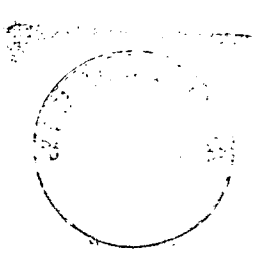
SYNTHESIS AND REACTIONS OF UNSTABLE ACTIVATED NITROGEN-CONTAINING ENOPHILES

James E. Mayo B.Sc.

Thesis presented for the degree of

Doctor of Philosophy

The University of Edinburgh **1998**



Declaration

I declare that this thesis is my own composition and that the work that it describes was carried out by myself unless specifically stated in the text. No part of this thesis has been submitted in any other application for a higher degree.

The thesis describes the results of research carried out in the Department of Chemistry of The University of Edinburgh, under the supervision of Dr. I. Gosney since 1st October 1993, the date of my admission as a research student.

James Mayo

For my parents and everyone else who has believed in me.

Acknowledgements

I would like to take this opportunity to thank my supervisor, Dr. Ian Gosney, for his supervision and encouragement throughout the course of this project. I would also like to thank Dr. Malcolm Banks for his advice and Neil Armstrong for help with the imine enophiles section of the project.

I am extremely grateful to the EPSRC for providing the main funding and to B.P. Chemicals, Grangemouth, for sponsoring the project as part of a CASE award. In particular I would like to thank Dr. Richard Blackborow for his help and assistance at BP chemicals.

I would also like to thank all of the technical staff within the Department of Chemistry, in particular, Mr. J. R. Millar and Mr. W. Kerr for running NMR spectra, Mr. A. Taylor and Miss E. Stevenson for mass spectra and Dr. A. J. Blake and Dr. S. Parsons for crystal structure determination. I would also like to thank my companions in the late lab 64 for making the research time so enjoyable, namely Tariq Abbas, Allan Doyle, Stuart Gebbie, Laurence Joly and Paul Thorburn.

Postgraduate Courses Attended

1. Medicinal Chemistry Lectures - Merck, Sharp and Dohme, Prof. R. Baker and Dr. P. Leeson, The University of Edinburgh, 1994, 1995 and 1996.
2. NMR Spectroscopy of Biological Molecules - Dr. P. Barlow and Dr. I. Sadler, The University of Edinburgh, 1995.
3. Chemical Development in the Pharmaceutical Industry - SmithKline Beecham, various speakers, The University of Edinburgh.
4. Industrial Fine Organic Chemistry - Prof. A. McKillop (University of East Anglia), The University of Edinburgh, 1996.
5. Hydrogen Peroxide and its Derivatives in Industry -Solvay Interox, various speakers, The University of Edinburgh, 1994.
6. Industrial Biocatalysts - SmithKline Beecham, various speakers, The University of Edinburgh, 1994
7. Industrial Chemistry - Zeneca Grangemouth, various speakers, The University of Edinburgh, 1995
8. Organic Research Seminars - various speakers, Chemistry Department, The University of Edinburgh, 3 years attendance
9. Current Topics in Organic Chemistry - various speakers, The University of Edinburgh, 2 years attendance
10. Royal Society of Chemistry, Perkin Division (Scottish Section) - annual meetings, various speakers, 3 years attendance.

11. Royal Society of Chemistry Annual Chemical Congress - various speakers, Heriot-Watt University, 1995

Abstract

The work described in this thesis has been concerned with investigations into the synthesis of activated cyclic enophiles attached by a linker group to a basic moiety and their reactivity in the ene reaction. The types of enophiles studied fall into three classes, *viz.* the five-membered triazolinediones, six-membered diazaquinones and the five-membered imidazolinediones. Also investigated was the amidoalkylation reaction of the acyclic activated imine, 1,2-diethoxycarbonyl aldimine ($EtO_2CN{=}CHCO_2Et$).

Hydrogenated precursors to the triazolinediones, i.e. urazoles, were synthesised by reaction of the relevant diamine with hydrazodicarbonamide because the normal synthetic routes using ethyl carbazate were found to be unsuccessful for basic functionalised urazoles. A variety of urazoles was synthesised and in turn subjected to chemical oxidation using a range of oxidants in the presence of an active alkene to bring about an ene reaction. No ene reaction was observed in any case and the triazolinedione reacted with itself to give complex mixtures. Hydrogenated precursors to the diazaquinones were synthesised from bromosuccinic anhydride, hydrazine and the required amine. These compounds also failed to give any ene reaction when reacted with alkenes normally active under such conditions. Reasons for this are discussed.

Progress was also made towards the synthesis of ethanolic precursors to the relevant cyclic imidazolinediones. Acyclic amine-containing compounds were prepared but these precursors failed to ring close without decomposition. This aspect was shown to be a key feature of such a ring structure by the successful synthesis of the non-ethanolic containing hydantoins.

Alcoholic precursors to the reactive intermediate 1,2-diethoxycarbonyl aldimine were synthesised and found to react in the presence of a catalytic amount of Lewis acid (BF_3) with suitable alkenes to form unexpected cyclic products, namely an azetidine and a γ-lactone ring structure. Whilst these products cannot be explained by invoking an ene reaction, they are shown to be the amidoalkylation products of either a [4+2]- or a [2+2]-cycloaddition reaction between the alkene and the imine. The [4+2]-cycloadducts are found to be unstable in the presence of moisture and readily lose ethanol to form a γ-lactone derivative. A step-wise mechanism involving a charged intermediate was invoked to explain both types of cycloaddition products. This proposal was supported by the high regioselectivity of the reaction outcome.

General Contents

Contents

Introduction

Contents

Discussion

Contents

Experimental

Introduction

1. Foreword

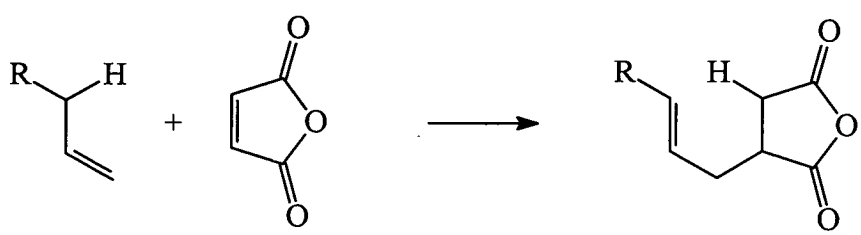
This thesis is concerned with the preparation of enophiles for use in the ene reaction, which is related to the Diels-Alder cycloaddition reaction and offers a wide synthetic scope in organic synthesis but perhaps due to its less favourable energetics remains largely neglected, especially in undergraduate textbooks. An overview of the reaction follows, with emphasis on the two types of enophile chosen for study in this project.

2. The Ene Reaction

The ene reaction is defined as the indirect addition of a compound containing a double bond (enophile) to an olefin possessing an allylic hydrogen (ene). As illustrated in Scheme 1, the reaction involves a transfer of the allylic hydrogen to the enophile, coupled with a bonding between the two unsaturated termini and concomitant allylic shift of the double bond[1]. The term was originally used exclusively for concerted reactions of this type, but the definition has been broadened to include any reaction that follows the general scheme.

Scheme 1

There have been some early isolated examples of the ene reaction; for example, the Prins reaction between olefins and carbonyl compounds[2], detailed later in this section, but the scope of the reaction was first realised in 1943 by Alder and co-workers[3] who utilised the process to functionalise alkenes with maleic anhydride **1** (Scheme 2).



1

Scheme 2

Thereafter, the reaction was left relatively obscure and unused until a break-through review article by Hoffmann in 1969[1]. Since then there have been several more specific reviews on certain aspects of the reaction[4-9] and the reaction has been subjected to several detailed mechanistic investigations[10-12].

2.1 Mechanism of the reaction

The ene reaction resembles the much better known Diels-Alder cycloaddition reaction in that both reactions may proceed through a cyclic transition state involving six electrons. The difference between the two reactions is that two of the π electrons of the diene from the Diels-Alder reaction are replaced by two σ electrons of the C-H bond allylic to the π bond. Consequently, the ene reaction is energetically less favourable and requires a greater activation energy with the need of harsher reaction conditions. Frontier molecular orbital (FMO) theory has been used[13] to describe the mode of addition as a suprafacial three-component interaction involving the HOMO of the π bond of the ene, the LUMO of the C-H bond allylic to the double bond and the LUMO of the enophile. Applications of the Woodward-Hoffmann orbital symmetry rules allow the involvement of a $[2\sigma+2\pi+2\pi]$ concerted reaction, and on this basis the reaction has been the subject of theoretical calculations using a modified version of the computer program CAMEO[7] to predict the feasibility and regiospecificity of the reaction.

An overall mechanism for the reaction has not yet been agreed upon and there is evidence for both a concerted and stepwise processes even with reactions involving the same enophile. Four possible reaction mechanisms can be proposed as outlined in Fig. 1. These involve either a diradical pathway (**A**), zwitterionic intermediate (**B**, **C**) or concerted reaction (**D**).

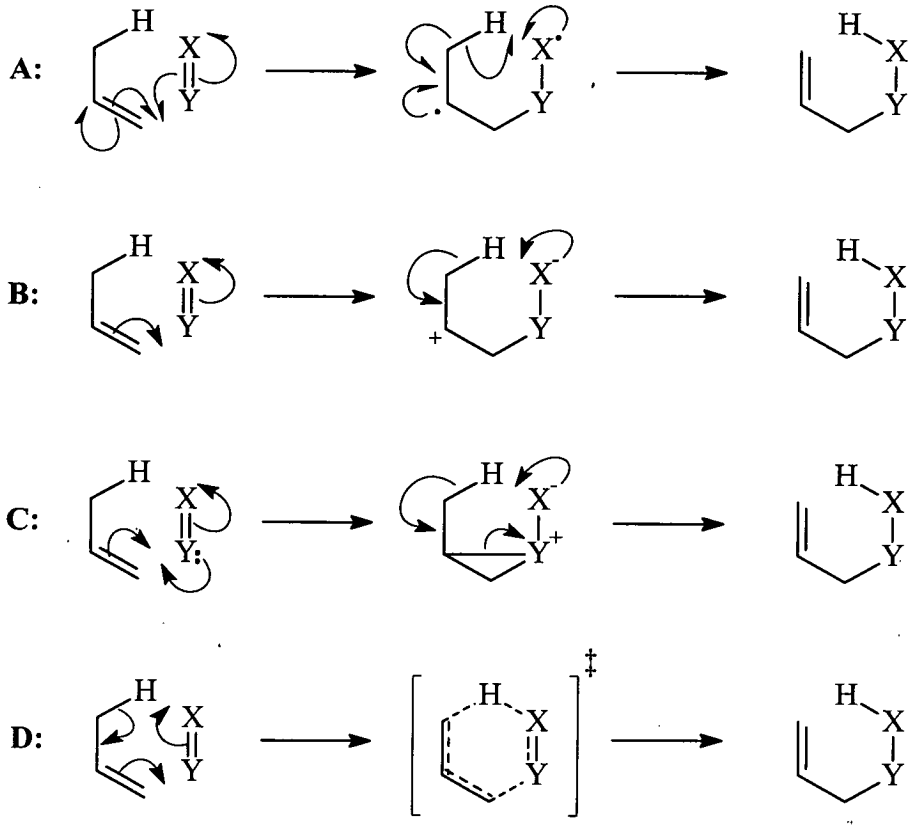
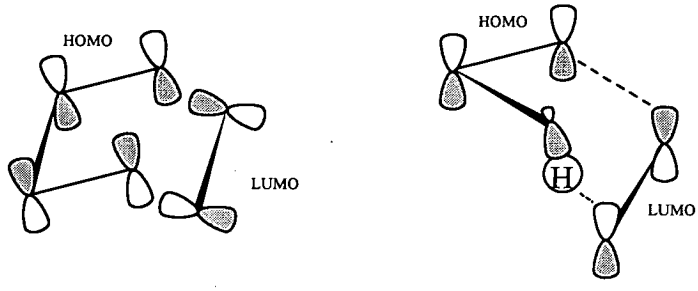


Figure 1. Possible mechanisms for ene reaction.

The mechanistic pathway proposed to involve a biradical intermediate, *i.e.* path **A**, is usually rejected due to a lack of rearrangements that lead to side products, which would be characteristic of biradicals. Nonetheless, the addition of free radical initiators and inhibitors have been shown to have an effect upon reactions involving cyclopentene or cyclohexene as ene component[14] and because of this, such a mechanism cannot be discounted. Similarly, the lack of observed products due to

rearrangements normally associated with carbocations makes the mechanism involving a simple acyclic zwitterionic intermediate (path **B**) also unlikely.

Following the first detailed stereochemical investigation into the reaction[15], a concerted mechanism (path **D**) was proposed as the most probable course of the reaction, especially in view of its high stereoselectivity. This pathway is consistent with similarities observed for the Diels-Alder cycloaddition reaction and with molecular orbital calculations. The proposed mechanism involves a suprafacial approach of the enophile to form a cyclic transition state as shown in Fig. 2 followed by formation of the product. There was also a lack of any observed solvent effects which combined with the high stereoselectivity would be consistent with such a concerted mechanism, but these factors alone do not prove the mechanism.

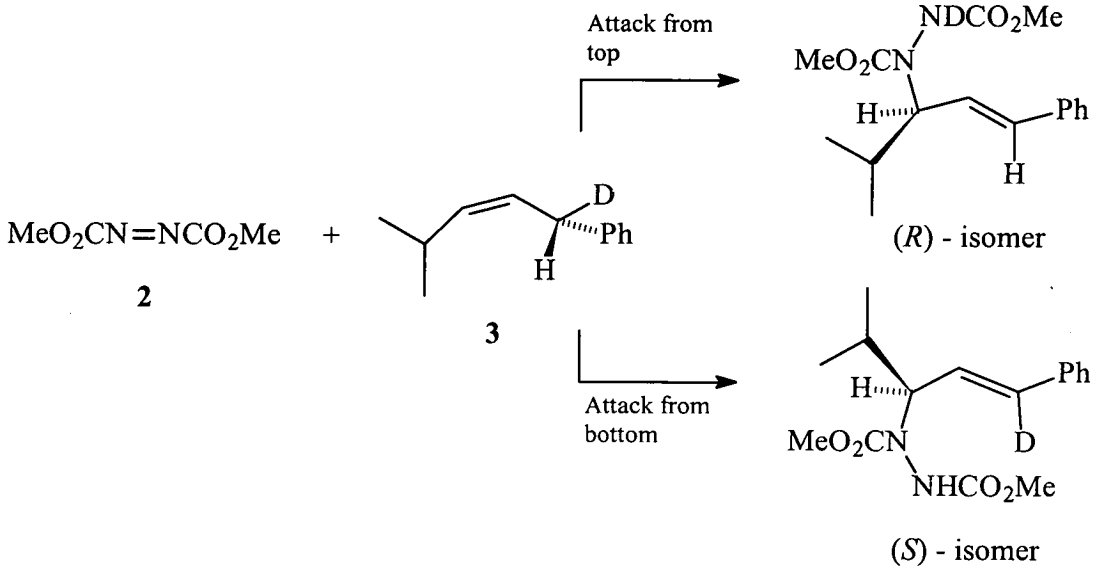


Diels-Alder Ene

Figure 2. Transition states in Diels-Alder and Ene Reactions

Experimental evidence for this mechanism was provided by the deuterium-labelling studies of Stephenson and Mattern[16] for the reaction between dimethyl azodicarboxylate **2** and methylphenylpentene **3** (Scheme 3). Essentially, attack from above the plane of the allylic bond gives rise to the (*R*)-isomer as the sole product,

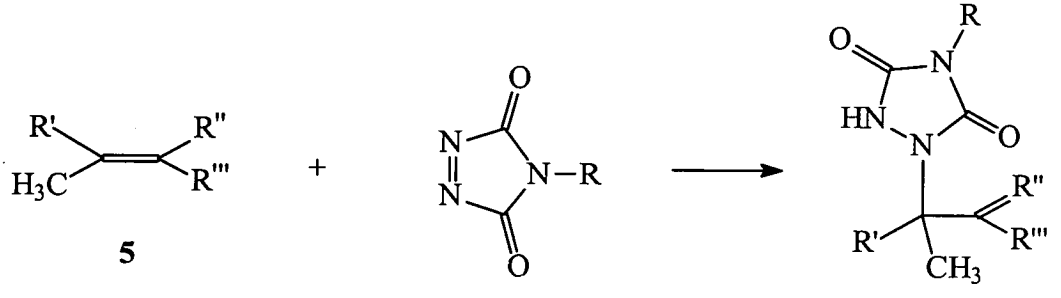
whilst attack from below leads to the (*S*)-isomer. Both of these products were observed in a ratio of 3.1:1 in favour of the (*S*)-isomer. In addition, the kinetic isotope effect for the abstraction of hydrogen from the benzylic centre was measured as 3.3. The coincidence of these numbers points strongly to a concerted mechanism, *i.e.* pathway **D** from Fig. 1.



Scheme 3

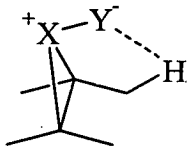
The second stepwise ionic mechanism described in Fig. 1 (path **C**) is also consistent with the stereochemical outcome of the reaction since the ene-enophile bond is formed initially and the intermediate formed is structurally rigid. Evidence for such an intermediate was found in the ene reaction of triazolinediones **4** (RTAD) with different isomers of tetramethylethylene-d_6 **5** (Scheme 4)[17]. The results obtained established a significant kinetic isotope effect (k_H/k_D = 3.7-3.8) for the *trans*-isomer

and not for the *cis* isomer. This outcome is inconsistent with the occurrence of a concerted pathway, which is expected to show an effect for both isomers. Instead, it is more consistent with the formation of a three-membered transition state (Fig.3) that allows hydrogen abstraction to occur on either side of the molecule and consequently is unaffected by the presence of the *cis* isomer.



Olefin **5**	RTAD **4**	k_H/k_D
R'=CD_3, R"=CD_3, R'"=CH_3	R=CH_3	1.08
(*cis*)	R=Ph	1.1
R'=CD_3, R"=CH_3, R'"=CD_3	R=CH_3	3.8
(*trans*)	R=Ph	3.7
R'=CH_3, R"=CD_3, R'"=CD_3	R=CH_3	5.7
(*geminal*)	R=Ph	5.8

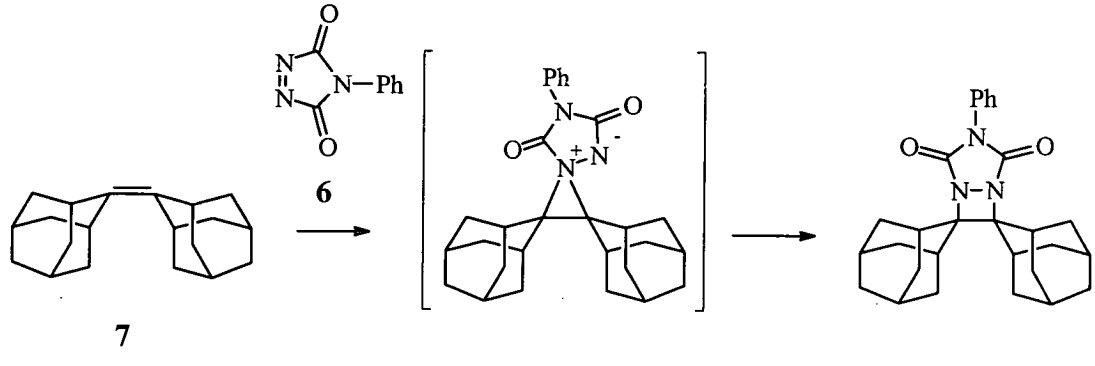
Scheme 4



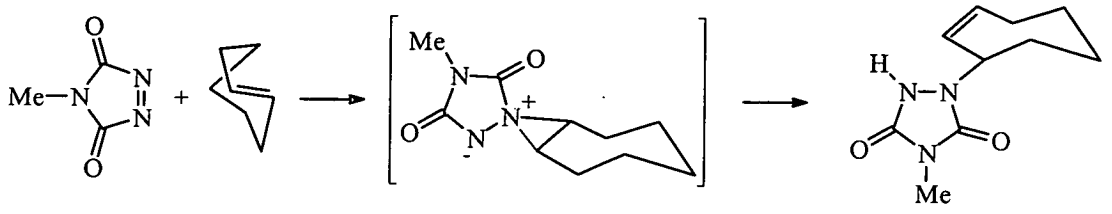
X
||
Y = Enophile

Figure 3. Proposed ene reaction intermediate

Additional support for such a mechanism is given by the direct observation of this cyclic intermediate. Thus, a three-membered pre-peroxide intermediate has been trapped in the reaction between singlet oxygen and adamantylideneadamantane in the presence of a phosphite[18]. Similarly, an aziridinium imide intermediate has been observed spectroscopically in the [2+2]-cycloaddition of 4-phenyltriazolinedione (PTAD) **6** with adamantylideneadamantane **7** (Scheme 5)[19, 20] and also in the ene reaction of 4-methyltriazolinedione (MTAD) **8** with cycloheptene **9** at -135°C (Scheme 6)[21].



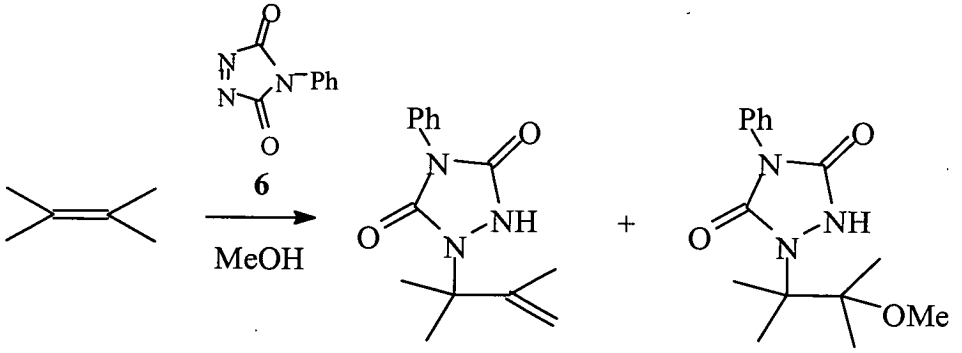
Scheme 5



8 **9**

Scheme 6

Further evidence for such a mechanism was also obtained when the ene reaction of PTAD **6** was carried out with tetramethylethylene in methanol. Both the ene product **A** and its methanol adduct **B** were obtained in different proportions depending on the temperature at which the reaction was performed[22] (Scheme 7).



A **B**

Temperature (°C)	%ene product, **A**	%methanol adduct, **B**
60	78	22
0	36	64
-40	17	83

Scheme 7

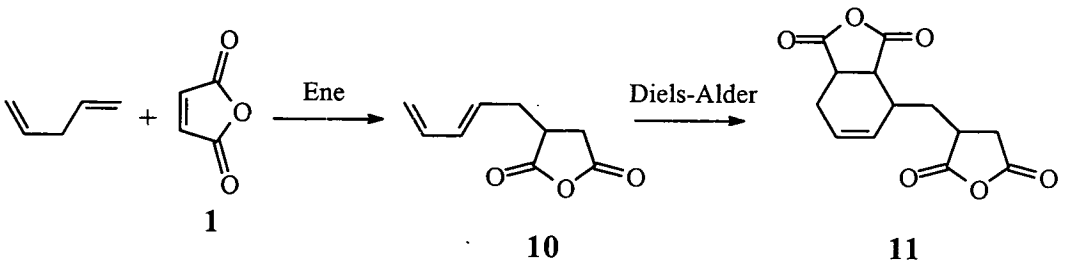
The two most commonly accepted of the reaction pathways shown in Fig. 1, *viz.* pathways **C** and **D**, have been calculated to be theoretically very similar in energy requirements[11] and, in essence, may account for the majority of ene reactions studied. The stereoselectivity of the stepwise mechanism is due to a combination of steric and electronic effects controlling the stereochemistry of the intermediate whereas the stereoselectivity of the concerted process is governed by the face of approach of the two molecules. Less reactive enophiles such as alkenes tend to react *via* the concerted process (pathway **D**), whereas the more reactive enophiles such as triazolinediones and singlet oxygen react *via* a three-membered ionic intermediate (pathway **C**)[20, 23].

The ene reaction can also generally be assisted by Lewis-acid catalysis[24]. For example, ene reactions involving formaldehyde as the enophile do not occur without a catalyst but can be carried out at room temperature in the presence of an alkyl aluminium halide[25]. This outcome is consistent with all of the proposed mechanistic routes shown in Fig. 1 since they are all made energetically more favourable by a lowering in energy of the LUMO of the enophile. The use of these catalysts can also have effects on the rate and mechanism of the reaction. Thus, Lewis-acid catalysed ene reactions have been found to follow both paths **C** and **D**[6] with the general rule being that the more reactive ene- or enophile-Lewis acid complexes react by a stepwise mechanism, whilst the less reactive complexes react *via* an asymmetric concerted mechanism[7, 26].

2.2 The ene component

The ene reaction has a wide scope and almost any olefin can be used as the ene component provided it possesses an allylic hydrogen. As has been shown in previous examples, simple alkenes have been extensively used, but other π-bonded molecules may also be utilised, including those containing allenic, acetylenic, aromatic and carbon-heteroatom unsaturated bonds. For the concerted ene reaction, the reactivity of the ene component depends upon the stability of the π- and σ- bonds with strained systems such as cyclopropene being particularly reactive. For the stepwise ene reaction, the reactivity is more dependent upon the ability of the central carbon to support a positive charge, and therefore alkenes with a disubstituted vinylic carbon are more reactive[7]. Since the product from an ene reaction will possess a double bond, if there is an abstractable hydrogen allylic to this bond, further ene reaction may occur and 2:1 adducts can often be formed as by-products[1].

With 1,3-dienes, there is also the possibility of competition from Diels-Alder cycloaddition reactions as every enophile may also function as a dienophile, and in such a situation, a sterically hindered diene or *trans*-enophile must be used to favour the ene pathway. A combination of the ene reaction and Diels-Alder cycloaddition is also possible, especially with 1,4-dienes, which may react as shown in Scheme 8 in an ene reaction to form a 1,3-diene such as **10,** followed by Diels-Alder reaction with another equivalent of the enophile, in this case with maleic anhydride **1**, to form the final bis-adduct **11**[27].



1 10 11

Scheme 8

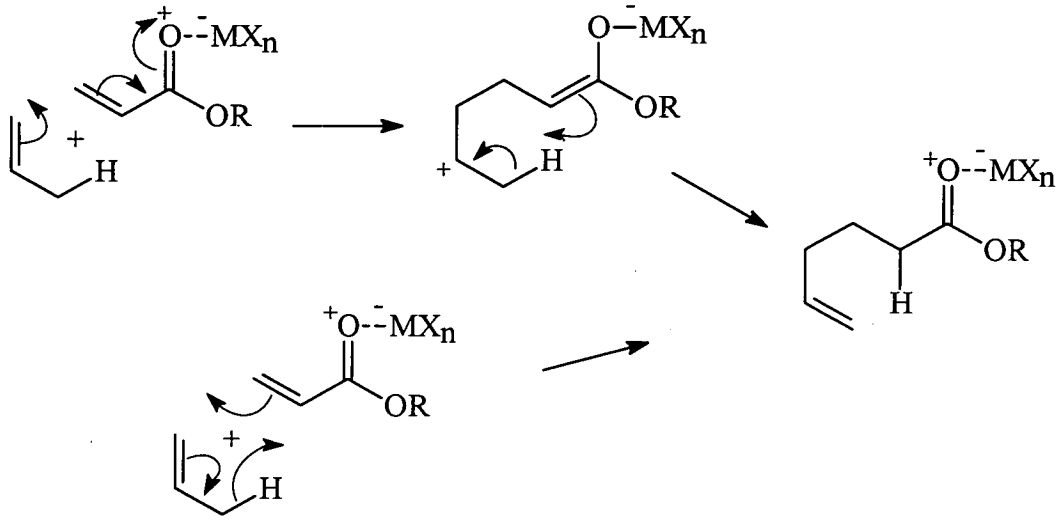
2.3 The enophile

There is a wide range of enophiles that can be employed in the ene reaction. Because of the energetics of the reaction, the most commonly used enophiles have characteristically low-lying LUMO states. These tend to be electron deficient π-bonded systems often with at least one electron-withdrawing substituent such as a carbonyl or sulfonyl group attached. Included are compounds containing alkene, alkyne, azo, imine, carbonyl and nitroso groups as well as singlet oxygen and charged species such as iminium ions[10]. Of particular interest to this project are the azo and imine enophiles, which will be discussed later in greater detail. The most reactive enophiles are those with the lowest energy LUMO and in particular those with more than one electron-withdrawing group.

2.3.1 Alkenes and alkynes

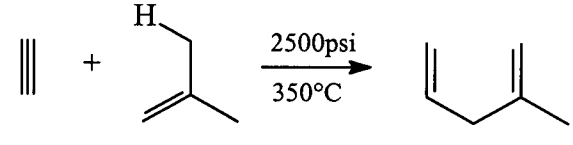
Simple alkenes do not normally function as enophiles and for the most simple ene reaction to occur, they usually require electron-withdrawing groups in one or more α-positions, *e.g.* maleic anhydride, methyl acrylate and tetracyanoethene[28]. Even with this level of activation, they are very inactive and require high temperatures and/or Lewis-acid catalysis to proceed at a reasonable rate. Maleic anhydride was one of the first enophiles to be extensively studied and it is commonly believed to react *via* a concerted mechanism with a preference for the *endo*-transition state[29].

Lewis-acid catalysis can be used with electron deficient alkenes such as α,β-unsaturated esters and other such functional groups and operates either by lowering the energy of the LUMO of the enophile by complexation to the oxygen of the carbonyl group in the transition state for a concerted mechanism, or by stabilising the intermediate formed by the stepwise mechanism (Scheme 9). The activation given by Lewis-acid catalysis is large enough to allow the reaction of esters at room temperature and can also influence the stereochemistry of the end products.



Scheme 9

Alkynes are considerably more reactive enophiles than alkenes, but non-activated alkynes will still require forcing conditions. For example, the relatively simple ene reaction between acetylene **12** and isobutene **13** can be achieved only in a flow reactor under high pressure (2500psi) and at the elevated temperature of 350°C (Scheme 10)[30].



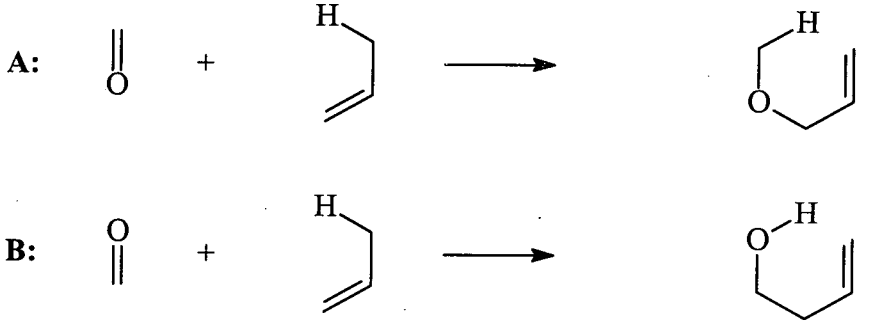
12 **13**

Scheme 10

This low reactivity can be augmented in a similar manner to alkene reactivity by the incorporation of electron-withdrawing substituents onto the acetylenic function, *e.g.* with dicyanoacetylene and hexafluorobutyne. Benzyne is also a very reactive enophile since the LUMO is considerably lowered in energy by the effects of ring strain.

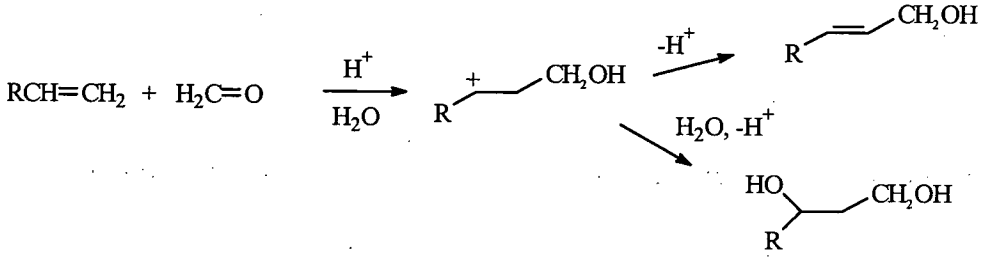
2.3.2 Carbonyl enophiles

Carbonyl compounds, *i.e.* ketones and aldehydes, possess a polarised reactive double bond, and in principle can react with alkenes *via* the ene reaction by two different pathways (Scheme 11). Thus, in theory, attachment to the oxygen atom can occur to form an allyl ether (path **A**), or to the carbon atom to form alcohols (path **B**). Due to more favourable energetics, carbon is always the site of addition and only alcohols are formed.



Scheme 11

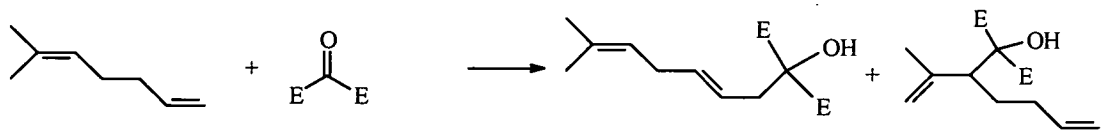
As is the case with carbon-carbon enophiles, simple aldehydes and ketones do not react under normal conditions and require electron-withdrawing groups or acid catalysis to function. Typical enophiles of the electron-withdrawing type include ethyl glyoxylate, hexafluoroacetone and carbonyl cyanide. An example of the use of Brønsted-acid catalysis is the Prins reaction in which the reactive species is thought to be a protonated aldehyde (Scheme 12). The complex formed by the addition of this species to the ene can react with other reagent present (for example water) to form other compounds as well as the standard ene product[31].



Scheme 12

Lewis-acid catalysis of carbonyl ene reactions has been widely studied and simple aldehydes and ketones, which will not react thermally, do so smoothly with alkenes in the presence of catalysts such as alkyl aluminium halides and tin tetrachloride. Kinetic isotope studies and analysis of reaction products have shown that the reaction mechanism is changed by the use of catalysis. In the example shown in Scheme 13, diethyl oxomalonate **14** is involved in an ene reaction with 2-methylhepta-2,6-diene **15**. The thermal reaction with no catalyst present follows a concerted pathway which

reacts slowly at the least hindered site to produce predominantly **A**, whereas when tin tetrachloride is used as a Lewis acid catalyst, the reaction is a much faster stepwise process involving a loosely bonded three-membered transition state which reacts at the site with the most stable carbocation so favours production of **B**[32, 33].



15 **14**: E = CO_2Et **A** **B**

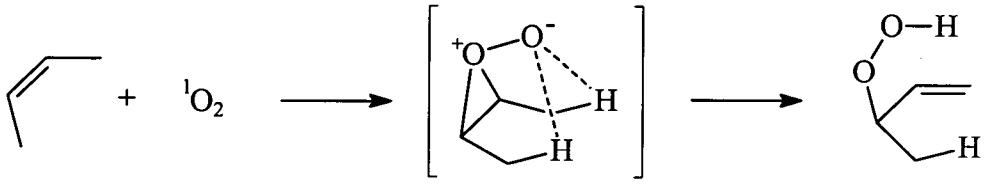
Conditions	% A	% B
180°C, 48hr	92	8
$SnCl_4$, 0°C, 5min.	3	97

Scheme 13

2.3.3 Singlet oxygen

When irradiated to its first excited (singlet) state, oxygen is a very reactive enophile, which reacts with almost any ene to produce an allylic hydroperoxide. Such products are often unstable and are usually studied by reduction to the corresponding alcohol with a hydride or phosphite reagent[34]. Singlet oxygen ($^1O_2$) is very similar in reactivity to triazolinediones which will be discussed later in the chapter, and it is

found that both enophiles are often studied together. Theoretical studies have been made on the mechanism of the addition, but showed very little difference in the energies of either concerted or stepwise routes.[10] Nonetheless, kinetic isotope studies show that $^1O_2$ normally reacts *via* a three-membered pre-peroxide transition state as illustrated in Scheme 14[35].



Scheme 14

Singlet oxygen is also a reactive dienophile and will readily undergo Diels-Alder [4+2]-cycloaddition reactions to form endo-peroxides. In addition, [2+2]-cycloadditions compete with the ene reaction and give rise to dioxetanes. These competing reactions are demonstrated by the photo-oxidation of indenes[36] and 1-vinylcycloalkenes[37], details of which are summarised in Fig. 4.

