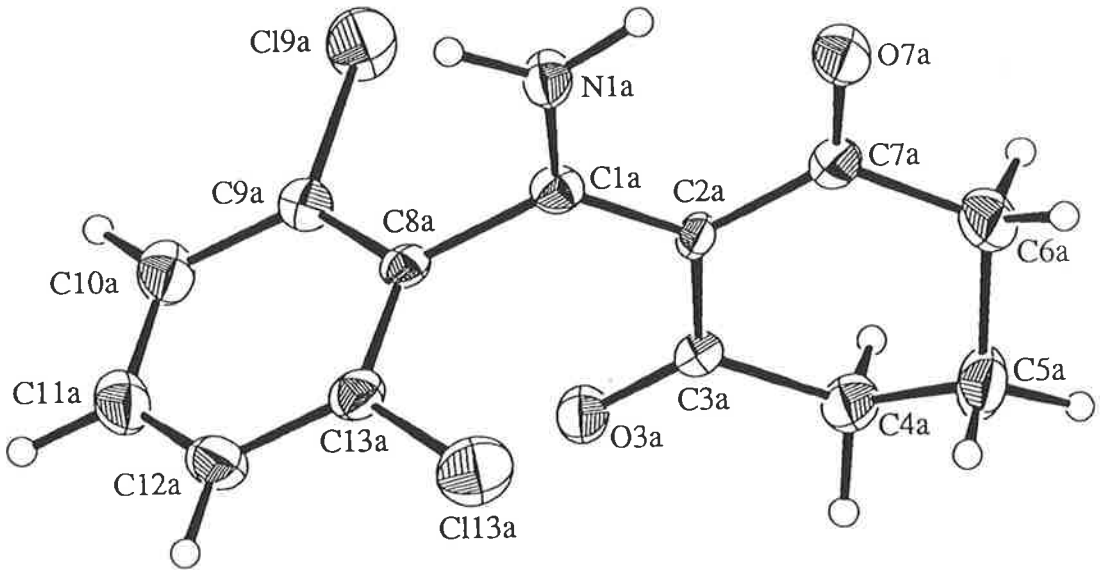
atom	atom	atom	angle
C(1b)	C(6b)	C(7b)	104.0(8)
C(5b)	C(6b)	C(7b)	136.5(9)
N(8a)	C(7a)	C(6a)	110.6(8)
N(8a)	C(7a)	C(71a)	120.7(8)
C(6a)	C(7a)	C(71a)	128.7(8)
N(8b)	C(7b)	C(6b)	112.0(8)
N(8b)	C(7b)	C(71b)	120.2(8)
C(6b)	C(7b)	C(71b)	127.8(9)
C(7a)	C(71a)	C(72a)	122.0(7)
C(7a)	C(71a)	C(76a)	120.9(7)
C(72a)	C(71a)	C(76a)	117.1(7)
C(7b)	C(71b)	C(72b)	123.1(8)
C(7b)	C(71b)	C(76b)	119.8(8)
C(72b)	C(71b)	C(76b)	117.0(7)
Cl(72a	C(72a)	C(71a)	120.1(7)
Cl(72a	C(72a)	C(73a)	118.3(7)
C(71a)	C(72a)	C(73a)	121.6(7)
Cl(72b	C(72b)	C(71b)	119.0(7)
Cl(72b	C(72b)	C(73b)	119.3(7)
C(71b)	C(72b)	C(73b)	121.7(8)
C(72b)	C(73b)	C(74b)	119.4(8)
C(72a)	C(73a)	C(74a)	120.1(7)
C(73a)	C(74a)	C(75a)	120.3(8)
C(73b)	C(74b)	C(75b)	121.1(8)
C(74b)	C(75b)	C(76b)	119.7(8)
C(74a)	C(75a)	C(76a)	118.9(7)

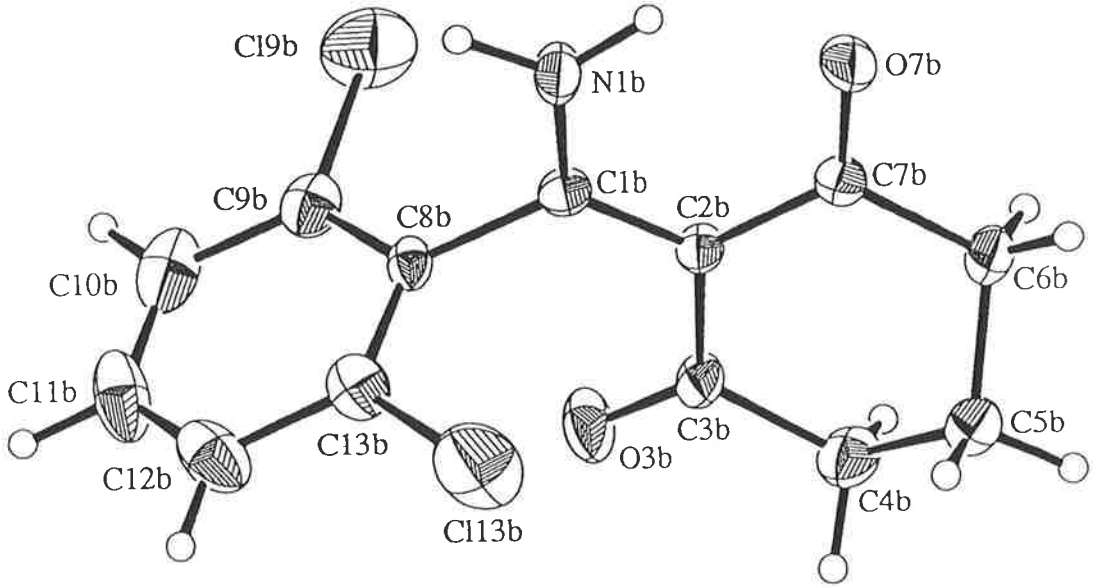
Cl(76a	C(76a)	C(71a)	120.0(7)
Cl(76a	C(76a)	C(75a)	118.0(7)
C(71a)	C(76a)	C(75a)	122.0(7)
Cl(76b	C(76b)	C(71b)	118.0(7)
Cl(76b	C(76b)	C(75b)	120.9(7)
C(71b)	C(76b)	C(75b)	121.1(8)

