SOME PERSPECTIVES ON THE DESIGN AND DISCOVERY OF NEW MULTI-COMPONENT REACTIONS

by

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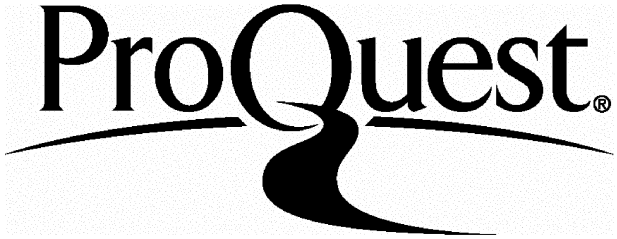

ABSTRACT

This thesis is divided into three parts. Part one presents an overview of multi-component reactions, contrasting isocyanide based and non-isocyanide based multi-component reactions, and gives examples of the most important examples of these types of reactions. In addition, a brief discussion of 1,3-dipolar cycloadditions is given to serve as a framework for the discussion in part two of the results obtained.

Part two is divided into three sections and discusses two conceptually different approaches to the development of new multi-component reactions. The first discusses the use of combinatorial methods for the generation and screening of reaction libraries and the limitations encountered in this approach. The second section deals with the use of isocyanides in a 1,4-cycloaddition followed by a 1,3-dipolar cycloaddition affording isoxazolines. A series of isocyanides were successfully employed both in an intra- and intermolecular fashion. Furthermore, the results gained from attempts using electron rich dipolarophiles as trapping agents in the latter 1,3-dipolar cycloaddition, suggest an alternative mechanism proceeding through an intermediate nitronate, rather than the nitrile oxide as previously assumed. The initial low yields were improved upon by the use of lithium perchlorate as a promoter of the cycloaddition reaction. The third section details the attempts made at utilising silylated nucleophiles to generate silylnitronates from nitroalkenes and their subsequent use in inter- and intramolecular 1,3-dipolar cycloadditions.

Part three describes the experimental procedures employed and results obtained.

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The time spent under Willie's wing has been exceptional in the happy personal chemistry that I have come to know in the lab. The joy of working in the lab is in no short measure thanks to the particularly friendly and talented people, past and present, in the group, who bring

with them a rich international flair into the lab. The past members of the group, who have gone before me, Ray, Marta, Mike, Tilly and Matt have been role models and heroes one and all! Working in Willie's group I have been blessed with being able to learn from the experience of some wonderful post-docs: Yvan, Pierre, Santi, Christoph, Isabelle B. and Isabelle G., Julien, Rosa. The current members of the group, Catherine, Rehan, Camilla, Beatrice, Marta, Karim, Charlotte, and post-docs Lynda and Geraldine I thank for the friendship they offered an oftentimes grumpy final year PhD student and making life in the lab the happy thing that it is. Particular thanks go to Catherine, Beatrice, Rehan, Lynda and Camilla for their keen proof reading.

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I thank my parents, without whose support none of this would have been possible.

And last but not least I thank my long-suffering wife, Sabrina: *fiep!*

ABBREVIATIONS

Ac	acetyl
APCI	atmospheric pressure chemical ionisation
Ar	aryl
b.p.	boiling point
BB-4CR	Bucherer-Bergs 4-component reaction
br	broad
CI	chemical ionisation
d	doublet
DABCO	diaza-bicylo-octane
DCM	dichloromethane
dd	double doublet
DMF	dimethyl formamide
DMSO	dimethylsulphoxide
dt	double triplet
EI	electron impact
equiv.	equivalents
Et	ethyl
EtOH	ethanol
FAB	fast atom bombardment
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infra red spectroscopy
J	coupling constant
LC/MS	liquid chromatography/mass spectrometry
m	multiplet (NMR) or medium (IR)
m.p.	melting point
MCC	multi-component condensation
MCR	multi-component reaction
Me	methyl
MeO	methoxy
MeOH	methanol
MS	mass spectrometry
***n*CR**	*n*-component reaction
NMR	nuclear magnetic resonance spectroscopy
noe	nuclear Overhauser effect
P-3CR	Passerini 3-Component Reaction
Ph	phenyl
ppm	parts per million

q	quartet
R	unspecified substituent
rt	room temperature
s	singlet (NMR) or strong (IR)
t	triplet
TBAF	tetrabutylammonium fluoride
tlc	thin layer chromatography
TMS	trimethylsilyl
TPA	tonnes per annum
Ts	tosyl
U-4CR	Ugi 4-component reaction
w	weak
Z	electron withdrawing group

Part 1:

INTRODUCTION

1.1 General Remarks

The present thesis is concerned with a search for new multi-component reactions (MCRs). A unifying theme has evolved during the course of this work inasmuch as the reactions described herein involve, in the first instance, the addition of either an isocyanide or a nucleophile to a nitroalkene, followed by a 1,3-dipolar cycloaddition.

It is therefore appropriate to discuss the concept and historical evolution of multi-component reactions, and to give some examples of the most important instances of this reaction type. Additionally a brief theoretical framework and background relating to selectivity in 1,3-dipolar cycloadditions is provided, since this is germane to the discussion of the results obtained.

Consequently, the introduction is divided into two chapters: The first chapter gives an overview of multi-component reactions and categorises them broadly into isocyanide based and non-isocyanide based multi-component reactions. The second chapter deals with the theoretical foundations of 1,3-dipolar cycloadditions, touching on the controversy between Huisgen and Firestone over the mechanistic details of the cycloaddition and then introducing the relevant concepts of frontier molecular orbital theory for a discussion of the selectivity in such cycloadditions.

1.2 Introduction and Definition of the Concept of Multi-Component Reactions

Within the area of invention and discovery of new reactions for organic synthesis, an especially promising area is the search for novel multi-component reactions.

MCRs belong to the most challenging areas of modern chemistry for several reasons. With MCRs, very complex target molecules can be synthesised in one operation from simple starting materials. These types of reactions can also be termed the most focused/convergent synthesis possible. Furthermore, by using appropriate components, certain properties of the target structure such as hydrophobicity, can be designed. With regard to yields and stereo selectivity, MCRs can often be superior to their multi step counterparts.

Within this context, we will define MCRs as *reactions involving at least three different functional groups, some of which may, however, be part of the same reagent molecule, yielding a product, which incorporates substantial portions of the starting materials.* As we shall see, examples of MCRs can be traced back almost as far as the beginnings of organic chemistry with reactions such as the Strecker synthesis of 1850, the Mannich condensation and the Bucherer-Bergs and Passerini reactions (*vide infra* 1.3.2). Multi million TPA processes such as the Roelen[1] reaction and Reppe[2] carbonylations also belong to the diverse group of MCRs, and although they utilise carbon monoxide instead of an isocyanide, they have been included in the group of isocyanide based MCRs because of the molecular orbital homology carbon monoxide shares with isocyanides.

1.2.1 Efficiency and Diversity of MCRs

Of all the tools available to the synthetic organic chemist, multi-component reactions (MCRs) are often claimed to be the most effective[3,4,5] with their proponents arguing that they are superior to all other reactions, not only by virtue of their atom economy, but also on aesthetic grounds.

Synthetic efficiency has been a topic of interest to chemists in general and synthetic organic chemists in particular, since the beginnings of the discipline. Over the past century, chemists have learned to synthesise increasingly complex molecules by ever more elegant means. The efficiency aspect of MCRs is linked to Trost's ideas on synthetic efficiency and atom economy[6]. Reducing waste products and incorporating as much material as possible from the starting materials into the products make for more efficient use of resources. As an example the Diels-Alder cycloaddition may be sited as an example of a reaction with 100% atom efficiency, all atoms of the starting materials are incorporated into the final product and the reaction does not necessarily require the use of solvents, thus reducing potential waste (Fig. 1).

Figure 1

A further point to be made in this context is that synthetically efficient processes form more than one new bond in a single step. Indeed, whilst the Diels-Alder reaction creates two new bonds in a single step, other reactions also share this feature of multiple bond formation. As we shall see later, the Ugi reaction is particularly noteworthy in this respect in being able to make up to eight new bonds in a single sequence.

A further important feature of MCRs, which is also linked to the concept of efficiency, may be summed-up by the key-words 'chemical diversity' and 'chemical library'. As many pharmacologically active

compounds are found by screening procedures and not by so called rational design, new and effective techniques to provide large libraries of new potential candidates based on MCRs are of interest to all pharmaceutical companies. Due to the limitations of chemists to tailor make drugs based on known characteristics, the number of tested compounds derived from traditional methods is relatively small. The new strategy is to produce a defined pool of target molecules by combining a given set of components by MCR and assay the resulting molecules in one step. Obviously, such procedures are much less time consuming and are able to enlarge the number of candidates to be tested in the screening pipeline. The goal is to produce as many new substances as possible from a pool of commercially available starting materials. Whilst many chemical libraries consist of nucleic acids and peptides, these compounds have the disadvantages of not being resistant towards enzymatic degradation and cannot therefore be taken orally. Classical drugs are small molecules, which do not have the disadvantages of nucleic acids and peptides. Ongoing efforts are being directed to creating small molecules with the aid of the combinatorial power of MCRs.

The combinatorial aspect of MCRs was first recognised by Ivar Ugi[7] in the early 60's, long before anyone conceptualised this kind of chemistry. Multi-component reactions have a very high combinatorial efficiency.

We can summarise the advantages of an ideal MCR *versus* a standard reaction as follows:

- Material savings
- Time savings
- Ease of purification

- Higher yields than in comparable multistep reactions
- Fewer by-products
- Higher atom economy
- Maximum convergence
- Generality
- Lack of intermediates requiring risk assessments in manufacturing processes (ecology)

1.2.2 Different Types of MCRs

The most noteworthy aspect of multi-component reactions is the presence of many chemical species, without the accumulation of any intermediates. MCRs share this characteristic with biochemical processes. The requirement here, as in biochemistry, is that all chemical species are in equilibrium with each other. A further commonality with biochemical reactions is the exothermicity of the product forming step. For preparative MCRs in which the product should accumulate, the further requirement of quasi irreversibility in the final step is added[8]. Ugi has classified multicomponent reactions into three types[8] as shown in Fig. 2:

- Type I reactions, which are a series of equilibria.

- Type II reactions in which a series of equilibria are followed by an irreversible product forming step.

- Type III reactions in which all steps are irreversible.

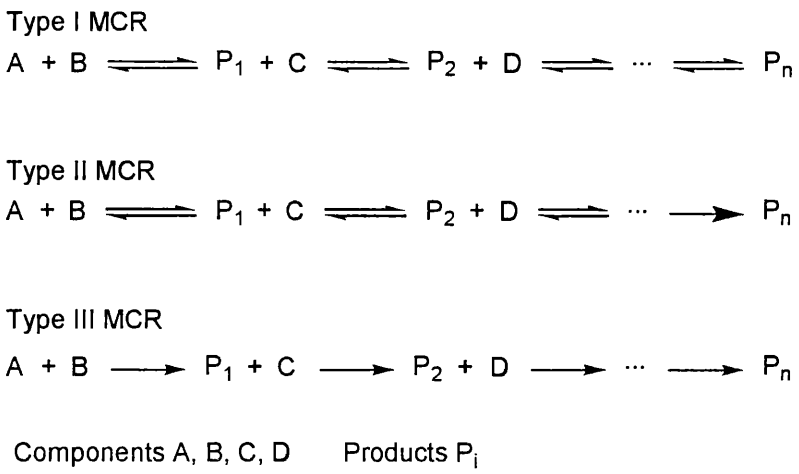


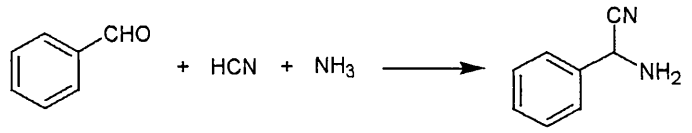
Figure 2: Ugi's classification of MCRs

1.2.3 Historically Important MCRs

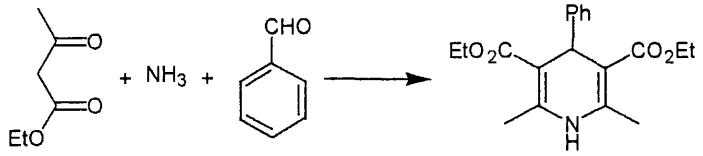
Historically, as tabulated in Figure 3 and Figure 4, a number of important non-isocyanide and isocyanide based multi-component reactions have been discovered. The earliest of these, although it was not termed as such until recently, was the Strecker reaction[9] in which ammonia and an aldehyde react with hydrogen cyanide to form a cyanohydrin, which can then be hydrolysed to the corresponding amino acid.

Most of these lead to heterocyclic systems. In Figure 4, the most relevant isocyanide based multi-component reactions are listed. Two of the most famous examples of this class of reaction are the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR). What sets these reactions apart from those in Figure 3, is that they utilize isocyanide or the isologous carbon monoxide, as a key reagent. Indeed, over the past 5-10 years interest has burgeoned in the discovery of new MCRs, many of which have involved the use of isocyanides.

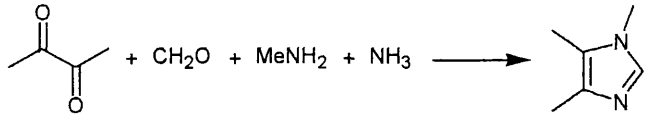
Strecker synthesis (1850)



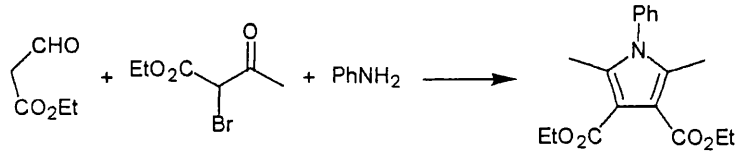
Hantzsch dihydropyridine synthesis (1882)



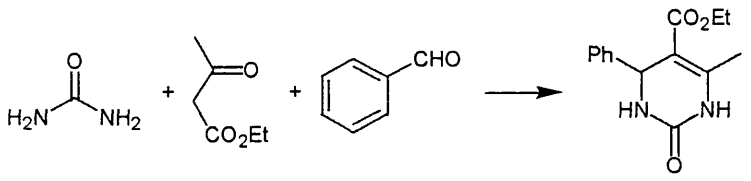
Radziszewski imidazole synthesis (1882)



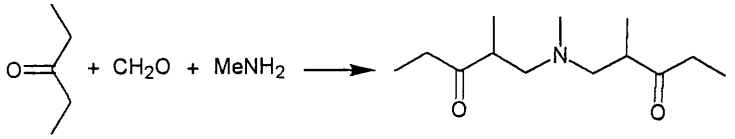
Hantzsch pyrrole synthesis (1890)



Biginelli reaction (1891)



Mannich reaction (1912)



Asinger condensation (1958)

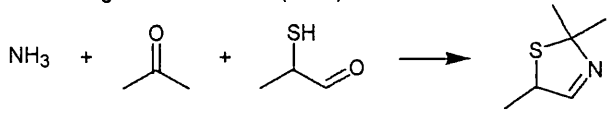
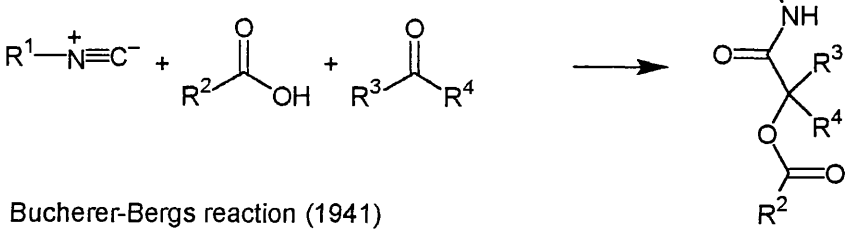
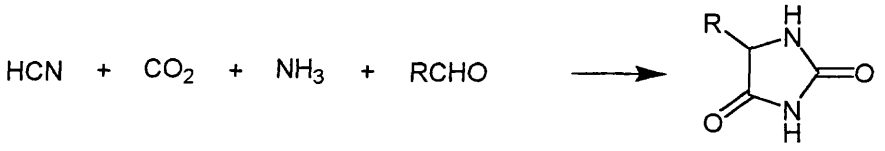


Figure 3

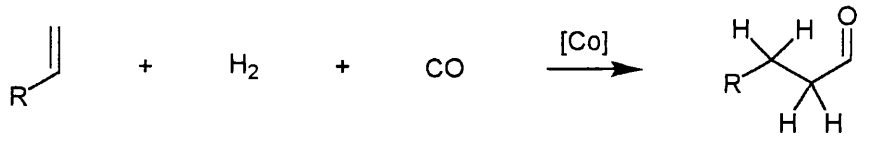
Passerini reaction (1921)



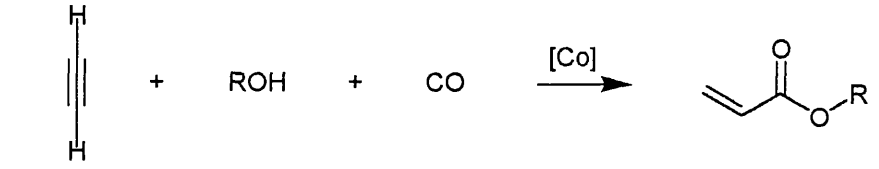
Bucherer-Bergs reaction (1941)



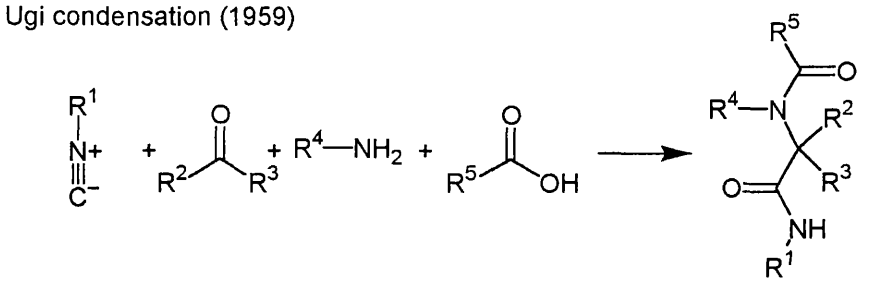
Roelen hydroformylation (1938)



Reppe carbonylation (1939)



Ugi condensation (1959)



Pauson-Khand reaction (1971)

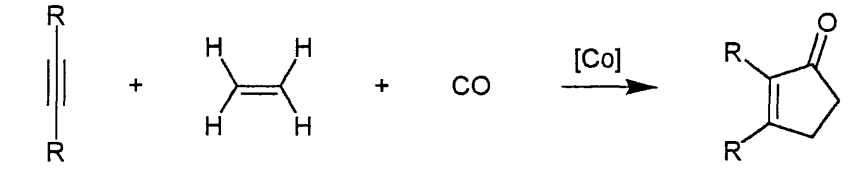


Figure 4: Isocyanide based MCRs

1.2.4 Biomimetic Aspects of MCRs

There are many remarkable parallels between MCRs and cellular biological processes. MCRs can, to some extent, be seen as biomimetic reactions and like most biochemical reactions they are of a consecutive nature, as they do not require the isolation of intermediates. It is often the case that many intermediates can coexist in different equilibria in biochemical transformations with the overall driving force being the coupling of energetically unfavourable reactions with energetically favourable ones. In MCRs, many equilibria also coexist, and the driving force in most cases is the final exothermic step. The biomimetic features of MCRs are twofold. In the first instance, there are biomimetically inspired syntheses such as Baldwin's synthesis of the Manzamines[10], among many more. However, the parallels with biology go beyond synthetic examples of bio-inspired chemistry – the entire concept of MCRs can be likened to the processes that occur in a living cell. All starting materials are present in the cell and are connected to each other under carefully controlled conditions to afford highly complex products in great purity and with complete control over regio- and stereoselectivity.

One of the earliest applications of multi-component chemistry was Robinson's synthesis of tropinone[11], a precursor of cocaine, by a Mannich 3-component condensation of succinic dialdehyde (**1**), methylamine (**2**) and acetone dicarboxylic acid (**3**) (Fig. 5). Indeed the Mannich reaction has remained a mainstay of synthetic organic chemistry to this day, in particular for alkaloid synthesis.

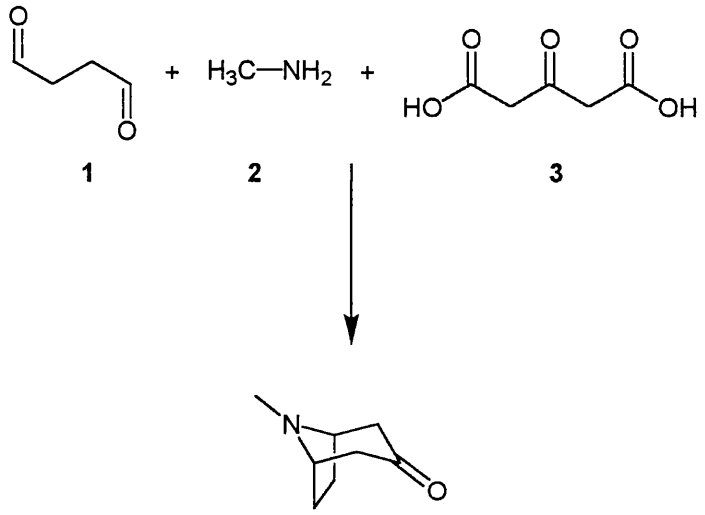


Figure 5

Two decades after Robinson performed his Tropinone synthesis, Schöpf[12] performed the Mannich reaction under physiological conditions.

1.3 Isocyanide Based Reactions

MCRs which employ isocyanides, such as the Ugi and Passerini reactions are amongst the most popular MCRs and, as a recent review[13] points out, some of the most efficient synthetic methods available to the preparative chemist. These reactions often constitute what might be termed a true MCR insofar that the reagents do not have to be added sequentially, as is often the case with other atom efficient procedures, such as domino reactions.

1.3.1 Special Features of Isocyanides

Like their isomers, the nitriles, isocyanides possess relatively acidic α-protons (Fig. 6). This has led to the use of α-metalated isocyanides in a

number of heterocyclic syntheses such as pyrroles[14], oxazolines[15], oxazoles[16] and imidazoles[17].

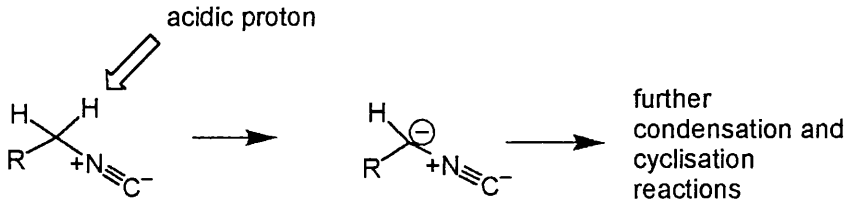


Figure 6

The unique feature about the chemistry of the isocyanides is of course that they belong to the very rare class of stable organic compounds with a formally divalent carbon (C^{II}). Their chemistry is therefore characterised by transformation to the tetravalent state (C^{IV}). The most striking feature of isocyanide chemistry is the ready α-addition this functional group undergoes (Fig. 7) to furnish imino derivatives (**4**). With heteroatom-hydrogen bonds this addition is catalysed by metals such as copper, silver or zinc to afford imino imidates (**5**)[18], phosphino imidates (**6**)[19], alkoxy imidates (**7**)[20] and thio imidates (**8**)[21]. Indeed, one of the first reactions of isocyanides was performed by Nef in which he treated an acyl chloride with an isocyanide to furnish a keto iminoyl chloride[22]. This reaction profile reveals that the isocyanide carbon can act as an 'ambiphile', inasmuch as it is both an electrophile and a nucleophile, whereas most other functional groups have their electrophilic and nucleophilic centres separated onto different atoms. Isocyanides share this ability to 'insert' into bonds with carbon monoxide and carbenes. Given the associated toxicity of carbon monoxide and the transience of short-lived carbenes, isocyanides therefore provide a superior ambiphile.