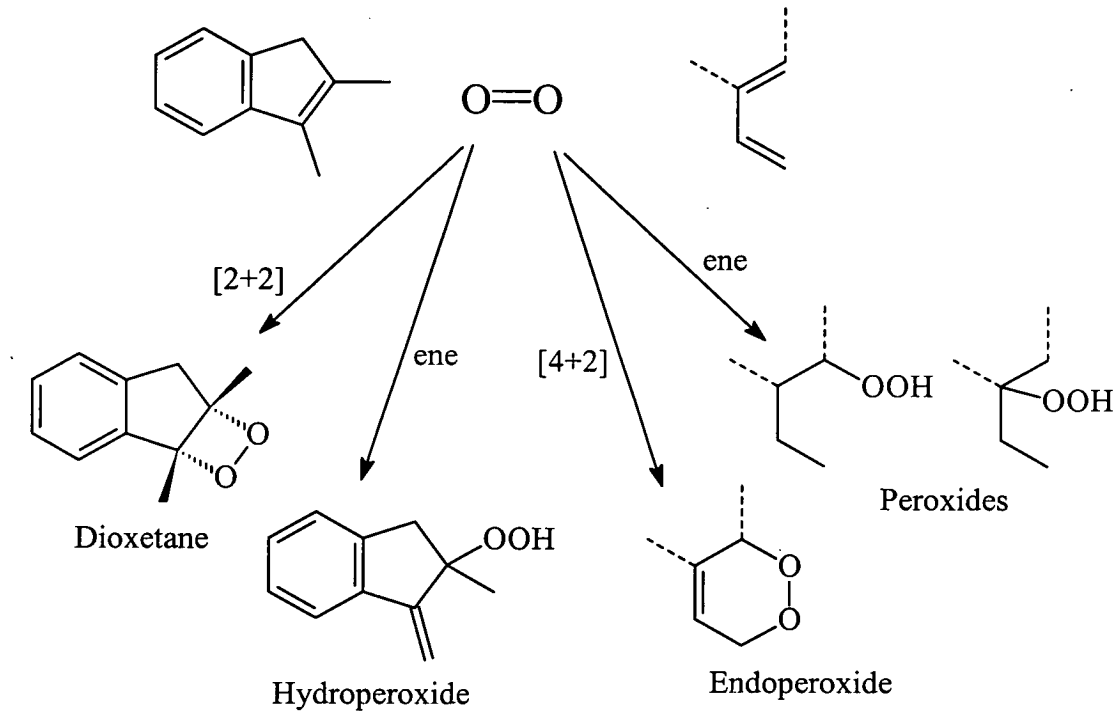
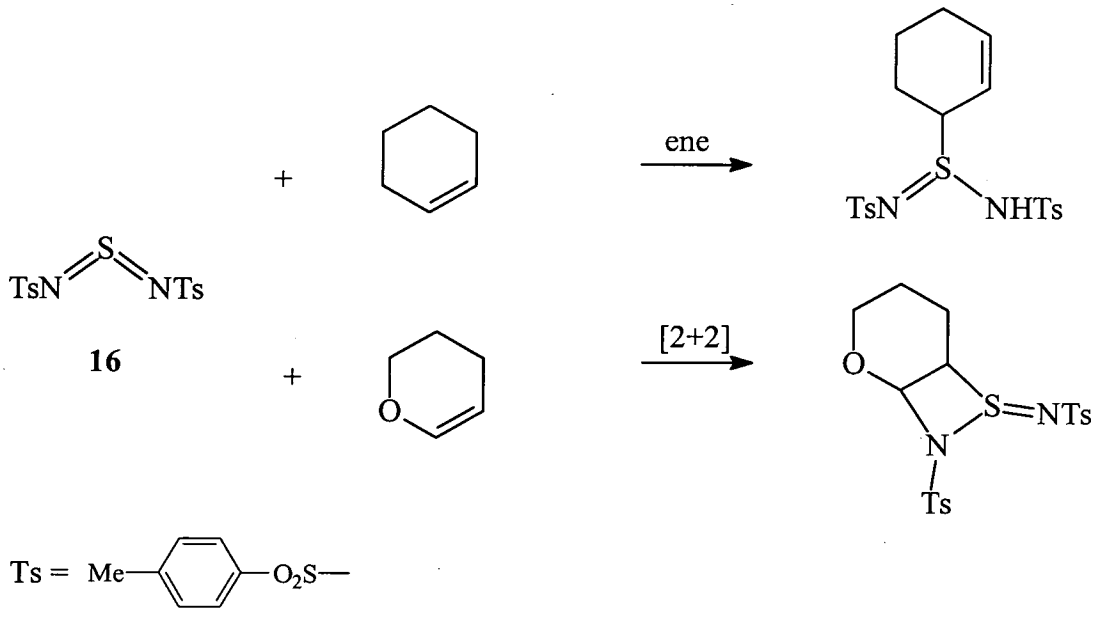


Figure 4. Examples of ene reaction of $^1O_2$, together with competing cycloaddition reactions

2.3.4 Other enophiles

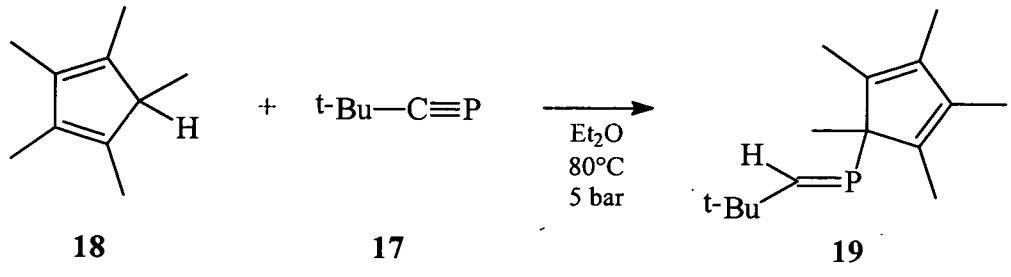
Other enophiles that have been used include sulfur-containing compounds such as thioketones, thionitroso compounds and sulfur-cumulated systems such as sulfur dioxide. *N*-Sulfinylarenesulfonamides and *N,N*-diaryl sulfurdiimides are particularly active enophiles, but suffer from competition from the corresponding [2+2]-cycloaddition reaction. For the reaction with cyclic alkenes, it has been found that di-*p*-toluenesulfonylsulfurdiimide **16** reacts either in an ene manner or by [2+2]-

cycloaddition depending on the identity of the neighbouring non-reactive allylic atom (Scheme 15)[38].



Scheme 15

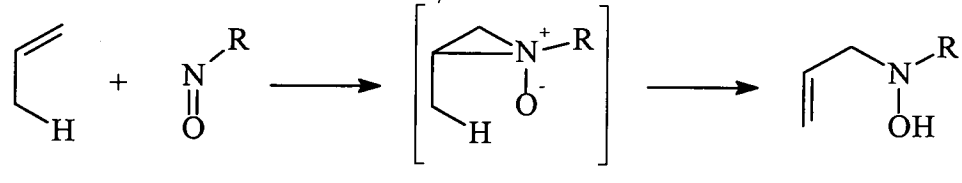
Phosphorus-containing compounds have also been found to be active as enophiles and these include the phosphaalkynes, which have been used both as dienophiles and enophiles, both with and without catalysis[39]. For example, in the reaction between *tert*-butyl phosphaalkyne **17** and pentamethylcyclopentadiene **18**, the expected Diels Alder [4+2]-cycloadduct is not formed due to steric hindrance, and instead the ene product phosphaalkene **19** is produced (Scheme 16)[40].



18 **17** **19**

Scheme 16

Nitroso compounds are similar in reactivity to azo-containing enophiles and have also been shown to react *via* a three-membered aziridine *N*-oxide to form hydroxylamines[41] (Scheme 17). Activated acyl nitroso compounds have also been studied, but due to poor stability they need to be generated *in situ*[42].

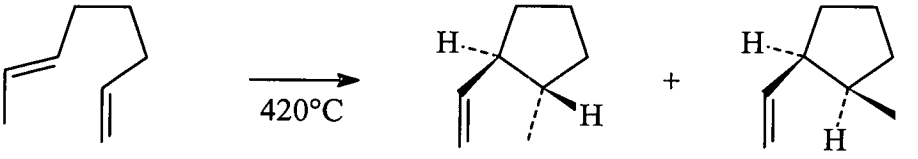


Scheme 17

2.4 Intra-molecular ene reactions

Intra-molecular ene reactions are also common, whereby a single molecule acts as both ene and enophile and the reaction results in ring closure[6]. The intramolecular

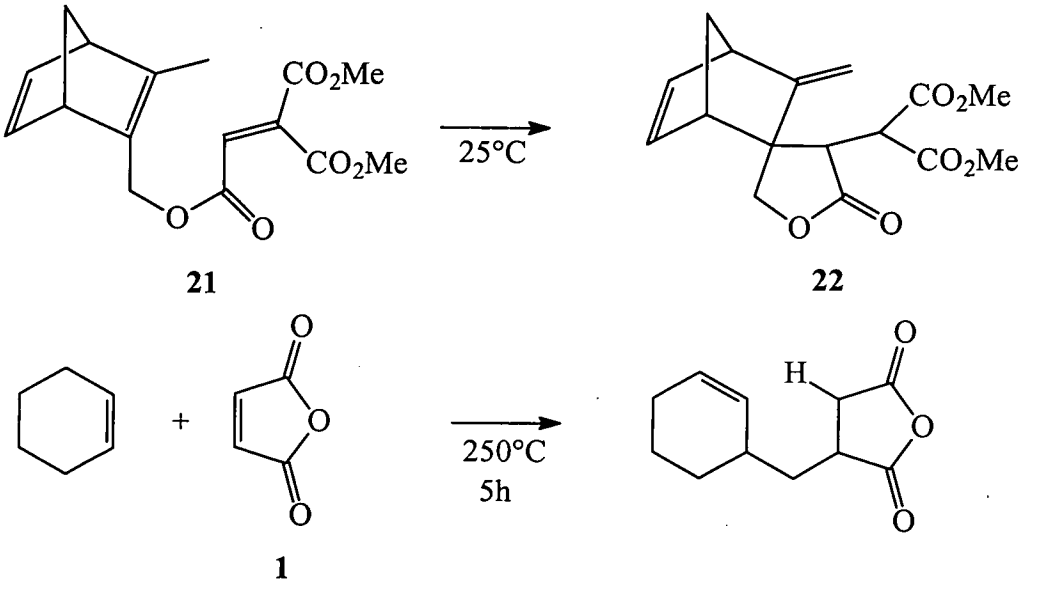
ene reaction, like the Diels-Alder cycloaddition, involves a loss in entropy[43] because the reaction involves the combination of two molecules. Consequently the reaction is highly favoured by an intra-molecular process due to entropic assistance.[5] This considerably lowered entropy requirement means that simple dienes will undergo an intramolecular ene reaction as illustrated by the pyrolysis of octa-1,6-diene **20** which cyclises to produce two isomers of the resulting vinyl substituted cyclopentane[44, 45] (Scheme 18).



20 1 : 14

Scheme 18

Ene reactions involving activated enophiles also benefit from the reduced entropy associated with the intra-molecular case. For example, the diene **21** in which the enophilic part of the molecule is activated by three carbonyl groups, will cyclise smoothly at room temperature immediately upon its formation to form a single spirolactone **22** (Scheme 19)[46]. By comparison, in the inter-molecular case, a similar enophile such as maleic anhydride **1** requires temperatures as high as 250°C to bring about reaction in a similar manner, *e.g.* with cyclohexene[3].



21 **22**

1

Scheme 19

There are three different types of cyclisation possible by the intra-molecular ene reaction. These are shown in Fig. 5 and correspond to the three centres of the allylic unit by which it is possible to attach the rest of the molecule. In cases where more than one type may occur, the order of reactivity is type 1 > type 2 > type 3.[5]

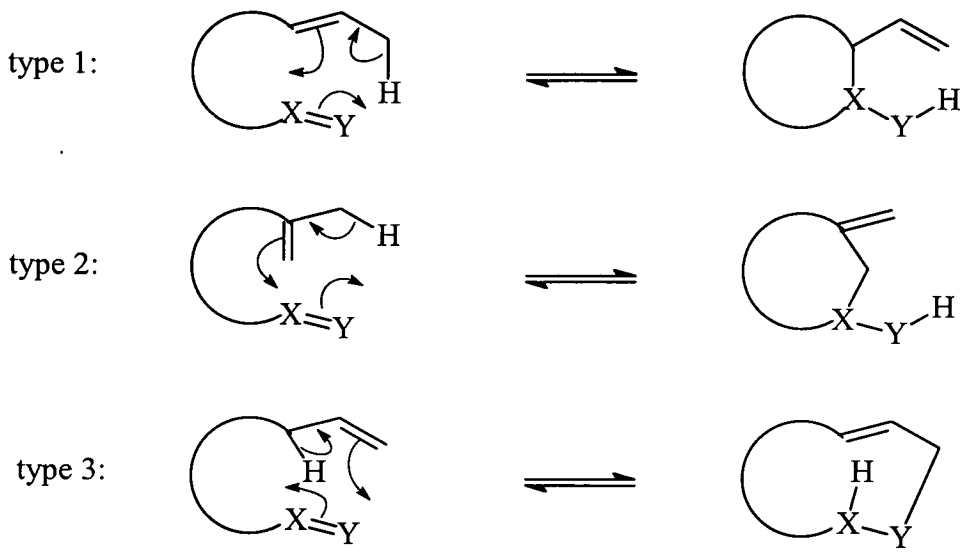
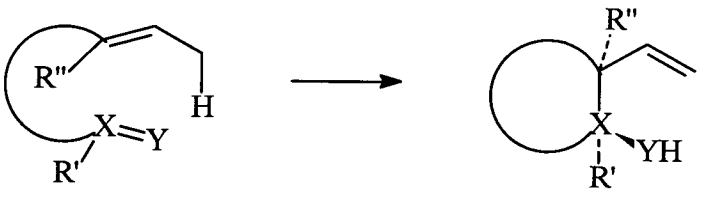


Figure 5. Different types of intra-molecular ene reaction.

The intra-molecular reaction also shows great specificity and is thought to proceed in a concerted manner *via* a highly ordered transition state.. Either an *exo-* or *endo-* transition state may be involved, depending on the chirality of the starting material or the placing of groups to direct steric hindrance. For example, in type 1 additions, where the hydrogen donor site is *cis* with respect to the enophilic chain, only a product in which the donor and acceptor site are *cis* to each other is formed as illustrated in Scheme 20.



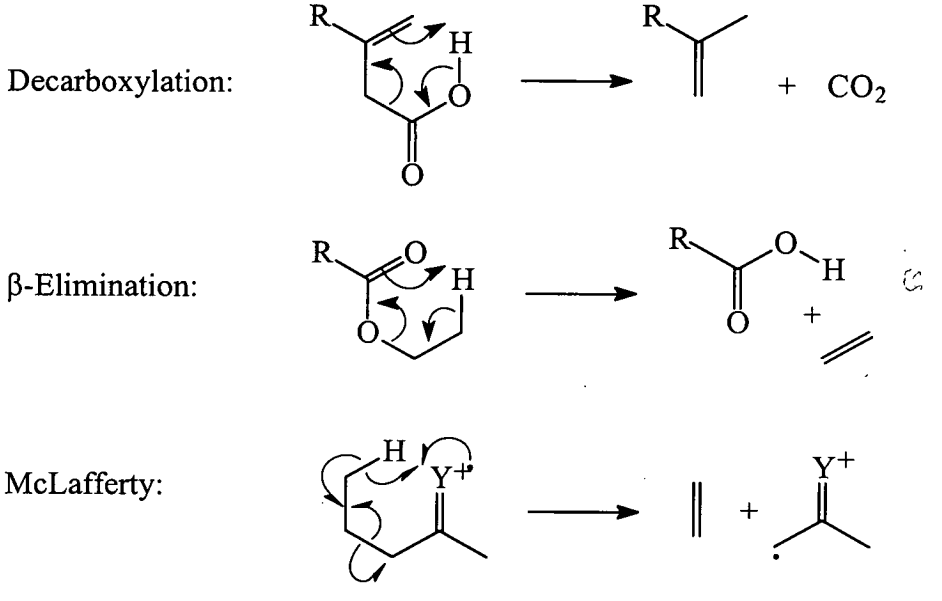
Scheme 20

2.5 Retro-ene reactions

The retro-ene reaction may be defined as the thermal reversion of the ene reaction where an unsaturated compound fragments to give two compounds with concomitant hydrogen shift. This outcome can normally be achieved by pyrolysis the relevant compound, either by normal thermolytic techniques such as heating, with or without a solvent, or by flash vacuum pyrolysis (FVP)*. As in the ene reaction, heteroatoms can be incorporated, either as attached activating groups or actually in the reactive centres, and double bonds may also react to be replaced by triple bonds. The reaction can be used in an intra-molecular fashion to achieve rearrangement, in the removal of specific groups or for generation of unsaturated reactive molecules in a similar way to the retro Diels-Alder reaction[47]. The topic has been covered in many of the other reviews previously mentioned[1, 4, 5, 7] and some synthetic applications have also been reviewed[48].

* see p. 87 for Fig. 13 illustrating FVP technique

There is no common mechanism governing all retro-ene reactions and suggested pathways have involved either a concerted or radical mechanism, with the former being most commonly suggested. Specific examples of the reaction include decarboxylation of β,γ-unsaturated acids[31], β-elimination of ketones, esters and similar compounds[49], and the McLafferty rearrangement which is commonly observed in mass spectroscopy (Scheme 21)[50].



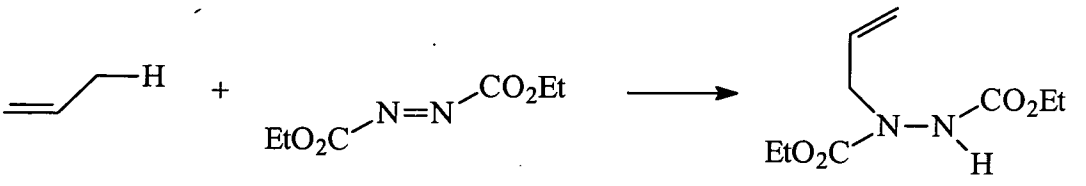
Scheme 21

3. Nitrogen-Containing Enophiles

As mentioned earlier, the specific enophiles relevant to this study are those that contain a nitrogen atom in the reactive centre, namely the azo-type and the imine-type.

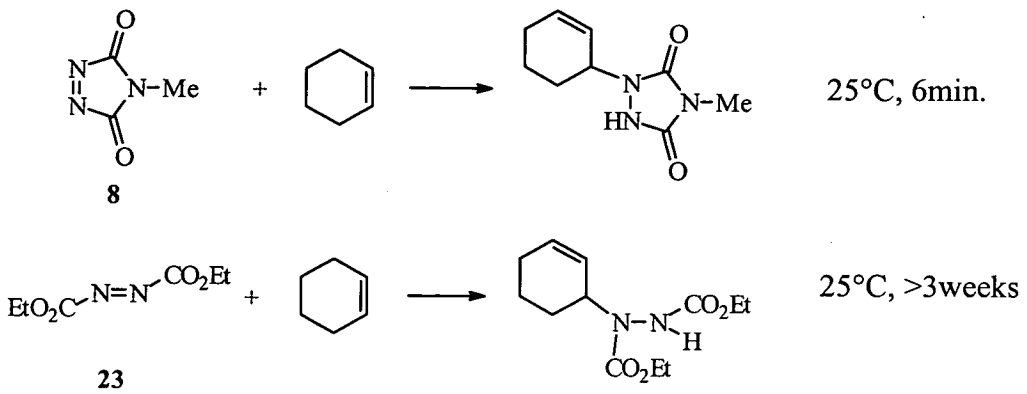
3.1 Azo-type enophiles

The azo-type enophiles are compounds in which the double bond that takes part in the ene reaction is a nitrogen-nitrogen double bond. In common with most enophiles that take part in the inter-molecular reaction, the azo-grouping requires electron-deficient activating groups connected to it. With such activation, these compounds are amongst the most reactive of enophiles and will react under very mild conditions[51]. The simplest azo enophiles are the azodicarboxylate esters such as *trans*-diethylazodicarboxylate **23** (DEAD), which was one of the first enophiles to be used in the reaction[52]. It will react with most allylic alkenes and heating to 80°C for a few hours is normally sufficient for complete reaction to produce a hydrazodicarboxylate such as **24** (Scheme 22).



Scheme 22

The ground state *trans* isomer of DEAD is not, however, ideally suited to the reaction and if photochemically generated *cis*-DEAD is used, the reaction is greatly improved[53]. Another way of achieving the *cis* configuration of the active bond is to use a cyclic equivalent, which is held permanently in the *cis* form, and very widely used in the ene reaction are the 1,2,4-triazoline-3,5-diones. 4-Phenyltriazolinedione, also known as Cookson's reagent[54] or PTAD **6**, and 4-methyltriazolinedione (MTAD) **8** have been extensively used both in Diels-Alder cycloadditions and ene reactions. These compounds are highly reactive enophiles; for example in the reaction with cyclohexene, MTAD **8** was found to react approximately 30,000 times faster than DEAD **23**[55], and will react smoothly at room temperature (Scheme 23). Due to this high reactivity, triazolinediones have been the subject of many studies including mechanistic and regio-chemical investigations[56-58], natural product syntheses[59] and polymer functionalisation[60].



Scheme 23

Triazolinediones have very similar reactivity in the ene reaction to singlet oxygen, both in mechanism and in products formed. Singlet oxygen and triazolinediones have both been shown to react in a step-wise mechanism involving the initial formation of a short-lived three-membered intermediate as shown in Fig. 3. In the case of the triazolinediones, the intermediate takes the form of an aziridinium imide (Fig. 6). This intermediate has been observed *in situ* (Scheme 5 and Scheme 6) and has been proved to be the intermediate by the Stephenson kinetic isotope test as described earlier in section 2.1

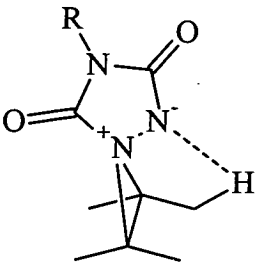
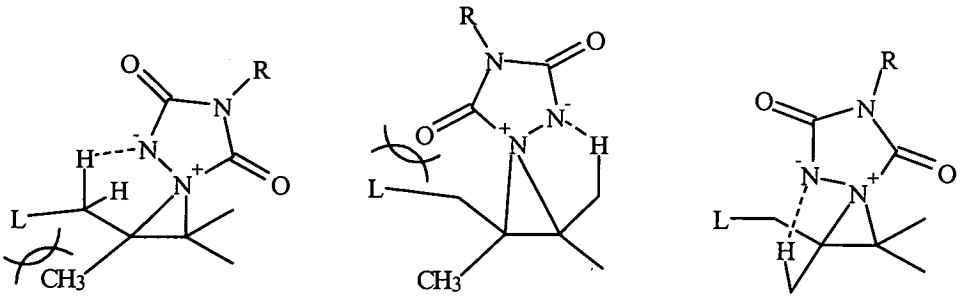


Figure 6. Aziridimium imide intermediate

In essence, there can be up to four allylic sites on the ene component that is used, and theoretically, hydrogen abstraction from any of these may lead to different products in the ene reaction. Triazolinediones react in a very regio-selective manner and preferentially abstract the allylic hydrogen geminal to the largest group on the double bond[61]. The dominant effect is steric hindrance, and electronic activation of any site has less effect than simply having a bulky alkyl group on one of the carbon atoms. This outcome is rationalised by considering the geometry of the intermediate involved in the reaction (Fig. 7). The intermediate where the hydrogen is geminal to the bulkiest group (structure **C**) has the least steric hindrance and is therefore the most favourable. The effect is very pronounced and accounts for up to 100% regioselectivity with *tert*-butyl substituted alkenes. For situations where there is no geminal allylic hydrogen, the transition state represented by structure **A** is favoured over the transition state represented by structure **B** and the hydrogen on the bulkiest group is abstracted.



A **B** **C**

Figure 7. Intermediates illustrating the geminal selectivity of PTAD

A: Abstraction from the bulkier group

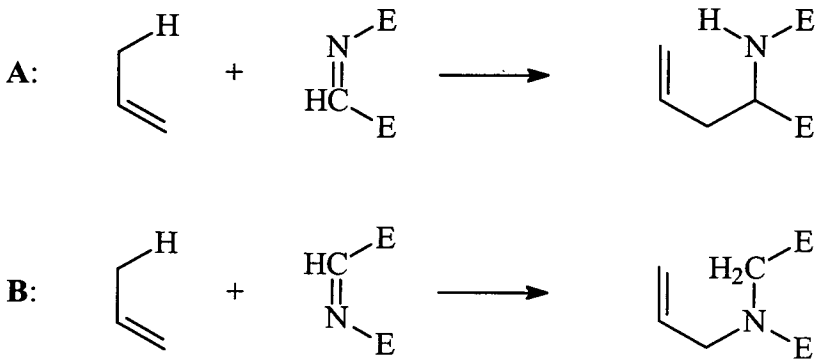
B: Abstraction from a non-geminal position

C: Abstraction from the geminal position

3.2 Imine type enophiles

The other class of nitrogen-containing enophiles relevant to this study are the imine enophiles, in which the bond participating in the reaction is a carbon-nitrogen double bond. Due to the asymmetric nature of this bond, two different types of reaction are possible, in which either a carbon-carbon bond is formed (**A**) or in which a carbon-nitrogen bond is formed (**B**) (Scheme 24). This possibility leads not only to complications in the reaction but potentially also extra synthetic potential. In practice, carbon-carbon bond formation (**A**) is more energetically favourable, and

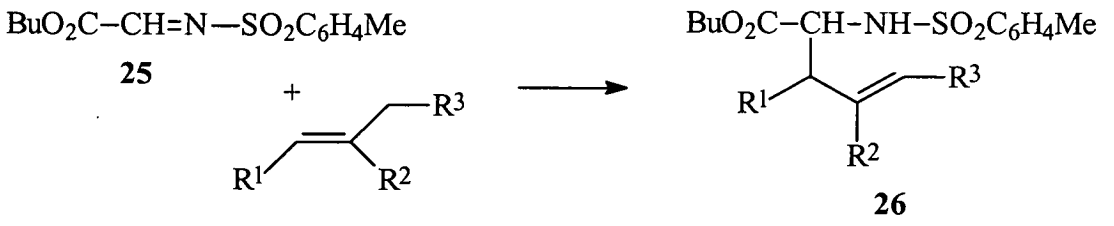
consequently in most cases, except when prohibited by geometric factors in intra-molecular reactions[62], reactions with imine enophiles usually follow this route[63].



Scheme 24

The theoretical overall energetics for the ene reaction with imine enophiles are very similar to that of carbon-carbon enophiles and likewise, electron-withdrawing (activating) groups attached to the bond and forcing conditions or catalysis are necessary for the inter-molecular reaction to occur[63]. The intra-molecular version requires less activation, but still tends to occur with some form of acyl activation to ensure success[62].

The first ene reaction with an imine enophile was carried out by Achmatowicz and Pietraszkewicz in 1981[64]. They found that butyl *N*-toluenesulfonyl iminoacetate **25** reacted with various alkenes at 120°C to form protected amino acids with vinyl substituents **26** (Scheme 25).



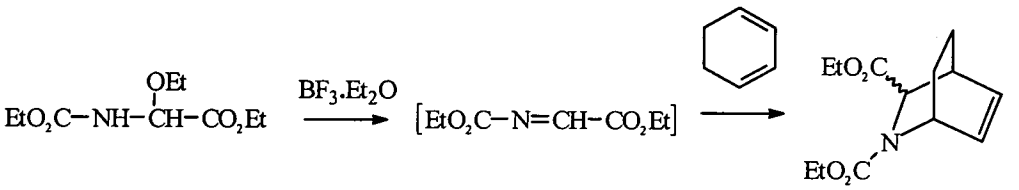
Scheme 25

The mechanism of the ene reaction with imine enophiles has not been investigated as thoroughly as in the case of the azo enophiles. In particular, kinetic isotope measurements have not been as conclusive, but recent evidence pointed towards a stepwise mechanism involving the formation of an ionic intermediate but the structure of the intermediate could not be inferred from the data[65].

Since this discovery, there has been comparatively little interest in this type of enophiles, probably due to the lack of reactivity of the pivotal bond. Experimentally, there have been very few examples of ene reactions involving imines as the enophile, despite a larger amount of work on imino-dienophiles in Diels-Alder reactions[66], and interest in some of the applications and stereochemistry of the reaction has only recently been shown.

To achieve a good comparison between the azo and imine enophiles, the activated enophiles chosen for this study were the acyl substituted imines. The main problem with these compounds is that they are generally only known as unstable

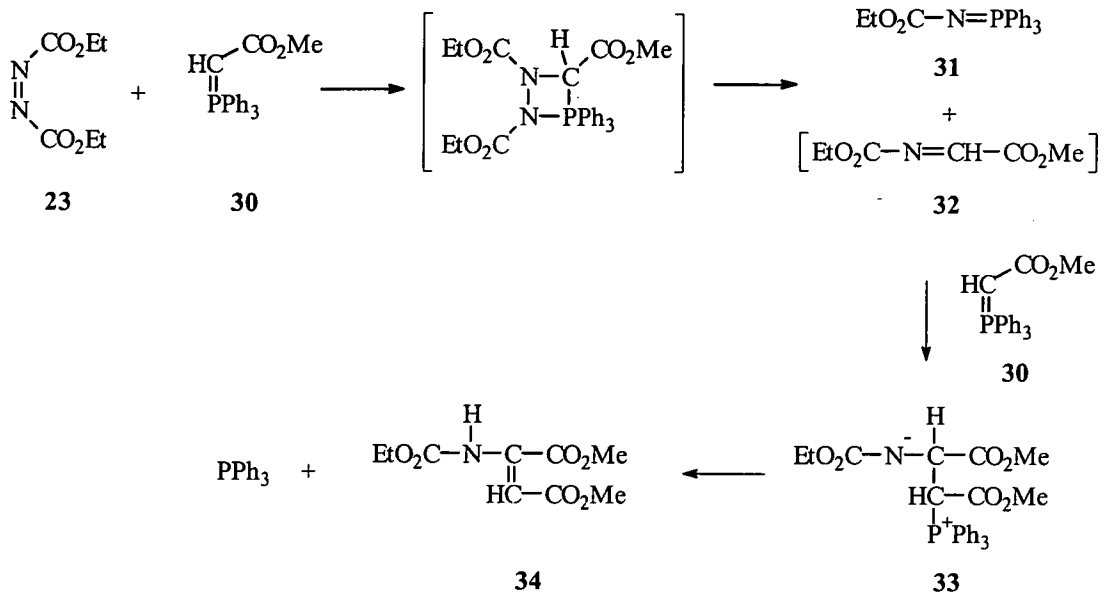
intermediates, and cannot be prepared as isolable compounds. The direct equivalents of DEAD and PTAD cannot be isolated and hitherto have been generated only from the appropriate precursor and trapped *in situ*[67, 68]. Diethoxycarbonyl imine **27** has been prepared by the addition of boron trifluoride etherate to its ethanolic precursor, ethyl ethoxycarbethoxyglycinate **28**. In this instance, the imine was trapped with cyclohexa-1,3-diene to form the Diels-Alder cycloadduct **29** (Scheme 26)[69].



28 **27** **29**

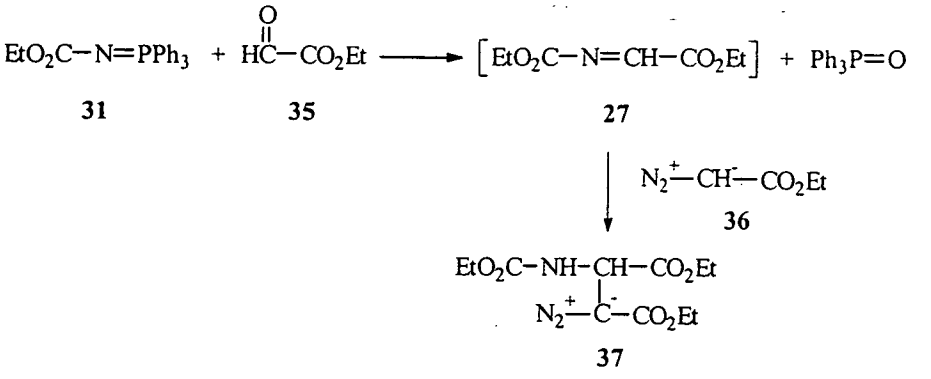
Scheme 26

An alternative synthesis of aldimines like **27** has been achieved with the aid of phosphorus chemistry[70]. Thus, the reaction between diethylazodicarboxylate **23** and the ylide **30** produced an unstable betaine intermediate which subsequently fragmented to give the triphenylphosphinimine **31** and the non-isolable imine **32**. In this case the imine was trapped by a second equivalent of ylide **30**, forming a charged intermediate **33** which subsequently rearranged to give the ethoxycarbonylaminomaleate diester **34** and triphenylphosphine (Scheme 27).



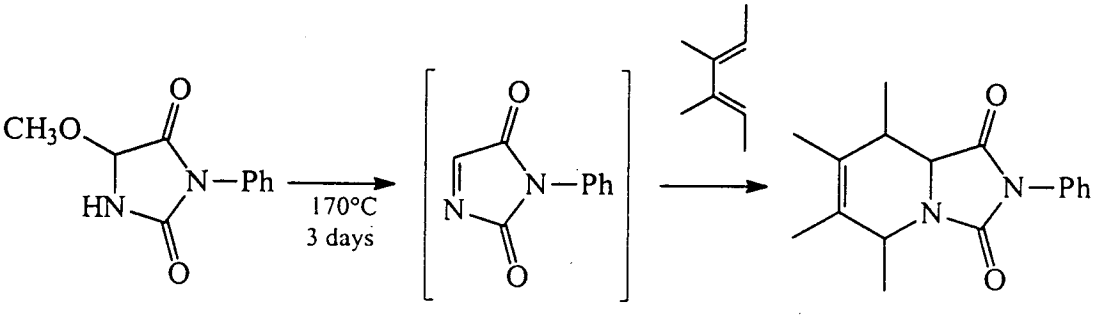
Scheme 27

In an alternative approach the triphenylphosphinimine **31** formed in the previous reaction can itself be used in an aza-Wittig reaction with ethyl glyoxylate **35** to generate the imine **27** with concomitant formation of triphenylphosphine oxide[71]. In this case, the imine was trapped with ethyl diazoacetate **36** to form the diazoester **37** (Scheme 28).



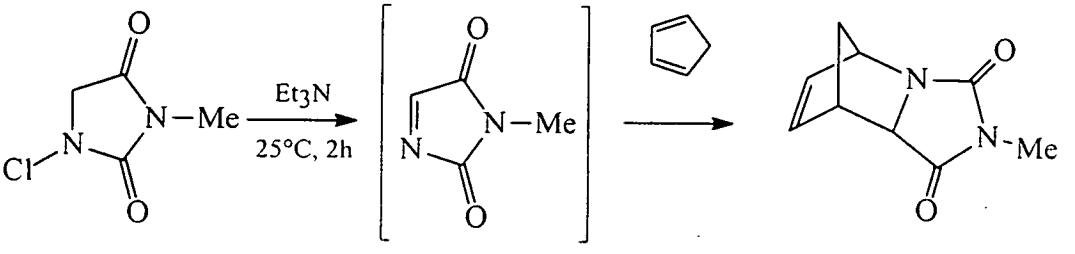
Scheme 28

Similarly, the imine equivalent of phenyltriazolinedione, *viz.* 3-phenylimidazoline-2,5-dione **38** has been prepared by loss of methanol from its precursor, 3-phenyl-5-methoxyhydantoin **39**, and reacted *in situ* with conjugated dienes such as tetramethylbutadiene to produce a cycloadduct **40** (Scheme 29)[67].



Scheme 29

Alternatively, these imidazolinediones may be prepared by treatment of an *N*-chlorinated hydantoin with an appropriate organic base, *e.g.* triethylamine. For example 3-methylimidazolinedione **41**, prepared from its *N*-chloro precursor **42** was also identified by *in situ* trapping in a Diels-Alder cycloaddition reaction with cyclopentadiene to produce the cycloadduct **43** (Scheme 30)[68].



42 **41** **43**

Scheme 30

4. Amidoalkylation

Another type of reaction that diacylimines as well as some of their precursors can take part in is α-amidoalkylation. This is a reaction in which an electron deficient amidoalkyl group reacts with a nucleophilic carbon atom of another molecule resulting in attachment of the two groups. In the reaction of saturated precursors to imines, this is accompanied by loss of the relevant leaving group. (Fig. 8).

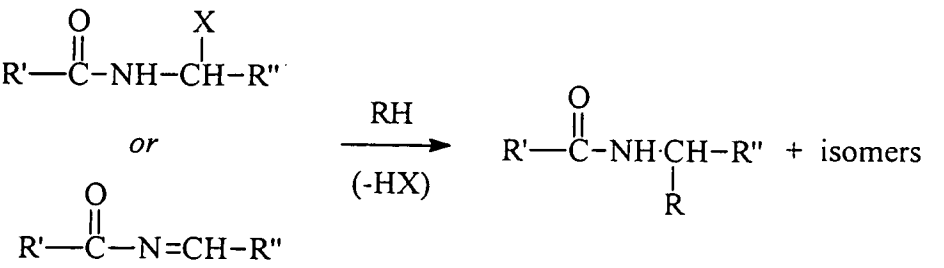
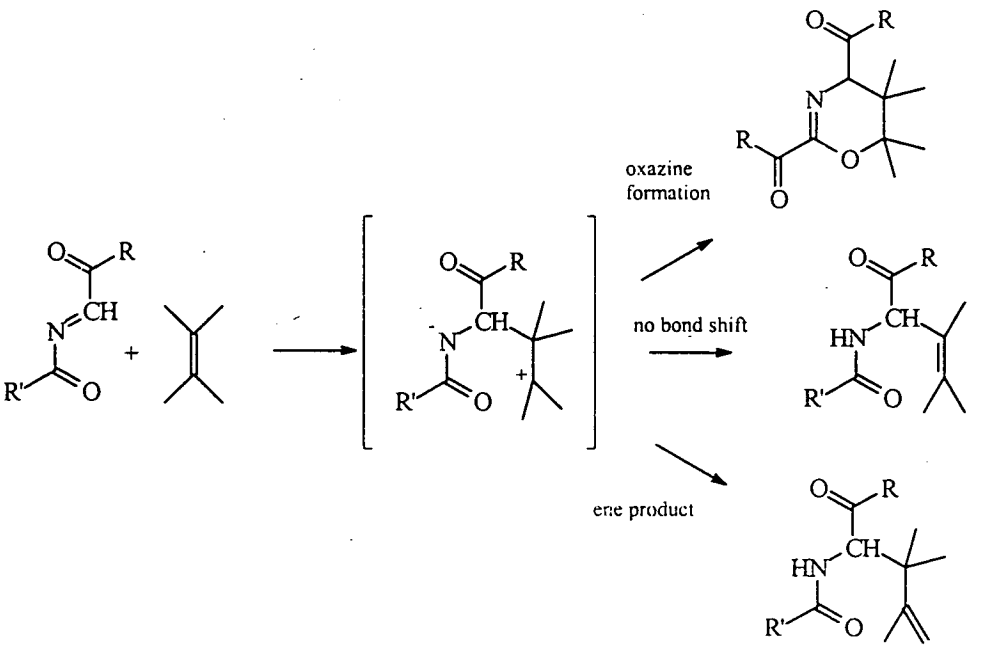


Figure 8. α-Amidoalkylation of a nucleophile RH

A large range of compounds with nucleophilic carbon atoms can be functionalised with this reaction including aromatic species, olefins, active methylene and organometallic compounds[72, 73]. Indeed, the ene reaction involving an acylimine can be regarded as a special case of α-amidoalkylation involving an allylic olefin.

In amidoalkylation of an olefin with a diacylimine, the two reagents will form an intermediate which can react in different ways depending on the structure of the imine (Scheme 31).