APPENDIX 8

Crystal structures of

α-amino-α-(2,6-dichlorophenyl)-cyclohexane-2,6-dione (80)





Bond distances (Å) for

α-amino-α-(2,6-dichlorophenyl)-cyclohexane-2,6-dione (80)

atom	atom	distance
Cl(9b)	C(9b)	1.703(8)
Cl(13b	C(13b)	1.703(8)
Cl(9a)	C(9a)	1.705(7)
Cl(13a	C(13a)	1.717(7)
O(3a)	C(3a)	1.227(7)
O(3b)	C(3b)	1.194(8)
O(7a)	C(7a)	1.217(8)
O(7b)	C(7b)	1.225(8)
N(1a)	C(1a)	1.285(7)
N(1b)	C(1b)	1.291(8)
C(1a)	C(2a)	1.394(8)
C(1a)	C(8a)	1.499(8)
C(1b)	C(2b)	1.378(9)
C(1b)	C(8b)	1.493(9)
C(2a)	C(3a)	1.433(9)
C(2a)	C(7a)	1.416(9)
C(2b)	C(3b)	1.441(9)
C(2b)	C(7b)	1.429(9)
C(3a)	C(4a)	1.481(9)

atom	atom	distance
C(3b)	C(4b)	1.49(1)
C(4a)	C(5a)	1.498(9)
C(4b)	C(5b)	1.486(9)
C(5b)	C(6b)	1.494(9)
C(5a)	C(6a)	1.49(1)
C(6b)	C(7b)	1.487(9)
C(6a)	C(7a)	1.49(1)
C(8b)	C(9b)	1.355(9)
C(8b)	C(13b)	1.361(8)
C(8a)	C(9a)	1.377(8)
C(8a)	C(13a)	1.359(8)
C(9a)	C(10a)	1.366(9)
C(9b)	C(10b)	1.36(1)
C(10b)	C(11b)	1.35(1)
C(10a)	C(11a)	1.365(9)
C(11b)	C(12b)	1.36(1)
C(11a)	C(12a)	1.36(1)
C(12a)	C(13a)	1.357(9)
C(12b)	C(13b)	1.38(1)

Bond angles (deg.) for

α-amino-α-(2,6-dichlorophenyl)-cyclohexane-2,6-dione (80)

atom	atom	atom	angle	atom	atom	atom	angle
N(1a)	C(1a)	C(2a)	122.0(7)	C(2b)	C(7b)	C(6b)	118.7(7)
N(1a)	C(1a)	C(8a)	113.8(7)	O(7a)	C(7a)	C(2a)	124.7(8)
C(2a)	C(1a)	C(8a)	124.2(7)	O(7a)	C(7a)	C(6a)	116.1(8)
N(1b)	C(1b)	C(2b)	122.1(8)	C(2a)	C(7a)	C(6a)	119.1(7)
N(1b)	C(1b)	C(8b)	113.7(7)	C(1b)	C(8b)	C(9b)	122.0(7)
C(2b)	C(1b)	C(8b)	124.1(7)	C(1b)	C(8b)	C(13b)	120.2(7)
C(1a)	C(2a)	C(3a)	119.7(7)	C(9b)	C(8b)	C(13b)	117.8(7)
C(1a)	C(2a)	C(7a)	119.4(7)	C(1a)	C(8a)	C(9a)	120.7(7)
C(3a)	C(2a)	C(7a)	120.9(7)	C(1a)	C(8a)	C(13a)	121.7(7)
C(1b)	C(2b)	C(3b)	119.1(8)	C(9a)	C(8a)	C(13a)	117.6(7)
C(1b)	C(2b)	C(7b)	120.5(7)	Cl(9a)	C(9a)	C(8a)	119.1(6)
C(3b)	C(2b)	C(7b)	120.5(7)	Cl(9a)	C(9a)	C(10a)	119.4(6)
O(3a)	C(3a)	C(2a)	123.2(7)	C(8a)	C(9a)	C(10a)	121.5(7)
O(3a)	C(3a)	C(4a)	117.6(7)	Cl(9b)	C(9b)	C(8b)	119.6(7)
C(2a)	C(3a)	C(4a)	119.2(7)	Cl(9b)	C(9b)	C(10b)	118.6(7)
O(3b)	C(3b)	C(2b)	122.9(8)	C(8b)	C(9b)	C(10b)	121.7(8)
O(3b)	C(3b)	C(4b)	119.1(8)	C(9b)	C(10b)	C(11b)	120.1(9)
C(2b)	C(3b)	C(4b)	118.0(8)	C(9a)	C(10a)	C(11a)	119.1(7)
C(3a)	C(4a)	C(5a)	112.4(6)	C(10b)	C(11b)	C(12b)	120(1)
C(3b)	C(4b)	C(5b)	114.7(7)	C(10a)	C(11a)	C(12a)	120.2(8)
C(4b)	C(5b)	C(6b)	109.2(6)	C(11a)	C(12a)	C(13a)	119.7(8)
C(4a)	C(5a)	C(6a)	110.8(7)	C(11b)	C(12b)	C(13b)	118.8(9)
C(5b)	C(6b)	C(7b)	112.7(6)	Cl(13b	C(13b)	C(8b)	119.7(7)
C(5a)	C(6a)	C(7a)	113.8(7)	Cl(13b	C(13b)	C(12b)	118.7(8)
O(7b)	C(7b)	C(2b)	123.4(8)	C(8b)	C(13b)	C(12b)	121.5(8)
O(7b)	C(7b)	C(6b)	117.8(8)	Cl(13a	C(13a)	C(8a)	119.0(7)
Cl(13a	C(13a)	C(12a)	119.1(7)				