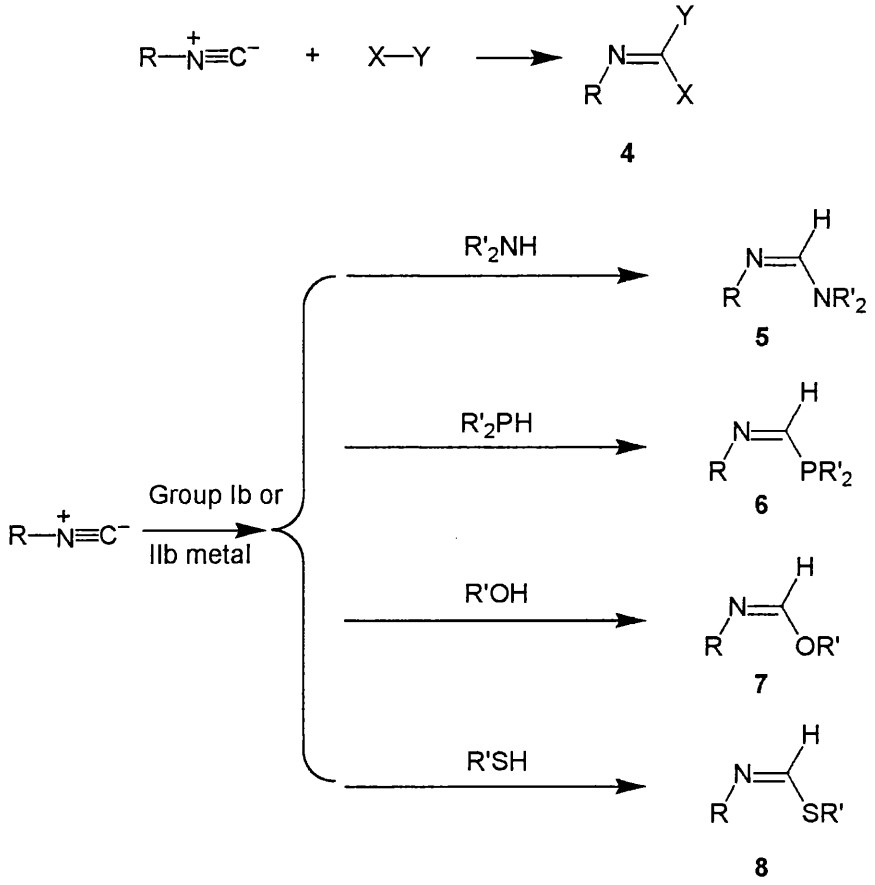


Figure 7: α-Addition Reactions of Isocyanides

From consideration of the important isocyanide based reactions in Figure 4 (p. 9) it becomes apparent that a number of reactions use isocyanides, cyanide or carbon monoxide as a key component. Their importance in these processes can be rationalised by contemplating the molecular orbital diagram of an isocyanide[23] (which is isolobal to carbon monoxide) and then comparing it with that of a nitrile (Fig.8). It is also significant to note that a number of MCRs with carbon monoxide have an isocyanide variant reaction, *e.g.* the isocyanide Pauson-Khand reaction[24].

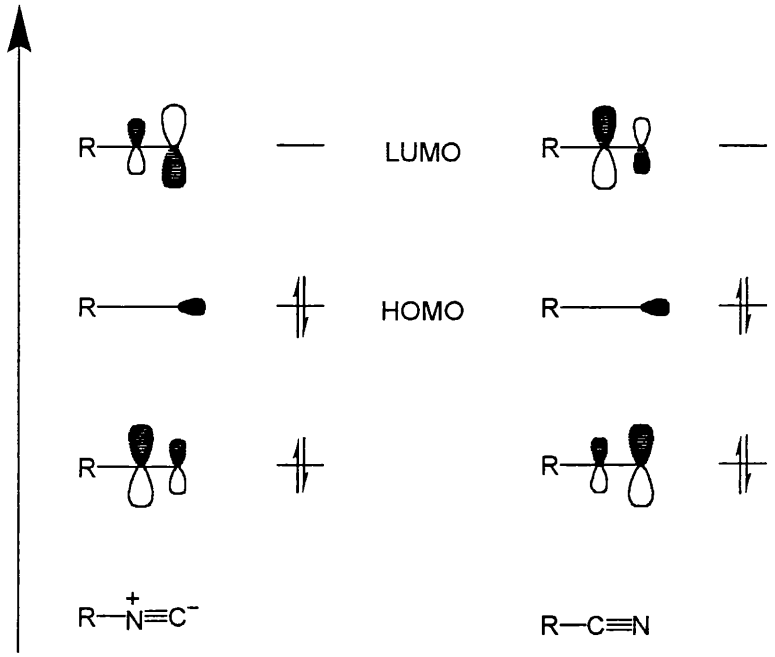


Figure 8: Frontier Molecular Orbitals of Isocyanide and Nitrile

Thus, it becomes apparent that the lone pair of electrons in the HOMO, *i.e.* the non-bonding σ-orbital, confers nucleophilic character onto the isocyanide, whereas the large LUMO orbital coefficient on the same carbon atom gives it its electrophilic nature. In contrast, the nucleophilic and electrophilic centres of the nitrile reside on different atoms. The nucleophilic HOMO is on the nitrogen atom, whereas the larger coefficient of the electrophilic LUMO is located on the carbon.

In the following sections we will introduce some of the most relevant isocyanide based MCRs, which illustrate their versatility and ambiphilic character.

1.3.2 Passerini Reaction

The Passerini reaction is the oldest isocyanide based MCR and was first performed in 1921. The reaction involves the formation of α-acyloxy amides from carboxylic acids (**9**), carbonyl compounds (**10**) and

isocyanides (Fig. 9). Polar protic solvents interfere with the reaction, suggesting an intermediate complex (**11**) with which the isocyanide undergoes α-addition to form (**12**) and then undergoes acyl migration to rearrange to the product (**13**).

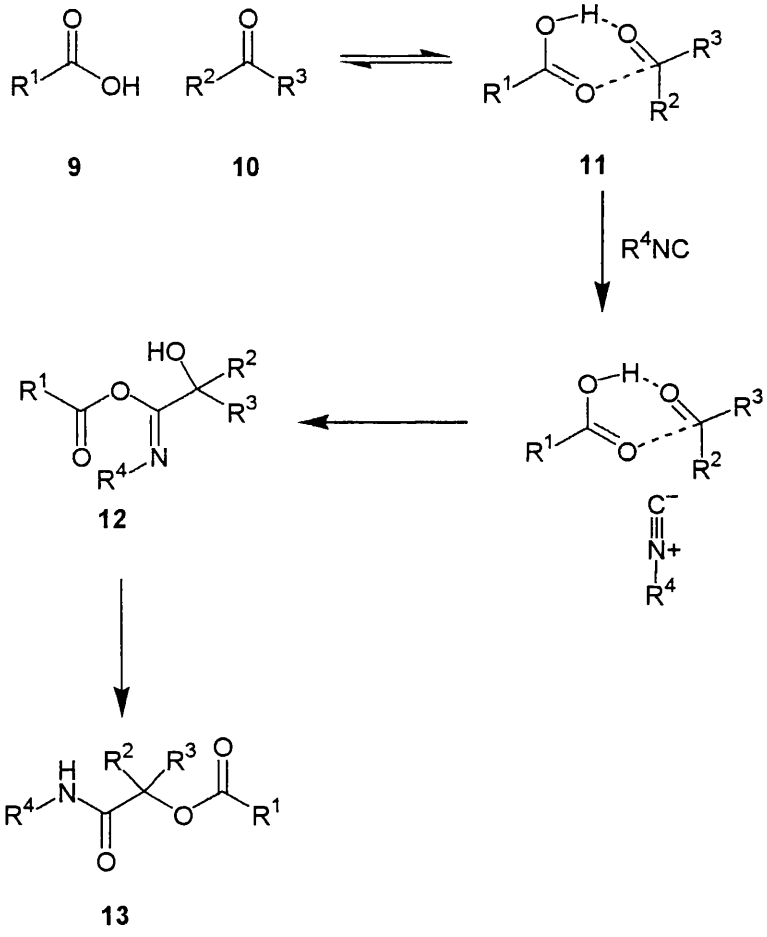
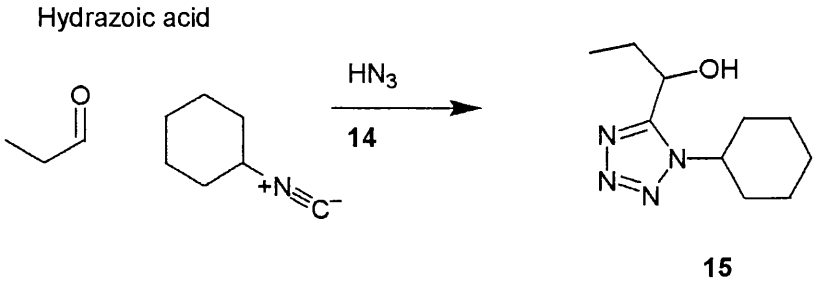
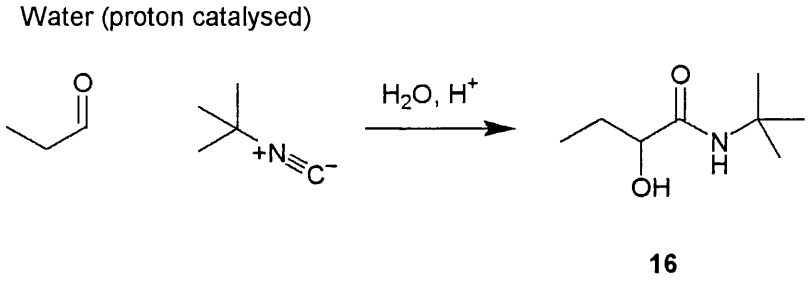


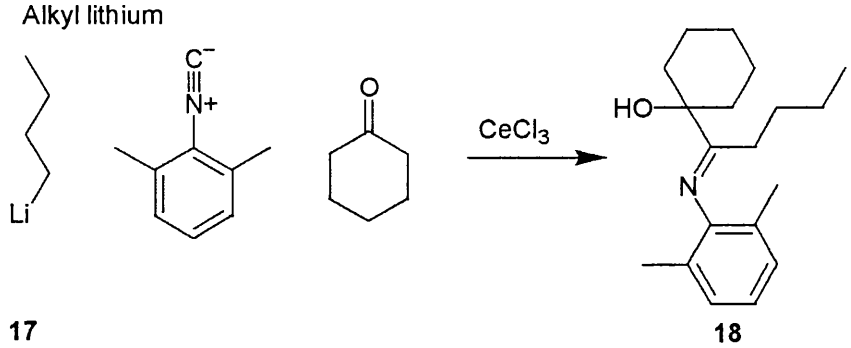
Figure 9: Mechanism of the Passerini Reaction

The Passerini reaction allows some variability in the type of reagents used. Notably, hydrazoic acid[25] (**14**), aqueous inorganic acids to catalyse the addition of water[26] and alkyllithium reagents[27] (**17**) can replace the carboxylic acid to afford tetrazoles (**15**), α-hydroxy amides (**16**) and α-

hydroxy imines (**18**) respectively (Fig. 10). Additionally, the carbonyl component can be exchanged for diphenylketene (**19**) to afford diketo amides (**20**)[28].


Hydrazoic acid
HN3
14
OH
N
N
N
N
15


Water (proton catalysed)
H2O, H+
O
N
H
OH
16


Alkyl lithium
Li
CeCl3
HO
N
17
18

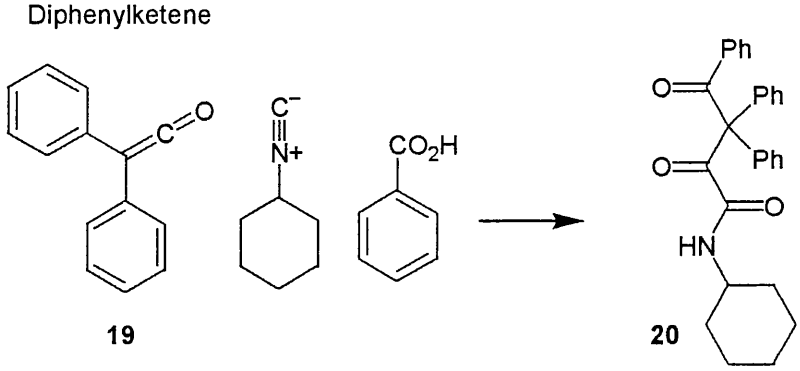
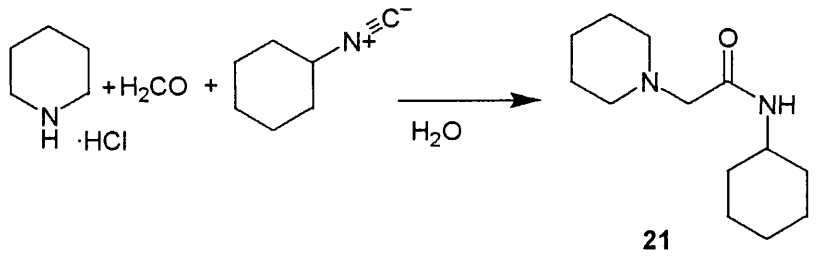

Diphenylketene
CO2H
Ph
Ph
Ph
HN
19
20

Figure 10

1.3.3 Ugi Reaction

The Ugi four-component condensation (U-4CC or U-4CR) was discovered in 1958 when Ivar Ugi instructed his student, Cornelius Steinbrückner to investigate the use of isocyanides as nucleophiles in the Mannich reaction[29]. The student duly treated a solution of piperidine hydrochloride with aqueous formaldehyde and cyclohexyl isocyanide and was surprised at the exothermicity of the reaction. Repeating the experiment (Fig. 11) at freezing bath temperature he was able to isolate the four-component product (**21**).



21

Figure 11

Within a short time, the reaction's scope and limitations were investigated, in particular with regard to the wide variety of acid and amine functionality that can be employed in the reaction. The result is a reaction of great scope, yielding heterocycles, such as tetrazoles and hydantoins, linear peptide-like structures, hydrazine derivatives and hydroxamic acid derivatives, to mention only a few (Fig. 12).

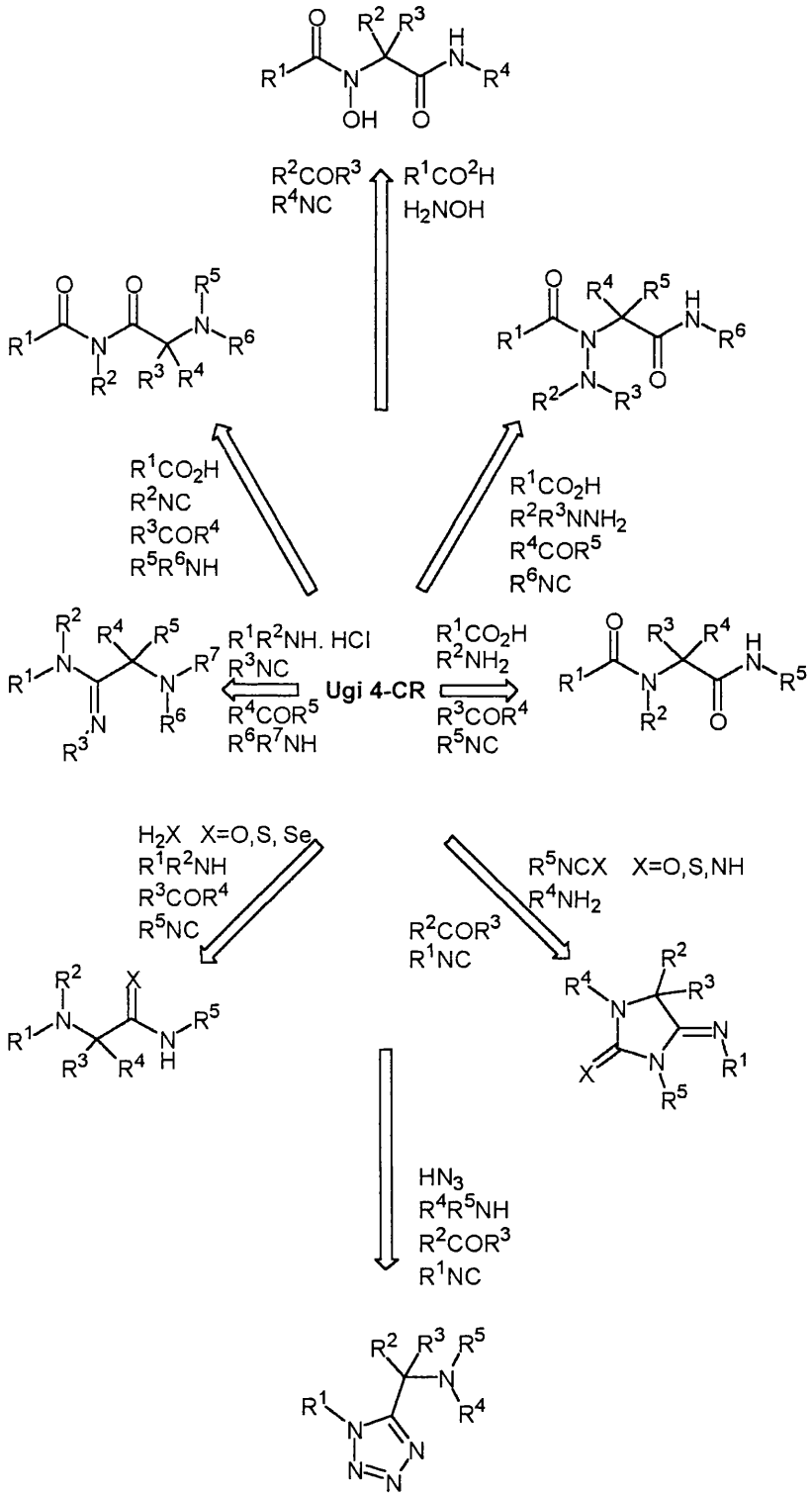
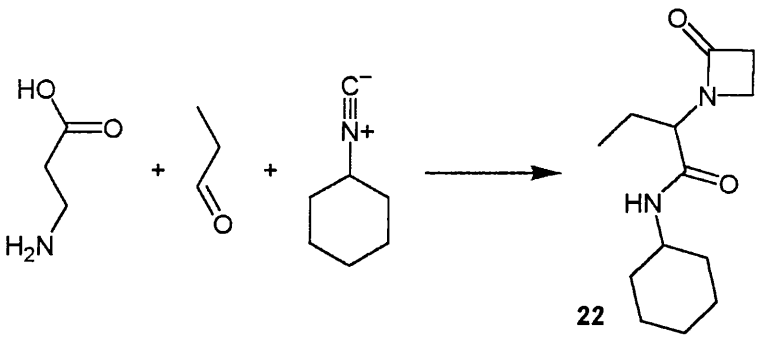


Figure 12: Scope and Variability of the Ugi-4CR

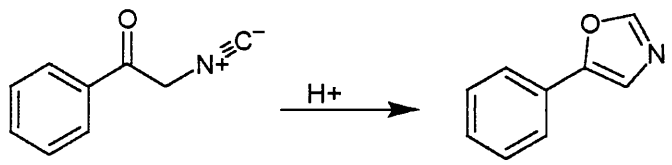
Moreover, the use of bifunctional reagents allows access to complex heterocycles such as the β-lactam (**22**) in one simple step (Fig. 13). Other structures arise from the use of keto carboxylic acids[30], isocyano carboxylic acids, amino carboxylic acids[31] or cyclic imines[32].



22

Figure 13

The only bifunctional reagents not to have been employed in the U-4CC are keto isocyanides. The latter compounds have not been synthesised, probably due to their inherent instability, as exemplified by the acid catalysed cyclisation of keto isocyanide (**23**) to form the corresponding oxazole derivative (**24**)[33] (Fig. 14).



23 **24**

Figure 14

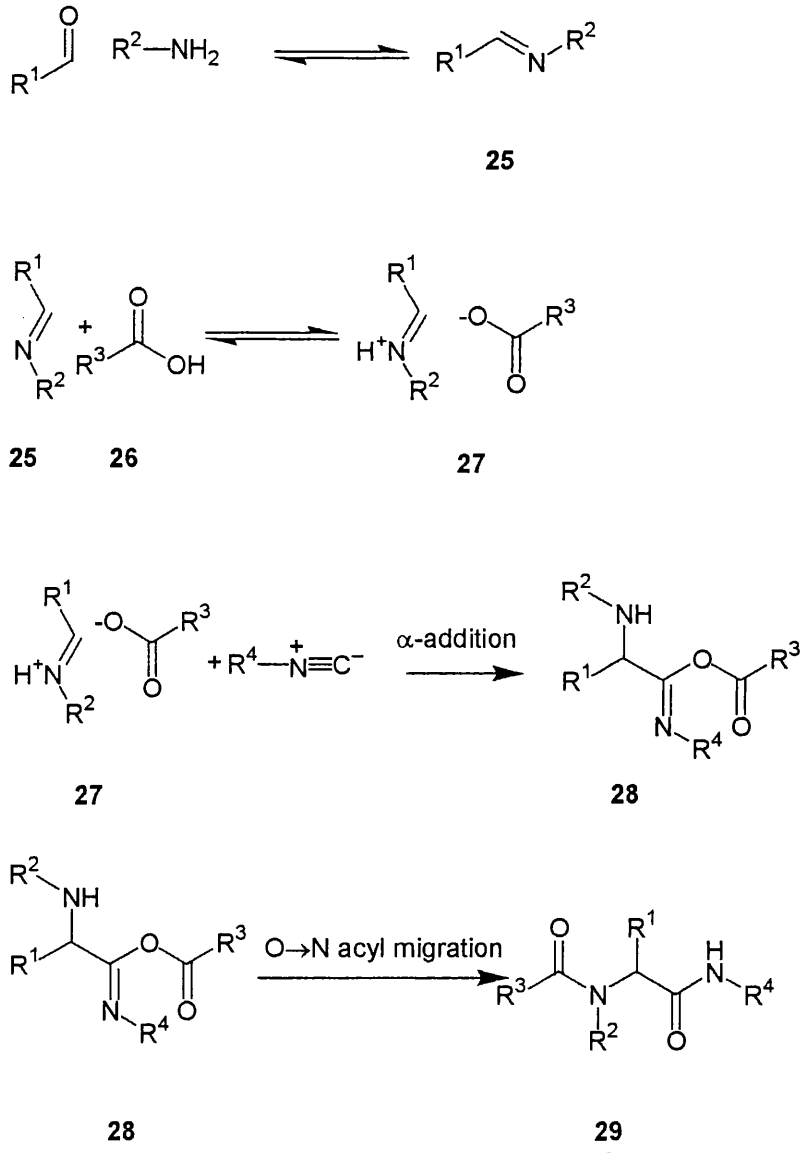
An intriguing point about the Ugi reaction is that the choice of solvent has an immense effect on the outcome of the reaction. When the reaction is carried out in methanol or a similar polar protic solvent the isolated product is the expected U-4CR product. However, when the reaction is carried out in a non-polar, non-protic solvent such as DCM, the amine does not take part in the reaction and the only product isolated is from the reaction of the acid, the carbonyl compound and the isocyanide, *i.e.* the Passerini product[34].