Scheme 31

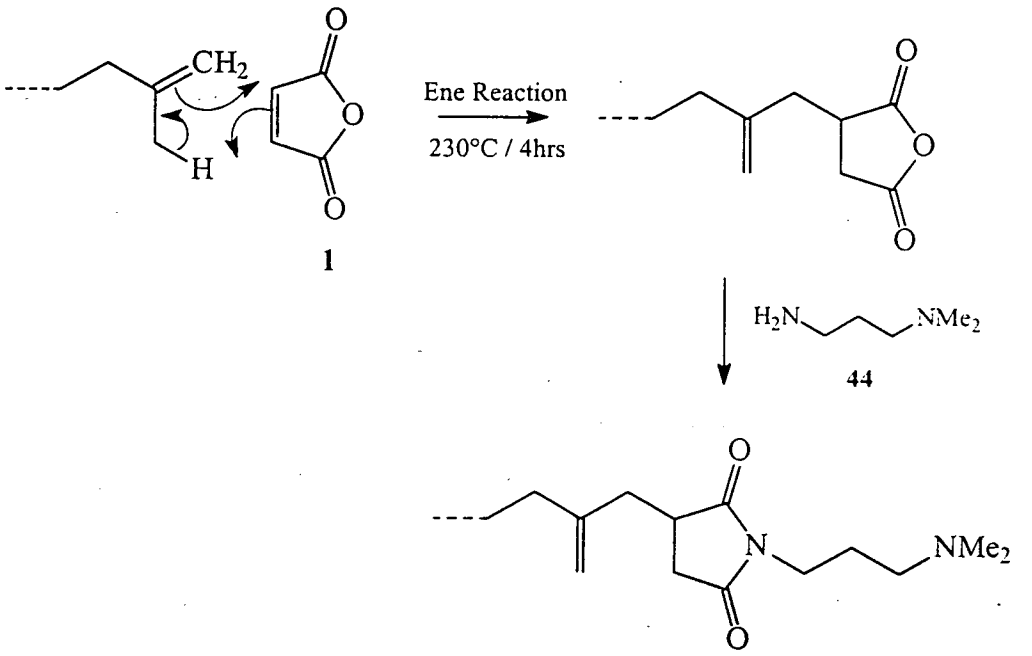
Since the imines that are being investigated in this study are diacylimines and may therefore also follow these pathways, it is important to consider the possibility of different products from amidoalkylation rather than just the product of the simple ene reaction.

5. Functionalised Polyisobutene

Polyisobutene is a well-defined homo-polymer, which can be prepared in a range of molecular weights depending on the type of polymerisation used and the conditions. Because of this control, physical properties can be tailored to suit the desired purpose. There are many uses for the pure polymer ranging from lubricants and paper adhesive to waxing of food products. A large use for the polymer is as a chemical intermediate for additive synthesis. Each polymer molecule contains a terminal unsaturated bond which may easily be functionalised after polymerisation, for uses ranging from sealants and coatings to oils and lubricants. Of particular interest to this project is their use as ashless dispersants and detergents for fuel additives. These chemicals, once added to the fuel, effectively clean the engine as it is being used. Particles of dirt or carbon deposits from inefficient burning are 'lifted off' the engine walls and valves and dispersed within the fuel. As a result, formation of rough deposits is inhibited and engine efficiency is maintained. Functionalised polyisobutene is particularly useful for this purpose as the polymer itself is very viscous and the terminal double bond can be easily functionalised with a great deal of control. The polymer must be functionalised with a polar, *e.g.* nitrogenous, head group to be an effective detergent; moreover, the product must burn cleanly and leave no residue to avoid clogging of the engine.

One way of achieving functionalisation is to utilise the ene reaction to place a linker group on the polymer which can be further functionalised with an amine to form the

desired detergent. An example of this process is the initial functionalisation of polyisobutene with maleic anhydride **1** followed by insertion of 3-(*N,N*-dimethylamino)propylamine **44** as illustrated in Scheme 32.

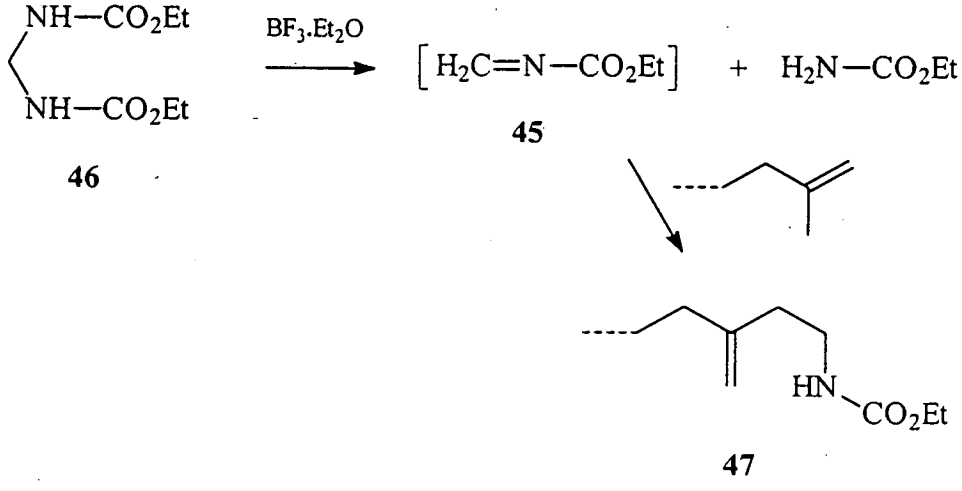


Scheme 32

A drawback to this process is the initial ene reaction which requires temperatures in excess of 230°C and high pressure. These conditions can cause self-polymerisation of the maleic anhydride in the presence of trace impurities, leading to a complicated and undesirable work-up procedure.

One solution to the problem was to improve on the ene used in the reaction. This has been achieved by using polyisobutene with a higher vinylidene content that has

recently become available due to improvements in the catalyst used for polymerisation. The vinylidene end group (as shown in Scheme 32) is particularly reactive in the ene reaction because of the availability of the allylic hydrogen. This approach can be complemented by improvement in the reactivity of the enophile that is used in the reaction. By using a nitrogenous enophile, such as an azo or an imine enophile, more nitrogen functionality can be introduced into the polymer, along with the increased reactivity that accompanies such enophiles. Azo functionalisation of polymers by means of the ene reaction has already been achieved with phenyltriazolinedione and diene polymers and was found to proceed under very mild conditions[60]. As illustrated in Scheme 33, imine functionalisation has been achieved with *N*-carboxymethyleneimine **45** which was generated *in situ* from methylene diurethane **46** by loss of urethane induced by using boron trifluoride as catalyst; subsequent reaction with polyisobutene led to the functionalised polymer **47**[74].



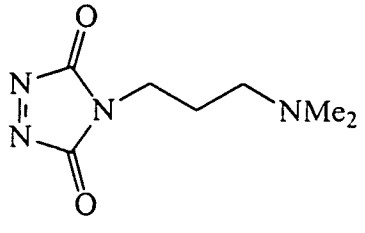
46 **45** **47**

Scheme 33

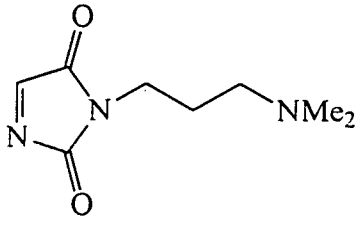
6. Objectives of the Research

When redesigning the enophile to be used, another consideration needs to be taken on board. This is to eliminate the requirement for a secondary functionalisation as shown in Scheme 32 and to incorporate the basic functionality at the other end of the molecule away from the reactive site. As a result, functionalisation of the polymer should be achieved in one simple step.

The ultimate goal of the project was to produce reactive ring systems which would participate easily in the ene reaction with model alkenes and eventually with polyisobutene. These reactive systems were to be attached to a basic moiety by an alkyl chain linker group. Consequently, two synthetic targets were chosen to be developed, 3'-(*N,N*-dimethylamino)propyltriazolinedione **48** and 3'-(*N,N*-dimethylamino)propylimidazolinedione **49**.



48



49

The project was pursued on a two pronged basis. Although it was hoped in the long run to compare the two systems, *viz.* azo and imine enophiles, and their reactivity in the ene reaction, it was apparent that the synthesis of the two ring systems would need different approaches. Therefore the discussion is split into two sections, one which deals with azo enophiles whilst the other is concerned with imine enophiles.

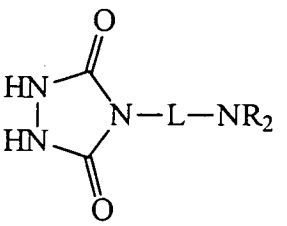
Discussion

1. Azo Enophiles

The azo enophiles chosen for study in this project are the five-membered triazolinediones, which are well known in the ene synthesis, and the less stable and correspondingly much less studied six-membered pyridazinediones. Based on precedent, both types of compound can be synthesised by oxidation of the corresponding hydrogenated precursors. Attention was therefore initially directed towards the synthesis of these precursors, then following this, the oxidation and ene reactions of these compounds.

1.1 Triazolinediones

A great deal is known about compounds containing the 1,2,4-triazolidine-3,5-dione ring structure, commonly known as urazoles. The parent compound, urazole itself, was originally prepared in 1894 by Thiele and Stange[75] and many alkyl and aryl derivatives have been subsequently prepared. The ring structure itself is quite acidic and may be ionised easily allowing most urazoles to dissolve in alkaline aqueous solution[76]. Perhaps due to this acidity, direct synthesis of a urazole attached by a linking group to a basic moiety, *e.g.* **50**, has not been accomplished so far.

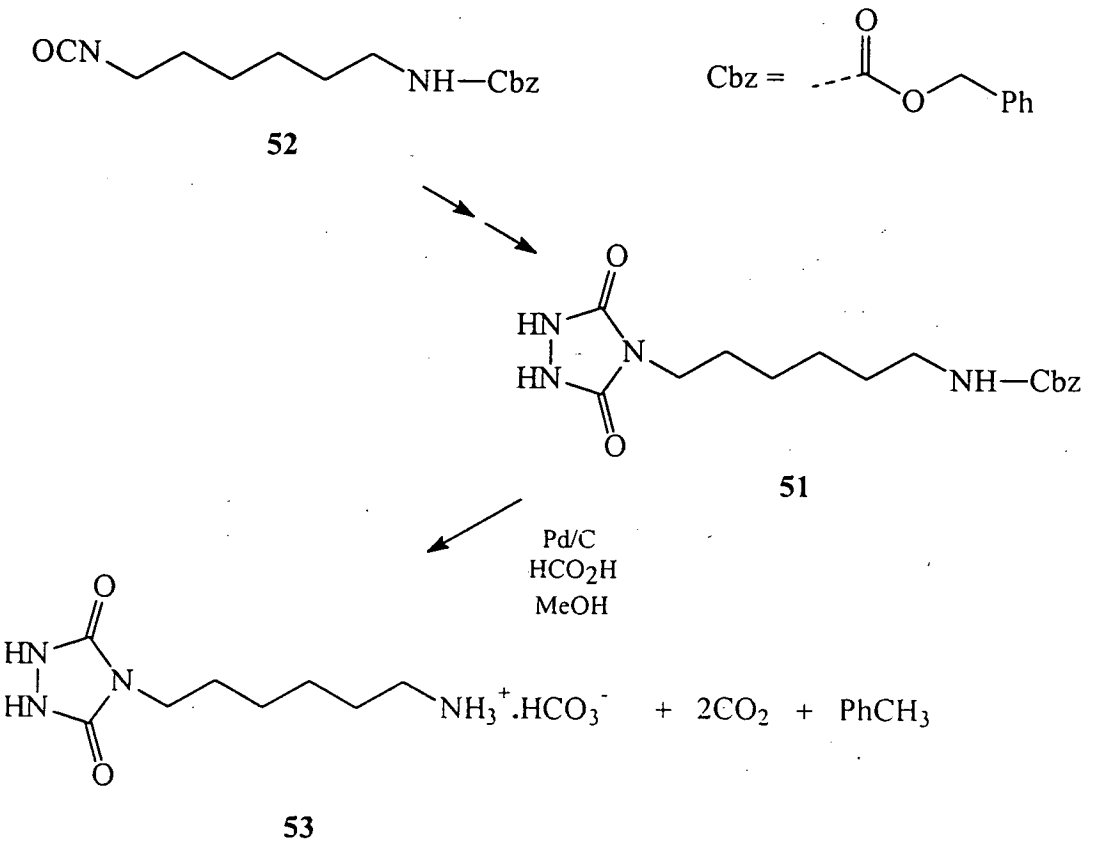


50

L = linker group

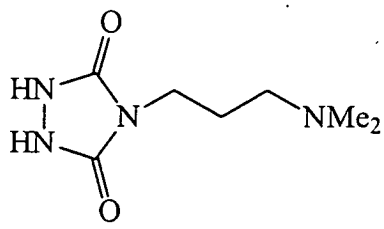
R = alkyl or aryl group

Indirect synthesis, *i.e.* synthesis of a protected base followed by deprotection, of a molecule of this type has only recently been achieved by standard synthesis methods. The carbobenzyloxy protected amino-urazole **51** was formed from the carbobenzyloxy protected isocyanate **52** (Scheme 34)[77]. The urazole was then deprotected by catalytic transfer hydrogenation to form the formate salt of the amino-urazole **53**.



Scheme 34

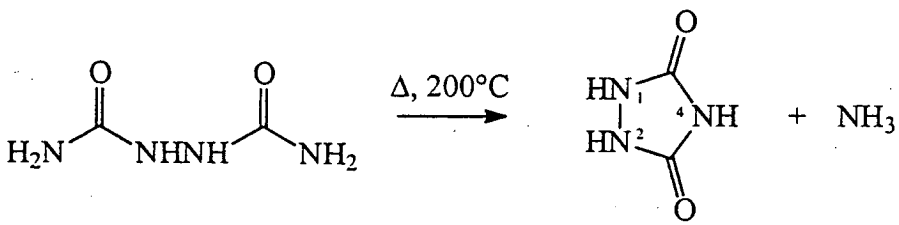
The aim of the project was to develop a general synthetic procedure for different types of amines, not just primary and secondary. The principal target, *viz.* 3-*(N,N*-dimethylamino)propyltriazolinedione **48**, requires access to 3-*(N,N*-dimethylamino)propylurazole **54** which contains a tertiary amine group and therefore cannot be prepared in this way.



54

1.1.1 Previous methods of urazole preparation

The parent compound, *viz.* 1,2,4-triazolidine-3,5-dione **55** was originally prepared by pyrolysis of hydrazodicarbonamide **56** at 200°C (Scheme 35)[75].

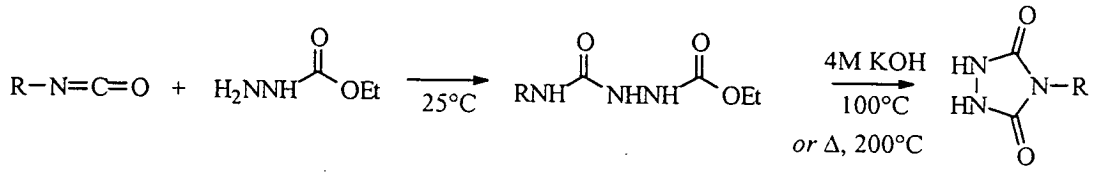


56 **55**

Scheme 35

The synthesis of 4-substituted urazoles **57** has traditionally followed a different pathway in order to achieve introduction of the relevant functional group. Thus the relevant isocyanate **58**, *e.g.* phenyl isocyanate for 4-phenyl-1,2,4-triazolidine-3,5-dione, is reacted with ethyl carbazate **59** at room temperature to form the

semicarbazide **60** which is then warmed in concentrated aqueous alkali until cyclisation is complete. The product can then be filtered off after neutralisation of the alkaline solution of the urazole **57** (Scheme 36)[78]. Alternatively, the final cyclisation step can be achieved by pyrolysis at *ca.* 200°C[75].



58 **59** **60** **57**

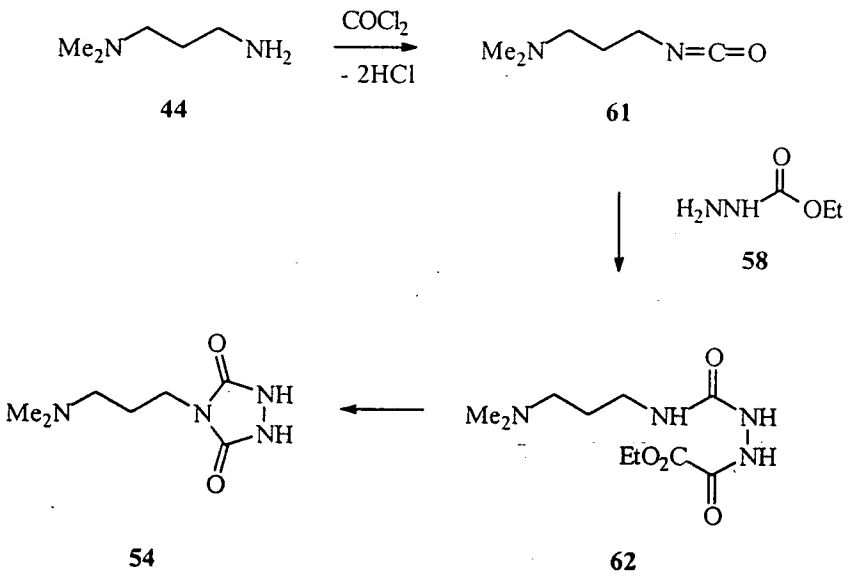
Scheme 36

The synthesis (known as the Cookson method) is a very robust one and has been used to prepare several types of urazoles, including 4-phenyl- and 4-methyl-urazole, the precursors to PTAD **6** and MTAD **8** respectively. Compounds with more complex end-group functionalisation such as chiral compounds[79] and amides[77] have also been synthesised using this method.

1.1.2 Attempted syntheses of basic urazoles

It was decided that due to literature precedence the Cookson method[78] of preparing urazoles would be utilised on the attempted synthesis of **54**, which contains the 3-

(N,N-dimethylamino)propyl group. This protocol involved initial preparation of the isocyanate **61** from 3-*(N,N*-dimethylamino)propylamine **44** by condensation with phosgene in toluene solution, followed by reaction with ethyl carbazate **58** to form the semicarbazide **62**. In the final step, treatment of the latter with alkali or alternatively pyrolysis would be used to bring about cyclisation to **54** (Scheme 37).



44 **61** **58** **54** **62**

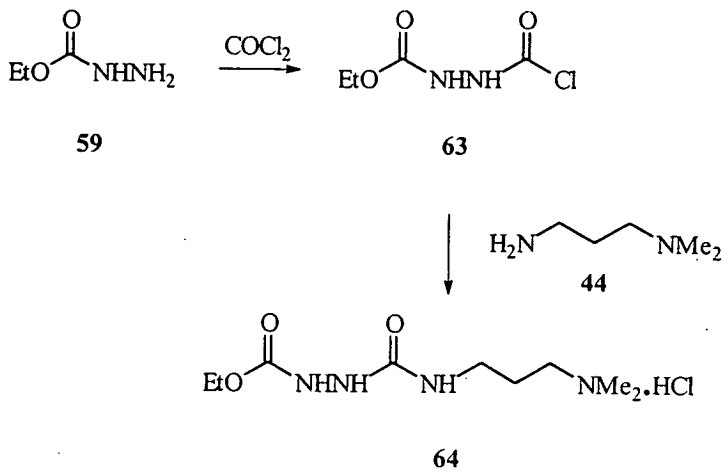
Scheme 37

Frustration was experienced in the first half of this approach, *viz.* the semi-carbazide preparation, which resulted only in polymeric residues and recovery of ethyl carbazate starting material. Further investigations showed that 3-*(N,N*-dimethylamino)propylisocyanate **61**, is very prone to self-polymerisation and cannot be prepared by the simple reaction of **44** with phosgene due to the basic moiety attached at the other end[80]. A phosgenation experiment utilising the dihydrochloride

salt of 3-*(N,N*-dimethylamino)propylamine was also attempted, but shielding of the base in this manner did not prevent similar polymerisation.

Whilst there are other ways of preparing isocyanates such as heating the relevant thiocarbamate[81] or removal of an alcohol function from the relevant urethane with chlorocatecholborane[82], it was felt that these areas had been investigated before and since the isocyanate was known to be difficult to isolate, an alternative strategy would prove more fruitful.

The approach then adopted involved exchanging the roles of the amine and the hydrazine (Scheme 38). Again, there is a potential problem since nitrogen-attached isocyanates are extremely unstable[83]. However, this can easily be overcome since the reaction between ethyl carbazate **59** and phosgene forms the chlorocarbazate **63**[84] which can then be used in place of the isocyanate to prepare the hydrochloride salt of the semicarbazide **64**.



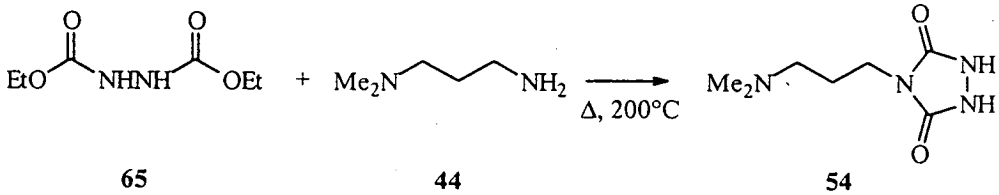
Scheme 38

The semicarbazide was prepared by this route in good yield, but poor purity as a hygroscopic yellow gum. Unfortunately, attempts to purify the gum led to almost complete failure. The use of chromatography did not succeed, either with alumina or silica, and with a range of solvents including triethylamine buffered; in all cases, the compound did not move off the baseline. Application of reverse phase TLC showed the presence of just a single spot, whilst analysis by NMR spectroscopy revealed that the compound was contaminated with a mixture of compounds. Thus chromatographic methods were unable to purify the compound.

Attempts to cyclise this crude product also failed. The standard Cookson[78] method of heating in aqueous alkali caused only partial cyclisation with many side-products being formed. Pyrolysis at 200°C also gave similar results. Separation of the products was attempted but various procedures failed to remove contamination with

polymeric residues and failed to provide discrete compounds even upon reverse-phase chromatography. This outcome indicated that polymerisation reactions were occurring in competition with the desired cyclisation. In an alternative approach, attempts at cyclisation by pyrolysis were made with the free base of the semicarbazide which was prepared by treatment with potassium carbonate. Disappointingly these attempts also gave polymeric residues.

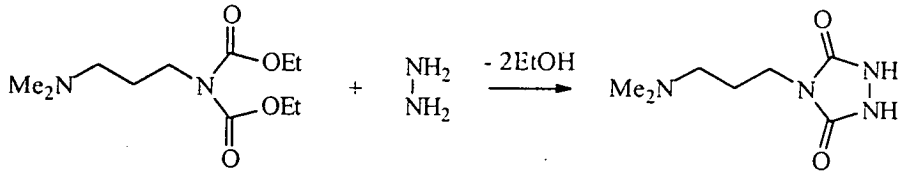
A different synthetic strategy was also being developed alongside the adapted Cookson route. This involved a simpler, one-pot synthesis in which the amine **44** was heated in the presence of hydrazine dicarboxylic acid diethyl ester **65** (Scheme 39). Although there is no literature precedence for this type of reaction, since the same type of chemistry is involved as the final cyclisation stage of the Cookson triazolidinedione synthesis, *i.e.* a condensation reaction involving loss of an ethanol molecule, it was hoped that this inter-molecular equivalent might be possible. Despite various attempts at different reaction temperatures and changing of reagent concentrations, no success was achieved even upon use of zeolite catalysis to promote the condensation by removal of ethanol.



65 **44** **54**

Scheme 39

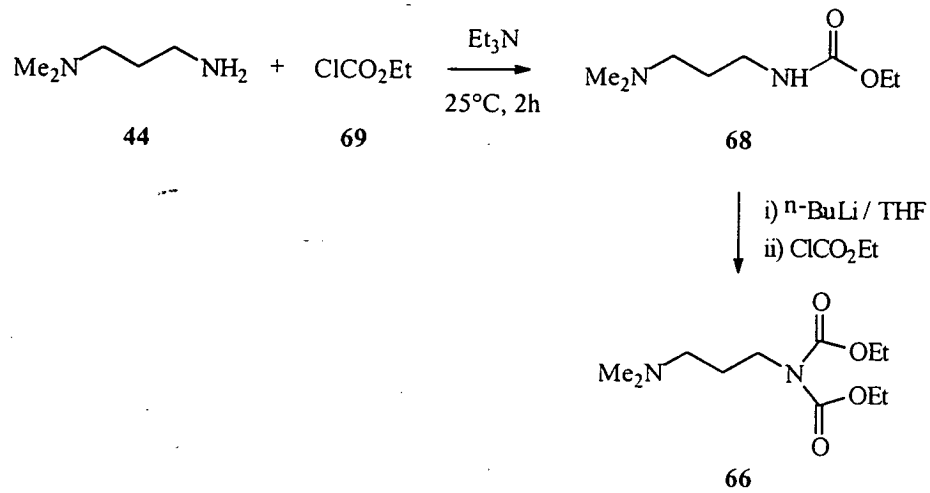
In an alternative approach, the synthesis was adapted in a similar way as before by reversing the roles of amine and hydrazine. It was hoped that the extra nucleophilicity of hydrazine would make the reaction more feasible This procedure involved the initial preparation of the dicarboxylate ester of 3-(*N,N*-dimethylamino)propylamine **66** and its reaction with anhydrous hydrazine **67** to form the desired urazole **54** by elimination of two moles of ethanol (Scheme 40).



66 **67** **54**

Scheme 40

The previously unknown dicarboxylate ester **66** was synthesised in two stages from 3-(*N,N*-dimethylamino)propylamine **44** (Scheme 41). In the first step, the mono ester **68** was prepared readily by simple condensation with ethyl chloroformate **69** using triethylamine as base. By contrast, addition of the second ester group was not so easily achieved, since the amide proton of the initial product **68** is considerably less labile and requires a much stronger base to bring about reaction. The bis-adduct **66** was prepared by initial formation of the lithium salt of the mono ester with butyl lithium followed by reaction with ethyl chloroformate **69**. This reaction was extremely clean and the novel isolated diester was sufficiently pure to use without further chromatographic purification.

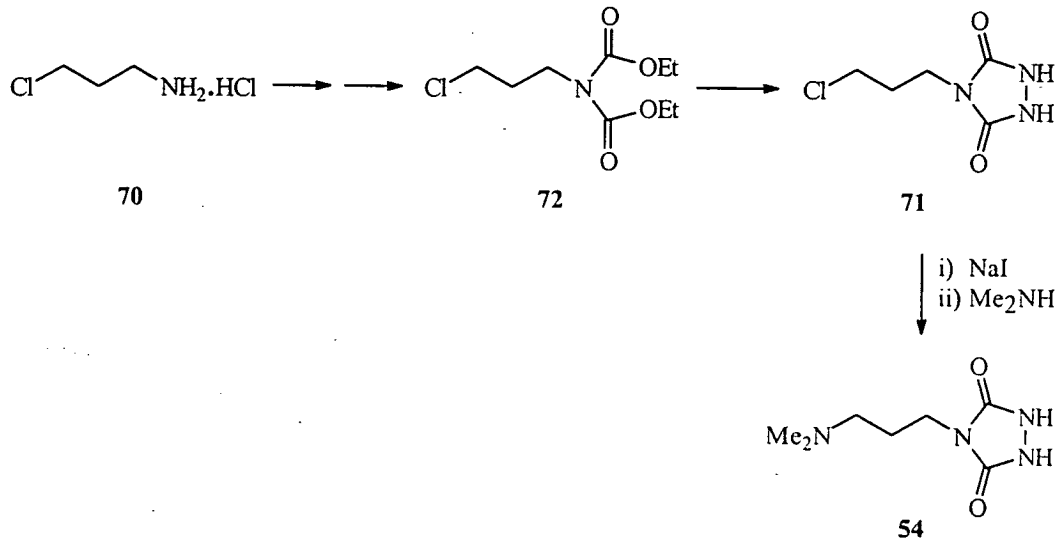


Scheme 41

The final condensation reaction was then attempted by heating the diester **66** in the presence of anhydrous hydrazine in ethanolic solution as described in Scheme 40. As the reaction progressed, analysis by infrared spectroscopy showed the loss of the carbonyl functionality completely pointing to a decomposition reaction rather than the expected cyclisation. Further evidence for this unintended reaction was also obtained by work-up which led to only polymeric residues.

Since this method was an entirely novel approach to the synthesis of triazolinediones, it was decided to extend the investigation further by following the path of the reaction with no interference from extraneous basic groups. Furthermore, by avoiding the use of a dibasic amine, column chromatography could be used to examine and purify the desired reaction products. The starting amine required for this development was 3-chloropropylamine hydrochloride **70** from which it was

hoped to synthesis 3-chloropropylurazole **71** *via* the dicarboxylate ester **72**. Introduction of the amino function in the final step as outlined in Scheme 42 would afford the target urazole **54**.



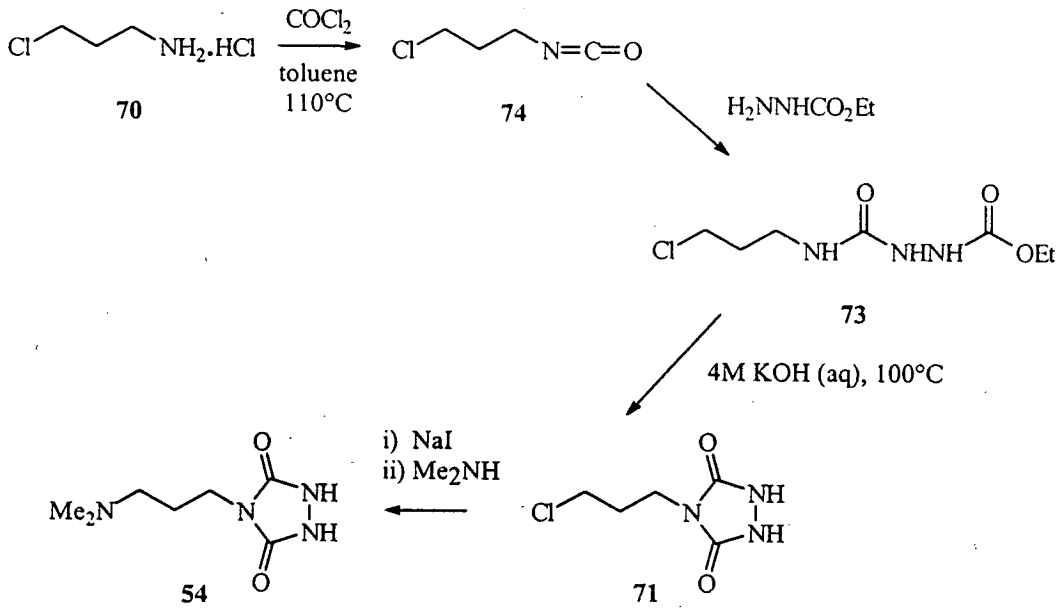
70 **72** **71** **54**

Scheme 42

The novel dicarboxylate ester **72** was prepared in good yield (80% overall) and high purity in a two step manner similar to that used previously in the 3-(*N,N*-dimethylamino)propyl case. In a subsequent step the addition and cyclisation reaction was also attempted with anhydrous hydrazine but again the carbonyl functionality was destroyed and only polymeric residues were obtained.

After recording the failure of these alternative routes, it was decided to revisit the Cookson method of urazole formation. The main problems previously experienced

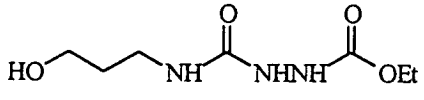
were thought to stem from the presence of the basic moiety. Hence, if the basic functionality could be introduced after urazole formation, it would not be present to interfere during the cyclisation stage nor would it give rise to the same purification problems. One way to achieve this outcome is *via* the initial formation of the chloro equivalent, *viz.* 3-chloropropylurazole **71** as mentioned earlier and subsequent reaction with dimethylamine to form the desired 3-(*N,N*-dimethylamino)propylurazole as shown in Scheme 43.



Scheme 43

Formation of the desired semicarbazide **73** was achieved by means of initial preparation of 3-chloropropyl isocyanate **74** from reaction of 3-chloropropylamine hydrochloride **70** with phosgene. It is necessary to use the amine hydrochloride in this step since the free base will self condense and polymerise. The phosgenation

was carried out in boiling toluene under reflux which gave a high enough temperature to generate small amounts of the free base by dissociation of the salt. Instead of isolating the sensitive and highly reactive isocyanate **74**, it was decided to use the reagent *in situ* by purging the system of excess phosgene with argon gas. After the removal was complete, the isocyanate was reacted with ethyl carbazate to form the semicarbazide **73** in good purity albeit in low yield (40%). In the penultimate step of the proposed synthesis, cyclisation of the semicarbazide was then accomplished to form the urazole **71** using 4M aqueous potassium hydroxide solution. The desired product was obtained after column chromatography but only in a low yield (11%) being accompanied by some (an additional 5%) non-cyclised semicarbazide **75**, which had been modified by substitution of the chloro group with a hydroxyl group.



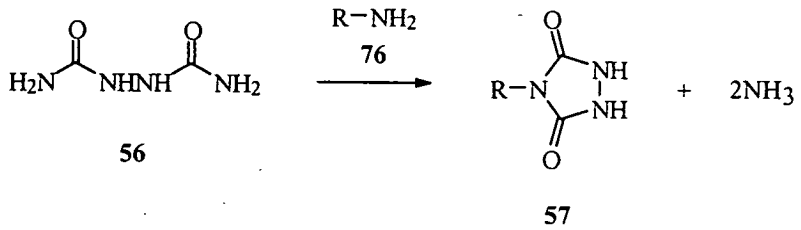
75

This type of substitution is unexpected and may be one of the key factors contributing to the low yield of cyclised product. No cyclised hydroxy-substituted urazole was isolated, even though it is very likely that some of this was formed in the reaction. It is possible that the bulk of the reaction mass not only undergoes cyclisation but also succumbs to hydrolysis to give the 4-(3'-hydroxypropyl)urazole which is then lost in aqueous work-up.

Despite the success of this particular route in preparing the desired 3-chloropropylurazole intermediate **71**, this outcome was achieved only in very low yield. In consequence, there was insufficient material to carry through the investigation to further stages and attention was diverted towards a more successful route. Nonetheless, given more time, it would have been desirable to investigate the feasibility of the proposed final stages in more detail, especially to improve the low yields observed for the cyclisation reaction by varying the reaction conditions or using pyrolysis instead of treatment with boiling alkali.

1.1.3 Synthesis of triazolidinediones

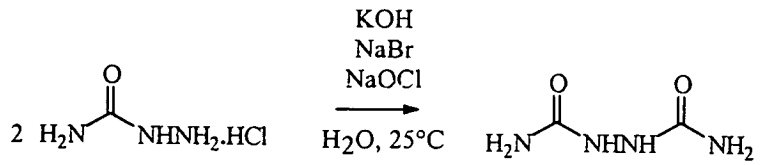
A successful scheme for the preparation of basic-substituted urazoles eventually came to light by considering the original synthesis of the parent compound from hydrazodicarbonamide as outlined in Scheme 35. In all of the reactions attempted so far, the leaving group involved in the cyclisation step is ethanol. However, in the original synthesis, a more volatile group, ammonia, is used as the leaving group. Incorporating this principle into the strategy, if the pyrolysis is performed in the presence of an amine **76** that contains the functionality that is to be incorporated into the urazole, formation of the desired substituted urazole may be achieved instead of the simple parent compound (Scheme 44).



Scheme 44

There are some examples in the older literature of the use of ammonia as a leaving group in the cyclisation step[75]. More recently a patent has been published giving details of this type of reaction for the formation of simple aryl- or acyl-functionalised urazoles[85]. The conditions described in this patent, *viz.* high temperatures and concentrations with dipolar aprotic solvents, were taken into account and a successful synthesis was developed.

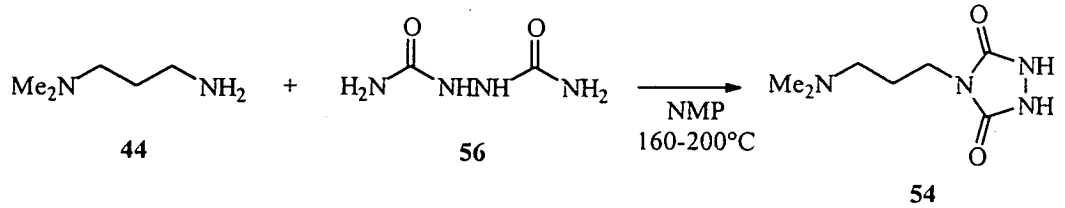
The key compound for the route developed, *viz.* hydrazodicarbonamide **56**, is commercially available but expensive. On this basis, the compound was prepared directly based on a literature method as shown in Scheme 45[86, 87] by the action of sodium hypochlorite solution on semicarbazide hydrochloride **77** in the presence of base. Catalytic amounts of sodium bromide were also added to the reaction to help the oxidation *via* the *in situ* formation of sodium hypobromite. It was also found that use of commercial material or crude product gave very poor results in the final cyclisation step. Consequently the hydrazodicarbonamide needed to be routinely recrystallised from boiling water and dried thoroughly before use in the next stage.



77 56

Scheme 45

The synthesis of the target urazole was then accomplished by heating of hydrazodicarbonamide **56** with 3-*N,N*-dimethylaminopropylamine **44** at temperatures of around 190°C using *N*-methylpyrrolidinone (NMP) as solvent (Scheme 46). The reaction was monitored by absorbing the ammonia evolved into water and titrating this solution with standard hydrochloric acid solution to keep the acidity of the solution at pH 4. The amount of ammonia detected over 4 hours corresponded to 99% of the theoretical amount, indicating that almost complete reaction had occurred. After cooling the solution, the product precipitated out, allowing easy isolation and avoiding the need for chromatography and the inherent problems that had been experienced with previous synthetic attempts. Further yield could be obtained by trituration with ethanol and the compound could be further purified by recrystallisation from ethanol.



Scheme 46

The product that was isolated from this reaction was very water soluble to the point of being hygroscopic, a condition that is not surprising considering the polarised nature of the molecule with a basic moiety attached to the acidic urazole. (Fig. 9).

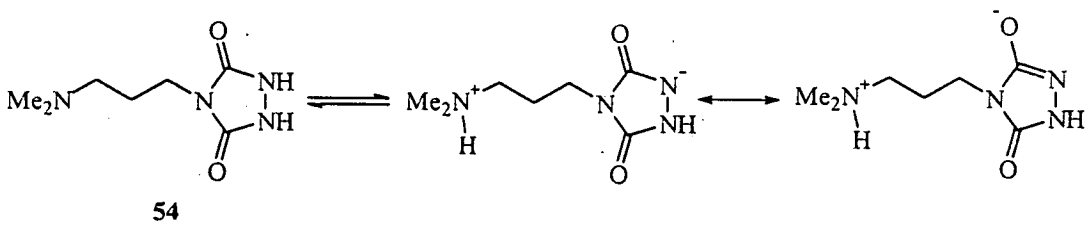


Figure 9. Potential ionised forms of 4-(3'-dimethylamino)propylurazole.

The possibility that 4-(3'-dimethylamino)propylurazole **54** existed in such an ionised state was investigated. A large crystal was grown from a solution in ethanol kept in an atmosphere of diethyl ether for 3 days. X-ray crystallography of the crystal showed the compound to be completely non-ionised in the solid state with bond

lengths and angles of the urazole group very similar to that of the urazole ring in other urazoles (Fig. 10)[88]. Full details of the structure are given in the Appendix.