Torsion Angles (deg) for

α-amino-α-(2,6-dichlorophenyl)-cyclohexane-2,6-dione (80)

(1)	(2)	(3)	(4)	angle
Cl(9bC	(9b)C	(8b)C	(1b)	1(1)
Cl(9bC	(9b)C	(8b)C	(13b	178.7(6)
Cl(9bC	(9b)C	(10bC	(11b	179.5(7)
Cl(13C	(13bC	(8b)C	(1b)	-3(1)
Cl(13C	(13bC	(8b)C	(9b)	179.4(6)
Cl(13C	(13bC	(12bC	(11b	-178.2(7)
Cl(9aC	(9a)C	(8a)C	(1a)	1.9(9)
Cl(9aC	(9a)C	(8a)C	(13a	179.7(5)
Cl(9aC	(9a)C	(10aC	(11a	179.8(6)
Cl(13C	(13aC	(8a)C	(1a)	0(1)
Cl(13C	(13aC	(8a)C	(9a)	-177.9(5)
Cl(13C	(13aC	(12aC	(11a	179.4(7)
O(3a)C	(3a)C	(2a)C	(1a)	3(1)
O(3a)C	(3a)C	(2a)C	(7a)	-176.0(6)
O(3a)C	(3a)C	(4a)C	(5a)	-153.8(7)
O(3b)C	(3b)C	(2b)C	(1b)	14(1)
O(3b)C	(3b)C	(2b)C	(7b)	-167.7(7)
O(3b)C	(3b)C	(4b)C	(5b)	-162.5(7)
O(7a)C	(7a)C	(2a)C	(1a)	-4(1)
O(7a)C	(7a)C	(2a)C	(3a)	174.7(7)
O(7a)C	(7a)C	(6a)C	(5a)	158.5(7)
O(7b)C	(7b)C	(2b)C	(1b)	-6(1)
O(7b)C	(7b)C	(2b)C	(3b)	176.1(7)
O(7b)C	(7b)C	(6b)C	(5b)	150.8(7)
N(1a)C	(1a)C	(2a)C	(3a)	-176.2(6)
N(1a)C	(1a)C	(8a)C	(9a)	84.7(8)
N(1a)C	(1a)C	(8a)C	(13a	-92.9(8)
N(1b)C	(1b)C	(2b)C	(3b)	-179.7(7)
N(1b)C	(1b)C	(2b)C	(7b)	2(1)
N(1b)C	(1b)C	(8b)C	(9b)	82.2(9)
N(1b)C	(1b)C	(8b)C	(13b	-95.1(9)
C(1a)C	(2a)C	(3a)C	(4a)	-179.6(6)
C(1a)C	(2a)C	(7a)C	(6a)	175.8(6)
C(1a)C	(8a)C	(9a)C	(10a	-179.6(7)
C(1a)C	(8a)C	(13aC	(12a	178.6(7)
C(1b)C	(2b)C	(3b)C	(4b)	-169.4(6)
C(1b)C	(2b)C	(7b)C	(6b)	173.4(6)
C(1b)C	(8b)C	(9b)C	(10b	-179.8(8)
C(1b)C	(8b)C	(13bC	(12b	-179.6(8)
C(2a)C	(1a)C	(8a)C	(9a)	-97.4(8)
C(2a)C	(1a)C	(8a)C	(13a	85.0(9)
C(2a)C	(3a)C	(4a)C	(5a)	29(1)
C(2a)C	(7a)C	(6a)C	(5a)	-21.6(9)
C(2b)C	(1b)C	(8b)C	(9b)	-100.5(9)
C(2b)C	(1b)C	(8b)C	(13b	82.2(9)
C(2b)C	(3b)C	(4b)C	(5b)	21(1)
C(2b)C	(7b)C	(6b)C	(5b)	-29(1)
C(3a)C	(2a)C	(1a)C	(8a)	6(1)
C(3a)C	(2a)C	(7a)C	(6a)	-5(1)
C(3a)C	(4a)C	(5a)C	(6a)	-54.1(9)