Mechanism of the U-4CR. Many reactions in organic chemistry are highly susceptible to the order in which reagents are added. The Ugi reaction however, exploits the inherent reactivity of each functional group employed and therefore the kinetics of each sub-reaction. This allows all four reagents to be present in the reaction mixture.

The mechanism for the reaction was elucidated and published in 1967[35]. This was done with the aid of one of the first commercially available computers. Ugi and Kaufhold found that the reaction proceeds according to Figure 15 and that the final step is irreversible. The Ugi reaction is thus a Type II MCR.

The crucial step in the mechanism (Fig. 15) is the formation if the imine (**25**), which in most cases is allowed to pre-condense before the other reagents are added to achieve optimum yields. In the presence of an acid (**26**), the imine is protonated to form the iminium salt (**27**). The isocyanide then undergoes an irreversible α-addition onto the iminium species to afford the *O*-acyl imine (**28**). Although this step includes the irreversible transformation of the divalent to the tetravalent carbon, the acyl imine cannot be isolated, but undergoes a spontaneous $O \rightarrow N$-acyl migration to form the Ugi product (**29**). The driving force for this

final step is probably the comparative strength of the amide bond over the *O*-acyl imine.



25 **26** **27** **28** **29**

Figure 15: Mechanism of the Ugi-4CR

Applications. In recent years, the Ugi reaction has found favour in the pharmaceutical industry due to its simplicity, reliability and diversity of products, making it an ideal reaction for the generation of compound libraries. Indeed, Ugi was probably the first to suggest the concept of

chemical compound libraries generated by the implementation of efficient reactions, allowing the compounds to be screened[36].

The peptide–like structure of many U-4CC products makes these compounds potentially biologically active. Indeed, one of the first applications of the U-4CC was the synthesis of a known commercial local anaesthetic, Xylocain ™ (**33**) from 2,6-dimethyl phenyl isocyanide (**30**), formaldehyde (**31**) and diethylamine (**32**)[37] (Fig.16) with water acting as the 'acid' component. This allowed many similar structures with similar pharmacological profiles, such as Lidofenin and Trimecain (Fig. 16) to be synthesised.

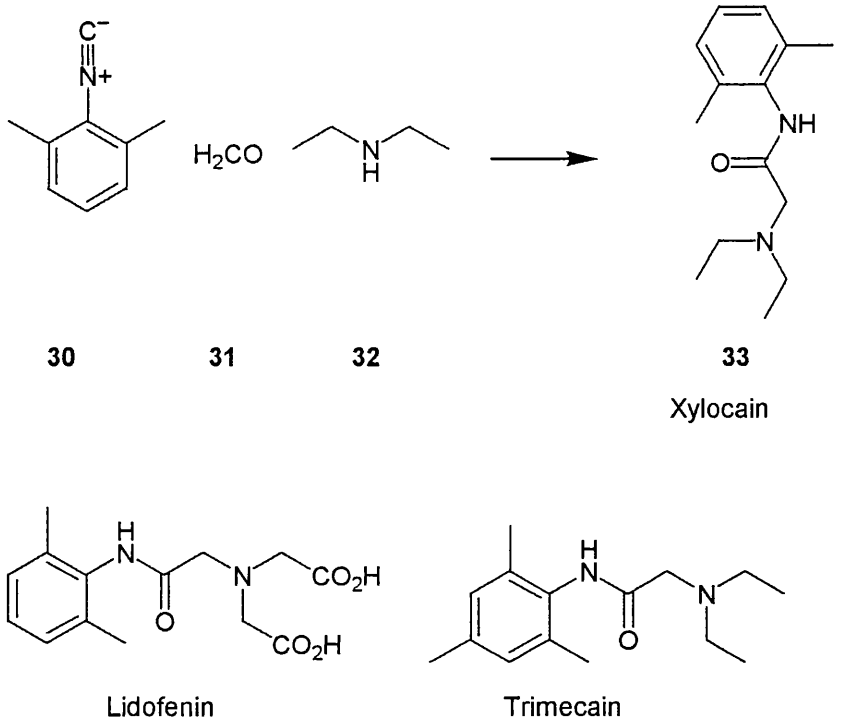
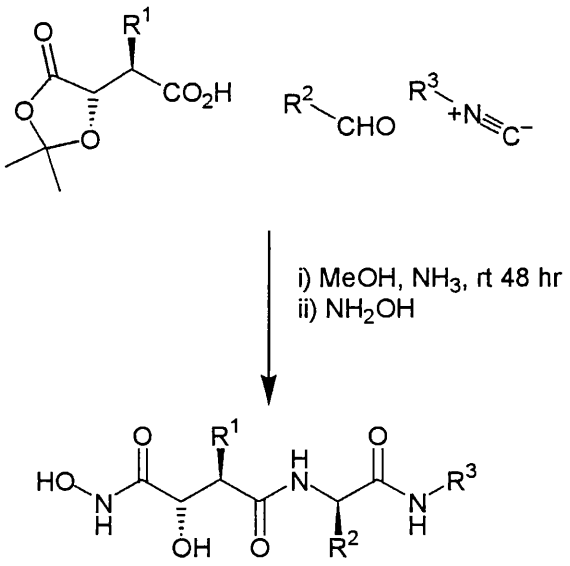


Figure 16

More recently, Pitlik and Townsend[38] have generated β-lactam libraries as potential inhibitors of leukocyte elastase inhibitors whereas, Floyd

and Whittaker at British Biotech have extended the Ugi reaction in a different way to generate libraries of hydroxamic acids (**34**), which were screened as potential metalloproteinase inhibitors[39] (Fig.17).



34

Figure 17

1.3.4 Other Isocyanide Based MCRs

The Ugi and Passerini reactions cover the largest part of isocyanide based MCRs. However, the first ever four-component condensation, the Bucherer-Bergs hydantoin synthesis, falls outwith the definition of the Ugi and Passerini reactions. Bucherer and Bergs[40] independently developed this hydantoin synthesis methodology (Fig. 18). In this reaction a ketone (**35**), ammonia (**36**), carbon dioxide (**37**) and hydrogen cyanide (**38**) (as the formal isocyanide) react to form hydantoin derivatives (**39**).

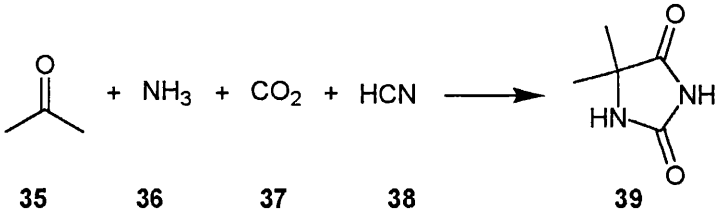


Figure 18

The drawback to this reaction is of course the use of highly toxic gases, although this can be partially circumvented by the use of ammonium carbonate and potassium cyanide to replace the gaseous reagents.

Recently three groups simultaneously published a new isocyanide based 3-CR[41]. All three groups discovered the same reaction by 'accident', when compound libraries had been generated by the Ugi reaction which involved the use of 2-amino pyridine (**40**). This did not furnish the expected four-component product but an unusual annulated 3-amino imidazole derivative (**43**) (Fig. 19) as exemplified for the case using benzaldehyde (**41**) and *tert.*-butylisocyanide (**42**).

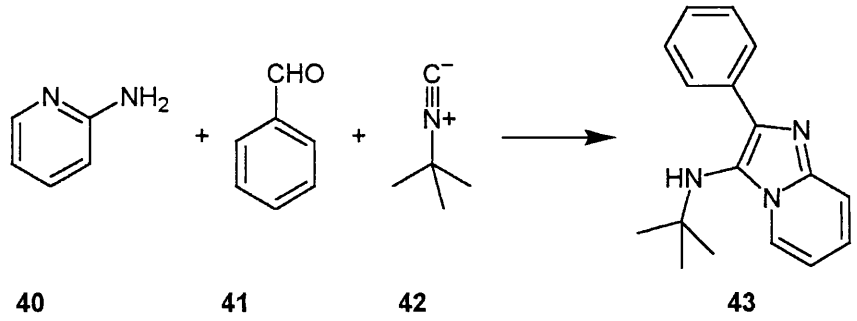


Figure 19

As we shall see, this serendipitous result also led Weber's group at Hoffmann-LaRoche to use a combinatorial approach to discover another 3-component reaction[42] (*vide infra* section 1.5.2)

1.4 Non-Isocyanide Based MCRs

From the reactions listed in Figure 3 (p. 8) it is apparent that a significant number of MCRs do not require the use of an isocyanide or its equivalent. Most of those illustrated involve a cyclisation step, but all require the presence of a nitrogen nucleophile and a carbonyl component to afford intermediate imines or imonium salts. These reactions, α-amino alkylations, will be discussed in the following section followed by an alternative and related group of atom efficient, sequential reactions, the domino reactions.

1.4.1 α-Amino Alkylations

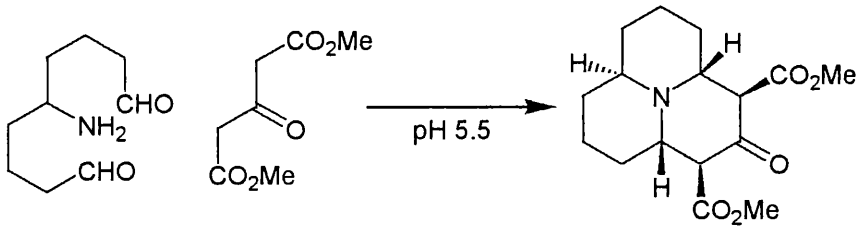
In 1960, Hellmann and Opitz classified a number of important multi-component processes[43], termed α-amino alkylations. The reactions, which they described, involved the condensation of an amine, an aldehyde or ketone and a protic acid or nucleophile.

In their review[43] of the literature covering over a century of chemistry, they list the most common alkylating agents in order of decreasing C-H acidity:

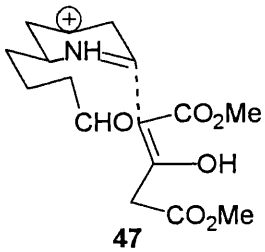
$H\text{-}CR_2\text{-}NO_2 > H\text{-}CR_2\text{-}CO_2R > H\text{-}CR_2\text{-}CN > H\text{-}CR_2\text{-}(CO)H$

The most important representative of this class of reactions is the Mannich three-component reaction (M-3CR).

The Mannich reaction. The Mannich 3-component condensation has been the workhorse of alkaloid chemistry ever since Robinson's Tropinone synthesis (*cf.* Fig. 1, p. 4). In fact, an impressive application of the Mannich reaction was performed by Stevens, some 60 years later, in his synthesis of a Coccinelline precursor (**46**)[44], in which the amino dialdehyde (**44**) dervived *in situ* from the deprotected dimethyl acetal, furnished a cyclic iminium cation, which undergoes stereoelectronically controlled axial alkylation (**47**) by the enolate of **45**, thus leading to the formation of four new carbon-carbon bonds and five stereocentres in a single reaction (Fig. 20).



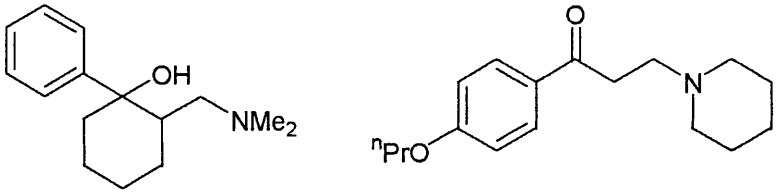
44 **45** **46**



47

Figure 20

The Mannich reaction, like the Ugi reaction, has found widespread application in industry. In particular, a number of Mannich reaction products such as those shown in Fig. 21, have found their way into the clinic.



Tramadol
Analgesic

Falicain
Anaesthetic

Figure 21

The Mannich reaction is probably one of the most important C-C bond forming reactions. Usually, the reaction is performed with an enolizable aldehyde or ketone as the C-H acid component. For most practical purposes, an amine hydrochloride salt is heated with formaldehyde and the carbonyl compound in a protic solvent. The amine (**48**) and formaldehyde (**31**) form the iminium salt (**50**), which in turn is alkylated by the enol form (**51'**) of the carbonyl compound (**51**) to afford the Mannich base (**52**) (Fig. 22).

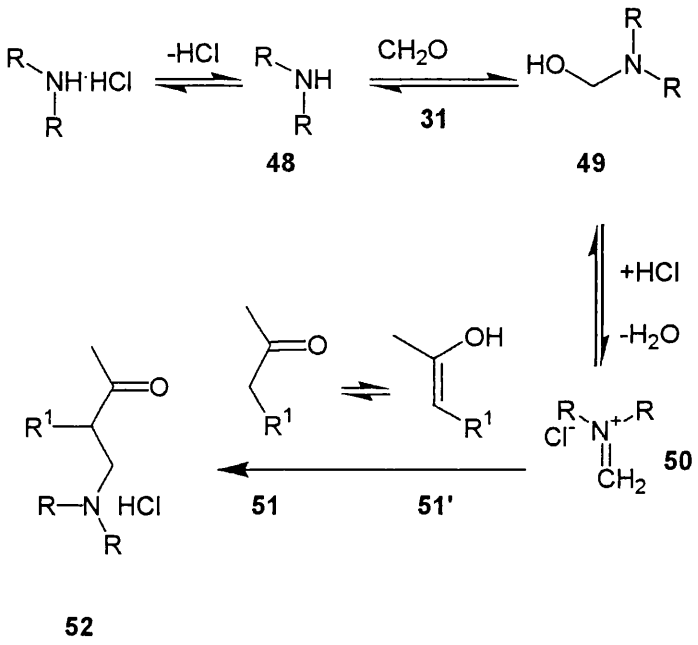
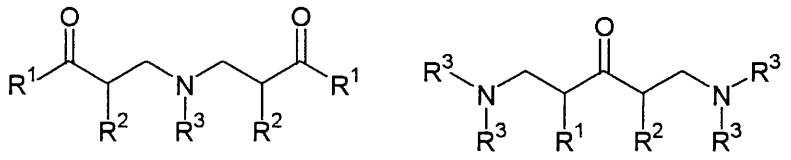


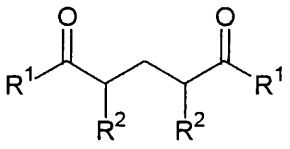
Figure 22

The resulting Mannich bases (**52**) can undergo a variety of useful subsequent reactions to furnish, for example, Michael acceptors, by elimination of the dialkyl amine, functionalised carbonyl compounds, by nucleophilic substitution of the quarternised amine, or γ-amino alcohols, by reduction or addition of a Grignard reagent to the carbonyl moiety.

However, it is this very nature of the reactivity profile of the Mannich bases which can lead to further interesting products (Fig. 23). Thus, when primary amines are employed, the resulting Mannich base can undergo a second reaction with formaldehyde and the carbonyl compound to yield Mannich bases of type **53**. When the carbonyl component used is unsymmetrical, bis-Mannich bases (**54**) can be formed. Use of the carbonyl compound in excess, leads to elimination followed by conjugate addition to yield 1,5 diketones (**55**).



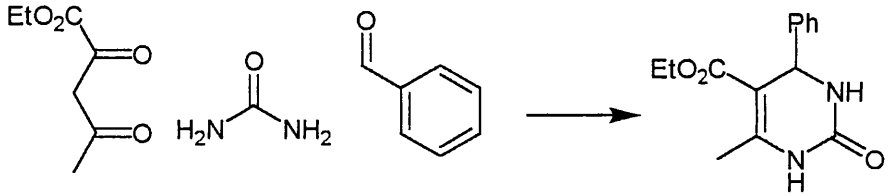
53 **54**



55

Figure 23

The Biginelli reaction, first described in 1893[45] is a 3-component condensation of an aldehyde (**41**), urea (**57**) and acetoacetate (**56**) to give a dihydropyrimidine (**58**) (Fig. 24). These heterocycles have found application in medicinal chemistry as calcium channel blockers and anti-hypertensive agents[46].



56 **57** **41** **58**

Figure 24

In this reaction, particularly high yields are achieved by selection of boron trifluoride etherate, cuprous chloride or acetic acid[47] as catalysts.

The proposed mechanism (Fig. 25) is thought to proceed through an initial aldol condensation, which under acid catalysis forms either the carbenium ion (**59**), or the potent Michael acceptor (**60**), which is then trapped by the urea to furnish intermediate **61**, prior to the final cyclisation to yield the Biginelli product (**58**).

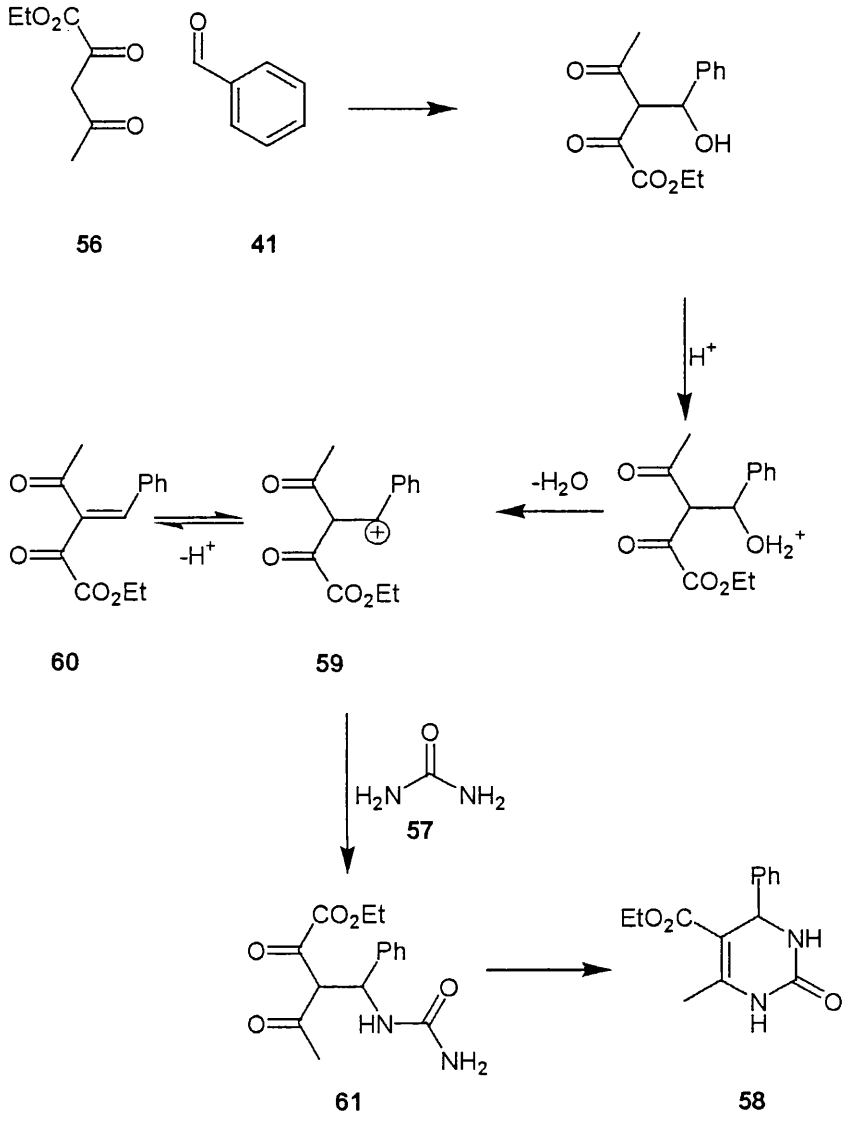


Figure 25

The proposed mechanism is supported by work done in Atwal's group[48]. In his modified version of the Biginelli reaction (Fig. 26), the aldehyde and keto-ester are pre-condensed to the unsaturated keto-ester (**60**) and reacted with the 'protected' urea (**62**). Indeed, this also allows the synthesis of 2-amino substituted pyrimidines (**64**) by use of guanidine or *N,N*-dimethyl guanidine (**63**) as the nucleophile.

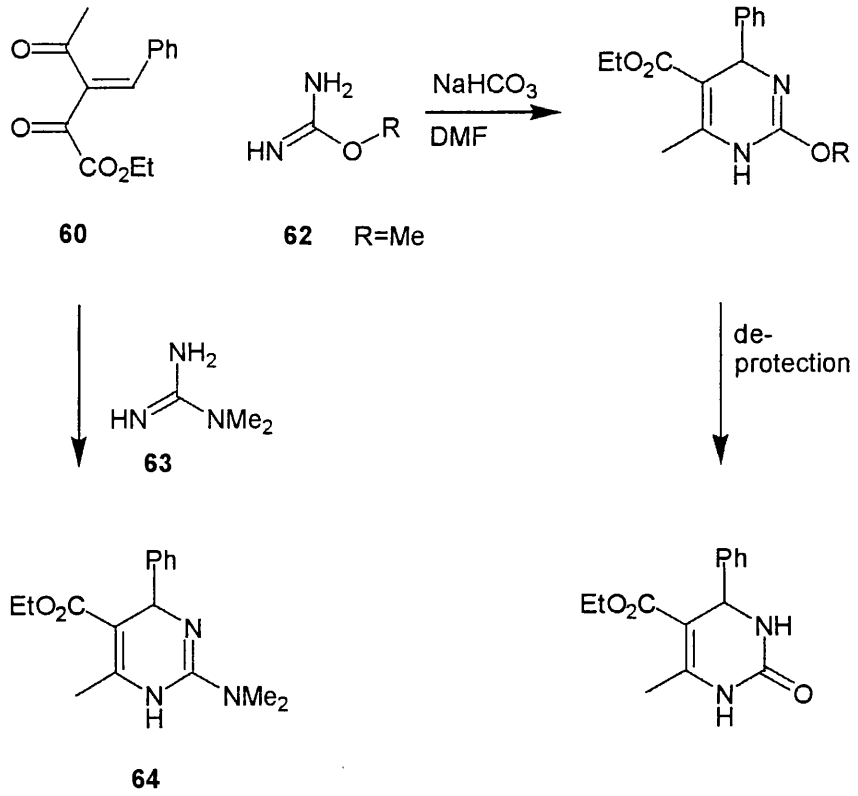
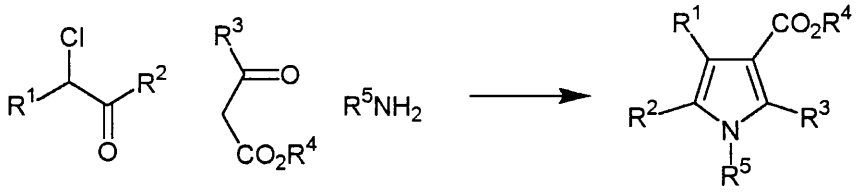


Figure 26

The Hantzsch pyrrole synthesis. The reaction of an α-halo ketone (**65**), β-keto ester (**66**) and an amine (**67**) to furnish a pyrrole (**68**) is called the Hantzsch pyrrole synthesis (Fig. 27)[49]. When two equivalents of the keto ester are used and the halo ketone is omitted, the reaction produces pyridines (*cf.* Fig. 29)[50].