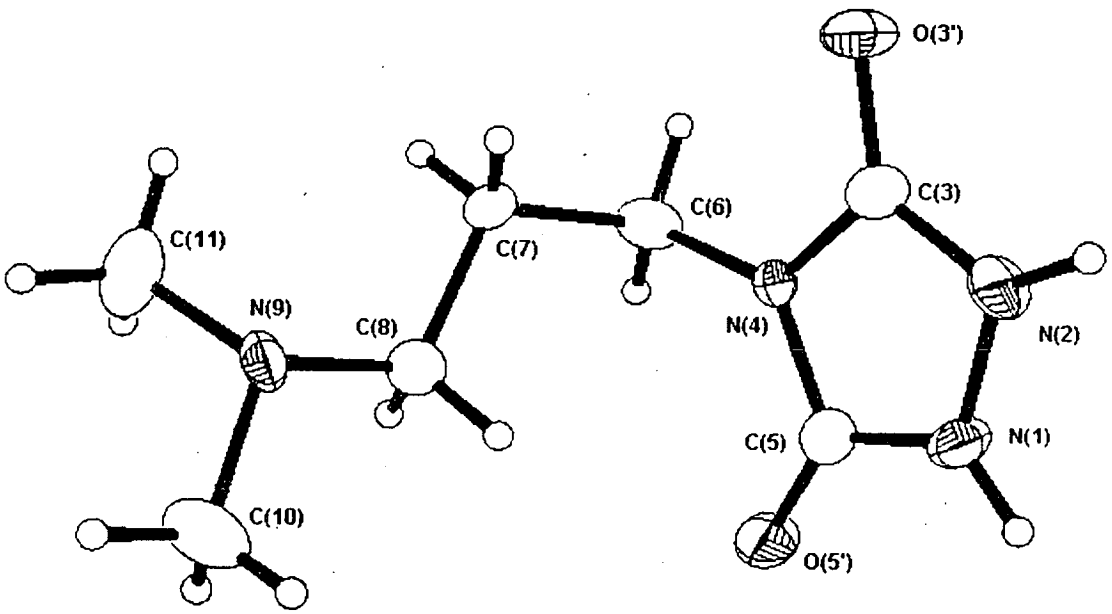
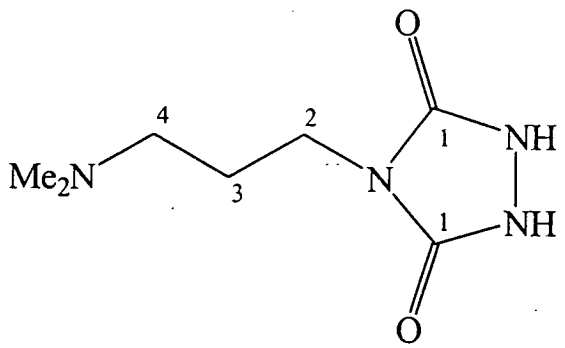


Figure 10. X-ray crystallographic structure of **54**

Carbon-13 NMR spectroscopy also revealed that in aqueous solution, the molecule is completely non-ionised with only slight deviation from the expected chemical shifts predicted by the computer program SpecInfo[89]. The small differences can be attributed to the electron-withdrawing nature of the basic moiety causing the predicted figures to be too low for the ring structure and too high for the linker chain (Fig. 11).

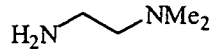
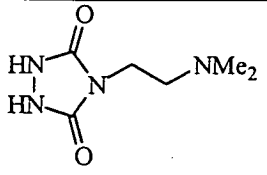
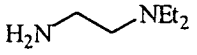
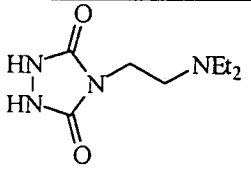
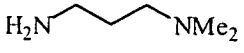
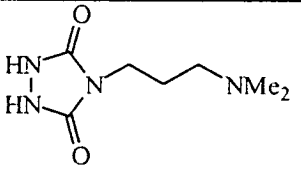
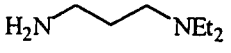
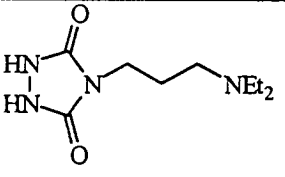
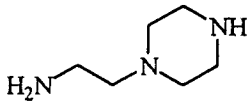
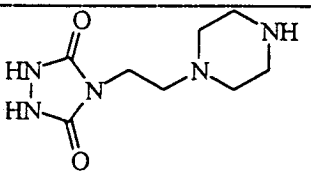
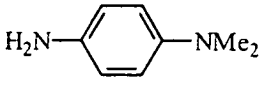
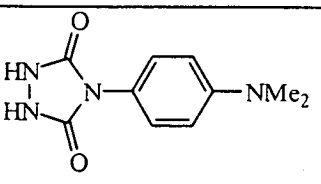
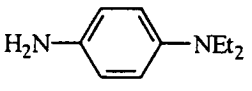
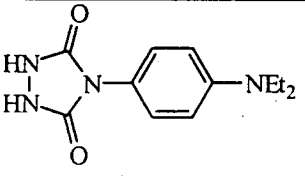


Atom No.	Predicted signal (ppm)	Actual signal (ppm)
1	152.4	156.1
2	37.5	35.2
3	25.6	23.6
4	57.2	54.7

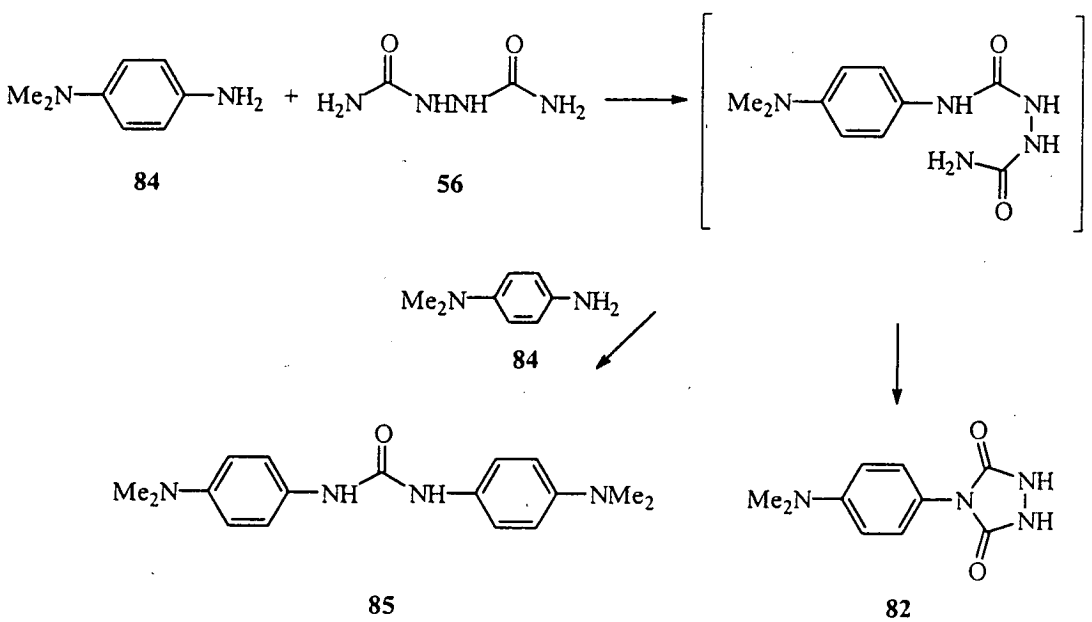
Figure 11. Predicted and actual values for ^{13}C NMR spectra of 3-(*N,N*-dimethylamino)propylurazole **54**.

Due to the fact that this was the first successful direct preparation of a base-connected urazole, it was decided to investigate the scope of the synthesis by subjecting a range of different amines to similar reaction conditions. Varying yields were found but all of the novel urazoles could be isolated in good purity by either filtration after cooling or trituration of the gum produced with ethanol (Table 1).

Table 1. Condensation of amines with hydrazodicarbonamide. Synthesis of 4-substituted urazoles.

Starting Amine	Product	Yield (%)
	 **78**	45
	 **79**	60
	 **54**	66
	 **80**	66
	 **81**	42
	 **82**	37
	 **83**	52

An interesting side-reaction was observed in the synthesis of urazole **82** by the reaction of *N,N*-dimethyl-*p*-phenylenediamine **84** with hydrazodicarbonamide. Also isolated along with the desired product **82** in 52% yield was bis-4-(*N,N*-dimethylamino)phenylurea **85** which is formed in 7% yield by displacement of semicarbazide as shown in Scheme 47. This outcome is presumably favoured by the lowering in nucleophilicity of the nitrogen through conjugation with the aryl ring. In consequence, intermolecular attack by the amine **84** on the intermediate is favoured. The ratio of products in the crude was determined by ^{1}H NMR spectroscopy using the ratios of the integrals of the aromatic signals to give a molar ratio of 7:1.



Scheme 47

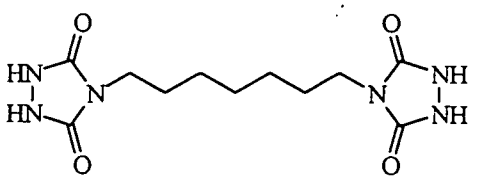
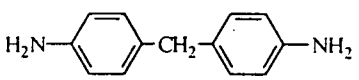
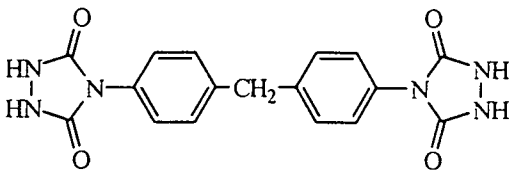
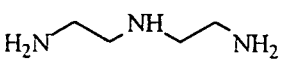
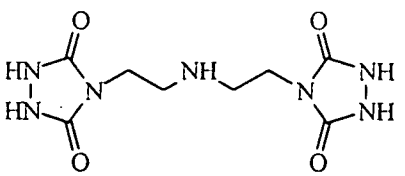
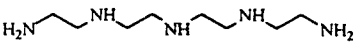
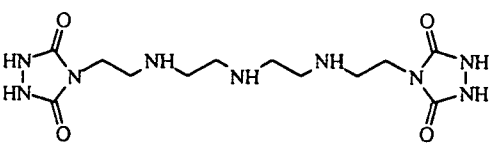
The ratio of products was increased in favour of **82** to 10:1 by dilution of the reaction mixture by a factor of two and since the urea could be removed easily by

recrystallisation, this side reaction did not present a problem to the synthesis. The fine balance of relative nucleophilicities of the nitrogen atoms is further highlighted by the finding that no urea is obtained in the corresponding reaction with *N*,*N*-diethyl-*p*-phenylenediamine to produce urazole **83** which is obtained in 52% yield. The reason why no urea was isolated from this reaction is of interest but lack of time prevented further investigations into the relationship between reaction conditions, the relative nucleophilicity of the amines involved and the amount of urea formed in the reaction.

1.1.4 Synthesis of bis-urazoles

Given that the original purpose of the project in hand was to use the triazolinediones prepared in the functionalisation of polymers, it was thought that some bifunctional triazolinediones separated by linker groups would be attractive synthetic targets. Such compounds could be used not only as detergent additives and dispersants, but also as polymer cross-linkers and hardening agents. In addition, this is another way to further investigate the flexibility of the adapted synthesis. A range of bis-amines chosen for conversion into bis-urazoles are shown in Table 2 together with the necessary precursor bis-amine.

Table 2. Proposed bis-urazoles

Starting bis-amine	Product bis-urazole
	 **86**
	 **87**
	 **88**
	 **89**

Of the triazolidinediones chosen to investigate, **86** and **87** have been synthesised previously using Cookson's method[90-92] but the other two, *viz.* **88** and **89**, cannot be synthesised in this way because of the basic nitrogen functions in their linking chains.

Despite repeated attempts under different reaction conditions, the outcome of the preparations proved to be disappointing and no pure product could be isolated. While ^{1}H NMR spectroscopy showed that partial reaction had occurred and that some

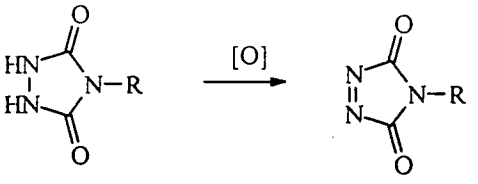
of the desired product was present, unfortunately side-reactions made separation of these hygroscopic crude products impossible.

In summary, the procedure developed in this section is established to be a good robust process with few limitations for the synthesis of mono-functional basic urazoles. For future work, there is much room for improvement and development, particularly in the case of the bis-urazoles with linker chains. Particular areas in need of further investigation are the relatively low yields and the competing formation of ureas. In particular the effect of different reaction temperatures and relative concentrations of reagents need to be investigated.

1.1.5 Oxidation of 4-substituted urazoles

A large variety of different oxidants have been reported in the literature as the reagent to carry out the oxidation of a urazole to the corresponding triazolinedione (Scheme 48). Initial oxidations were performed by the action of lead peroxide on urazoles[75] in dilute sulfuric acid solution. Subsequently the reaction has been achieved by the addition of iodine to heavy metal salts of urazoles[93], or more simply by the action of more traditional oxidants such as *tert*-butyl hypochlorite[78], lead tetra-acetate[94], manganese dioxide, calcium hypochlorite, nitrogen dioxide[95] and *N*-bromosuccinimide[96]. Also employed has been less common methods of oxidation such as treatment with benzeneseleninic anhydride[97] or *p*-toulenesulfonyl isocyanate in dimethylsulfoxide solution[98]. Electrolysis in acetonitrile solution[99] has also been

used to achieve such an oxidation. The oxidants that gave the best yields as well as clean products and ease of use were *N*-bromosuccinimide and nitrogen dioxide, which are sufficiently clean reagents to allow preparation of the highly reactive parent compound, *viz.* triazolinedione which bears only an hydrogen atom in the 4-position[100]. These oxidants were specifically chosen for use in the project, whilst some trials were conducted with manganese dioxide, mercuric oxide, and *p*-toluenesulfonyl isocyanate and the more conventional oxidants, such as chlorine and bromine.

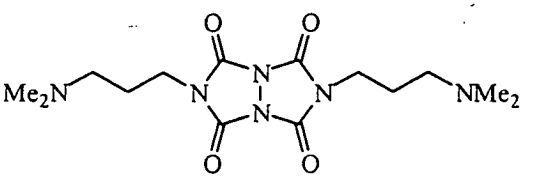


Scheme 48

The oxidation was carried out originally with *N*-bromosuccinimide using dichloromethane as solvent in an attempt to prepare a sample of the desired triazolinedione. The characteristic pink colour associated with the triazolinedione group was observed as soon as the oxidant was added to the solution of urazole. Unfortunately aqueous work-up caused the solution to decolourise instantaneously, thereby demonstrating the target compound's high affinity for and reactivity with water. No discernible product was obtained from this reaction, only a complex mixture. In a different approach, nitrogen dioxide was used as oxidant and no

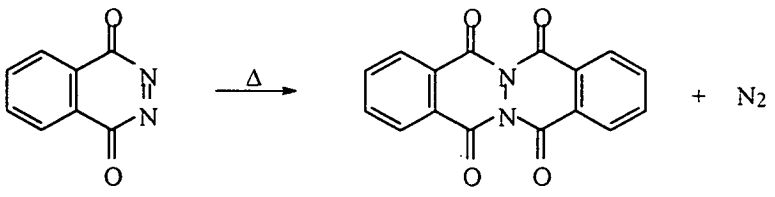
aqueous work-up was employed and alternatively, the inorganic salts were filtered off and the solution was evaporated to dryness to yield a pink gum which decolourised slowly with effervescence, even when contained under a nitrogen atmosphere.

The residue from this oxidation was examined by high field NMR spectroscopy and was found to contain a very crude mixture of compounds, in which the 3-(*N,N*-dimethylamino)propyl region was mostly preserved. Disappointingly, separation of the mixture could not be achieved as thin-layer chromatography pointed to an inseparable polymeric mixture of compounds. In fact, due to decomposition occurring mostly upon concentration of the mixture, it would appear that the desired compound is reacting with itself, by loss of nitrogen most likely to form a mixture of oligomers, but formation of the bis-adduct **90** is also possible.



90

Bis-adducts of this type are known as side-products from reactions involving the six-membered pyridazinedione ring systems when no trapping agent is introduced into the reaction[46]. As shown in Scheme 49, nitrogen is evolved and the reactive intermediate reacts with itself to form the bis-adduct. So far this type of product is unknown from usage of triazolinediones.



Scheme 49

These proposed reactions are all thought to be brought about by the influence of the attached basic moiety upon the highly reactive triazolinedione centre. It is possible that the influence may be either intramolecular or intermolecular. Indeed, inspection of molecular models shows that the flexibility of the alkyl chain in 3-*(N,N*-dimethylamino)propyl urazole allows the basic group to be in close proximity to the triazolinedione ring, which due to its electron deficient nature, would certainly attract the lone pair of the basic nitrogen. This influence is best described by considering other canonical forms of the resonance stabilised triazolinedione ring as shown in Fig. 12.

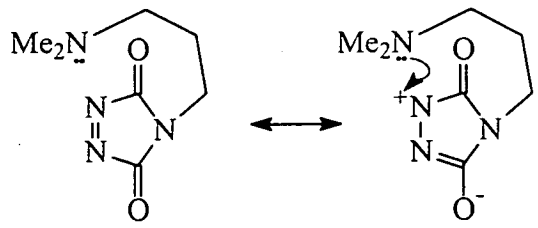


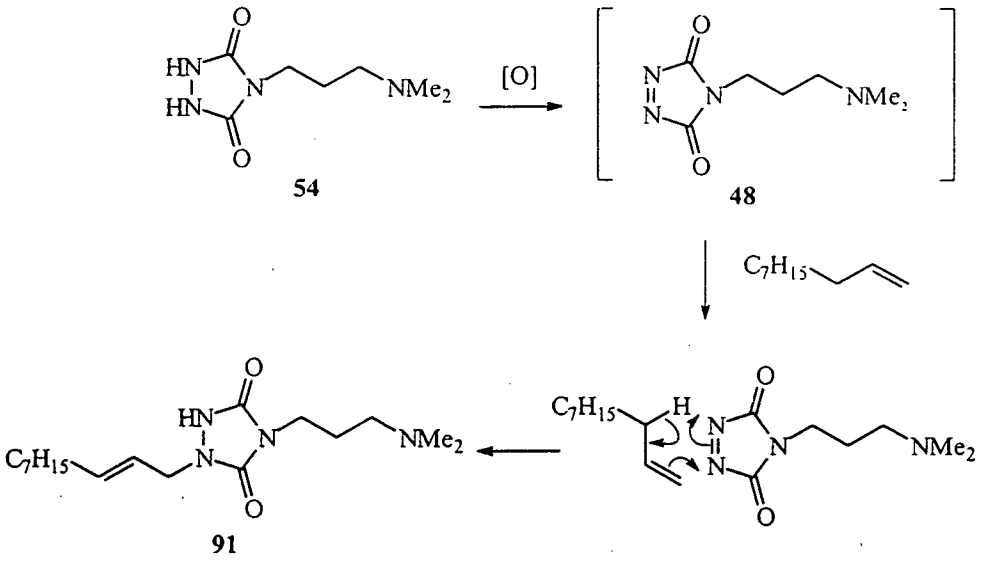
Figure 12. Possible canonical forms of **54**

The distinction between intramolecular and intermolecular effects can be examined by oxidation of the other urazoles that were prepared in section 1.1.3. The oxidations were carried out with *N*-bromosuccinimide and nitrogen dioxide as described previously and, in the same manner, all of the triazolinediones formed were found to decompose upon concentration of the solution.

In particular, both the urazoles with the dialkylaminoethyl group, which are prevented from intramolecular interactions by a shorter chain length and those with the dialkylaminophenyl groups, which have no chain flexibility at all, decomposed, pointing to an intermolecular effect causing the instability. Consistent with this is the evidence that the decomposition reaction appears to be accelerated by concentration of the compound.

Since the isolation of the basic-functionalised triazolinediones was proving impossible to achieve, it was decided to regard the compounds as reactive

intermediates and attempt to trap them without isolation by an *in situ* ene reaction. The initial oxidation of 3-*(N,N*-dimethylamino)propyl urazole **54** with *N*-bromosuccinimide was repeated in the presence of 1-decene (Scheme 50), but no reaction to form the expected ene product **91** was observed. A range of conditions and oxidants were therefore tried out as summarised in Table 3.



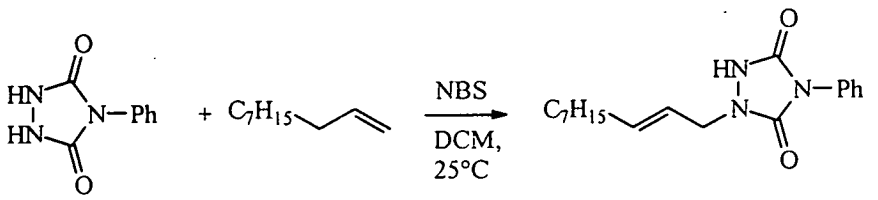
Scheme 50

Table 3. Conditions employed for *in situ* oxidation and ene reactions of **54** in the presence of 1-decene

Oxidising agent	Solvent	Temperature
NBS	DCM	25°C
NBS	DCM	0°C
NBS	CH_3CN	25°C
NBS	CH_3CN	0°C
NBS	DMSO	25°C
NBS	DMF	25°C
NBS	DMF	0°C
N_2O_4	DCM	0°C
N_2O_4	DMF	0°C
HgO	DCM	25°C
TsNCO	DMSO	25°C
Cl_2	DCM	25°C
Br_2	DCM	25°C
Br_2	DCM	0°C
Br_2	DMF	25°C
Br_2	DMF	0°C

NBS = *N*-bromosuccinimide; TsNCO = *p*-toluenesulfonyl isocyanate;
DCM = dichloromethane; DMF = *N*,*N*-dimethylformamide;
DMSO = dimethylsulfoxide;

All of these reactions resulted in slow decolouration of the initially formed triazolinedione **48**, but only unreacted decene and polymeric residues were detected at the end of the reaction. It was decided to verify that the conditions used were of a nature sufficient to promote the ene reaction by carrying out a parallel control experiment in which both 4-(3'-*(N,N*-dimethylamino)propyl)urazole **54** and 4-phenylurazole **92** were oxidised with *N*-bromosuccinimide in the presence of 1-decene under exactly the same conditions (Scheme 51).



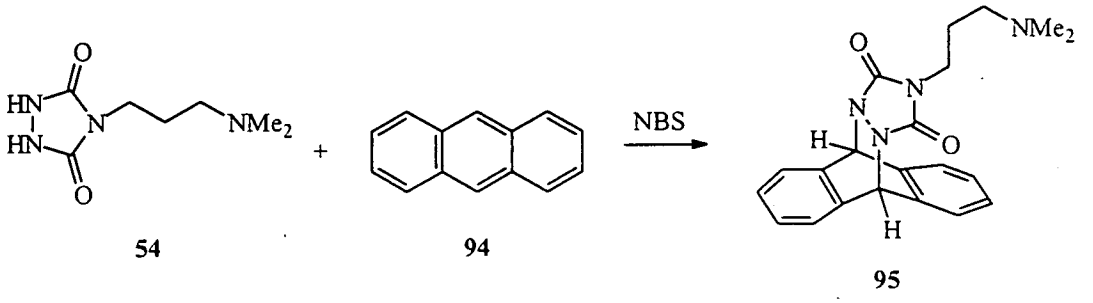
92 **93**

Scheme 51

The outcome was that the 3'-*(N,N*-dimethylamino)propyltriazolinedione produced by the addition of *N*-bromosuccinimide was decolourised within 1 hour, much faster than the case with the phenyltriazolinedione (PTAD) produced which took *ca.* 10 hours. In contrast also, the PTAD produced an easily extractable novel monofunctionalised pure ene product **93** in 46% yield whereas no discernible organic products could be isolated from the oxidation and attempted ene reaction of 3'-*(N,N*-dimethylamino)propylurazole. This was taken as further evidence that specifically the base-functionalised triazolinediones were either decomposing to form complex mixtures or reacting with themselves preferentially in a polymeric manner rather than undergo the ene reaction.

In a further attempt to test the reactivity of the generated triazolinediones, 3'-*(N,N*-dimethylamino)propylurazole was subjected to an *in situ* oxidation with *N*-bromosuccinimide and trapping in a Diels-Alder cycloaddition reaction with anthracene **94** (Scheme 52). Anthracene was chosen as the diene because the expected product **95** from this reaction with the triazolinedione possesses aromatic

groupings, which should promote organic solubility and help with the work-up of the reaction.



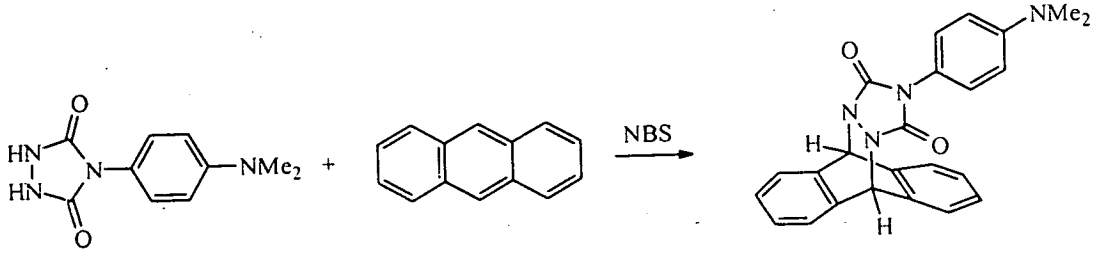
54 94 95

Scheme 52

The triazolinedione formed from **54** when the *N*-bromosuccinimide was added , 4-(3'-*(N,N*-dimethylamino)propyl)-1,2,4-triazoline-3,5-dione **48** reacted almost instantly and very little of the pink colour generated was observed after addition was complete. Nonetheless, upon preparation for chromatographic work-up, the product decomposed to a black tar, analysis of which by NMR and infra-red spectroscopy did not show any of the expected Diels-Alder adduct **95** and instead only a complex mix of compounds that could not be separated and subsequently whose structure could not be identified.

The same cycloaddition reaction was then repeated with 4-(*N,N*-dimethyl-*p*-aminophenyl)-urazole **82** and on this occasion the product obtained did not decompose totally allowing the mixture to be separated to give the expected

cycloadduct **96** in a reasonably low yield of 29% in the form of its hydrobromide salt (Scheme 53). This low yield points to the instability of the triazolinedione and despite the presence of a very active trapping agent, side reactions involving decomposition are probably also at work. The structure of **96** is confirmed by ^{1}H and ^{13}C NMR spectroscopy which showed typical absorptions for the chemically identical bridgehead carbons at 6.31 ppm and 60.4 ppm respectively.



82 **94** **96**

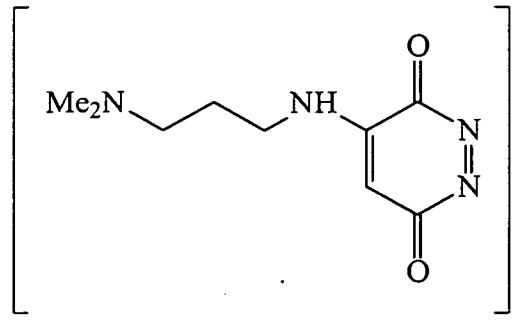
Scheme 53

The success of the aromatic Diels-Alder cycloaddition (with respect to the failure of the aliphatic case) may be explained in two ways. Either the initial Diels-Alder product from the aliphatic case is too unstable to be isolated, *i.e.* the aryl substituted product **96** is more stable than the product **95** bearing the propyl group as linker, or the reaction is prevented from occurring by the influence of the groups attached to the nitrogen base with the alkylamine group having more of an effect than the weaker arylamine group.

In conclusion, it would appear from the results that the base-functionalised triazolinediones are too reactive towards themselves to give straight-forward ene adducts, or also possible, the products of the ene reaction are themselves too unstable and decompose upon their generation. Diels-Alder cycloaddition reactions involving triazolinediones were only a little more successful with only a small amount of one adduct isolated. In similar reactions carried out with the hydrobromide salt of 4-(3'-*(N,N*-dimethylamino)propyl)urazole, failure also occurred and it seems unlikely that shielding of the basic entity as a salt can have a beneficial effect.

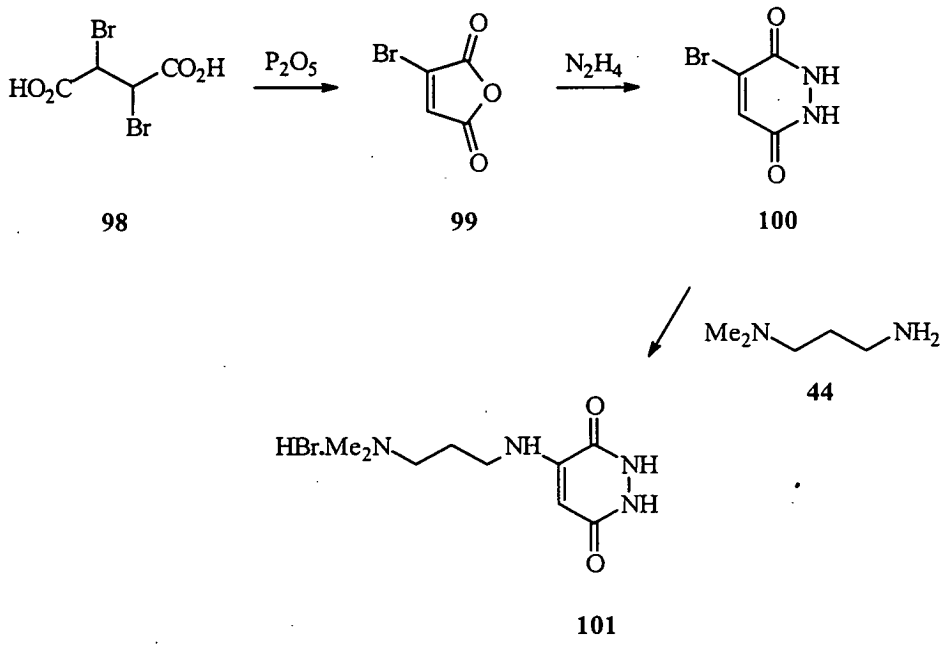
1.2 Diazaquinones

In view of difficulties experienced with the generation of urazole precursors, another way of introducing the 3-*(N,N*-dimethylamino)propyl group to alkenes *via* the ene reaction was sought. An alternative route is to employ the six-membered equivalent of the triazolinedione, *viz.* the pyridazinedione (diazaquinone) moiety as depicted in structure **97**. This class of compounds are similarly synthesised by the oxidation of their hydrogenated precursor[101] but are known to be unstable at room temperature and consequently can only be prepared either *in situ* or at temperatures below -50°C[101, 102]. No studies, as yet, have appeared in which diazaquinones have been tested in an ene reaction.



97

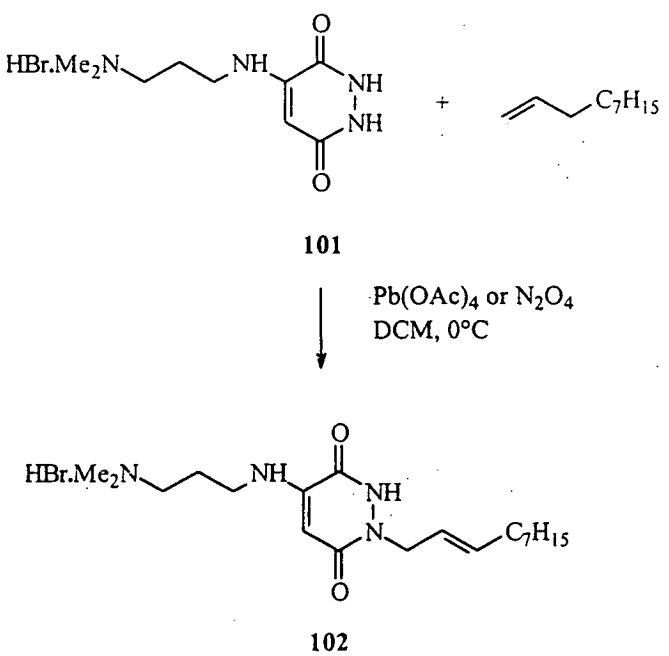
The planned synthetic route to the desired diazaquinone **97** is outlined in Scheme 54 and proceeds from dibromosuccinic acid **98** *via* bromomaleic anhydride **99** and subsequent conversion of the latter into bromomaleic hydrazide **100** by treatment with hydrazine. Reaction of **100** with 3-*(N,N*-dimethylamino)propylamine **44** would lead to isolation of hydrazide **97** probably as its hydrobromide salt **101** which could be oxidised when required to give the diazaquinone **97**.



Scheme 54

In practice, all stages of the synthesis proceeded in reasonable yield and in good purity with no further purification being required before isolation of the precursor as its hydrobromide salt **101** was achieved in 72% yield overall from dibromosuccinic acid. It was reasoned that preparation of the free base was not be necessary since the extra protection that would be provided by the hydrobromide group would only assist in the stability of the reactive diazaquinone intermediate upon its generation. Consequently the free base was not prepared. The structure of the hydrobromide salt was confirmed by NMR spectroscopy which showed incorporation of the 3-*(N,N*-dimethylamino)propyl group combined with the unsaturated CH at the 5-position and mass spectroscopy which showed it to be a stable hydrobromide salt by the isotope distribution pattern.

The maleic hydrazide precursor **101** was reacted in an oxidation and *in situ* ene reaction with 1-decene using Clement's conditions[101] in which a slurry of the compound in dichloromethane solution containing the alkene starting material a small amount of glacial acetic acid at 0°C was treated slowly with lead tetraacetate. Effervescence was observed and after filtration of the solution to remove the lead acetate by-product, the solvent was removed *in vacuo* to give a yellow gum. No distinct reaction products were observed and there was no distinct evidence for the formation of **102** (Scheme 55).

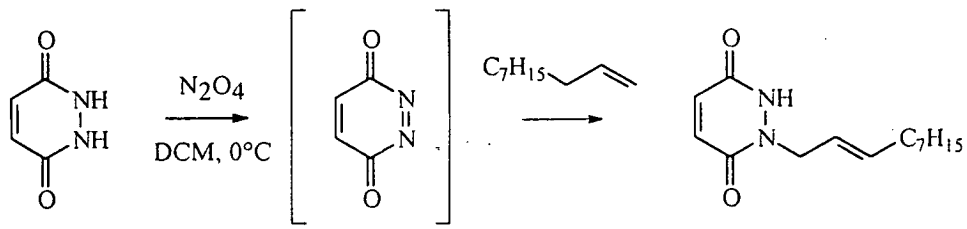


Scheme 55

The oxidation was then repeated using lab-generated nitrogen dioxide at 0°C, again in dichloromethane solution, with sodium sulfate present to remove the nitric acid

produced by the oxidising gas by conversion into sodium nitrate and sodium bisulfate. Again no distinct reaction product was detected with only starting material alkene and polymeric residues recovered.

Since the ene reaction has no precedence with this type of molecule, it was decided to repeat the oxidation procedure and attempted ene reaction by using the parent compound itself, maleic hydrazide **103**, as the enophile precursor (Scheme 56).



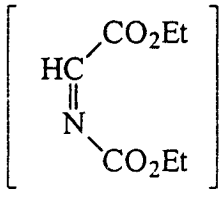
103 **104**

Scheme 56

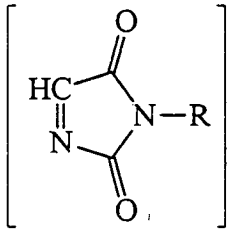
Both types of reaction conditions were tried, but once again none of the ene product **104** was observed when 1-decene was present and upon work-up the latter was recovered unchanged along with polymeric residues. It was decided at this point that the diazaquinones were also unreactive in the ene reaction and instead preferred to decompose by self condensation like the basic urazoles. Since some success had been achieved by this time in a synthesis for the basic-functionalised urazoles, it was decided to concentrate efforts in that area.

2. Imine Enophiles

The imines chosen for study in this project are the unstable diacylimines similar in structure to diethyl azodicarboxylate and *N*-substituted triazolinediones, *viz.* diethoxycarbonyl aldimine **105** and dehydrohydantoins **106**. In the acyclic case, synthesis of the imine precursor was straight-forward and consequently most attention was directed towards studying its potential in the ene reaction and also amidoalkylation. By contrast, in the cyclic case the synthesis of a basic function attached to a 4-methoxyhydantoin moiety had never been achieved before, and in this instance most of the attention was focused on the synthesis of precursors to the imines.



105



106

2.1 Acyclic imines

2.1.1 Attempted formation *via* flash vacuum pyrolysis method

Although a recognised route to diethoxycarbonyl aldimine **105** exists *via* an ethanolic precursor[69], it was decided initially to investigate an alternative method for generating the unstable imine without having any other reagents present, *viz.* flash vacuum pyrolysis (FVP, Fig. 13) of the hydrogenated precursor, ethyl ethoxycarbonyl glycinate **107**, over a palladium/ alumina catalyst (Scheme 57). It was hoped that the imine **105** formed by the removal of hydrogen could be trapped *in situ* by a Diels-Alder cycloaddition reaction with cyclopentadiene upon allowing the collection trap containing the latter to warm up to room temperature.