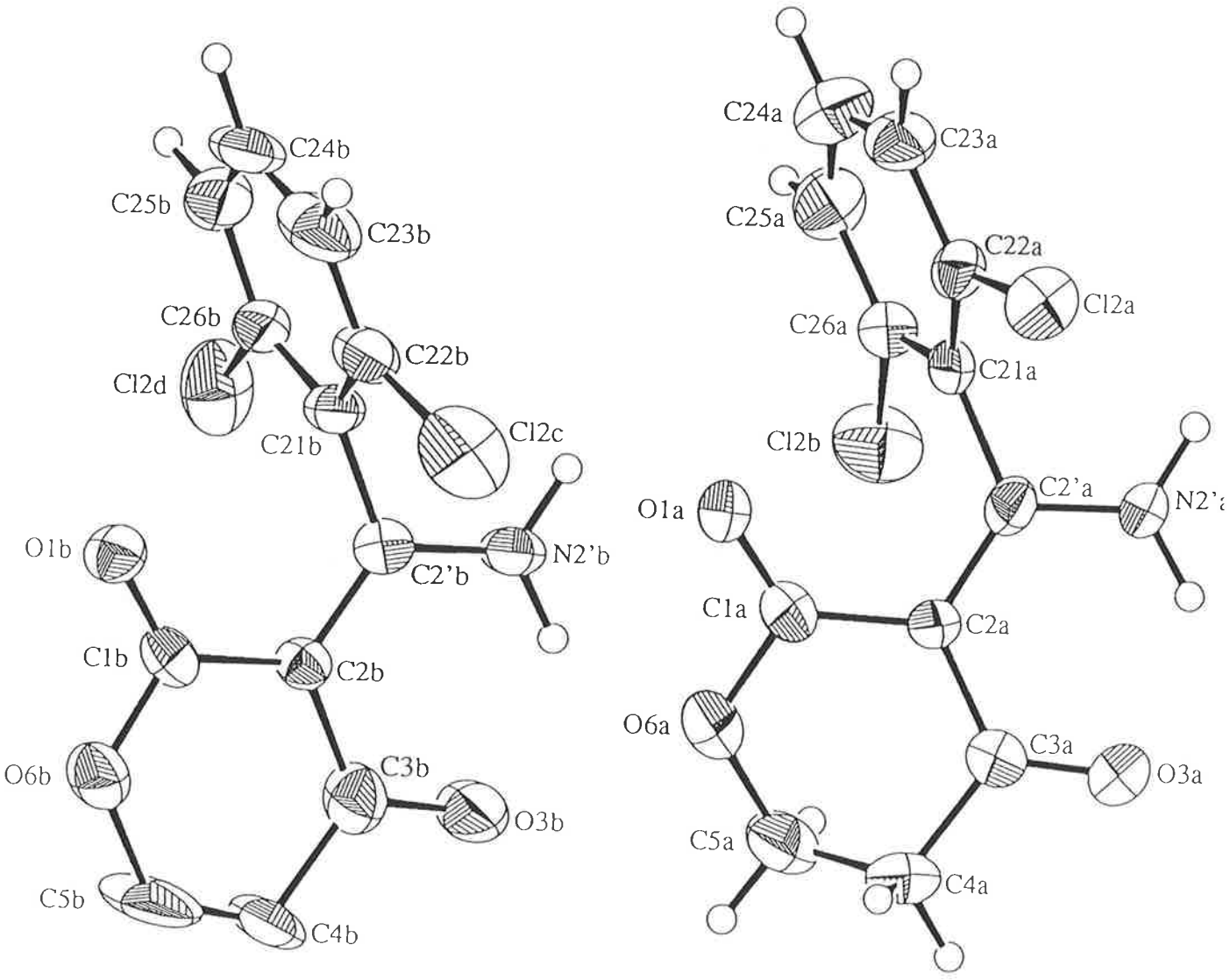
N(1a)C(1a)C(2a)C(7a)	3(1)	C(3b)C(2b)C(1b)C(8b)	3(1)
C(3b)C(2b)C(7b)C(6b)	-4(1)		
C(3b)C(4b)C(5b)C(6b)	-52.9(9)		
C(4a)C(3a)C(2a)C(7a)	1(1)		
C(4a)C(5a)C(6a)C(7a)	50.9(9)		
C(4b)C(3b)C(2b)C(7b)	9(1)		
C(4b)C(5b)C(6b)C(7b)	56.3(9)		
C(7b)C(2b)C(1b)C(8b)	-174.7(7)		
C(7a)C(2a)C(1a)C(8a)	-175.0(6)		
C(8b)C(9b)C(10bC(11b	1(1)		
C(8b)C(13bC(12bC(11b	-2(1)		
C(8a)C(9a)C(10aC(11a	1(1)		
C(8a)C(13aC(12aC(11a	1(1)		
C(9a)C(8a)C(13aC(12a	1(1)		
C(9a)C(10aC(11aC(12a	0(1)		
C(9b)C(8b)C(13bC(12b	3(1)		
C(9b)C(10bC(11bC(12b	1(2)		
C(10bC(9b)C(8b)C(13b	-2(1)		
C(10bC(11bC(12bC(13b	0(1)		
C(10aC(9a)C(8a)C(13a	-2(1)		
C(10aC(11aC(12aC(13a	-1(1)		

	Intermolecular Hydrogen bonding	Intramolecular Hydrogen bonding
Molecule a	1.84Å	1.83Å
Molecule b	1.79Å	1.84Å