65 **66** **67** **68**

Figure 27

The mechanism of pyrrole formation is shown in Figure 28 and proceeds *via* an initial halide displacement by the keto ester to afford an intermediate 1,4-diketone (**69**). This then undergoes cyclisation with the amine, similar to the Knorr pyrrole synthesis[51], *via* formation of carbinolamine (**70**) and enamine (**71**).

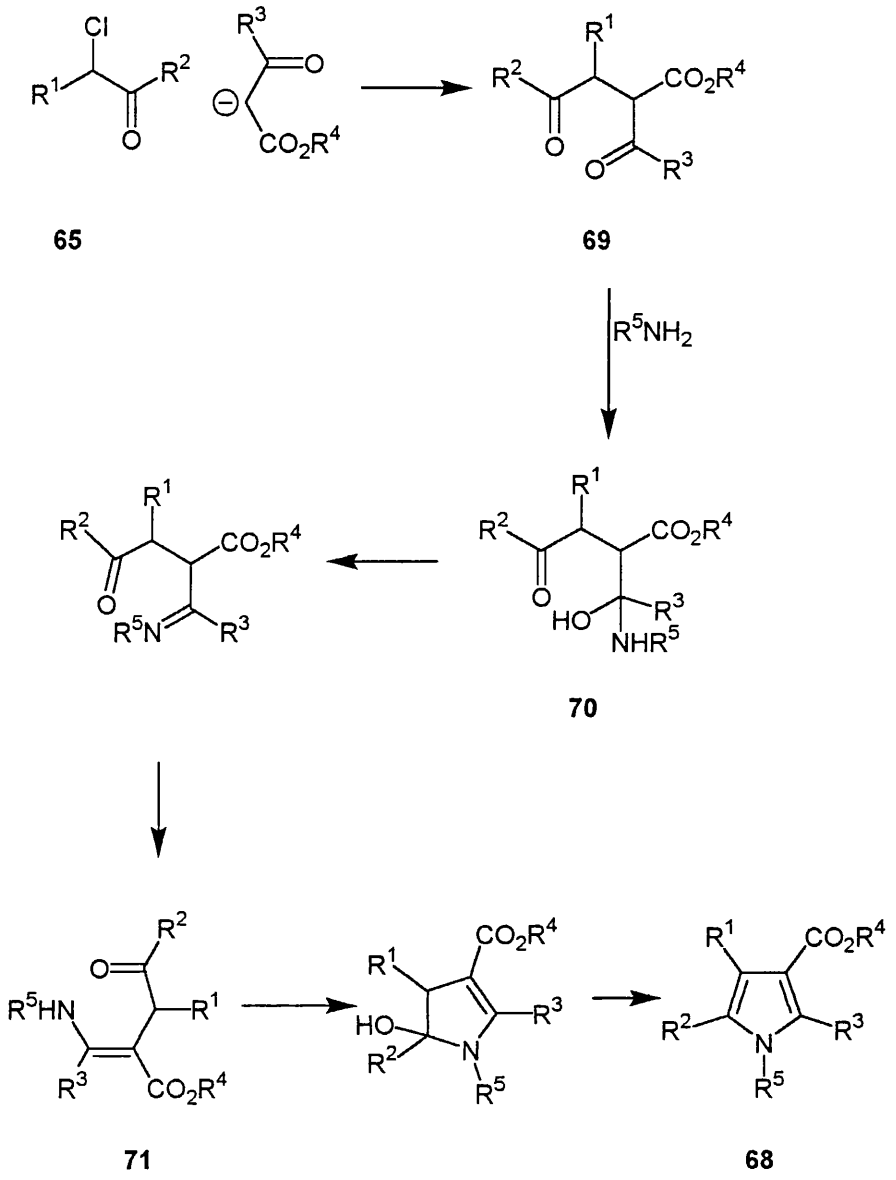
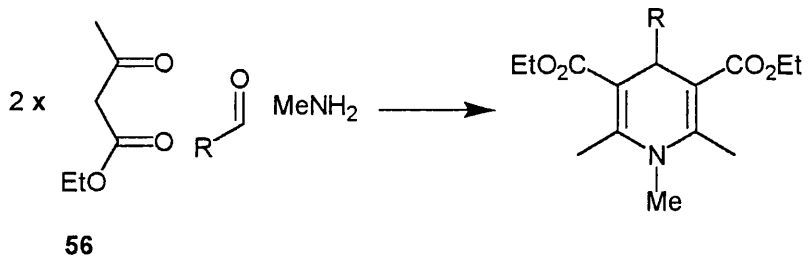


Figure 28

The Hantzsch dihydropyridine synthesis. The product of this dihydropyridine synthesis is, by necessity, symmetrical due to the use of two equivalents of the keto ester (Fig. 29).



56

Figure 29

It is nevertheless possible to produce an unsymmetrical dihydropyridine by separating out the mechanistic steps of the reaction (Fig. 30), *i.e.* by pre-forming and isolating the aldol (**73**) and enamine (**72**) intermediates and combining these in turn to afford an unsymmetrical dihydropyridine such as (**74**)[52].

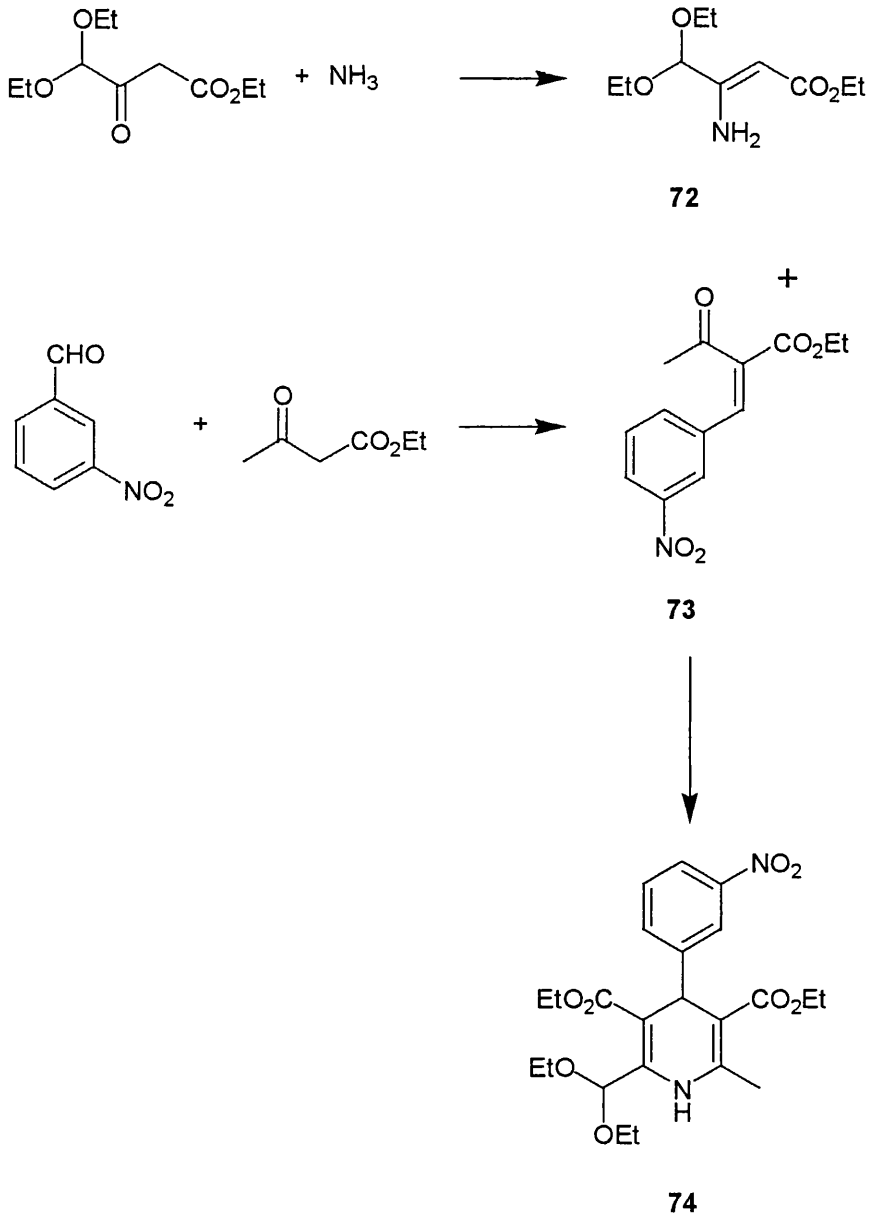
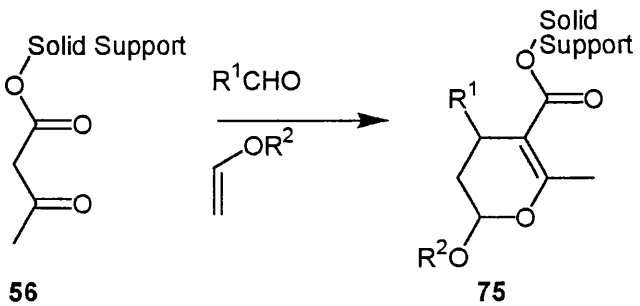


Figure 30

1.4.2 Domino Reactions

It is instructive to consider isocyanide based MCRs in relation to tandem, domino or cascade reactions, which are often encountered in modern day organic synthesis. These latter three names are often used interchangeably in fact, and cover a wide variety of reaction types.

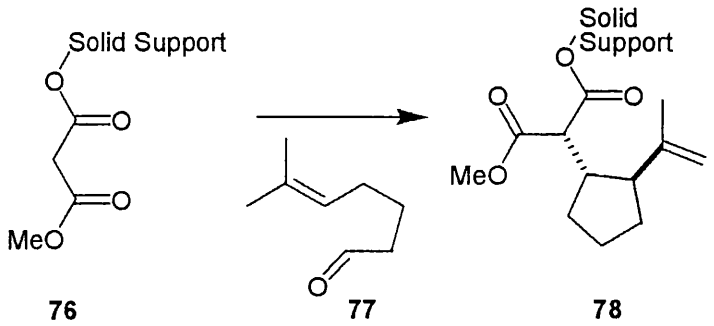
In essence however, these are reactions that occur in succession. An example is the Michael addition of a 1,3-diketone onto an acrylate followed by alkylation of the resultant enolate. A fundamental aspect of this type of chemistry is the requirement for step-wise introduction of reagents, with all reagents contributing to the final product[53]. Nevertheless, in spite of these reactions giving access to new connectivities they do not usually involve fundamentally new reactions, but tend to rely on less common sequences of known reactions. The strength of this approach lies in the vast number of possible permutations of known reactions, *i.e.* combining anionic-anionic, pericyclic-pericyclic or anionic-pericylic reactions to develop new domino reactions. At the present time, the Tietze group is one of the most productive research groups in this field. They have developed a number of domino reactions and used them in solid phase synthesis for combinatorial chemistry, as exemplified by the three component Knoevenagel-hetero Diels-Alder reaction (Fig. 31)[54] to furnish dihydropyrans (**75**), in which polymer bound acetoacetate (**56**) is condensed with an aliphatic aldehyde followed by a cycloaddition with an enol ether to afford the dihydropyran (**75**). These compounds are of interest as they can be transformed in a number of ways, in particular by hydrogenation or hydroxylation to afford novel carbohydrates.



56 **75**

Figure 31

In related work, Tietze's group has also developed the Knoevenagel-Ene reaction (Fig. 32) to afford cycloalkanes[55] (**78**) from keto esters (**76**) and unsaturated aldehydes (**77**).



76 **77** **78**

Figure 32

Domino reactions are often intramolecular processes and frequently rely on a fully-fledged ionic charge to 'migrate' through a molecule in the key bond forming steps. This is particularly true of the early examples, which took their inspiration from Nature. The elegant work of W. S. Johnson in the late 1960's on biogenetic-like olefinic cyclisations[56], such as that shown in Figure 33, demonstrate the preparative potential of such a strategy. These have their equivalent in Nature, as in the conversion of squalene to the lanosterol skeleton[56].

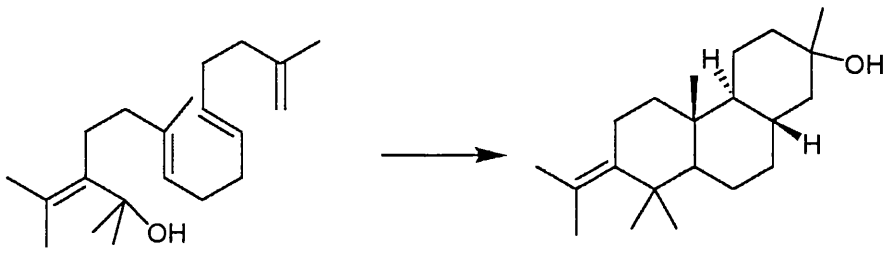
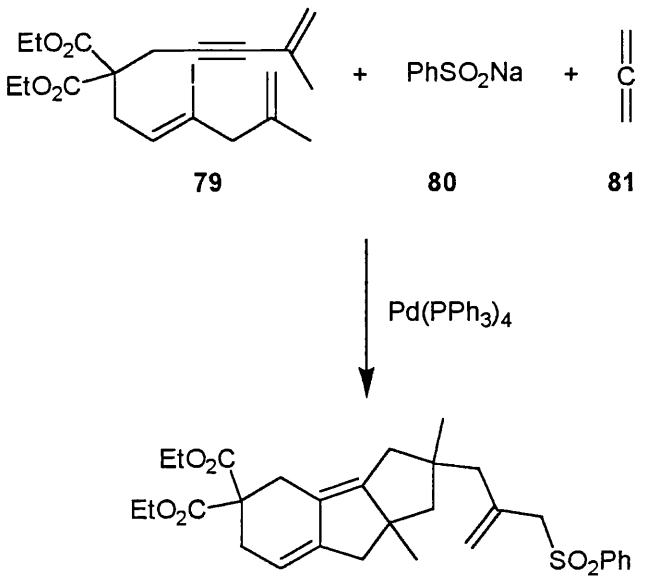


Figure 33

A further aspect covered by these terms is that of the initial reaction triggering the introduction either of functionality or of a functionalised (*e.g.* organometallic) intermediate, for the second reaction step, which in turn generates the functionality for a further reaction step. Of particular note in this respect is Grigg's[57] work in developing metal catalysed cascade reactions. In this case, an appropriate starter moiety, such as a vinyl, aryl or allyl halide, in combination with a palladium catalyst, is reacted with acceptor molecules such as alkene, alkyne, allene, enyne, diene or carbon monoxide. The latter is particularly valuable as a single carbon acceptor molecule.

In Figure 34 the open chain polyene (**79**) undergoes palladium catalysed cyclisation[57]. Rather than undergo reductive elimination at this stage, the Pd-carbon bound intermediate adds to allene (**81**) and the reaction is then terminated by the sulphinate nucleophile (**80**) to afford **82**.



79 **80** **81**

82

Figure 34

A popular approach in the chemistry of domino reactions appears to be the use of successive cycloadditions.

Thus, Tsuge has developed a method for the formation of tricyclic heterocycles starting from pyridinium alkyl ylides[58]. The products are formed by successive 1,3-dipolar cycloadditions (Fig. 35), in the first instance on the azomethine ylide derived from the pyridinium chloride (**83**) and this is then followed by the generation of a nitrile oxide from **85**, which reacts with the dihydropyridine (**84**) to furnish the product (**86**).

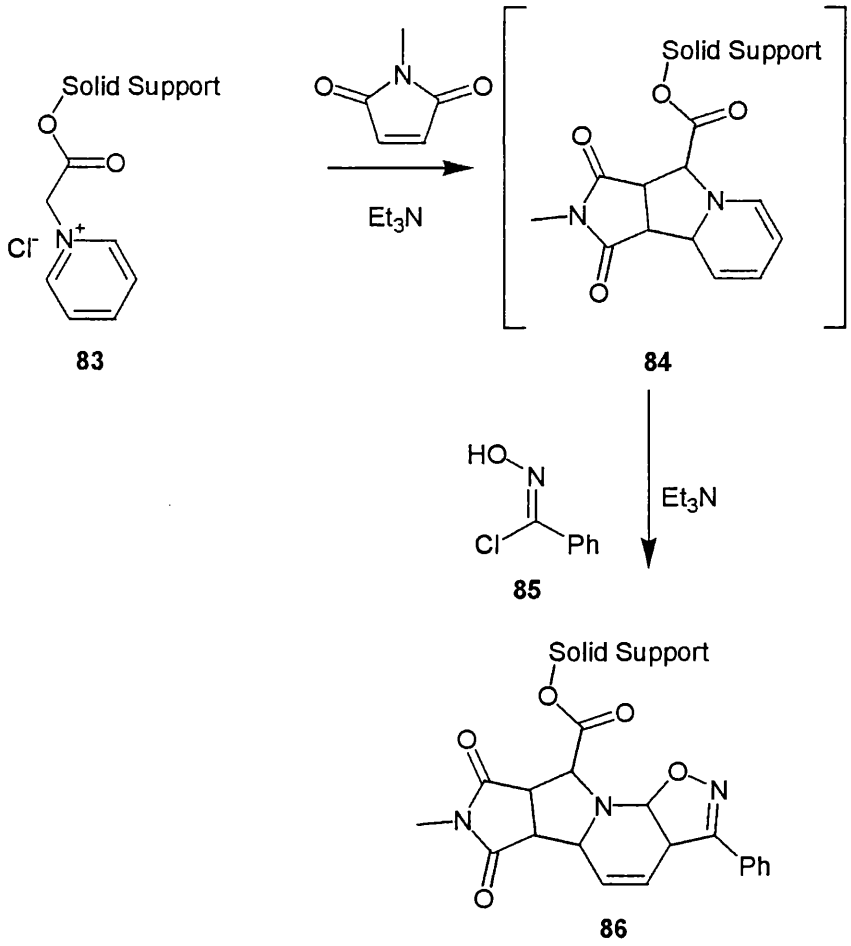


Figure 35

In a similar fashion, Fokas and his group at ArQule have prepared a library of spiro-pyrollidinone oxindoles[59] using the 1,3-dipolar cycloaddition theme (Fig. 36). The reaction of isatin (**87**), amino acids (**88**) and chalcone (**90**), *via* the formation of azomethine ylide (**89**) resulted in the formation of the spiro heterocycle (**91**).

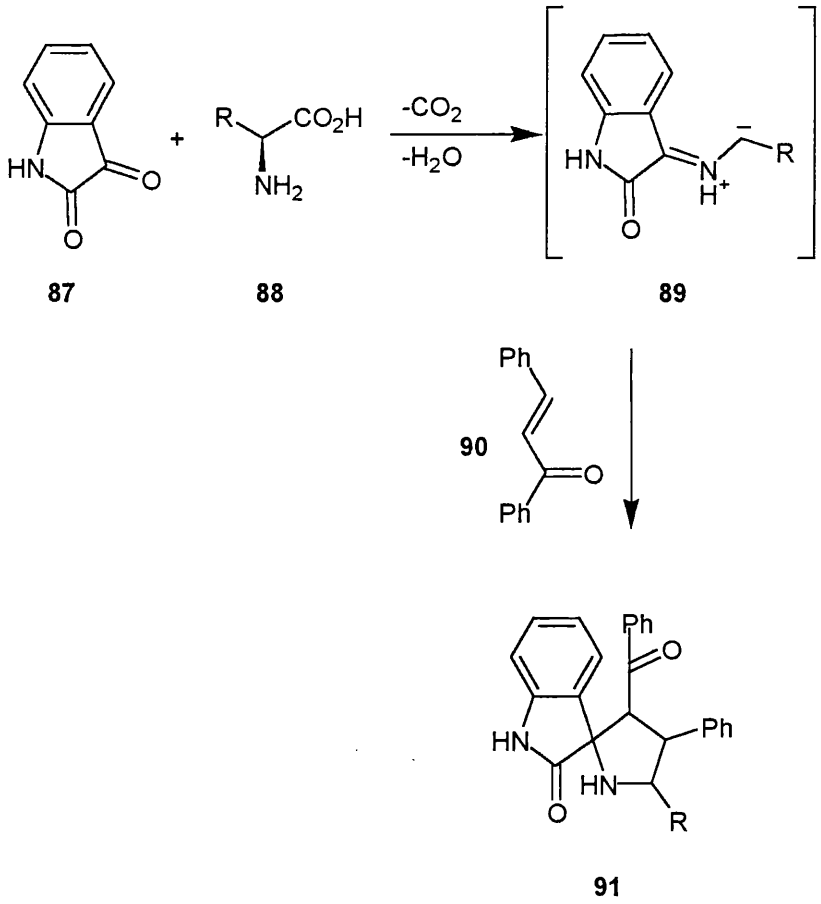
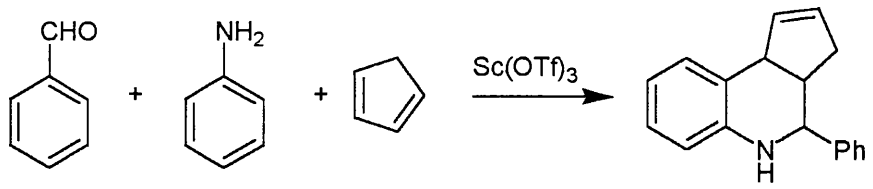


Figure 36

In a similar vein, an aza Diels-Alder reaction can be performed in a three component fashion[61]. This reaction has been called the Grieco 3-component reaction. The reaction involves the condensation of an aromatic aldehyde (**41**), an amine (**92**) and a dienophile (**93**) to furnish six-membered nitrogen containing heterocycles (**94**)(Fig. 37).



41 92 93 94

Figure 37

1.5 Outline of Approaches for the Discovery of New MCRs

As we have already argued, the requirements of commercially driven research are geared towards efficiency and novelty, and these have led to a growing interest in the use of MCRs as research tools for the discovery of new therapeutic agents. With so many research groups using the same chemistry to generate lead structures, chemists have found the need to develop and discover new and efficient MCR methodologies. This has spurred the quest for major routes to new MCRs, and in the following section, some of the approaches taken are delineated.

1.5.1 Secondary Reactions of MCRs and Unions of MCRs

Secondary Reactions. One of the most obvious ways of generating diversity and novelty in MCR products is to subject the initial product to a subsequent reaction in order to produce compounds that are not initially accessible by the primary reaction. Most often, this is achieved by cyclisation. One of the most straightforward examples of this tactic is the reaction of aldehyde (**95**), isocyanide (**96**) and amino acid (**97**), which under standard U-4CR conditions furnishes the α-amino amide (**99**). Addition of a base then leads to cyclisation to form piperazidinones (**98**)(Fig. 38)[60].