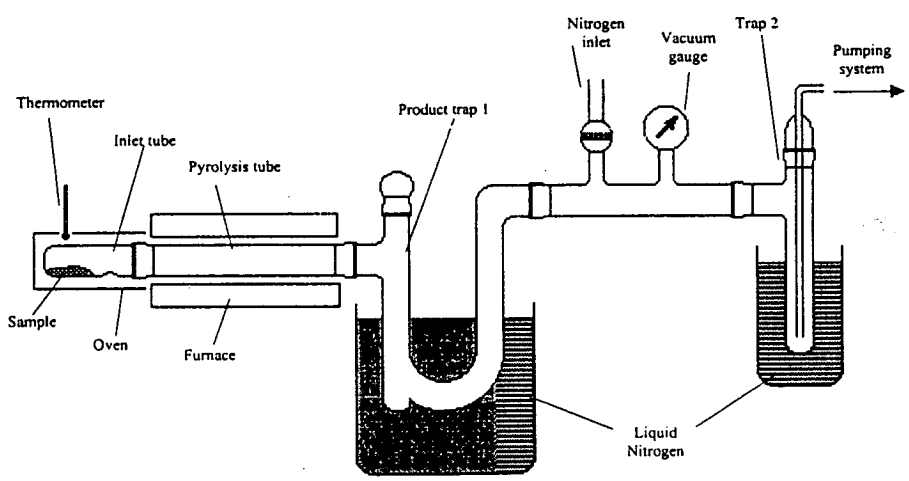
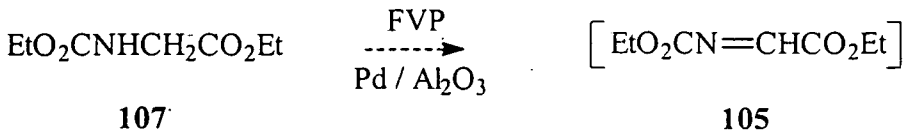


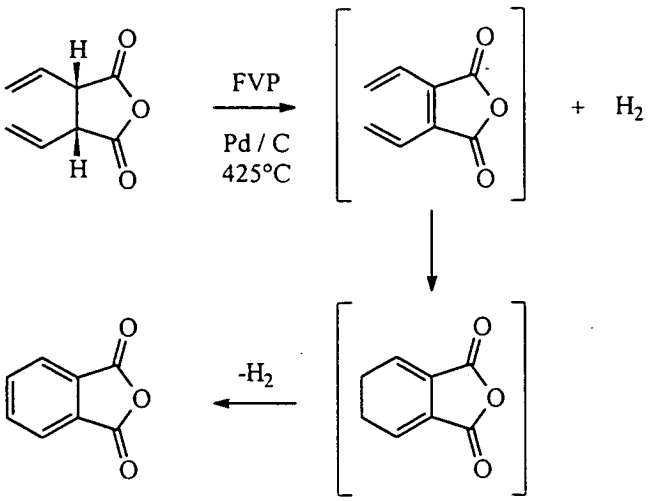
Figure 13. Typical FVP apparatus



107 **105**

Scheme 57

The procedure was carried out several times by varying the furnace temperatures from 400°C to 600°C, but no products of a reaction involving an imine were detected and only cyclopentadiene and its dimer, dicyclopentadiene, were recovered. It was presumed that, despite using comparatively low FVP temperatures, the extra contact time afforded by the catalyst was sufficient to cause total decomposition of the precursor rather than formation of the desired imine product. In retrospect, this was perhaps not too surprising a result since FVP is normally used to carry out selective fragmentation of a precursor rather than dehydrogenation. Hydrogen gas is not a very good leaving group for this purpose, although this type of process has been accomplished previously in this laboratory in the pyrolysis of cis-2,3-divinylsuccinic anhydride into phthalic anhydride with the loss of 2 equivalents of hydrogen as shown in Scheme 58[103].



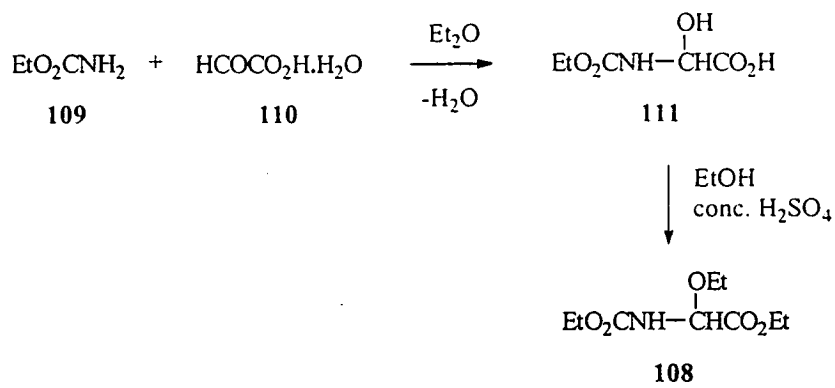
Scheme 58

2.1.2 Successful preparation of imine 105 *via* ethanolic precursor method

In a different approach, the imine could be generated from an alcoholic precursor as described in Scheme 26. Therefore research into the preparation of the ethanolic precursor to the target imine **105** was undertaken. Whilst the precursor, ethyl ethoxy-*N*-ethoxycarbonylglycinate **108**, had been prepared for use by Krow *et al.*[69], no full identification or actual synthesis of the compound was to be found in the chemical literature.

The strategy adopted to synthesise this precursor involved an adaptation of Zoller and Ben Ishai's preparation of methyl methoxyhippurate[104] and commenced with reaction of ethyl carbamate **109** with the hydrate of glyoxylic acid **110** to form

hydroxy-*N*-ethoxycarbonyl glycine **111** using boiling diethyl ether as solvent This coupling could be promoted by the use of a Soxhlet apparatus containing calcium hydroxide to rigorously remove water freed up by reaction of the hydrate. This was then followed by esterification at room temperature in ethanol with catalytic amounts of concentrated sulfuric acid.(Scheme 59). Upon aqueous work-up, the glycinate **108** was obtained in 88% overall yield and required no further purification before use as a precursor to the imine.

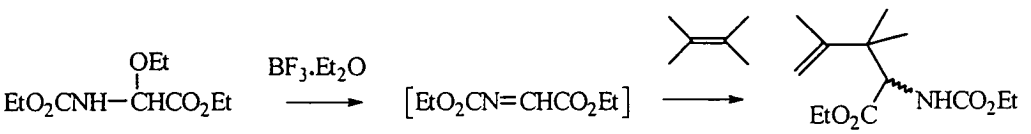


Scheme 59

2.1.3 Attempted ene reactions

Once the glycinate **108** had been prepared, conditions were selected to promote the formation of the imine **105** in the hope of carrying out a subsequent ene reaction. The conditions chosen involved heating the precursor **108** in dry chloroform under

reflux with an appropriate alkene in the presence of boron trifluoride etherate as catalyst (Scheme 60). The alkene chosen for initial study was tetramethylethylene due to its high symmetry which would lead to a less complex product mixture and consequently products of the reaction would be easier to identify.



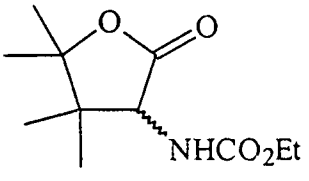
108 **105** **112**

Scheme 60

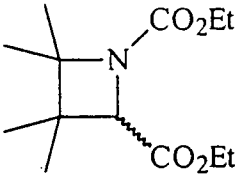
Three equivalents of boron trifluoride etherate were originally selected as it was not known whether the acid would functionalise solely as a catalyst or be consumed in the reaction. Two equivalents were needed to activate one carbonyl group each, leaving the third equivalent to induce loss of the ethoxy group and formation of the imine.

When the reaction was performed, none of the expected unsaturated ene product **112** was observed. Instead two completely unexpected and novel compounds were isolated, *viz.* γ-lactone **113** and azetidine **114**, two types of compound which had not previously been observed from an amidoalkylation with a diester such as **108**[73]. Both products were identified using a range of spectroscopic techniques. The γ-lactone **113** has a characteristic absorbancies at 59ppm and 87ppm, corresponding to

the CH in the 3-position and the quaternary carbon in the 5-position respectively, and has an IR absorbance at 1694 cm^{-1}, consistent with the carbonyl group of a lactone ring and a molecular weight 28 units below that of a direct adduct indicating the loss of an ethyl group. The azetidine **114** is characterised by the lack of any coupling in the ^1H NMR spectrum with the ring CH in the 2-position and by its characteristic ring carbons in the corresponding ^{13}C NMR spectrum. The azetidine can be distinguished from its isomeric oxazine by IR absorptions at 1751cm^{-1} and 1724cm^{-1}, characteristic of two esters rather than the imine absorption produced by an oxazine which would occur at approximately. 1640cm^{-1}.



113

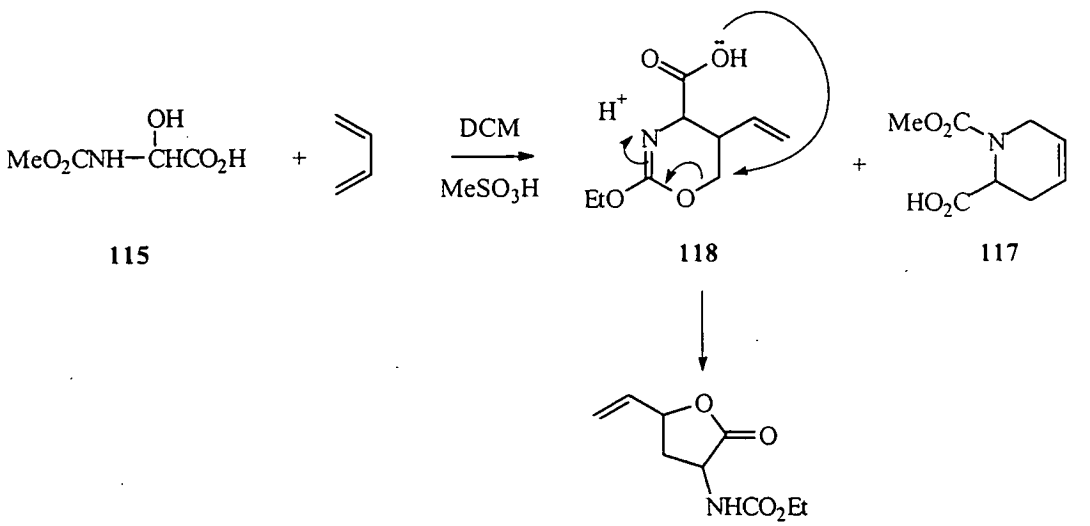


114

The azetidine **114** is a simple [2+2]-cycloadduct that is the product of an entirely possible but uncommon cycloaddition reaction which can occur in competition with the ene reaction[1]. The γ-lactone product **113** lacks one of the ethyl groups of the starting material and so is likely to have been formed by hydrolysis of an initial product which probably occurred upon aqueous work-up prior to chromatography.

It is known that the Brønsted acid-catalysed amidoalkylation reaction between hydroxy-*N*-methoxycarbonylglycine **115**, an analogue of the free acid of the chosen

precursor **108**, and butadiene produces a γ-lactone **116** in a similar way to the reaction related here in a yield of 75% (Scheme 61)[105]. However, in this case, no [2+2]-cycloadduct was formed and instead a small amount (7%) of the expected Diels Alder cycloadduct, *viz.* the tetrahydropyridine **117**, was isolated.



115 **118** **117**

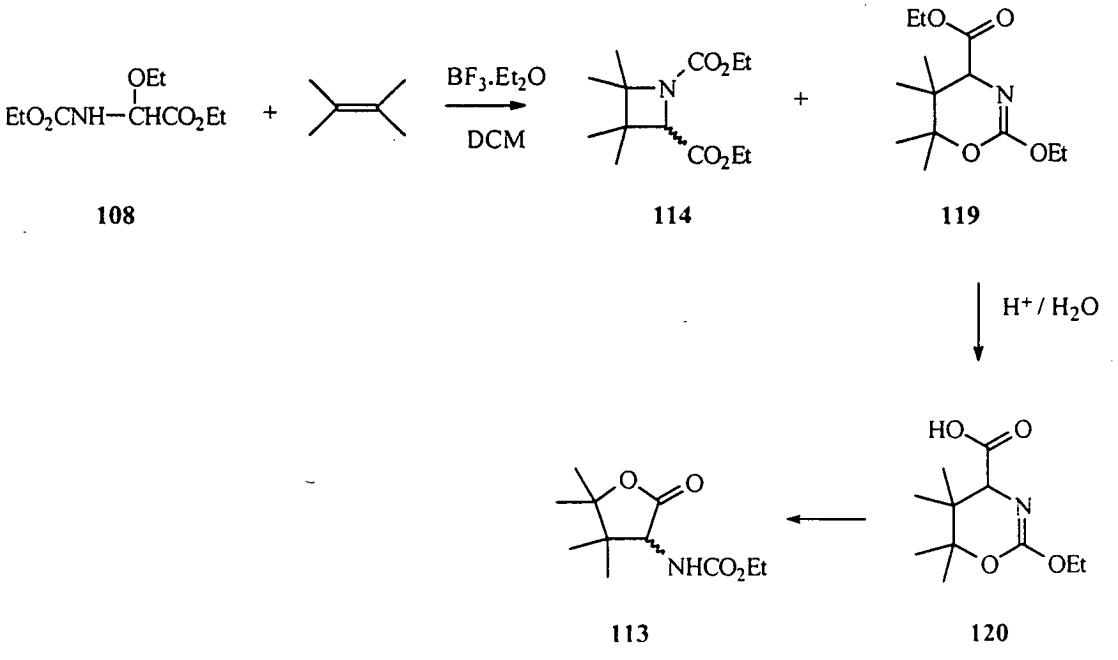
116

Scheme 61

The initial product is presumed to be the 1,3-oxazine **118**, which is formed by a [2+4]-cycloaddition reaction between the acylimine generated from **115** and butadiene and subsequently rearranges to give the γ-lactone **116** by a mechanism involving ring opening and concomitant ring closing as depicted. The similarity of this reaction and its product to that which produced compound **113** would indicate a similar reaction pathway between the two reactions. This rearrangement of an oxazine to a lactone is also known for more stable isolable oxazine esters when

heated in acidic media[106]. These literature results add further weight to the argument that hydrolysis in the work-up leads to the formation of the five membered γ-lactone product, the driving force of which is the latter's greater stability compared to the six membered unsaturated 1,3-oxazine.

The pathway of the reaction initially proposed in Scheme 60 turned out as shown in Scheme 62, whereby both the azetidine **114** and the 1,3-oxazine **119** are being formed in the reaction. The azetidine was recovered in 47% yield but work-up conditions have then caused hydrolysis and rearrangement of the 1,3-oxazine to form the racemic γ-lactone **113** which is isolated in 30% yield, a ratio of 1.57:1. Reduction of the catalyst charge to 1 equivalent resulted in a lowering of yield to 38% of azetidine and 23% γ-lactone and an altering of ratio to 1.65:1.



108 **114** **119** **113** **120**

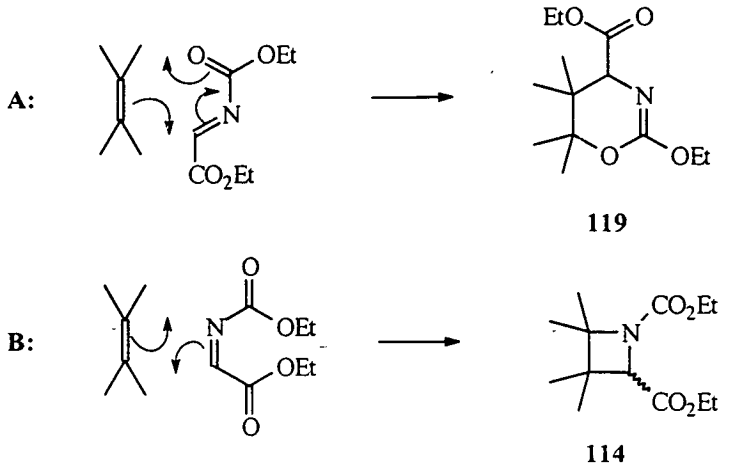
Scheme 62

The reaction was also carried with no aqueous work-up but instead with direct separation of the reaction products by column chromatography on silica. The outcome was isolation of the γ-lactone and azetidine in a similar ratio (1.5:1 azetidine : lactone) giving strong evidence that silica itself would also bring about hydrolysis to the oxazine product **120** which then rearranges to give the γ-lactone.

A separate experiment performed in an NMR tube gave further evidence for the oxazine formation by *in-situ* ^{1}H NMR spectroscopy which showed no signals exclusive to the spectrum corresponding to the lactone despite disappearance of the starting material and apparent production of a crude mix containing the azetidine.

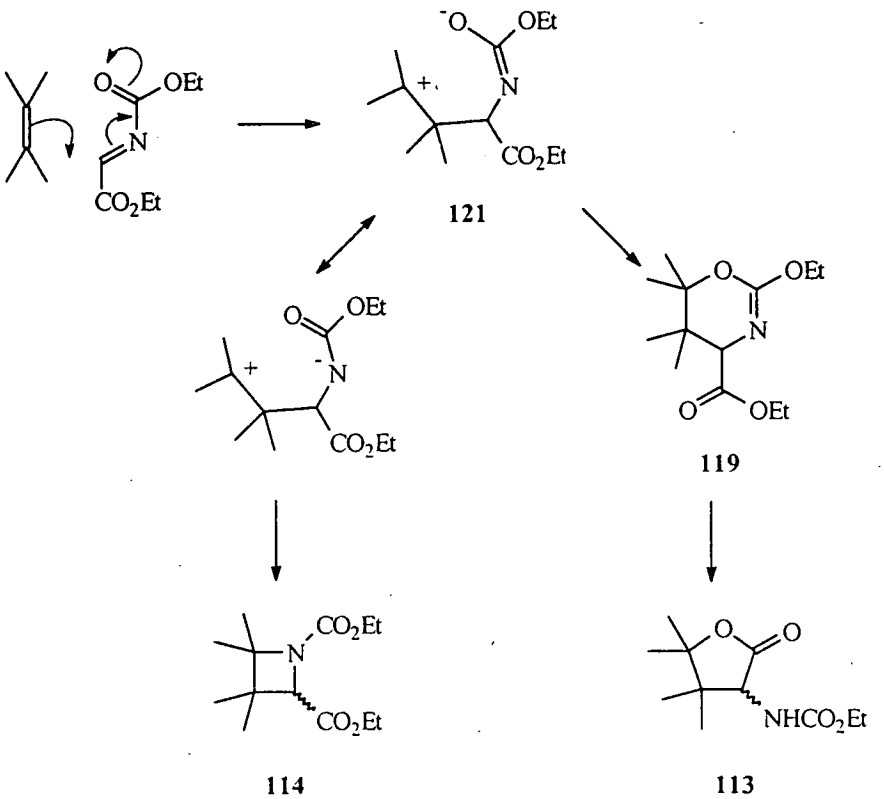
The formation of two different types of product in a *ca.* 1.5:1 ratio gives rise to some indications about the mechanism of the reaction. In essence, there are two possible pathways that can account for both types of product formation, *viz.* concerted and step-wise.

It is possible that two different concerted cycloaddition reactions are occurring competitively as illustrated in Scheme 63, *i.e.* one to form the [4+2]-Diels-Alder cycloadduct (path **A**), and another less likely cycloaddition to form the more strained [2+2]-cycloadduct (path **B**).



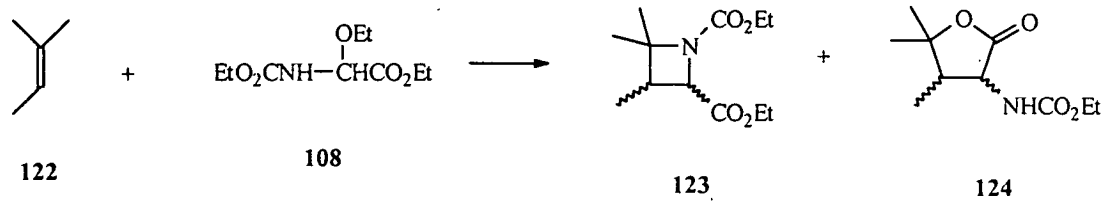
Scheme 63

There is likely to be a large difference in activation energies between these two processes and the considerably more favourable Diels-Alder cycloaddition (path **A**)is likely to form more product than the less favourable path **B**. Since there is not significantly more of the product associated with oxazine formation isolated, these two concerted pathways seem less likely than a step-wise mechanism which can account for both types of product from the same intermediate as shown in Scheme 64. Essentially, the imine reacts initially with the alkene to form an ionic intermediate **121** which can cyclise from one of two resonance forms to produce either the azetidine or the oxazine.



Scheme 64

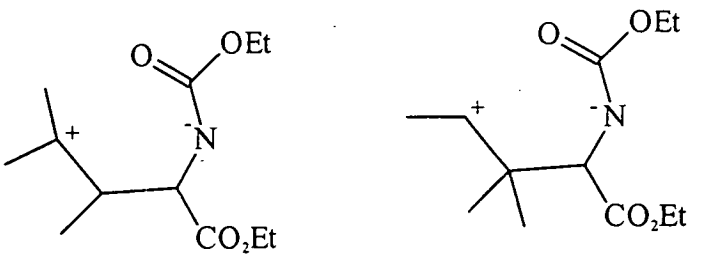
A further experiment was carried out to provide further evidence on which of the two different mechanistic pathways was occurring in the reaction. For this purpose an asymmetrical alkene with one methyl group removed compared to tetramethylethylene, *viz.* 2-methylbut-2-ene **122**, was subjected to the same reaction with ethyl ethoxy-*N*-ethoxycarbonylglycinate **108** and was found to give the expected azetidine **123** together with the γ-lactone **124** in a yield of 29% and 28% respectively which corresponds to a ratio of approximately 1:1 azetidine to γ-lactone (Scheme 65).



122 108 123 124

Scheme 65

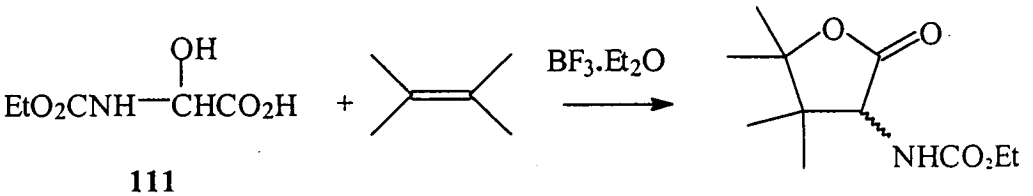
Only one regioisomer of each type of product was observed according to ^{1}H and ^{13}C NMR spectroscopy. The presence of only single regioisomer of the azetidine formed **123** was established by a signal in the $\pi/2$ DEPT ^{13}C NMR spectrum which showed that the ring carbon which absorbs at 35ppm (position 3) had changed from a quaternary to a CH grouping and no corresponding signal in the spectrum for the ring carbon absorbing at 80ppm (position 4). This specificity of reaction can be explained best by a step-wise mechanism, since the concerted mechanism would lead to both regioisomers of each product, *i.e.* four compounds overall. Steric hindrance might bring about a slight difference in ratio between isomers, but nonetheless, only a step-wise process with a highly structured intermediate can account for the explicit regioselectivity. The proposed intermediate, **125**, which is shown in Fig. 14 is favoured both by the least obstructed site of attachment and by the fact that the most stable carbocation is generated in the intermediate. On the other hand, the isomeric form **126** is much less likely to occur since not only is it more hindered at that site, but also the carbocation formed is less stable.



125 **126**

Figure 14. Carbocation intermediates

Another investigation was also made to determine whether the γ-lactone **113** could be formed directly under the reaction conditions rather than by the work-up procedure afterwards. Consequently the reaction was repeated with tetramethylethylene under identical conditions using the unprotected acid form, 2-hydroxy-*N*-ethoxycarbonylglycine **111** of the previous imine precursor **108** (Scheme 66).



111 **113**

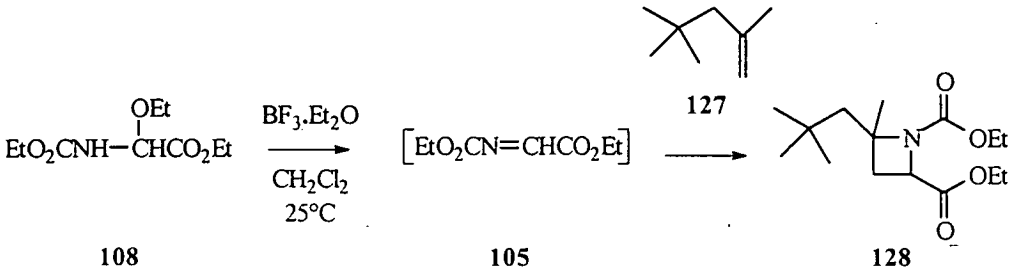
Scheme 66

The outcome of this reaction was surprising in that no azetidine was isolated, but only the γ-lactone **113**, which was obtained without chromatography being required.

A probable reason for the absence of azetidine is because the γ-lactone can be produced directly in the reaction without the need for hydrolysis in the work-up. This provides an extra driving force for the production of the γ-lactone and so the less favourable azetidine is not formed. Another contributing factor could have been that an acid grouping is more electronegative than an ester group and withdrew charge onto the oxygen atom more effectively than the ester group thus leading to preferential oxazine and therefore γ-lactone formation.

A further anomaly was found when a different alkene to the simple substituted butenes was used in the reaction. Since one of the principle aims of the project was to functionalise polyisobutene, specifically that with a high level of reactive vinylidene end-groups, the reaction of the diester **108** which is the precursor to the reactive aldimine **105** was carried out with α-di-isobutene **127** under the same conditions. On this occasion, only the azetidine **128** was recovered with no evidence being found for oxazine formation presumably due to steric hindrance caused by the extra alkyl groups on the alkene. Evidence for the structure of **128** is provided by NMR and IR spectroscopy which is consistent with accurate mass data. In particular ^{1}H NMR spectroscopy shows absorbancies at 1.80ppm and 1.95ppm, corresponding to two geminally split signals from the CH_2 group at the 3- position of the azetidine ring. This geminal coupling is caused by the *tert*-butyl group in the product combining with the presence of the ring to produce different environments for the two protons. The other isomer could not produce a similar complex signal as there would be no vicinal proton to couple with. The structure is also confirmed by predictions for the ^{13}C NMR spectrum of **128** from the computer program SpecInfo[89]

which match the spectrum of the product accurately whereas the program predicts very different signals corresponding to the ring carbons of the other regioisomer .



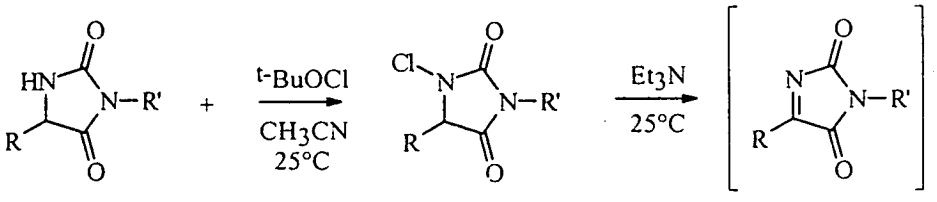
108 105 128

Scheme 67

In summary, the amidoalkylation reactions of an imine precursor such as **108** with substituted alkenes to bring about formation of a γ-lactone such as **113** with a Lewis acid is not only novel but has also brought about the unexpected formation of azetidines. Insufficient time has prevented further investigation into the mechanism of formation of these products, especially why the reaction gives only one or the other product with certain reactants and, on the other hand, both products with other reactants. At this stage, the mechanism of the amidoalkylation is best described as a step-wise process involving the initial formation of a charged intermediate as described in Scheme 64, although it is not clear why each particular selectivity is followed. It would also have been of interest to explore the use of alternative Lewis acids in the reaction and this avenue may be one of several areas for future work.

2.2 Cyclic acylimines

The cyclic acylimines chosen for this study were the unstable imidazolinediones (or dehydrohydantoins) **129** which were first studied by Evnin and Blyskal in 1970[68] who generated several dehydrohydantoins from their respective hydantoins **130** by formation of the *N*-chloro precursors **131**, as shown in Scheme 68, followed by dehydrochlorination with triethylamine.

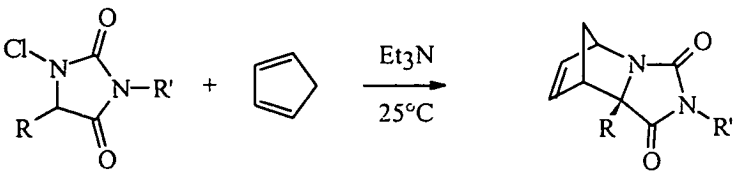


130 **131** **129**

R=H, R'=CH_3;
R=CO_2Me, R'=CH_2Ph;
132: R=Ph, R'=CH_3

Scheme 68

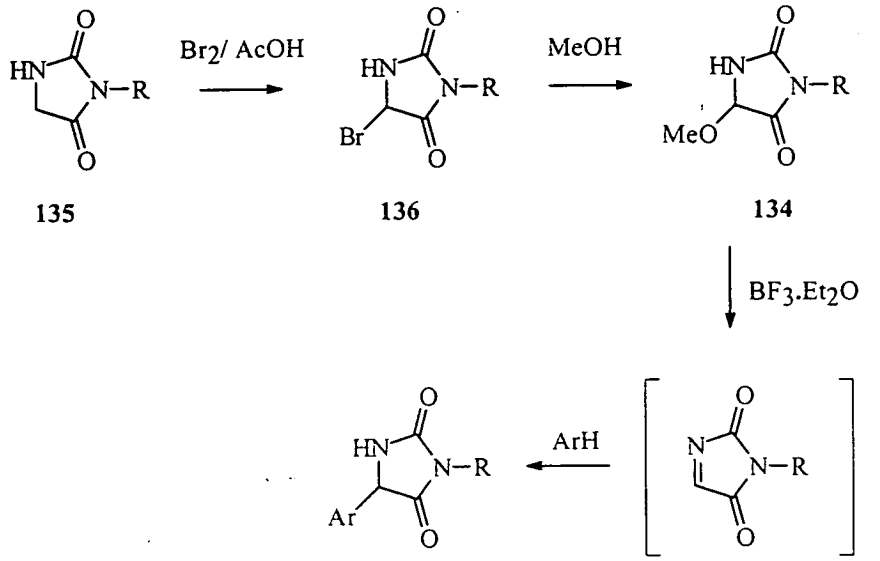
Unfortunately, only 5-phenyl-3-methylhydantoin **132** was found to be stable at room temperature and even then was extremely sensitive to the atmosphere. As shown in Scheme 69, the other dehydrohydantoins prepared in this way were generated and trapped *in situ* by Diels-Alder reaction with *e.g.* cyclopentadiene to form a *endo* specific cycloadduct **133**.



131 133

Scheme 69

In a different approach, Ben Ishai and co-workers[107] functionalised the carbon of the potential imine with an alcoholic leaving group, which was removed under acidic conditions to form the dehydrohydantoin when desired. Thus, synthesis of the precursor, methoxyhydantoin **134**, was accomplished from the hydantoin **135**, *via* bromination to form the bromohydantoin **136** followed by substitution with methanol (Scheme 70). In the final stage the dehydrohydantoin was generated by the action of boron trifluoride etherate in either boiling toluene or chloroform under reflux. Isolation of the reactive dehydrohydantoin was not attempted, but successful trapping of the intermediate was accomplished by amidoalkylation with an aromatic compound.



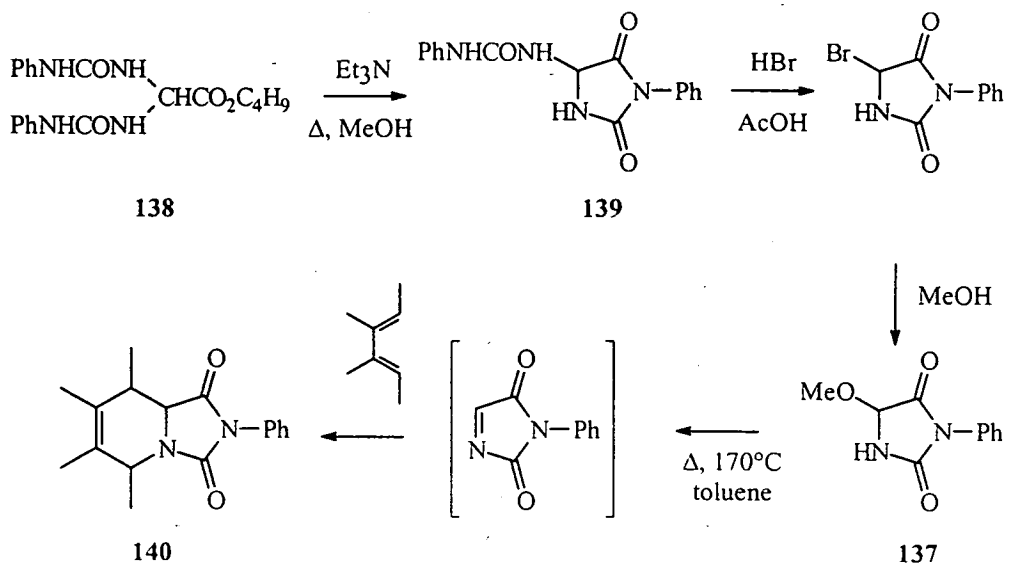
135 136 134

R = H, $C_6H_5CH_2$, *p*-ClC_6H_4

Ar = C_6H_5, $C_{14}H_9$, $CH_3C_6H_5$

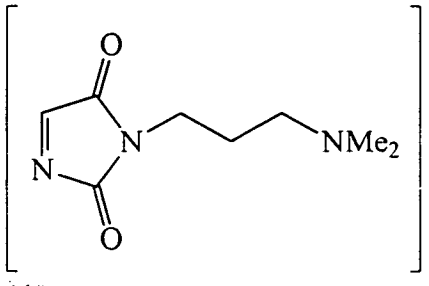
Scheme 70

Dehydrohydantoins synthesised in this way have been used as activated imine dienophiles in Diels-Alder reactions as well as for amidoalkylations, proving that the imine was indeed being formed as a reactive intermediate. In one particular case, the alcoholic precursor **137** was formed from the bisurea **138** *via* the ureido-functionalised hydantoin **139** as shown in Scheme 71[67]. Subsequently the precursor was reacted with tetramethylbutadiene in toluene solution by heating in a sealed tube at 170°C to form the desired cycloadduct **140** in 49% yield based on the bisurea.



Scheme 71

While both of these ways of generating dehydrohydantoins are successful for this particular type of product, the methods were thought to be unsuitable for the target molecule in hand, *viz.* 3-*(N,N*-dimethylamino)propylimidazolinedione **141**.



141

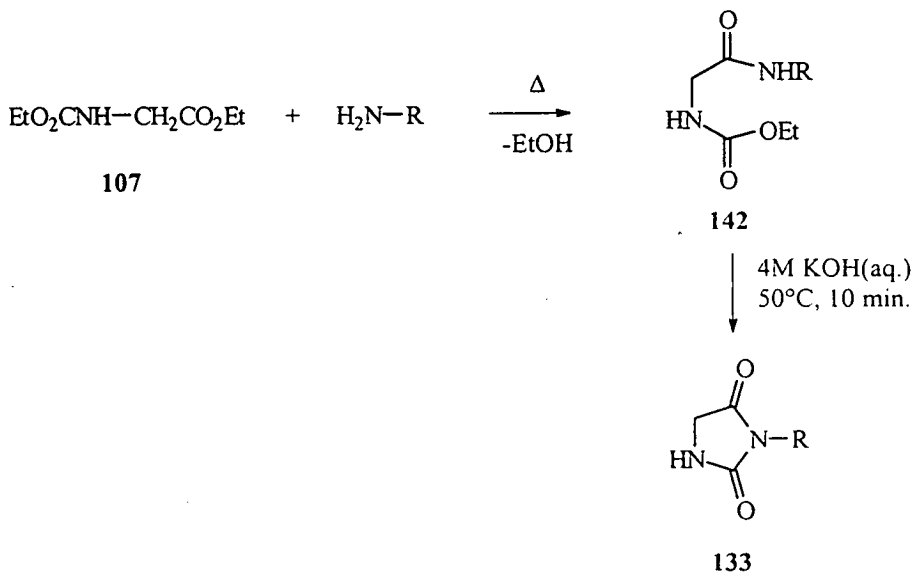
Specifically, the chlorohydantoin route was considered to be unsuitable for a compound with a basic moiety connected to the ring *via* the propyl group since it would react, either with itself or with a neighbouring molecule, as soon as it was generated by removal of hydrogen chloride. Furthermore, it was also feared that the attached *N,N*-dimethylamino group would not survive the harsh oxidising conditions required for chlorination. Because of these considerations, the alternative route involving alkoxy hydantoins was chosen to generate the target precursor. An added benefit to this approach is that experience had already been gained in the synthesis of the imine enophiles which relied on a similar elimination of an alcohol.

The literature preparations[15, 16, 68] for alkoxy precursors from hydantoins as outlined in schemes 70 and 71 are not considered to be suitable for examples bearing a basic grouping. It was thought that the *N,N*-dimethylamino functionality would be incompatible with a brominated intermediate needed in both processes due to the possibility of *in situ* dehydrobromination. Consequently, it was decided to investigate the direct synthesis of the 5-alkoxyhydantoin ring system such as **137** rather than carry out functionalisation of the pre-formed ring.

2.2.1 Preliminary attempts to synthesise 4-alkoxy hydantoins

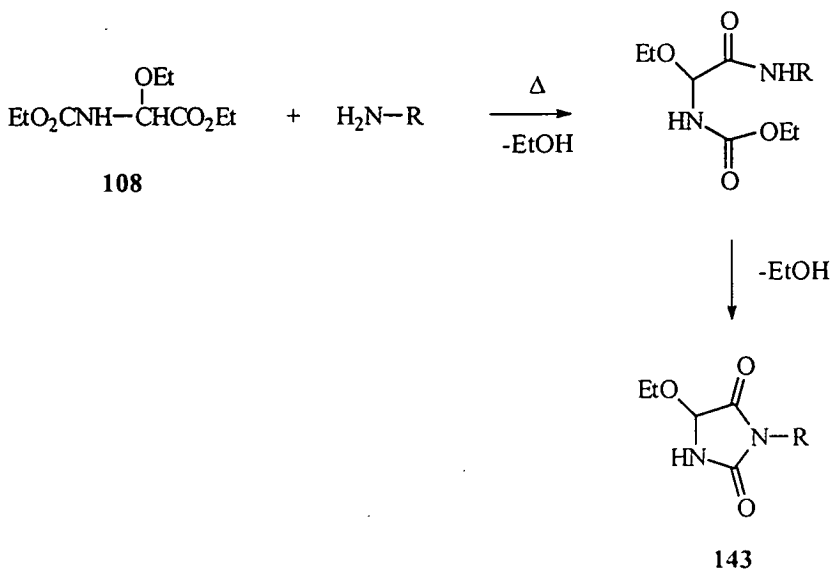
By analogy to Cookson's synthesis described earlier in this thesis, one of the routes to a direct synthesis of non-hydroxy hydantoins **135** is *via* ethyl carbethoxyglycinate **107**. Specifically, the diester is heated with the relevant amine to cause formation of

the ureido acetate **142** which is then dissolved in alkali and warmed to *ca.* 50°C to achieve cyclisation as depicted in Scheme 72 where R is aryl or alkyl[108].



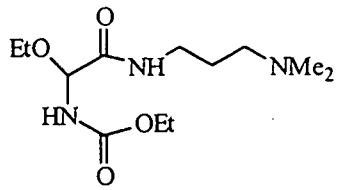
Scheme 72

Adapting this synthesis, it should be feasible to prepare the corresponding 4-alkoxy hydantoin derivative by heating the diester precursor of the hydantoin, *viz.* ethyl ethoxycarbethoxyglycinate **108**, with the relevant amine to form the desired compound **143** (Scheme 73).