APPENDIX 9

Crystal structures of

α-amino-α-(2,6-dichlorophenyl)-3-oxacyclohexane-2,6-dione **(82)**



Bond distances (Å) for

α-amino-α-(2,6-dichlorophenyl)-3-oxacyclohexane-2,6-dione (82)

atom	atom	distance	atom	atom	distance
Cl(2d)	C(26b)	1.704(8)	C(2a)	C(3a)	1.445(8)
Cl(2c)	C(22b)	1.727(7)	C(2'a)	C(21a)	1.492(8)
Cl(2a)	C(22a)	1.717(6)	C(2'b)	C(21b)	1.473(7)
Cl(2b)	C(26a)	1.731(6)	C(3a)	C(4a)	1.499(8)
O(1a)	C(1a)	1.210(7)	C(3b)	C(4b)	1.508(8)
O(1b)	C(1b)	1.215(6)	C(4a)	C(5a)	1.492(9)
O(3a)	C(3a)	1.235(7)	C(4b)	C(5b)	1.252(9)
O(3b)	C(3b)	1.240(6)	C(21a)	C(22a)	1.375(7)
O(6a)	C(1a)	1.364(7)	C(21a)	C(26a)	1.373(8)
O(6a)	C(5a)	1.442(7)	C(21b)	C(22b)	1.377(8)
O(6b)	C(1b)	1.360(6)	C(21b)	C(26b)	1.393(8)
O(6b)	C(5b)	1.438(8)	C(22b)	C(23b)	1.39(1)
N(2'a)	C(2'a)	1.322(7)	C(22a)	C(23a)	1.400(8)
N(2'b)	C(2'b)	1.312(6)	C(23a)	C(24a)	1.374(9)
C(1a)	C(2a)	1.459(8)	C(23b)	C(24b)	1.37(1)
C(1b)	C(2b)	1.450(7)	C(24a)	C(25a)	1.360(9)
C(2b)	C(2'b)	1.392(7)	C(24b)	C(25b)	1.36(1)
C(2b)	C(3b)	1.463(8)	C(25a)	C(26a)	1.373(8)
C(2a)	C(2'a)	1.396(8)	C(25b)	C(26b)	1.37(1)

	Intermolecular Hydrogen bonding	Intramolecular Hydrogen bonding
Molecule a	1.83Å	1.88Å
Molecule b	1.99Å	1.84Å

Bond angles (deg.) for

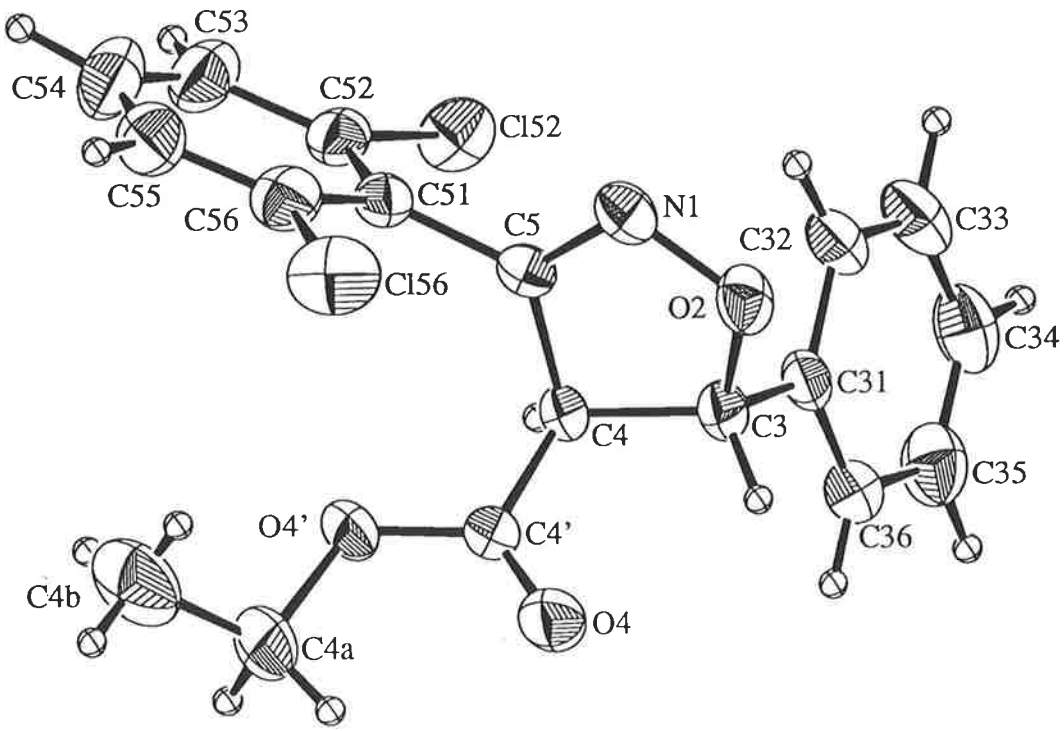
α-amino-α-(2,6-dichlorophenyl)-3-oxacyclohexane-2,6-dione (82)