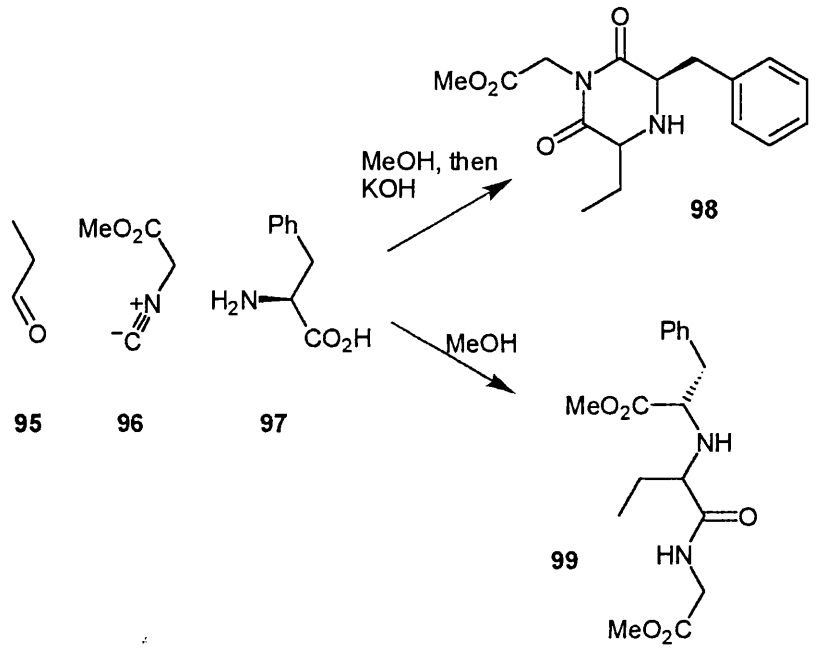


Figure 38

The major drawback of the Ugi reaction is the comparative dearth of commercially available isocyanides. This led Armstrong to develop the use of cyclohexenyl isocyanide (**100**), as the 'universal' isocyanide[62]. The importance of this reagent lies in the series of facile acid catalysed conversions of the resulting ene-amide (**101**) into a diverse range of secondary compounds (Fig. 39).

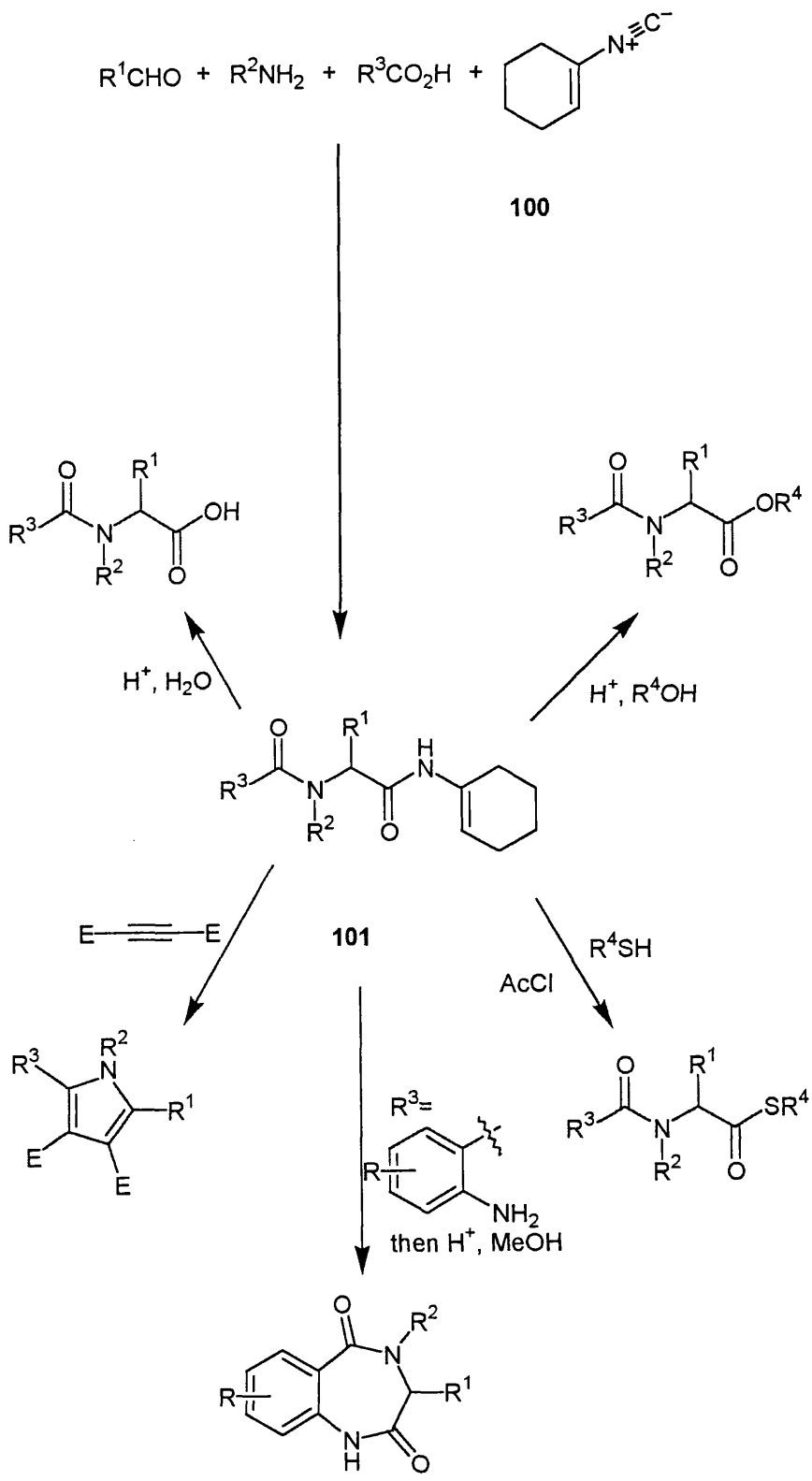

R1CHO + R2NH2 + R3CO2H +
100
H+, H2O
H+, R4OH
101
E—≡—E
R4SH
AcCl
R3=
NH2
then H+, MeOH

Figure 39

Unions of Known MCRs. Ugi and Dömling have developed the union concept of MCRs to generate 'higher order MCRs'. This involves the combination of reactions. The sequences involved are MCRs, giving rise to 5, 6 and 7 component reactions. The earliest example of a U-5CR (Fig. 40) is the use of CO_2 and an alcohol to furnish an 'alkoxy carboxylic acid' as the acid component to give rise to the corresponding urethane (**102**)[36].

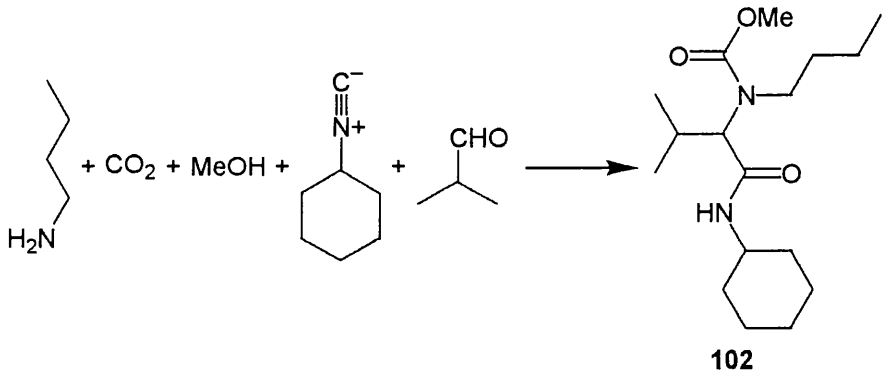


Figure 40

In conceptual terms the U-4CR itself can be seen as a union of the Passerini and Mannich reactions[63] and can be represented symbolically by a Venn-Diagram as shown in Figure 41.

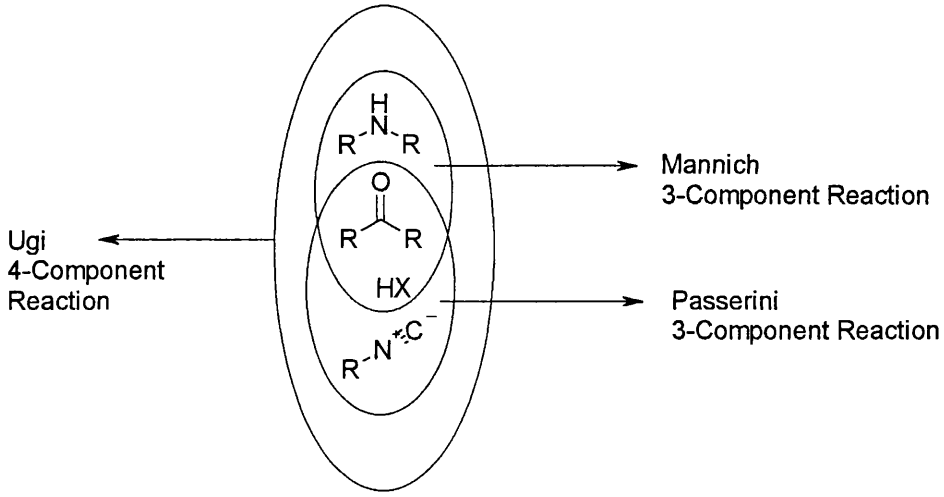


Figure 41

This approach has been so successful that it has given rise to a record breaking 7-component reaction[64]. By combining an Asinger 4-component reaction with an Ugi-5CR, Ugi and Dömling were able to prepare highly substituted thiazoles (**107**) in modest yields (Fig. 42). The mechanism proceeds *via* an imine (**103**) and α-mercapto aldehyde (**104**) to form an intermediate thiazoline (**106**). This is protonated by methyl carbonic acid (**105**) and undergoes α-addition and subsequent rearrangement with the isocyanide (**42**) to furnish (**107**) in a one-pot procedure.

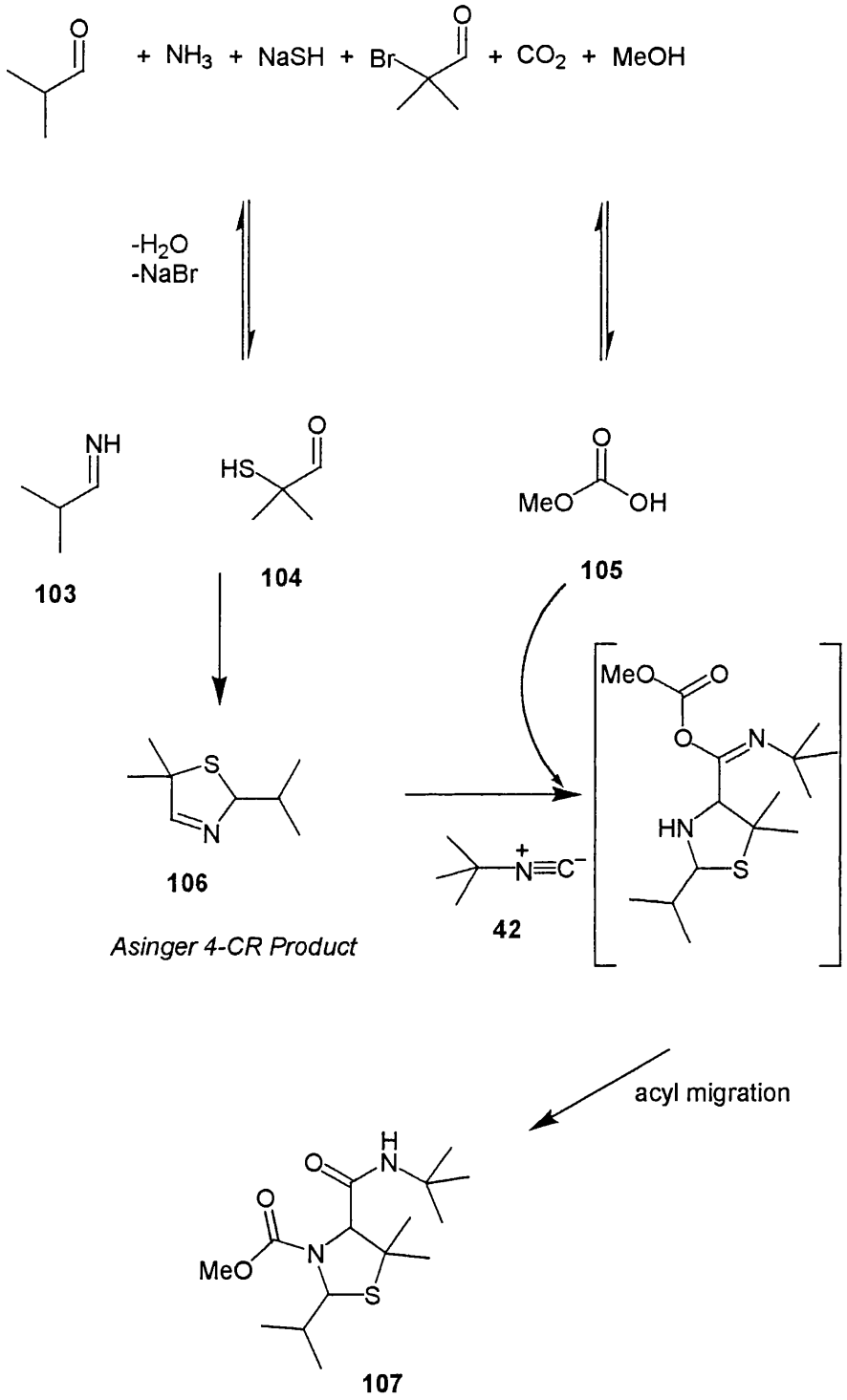


Figure 42: Ugi-7CR

The first stages of the reaction, formation of the imine (**103**) and methyl carbonic acid (**105**), are equilibria. Cyclisation to the thiazoline (**106**) is a

quasi-irreversible sub-reaction. This is followed by reversible protonation of the thiazoline (**106**) by the methyl carbonic acid (**105**) and finally by the irreversible, product forming steps of the reaction involving the usual participation of isocyanide (**42**) and acyl migration.

Fundamental to the success of the reaction is the final irreversible conversion of C^{II} to C^{IV}, *i.e.* that the entire process can be seen as a Type II MCR.

1.5.2 Combinatorial Reaction Libraries

The methods described above have their foundation in the rational and logical connection of known reactions. By way of contrast, there have also been reports on the 'chance' discovery of new MCRs. Weber and Lack have pioneered the use of combinatorial methods in the discovery of new reactions[42]. The advantage here lies in the conceptual possibility of discovering fundamentally new multi-component reactions. The inspiration for the generation of combinatorial reaction libraries (as opposed to compound libraries) appears to have come from the serendipitous discovery of a new 3-component reaction by two industrially based research groups simultaneously[41], even though this was published after Lack and Weber's reaction library, and in all probability was due to the commercial value of the compounds synthesised[65]. Both Weber's group and Blackburn's group found that in the generation of Ugi-type compound libraries the products formed depended on the amine employed (Fig. 43), *i.e.* by using 2-amino pyridine (**40**) they were able to generate imidazo pyridines (**108**) rather than the expected U-4CR product (**109**).

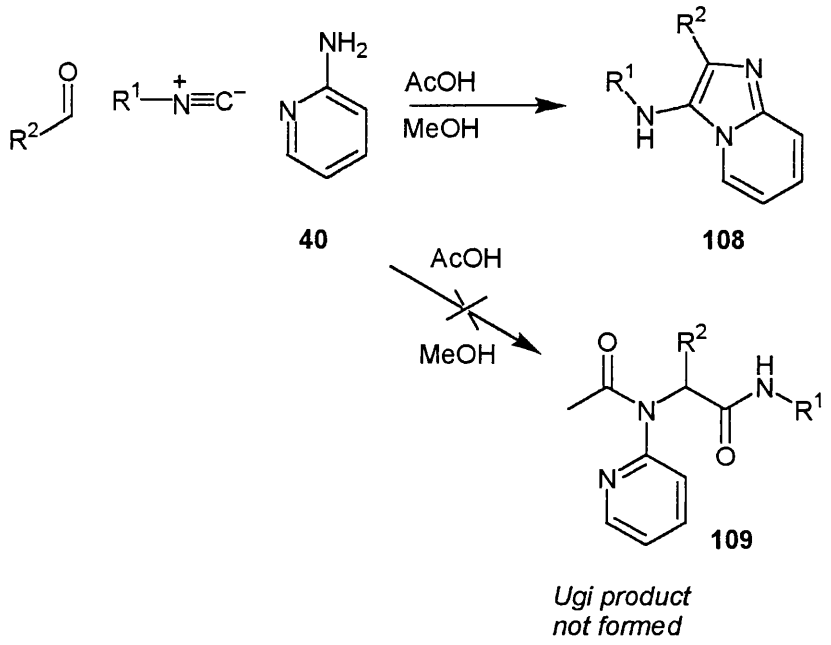


Figure 43

Prior to the publication of the serendipitous discovery of this three component reaction, Weber explicitly chose ten commercially available reagents (Fig. 44) and reacted them combinatorially, generating a library of 1013 reactions. These are 2-component, 3-component, 4-component and, in the best possible case, a 10-component reaction. The reactions were analysed by HPLC and the peaks corresponding to starting materials were subtracted from the HPLC trace, leaving only peaks corresponding to a reaction having taken place. The HPLC trace showed the 're-discovery' of old reactions, but also suggested the existence of a new 3-component reaction (Fig. 45). This was then verified by repeating the reaction on a preparative scale, with the standard isolation and full characterisation of the new compound (**113**).

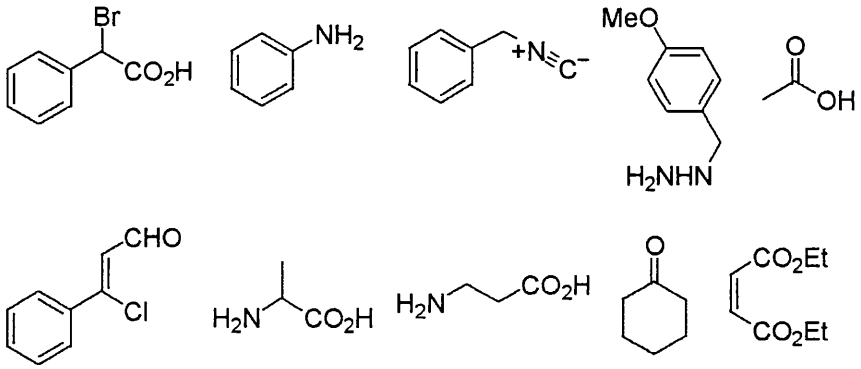
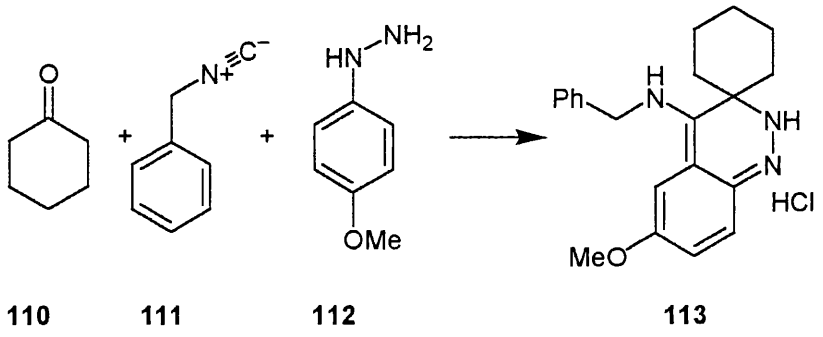


Figure 44

In this position, from the reaction library generated, Weber was able to show the existence of a new 3-component reaction featuring the reaction of an aromatic hydrazine (**112**), a ketone (**110**) and an isocyanide (**111**), in the presence of acetic acid which gave rise to a dihydrocinnoline (**113**) (Fig. 45).



110 **111** **112** **113**

Figure 45

1.6 Conclusions

In synthetic organic chemistry, great importance is placed on the ability to construct complex, highly functionalised molecules rapidly and with little effort. MCRs fulfil the important requirement of the industrial

chemist to access a vast range of complex, heteroatom containing molecules.

From the foregoing overview, the advantages of multi-component reactions are apparent. Nevertheless, given the lack of fundamental knowledge of the rates and reversibilities of many reaction types, it is clear that premeditated invention of a new MCR is inherently difficult. For this reason, save for the totally 'chance driven' approach of Weber, most research groups have preferred to focus in recent times on the clever combination of existing reactions to give new products, as in the development of domino processes or the Ugi union concept and secondary reactions. Indeed, even Ugi's formidable contributions to the field of multi-component reactions are founded on decades of experience of isocyanide chemistry.

CHAPTER 2

Since the overall concept of developing reactions in which several bonds can be formed is a primary objective of the present thesis, it is also relevant to discuss one of the subsets of pericylic reactions, which is most often used for heterocycle construction, the 1,3-dipolar cycloaddition strategy.

2.1 1,3-Dipolar Cycloadditions

If Ivar Ugi is the Father of MCRs[66] then his PhD supervisor Rolf Huisgen may well be considered the Grandfather of a similarly atom efficient reaction type, the 1,3-dipolar cycloadditions.

Cycloadditions in general are one of the most efficient methods for ring construction. The most famous example, the Diels-Alder reaction, has proved to be a very rich area of research and has been applied to an incredible number of complex natural products containing carbocyclic 6-membered rings. Equally, over the past 50 years, 1,3-dipolar cycloadditions have gained in importance. In contrast to Diels-Alder reactions, these methods afford 5-membered heterocyclic rings, which allow further manipulation to offer access to 1,3-substituted acyclic compounds. In common with the Diels-Alder reaction, dipolar cycloadditions proceed via a 6-electron aromatic transition state. The resulting products and the regioselectivity and stereoselectivity can be rationalised in terms of frontier orbital interactions[67].

In common with the discussion on MCRs in the previous section, cycloaddition reactions have the potential for high atom economy.

Thus, both are multiple bond forming processes. In general terms, further advantages relating to 1,3-dipolar cycloadditions are that they are easily prepared from simple starting materials and that the products contain masked functionality which is amenable to further stereocontrolled functionalisation and elaboration.

2.2 Definition of 1,3-Dipoles

1,3-Dipoles are compounds in which a sequence of three atoms (a-b-c) can be expressed with charges formally separated. This is the result of one of the atoms only possessing a sextet of electrons, with one of the other atoms possessing an unshared pair of non-bonding electrons (Fig. 46). These reagents thus contain 4π-electrons spread over three atoms.

Huisgen has categorised 1,3-dipoles according to their geometrical structure and, by extension, their electronic structure (Fig. 46). The propargyl-allyl type dipoles can be drawn as resonance hybrids in which one canonical form contains a triple bond and the other cumulated double bonds. Application of VSEPR-theory suggests these compounds to be geometrically linear.

The allyl group of compounds, by contrast are bent, and contain a single and a double bond.