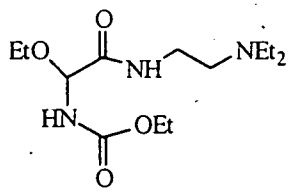


Scheme 73

This reaction was tried out with two amines; 3-*(N,N*-dimethylamino)propylamine and 2-(*N,N*-diethylamino)ethylamine, in each case the initial condensation proceeded in quantitative yield to afford the required ethoxyureidoacetate esters **144** and **145**, respectively. Unfortunately, the final cyclisation step did not occur either upon pyrolysis at 140°C or by treatment with 4M aqueous potassium hydroxide and only decomposition resulted as shown by both IR and NMR spectroscopy, which recorded loss of the carbonyl functionality altogether.

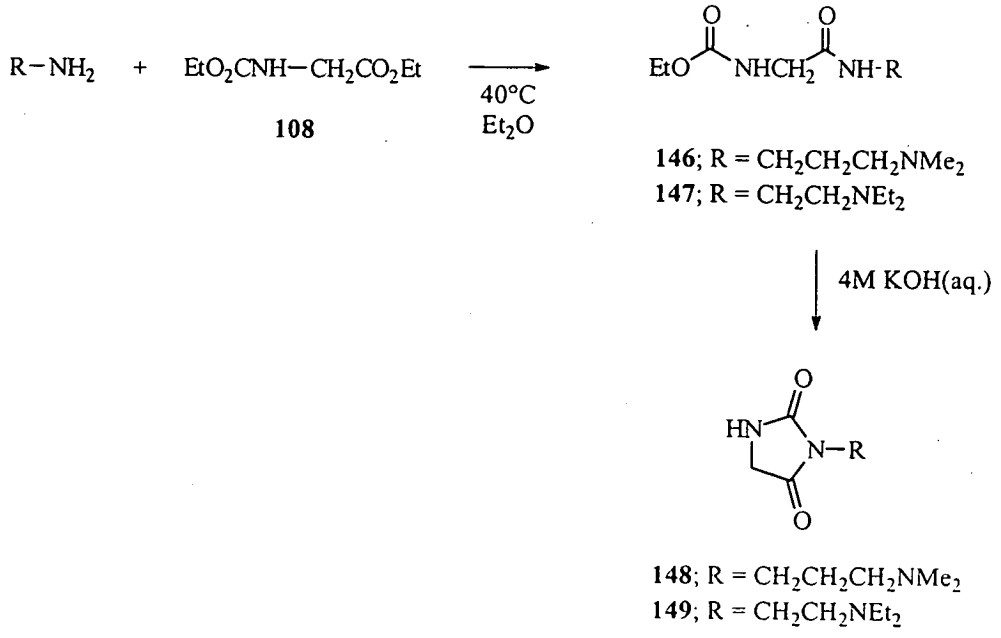


144



145

In order to confirm that the failure of cyclisation was a feature specific to the 4-alkoxyhydantoins, the reaction outlined in Scheme 72 was carried out with the two amines used previously, *viz.* 3-*(N,N*-dimethylamino)propylamine and 2-(*N,N*-diethylamino)ethylamine. The initial condensation proceeded in a similar manner and work-up led to the isolation of the ethyl ureidoacetate esters **146** and **147** in virtually quantitative yield. The cyclisation steps were then performed with 4M aqueous potassium hydroxide and both 1-(3'-(*N,N*-dimethylamino)propyl)hydantoin **148** and 1-(2'-(*N,N*-diethylamino)ethyl)hydantoin **149** were isolated as their hydrochloride salts in a yield of 59% and 42%, respectively (Scheme 74). In the first case, the free base was prepared in order to verify that the hydrochloride salts had been isolated initially.

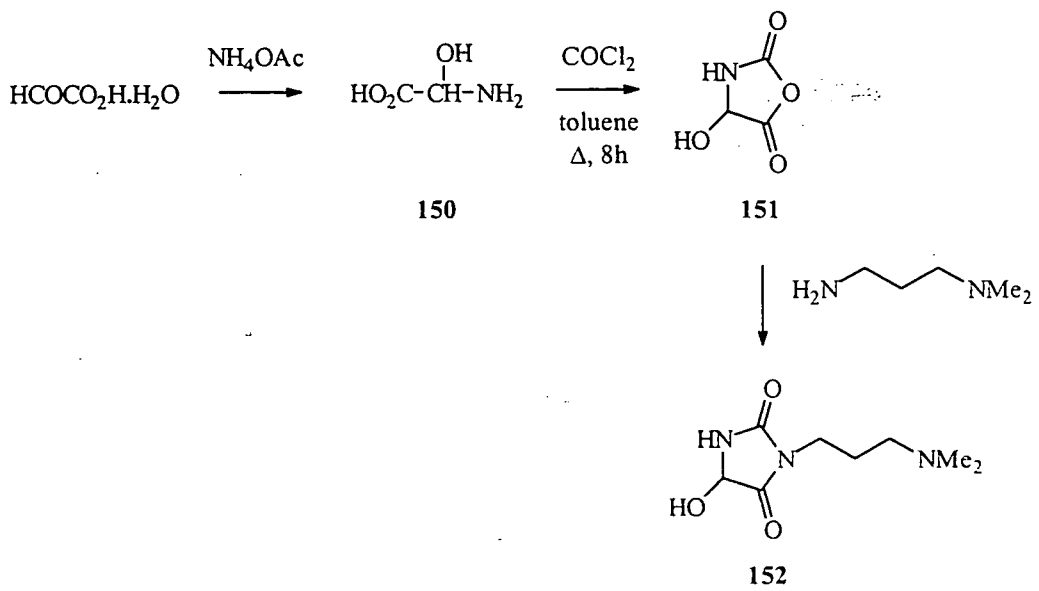


Scheme 74

The success of this synthesis compared to the failure of the synthesis of 4-ethoxyhydantoins recorded in Scheme 73 shows that while this approach is sound for more simple hydantoins, *i.e.* without an alkoxy functional group, the final cyclisation step requires harsh conditions of either high temperature or high alkalinity which appear to cause decomposition. Whether it is the case that the starting material decomposes without cyclisation or that the cyclised product is not stable under these reaction conditions is not clear at this stage of the work.

Another synthetic route that was explored next was one involving α-hydroxyglycine as an intermediate and details are given in Scheme 75. Initially, glyoxylic acid was reacted with aqueous ammonium acetate at room temperature to form α-

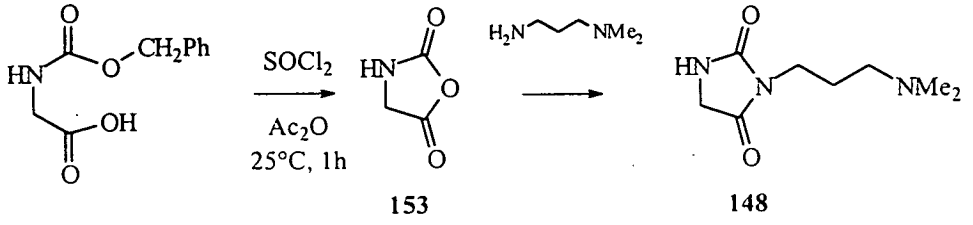
150[109] in 86% yield, which was added to phosgene in toluene and heated under reflux to form 4-hydroxyoxazolidinedione **151**.



Scheme 75

After evaporating off the solvent and excess phosgene, this air-sensitive compound was identified as an anhydride by its IR spectrum and, without further purification, was then reacted with 3-*(N,N*-dimethylamino)propylamine in methanol solution at room temperature. Unfortunately, the desired 4-hydroxyhydantoin **152** was not formed and only an intractable mixture of polymeric residues was isolated. This outcome is unlike the reaction between maleic anhydride and 3-*(N,N*-dimethylamino)propylamine[110], which gives the product without many unwanted side reactions. With this information in hand, the failure of this route is unexpected, and consequently a similar approach to the previous method of hydantoin formation

was adopted, *i.e.* to synthesise the hydantoin without an hydroxy functional group as shown in Scheme 76.

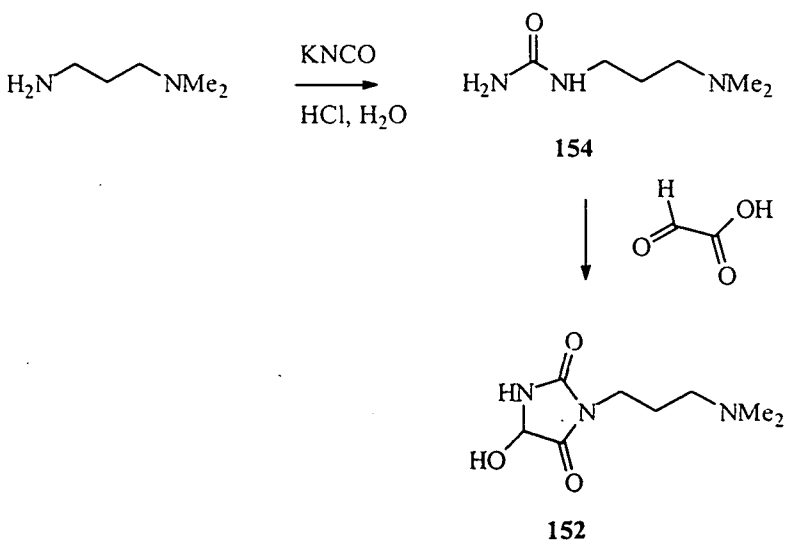


Scheme 76

The method involved a preparation of the unsubstituted anhydride **153** from *N*-carbobenzyloxyglycine by treatment with thionyl chloride in acetic anhydride solution at room temperature followed by brief heating to bring about cyclisation[111]. The anhydride prepared in this way was identified by its melting point and, after isolation, was reacted with 3-*(N,N*-dimethylamino)propylamine in anhydrous ether at room temperature for 16 hours. During reaction, a precipitate formed and, from spectroscopic studies, was identified only as a polymeric residue with no evidence being found to show formation of the desired product **148**. This demonstrates that the route is unlikely to be useful for hydantoin synthesis.

A final avenue to be explored in this area involved the synthetic route outlined in Scheme 77 whereby initial preparation of the corresponding urea **154** of 3-*(N,N*-dimethylamino)propylamine was followed by functionalisation and concomitant

condensation/ cyclisation with glyoxylic acid by Ben Ishai *et al.*[112] to form the 4-hydroxyhydantoin **152**. This synthetic route has previously been used to prepare non-basic functionalised 4-methoxyhydantoins, and in the present context, was thought to be a promising synthetic pathway.



Scheme 77

The urea **154** was obtained in only 25% yield largely due to the need of a distillation purification step. After addition of the urea to a solution of glyoxylic acid in ethanol, the solution was stirred at room temperature for three days, but unfortunately upon work-up, no discernible product was isolated, again polymeric residues being formed instead of the target hydroxyhydantoin **152**.

The same route was looked at again to investigate whether the synthesis could be applied successfully to different amines. The amine chosen was 2-(*N,N*-diethylamino)ethylamine, the urea of which can be prepared in a much higher yield of 97%[113]. Unfortunately, the final step with glyoxylic acid also led to no discernible products being recovered.

In summary, all of the synthetic routes examined for the preparation of dehydrohydantoins have failed to produce any discrete product. Despite this failure, one of the routes proved to be suitable for the preparation of non-alkoxy hydantoins, and consequently offers the possibility in the future of providing an alternative strategy for functionalising the hydantoin ring, rather than attempting to prepare the activated ring directly.

3. Conclusion and Future Work

A general route to previously unknown base-functionalised mono-urazoles has been developed and successfully implemented with several amine precursors, but less success is achieved in the attempted synthesis of bis-urazoles in a similar manner. Oxidation of some of the mono-urazoles has resulted in the formation of unstable intermediates, which are found to be generally too reactive and condense with themselves rather than serve as effective enophiles and dienophiles.

The use of imine enophiles in amidoalkylation has been augmented by the generation of 1,2-diethoxycarbonylaldimine by the action of a Lewis acid in the presence of an alkene. The recovery of a lactone by hydrolysis in the work-up is an unexpected product from amidoalkylation, whilst the formation of a [2+2]-cycloadduct is previously unknown in this type of reaction. The isolation of such products, coupled with the regiospecificity of the reaction, points to a step-wise mechanism involving an ionic intermediate that can cyclise in two different ways to afford either product.

In short, there is considerable room for future work in both the azo and imine areas of this thesis. Further knowledge of azo enophiles could be gained from a study of their concomitant dienophilic character in more detail, specifically if trapping agents other than anthracene were employed. By studying the imine area in greater detail, particularly the effect of changing the imine precursor, as well as using different

alkene substrates and catalysts, it is hoped to gain a better understanding of the mechanism of the reaction and its synthetic potential.

An investigation into several different potential synthetic pathways to the cyclic acylimines disappointingly failed to produce the required alcoholic precursors, and future work will require a different approach to the preparation of base-functionalised alkoxyhydantoins. Their successful synthesis is not likely to involve ring-formation at a later stage and an investigation into direct functionalisation of the hydantoin ring system would seem to be the logical way forward.

Experimental

1. Instrumentation and General Techniques

1.1 Glossary of terms, symbols and abbreviations

Ar	aromatic
EI	electron impact
Et	ethyl group
FAB	fast atom bombardment
FT IR	fourier transform infra-red spectroscopy
FVP	flash vacuum pyrolysis
J	coupling constant
Lit.	literature value
M	moles per litre
M^+	molecular ion
Me	methyl group
MP	melting point
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl group

TLC	thin Layer Chromatography
THF	tetrahydrofuran
b	broad singlet
cm	complex multiplet
d	doublet
δ	chemical shift in parts per million
dec	decomposed upon melting.
dt	doublet of triplets
eq	equivalents
mmol	millimoles
q	quartet
p	pentet
ppm	parts per million
s	singlet
t	triplet
tt	triplet of triplets
mm Hg	pressure in millimetres of mercury
ν_{max}	wavenumber of maximum absorbance

1.2 Instrumentation

1.2.1 NMR spectroscopy

Routine ^{1}H NMR spectra were obtained using a Jeol PMX-60 spectrometer operating at 60MHz. Higher field spectra were obtained on a Bruker WP-200 SW spectrometer at 200.13MHz for ^{1}H and at 50.32MHz for ^{13}C, operated by Mr. W. Kerr, on a Bruker AC-250 spectrometer operating at 250.13MHz for ^{1}H and at 62.90MHz for ^{13}C operated by Mr. J. R. A. Millar or on a self operated Varian Gemini 2000 spectrometer operating at 199.97MHz for ^{1}H and at 50.28MHz for ^{13}C

Chemical shifts are reported in parts per million using tetramethylsilane ($\delta = 0.00$) as a reference.

1.2.2 Infrared spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer. Liquid samples were run as thin films and solid samples as nujol mulls or dichloromethane solution thin films, both on sodium chloride plates. Air sensitive liquids and solutions *e.g.* isocycanates and volatile liquids *e.g.* phosgene were recorded using a sodium chloride solution-cell with a 25μm. Teflon spacer.

1.2.3 Mass spectroscopy

FAB and accurate mass measurements (results given as protonated molecular ion, MH^+) were obtained on a Kratos MS-50 TC spectrometer, operated by Mr. A. Taylor. EI measurements were obtained on a Kratos MS902 spectrometer or on a Finnegan 4500 spectrometer operated by Miss E. Stevenson.

1.2.4 Melting points

Melting Points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected.

1.3 General practices

1.3.1 Flash column chromatography

Wet flash chromatography was routinely carried out using Merck silica gel 60 (mesh size 0.040-0.063mm) as solid support with a pressure of 10psi. of compressed air to aid elution of solvent.

1.3.2 Thin layer chromatography

Analytical TLC was carried out on Merck 5554 aluminium backed plates coated with a 0.2mm layer of Kieselgel GF_{254} silica. Detection was achieved by ultra violet radiation at 254nm, iodine vapour and dipping into either 5% sulfuric acid/ ethanol mixture or 1M acidified $KMnO_4$ solution followed by gentle heating.

1.3.3 Purification and drying of solvents

Dichloromethane, toluene, acetonitrile, methanol, isopropanol and dimethylformamide were all dried by distillation from finely divided calcium hydride under an argon atmosphere. Diethyl ether and tetrahydrofuran were dried by distillation from sodium and benzophenone under an argon atmosphere. Ethanol was dried by distillation from magnesium and ethyl bromide to give 'super dry' ethanol. Chloroform was dried with anhydrous $CaCl_2$ followed by filtration and acetone was dried with anhydrous $CaCO_3$ followed by filtration and distillation. All solvents were purified as they were required and used immediately.

1.3.4 Drying of glassware and inert gases

For moisture and air sensitive reactions, reaction flasks were dried thoroughly by heating with a strong Bunsen flame while flushing with a strong flow of argon.

Argon gas used for reactions and purging was dried through sulphuric acid, calcium chloride and self indicating silica gel dreschel bottles.

1.3.5 Preparation of oxidising gases

Chlorine gas was prepared as required by strong heating of cuprous chloride in a stream of argon gas. The gas was dried by passing through a trap kept at -78°C by a dry ice/acetone bath before use. Nitrogen dioxide was prepared by strong heating of lead nitrate. The gas formed was passed through a column of phosphorus pentoxide before collection in a flask cooled in a dry ice/acetone bath. The gas was used by warming the flask to room temperature and passing argon through the flask and out through a second column of phosphorus pentoxide then through a sintered gas bubbler into the reaction mixture.

1.3.6 Flash vacuum pyrolysis (FVP)

Flash Vacuum Pyrolysis is the process where the precursor to the desired product is sublimed through a quartz tube placed in a furnace heated to temperatures of typically around 600°C and then collected in a trap cooled by liquid nitrogen. The whole system is kept under high vacuum by means of a rotary oil pump. Any catalyst required is placed in the quartz tube and held with quartz wool.

2. Azo Enophiles

2.1 Attempted preparation of urazoles

2.1.1 Ethyl chlorocarbamoylcarbazate 63

Ethyl carbazate (2.05g, 19.7 mmol) was dissolved in dry diethyl ether (40ml) under argon and added dropwise with stirring to an ice cooled solution of phosgene in toluene (50ml, 1.93M, 97mmol) over 5 minutes. The mixture was allowed to warm to room temperature, stirred for 1 hour and then evaporated to dryness to give 3.18g (97%) of white solid **M.P.** 77.6-79.4°C (Lit.. 78-80°C)[84]

2.1.2 4-(3'-(*N,N*-dimethylamino)propyl)-1-carbethoxy semicarbazide 64

Ethyl chlorocarbamoylcarbazate **63** (3.15g, 19mmol) was partially dissolved in dry dichloromethane (25ml) under argon and cooled in an ice bath. After 10 minutes, 3-(*N,N*-dimethylamino)propylamine (2.4ml, 1.87g, 19.3 mmol) was added dropwise over 15 minutes by syringe pump. After 2 hours, the mix was evaporated to dryness to give 5.00g (100%). of the hydrochloride **64** as a yellow gum. A sample of the free base was prepared by reaction of the hydrochloride (1.10g, 4.1mmol) with saturated aqueous sodium bicarbonate (50ml) followed by continuous extraction for 24 hours

with dichloromethane (500ml) to give a brown oil (0.62g., 2.6 mmol, 64%). **^{1}H NMR** (250.13 MHz, $CDCl_3$) δ 10.51 (s, 1H, NH), 7.06 (s, 2H, NH), 4.05 (q, 2H, ^{3}J=7.1Hz, $CH_3C\underline{H}_2O$), 3.72 (t, 2H, ^{3}J=5.8Hz, $C\underline{H}_2NMe_2$), 3.22 (t, 2H, ^{3}J=6.0Hz, $C\underline{H}_2NH$), 2.86 (s, 6H, $N(CH_3)_2$), 1.88 (tt, 2H, ^{3}J=6.0, 5.8Hz, $CH_2C\underline{H}_2CH_2$), 1.13 (t, 3H, ^{3}J=7.1Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (62.896 Hz, $CDCl_3$) δ 156.4(C=O), 154.3 (C=O), 61.3 (CH_2), 48.1 (CH_2), 41.8 (CH_2), 35.5 ($2CH_3$) 21.1 (CH_2) 14.0 (CH_3); **FT IR** ν_{max}/cm^{-1}: 3273 (NH), 1740 (C=O), 1689 (C=O); **Accurate Mass** found 233.16158, (MH^+) $C_9H_{20}N_4O_3$ requires 233.16137.

2.1.3 Attempted cyclisations of 4-(3'-(*N,N*-dimethylamino)propyl)-1-carbethoxysemicarbazide 64

Semicarbazide hydrochloride **64** (1.89g, 7mmol) was dissolved in aqueous KOH (4M, 10ml, 40mmol) and boiled under reflux for 8 hours. After cooling to room temperature and neutralisation, extraction of the solution with dichloromethane (2x50ml) gave no product so the solution was evaporated to dryness and freeze dried for 15 hours at 2mm Hg. The residue was triturated with ethanol and examined by ^{1}H NMR spectroscopy and found to contain a crude mix with evidence for some cyclised product. TLC examination of the product with ethanol buffered with 10% triethylamine showed only one spot on the baseline so chromatographic separation was not attempted.

In three separate experiments, semicarbazide hydrochloride **64** (3.34g, 12mmol) was heated neat at 140°C, 160°C and 200°C for 6 hours. Examination of the residue after cooling by ^{1}H NMR spectroscopy showed only a crude mixture of products. Again TLC examination of these residues showed that separation by chromatography was not feasible.

The free base, semicarbazide **64**, (0.46g, 2mmol) was heated neat to 160°C for 6 hours then cooled and examined by ^{1}H NMR spectroscopy. Similar results to the previous experiment were observed and separation of the mixture was not attempted.

2.1.4 Attempted preparation of 4-(3'-(*N,N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione 54 from diethoxycarbonylhydrazine 65

Dicarbethoxycarbonylhydrazine **65** (1.63g, 10mmol) was dissolved in 3-(*N,N*-dimethylamino)propylamine (50ml, 40.6g, 400mmol) and the solution was boiled under reflux for 24 hours. The reaction was monitored by loss of the carbonyl absorption at 1722 cm^{-1} in the FT IR spectrum of the crude solution. After this had completed, the excess 3-(*N,N*-dimethylamino)propylamine was removed *in vacuo* to give 3.96g of orange gum. Analysis of this residue by ^{13}C NMR spectroscopy indicated that carbonyl functionality had been lost completely and only side products had formed. The experiment was repeated with 5A molecular sieves in order to aid removal of the ethanol but with similar results.

2.1.5 Ethyl *N*-(3-(*N,N*-dimethylamino)propyl)carbamate 68

3-(*N,N*-Dimethylamino)propylamine (1.25ml, 1.02g, 10mmol) was dissolved in dry toluene (50ml) under argon and stirred at room temperature while triethylamine (1.6ml, 2.20g, 22mmol) was added followed by ethyl chloroformate (1.4ml, 1.6g, 14.6mmol, 1.5 eq) dropwise over 5 minutes. The mixture was stirred for 18 hours then filtered. The filtrate was evaporated *in vacuo* to give the product as a clear liquid (1.51g, 87%). **^{1}H NMR** (250.132MHz, $CDCl_3$) δ 5.79 (b, 1H, NH), 3.91 (q, 2H, ^{3}J=7.1Hz), $CH_3C\underline{H}_2O_2C$), 3.03 (q, 2H, ^{3}J=6.3Hz, $NHC\underline{H}_2CH_2$), 2.15 (t, 2H, ^{3}J=6.9Hz, $CH_2C\underline{H}_2N(CH_3)_2$), 2.03 (s, 6H, $N(CH_3)_2$), 1.47 (p, 2H, ^{3}J=6.9Hz, $CH_2C\underline{H}_2CH_2$), 1.05 (t, 3H, ^{3}J=7.1Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (62.896MHz, $CDCl_3$), δ 156.4 (C=O), 59.91 (CH_2), 57.39 (CH_2), 44.96 (2(CH_3)), 39.52 (CH_2) 26.88 (CH_2), 14.24 (CH_3); **FT IR** ν_{max}/cm^{-1} 3331 (NH), 1699 (C=O); **M.S.** 175 (MH^+, 66%), 130 (43%), 102 (49%), 84 (50%), 72 (46), 58 (76), 45 (77), 29 (100%)[114]

2.1.6 Diethyl 3-(*N,N*-dimethylamino)propylamine-1,1-dicarboxylate 66

Ethyl *N*-(3-(*N,N*-dimethylamino)propyl)carbamate **68** (0.85g, 4.89mmol) was dissolved in dry THF under argon and cooled in an ice bath for 15 minutes. n-Butyl lithium in hexane solution (1.6M, 3.3ml, 5.28mmol, 1.1eq) was added slowly and the mixture was cooled in a dry ice/ acetone bath at -78°C for 1 hour. Ethyl chloroformate (0.48ml, 0.54g, 5mmol) was added with stirring and the mixture was allowed to warm slowly to room temperature and stirred for 16 hours. The mixture

was then quenched with water (25ml) and stirred for 30 minutes. The THF was removed by rotary evaporator and the residues extracted with dichloromethane (3x25ml), washed (H_2O, 25ml), dried over $MgSO_4$ and concentrated to give the product as a pale yellow oil (1.03g, 84%). **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 4.10 (q, 4H, ^{3}J=7.1Hz, $CH_3C\underline{H}_2$), 3.56 (t, 2H, ^{3}J=7.6Hz, $CH_2N(CO)_2$), 2.13 (t, 2H, ^{3}J=7.3 Hz, $C\underline{H}_2NMe_2$), 2.05 (s, 6H, $N(C\underline{H}_3)_2$), 1.64 (p, 2H, ^{3}J=7.4Hz, $CH_2C\underline{H}_2CH_2$), 1.17 (t, 6H, ^{3}J=7.1Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 153.2 (2(C=O)), 62.38 ($2(CH_2)$), 56.44 (CH_2), 44.88 ($2(CH_3)$), 44.45 (CH_2), 26.47 (CH_2), 13.67 ($2(CH_3)$); **FT IR** ν_{max}/cm^{-1} 1750, 1700 (C=O); **Accurate Mass** found 247.16459 (MH^+), $C_{11}H_{23}N_2O_4$ requires 247.16578

2.1.7 Attempted preparation of 4-(3'-(*N,N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione 54 from dicarboxylate ester 66

Diethyl 3-(*N,N*-dimethylamino)propylamine-1,1-dicarboxylate **66** (0.738g, 3.0mmol) was dissolved in super dry ethanol (50ml). Anhydrous hydrazine (100μl, 98mg, 3mmol) was added by microsyringe and the mixture was boiled under reflux. The reaction was monitored during this heating by FT IR spectroscopy which indicated a loss of absorbance in the carbonyl region of the spectra. After 6 hours, the reaction was judged to be complete and the mixture was evaporated to dryness. ^{1}H and ^{13}C NMR spectroscopy indicated that there was no clear product and only a polymeric mixture was present.

2.1.8 Ethyl *N*-(3-chloropropyl)carbamate

3-Chloropropylamine hydrochloride (1.30g, 10mmol) was added to dry diethyl ether (50ml) under argon and stirred in an ice bath. Triethylamine (4.5ml, 3.26g, 32mmol) in diethyl ether (10ml) was added and the mixture was stirred for 5 minutes. Ethyl chloroformate (1.4ml, 1.6g, 14.6mmol, 1.5 eq) in diethyl ether (10ml) was added dropwise over 5 minutes. The mixture was stirred for 1 hour then filtered. The filtrate was evaporated *in vacuo* to give the product as a clear liquid (1.51g, 87%). **^{1}H NMR** (250.133MHz, $CDCl_3$), δ 5.58 (b, 1H, NH), 3.92 (q, 2H, ^{3}J=7.1Hz $CH_3C\underline{H}_2$), 3.40 (t, 2H, ^{3}J=6.4Hz, CH_2Cl), 3.11 (q, 2H, ^{3}J=6.4Hz, $NHC\underline{H}_2$), 1.78 (p, 2H, ^{3}J=6.5Hz, $CH_2C\underline{H}_2CH_2$), 1.02 (t, 3H, ^{3}J=7.0Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (62.986MHz, $CDCl_3$), δ 156.5 (C=O), 60.03 (CH_2), 41.75 (CH_2), 37.57 (CH_2), 32.05 (CH_2), 13.99 (CH_3); **FT IR** ν_{max}/cm^{-1} 3333 (NH), 1699 (C=O); **Accurate Mass** found 166.06335 (MH^+, ^{35}Cl), 168.06144 (MH^+, ^{37}Cl), $C_6H_{13}ClNO_4$ requires 166.06348 and 168.06053 respectively.

2.1.9 Diethyl 3-chloropropylamine-1,1-dicarboxylate 72

Ethyl *N*-(3-chloropropyl)carbamate (1.024g, 6.2mmol) was dissolved in dry THF under argon and cooled in an ice bath for 15 minutes. *n*-Butyl lithium in hexane solution (1.6M, 4.4ml, 7.07mmol, 1.1eq) was added and the mixture was cooled in a dry ice/ acetone bath at -78°C for 1 hour. Ethyl chloroformate (0.68ml, 0.67g, 6.3mmol) was added with stirring and the mixture was allowed to warm slowly to

room temperature and stirred for 3 hours. The mixture was then quenched with water (25ml) and stirred for 30 minutes: The THF was removed by rotary evaporator and the remaining aqueous solution extracted with dichloromethane (3x25ml), washed (H_2O, 2x25ml), dried over $MgSO_4$ and concentrated to give the product as a pale yellow oil (1.36g, 92%). **^{1}H NMR** (250.133MHz, $CDCl_3$) δ 4.03 (q, 4H, ^{3}J=7.1Hz, $(CH_3C\underline{H}_2O_2C)_2N$), 3.61 (t, 2H, ^{3}J=6.9Hz, CH_2Cl), 3.33 (t, 2H, ^{3}J=6.5Hz, NCH_2), 1.84 (p, 2H, ^{3}J=6.9Hz, $CH_2C\underline{H}_2CH_2$), 1.10 (t, 6H, ^{3}J=7.1Hz, $(C\underline{H}_3CH_2O_2C)_2N$); **^{13}C NMR** (62.896MHz, $CDCl_3$) δ 152.7 (C=O), 62.28 (2(CH_2)), 43.47 (CH_2), 41.49 (CH_2), 31.21 (CH_2), 13.43 (2(CH_3)); **FT IR** ν_{max}/cm^{-1} 1753 (C=O), 1699 (C=O); **Accurate Mass** found 238.08446 (MH^+, ^{35}Cl), 240.08299 (MH^+, ^{37}Cl), $C_9H_{17}ClNO_4$ requires 238.08461 and 240.08166 respectively.

2.1.10 Attempted preparation of 4-(3'-chloropropyl)-1,2,4-triazolidine-3,5-dione 71 from dicarboxylate ester 72

Diethyl 3-chloropropylamine-1,1-dicarboxylate **72** (0.710g, 3.0mmol) was dissolved in super dry ethanol (50ml). Anhydrous hydrazine (98μl, 96mg, 3mmol) was added and the mixture was boiled under reflux for 6 hours. Thin layer chromatography indicated that all starting material had been consumed and only baseline material was apparent. After this time, the mixture was evaporated to dryness and subjected to NMR and FT IR analysis. No evidence of starting material or desired urazole was detected and only polymeric residues were obtained.

2.1.11 4-(3'-Chloropropyl)-1-ethoxycarbonyl semicarbazide 73

3-Chloropropylamine hydrochloride (2.61g, 20mmol) was added to 150ml of dried toluene. The mixture was boiled under reflux for 3 hours, during which phosgene in toluene solution (1.93M, 30ml, 54mmol, 2.7eq) was added by syringe pump over 2.5 hours. After cooling to room temperature, the mixture was purged with argon for 90 minutes. Solution phase IR indicated only 3-chloropropylisocyanate **74** (ν_{max}/cm^{-1} = 2263), and no phosgene left (ν_{max}/cm^{-1} =1747). A solution of ethyl carbazate (2.08g, 20mmol) in dichloromethane (20ml) was added to the solution and stirred for 30 minutes. The solution was then washed with water (100ml), the aqueous layer extracted with dichloromethane (3x100ml) and the combined organics dried over $MgSO_4$ and evaporated to dryness under vacuum to give 1.75g (40%) of product as a white solid **M.P.** 102.2-102.7°C; **^{1}H NMR** (250.134MHz, $(CD_3)_2CO$) δ 4.09 (q, 2H, ^{3}J=7.1Hz, $CH_3\underline{CH_2}O_2C$), 3.64 (t, 2H, ^{3}J=6.7Hz, $ClC\underline{H_2}CH_2$), 3.30 (t, 2H, ^{3}J=6.6Hz, $C\underline{H_2}NH$), 1.95 (p.2H, ^{3}J=6.8Hz, $CH_2C\underline{H_2}CH_2$), 1.21 (t, 3H, ^{3}J=7.1Hz, $C\underline{H_3}CH_2$); **^{13}C NMR** (62.896MHz, $(CD_3)_2CO$) 158.0 (C=O), 156.2 (C=O), 60.05 (CH_2), 41.60 (CH_2), 35.95 (CH_2), 32.23 (CH_2), 13.06 (CH_3); **FT IR** ν_{max}/cm^{-1} 3313 (NH), 3266 (NH), 3167 (NH), 1712 (C=O), 1644 (C=O); **Accurate Mass** found 224.08066 (MH^+, ^{35}Cl), 226.06456 (MH^+, ^{37}Cl), $C_7H_{15}ClN_3O_3$ requires 224.08019 and 226.07724.

2.1.12 Cyclisation of 4-(3'-chloropropyl)-1-ethoxycarbonyl semicarbazide 73

4-(3'-Chloropropyl)ethoxycarbonyl semicarbazide **73** (1.113g, 5mmol) was dissolved in aqueous potassium hydroxide solution (4M, 2.5ml, 10mmol). The solution was heated by a water bath at 70°C for 2 hours. The mixture was acidified to pH.1 with concentrated HCl (0.5ml) then extracted with dichloromethane (3x40ml) which was dried over $MgSO_4$, filtered and evaporated to give 0.37g of white hygroscopic solid. Purification of this by column chromatography using ethyl acetate as eluent gave a clear gum (98mg,11%) which was identified as the cyclised product, 4-(3'-chloropropyl)-1,2,4-triazolidine-3,5-dione **71**; **^{1}H NMR** (200.13MHz, $(CD_3)_2CO$) δ 9.5-8.0 (b,2H,HNNH), 3.67 (t, 2H, ^{3}J=6.7Hz, $C\underline{H}_2Cl$), 3.63 (t, 2H, ^{3}J=6.8Hz, $C\underline{H}_2N$), 2.12 (p, 2H, ^{3}J=6.7Hz, $CH_2C\underline{H}_2CH_2$); **^{13}C NMR** (50.32 MHz, $(CD_3)_2CO$) δ 155.1 (C=O), 41.25 (CH_2), 35.30 (CH_2), 30.15 (CH_2); **FT IR** ν_{max}/cm^{-1} 3166 (NH), 1663 (C=O); **Accurate Mass** found 178.04994 (MH^+, ^{35}Cl), 180.03521 (MH^+, ^{37}Cl), $C_5H_8ClN_3O_3$ requires 178.03833 and 180.03538 respectively. Also isolated was the hydroxy substituted semicarbazide, 4-(3'-Hydroxypropyl)-1-ethoxycarbonylsemicarbazide **75** as a white solid (51mg, 0.25mmol, 5%). **^{1}H NMR** (250.134MHz, $CDCl_3$) δ 10.1-8.6 (b, 2H, NHNH), 7.81 (s, 1H), 5.97 (s, 1H) 4.12 (q, 2H, ^{3}J=7.1Hz, $CH_3C\underline{H}_2O_2C$), 3.61-3.47 (cm, 2H, $C\underline{H}_2OH$), 3.37-3.21 (cm, 2H, $C\underline{H}_2NH$), 1.97 (p.2H, ^{3}J=6.8Hz, $CH_2C\underline{H}_2CH_2$), 1.21 (t, 3H, ^{3}J=7.1Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (50.32 MHz, $CDCl_3$) 156.9 (C=O), 156.7 (C=O), 61.47 (CH_2), 49.48 (CH_2), 39.83 (CH_2), 22.16 (CH_2), 13.06 (CH_3); **FT IR** ν_{max}/cm^{-1} 3313 (NH), 3266 (NH),1742 (C=O), 1676 (C=O); **Accurate Mass** found 206.11433 (MH^+), $C_7H_{15}N_3O_4$ requires 206.11408.

2.2 Preparation of *N,N*-dimethylamino functionalised urazoles

2.2.1 Hydrazodicarbonamide 56

Semicarbazide hydrochloride (22.35g, 200mmol) and sodium bromide (5.45g, 50mmol, 0.25eq) were dissolved in water (100ml) and cooled for 1 hour in an ice bath. Sodium hydroxide (7.99g, 200mmol) was dissolved in water (50ml) and added to aqueous sodium hypochlorite solution (140ml, 2.15M, 300mmol, 1.5eq). This solution was cooled for 1 hour before being added dropwise to the semicarbazide solution in an ice bath with rapid stirring. After addition was complete, the mixture was filtered. The solid collected was washed with water (50ml), and recrystallised from boiling water (1100ml) to give the product as a white crystalline solid (6.85g, 58%), **M.P.** 257.2-257.6°C (Lit. 256°C)[86].

2.2.2 4-(3'-(*N,N*-Dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione 54

Hydrazodicarbonamide **56** (13.13g, 111mmol) was added to a solution of 3-(*N,N*-dimethylamino)propylamine **44** (14.2ml, 11.54g, 113mmol) in dry *N*-methylpyrrolidinone (21ml). The mixture was then heated with stirring to an internal temperature of 160°C with a carbon bath. As the reaction progressed, production of ammonia was monitored by passing argon over the solution into aqueous hydrochloric acid (1.0M). After 4 hours at 160-170°C, the temperature was raised to

190°C. After a further 2 hours at 190°C, the production of ammonia had ceased (total 218mmol, 99%) and the mixture was allowed to cool overnight. The precipitate formed was filtered off and washed with ethanol (2x20ml) and diethyl ether (20ml) before being dried for 18 hours at 100°C, 1mm Hg to give 13.45g (66%) of product as an off-white solid. **M.P.** 183.1-183.7°C; **^{1}H NMR** (250.133MHz, D_2O) δ 3.41 (t, 2H, ^{3}J=6.7Hz, $CH_2N(CO)_2$), 2.98 (t, 2H, ^{3}J=7.2Hz, CH_2NMe_2), 2.71 (s, 6H, $N(CH_3)_2$), 1.89 (p, 2H, ^{3}J=7.2Hz, $CH_2C\underline{H}_2CH_2$);**^{13}C NMR** (62.896MHz, D_2O) δ 156.1 (C=O), 54.73 (CH_2) 42.51 ($2CH_3$), 35.20 (CH_2) 23.63 (CH_2); **FT IR** ν_{max}/cm^{-1} 3162 (NH), 1692 (C=O); **Accurate Mass** 187.11936 (MH^+), $C_7H_{15}N_4O_2$ requires 187.11950.