atom	atom	atom	angle
C(1a)	O(6a)	C(5a)	117.6(5)
C(1b)	O(6b)	C(5b)	118.6(5)
O(1a)	C(1a)	O(6a)	115.6(6)
O(1a)	C(1a)	C(2a)	126.6(6)
O(6a)	C(1a)	C(2a)	117.8(6)
O(1b)	C(1b)	O(6b)	115.0(5)
O(1b)	C(1b)	C(2b)	125.8(6)
O(6b)	C(1b)	C(2b)	119.2(6)
C(1b)	C(2b)	C(2'b)	120.4(5)
C(1b)	C(2b)	C(3b)	118.6(6)
C(2'b)	C(2b)	C(3b)	120.9(5)
C(1a)	C(2a)	C(2'a)	119.3(6)
C(1a)	C(2a)	C(3a)	119.9(6)
C(2'a)	C(2a)	C(3a)	120.8(6)
N(2'a)	C(2'a)	C(2a)	121.7(6)
N(2'a)	C(2'a)	C(21a)	115.1(6)
C(2a)	C(2'a)	C(21a)	123.2(5)
N(2'b)	C(2'b)	C(2b)	121.6(5)
N(2'b)	C(2'b)	C(21b)	115.1(5)
C(2b)	C(2'b)	C(21b)	123.3(5)
O(3a)	C(3a)	C(2a)	123.5(6)
O(3a)	C(3a)	C(4a)	121.1(6)
C(2a)	C(3a)	C(4a)	115.4(6)
O(3b)	C(3b)	C(2b)	121.7(6)
O(3b)	C(3b)	C(4b)	119.7(6)
C(2b)	C(3b)	C(4b)	118.5(6)
Cl(2d)	C(26b)	C(25b)	119.3(7)
C(3a)	C(4a)	C(5a)	109.1(6)
C(3b)	C(4b)	C(5b)	115.8(7)
O(6a)	C(5a)	C(4a)	110.5(5)
O(6b)	C(5b)	C(4b)	128.0(7)
C(2'a)	C(21a)	C(22a)	121.4(6)
C(2'a)	C(21a)	C(26a)	121.4(5)
C(22a)	C(21a)	C(26a)	117.2(6)
C(2'b)	C(21b)	C(22b)	121.2(6)
C(2'b)	C(21b)	C(26b)	121.1(6)
C(22b)	C(21b)	C(26b)	117.7(6)
Cl(2c)	C(22b)	C(21b)	118.9(5)
Cl(2c)	C(22b)	C(23b)	118.7(7)
C(21b)	C(22b)	C(23b)	122.3(7)
Cl(2a)	C(22a)	C(21a)	120.8(5)
Cl(2a)	C(22a)	C(23a)	117.6(5)
C(21a)	C(22a)	C(23a)	121.6(6)
C(22a)	C(23a)	C(24a)	118.7(6)
C(22b)	C(23b)	C(24b)	118.1(9)
C(23a)	C(24a)	C(25a)	120.6(7)
C(23b)	C(24b)	C(25b)	120.8(9)
C(24a)	C(25a)	C(26a)	119.6(7)
C(24b)	C(25b)	C(26b)	120.9(9)
Cl(2b)	C(26a)	C(21a)	120.5(5)
Cl(2b)	C(26a)	C(25a)	117.2(6)
C(21a)	C(26a)	C(25a)	122.4(6)
Cl(2d)	C(26b)	C(21b)	120.5(5)

APPENDIX 10

Crystal structures of

ethyl 5-(2,6-dichlorophenyl)-3-phenyl-Δ^2-isoxazoline-4-carboxylate (**56**)



Bond distances (Å) for

ethyl 5-(2,6-dichlorophenyl)-3-phenyl-Δ^2-isoxazoline-4-carboxylate (56)

atom	atom	distance
Cl(52)	C(52)	1.726(4)
Cl(56)	C(56)	1.741(5)
O(2)	N(1)	1.403(4)
O(2)	C(3)	1.456(4)
O(4)	C(4')	1.201(4)
O(4')	C(4')	1.321(5)
O(4')	C(4a)	1.471(6)
N(1)	C(5)	1.269(4)
C(3)	C(4)	1.533(5)
C(3)	C(31)	1.507(5)
C(3)	H(3)	1.01(4)
C(4)	C(4')	1.506(6)
C(4)	C(5)	1.512(5)
C(4)	H(4)	0.90(3)
C(4a)	C(4b)	1.43(1)
C(4a)	H(4a)	0.94(8)
C(4a)	H(4b)	0.9(1)
C(4b)	H(4c)	0.82(8)
C(4b)	H(4d)	0.81(6)
C(4b)	H(4e)	0.87(8)
C(5)	C(51)	1.482(5)
C(31)	C(32)	1.390(6)
C(31)	C(36)	1.380(6)
C(32)	C(33)	1.372(7)
C(32)	H(32)	0.97(4)
C(33)	C(34)	1.361(8)
C(33)	H(33)	0.96(5)
C(34)	C(35)	1.358(7)
C(34)	H(34)	0.99(5)
C(35)	C(36)	1.394(7)
C(35)	H(35)	0.98(4)
C(36)	H(36)	0.93(4)
C(51)	C(52)	1.397(5)
C(51)	C(56)	1.381(6)
C(52)	C(53)	1.375(6)
C(53)	C(54)	1.375(8)
C(53)	H(53)	0.97(5)
C(54)	C(55)	1.366(8)
C(54)	H(54)	0.98(5)
C(55)	C(56)	1.375(7)
C(55)	H(55)	0.96(4)

Bond angles (deg.) for

ethyl 5-(2,6-dichlorophenyl)-3-phenyl-Δ^2-isoxazoline-4-carboxylate (56)