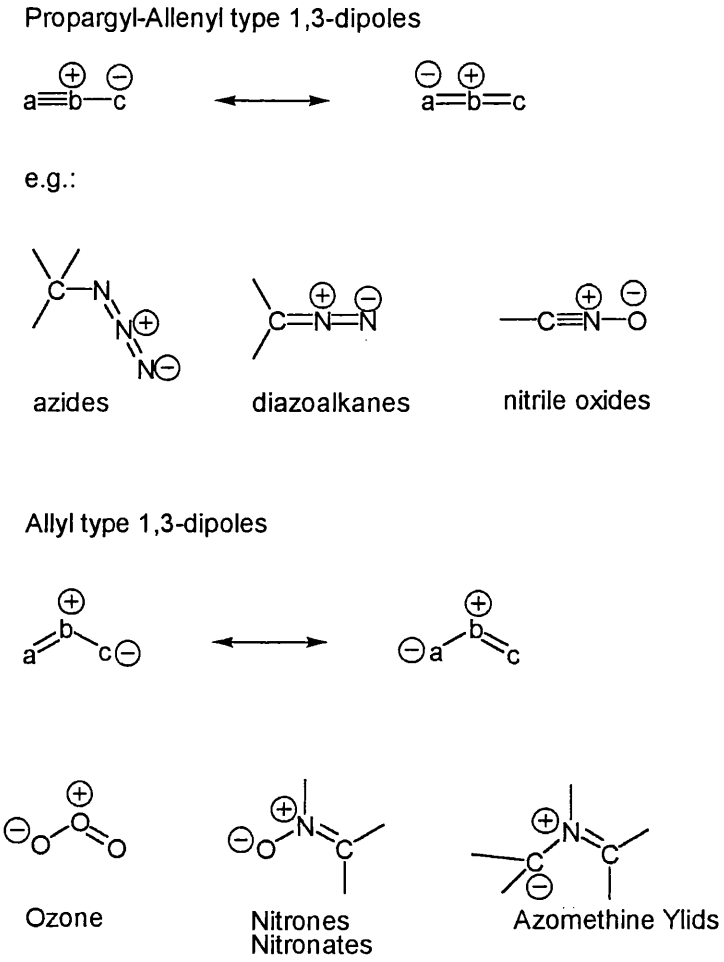


Figure 46

2.3 Mechanistic Considerations

Since the predictive usefulness of a reaction is dependent on the depth of mechanistic insight, it is not surprising that the mechanism of 1,3-dipolar cycloadditions has been thoroughly studied, in particular by Huisgen's group. In the early days of the reaction, there was some controversy as to the synchronicity of bond formation in the reaction.

Thus, Huisgen championed a concerted, asynchronous process in which both bonds are formed in the same step leading to a single transition state (Fig. 47).

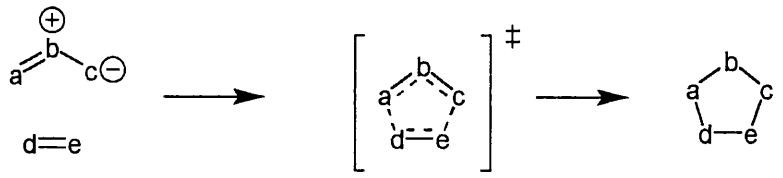
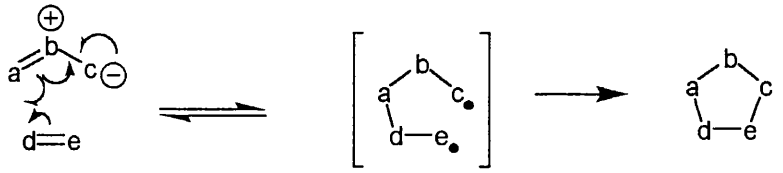


Figure 47

In contrast, Firestone[68] proposed a two step pathway with a discreet spin paired diradical intermediate (**114**), the formation of which is the rate determining step (Fig. 48).



114

Figure 48

Huisgen's mechanistic investigations in the 1960's and 1970's showed that dipolar cycloadditions are insensitive to solvent polarity. This suggested the absence of a zwitterionic intermediate. They were also able to show that the reactions proceed with a high negative entropy of activation[69] and that the reaction proceeds *via* an early highly ordered transition state. These findings together with the observed high regiospecificity and stereospecificity brought Huisgen to the conclusion that the reaction proceeds in a single step, in which both new bonds are formed in an early transition state, albeit asynchronously.

One of the major criticisms levelled against the diradical mechanism, is the observation that there is complete transfer of stereochemical information from the dipolarophile to the cycloadduct. Thus, the products of a reaction with an *E*-alkene will invariably lead to a *trans* product, while with the *Z*-alkene provides the *cis*-product. This observation further undermined a biradical or zwitterionic intermediate, as these intermediates would be able to undergo rotation around the σ-bond, hence destroying any prior stereochemical information from the dipolarophile. Furthermore, if the orientation of the diradical is poor and disfavours cyclisation, Firestone was forced to suggest that the intermediate (**114**) reverts to starting material, without loss of stereochemical information[68] (Fig. 48). To preserve any stereochemical information the barrier to rotation about the single bonds would have to be greater than the activation barrier for ring closure.

It was argued that the high stereospecificity of 1,3-dipolar cycloadditions provided compelling proof that the reaction proceeded in concerted fashion, *i.e.* that the nature of the stereochemical information of the double bond is preserved in the product[70]. Firestone suggested that this did not conclusively disprove a diradical pathway. He argued (Fig. 49) that if the rate constant for rotation (k_r) around bond *a* (**116** to **117**) was smaller than the rate constant for cyclisation (k_c), then high stereospecificity would still be observed[68].

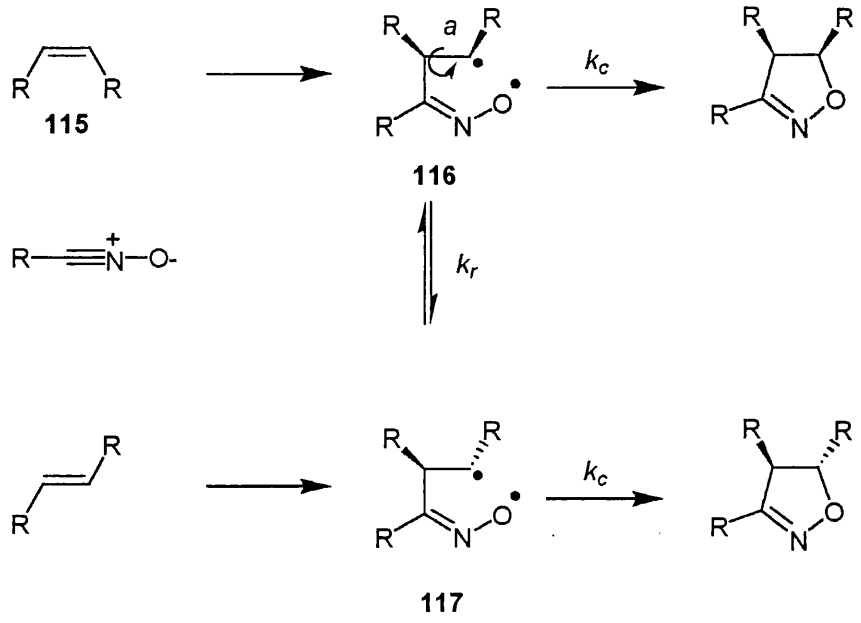


Figure 49

Finally however, Houk and Firestone himself in 1985 delivered experimental evidence against the diradical mechanism[71]. By performing the 1,3-dipolar cycloaddition (Fig. 49, **115**, R=D) of *p*-nitro benzonitrile with *cis* and *trans*-dideutero ethylene, they showed that the barrier to rotation has to be 2.3 kcal/mol (~9.2 kJ/mol) higher than the cyclisation barrier. Intermediate (**117**), a deuterated primary radical, would have a rotational barrier about bond *a* of no more than 0.4 kcal/mol. With such a low rotational barrier one would not expect the observed stereospecificity of 98%. Therefore, the most reasonable mechanism is a concerted one.

The advent of the Woodward-Hoffmann rules and the concepts of frontier molecular orbital interactions by Fukui, gave synthetic chemists a powerful explanatory and predictive tool, which validated a concerted reaction pathway. This allowed practitioners the use of a theoretical tool for the understanding of regiochemical and stereochemical control

where there had previously not been any understanding of selectivity in the reaction. Hence, it has become common to discuss cycloaddition reactions in general and 1,3-dipolar cycloadditions in particular in terms of frontier molecular orbital theory (FMO).

FMO Theory. A coherent mechanistic picture for dipolar cycloadditions emerged with the development of frontier molecular orbital theory[72]. The principle behind this theory is that a reaction proceeds when there is an agreement of orbital symmetry between reactants and products leading to a conservation of orbital symmetry. The highest occupied molecular orbital (HOMO) of one of the reagents is seen to 'donate' its electrons to the lowest unoccupied molecular orbital (LUMO) of the other (Fig. 50). This leads to an allowed [$4_{\pi s}$ + $2_{\pi s}$] process, according to the Woodward-Hofmann rules.

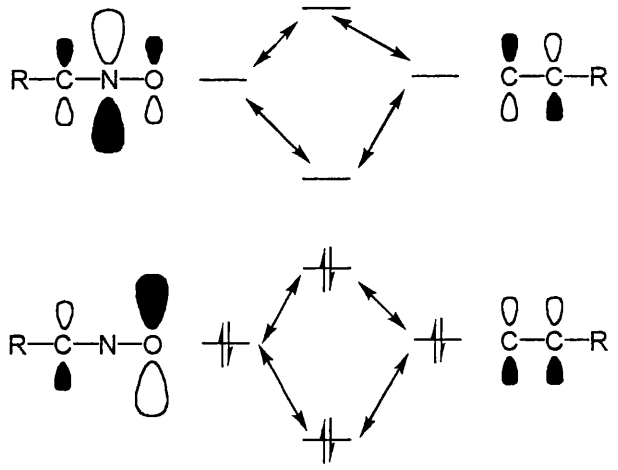
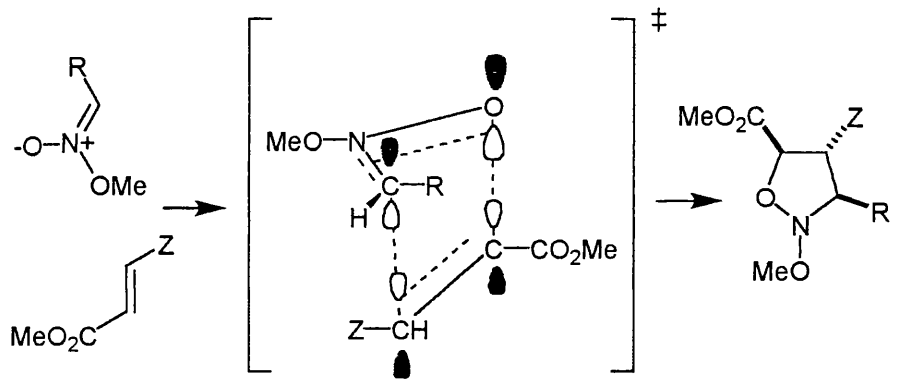


Figure 50

Irrespective of the dipoles and dipolarophile involved, the cycloaddition proceeds with the reactants in a bi-planar, 'envelope-like' complex (Fig.

51, **118**). This brings the π-orbitals into proximity permitting their interaction via a 4 πs-2 πs process.



118

Figure 51

Importantly FMO theory also correctly predicts and explains the regioselectivity of dipolar cycloadditions.

Substituents at the dipole and dipolarophile affect the energy of the molecule's frontier orbitals. These changes in the orbital coefficients lead to changes in regioselectivity and an increase or decrease in reaction rate, depending on whether the energy gap between the frontier orbitals is increased or decreased by the substitution.

On the whole, electron withdrawing substituents lower the level of both the HOMO and LUMO, whereas electron donating substituents increase both orbital energy levels and conjugated substituents tend to raise the HOMO and lower the LUMO energy[67].

Sustmann[73] classified 1,3-dipolar cycloadditions according to the predominant and controlling, orbital interactions between reagent and dipole (Fig. 52).

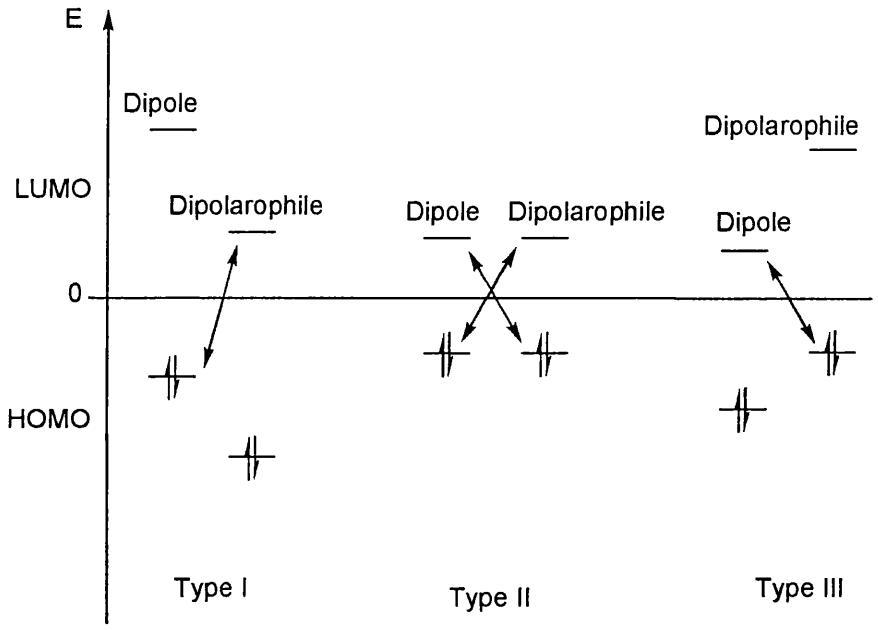


Figure 52

Thus cycloadditions with relatively electron rich dipoles, such as azomethine ylides, are Type I 1,3-dipolar cycloadditions and are controlled by the predominant interaction of $HOMO_{dipole}$ – $LUMO_{dipolarophile}$. By contrast, the reactions of nitrile oxides with dipolarophiles are Type II 1,3-dipolar cycloadditions. They are controlled by either HOMU-LUMO interaction and thus will react with both electron rich and electron poor dipolarophiles. Finally, reactions involving very electron deficient dipoles are governed by $LUMO_{dipole}$ - $HOMO_{dipolarophile}$ interactions and thus belong to Type III 1,3-dipolar cycloadditions.

Most 1,3-dipolar cycloadditions, in particular those with nitrile oxides, fall into the 2nd category, in which the reaction may be controlled by either the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ or the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction, depending on the substitution of the dipole. Therefore, both electron donating and electron withdrawing groups on the dipolarophile will accelerate the reaction.

With the identification of the dominant orbital interaction, i.e. the lowest energy interaction, it is possible to predict and explain the regiochemical outcome of any given cycloaddition reaction. Even where two different regiochemical outcomes are possible from a purely qualitative analysis, it is possible to assign and predict a regiochemical outcome based on the union of atoms with the largest orbital coefficient.

These arguments formalised the mechanism of dipolar cycloadditions as a concerted nonsynchronous process, driven by orbital overlap at the pertinent reaction centres. The strength of this theory lies in its ability to go beyond standard electronic and steric arguments.

At this stage, it is especially relevant to comment on the chemistry of the particular 1,3-dipoles which form the experimental framework of our own research programme.

2.4 Nitronates

This section will provide a brief overview of the chemistry of nitronate and silyl nitronate esters but with a focus on 1,3-dipolar cycloaddition reactions. Nitronates are derivatives of nitronic acids (**119**), which are in tautomeric equilibrium with the parent nitro alkane (Fig. 53). The latter can be alkylated with a suitable alkylating agent such as

trimethyloxonium tetrafluoroborate or alternatively undergo silylation with chlorotrimethylsilane and triethylamine.

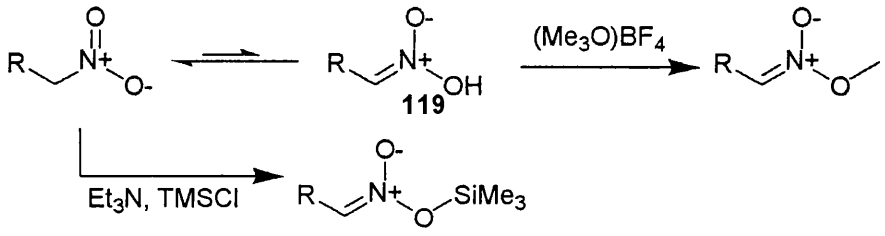


Figure 53

The preceding examples show the nucleophilicity of the hard oxygen atom of the nitro group in the generation of nitronates using hard electrophiles. Beyond this, nitronate anions generated from nitroalkanes (**120**) and base, can also function as carbon nucleophiles with soft electrophiles. The most important reaction of this type is the use of nitronates in an Aldol-type reaction with aldehydes or ketones (**121**). The drawback with this methodology is the subsequent elimination of water to furnish nitroalkene (**122**). However, this can be avoided by making the dianion of the nitroalkane, or employing Seebach's silyl nitronate method[74] (Fig. 54). Additionally, α,β-unsaturated carbonyl compounds (**123**) can also act as electrophiles to furnish γ-nitro ketones (**124**).

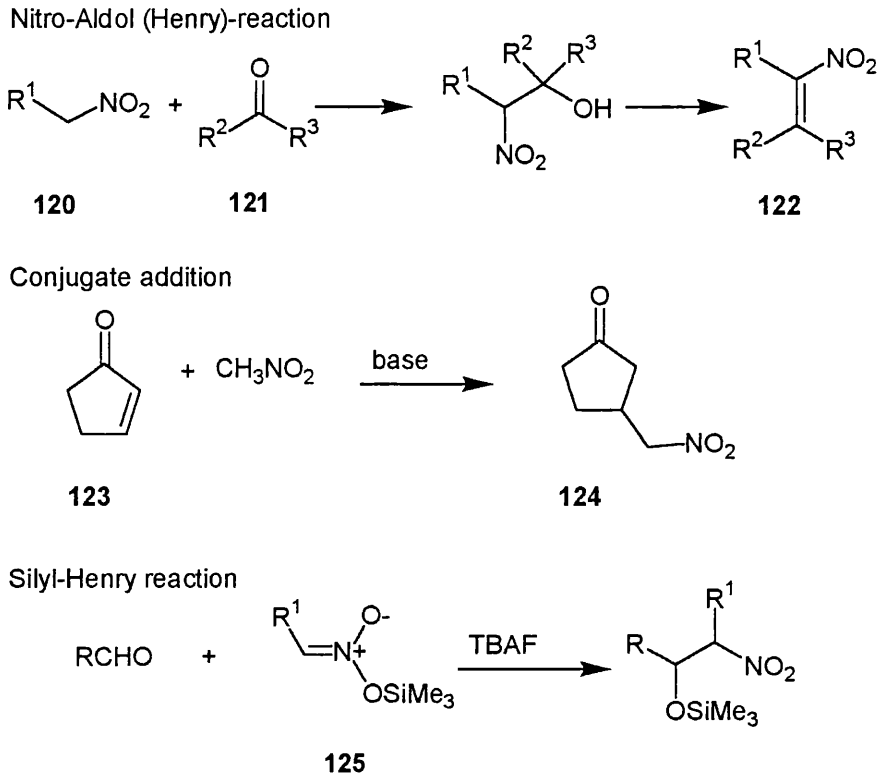


Figure 54

Neutral nitronates (**125**) generated in the in the above fashion (Fig. 54) are not only carbon or oxygen nucleophiles, but also 1,3-dipoles of the bent allyl type (*cf.* section 2.2)

Cycloaddition reactions between a nitronate and a dipolarophile yield 5-substituted isoxazolines (Fig. 55). Furthermore, 1,2-disubstituted alkenes, such as methyl crotonate (**126**), exclusively yield the isoxazolines with the electron-withdrawing group in the 5-position (**127**). The cycloaddition can be catalysed by boron trifluoride[75].

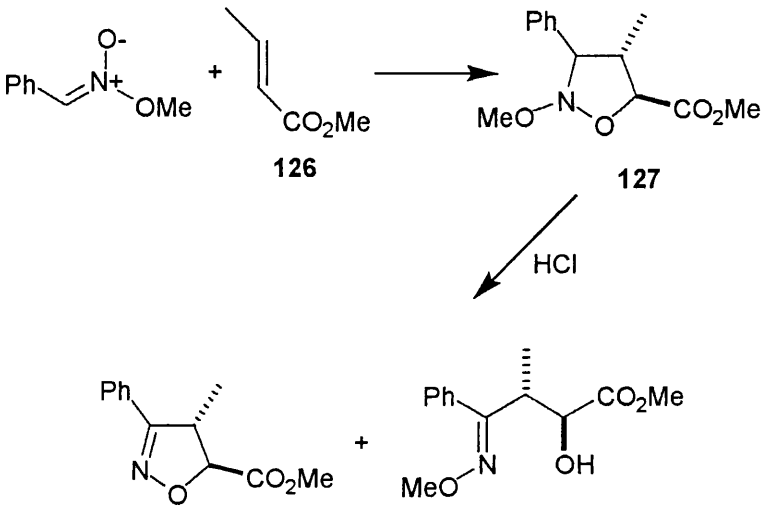


Figure 55

Tandem [4+2][3+2] cycloadditions of vinyl nitronates have emerged recently as a useful tool to access heterocyclic compounds. The power of the reaction lies in the generation of four new bonds and a number of chiral centres. Permutations of both cycloadditions (*inter/intra*) allow the construction of diverse compound sets[76].

Denmark's group has usefully employed these cascade reactions in the synthesis of Mesembrine and other alkaloids.

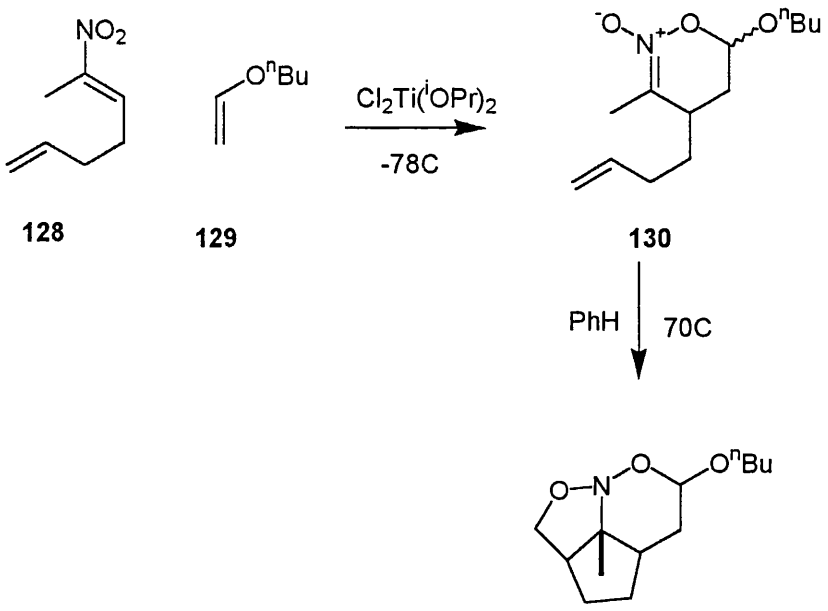


Figure 56

In Denmark's work (Fig. 56) the initial [4+2] addition of butyl vinyl ether to nitroalkene (**128**) is governed by inverse electron demand[77] requiring an electron rich dienophile (**129**). The resulting cyclic alkyl nitronate (**130**) is better suited to an electron neutral olefin for the subsequent [3+2] cycloaddition. This allowed the alkene to be tethered to the nitro olefin without interfering in the initial [4+2] cycloaddition.

Nitronate cycloaddition chemistry is not limited to alkyl nitronates. Torsell's group[78] has used silyl nitronates in the synthesis of isoxazolidines (Fig. 57). Silyl nitronates (**131**) are best generated from a nitroalkane (**120**), base (*e.g.* triethylamine) and chlorotrimethylsilane. Usually, the silyl nitronate is generated *in situ* due to their easy hydrolysis with water and then treated with the dipolarophile. However, Seebach and Colvin have isolated simple silyl nitronates by distillation and characterised them[79].