2.2.3 4-(2'-(*N,N*-Dimethylamino)ethyl)-1,2,4-triazolidine-3,5-dione 78

Hydrazodicarbonamide (2.36g, 20mmol) was added to a solution of 2-(*N,N*-dimethylamino)-ethylamine (2.20ml, 1.76g, 20mmol) in *N*-methylpyrrolidinone (6ml). The mixture was heated at 150°C for 2 hours and then heated to 180°C for a further 5 hours. Ammonia produced by the reaction was monitored by litmus testing of argon passed over the mixture and showed complete reaction after this time. The yellow solution formed was then allowed to cool and stirred overnight. The solvent was then removed by Kügelrohr bulb to bulb distillation at 120°C, 1mm Hg and the residue was triturated with ethanol (30ml). The initial solid formed was filtered off to give a white hygroscopic solid (100mg) which was discarded. The filtrate was then left for 3 days at room temperature, during which time a precipitate developed.

This was filtered to give the product as a white crystalline solid (1.54g, 45%). **M.P.** 154.2-156.3°C; **^{1}H NMR** (250.134MHz, $(CD_3)_2SO$) δ 8.97 (b, 2H, NHNH), 3.41 (t, 2H, ^{3}J=6.4Hz, $C\underline{H}_2N(CO)_2$), 2.42 (t, 2H, ^{3}J=6.4Hz, CH_2NMe_2), 2.14 (s, 6H, $N(CH_3)_2$); **^{13}C NMR** (62.896MHz, $(CD_3)_2SO$); δ 155.3 (C=O), 56.14 (CH_2) 45.11 ($2CH_3$) 36.14 (CH_2); **FT IR** ν_{max}/cm^{-1} 3200 (NH), 1698 (C=O); **Accurate Mass** 173.10342 (MH^+) $C_6H_{13}N_4O_2$ requires 173.10385.

2.2.4 4-(2'-(*N,N*-Diethylamino)ethyl)-1,2,4-triazolidine-3,5-dione 79

Hydrazodicarbonamide (2.11g, 18mmol) was added to a solution of 2-(*N,N*-dimethylamino)-ethylamine (2.5ml, 2.07g, 18mmol) in *N*-methylpyrrolidinone (6ml). The mixture was heated to 185°C by carbon bath during which ammonia production was monitored by litmus paper. After ammonia production had ceased (4.5 hours) the mix was then allowed to cool and left overnight. The resulting liquid was evaporated to dryness under vacuum in a Kügelrohr oven at 120°C and triturated with ethanol to give the product as a white crystalline solid (2.15g, 60%): **M.P.** 143.1-144.7°C; **^{1}H NMR** (250.134MHz, $(CD_3)_2SO$) δ 3.40 (t, 2H, ^{3}J=6.6Hz, $C\underline{H}_2N(CO)_2$), 2.56 (t, 2H, ^{3}J=6.6Hz, CH_2NEt_2), 2.46 (q, 4H, ^{3}J=7.2Hz, $(CH_3C\underline{H}_2)_2N$), 0.91 (t, 6H, $(C\underline{H}_3CH_2)_2N$); **^{13}C NMR** (62.896MHz, $(CD_3)_2SO$) δ 155.4 (C=O), 48.66 (CH_2) 46.65 ($2CH_2$) 36.28 (CH_2), 11.90 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} 3198 (NH), 1703 (C=O); **Accurate Mass** 201.13472 (MH^+) $C_8H_{17}N_4O_2$ requires 201.13515.

2.2.5 4-(3'-(*N,N*-Diethylamino)propyl)-1,2,4-triazolidine-3,5-dione 80

Hydrazodicarbonamide (2.359g, 20mmol) was added to a solution of 3-(*N,N*-diethylamino)propylamine (3.15ml, 2.65g, 20mmol) in dry *N*-methylpyrrolidinone (5ml). The mixture was heated to 185°C by carbon bath during which ammonia production was monitored by litmus paper. After the production of ammonia had ceased (9 hours) the mixture was allowed to cool overnight. The resulting liquid was triturated with ethanol (50ml) and the resulting solid was filtered off, washed (2x5ml EtOH) and dried under vacuum to give the product as a colourless solid (2.633g, 66%). **M.P.** 160.8-162.1°C; **^{1}H NMR** (250.133MHz, D_2O) δ 3.50 (t, 2H, ^{3}J=6.5Hz, $CH_2N(CO)_2$), 3.13 (q, 4H, ^{3}J=7.3Hz, $(CH_3C\underline{H}_2)_2N$) 3.06 (t, 2H, ^{3}J=5.6Hz, $C\underline{H}_2NEt_2$), 1.96 (p, 2H, ^{3}J=6.2Hz, $CH_2C\underline{H}_2CH_2$) 1.18 (t, 6H, $(C\underline{H}_3CH_2)_2N$); **^{13}C NMR** (62.896MHz, D_2O) δ 156.1 (C=O), 48.61 (CH_2) 47.04 ($2CH_2$), 35.45 (CH_2), 22.87 (CH_2) 8.02 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} (NH), 1693 (C=O); **Accurate Mass** 215.15199, (MH^+) $C_9H_{19}N_4O_2$ requires 215.15080

2.2.6 4-(2'-Piperazinoethyl)-1,2,4-triazolidine-3,5-dione 81

Hydrazodicarbonamide (2.356g, 20mmol) was added to a solution of *N*-(2'-aminoethyl)piperazine (2.6ml, 2.58g, 20mmol) in *N*-methylpyrrolidinone (5ml). The mixture was heated to 185°C by carbon bath during which ammonia production was monitored by litmus paper. After ammonia production had ceased (8 hours) the mix was then allowed to cool and left overnight. The resulting liquid was triturated with

ethanol (100ml) and washed with ethanol to give the product as a white crystalline solid (1.762g, 42%): **M.P.** 251.2-253.3 °C (dec); **^{1}H NMR** (250.133MHz, D_2O) δ 3.52 (t, 2H, ^{3}J=6.7Hz, $C\underline{H}_2N(CO)_2$), 3.14 (t, 4H, ^{3}J=5.1Hz, $(C\underline{H}_2)_2N$), 2.73 (t, 4H, ^{3}J=5.1Hz, $(C\underline{H}_2)_2N$), 2.62 (t, 2H, $(CH_2)_2NC\underline{H}_2$); **^{13}C NMR** (62.896MHz, D_2O); δ 156.2 (C=O), 54.65 (CH_2) 48.82 ($2CH_2$), 42.91 ($2CH_2$), 35.26 (CH_2); **FT IR** ν_{max}/cm^{-1} 1691 (C=O); **Accurate Mass** 214.13030 (MH^+) $C_8H_{16}N_5O_2$ requires 214.13040

2.2.7 4-(4'-(*N,N*-Dimethylamino)phenyl)-1,2,4-triazolidine-3,5-dione 82

N,N-Dimethyl-*p*-phenylenediamine was purified by distillation from calcium hydride prior to use. Hydrazodicarbonamide (2.38g, 20mmol) was added to a solution of *N,N*-dimethyl-*p*-phenylenediamine (2.715g, 20mmol) in *N*-methylpyrrolidinone (10ml). The mixture was heated to 190°C by carbon bath during which ammonia production was monitored by litmus paper. After ammonia production had ceased (5 hours) the mix was then allowed to cool and left overnight. The solid formed in the flask was extracted by trituration with ethanol. This gave 2.71g of a 7:1 mixture of the desired product (52%) and *N,N'*-bis-(4-(*N,N*-dimethylamino)phenyl)-urea **85** (7%): **^{1}H NMR** (250.134MHz, $(CD_3)_2SO$) δ 8.14 (s, 2H, NHCONH), 7.25 (d, 4H, ^{3}J=9.0Hz, Ar), 6.68 (d, 4H, ^{3}J=9.0Hz, Ar), 2.81 (s, 12H, $2N(CH_3)_2$); **^{13}C NMR** (62.896MHz, $(CD_3)_2SO$) δ 153.3 (C=O), 146.3 (2C), 130.1 (2C), 120.4 (4CH), 113.4 (4CH), 40.90 ($4CH_3$); This compound could however be removed by recrystallisation from ethanol to give the pure product (1.37g, 32% overall). **M.P.** 229.1-230.0°C; **^{1}H NMR** (250.133MHz, $(CD_3)_2SO$) δ 10.27 (s, 2H, NHNH), 7.16 (d,

2H, ^{3}J=8.9 Hz, Ar), 6.75 (d, 2H, ^{3}J=9.0Hz, Ar), 2.91 (s, 6H, N(CH_3)$_2$); **^{13}C NMR** (62.896MHz, (CD_3)$_2$SO) δ 154.4 (C=O), 150.0 (C),127.4 (2CH), 120.1 (C), 112.17 (2CH), 40.27 (2CH_3); **FT IR** ν_{max}/cm^{-1} 1702 (C=O); **Accurate Mass** found m/z 221.10273 (MH^+), $C_{10}H_{13}N_4O_2$ requires 221.10385.

2.2.8 4-(4'-(*N,N*-Diethylamino)phenyl)-1,2,4-triazolidine-3,5-dione 83

N,N-Diethyl-*p*-phenylenediamine was prepared by extraction from a solution of the hydrochloride salt in 2M aqueous sodium hydroxide solution followed by distillation at 200°C, 0.2mm Hg. Some of the freshly prepared amine (3.3ml, 3.26g, 20mmol) was then dissolved in *N*-methylpyrrolidinone (5ml) and hydrazodicarbonamide (2.37g, 20mmol) was added. The mixture was heated to 195°C by carbon bath during which ammonia production was monitored by litmus paper. After ammonia production had ceased (4.5 hours) the mix was then allowed to cool and left overnight. The resulting liquid was added to water (150ml) and the solid was filtered off and dried to give the product as a grey solid (1.78g, 36%). The mother liquor was then evaporated to dryness under vacuum in a Kügelrohr oven and triturated with ethanol to give more grey solid (0.79g, 16%). These were combined and recrystallised to give 2.31g (47%) of product: **M.P.** 223.1-224.1°C; **^{1}H NMR** (250.134MHz, (CD_3)$_2$SO) δ 10.23 (s, 2H, NHNH), 7.10 (d, 2H, ^{3}J=9.1Hz, Ar), 6.68 (d, 2H, ^{3}J=9.1Hz, Ar) 3.35 (q, 4H, ^{3}J=7.1Hz, ($CH_3C\underline{H}_2$)$_2$N), 1.06 (t, 6H, ^{3}J=7.0Hz, ($C\underline{H}_3CH_2$)$_2$N); **^{13}C NMR** (62.896MHz, (CD_3)$_2$SO) δ 154.5 (C=O), 147.0 (C),127.8 (2CH), 119.1 (C), 111.2 (2CH), 43.94 (2CH_2) 12.48 (2CH_3); **FT IR** ν_{max}/cm^{-1} 1678

(C=O); **Accurate Mass** found m/z 259.13518 (MH^+), $C_{12}H_{17}N_4O_2$ requires 249.13515.

2.3 Oxidation of urazoles

2.3.1 Oxidation of 4-(3'-(*N,N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione 54

4-(3'-(*N,N*-Dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione **54** (187mg, 1mmol) was slurried in dry dichloromethane (50ml) under argon at room temperature. *N*-Bromosuccinimide (360mg, 2mmol) was added slowly over five minutes. All solids dissolved in the dichloromethane to give a pink-red solution corresponding to 4-(3'-(*N,N*-dimethylamino)propyl)-1,2,4-triazoline-3,5-dione. The solution was washed with water (50ml) upon which the solution decolourised. The organic layer was dried over magnesium sulfate and evaporated to give 96.9mg of yellow solid which could not be identified by spectroscopic or chromatographic methods.

In an alternative oxidation, 4-(3'-(*N,N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione **54** (0.92g, 4.8mmol) was slurried in dry dichloromethane (70ml) with sodium sulfate (10.3g) and the mixture was cooled to 0°C. Nitrogen dioxide (1.38g, 15mmol) which had previously been prepared and isolated at -50°C from 6.3g of lead nitrate was added by warming the flask to 0°C and passing argon over the frozen gas

and into the reaction mixture which became red in colour. The mix was stirred for 1 hour then warmed to room temperature and purged of excess nitrogen dioxide with argon. The mix was then filtered and the organic phase was concentrated *in vacuo* to give 0.63g of red gum which decolourised slowly with effervescence to a yellow colour and could not be identified by chromatographic or spectroscopic methods.

2.3.2 Oxidation of 4-(2'-(*N*,*N*-dimethylamino)ethyl)-1,2,4-triazolidine-3,5-dione 78 and 4-(4'-(*N*,*N*-dimethylamino)phenyl)-1,2,4-triazolidine-3,5-dione 82

The two other urazoles were oxidised in a similar way to 4-(3'-(*N*,*N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione with both *N*-bromosuccinimide and nitrogen dioxide in similar product ratios. Upon aqueous extraction or concentration of the organics, the red liquid that was formed in each case decolourised and could not be identified spectroscopically or separated by chromatographic means.

2.3.3 Oxidation and *in situ* ene reaction of base functionalised urazoles with 1-decene

A range of conditions were employed for the oxidations as given in table 3 in the discussion section. Varying temperatures, solvents and reagents were used but they all followed a general reaction schematic.

4-(3'-(*N,N*-Dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione **54** (186mg, 1mmol) was dissolved or slurried up in the solvent used (typically 25ml) under argon, 1-decene (0.2ml, 0.148g, 1.05mmol) was added and the mixture was stirred at the desired temperature while the relevant oxidant was added. In the case of solid or liquid oxidants, the addition was made while purging the system with argon and in the case of gaseous oxidants, the gas was introduced to the reaction through a sintered glass bubbler in the form of a mixture with argon. After addition of the oxidant, the mixture was stirred at the required temperature until the mix had fully decolourised. The mixture was then filtered if necessary and extracted into dichloromethane and washed with water. The organic phase was dried over anhydrous magnesium sulfate, the solvents removed *in vacuo* and the mixture examined by TLC and NMR. Only baseline material and starting material were observed in TLC and NMR spectroscopy showed only a complex mixture of compounds.

2.3.4 Oxidation and *in situ* ene reaction of 4-phenyl-1,2,4-triazolidine-3,5-dione with 1-decene

Sodium bicarbonate (1.4g, 17mmol, 4eq) and 4-phenyl-1,2,4-triazolidine-3,5-dione (354mg, 2mmol) were slurried in a solution of 1-decene (0.4ml, 295mg, 1.05eq) in dry dichloromethane under argon. *N*-Bromosuccinimide (712mg, 4mmol, 1eq) was added and the red mixture was stirred for 10 hours during which it decolourised fully.

The mixture was then filtered and washed with water (3x40ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 1-dec-2'-enyl-4-phenyl-1,2,4-triazolidine-3,5-dione **93** as a white solid (285mg, 46%): **M.P.** 94.6-95.3°C; **^{1}H NMR** (250.133MHz, ($CDCl_3$) δ 10.00-9.5 (b, 1H, NH), 7.50-7.31 (cm, 5H, Ph), 5.72 (dt, 1H, ^{3}J(d)=14.7Hz, ^{3}J(t)=6.8Hz, C<u>H</u>=CH), 5.40 (dt, 1H, ^{3}J(d)=14.7Hz, ^{3}J(t)=6.8Hz, C<u>H</u>=CH) 4.07 (d, 2H, ^{3}J=6.7Hz, CHC<u>H$_2$</u>N), 1.96 (q, 2H, ^{3}J=6.8Hz, CHC<u>H$_2$</u>CH$_2$), 1.23 (s, 10H, 5CH_2), 1.06 (t, 3H, ^{3}J=6.8Hz, CH_3); **^{13}C NMR** (62.896MHz, $(CD_3)_2SO$) δ 153.2 (C=O), 151.8 (C), 138.2 (CH),131.0 (C), 128.8 (2CH), 127.9 (CH) 125.3 (2CH), 121.0 (CH), 48.09 (CH_2), 31.91 (CH_2), 31.53 (CH_2), 28.84 (CH_2), 28.82 (CH_2), 28.45 (CH_2), 22.37 (CH_2), 13.84 (CH_3); **FT IR** ν_{max}/cm^{-1} 3160 (NH), 1679 (C=O); **Accurate Mass** found m/z 316.20388 (MH^+) $C_{18}H_{26}N_3O_2$ requires 316.20250

2.3.5 Oxidation and *in situ* Diels Alder reaction of 4-(3'-(*N*,*N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione 54 with anthracene

Anthracene (89mg, 0.5mmol) and *N*-bromosuccinimide (178mg, 1mmol) were dissolved in dry dichloromethane (50ml) under argon, cooled to 0°C and stirred while 4-(3'-(*N*,*N*-dimethylamino)propyl)-1,2,4-triazolidine-3,5-dione (93mg, 0.5mmol) was added. Pink colour was observed as the triazolidinedione reacted and dissolved but was decolourised almost instantly to give a light yellow solution cloudy with a small amount of white precipitate. The mixture was stirred overnight , then filtered, washed, dried over magnesium sulfate and evaporated *in vacuo* to give

150mg of yellow gum. Purification of this gum by flash chromatography on silica using a diethyl ether and ethyl acetate gradient as eluent yielded no identifiable products.

2.3.6 Oxidation and *in situ* Diels Alder reaction of 4-(4'-(*N,N*-dimethylamino)phenyl)-1,2,4-triazolidine-3,5-dione 82 with anthracene

Anthracene (178mg, 1mmol) and *N*-bromosuccinimide (254mg, 2mmol) were dissolved in dry dichloromethane under argon and stirred at 0°C while 4-(4'-(*N,N*-dimethylamino)phenyl)-1,2,4-triazolidine-3,5-dione (219mg, 1mmol) was added. The urazole reacted and dissolved to afford a dark red solution which decolourised within 1 minute to give a light purple colour with grey precipitate. The mixture was stirred for 12 hours then filtered, washed, dried over sodium sulfate, filtered and concentrated *in vacuo* to give 312mg of a grey gum. This gum was purified by column chromatography using a diethyl ether and ethyl acetate gradient as eluent with diethyl ether and filtered to give the hydrobromide salt of the Diels Alder cycloadduct 4-(4'-(*N,N*-dimethylamino)phenyl)-3,5-dioxo-2,4,6-triaza-8,9:10,11-dibenzo-tricyclo[5.2.2.$0^{2,6}$]-undeca-8,10-diene **96** as an off-white solid (110mg, 23%). **M.P.**130°C (d); **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 7.91-7.87 (cm, 2H, Ar), 7.51-7.26 (cm, 10H, Ar), 6.31 (s, 2H, bridgehead CH), 2.75 (s, 6H, $N(CH_3)_2$); **^{13}C NMR** (62.896MHz, $CDCl_3$) δ 155.6 (2C=O), 137.5 (C), 136.3 (4C), 135.2 (C), 129.2 (2CH), 128.3 (4CH), 124.0 (4CH), 123.3 (2CH), 60.39 (2CH) 43.89 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} 1700 (C=O); **Accurate Mass** found m/z 475.07708 ($M\text{-}H^+$, ^{79}Br),

477.07577 ($M-H^+$, ^{81}Br), $C_{24}H_{20}BrN_4O_2$ requires 475.07696 and 477.07577 respectively.

2.4 Pyridazinediones

2.4.1 Bromomaleic anhydride 99

Dibromosuccinic acid (31.5g 114mmol) was heated over phosphorus pentoxide (19.5g, 140mmol) until the anhydride was formed and distilled off as a yellow oil (16.63g, 94.3mmol 85% b.p. 150°C (Lit. 150-152)[115]). The product was identified by its boiling point and used directly in the next step without further characterisation.

2.4.2 Bromomaleic hydrazide 100

Bromomaleic anhydride **99** was added dropwise over 20 minutes to a solution of hydrazine hydrate (12.23g, 94.3 mmol) in water (50ml). The solution was then heated under reflux for 90 minutes and stirred for 18 hours at room temperature to allow full precipitation of the product. The mixture was filtered and the solid washed with water (2x20ml) and ethanol (20ml). After drying in a vacuum desiccator at 80°C for 6 hours, the product was obtained in 84% yield (72% from dibromosuccinic acid). It was identified by IR spectroscopy and melting point (253-254°C, Lit. 255-256°C)[115] and was judged pure enough to use in the next step without further purification.

2.4.3 4-(3-*N,N*-Dimethylamino)propylamino-1,2,3,6-tetrahydropyridazine-3,6-dione 101

To a slurry of 3-Bromomaleic hydrazide **100** (3.347g, 17.5mmol) in super dry ethanol (25ml) was added a solution of 3-(*N,N*-dimethylamino)propylamine **44** (2.20ml, 1.78g, 17.5mmol) in ethanol (5ml). After 5 minutes stirring, a clear yellow solution had developed. This was evaporated to dryness to give the product in the form of its hydrobromide salt as a cream solid (5.123g, 100%). NMR spectroscopy indicated that no further purification was necessary. **^{1}H NMR** (250.133MHz, D_2O) δ 7.19 (s, 1H, CH=C), 2.78 (t, 2H, ^{3}J=7.3Hz, $C\underline{H}_2NH$), 2.49 (t, 2H, ^{3}J=7.3Hz, $C\underline{H}_2N(CH_3)_2$), 2.25 (s, 6H, $N(CH_3)_2$), 1.69 (p, 2H, ^{3}J=7.0 Hz, $CH_2C\underline{H}_2CH_2$); **^{13}C NMR** (62.896MHz, D_2O) δ 159.8 (C=O), 158.9 (C=O), 133.2 (C), 132.6 (CH), 55.11 (CH_2), 43.23 (2(CH_3)), 37.54 (CH_2) 24.46 (CH_2); **FT IR** ν_{max}/cm^{-1} 1647 (C=O); **Accurate Mass** found m/z 293.07773 (M^+, ^{79}Br), 295.05919 (M^+, ^{81}Br), $C_9H_{17}BrN_4O_2$ requires 293.06131 and 295.05940 respectively.

2.4.4 Oxidation and *in situ* ene reactions of pyridazinediones with 1-decene

3'-(*N,N*-Dimethylamino)propylamino-1,2-pyridazine-3,6-dione hydrobromide **101** (293mg, 1mmol) was slurried in a solution of 1-decene (0.2ml, 148mg,1.05eq) and acetic acid (1ml) in dry dichloromethane (50ml) at 0°C. Freshly recrystallised lead

tetraacetate (444g, 1mmol) was added and the mixture was stirred for 16 hours. The mixture was then washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 153mg of yellow gum. Analysis of the product by TLC and IR spectroscopy showed only some starting alkene and a complex mixture of decomposition products which could not be resolved by chromatographic means.

The oxidation and in situ ene reaction was repeated using maleic hydrazide **103** (175mg, 1.5mmol), 1-decene (0.35ml, 260mg, 1.8mmol), and lead tetraacetate (692mg, 1.5mmol) in dichloromethane (50ml) under the same conditions and the same results were produced.

3. Imine Enophiles

3.1 Attempted preparation of diacylimine by dehydrogenative FVP

3.1.1 Ethyl ethoxycarbonylglycinate 107

Glycine ethyl ester (2.52g, 18mmol) was dissolved in water (2.5ml) and cooled in an ice bath. Aqueous sodium hydroxide solution (1.8ml, 10N, 18mmol) was added slowly with stirring. Ethyl chloroformate (2.01g, 18mmol) was added slowly by syringe pump followed by aqueous sodium carbonate (1.01g. in 5ml, 9 mmol). The solution was allowed to warm to room temperature and stirred for 1 hour. The two layered mixture that resulted was extracted with diethyl ether (2x20ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 2.77g (88%) of clear liquid. This was purified by bulb to bulb distillation to yield slowly solidifying white solid (2.34g., 75%); **M.P.** 26.5-28°C. (Lit.[116] 27-28°C)

3.1.2 FVP of ethyl ethoxycarbonylglycinate 107 over 5%Pd on Alumina

Ethyl ethoxycarbonylglycinate (100mg) was distilled at 70-100°C, $4x10^{-2}$mm Hg through a silica tube containing 2.5g of 5% Pd/Al_2O_3 catalyst packed with quartz wool, into a U-tube cooled by liquid nitrogen. The experiment was performed twice

with the silica tube heated to either 600°C or 400°C but no evidence of product or starting material was observed on warming the collection tube to room temperature. Another experiment involving *in situ* trapping was also attempted with cyclopentadiene but only dicyclopentadiene was observed.

3.2 Preparation of alkoxy diacylimine precursor 108

3.2.1 2-hydroxy-*N*-ethoxycarbonylglycine 111

Ethyl carbamate (8.91g, 10mmol) and glyoxylic acid monohydrate (9.22g., 10mmol) were dissolved in diethyl ether (150ml). A soxhlet extractor containing CaH_2 (1g) was fitted to remove the water formed in the reaction and the mixture was boiled under reflux for 6 hours, then stirred at room temperature for 18 hours. The white precipitate produced was filtered and dried under vacuum to give 15.44g (95%) of product **M.P.** 85.1-85.7°C (Lit. 80-82°C)[117]; ν_{max}/cm^{-1} 3341 (NH, OH), 1705 (C=O)

3.2.2 Ethyl ethoxy-*N*-ethoxycarbonylglycinate 108

2-hydroxy-*N*-ethoxycarbonylglycine (26.5g, 162mmol) was dissolved in absolute ethanol (300ml) with stirring at 0°C. Concentrated sulfuric acid (10ml) was added slowly. The mix was allowed to warm to room temperature and stirred for 20 hours.

The reaction was then quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (100ml, 2x50ml), washed with water (20ml), dried over $MgSO_4$ and evaporated to dryness to yield 32.31g (93%) of clear liquid. This was then purified by bulb to bulb distillation at 200°C, 2mm Hg. to give 18.03g.(51%) of pure product, **M.P.** 13-14°C;**^{1}H NMR** (200.13Hz., $CDCl_3$) δ 6.01 (d, 1H, NH, ^{3}J=9.7 Hz.), 5.24 (d, 1H, CHNH, ^{3}J=9.7Hz), 4.11 (q, 2H, CH_2O_2C, ^{3}J=7.1Hz), 4.02 (q, 2H, CH_2O_2C, ^{3}J=7.1Hz), 3.53 (q, 2H, CH_2OCH, ^{3}J=6.9Hz), 1.05-1.21 (cm, 9H, $3CH_3CH_2$) ; **^{13}C NMR** (50.32Hz, $CDCl_3$) δ 167.6 (C=O), 155.6 (C=O), 79.0 (CH), 64.0 (CH_2), 61.5 (CH_2), 61.1 (CH_2), 14.5 (CH_3), 14.0 (CH_3), 13.6 (CH_3); **FT IR** ν_{max}/cm^{-1} 3334 (NH), 1727 (C=O) ; **Accurate Mass** found 220.11861(MH^+), $C_9H_{18}NO_4$ requires 220.11850

3.3 Reactions of imine esters with alkenes

3.3.1 Reactions of ethyl ethoxy-*N*-ethoxycarbonylglycinate 108 with 2,3-dimethyl-2-butene

With 3 equivalents of boron trifluoride:

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (1.10g, 5.0mmol), and 2,3-dimethyl but-2-ene (0.42g, 5.0mmol) were dissolved in dry chloroform (80ml) under argon. Boron trifluoride-etherate (1.9ml, 15.4mmol, 3eq) was added by syringe and the mixture was boiled under reflux for 4 hours. It was then quenched with concentrated

ammonia solution (10ml), extracted with dichloromethane (50ml), washed with water (25ml), dried over $MgSO_4$, filtered and evaporated to dryness to give 1.14g of colourless oil. The products were then separated by column chromatography using hexane and diethyl ether as eluent to yield 320mg (30%) of 4,4,5,5-tetramethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **113** and 600mg (47%) of diethyl 3,3,4,4-tetramethylazetidine-1,2-dicarboxylate **114**.

With 1 equivalent of boron trifluoride:

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (1.10g, 5.0mmol), and 2,3-dimethyl but-2-ene (0.42g, 5.0mmol) were dissolved in dry chloroform (50ml) under argon. Boron trifluoride-etherate (0.7ml, 0.81g, 5.7mmol) was syringed in and the mixture was boiled under reflux for 6 hours. It was then quenched with concentrated ammonia solution (10ml), extracted with dichloromethane (50ml), washed with water (25ml), dried over $MgSO_4$, filtered and evaporated to dryness to give 1.17g of colourless oil. The products were then separated by column chromatography using hexane and diethyl ether as eluent to yield 240mg (23%) of 4,4,5,5-tetramethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **113** and 490mg (38%) of diethyl 3,3,4,4-tetramethylazetidine-1,2-dicarboxylate **114**.

Data for compounds:

4,4,5,5-tetramethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **113**: **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 5.13 (d, 1H, ^{3}J=7.6Hz, NH), 4.66 (d, 1H, ^{3}J=8.3Hz, C<u>H</u>NH), 4.09 (q, 2H, ^{3}J=7.1Hz, OC<u>H</u>$_2$CH$_3$), 1.39 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.23 (t, 3H, ^{3}J=7.16 Hz, C<u>H</u>$_3$CH$_2$O), 1.09 (s, 3H, CH_3), 0.87 (3H, s); **^{13}C NMR** δ 174.0 (C=O), 156.71 (C=O), 86.98 (C), 61.45 (CH_2), 59.30 (CH), 45.13 (C), 23.79 (CH_3), 22.38 (CH_3), 20.43 (CH_3), 18.04 (CH_3), 14.28 (CH_3); **FT IR** ν_{max}/cm^{-1} 3320 (NH), 1770 (C=O), 1694 (C=O); **Accurate mass**: Found ((MH$^+$) 230.13957, $C_{11}H_{20}NO_4$ requires 230.13923.

Diethyl 3,3,4,4-tetramethylazetidine-1,2-dicarboxylate **114**: **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 4.18-3.97 (cm, 4H, 2CH_2), 1.33 (s, 1H, CH), 1.24-1.17 (cm, 12H, 4CH_3), 1.00 (s, 3H, CH_3), 0.79 (s, 3H, CH_3); **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 172.27 (C=O), 151.76 (C=O), 83.10 (C), 63.19 (CH_2), 60.57 (CH_2), 57.74 (CH), 35.62 (C), 22.93 (CH_3), 22.41 (CH_3), 21.88 (CH_3), 17.45 (CH_3), 14.19 (2CH_3); **FT IR** ν_{max}/cm^{-1} 1751 (C=O), 1724 (C=O); **Accurate mass**: Found (MH$^+$) 258.17014, $C_{13}H_{24}NO_4$ requires 258.17053.

3.3.2 Reaction of ethyl ethoxy-*N*-ethoxycarbonylglycinate 108 with 2,3-dimethyl-2-butene with 3 equivalents of boron trifluoride monitored by *in situ* NMR spectroscopy

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (0.015g, 0.06mmol), and 2,3-dimethyl but-2-ene (7.5μl, 0.0059g, 0.07mmol) were dissolved in deuterated chloroform (0.25ml). Boron trifluoride-etherate (27μl, 0.031g, 0.23mmol) was syringed in, the tube was purged with argon gas and sealed and the solution was agitated by shaking. ^{1}H NMR spectroscopy was performed immediately, after 1 hour and the following day. Interpretation of the result showed no change after 1 hour, indicating that reaction was complete by 1 hour and formation of azetidine with no corresponding evidence for any γ-lactone formation.

3.3.3 Reaction of ethyl ethoxy-*N*-ethoxycarbonylglycinate 108 with 2-methyl-2-butene with 3 equivalents of boron trifluoride

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (1.55g, 7.1mmol), and 2-methyl-2-butene (0.51g, 7.2mmol) were dissolved in dry chloroform (50ml). Boron trifluoride-etherate (2.8ml, 3.23g, 22.4mmol) was syringed in and the mixture was stirred at room temperature for 6 hours. It was then quenched with concentrated ammonia solution (10ml), extracted with dichloromethane (50ml), washed with water (25ml), dried over $MgSO_4$, filtered and evaporated to dryness to give 1.53g of colourless oil. The products were then separated by column chromatography using hexane and

diethyl ether as eluent to yield 430mg (28%) of 4,4,5-trimethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **124** and 510mg (29%) of diethyl 3,4,4-trimethyl-1,2-azetidinedicarboxylate **123**.

Data for compounds:

4,4,5-trimethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **124**: **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 5.59 (d, 1H, ^{3}J=8.1Hz, NH), 4.19-4.02 (cm, 3H, C<u>H</u>NH, O<u>CH$_2$</u>CH$_3$), 2.24-2.16 (cm, 1H, CHC<u>H</u>CH$_3$), 1.36 (s, 3H, CH$_3$), 1.22 (s, 3H, CH$_3$), 1.16 (t, 3H, ^{3}J=7.4 Hz, <u>CH$_3$</u>CH$_2$O), 1.05 (d, 3H, ^{3}J=6.8Hz, <u>CH$_3$</u>CH); **^{13}C NMR** δ 173.9 (C=O), 156.5 (C=O), 84.54 (C), 61.15 (CH_2), 56.45 (CH), 46.20 (CH), 26.90 (CH_3), 21.57 (CH_3), 14.17 (CH_3), 11.67 (CH_3); **FT IR** ν_{max}/cm^{-1} 3320 (NH), 1770 (C=O), 1694 (C=O); **Accurate mass**: Found (MH^+) 216.12454, $C_{10}H_{18}NO_4$ requires 216.12358.

Diethyl 3,4,4-trimethylazetidine-1,2-dicarboxylate **123**: **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 4.29 (d, 1H, ^{3}J=4.9Hz, NCH), 4.20-4.07 (cm, 4H, 2(CH_3<u>CH_2</u>)), 1.98-1.93 (cm, 1H, CHC<u>H</u>CH$_3$), 1.29 (s, CH_3), 1.24 (s, CH_3), 1.20-1.14 (cm, 6H, 2CH_3), 0.73 (d, 3H, ^{3}J=7.0Hz, CH_3); **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 172.3 (C=O), 151.9 (C=O), 79.49 (C), 63.06 (CH_2), 60.54 (CH_2), 57.52 (CH), 35.16 (CH), 26.89 (CH_3), 25.33 (CH_3), 14.03 (CH_3), 13.87 (CH_3), 9.55 (CH_3); **FT IR** ν_{max}/cm^{-1} 1751 (C=O), 1724 (C=O); **Accurate mass**: Found (MH^+) 244.1551, $C_{12}H_{22}NO_4$ requires 244.15488.

3.3.4 Reaction of ethoxy-*N*-hydroxycarbonylglycine 107 with 2,3-dimethyl-2-butene

Ethoxy-*N*-hydroxycarbonylglycine **107** (2.19g, 10mmol), and 2,3-dimethyl but-2-ene (0.943g, 11.2mmol) were dissolved in dry diethyl ether (80ml) under argon. Boron trifluoride-etherate (4.15ml, 33mmol, 3eq) was syringed in and the mixture was stirred overnight for 16 hours. It was then quenched with concentrated ammonia solution (10ml), extracted with dichloromethane (50ml), washed with water (25ml), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give 0.84g (40%) of white solid which was identified by its 1H NMR spectrum as 4,4,5,5-tetramethyl-3-ethoxycarbonylamino-2(*3H*)-dihydrofuranone **113**.

3.3.5 Diethyl 4-methyl-4-(2',2'-dimethylpropyl)azetidine-1,2-dicarboxylate 128

Ethyl ethoxy-*N*-ethoxycarbonylglycinate **108** (2.07g, 9.5 mmol) was dissolved in a solution of α-diisobutene **127** (1.06g, 95 mmol) in dried chloroform (50ml) under argon. Boron trifluoride-etherate (5.5ml, 4.77g, 34mmol, 3.5eq) was syringed in and the mixture was boiled under reflux for 5 hours. The mixture was then quenched with concentrated ammonia solution (20ml), extracted with dichloromethane (2x50ml), dried over $MgSO_4$ and evaporated to dryness to give 2.54g of yellow oil. The mixture was then purified by flash chromatography using hexane/diethyl ether as eluent to yield the product as a yellow oil (1.73g, 61%). **^{1}H NMR** (250.133MHz,

$CDCl_3$) δ 4.21-4.04 (cm, 5H, $2CH_3C\underline{H}_2O$, C<u>H</u>N), 1.95 (dd, 1H, ^2J=13.4Hz, ^3J=5.2Hz, ring CH), 1.80 (dd, 1H ^2J=11.9Hz, ^3J=11.4Hz, ring CH) 1.62 (s, 2H, $^tBuC\underline{H}_2$), 1.33 (s, 3H, CH_3CN), 1.25 (t, 3H, ^3J=7.1Hz, $C\underline{H}_3CH_2O$), 1.24 (t, 3H, ^3J=7.1Hz, $C\underline{H}_3CH_2O$), 0.99 (9H, $(CH_3)_3C$); **^{13}C NMR** (62.896MHz, $CDCl_3$) δ 173.2 (C=O), 153.0 (C=O), 80.39 (C), 63.00 (CH_2), 60.82 (CH_2), 54.04 (CH_2), 53.38 (CH), 35.06 (CH_2), 31.26 ($3CH_3$), 30.79 (C), 24.92 (CH_3), 14.00 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} 1724 (broad, C=O); **Accurate mass** found 286.20057 (MH^+), $C_{15}H_{28}NO_4$ requires 286.20183.

3.4 Preparation of acyclic amino functionalised imine enophile precursors

3.4.1 Ethyl 2-ethoxy-[3-(3'-(*N,N*-dimethylamino)propyl)ureido]-acetate 144

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (1.025g, 4.7mmol) and 3-(*N,N*-dimethylamino)propylamine (0.6ml, 0.48g, 4.7mmol) were mixed together under anhydrous conditions. The solution was warmed by an oil bath at 85°C for 8 hours then allowed to cool to room temperature and stirred overnight. Removal of the ethanol produced by the reaction under high vacuum gave the product as a clear oil (1.291g, 4.7mmol, 100%). **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 7.87 (b, 1H, $N\underline{H}CH_2CH_2$), 6.04 (d, 1H, ^3J=8.4Hz, N<u>H</u>CH), 5.21 (d, 1H, ^3J=7.8Hz, C<u>H</u>NH), 4.07 (q, 2H, ^3J=7.0Hz, $CH_3C\underline{H}_2O_2C$), 3.61 (q, 2H, ^3J= 7.0Hz, $OC\underline{H}_2CH_3$), 3.28 (q, 2H, ^3J=6.0Hz, $NHC\underline{H}_2CH_2$), 2.32 (t, 2H, ^3J=6.3Hz, $C\underline{H}_2NMe_2$), 2.17 (s, 6H, $N(C\underline{H}_3)_2$), 1.61 (p, 2H, ^3J=6.3Hz $CH_2C\underline{H}_2CH_2$), 1.24-1.11 (cm, 6H, $2(C\underline{H}_3CH_2)$); **^{13}C NMR**

(50.283MHz, $CDCl_3$) δ 168.0 (C=O), 155.0 (C=O), 82.71 (CH), 59.70 (CH_2), 56.32 (CH_2), 43.72 ($2CH_3$), 42.95 (CH_2), 37.61 (CH_2), 24.42 (CH_2), 13.06 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} 1697 (C=O)[108].