atom	atom	atom	angle	atom	atom	atom	angle
N(1)	O(2)	C(3)	108.9(3)	C(4a)	C(4b)	H(4e)	106(6)
C(4')	O(4')	C(4a)	116.2(4)	H(4c)	C(4b)	H(4d)	113(8)
O(2)	N(1)	C(5)	109.8(3)	H(4c)	C(4b)	H(4e)	120(9)
O(2)	C(3)	C(4)	104.4(3)	H(4d)	C(4b)	H(4e)	111(8)
O(2)	C(3)	C(31)	110.4(3)	N(1)	C(5)	C(4)	114.1(4)
O(2)	C(3)	H(3)	104(2)	N(1)	C(5)	C(51)	120.6(4)
C(4)	C(3)	C(31)	114.5(3)	C(4)	C(5)	C(51)	125.2(3)
C(4)	C(3)	H(3)	113(2)	C(3)	C(31)	C(32)	121.5(4)
C(31)	C(3)	H(3)	110(2)	C(3)	C(31)	C(36)	119.5(4)
C(3)	C(4)	C(4')	113.1(3)	C(32)	C(31)	C(36)	119.0(4)
C(3)	C(4)	C(5)	99.4(3)	C(31)	C(32)	C(33)	120.0(5)
C(3)	C(4)	H(4)	114(2)	C(31)	C(32)	H(32)	117(3)
C(4')	C(4)	C(5)	111.5(3)	C(33)	C(32)	H(32)	123(3)
C(4')	C(4)	H(4)	107(2)	C(32)	C(33)	C(34)	120.6(6)
C(5)	C(4)	H(4)	111(2)	C(32)	C(33)	H(33)	118(3)
O(4)	C(4')	O(4')	124.1(4)	C(34)	C(33)	H(33)	121(3)
O(4)	C(4')	C(4)	124.6(4)	C(33)	C(34)	C(35)	120.7(6)
O(4')	C(4')	C(4)	111.3(3)	C(33)	C(34)	H(34)	114(3)
O(4')	C(4a)	C(4b)	109.6(5)	C(35)	C(34)	H(34)	125(3)
O(4')	C(4a)	H(4a)	109(6)	C(34)	C(35)	C(36)	119.7(6)
O(4')	C(4a)	H(4b)	105(7)	C(34)	C(35)	H(35)	124(3)
C(4b)	C(4a)	H(4a)	129(6)	C(36)	C(35)	H(35)	117(3)
C(4b)	C(4a)	H(4b)	101(7)	C(31)	C(36)	C(35)	120.0(5)
H(4a)	C(4a)	H(4b)	99(8)	C(31)	C(36)	H(36)	118(2)
C(4a)	C(4b)	H(4c)	95(7)	C(35)	C(36)	H(36)	122(2)
C(4a)	C(4b)	H(4d)	111(5)	C(5)	C(51)	C(52)	120.6(4)

C(5)	C(51)	C(56)	122.5(4)
C(52)	C(51)	C(56)	116.9(4)
Cl(52)	C(52)	C(51)	119.0(3)
Cl(52)	C(52)	C(53)	119.1(4)
C(51)	C(52)	C(53)	121.9(5)
C(52)	C(53)	C(54)	119.2(5)
C(52)	C(53)	H(53)	120(3)
C(54)	C(53)	H(53)	120(3)
C(53)	C(54)	C(55)	120.3(6)
C(53)	C(54)	H(54)	118(3)
C(55)	C(54)	H(54)	121(3)
C(54)	C(55)	C(56)	120.1(6)
C(54)	C(55)	H(55)	129(3)
C(56)	C(55)	H(55)	111(3)
Cl(56)	C(56)	C(51)	119.5(4)
Cl(56)	C(56)	C(55)	118.9(4)
C(51)	C(56)	C(55)	121.6(5)

Torsion Angles (deg) for

ethyl 5-(2,6-dichlorophenyl)-3-phenyl-Δ^2-isoxazoline-4-carboxylate (**56**)

(1)	(2)	(3)	(4)	angle
Cl(52	C(52)	C(51)	C(5)	-2.9(6)
Cl(52	C(52)	C(51)	C(56)	179.4(3)
Cl(52	C(52)	C(53)	C(54)	179.8(4)
Cl(56	C(56)	C(51)	C(5)	2.2(6)
Cl(56	C(56)	C(51)	C(52)	179.8(3)
Cl(56	C(56)	C(55)	C(54)	-179.9(5)
O(2)	N(1)	C(5)	C(4)	1.8(4)
O(2)	N(1)	C(5)	C(51)	179.8(3)
O(2)	C(3)	C(4)	C(4')	-101.4(4)
O(2)	C(3)	C(4)	C(5)	17.0(4)
O(2)	C(3)	C(31)	C(32)	-30.1(5)
O(2)	C(3)	C(31)	C(36)	150.5(4)
O(4)	C(4')	O(4')	C(4a)	-0.5(7)
O(4)	C(4')	C(4)	C(3)	0.1(6)
O(4)	C(4')	C(4)	C(5)	-111.0(5)
O(4')	C(4')	C(4)	C(3)	179.1(3)
O(4')	C(4')	C(4)	C(5)	68.0(4)
N(1)	O(2)	C(3)	C(4)	-17.7(4)
N(1)	O(2)	C(3)	C(31)	105.9(3)
N(1)	C(5)	C(4)	C(3)	-12.3(4)
N(1)	C(5)	C(4)	C(4')	107.3(4)
N(1)	C(5)	C(51)	C(52)	107.8(5)
N(1)	C(5)	C(51)	C(56)	-74.7(5)
C(3)	O(2)	N(1)	C(5)	10.5(4)
C(3)	C(4)	C(5)	C(51)	169.8(4)
C(3)	C(31)	C(32)	C(33)	179.0(4)
C(3)	C(31)	C(36)	C(35)	-179.1(4)
C(4)	C(3)	C(31)	C(32)	87.4(5)
C(4)	C(3)	C(31)	C(36)	-92.0(5)
C(4)	C(4')	O(4')	C(4a)	-179.5(5)
C(4)	C(5)	C(51)	C(52)	-74.4(5)
C(4)	C(5)	C(51)	C(56)	103.1(5)
C(4')	O(4')	C(4a)	C(4b)	138.2(6)
C(4')	C(4)	C(3)	C(31)	137.7(4)
C(4')	C(4)	C(5)	C(51)	-70.6(5)
C(5)	C(4)	C(3)	C(31)	-103.9(4)
C(5)	C(51)	C(52)	C(53)	177.4(4)
C(5)	C(51)	C(56)	C(55)	-176.6(4)
C(31)	C(32)	C(33)	C(34)	0.1(8)
C(31)	C(36)	C(35)	C(34)	0.0(8)
C(32)	C(31)	C(36)	C(35)	1.5(7)
C(32)	C(33)	C(34)	C(35)	1.4(8)
C(33)	C(32)	C(31)	C(36)	-1.6(6)
C(33)	C(34)	C(35)	C(36)	-1.5(9)
C(51)	C(52)	C(53)	C(54)	-0.5(8)
C(51)	C(56)	C(55)	C(54)	-1.1(8)
C(52)	C(51)	C(56)	C(55)	1.0(7)
C(52)	C(53)	C(54)	C(55)	0.5(9)
C(53)	C(52)	C(51)	C(56)	-0.2(7)
C(53)	C(54)	C(55)	C(56)	0.3(9)