In contrast to *N*-alkoxy isoxazolines, the resulting *N*-silyloxy isoxazolines (**132**) easily eliminate the silanol under acid catalysis, to furnish the corresponding isoxazoline (**133**) exclusively, without concomitant ring opening (Fig. 57).

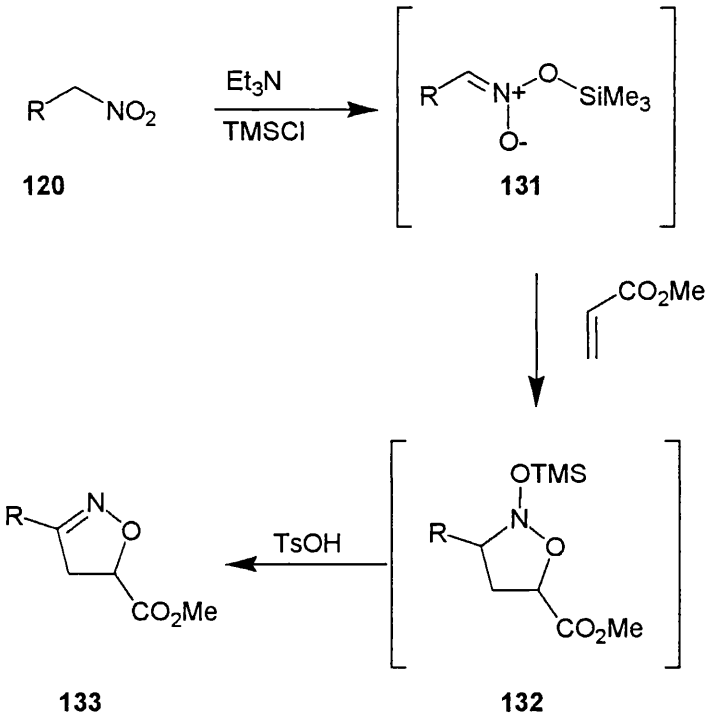


Figure 57

Whereas simple alkyl nitronates preferentially react with electron poor dipolarophiles, Torsell[78] has shown that silyl nitronates react equally well with electron rich dipolarophiles, such as ethyl vinyl ether. Thus, it appears that the substitution of the nitronate oxygen atom is crucial to its reactivity profile. This reactivity profile is most probably due to the more electronegative character of silicon relative to carbon. Additionally, silicon has vacant d-orbitals which may undergo back bonding with the lone pair of electrons on oxygen (Fig. 58), making the

silyl nitronate more electron poor and thus facilitating reaction with electron rich dipolarophiles.

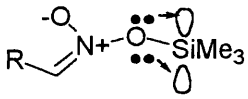
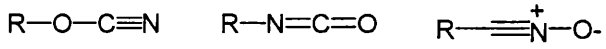


Figure 58

2.5 Nitrile Oxides

Nitrile oxides (**136**) are linear dipolarophiles. They are isomeric both with cyanates (**134**) and isocyanates (**138**) (Fig. 59).



134 **135** **136**

Figure 59

Nitrile oxides (**136**) are highly reactive species, with a half-life of the order of minutes, and in the absence of a dipolarophile, they will undergo dimerisation (Fig. 60) to form furoxans (**137**), isomerisation to the corresponding isocyanate (**139**), or polymerisation. However, in the presence of an appropriate dipolarophilic trapping agent such as an alkene (**140**), nitrile oxides furnish isoxazolines (**138**).

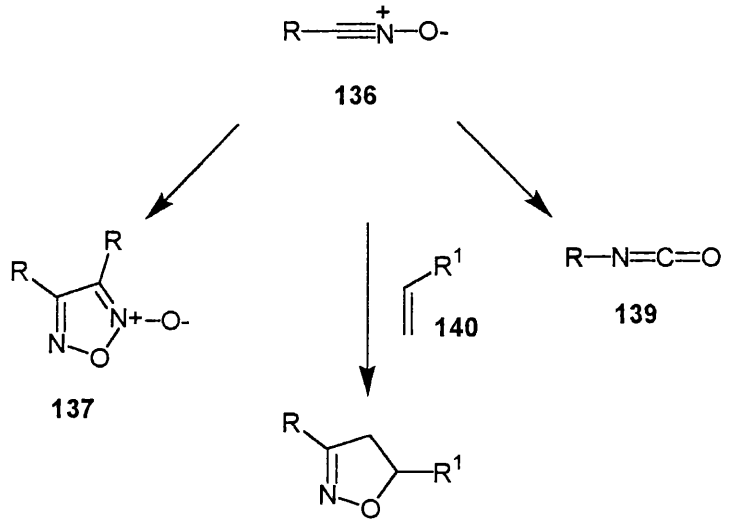


Figure 60

The earliest example of a nitrile oxide (**136**) used in a cycloaddition reaction was Grünanger's publication in 1950[80], although the generation of benzonitrile oxide goes back to Gabriel's work[81] in 1886. In some rare cases appropriately substituted nitrile oxides have been isolated[82]. Over the past 50 years the generation and reaction of nitrile oxides has become a staple reaction in the organic chemist's tool kit.

The most convenient way of generating nitrile oxides (**136**, Fig. 61) is by dehydrohalogenation of the corresponding hydroximinoyl halide (**142**). These in turn are generated from the parent aldoximes (**141**) with *N*-chloro or *N*-bromo succinimide, chlorine or sodium hypochlorite.

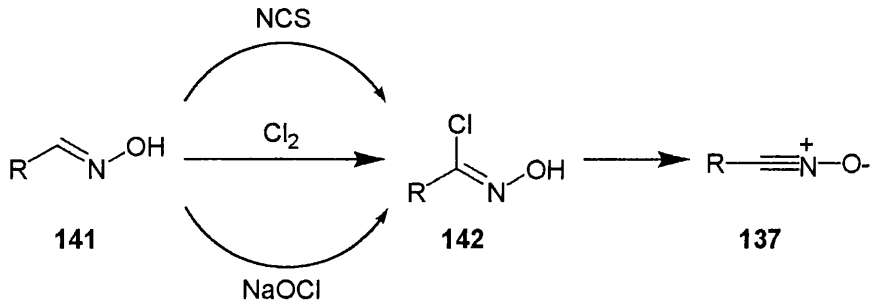


Figure 61

An alternative method is the dehydration of primary nitro compounds (**120**) with phenylisocyanate in the presence of a catalytic amount of triethylamine[83] (Fig. 62). This method is known as the Mukaiyama-Hishimo procedure and has the advantage of avoiding the chlorination step.

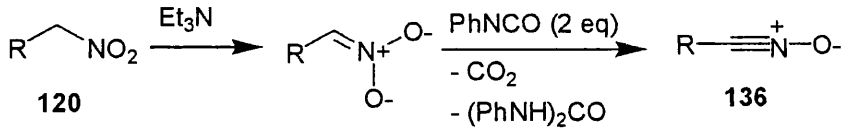


Figure 62

Nitrile oxides (**136**) have been shown to undergo cycloaddition reactions with a number of carbon-carbon and carbon-hetero atom double bonds to afford isoxazolines and hetero-isoxazolines.

Where the dipolarophile is mono-substituted the result is in most cases the 5-substituted heterocycle, except in cases in which the dipolarophile is especially electron poor, such as sulphones.

Reaction of nitrile oxides with electron rich and conjugated alkenes is LUMO controlled (Type III reaction). With electron deficient alkenes the reaction is usually HOMO (Type I reaction) (Fig. 63). Both of these reactions lead to the formation of 5-substituted isoxazolines.

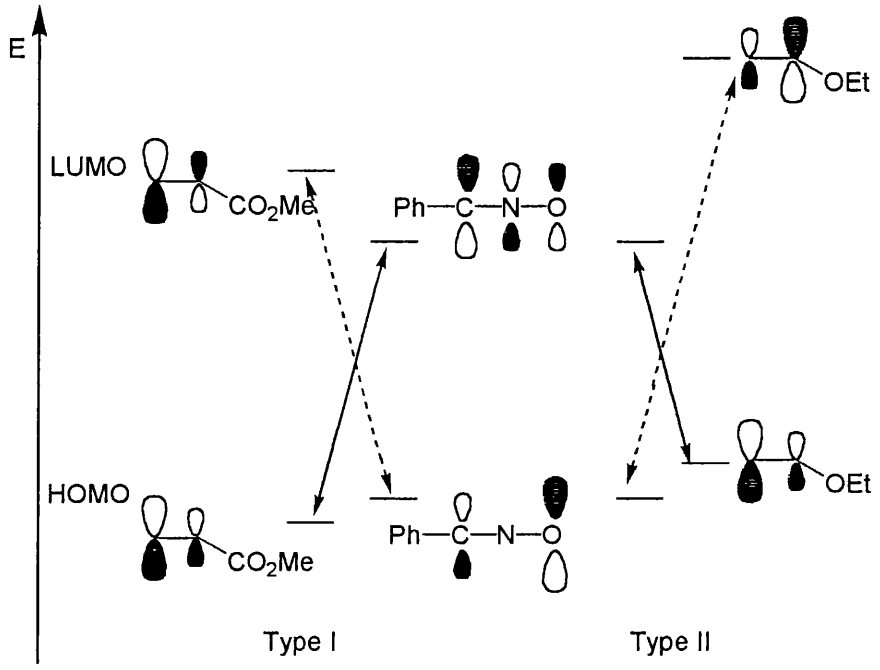


Figure 63

2.6 Conclusion

The usefulness of 1,3-dipolar cycloaddition chemistry in synthetic chemistry has been proven over many decades. The strength of the reaction lies in the first instance on the ease of preparation of the dipoles and then in the 'convergent' nature of bond formation, coupled with the versatility of the heterocyclic products formed for further synthetic elaboration

From the foregoing overview, which has exemplified the utility of 1,3-dipolar cycloadditions with particular reference to nitronates and nitrile oxides, it is clear that the use of FMO theory in terms of understanding the contrasting reactivities of these two 1,3-dipoles has been paramount.

Part 2:

RESULTS AND DISCUSSION

CHAPTER 1

1 Introduction and Overview

The objective of the present thesis is the development of a new multi-component reaction. Two conceptually different approaches have been adopted, the first being an 'irrational' discovery method whilst the second follows the more traditional 'rational' design method. Within the constraints of the project was also the wish to develop a robust and versatile methodology for particular use in an industrial setting, and in particular for parallel synthesis and high diversity combinatorial chemistry. In an ideal world, we wished to investigate and expand the types of methodology amenable to us in the development of new multi-component processes with the aim of producing more 'convergent reactions'. Known MCRs, such as the Ugi reaction, are often highly versatile and robust reactions amenable to robotic synthesis. As such, they possess the advantage that they do not require the employment of an inert atmosphere and specially dried solvents. However, most current MCR methods are relatively limited in their use of heteroatoms and, by implication, produce compounds of only limited diversity. Additionally, the reactions involved often rely on the equilibration of starting materials and the sequential addition of reagents. This property is a particular disadvantage for robotic implementation of a method as reaction rates vary considerably as a function of substrate structure and, in consequence, yields are seldom at their optimum.

CHAPTER 2

2.1 Extension of the Combinatorial Principle: A Combinatorial Approach to Multi-Component Reactions

Within the past 5-10 years, synthetic chemists have been using the related techniques of combinatorial chemistry and parallel synthesis in academe and especially in the pharmaceutical industry to generate very large numbers of compounds to screen against biological assays. Early efforts concentrated on simply generating large numbers of compounds on a peptide scaffold or similarly simple compounds, and used only conventional peptide coupling chemistry. More recently, efforts have been directed towards using these techniques to develop new catalysts[84] and also to discover[85] and optimise[86] new reactions.

In some respects, developing new reactions, i.e. by postulating a mechanism and then testing the hypotheses, is a hit and miss procedure. This suggests that there is no analytical solution to make the problem tractable by either a formal or a mathematical method. Problems which elude analytical solutions are called NP-complete[87] (**n**on-**p**olynomially complete), that is they cannot be solved in a reasonable amount of time (such as the life-time of the experimenter). NP-complete problems are best tackled using heuristics*[88]. The two situations in which heuristic methods are invoked generally occur either when there is not enough information to formulate an axiomatic algorithm, or when a problem possesses too great a complexity to be solved by an axiomatic algorithm.

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* ευρισκιεν: to find

In cases for which insufficient information is available to formulate a theory, the basis to formulate a deductive algorithm is also missing. In other words, where the connection between observed facts is unknown then the problem cannot be solved deductively or analytically. Heuristics in this context becomes a bye-word for 'don't know'.

Alternatively, at issue may be that the problem is complex to the degree that it becomes intractable. This situation arises, if there are in principle, too many solutions that require evaluation. Deduction then becomes too complex and time consuming a task to be a reasonable option.

It could be argued that multi-component reactions are systems of a level of complexity in which to postulate a mechanism *a priori* would be futile. Thus finding new multi-component reactions is ultimately best solved by the *Monte-Carlo* method, *i.e.* by pure chance.

With this in mind, it seemed reasonable not just to generate combinatorial product libraries, but also libraries containing (attempted) reactions. The most efficient approach to this kind of parallel synthesis requires automation both in the synthesis and in the analysis.

2.1.1 Outline of the Genetic Algorithm

The genetic algorithm[89] is a search procedure, which mimics natural selection or evolution. The procedure translates real data into abstract 'string structures' (units of computer information), subjects these structures to a fitness function and randomised information exchange, thus allowing the evolution of optimised information structures[89], *i.e.*

it is fundamentally a stochastic procedure, rather than a deterministic one. It is therefore suited to problems with a great deal of data and with many possible optimal or near optimal solutions.

An evolutionary system is composed of two levels, *viz.* the encoding level and realisation level. The two layers are connected by an operator, which allows the encoded level to be realised. The two levels mirror the genotypic and phenotypic levels of genetics respectively. A fitness function tests the phenotypes from which in turn a new generation of genotypes evolves through a feedback loop.

Using this concept, Weber synthesised a virtual compound library of test compounds *'in silico'*, and tested it for a best fit against a thrombin inhibitory assay[90] with the aid of a computer programme. From an initial reagent pool of 10 isocyanides, 40 aldehydes, 10 amines and 40 carboxylic acids, which would generate a library of 160000 Ugi 4-CC compounds, a starting generation of only 20 were chosen at random. These were tested against the fitness function. The compounds which scored highly against the fitness function were allowed to undergo mutation and crossover, *i.e.* exchanging elements from their encoded level (*genes*). This produced a second generation, which underwent the same test, and again the compounds with the highest inhibition underwent crossover and mutation to produce the following generation. The result was that after only 16 cycles or generations (representing 400 reactions), the average inhibitory concentration was below 1μM. This meant that only a handful of compounds actually had to be synthesised and tested in the lab, rather that all 160000 compounds.

The two crucial features of the genetic algorithm are (i) recursiveness and (ii) the use of a fitness function to measure the quality of each individual in a generation.

Applied to the generation of a reaction library neither feature can be satisfactorily integrated in the search for new reactions. The recursivity feature would suggest that certain functional groups are better suited to the development of new reactions than others are, when the reactivity of a functional group depends on the conditions to which it is subjected and the interactions with other functional groups which it can undergo.

The fitness function poses an equally impenetrable problem when applied to the discovery of new reactions. The progress of a reaction cannot be measured incrementally. A new bond either forms or it does not, and hence a new reaction cannot partially take place. Therefore, if a reaction takes place, the fitness function becomes obsolete in the search for new reactions. Furthermore, the function cannot help determine which reagents should be kept for the next round of tests out of those which did not produce a new reaction.

Thus, although genetic algorithms have been applied to numerous problems in chemistry and biology, on the basis of the foregoing analysis it would appear that they were not appropriate in the present context.

2.2 Combinatorial Reaction Library

Our initial studies therefore focused on a combinatorial approach in which groups of reagents were reacted with each other in a combinatorial manner to generate a reaction library. To the best of

our knowledge, there had been only one recent example of this approach to the development of new MCRs[42]. Since the concept of screening large compound libraries was well documented in the literature[91], we reasoned that the screening of even crude reaction mixtures by mass spectroscopy for identification of molecular masses equivalent to more than two reagent masses could provide a lead to the discovery of new reactions.

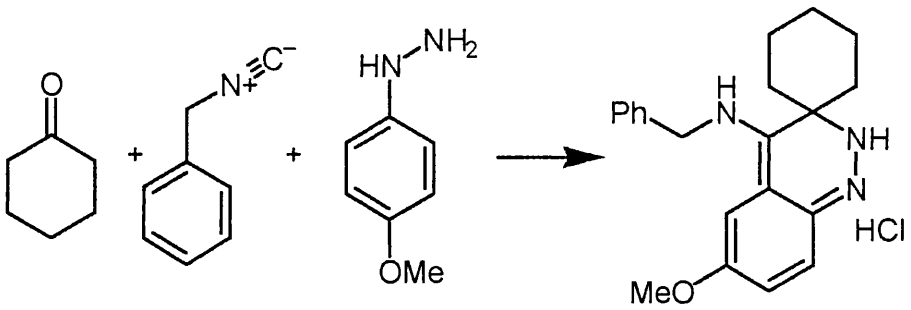


Figure 64

Weber and Lack[42] have successfully used a similar approach in which they screened a small reaction library consisting of 1013 reactions, using HPLC to develop a new 3-component reaction based on isocyanide chemistry (Fig. 64). The ten different reactants (Fig. 65) were reacted with each other in combinatorial fashion. The crude reaction mixtures were then analysed by HPLC, and those peaks corresponding to the starting materials and simple 2-component reactions were discounted. This left only the more complex products to analyse and resulted in the discovery of a new reaction.

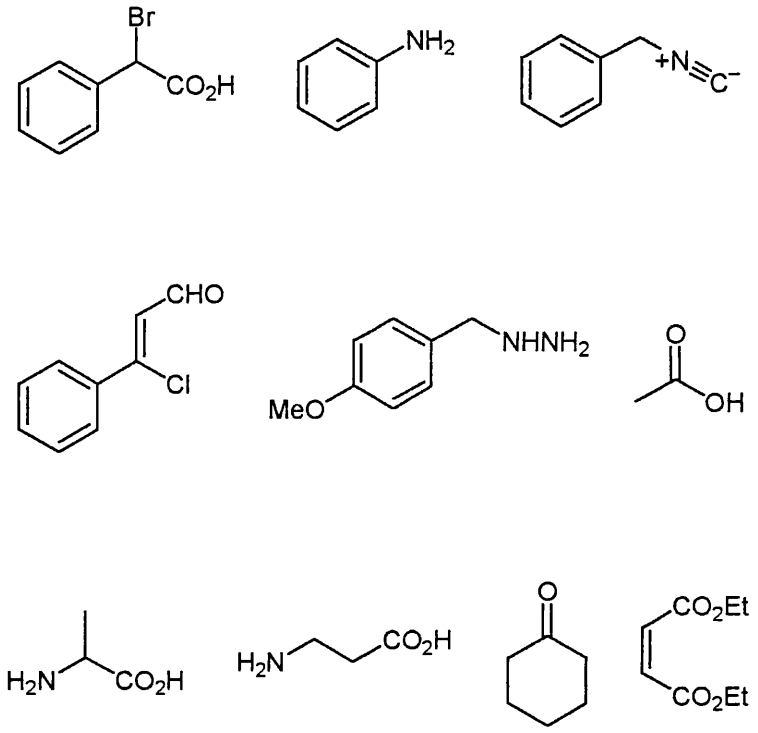


Figure 65

The ten reagents (Fig. 65) give rise to a total of 1013 possible reactions, ranging from 45 2-component reactions to one possible 10-component reaction (Table 1) according to the formula of possible combinations of elements without repetition[92] (Eq. 1), where ***C*** is the number of reactions using ***r*** reagents out of a total of ***k*** reagents.

$$C^{k}_{r}=\frac{k!}{r!(k-r)!}$$ Equation 1

Number of Components	10	9	8	7	6	5	4	3	2	
Number of Combinations	1	10	45	120	210	252	210	120	45	Total=1013

Table 1

2.2.1 Choice of Reagents

In Weber's work[42], no classification of reagents was attempted, *i.e.* each reagent was treated as being unique to its set. This implies a view that each reagent has a unique reactivity profile. However, it could be argued that any given choice of reagents have a number of qualities in common which might mark them out as possessing a common reactivity profile. Thus, Weber's 10 reagents (Fig. 65) might be grouped into sets. For example aniline and *p*-methoxyphenylhydrazine can be classed as nucleophiles, or α-chlorocinnamaldehyde and diethyl maleate can be grouped together as dienophiles, dipolarophiles or Michael acceptors. This simply reflects some of the chemistry each compound is capable of and therefore some of the chemistry which could be expected in a reaction library.

At the heart of this argument is the concept of diversity. Grouping reagents together such as amines may lead to a set of compounds containing all commercially available amines, but very little diversity. Commercially generated libraries prepared for screening against biological assays are concerned with generating diversity with regard to the products obtained, however in our case the diversity argument focuses on the starting materials rather than the products. Just as combinatorial libraries are differentiated into distinct structural classes according to their core templates[93], we reasoned that it might be logical to differentiate reagents into distinct classes according to their intrinsic reactivities. Indeed, any undergraduate textbook on organic chemistry does so by discussing each functional group separately. We were aware however that grouping our starting materials along these classical lines might only result in finding known reactions, as in the reaction of an

ester with an amine to afford an amide, or at best unusual, but not generally applicable exceptions to known chemistry.

Thus, in our own choice of reagents we elected not only to group starting materials together in a way which might reflect their reactivity, but also at the same time allow us to cover as many combinations of functional groups reacting with each other. Such a choice of reagents is not entirely random. Moreover, the use of bifunctional reagents leads to an increase of complexity. Conceptually, the use of a *bis*-electrophile and a *bis*-nucleophile involving four different functional groups can be interpreted as a four-component reaction.

It is common in chemistry to differentiate molecules by grouping them into different classes. This differentiation is usually based on functional groups, or on physico-chemical properties such as acidity, basicity or on the physical state of the material. In attempting to group reagents together our aim was to match reagents to exploit their reactivity and thus attempt to ensure adequate coverage of the 'reaction space', *i.e.* the effort was made to cover as many possible and unusual combinations of functional groups. It was clear that there was no unique solution to the problem posed. The success of the project required the total scheme, from choice of compounds, conditions, automation, analysis and data evaluation to work together.

Rather than group reagents together simply by functionality, we elected to group them along more general principles as shown in Figure 66. Thus, group 1 contains trifunctional reagents, group 2 bifunctional reagents, group 3 monofunctional reagents and group 4 nitrogen containing reagents. Additionally, in order to encourage reaction, α-pyridone and triphenylphosphine were considered as

potentially useful additives, which could function respectively as acid-base and nucleophilic catalysts of some degree of generality. This allowed us in principle to access the reactivity of more than one functional group in any given reaction and thus effectively increase the diversity covered. Additionally, increased reaction diversity was to be achieved by subjecting the reaction to different conditions: each reaction was performed twice, each time on a separate 96-well plate. One plate was allowed to react at room temperature, whilst the other was subjected to microwave irradiation.