3.4.2 Ethyl 2-ethoxy-[3-(3'-(*N,N*-diethylamino)ethyl)ureido]-acetate 145

Ethyl ethoxy-*N*-ethoxycarbonylglycinate (1.029g, 4.7mmol) and 3-(*N,N*-diethylamino)propylamine (0.74ml, 0.61g, 4.7mmol) were placed in a 5 ml flask and warmed in an oil bath at 100°C for 8 hours under anhydrous conditions. The mixture was then cooled to room temperature and evaporated to dryness under high vacuum to yield the product as a yellow oil (1.360g, 4.7mmol, 100%). **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 7.26 (b, 1H, $N\underline{H}CH_2CH_2$), 6.06 (d, 1H, ^3J=8.0Hz, $N\underline{H}CH$), 5.24 (d, 1H, ^3J=7.3Hz, $C\underline{H}NH$), 4.07 (q, 2H, ^3J=7.0Hz, $CH_3C\underline{H}_2O_2C$), 3.61 (q, 2H, ^3J= 7.0Hz, $OC\underline{H}_2CH_3$), 3.25 (q, 2H, ^3J=5.5Hz, $NHC\underline{H}_2CH_2$), 2.54-2.43 (cm, 6H, $C\underline{H}_2N(C\underline{H}_2)_2$), 1.22-1.11 (cm, 6H, $2(C\underline{H}_3CH_2O_2C)$, 0.95 (t, 6H, ^3J=7.2Hz, $(C\underline{H}_3CH_2)_2N$); **^{13}C NMR** (50.283MHz, $CDCl_3$) δ 166.6 (C=O), 155.5 (C=O), 78.84 (CH), 62.37 (CH_2), 59.85 (CH_2), 49.78 (CH_2), 45.27 ($2CH_2$), 35.38 (CH_2), 13.49 (CH_3), 12.91 (CH_3), 9.93 ($2CH_3$); **FT IR** ν_{max}/cm^{-1} 1704 (C=O); **Accurate mass** found 290.20750, $C_{13}H_{28}N_3O_4$ requires 290.20798.

3.5 Attempted preparation of alkoxy functionalised imidazolidinediones

3.5.1 Attempted cyclisation of ethyl 2-ethoxy-[3-(3'-(*N,N*-dimethylamino)propyl)ureido]-acetate 144

Ethyl 2-ethoxy-[3-(3'-(*N,N*-dimethylamino)propyl)ureido]-acetate **144** (1.29g, 4.7mmol) was prepared as described earlier. Further heating of the compound for an additional 40 hours at 80°C gave no cyclisation, but a slight decomposition. The mixture was heated to 140°C for 5 hours but no cyclisation and only decomposition was observed. Starting material (1.29g, 4.7mmol) was also heated with aqueous potassium hydroxide solution (4M, 5ml) but only decomposition products were observed. Experiments were also tried stirring a solution of the precursor in methanol with an excess of potassium hydroxide or potassium bicarbonate but again only decomposition products were observed.

3.5.2 Hydroxyglycine route

Hydroxyglycine

Glyoxylic acid monohydrate (4.60g, 50mmol) was dissolved in water (10ml) and cooled in an ice bath. An ice cooled solution of ammonium acetate (9.50g, 100mmol) was added in slowly and the mixture was stirred for 2 hours. The solid produced was then filtered off, washed with water and ethanol and dried under

vacuum to give the product as a white solid (3.91g, 43mmol, 86%). **M.P.** (dec). 103.9-104.8°C (Lit. 105-106°C[109]).

Reaction of hydroxyglycine with 3-(*N,N*-dimethylamino)propylamine *via* 4-hydroxyoxazolidine-2,5-dione 151

Hydroxyglycine (0.912g, 10mmol) was added to a solution of phosgene in toluene (1.93M, 20ml, 38mmol) and boiled under reflux for 8 hours. The mixture was evaporated to dryness to give 1.15g of brown gum. A solution of 3-(*N,N*-dimethylamino)propylamine (1.25ml, 1.02g, 10mmol) in methanol (20ml) was added slowly and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated to give 2.01g of brown gum. Analysis by ^{1}H NMR spectroscopy showed the gum to be a crude polymeric mixture.

3.5.3 Reaction of ureas with glyoxylic acid

3-(*N,N*-Dimethylamino)propylurea 154

3-(*N,N*-Dimethylamino)propylamine (5ml, 4.08g, 40mmol) and potassium isocyanate (3.233g, 40mmol) were dissolved in water (20ml). Aqueous hydrochloric acid (2M, 20ml) was added slowly over 15 minutes with stirring and cooling in a room temperature water bath. The mixture was evaporated to dryness and ethanol (40ml) was added. The mixture was then filtered and evaporated to dryness again.

The liquid residue was then purified by Kügelrohr distillation (250°C, 0.2mm Hg) to give the product as a clear liquid (1.45g, 10mmol, 25%). **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 5.86 (b, 2H, $N\underline{H}_2$), 5.39 (b, 1H, NH), 3.09 (t, 2H, ^{3}J=5.9Hz, $C\underline{H}_2NH$), 2.24 (t, 2H, ^{3}J=6.7Hz, $C\underline{H}_2N(CH_3)_2$), 2.12 (t, 6H, ^{3}J=1.4Hz, $(C\underline{H}_3)_2N$), 1.58 (p, 2H, ^{3}J=6.6Hz, $CH_2C\underline{H}_2CH_2$); **^{13}C NMR** (50.283MHz, $CDCl_3$) δ 158.3 (C=O), 43.81 ($2CH_3$), 43.67 (CH_2), 37.70 (CH_2), 26.20 (CH_2)[108];

Reaction of 3-(*N,N*-dimethylamino)propylurea with glyoxylic acid

3-(*N,N*-Dimethylamino)propylurea (1.448g, 10mmol) was dissolved in ethanol (25ml) and treated with glyoxylic acid monohydrate (1.841g, 20mmol, 2eq) The mixture was stirred at room temperature for 5 days. Analysis of the crude reaction mixture showed that there was potentially some product in the mixture but it was heavily contaminated. Various extractions and trituration attempts could not separate the mixture, which was only baseline in thin layer chromatography hence could not be purified by chromatographic methods.

2-(*N,N*-Dimethylamino)-ethyl-urea

2-(*N,N*-Dimethylamino)-ethylamine (4.4ml, 3.52g, 40mmol) was dissolved in aqueous hydrochloric acid (17ml, 2.3M, 40mmol). This solution was cooled in ice and added dropwise with stirring to an ice cooled solution of potassium isocyanate (3.24g, 40mmol) in water (10ml). The mixture was then allowed to warm to room temperature then evaporated to dryness. The residue was treated with ethanol (40ml)

and filtered. Evaporation to dryness and slow solidification gave the product as a hygroscopic white solid (5.09g, 38.9mmol, 97%). **M.P.** 48.2-49.3°C (Lit. 38-40°C)[113].

3.6 Preparation of non-functionalised imidazolidinediones

3.6.1 1-(3'-(*N,N*-Dimethylamino)propyl)imidazolidine-2,5-dione 148

3-(*N,N*-Dimethylamino)propylamine (2.5ml, 2.03g, 20mmol) and ethyl-*N*-ethoxycarbonylglycinate (3.502g, 20mmol) were added together and heated in an oil bath at 105°C for 9 hours. An aliquot of the liquid (100mg) was removed and found to be ethyl (3-(*N,N*-dimethylamino)propyl)ureidoacetate **146**. **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 7.73 (b, 1H, $N\underline{H}CH_2CH_2$), 5.90 (b, 1H, $N\underline{H}CO_2Et$), 4.02 (q, 2H, ^3J=7.1Hz, $CH_3C\underline{H}_2O_2C$), 3.70 (d, 2H, ^3J= 5.5Hz, $COC\underline{H}_2NH$), 3.22 (q, 2H, ^3J=6.3Hz, $NHC\underline{H}_2CH_2$), 2.27 (t, 2H, ^3J=6.3Hz, CH_2NMe_2), 2.11 (s, 6H, $N(C\underline{H}_3)_2$), 1.56 (p, 2H, ^3J=6.3Hz $CH_2C\underline{H}_2CH_2$), 1.11 (t, 3H, ^3J=7.1Hz, $C\underline{H}_3CH_2$); **^{13}C NMR** (50.283MHz, $CDCl_3$) δ 168.0 (C=O), 155.0 (C=O), 59.70 (CH_2), 56.32 (CH_2), 43.72 ($2CH_3$), 42.95 (CH_2), 37.61 (CH_2), 24.42 (CH_2), 13.06 (CH_3); **Accurate mass** found 232.16602 (MH^+), $C_{10}H_{22}N_3O_3$ requires 232.16612.

The remaining compound was dissolved in a solution of potassium hydroxide (12g) in water (25ml) and warmed at 40°C for 10 minutes. After cooling, the mixture was acidified with concentrated hydrochloric acid (16ml) in water (6ml) before being evaporated to dryness. The residue (12.2g) was extracted with methanol (3x30ml),

filtered and evaporated to dryness to give 4.35g of hygroscopic yellow solid. This was then recrystallised from anhydrous isopropanol to give 2.63g (59%) of the product in the form of a yellow hygroscopic hydrochloride salt. A 200mg aliquot was taken and treated with aqueous silver nitrate solution (1M, 25ml), filtered and evaporated. Trituration of the residue with isopropanol followed by recrystallisation gave 50mg of the free base of **148** as a white hygroscopic solid. **M.P.** 119.1-120.3°C; **^{1}H NMR** (199.974MHz, D_2O) δ 3.68 (s, 2H, $C\underline{H}_2NH$), 3.28-3.14 (cm, 4H, $C\underline{H}_2CH_2\underline{C}H_2$), 2.90 (s, 6H, $N(C\underline{H}_3)_2$), 1.92 (p, 2H, ^{3}J=7.4Hz $CH_2C\underline{H}_2CH_2$); **^{13}C NMR** (50.283MHz, D_2O) δ 181.2 (C=O), 163.5 (C=O), 58.18 (CH_2), 46.71 (CH_2), 45.56 ($2CH_3$), 39.25 (CH_2), 27.83 (CH_2)); **FT IR** ν_{max}/cm^{-1} 1715 (C=O);

3.6.2 1-(3'-(*N,N*-Diethylamino)ethyl)-imidazolidine-2,5-dione 149

2-(*N,N*-Diethylamino)ethylamine (0.74ml, 0.61g, 4.7mmol) and ethyl *N*-ethoxycarbonylglycinate (0.821g, 4.7mmol) were added together and heated in an oil bath at 100°C for 8 hours. An aliquot of the liquid (100mg) was removed and identified as ethyl (3-(*N,N*-diethylamino)ethyl)ureidoacetate **147**. **^{1}H NMR** (199.974MHz, $CDCl_3$) δ 6.95 (b, 1H, $N\underline{H}CH_2CH_2$), 6.01 (b, 1H, $N\underline{H}CO_2Et$), 3.99 (q, 2H, ^{3}J=7.1Hz, $CH_3C\underline{H}_2O_2C$), 3.69 (d, 2H, ^{3}J= 5.8Hz, $COC\underline{H}_2NH$), 3.19 (q, 2H, ^{3}J=5.8Hz, $NHC\underline{H}_2CH_2$), 2.46-2.35 (cm, 6H, $C\underline{H}_2N(C\underline{H}_2)_2$), 1.12 (t, 3H, ^{3}J=7.1Hz, $C\underline{H}_3CH_2$) 0.88 (t, 6H, ^{3}J=7.0Hz, $N(CH_2C\underline{H}_3)_2$); **^{13}C NMR** (50.283MHz, $CDCl_3$) δ 168.2 (C=O), 155.6 (C=O), 59.70 (CH_2), 49.92 (CH_2), 45.22 ($2CH_2$), 42.95 (CH_2),

35.29 (CH_2), 13.03 (CH_3), 9.84 ($2CH_3$); **Accurate mass** found 246.18284 (MH^+), $C_{11}H_{24}N_3O_3$ requires 246.18177.

The remaining compound was dissolved in a solution of potassium hydroxide (3g) in water (15ml) and warmed at 40°C for 5 minutes. After cooling, the mixture was acidified with aqueous hydrochloric acid (4M, 6ml) and then evaporated to dryness. The residue was extracted with methanol (3x20ml), filtered and evaporated to dryness to give 0.47g (42%) of hygroscopic white solid This was identified as the product **149** in the form of its hydrochloride salt. **^{1}H NMR** (199.974MHz, D_2O) δ 3.85 (s, 2H, $C\underline{H}_2NH$), 3.52 (t, ^3J=5.8Hz, 2H, $NHC\underline{H}_2CH_2$), 3.34-3.21 (cm, 6H, $C\underline{H}_2N(C\underline{H}_2)_2$), 1.29 (t, 6H, ^3J=7.3 Hz, $N(CH_2C\underline{H}_3)_2$); **^{13}C NMR** (50.283MHz, D_2O) δ 175.3 (C=O), 160.1 (C=O), 51.64 (CH_2), 47.37 ($2CH_2$), 41.72 (CH_2), 34.63 (CH_2), 7.69 ($2CH_3$).

3.6.3 Attempted preparation of 1-(3'-(*N,N*-Dimethylamino)propyl)imidazolidene-2,5-dione *via* oxazolidine-2,5-dione

Oxazolidine-2,5-dione

Carbobenzyloxyglycine (2.51g, 36mmol) was added to a mixture of thionyl chloride (3.5ml) and acetic anhydride (7.5ml). The mixture was warmed by a water bath at 40°C and stirred for 20 minutes during which the solid dissolved. The solution was then heated to boiling for 1 minute then cooled in an ice bath for 1 hour and filtered.

The solid was washed with diethyl ether and dried on a vacuum desiccator to give the anhydride as a white solid (1.13g, 11.2mmol, 31%). **M.P.** 100-101°C. (dec) (Lit. 100°C)[118].

Reaction of oxazolidine-2,5-dione with 3-(*N,N*-dimethylamino)propylamine

Oxazolidine-2,5-dione (1.01g, 10mmol) was added to dry diethyl ether (20ml). 3-(*N,N*-Dimethylamino)propylamine (1.25ml, 1.02g, 10mmol) was added slowly. The mixture was then stirred overnight before being filtered. The hygroscopic solid was washed with methanol (5ml) and dried in a vacuum desiccator. The solid was not, however, the desired product but a mixture of polymeric residues. Evaporation of the solution phase of the reaction mixture also yielded polymeric residues.

References

1. H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, 1969, **8**, 556.

2. H. J. Prins, *Chem. Wekblad.*, 1919, **16**, 1510.

3. K. Alder, F. Pascher and A. Schmitz, *Ber. Dtsch. Chem. Ges.*, 1943, **76**, 27.

4. J. Dubac and A. Laporterie, *Chem. Rev.*, 1987, **87**, 319.

5. W. Oppolzer and V. Snieckus, *Angew. Chem. Int. Ed. Engl.*, 1978, **17**, 476.

6. B. B. Snider, *Acc. Chem. Res.*, 1980, **13**, 426.

7. G. D. Paderes and W. L. Jorgensen, *J. Org. Chem.*, 1992, **57**, 1904.

8. E. C. Keung and K. Alper, *J. Chem. Educ.*, 1972, **49**, 97.

9. K. Mikami and M. Shimuzu, *Chem. Rev.*, 1992, **92**, 1021.

10. A. G. Davies and C. H. Schiesser, *Tetrahedron*, 1991, **47**, 1907.

11. G. Desimoni, G. Faita, P. P. Righetti, A. Sfulcini and D. Tsyganov., *Tetrahedron*, 1994, **50**, 1821.

12. Y. Elemes and C. S. Foote, *J. Am. Chem. Soc.*, 1992, **114**, 6044.

13. S. Inagake, H. Fujimoto and K. Fukui, *J. Am. Chem. Soc.*, 1976, **98**, 4693.

14. R. Huisgen and H. Pohl, *Chem. Ber.*, 1960, **93**, 527.

15. R. T. Arnold and J. S. Showell, *J. Am. Chem. Soc.*, 1957, **79**, 419.

16. L. M. Stephenson and D. L. Mattern, *J. Org. Chem.*, 1976, **41**, 3164.

17. C. C. Cheng, C. A. Seymour, M. A. Petti and F. D. Greene, *J. Org. Chem.*, 1984, **49**, 2910.

18. M. Stratakis, M. Orfanopoulos and C. S. Foote, *Tetrahedron Lett.*, 1991, **32**, 863.

19. M. Squillacote, M. Mooney and J. de Felippis, *J. Am. Chem. Soc.*, 1990, **112**, 5364.

20. C. A. Seymour and F. D. Greene, *J. Am. Chem. Soc.*, 1980, **102**, 6384.

21. S. F. Nelsen and D. L. Kapp, *J. Am. Chem. Soc.*, 1985, **107**, 5548.

22. Y. Elemes and M. Orfanopoulos, *Tetrahedron Lett.*, 1991, **32**, 2667.

23. S. Dang and A. G. Davies, *J. Chem. Soc. Perkin Trans. 2*, 1991, **72**, 721.

24. M. Santellé and J.-M. Pons, 'Lewis Acids and Selectivity in Organic Synthesis', CRC Press, London, 1996.

25. B. B. Snider and E. Ron, *J. Am. Chem. Soc.*, 1985, **107**, 8160.

26. B. B. Snider, in 'Comprehensive Organic Synthesis', ed. B. M. Trost, Vol. 5, p1, Pergammon, Oxford, 1991.

27. R. K. Hill and H. J. Barger Jnr., *J. Org. Chem.*, 1965, **30**, 2558.

28. A. N. Lautzenheiser and P. W. LeQuesne, *Tetrahedron Lett.*, 1969, 207.

29. S. H. Nahm and H. N. Cheng, *J. Org. Chem.*, 1986, **51**, 5093.

30. N. F. Cywinski, *J. Org. Chem.*, 1965, **30**, 361.

31. J. March, 'Advanced Organic Chemistry', McGraw-Hill, Tokyo, 1977.

32. M. F. Salomon, S. N. Pardo and R. G. Salomon, *J. Am. Chem. Soc.*, 1980, **102**, 2473.

33. L. M. Stephenson and M. Orfanopoulos, *J. Org. Chem.*, 1981, **46**, 2200.

34. L. M. Stephenson, M. J. Grdina and M. Orfanopoulos, *Acc. Chem. Res.*, 1980, **13**, 411.

35. Y. Elemes, M. Stratakis and M. Orfanopoulos, *Tetrahedron Lett.*, 1989, **30**, 6903.

36. J. Zhang and C. S. Foote, *Tetrahedron Lett.*, 1986, **27**, 6153.

37. W. Herz and R.-R. Jio, *J. Am. Chem. Soc.*, 1985, **50**, 618.

38. R. Schönberger and G. Kresze, *Liebigs Ann. Chem.*, 1975, 1725.

39. A. Marinetti, L. Ricard, F. Nathey, M. Slany and M. Regitz, *Tetrahedron*, 1993, **49**, 10279.

40. U. Annen and M. Regitz, *Tetrahedron Lett.*, 1988, **29**, 1681.

41. C. A. Seymour and F. D. Greene, *J. Org. Chem.*, 1982, **47**, 5227.

42. G. E. Keck, R. R. Webb and J. B. Yates, *Tetrahedron*, 1981, **37**, 4007.

43. F. R. Benn, J. Dwyer and I. Chappel, *J. Chem. Soc. Perkin Trans. 2*, 1977, 533.

44. W. D. Huntsman and T. H. Curry, *J. Am. Chem. Soc.*, 1958, **80**, 2252.

45. W. D. Huntsman, V. C. Solomon and D. Eros, *J. Am. Chem. Soc.*, 1958, **80**, 5455.

46. T. R. Kelly, *Tetrahedron Lett.*, 1973, **14**, 437.

47. M. C. Lasne and J. L. Ripoll, *Synthesis*, 1985, 121.

48. J.-L. Ripoll and Y. Valée, *Synthesis*, 1993, 659.

49. R. F. C. Brown, 'Pyrolytic Methods in Organic Chemistry', ed. Wassermann, Academic, New York, 1980.

50. D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry', McGraw-Hill, London, 1989.

51. C. J. Moody, *Adv. Het. Chem.*, 1982, **30**, 1.

52. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1927, **450**, 237.

53. R. Askani, *Chem. Ber.*, 1965, **98**, 2551.

54. D. Barton, X. Lusinchi and J. S. Ramírez, *Tetrahedron Lett.*, 1983, **24**, 2995.

55. W. H. Pirkle and J. C. Stickler, *J. Chem. Soc. Chem. Commun.*, 1967, 760.

56. S. Ohashi, K. Leong, K. Matyaszewski and G. B. Butler, *J. Org. Chem.*, 1980, **45**, 3467.

57. S. Ohashi and G. B. Butler, *J. Org. Chem.*, 1980, **45**, 3472.

58. F. Jensen and C. S. Foote, *J. Am. Chem. Soc.*, 1987, **109**, 6576.

59. E. J. Corey and B. B. Snider, *Tetrahedron Lett.*, 1973, **14**, 3091.

60. T. S. Chen and G. B. Butler, *J. Macromol. Sci.-Chem. A16*, 1981, 757.

61. M. Orfanopoulos, Y. Elemes and M. Stratakis, *Tetrahedron Lett.*, 1990, **31**, 5775.

62. R. M. Borzilleri and S. M. Weinreb, *Synthesis*, 1995, 347.

63. J.-M. Lin, K. Koch and F. W. Fowler, *J. Org. Chem.*, 1986, **51**, 167.

64. O. Achmatowicz, Jnr. and M. Pietraszkewicz, *J. Chem. Soc. Perkin Trans. 1*, 1981, 2680.

65. W. Starflinger, G. Kresze and K. Huss, *J. Org. Chem.*, 1986, **51**, 37.

66. S. M. Weinreb and J. I. Levin, *Heterocycles*, 1979, **12**, 949.

67. D. Ben Ishai and E. Goldstein, *Tetrahedron*, 1971, **27**, 3119.

68. B. Evnin, A. Lam and J. Blyskal, *J. Org. Chem.*, 1970, **35**, 3097.

69. G. R. Krow, C. Johnson and M. Boyle, *Tetrahedron Lett.*, 1978, **23**, 1971.

70. H. J. Bestmann and R. Zimmermann, *Chem. Ber.*, 1968, **101**, 2185.

71. H. Plieninger and D. vor der Brück, *Tetrahedron Lett.*, 1968, 4371.

72. H. E. Zaugg, *Synthesis*, 1993, 85.

73. H. E. Zaugg, *Synthesis*, 1993, 181.

74. P. B. Valkovitch and K. J. Chou, USA, US4,973,732, 1990, 77pp.

75. J. Thiele and O. Stange, *Justus Liebigs Ann. Chem.*, 1894, **283**, 1.

76. M. J. Bausch, B. David, P. Dobrowolski, C. Guadalupe-Fasano, R. Gostowski, D. Selmarten, V. Prasad, A. Vaughn and L.-H. Wang, *J. Org. Chem.*, 1991, **56**, 5643.

77. G. Read and N. R. Richardson, *J. Chem. Soc. Perkin Trans. I*, 1996, 167.

78. R. C. Cookson, S. S. Gupte, I. D. R. Stevens and C. T. Watts, *Org. Synth.*, 1971, **51**, 121.

79. L. A. Paquette and J. Döhner, *J. Org. Chem.*, 1980, **45**, 5105.

80. W. Bunge, *Angew. Chem.*, 1960, **72**, 1002.

81. H. Pelster, E. Muehlbauer and D. Delfs, Belgium, Belg. 631,961, 1963, 42pp.

82. V. L. K. Valli and H. Alper, *J. Org. Chem.*, 1995, **60**, 257.

83. S. Patai, 'Chemistry of Cyanates and their Thio Derivatives Parts I and II' from 'The Chemistry of Functional Groups', ed. S. Patai, Wiley, Chichester, UK, 1977.

84. D. D. Hurd and F. F. Cesark, *J. Am. Chem. Soc.*, 1967, **89**, 1417.

85. H. Giesecke, R. Merten and L. Rottmaier, Germany, DE 3027612 A1, 1982, 23pp.

86. F. W. Linch, *J. Chem. Soc. (London)*, 1912, **101**, 1755.

87. R. Stollé, *Ber. Dtsch. Chem. Ges.*, 1913, **46**, 260.

88. S. E. Malakpour, G. B. Butler, H. Aghabozorg and G. J. Palenik, *Macromolecules*, 1985, **18**, 342.

89. SpecInfo version 3, © Chemical Concepts, Germany, used courtesy of Daresbury Laboratory, 1996

90. P. Ashkenazi, R. D. Macfarlane, W. A. Örtling, H. Wamhoff, K. M. Wald and D. Ginsburg, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 933.

91. P. Ashkenazi, R. D. Macfarlane, W. A. Örtling, H. Wamhoff, K. M. Wald and D. Ginsburg, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 936.

92. B. Saville, *J. Chem. Soc. Chem. Commun.*, 1971, 635.

93. R. Stollé, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 273.

94. B. T. Gillis and J. D. Haggarty, *J. Org. Chem.*, 1967, **32**, 330.

95. J. C. Stickler and W. H. Pirkle, *J. Chem. Soc.*, 1966, **31**, 3442.

96. H. Wamhoff and K. Wald, *Org. Prep. Proc. Int.*, 1975, **7**, 251.

97. T. G. Back, S. Collins and R. G. Kerr, *J. Org. Chem.*, 1981, **46**, 1564.

98. J. A. Moore, R. Muth and R. Sorace, *J. Org. Chem.*, 1974, **39**, 3799.

99. H. Wamhoff and G. Kunz, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 797.

100. J. E. Herweh and R. M. Fantazier, *Tetrahedron Lett.*, 1973, **14**, 2101.

101. R. A. Clement, *J. Org. Chem.*, 1962, **27**, 1115.

102. T. J. Kealy, *J. Am. Chem. Soc.*, 1962, **84**, 966.

103. C. M. Buchan, J. I. G. Cadogan, I. Gosney, B. J. Hamill, S. F. Newlands and D. A. Whan, *J. Chem. Soc. Chem. Commun.*, 1983, 725.

104. U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863.

105. D. Ben Ishai and S. Hirsch, *Tetrahedron Lett.*, 1983, **24**, 955.

106. D. Ben Ishai, R. Moshenberg and J. Altmann, *Tetrahedron*, 1977, **33**, 1533.

107. D. Ben Ishai, G. Ben-Et and A. Warshawsky, *J. Het. Chem.*, 1970, **7**, 1289.

108. K. Lempert, L.-S. M., I. Patakey and K. Pfeifer, *Magyar Kém. Folyoirat*, 1959, **65**, 107.

109. A. J. Hoefnagel, H. van Bekkum and J. A. Peters, *J. Org. Chem.*, 1992, **57**, 3916.

110. L. M. Rice, C. H. Grogan and E. E. Reid, *J. Am. Chem. Soc.*, 1953, **75**, 2261.

111. A. C. Farthing, *J. Am. Chem. Soc.*, 1950, **72**, 3213.

112. D. Ben Ishai, J. Altmann and Z. Bernstein, *Tetrahedron*, 1977, **33**, 1191.

113. W. Chiti and R. Selleri, *Il Farmaco Ed. Sci.*, 1956, **11**, 607.

114. C. Rav-acha, I. Ringel, S. Sarel and J. Katzenhendler, *Tetrahedron*, 1988, **44**, 5879.

115. Y. A. Baskakov and N. N. Melnikov, *Zhur. Obshchei Khim.*, 1954, **24**, 1216.

116. E. Fischer and E. Otto, *Ber. Dtsch. Chem. Ges.*, 1901, **36**, 2106.

117. A. Schouteeten and Y. Christidis, Germany, Ger. Offen 2,748,072, 1978, 17pp.

118. H. Leuchs, *Ber. Dtsch. Chem. Ges.*, 1907, **37**, 738.

Appendix

Crystal structure of 4-(3'-(*N,N*-dimethylamino)propyl-1,2,4-triazolidine-3,5-dione

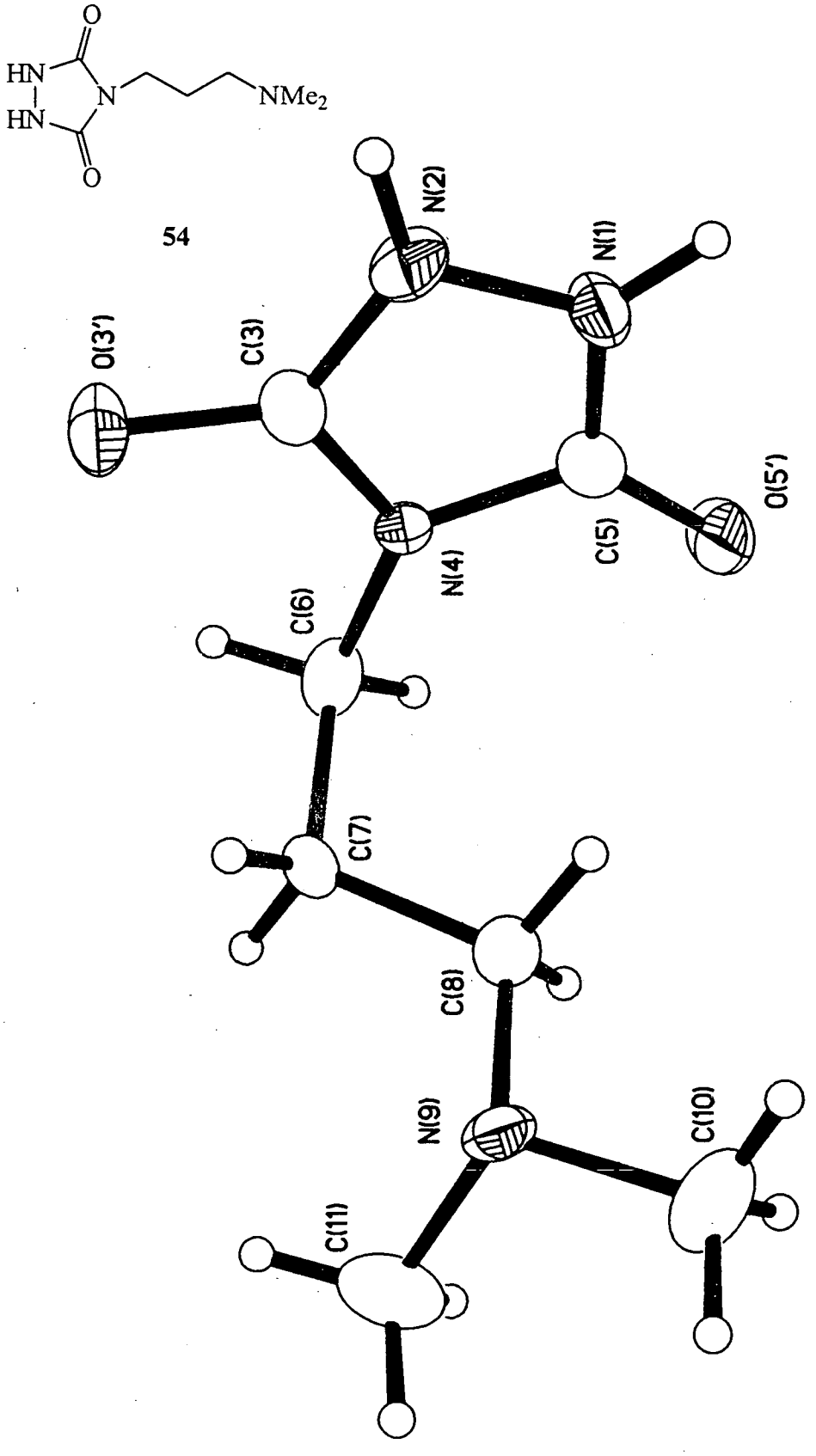

HN
HN
N
NMe2
O
O
54
N(2)
N(1)
O(3')
C(3)
O(5')
C(5)
N(4)
C(6)
C(7)
C(8)
N(9)
C(10)
C(11)

Table 1. Crystal data and structure refinement for 1.

Identification code	c7n4o2
Empirical formula	C7 H14 N4 O2
Formula weight	186.22
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 5.662(2) A alpha = 90 deg. b = 15.584(4) A beta = 97.12(2) deg. c = 10.791(3) A gamma = 90 deg.
Volume	944.8(5) A^3
Z	4
Density (calculated)	1.309 Mg/m^3
Absorption coefficient	0.098 mm^-1
F(000)	400
Crystal size	0.60 x 0.23 x 0.12 mm
Theta range for data collection	2.61 to 22.53 deg.
Index ranges	-6<=h<=6, 0<=k<=16, 0<=l<=11
Reflections collected	1239
Independent reflections	1239 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1233 / 0 / 120
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0853, wR2 = 0.1607
R indices (all data)	R1 = 0.2252, wR2 = 0.2304
Largest diff. peak and hole	0.241 and -0.368 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	5104(13)	531(5)	1434(6)	45(2)
N(2)	5251(13)	1123(4)	2400(7)	45(2)
C(3)	3630(15)	887(6)	3083(8)	36(2)
O(3')	3056(10)	1249(4)	4072(6)	49(2)
N(4)	2427(13)	171(4)	2558(6)	33(2)
C(5)	3388(18)	-38(6)	1490(8)	44(2)
O(5')	2816(12)	-656(4)	803(6)	62(2)
C(6)	494(15)	-258(5)	3031(8)	40(2)
C(7)	1308(15)	-890(5)	4078(7)	41(2)
C(8)	2613(15)	-1653(5)	3598(8)	45(3)
N(9)	3896(13)	-2183(4)	4615(6)	37(2)
C(10)	5358(16)	-2836(6)	4073(9)	62(3)
C(11)	2178(17)	-2604(6)	5386(8)	64(3)

Table 3. Bond lengths [A], angles and torsions [deg] for 1.

N(1)-C(5)	1.322(10)
N(1)-N(2)	1.386(8)
N(2)-C(3)	1.299(10)
C(3)-O(3')	1.284(9)
C(3)-N(4)	1.390(9)
N(4)-C(5)	1.373(10)
N(4)-C(6)	1.430(10)
C(5)-O(5')	1.234(10)
C(6)-C(7)	1.526(10)
C(7)-C(8)	1.524(10)
C(8)-N(9)	1.488(9)
N(9)-C(10)	1.477(10)
N(9)-C(11)	1.507(9)
C(5)-N(1)-N(2)	112.8(7)
C(3)-N(2)-N(1)	104.9(7)
O(3')-C(3)-N(2)	128.0(8)
O(3')-C(3)-N(4)	122.0(8)
N(2)-C(3)-N(4)	109.9(7)
C(5)-N(4)-C(3)	107.9(7)
C(5)-N(4)-C(6)	126.1(7)
C(3)-N(4)-C(6)	126.0(7)
O(5')-C(5)-N(1)	129.5(9)
O(5')-C(5)-N(4)	126.0(9)
N(1)-C(5)-N(4)	104.4(8)
N(4)-C(6)-C(7)	113.1(7)
C(8)-C(7)-C(6)	111.5(6)
N(9)-C(8)-C(7)	113.3(6)
C(10)-N(9)-C(8)	109.7(7)
C(10)-N(9)-C(11)	110.5(7)
C(8)-N(9)-C(11)	111.0(7)
C(5)-N(1)-N(2)-C(3)	2.2(10)
N(1)-N(2)-C(3)-O(3')	-178.4(8)
N(1)-N(2)-C(3)-N(4)	-1.3(9)
O(3')-C(3)-N(4)-C(5)	177.4(8)
N(2)-C(3)-N(4)-C(5)	0.1(9)
O(3')-C(3)-N(4)-C(6)	-1.3(12)
N(2)-C(3)-N(4)-C(6)	-178.6(7)
N(2)-N(1)-C(5)-O(5')	-178.1(9)
N(2)-N(1)-C(5)-N(4)	-2.1(10)
C(3)-N(4)-C(5)-O(5')	177.4(9)
C(6)-N(4)-C(5)-O(5')	-3.9(14)
C(3)-N(4)-C(5)-N(1)	1.2(9)
C(6)-N(4)-C(5)-N(1)	179.9(7)
C(5)-N(4)-C(6)-C(7)	99.5(9)
C(3)-N(4)-C(6)-C(7)	-82.1(9)
N(4)-C(6)-C(7)-C(8)	-67.7(9)
C(6)-C(7)-C(8)-N(9)	167.2(7)
C(7)-C(8)-N(9)-C(10)	-172.6(7)
C(7)-C(8)-N(9)-C(11)	65.0(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	55(6)	47(5)	39(5)	-14(4)	23(4)	-17(4)
N(2)	48(5)	34(5)	53(5)	-14(4)	5(4)	-19(4)
C(3)	33(6)	44(6)	30(5)	-2(5)	1(5)	3(5)
O(3')	47(4)	57(4)	45(4)	-21(3)	16(3)	-4(3)
N(4)	42(5)	23(4)	35(4)	-2(4)	15(4)	-8(4)
C(5)	63(7)	41(6)	26(5)	2(5)	5(5)	2(6)
O(5')	97(6)	47(4)	45(4)	-22(4)	28(4)	-26(4)
C(6)	31(6)	46(6)	42(6)	-12(5)	-3(5)	6(5)
C(7)	51(6)	39(6)	36(5)	2(4)	23(5)	4(5)
C(8)	47(7)	42(6)	49(6)	0(5)	16(5)	2(5)
N(9)	51(5)	24(4)	35(4)	5(4)	-2(4)	4(4)
C(10)	59(7)	54(7)	69(7)	-20(6)	-10(6)	14(6)
C(11)	67(8)	68(7)	54(7)	16(6)	-4(6)	-28(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(1)	6030(13)	534(5)	860(6)	54
H(2)	6205(13)	1553(4)	2521(7)	54
H(6A)	-427(15)	-565(5)	2353(8)	48
H(6B)	-540(15)	166(5)	3341(8)	48
H(7A)	2355(15)	-599(5)	4723(7)	49
H(7B)	-65(15)	-1094(5)	4446(7)	49
H(8A)	1471(15)	-2013(5)	3094(8)	54
H(8B)	3747(15)	-1445(5)	3065(8)	54
H(10A)	6102(84)	-3200(24)	4726(11)	93
H(10B)	6560(68)	-2557(6)	3665(48)	93
H(10C)	4362(24)	-3175(25)	3478(41)	93
H(11A)	1395(79)	-2171(6)	5821(45)	96
H(11B)	3029(24)	-2986(29)	5980(39)	96
H(11C)	1013(67)	-2922(33)	4848(10)	96