APPENDIX 11

Easton, C.J., Hughes, C.M., Tiekink, E.R.T., Lubin, C.E., Savage, G.P. and Simpson, G.W. (1994) Reversal of regiochemistry in the synthesis of isoxazoles by nitrile oxide cycloadditions.
Tetrahedron Letters, v. 35 (21), pp. 3589–3592, May 1994

APPENDIX 12

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Yeast-catalysed Reductive Ring-opening of Isoxazoles

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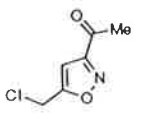
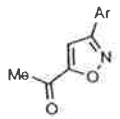
A novel reductive cleavage of the N–O bond of the isoxazoles **3a, b** and **5**, using actively fermenting baker's yeast, is described.

The use of actively fermenting baker's yeast (sp. *Saccharomyces cerevisiae*) is now a well established technique in organic chemistry.[1,2] Numerous synthetic transformations have been reported, including ester hydrolysis, condensations, and of particular importance the reduction of carbonyl compounds. The latter has been exploited in isoxazole chemistry, in the enantioselective reduction of the carbonyl groups of compounds such as the 3- and 5-acetyl-substituted isoxazoles **1** and **2**.[3] By contrast, we have now observed that the isoxazoles **3a**, **b**[4] and **5** undergo reductive ring-opening to give **4a**, **b** and **6**, respectively, under analogous conditions. This is the first example of a yeast-catalysed reductive cleavage of either an aromatic ring or a single bond.

The isoxazole **3a** (0.5 g) was added to a fermenting mixture prepared from dried baker's yeast (Fermipan, Gist-brocades Holland, 10 g) and sucrose (75 g) in water (400 ml) at 37 °C. After 24 h, standard work-up gave the ring-opened product **4a** [0.12 g; ^{1}H NMR ($CDCl_3$) δ 1.92 (br s, 1H), 1.97 (quint., *J* 6.5 Hz, 2H), 2.43 (t, *J* 6.5 Hz, 2H), 2.65 (t, *J* 6.5 Hz, 2H), 6.06 (br s, 1H), 7.35 (m, 3H)].† X-Ray crystallographic analysis established that the product **4a** exists as the dione–enamine tautomer in the solid state, the difference between the solution and solid structures being attributable to intermolecular hydrogen bonding in the crystal form.[5]



1



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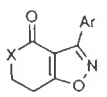

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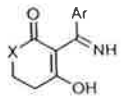
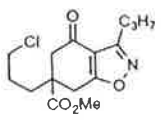
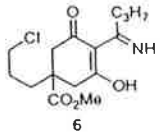


4

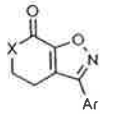
a; X = CH_2
b; X = O
Ar = 2,6-dichlorophenyl



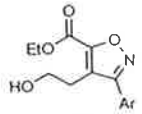
5



6



7a; X = CH_2
7b; X = O



8

Ar = 2,6-dichlorophenyl

Although the absolute yield of **4a** was only modest, the process yield was 75%, based on recovered starting material (0.34 g), and these conditions were found to be optimal for the quantity of yeast, sucrose and the substrate **3a**, and the reaction time. Other strains of yeast (*e.g.*, Munich lager yeast and Balmoral ale yeast) also catalysed the conversion of **3a** to **4a** but the product was more difficult to isolate from organic material contained by the yeasts. The isoxazoles **3b** and **5** also underwent reductive ring-opening to give **4b** and **6** respectively. In each case the absolute and process yields were similar to that of **4a**.

Incubation of the isoxazoles **7a**, **b**,[4] regioisomers of **3a**, **b**, with baker's yeast gave only recovered starting material (67%) in the former case, and starting material (27%) and the transesterification product **8** (2%) in the latter; there was no evidence of reductive ring cleavage. Although there is no obvious explanation for the difference in reactivity of **3a**, **b** compared with **7a**, **b**, it is interesting to note that the compounds **3a**, **b** with the lower reduction potentials underwent reductive ring cleavage. The reduction potentials of **3a**, **b** and **7a**, **b** were measured in acetonitrile, with Ag/AgCl as the reference electrode, and found to be −2.15, −2.2, −2.5 and −2.5 V, respectively.

The reductive cleavage of isoxazoles is an important method for the construction of β-diketones, β-ketoimines and β-ketoesters and their derivatives, and is normally carried out by metal-catalysed (nickel, palladium) hydrogenolysis.[6] These methods fail when other sensitive groups or catalyst poisons are present in the molecule. Now, baker's yeast provides an alternative method for this transformation.

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Footnote

† All new compounds were fully characterised.

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APPENDIX 13

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