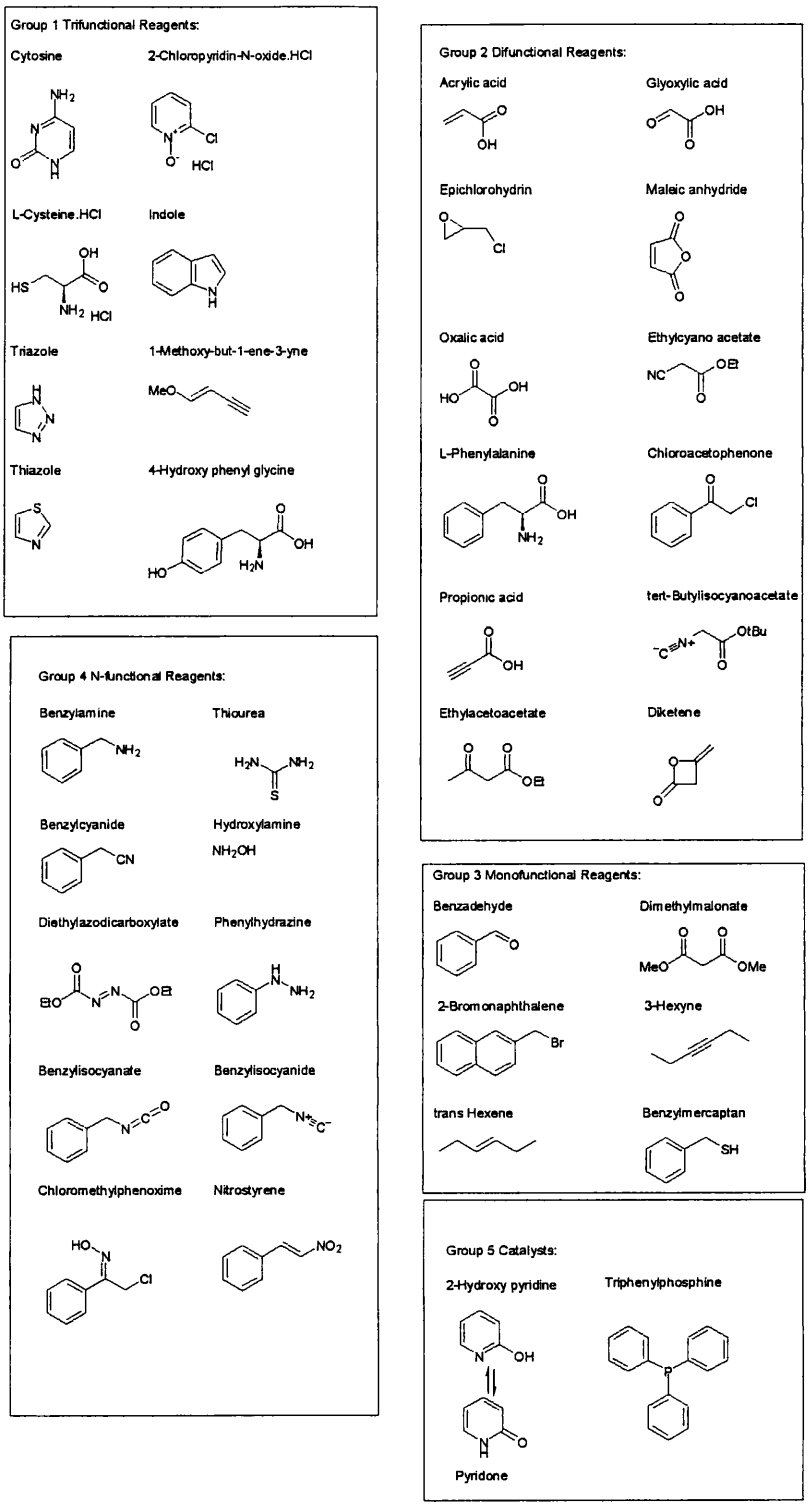
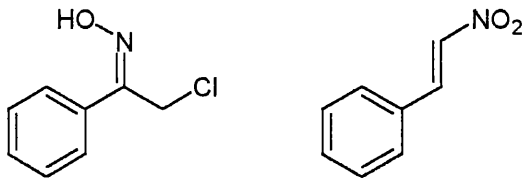

Group 1 Trifunctional Reagents:
Cytosine
2-Chloropyridin-N-oxide.HCl
L-Cysteine.HCl
Indole
Triazole
1-Methoxy-but-1-ene-3-yne
Thiazole
4-Hydroxy phenyl glycine
Group 2 Difunctional Reagents:
Acrylic acid
Glyoxylic acid
Epichlorohydrin
Maleic anhydride
Oxalic acid
Ethylcyano acetate
L-Phenylalanine
Chloroacetophenone
Propionic acid
tert-Butylisocyanoacetate
Ethylacetoacetate
Diketene
Group 3 Monofunctional Reagents:
Benzadehyde
Dimethylmalonate
2-Bromonaphthalene
3-Hexyne
trans Hexene
Benzylmercaptan
Group 4 N-functional Reagents:
Benzylamine
Thiourea
Benzylcyanide
Hydroxylamine
Diethylazodicarboxylate
Phenylhydrazine
Benzylisocyanate
Benzylisocyanide
Chloromethylphenoxime
Nitrostyrene
Group 5 Catalysts:
2-Hydroxy pyridine
Triphenylphosphine
Pyridone

Figure 66

Moreover, it appeared highly unlikely to discover a reaction of more than four components. In spite of the largest number of reactions arising from combinations of six reagents in Weber's work, with the implicit corollary of the chances of finding a potential 6-component reaction being relatively high, we felt that discovering a 3-, or 4-component reaction was considerably more likely. Hence, we opted to investigate only possible 4-component reactions, which in theory at least would still allow us to discover any given 3-component reaction as a subset of the four reagents used.

In addition to our thoughts on reagent classification, we also considered that the use of non-commercially available reagents or those less commonly used, would by its very nature, encourage novelty. Hence, the reagent list contains α-chloro acetophenone oxime (**143**) and nitrostyrene (**144**, Fig. 67). Both reagents are easily accessible from commonly available starting materials and require only one simple reaction in their synthesis. Both compounds were chosen for their rich and sometimes unusual chemistry.



143 **144**

Figure 67

Thus, for example, in the presence of base, an α-chloro oxime will eliminate HCl to produce a highly reactive nitroso alkene. Indeed, so reactive are these species that it was not until 1960 that the first stable compound of this type, trifluoro nitroso ethylene, was synthesised[94].

Nevertheless, nitroso alkenes can be formed in solution as reactive intermediates and can then undergo a variety of reactions including [4+2] cycloadditions and reaction with activated methylene compounds to form imines. When conjugated to an unsaturated moiety the nitroso group exerts a powerful effect as an electron withdrawing substituent.

Equally, the chemistry of nitroalkenes has a rich literature associated with it[95]. Again at the forefront stand [4+2] cycloadditions with the nitroalkene acting as either the 2π or the 4π component (*vide infra*). Additionally the reactivity of nitroalkenes is characterized by the electrophilic nature of the alkene double bond and the ability of the nitro group to stabilize a negative charge, thus allowing it to undergo Michael additions and subsequent aldol type reactions[96].

The synthesis of α-chloro acetophenone oxime (**143**) proceeded without difficulty and was carried out easily and in good yield[97]. In the case of a nitroalkene, we encountered some difficulty at first, as our intention was to prepare 1-nitromethylene cyclopentane by adapting methodology developed in the Barton group for the synthesis of steroidal nitroalkenes[98] (Fig. 68).

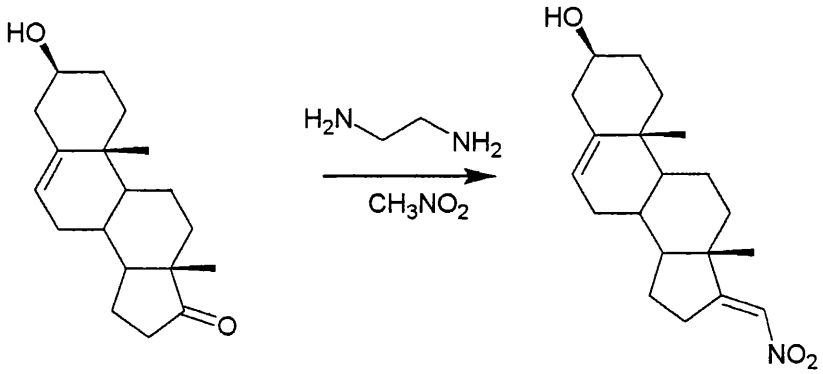


Figure 68

In our hands, the reaction of cyclopentanone with nitromethane in the presence of a catalytic amount of ethylene diamine yielded a mixture of vinylic and allylic nitro alkenes, which could not be separated, and thus was of no further use for our combinatorial study. The formation of the mixture can be rationalised by the fact that the endocyclic double bond is thermodynamically favoured. It was thus decided that a non-enolizable aldehyde should be employed to avoid such a problem of double bond migration, and indeed, the classical reaction of nitromethane with benzaldehyde using potassium hydroxide[99] to give nitrostyrene (**144**) proved to be highly efficient and subsequently offered easy access to large quantities of nitrostyrene.

2.2.2 Validation of Analytical Methods

To ensure that the automation, programming and analytical equipment functioned appropriately, a series of test experiments were set up to validate the methods and techniques employed, thus testing the system and generating guidelines for a general operating procedure protocol. The goals of the former were to make sure that the robotics programme was faultless and dispensed the correct reagent to the correct well in the correct amount. The goals of the latter were to determine the best solvent to be used, the amount of microwave irradiation which could be tolerated by the 96 well plate, the chosen solvent, the reagents and finally the degree of dilution of the crude sample to allow for reliable mass spectroscopy.

A number of known reactions were chosen to assess the reliability of the methodology. The use of these reactions in the context of automated synthesis is well established[100]. A common approach to combinatorial organic synthesis is to use spatially addressable synthesis,

where reagent building blocks are reacted systematically in individual reaction wells to form discreet molecules[101].

Amongst these, one of the most widely used reactions in automated parallel synthesis is the Ugi reaction. It is particularly suited to application in a robotic synthesis as the reaction does not require anhydrous or oxygen free conditions. Other reactions suited to these kinds of conditions are the Passerini[102], Biginelli[103], and Grieco[104] reactions (*cf.* Part I, sections 1.1.2, 1.2.1 & 1.2.2 respectively). These were employed to create discreet and comparatively pure test compounds.

Thus, after the series of trials detailed below, it was possible to detect the Ugi product (**146**) and its dimer (**147**) from the reaction of benzaldehyde (**41**), glycine (**145**), *tert.*-butyl isocyanide (**42**) and the solvent ethylene glycol (Fig. 69).

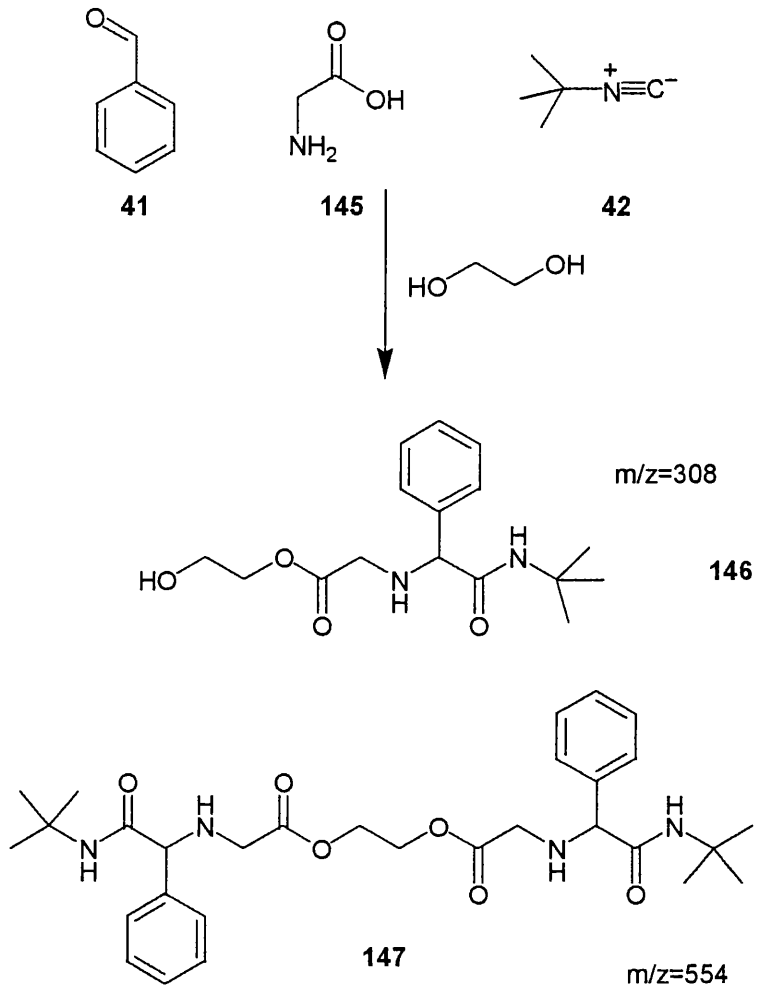


Figure 69

This crucial test confirmed that the programming, robotics and a satisfactory analytical method were in place and in working properly in order to allow us to proceed with the preparation of the reaction library itself.

The test reactions, which were carried out in different solvents allowed us to assess which solvent possessed the most desirable combination of characteristics for the robotic protocol. From this, it was apparent that ethylene glycol was an appropriate solvent, not only because most of the reagents were soluble in the amount required but also because its

dielectric constant allowed it to be used in conjunction with microwave irradiation. The plates were also subjected to various amounts of time in the microwave oven to give an indication of temperature each solvent reached, and whether the degree of microwave irradiation had any effect on the analytical characteristics of the plate, for example by degradation or polymerisation of reagents or products.

Within the past two decades interest in microwave assisted reactions has grown and has been extensively reviewed[105]. The application of microwaves to organic synthesis has given rise to some startling increases in yield and purity of reactions such as the Diels-Alder reaction between dimethyl fumarate (**149**) and anthracene (**148**)[106] (Fig. 70).

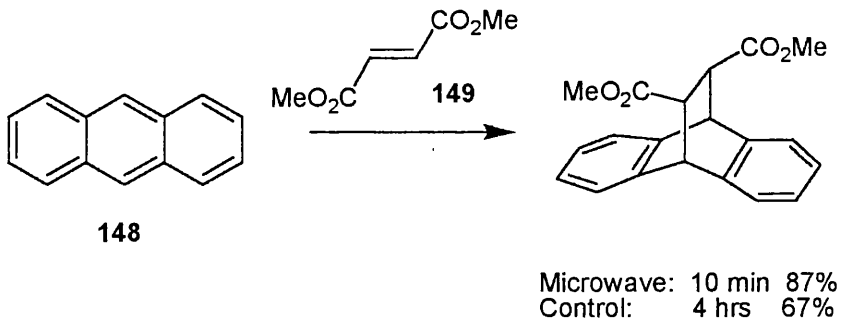


Figure 70

The microwave effect is the result of highly efficient internal heating, generated by the alignment of the dipole moments of the reagents with the oscillation of the alternating external electric field from the microwave oven. The major advantages presumed to arise from this effect are that the energy transfer (heating) is almost instantaneous at the core without any of the local over heating associated with normal

heating. This leads to shorter reaction times, higher yields and increased purity of product.

The solvents employed were ethylene glycol, DMF, THF, MeOH, acetonitrile and hexane. The plates were subjected to microwave radiation for 30 sec, 60 sec, 90 sec and 120 sec. The temperature of the plates was measured with a thermometer at two opposing corners, in the centre and two intermediate points in between, of the plate. The first observation to be made was that heating was very uneven across the plate depending on the exact site within the microwave oven where the well was actually located. This suggested that the microwave radiation was not evenly dispersed through the oven, leading to temperature differentials of as much as 50°C between wells at the focus point of the radiation and those at the edge of the plate. Without access to a highly specialised microwave oven in which the microwaves are focused and evenly dispersed, we were unable to resolve the problem of uneven heating.

Excess microwave radiation led to evaporation of the more volatile solvents, such as MeOH, THF and acetonitrile, with the result that the reagents themselves were radiated without the attenuating effect, which the solvent had by dispersing excess heat efficiently. This in turn led to a tarring of the reagents and potential products, which could not then be dissolved sufficiently well to allow analysis by mass spectrometry.

In the case of the higher boiling solvents, such as ethylene glycol and DMF, it was found that the solvents reached their boiling points within 90 sec of microwave radiation. With longer microwave irradiation, the heat from the boiling liquid was transferred to the

polypropylene plates and destroyed the plates! Therefore, a compromise had to be achieved with regard to exposure of the reactions to microwave heating and the integrity of the plates. Thus, in the event the plates were microwaved twice for 45 seconds and allowed to cool in between.

The solvents and volatile starting materials were then removed from the plates under reduced pressure. In a further robotic manipulation, the dried compounds in the plates were then dissolved and diluted to a concentration of 0.6 mg/ml in MeOH and submitted for automated mass spectrometry. The mass spectrometry was carried out in both positive and negative ion mode generated by electron impact.

2.2.3 Library Generation

The preceding test phase using the Ugi reaction had therefore ensured that that the robotic systems and operating procedures were in place and functioning, thus allowing us to proceed with the generation of our novel reaction library.

Hence, with reference to our chosen groupings, (Fig. 66, p. 80), the reagents from group one were pipetted into each well of the 8 rows of the plate and those from group two into each well of the 12 columns of the plate. One reagent each from groups three and four was added to each well of the plate, that is, these were kept constant across the plate. Therefore well A1, for example always contained cytosine and acrylic acid, well H12 always contained 4-hydroxy phenyl glycine and diketene. To both of these wells the same reagent from groups three and four were added, e.g. benzaldehyde and benzylamine.

Combinatorial variation of the 16 reagents solely from groups three and four, with the remaining 20 identical to each plate, would lead alone to 60 plates being generated. With the added variations of using a catalyst and employing microwaves (6 x 10 x 2 x 2 x 2=) 360 plates were therefore prepared in total. Overall, this represents 96 x 360=34560 reactions, which were prepared for mass spectroscopic analysis.

The following flow chart (Fig. 71) gives a brief overview of the steps involved.

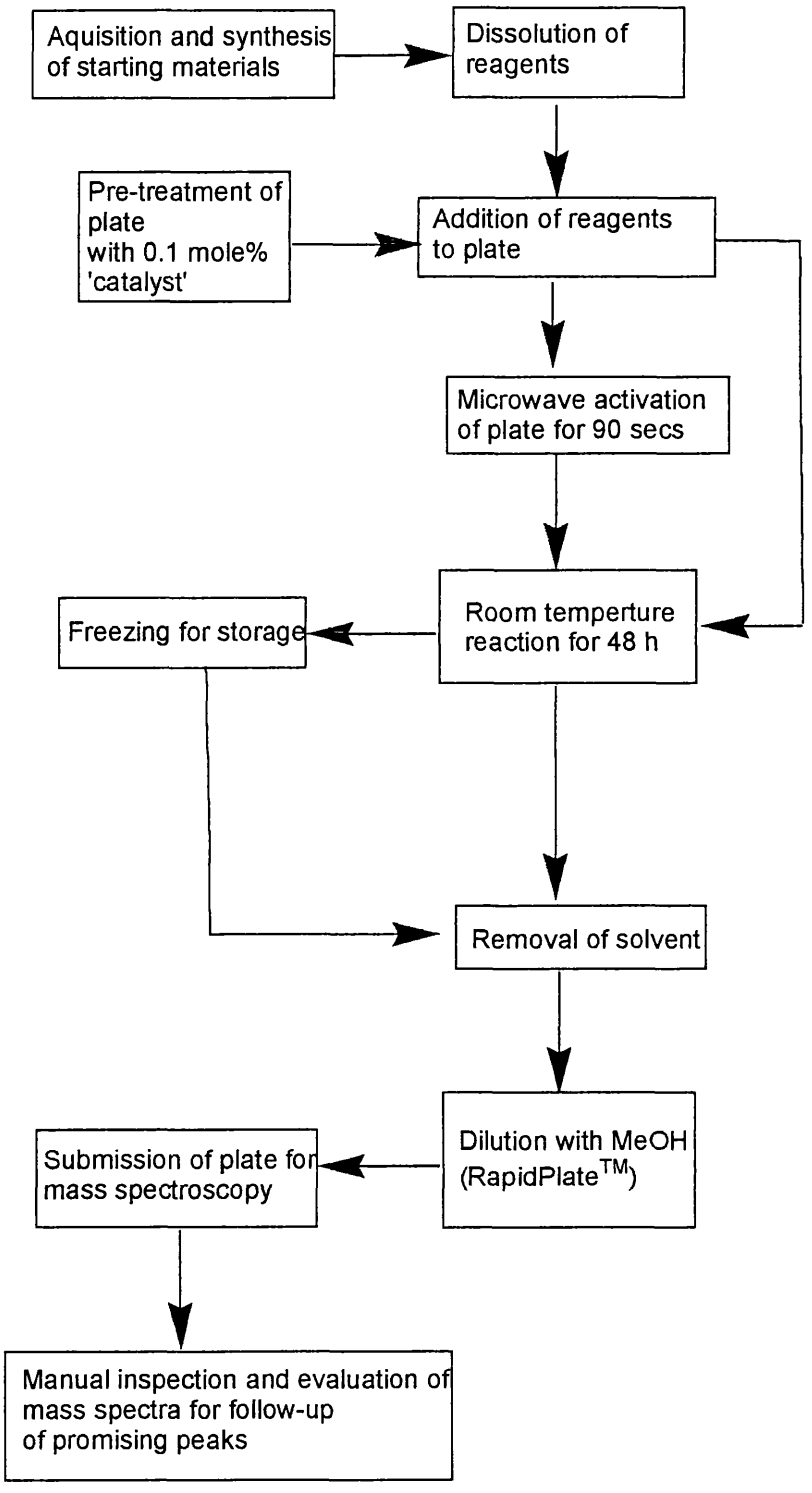

Aquisition and synthesis of starting materials
Dissolution of reagents
Pre-treatment of plate with 0.1 mole% 'catalyst'
Addition of reagents to plate
Microwave activation of plate for 90 secs
Freezing for storage
Room temperture reaction for 48 h
Removal of solvent
Dilution with MeOH (RapidPlate™)
Submission of plate for mass spectroscopy
Manual inspection and evaluation of mass spectra for follow-up of promising peaks

Figure 71

2.2.3.1 Data Collection and Analysis

We then proceeded to the final phase of the protocol which we had established, and in the event as outlined below, this proved to be our '*bête-noire*'. Thus, analysis of the mass spectra of each crude reaction mixture showed masses equivalent to a 2-component reaction, *e.g.* Michael additions of amines onto methyl acrylate. These peaks were usually predominant, thus making the detection of other reactions difficult by virtue of their smaller peak sizes. More disturbingly, however, the spectra were not reproducible. A large number of spectra were highly complex. At first, we believed this to be a result of improper sample preparation, *i.e.* samples submitted of too high or too low concentration for mass spectroscopy. The plates were re-synthesised and re-submitted only to yield a completely different spectrum. Some of the major peaks, corresponding to 2-component masses, were still present, yet lower intensity peaks had appeared and others disappeared. The irreproducibility of the crude reaction mixtures was a severe drawback. We believed that a major disadvantage of our approach had been to use crude samples for analysis. However, the alternative option of performing LC/MS on the reaction library, in order to partially purify the crude reaction mixtures, was too time consuming to be viable with the equipment constraints placed upon us by our industrial partner. Even without purification, the mass spectrum for each well took 5 minutes to run, *i.e.* 8 hours for each plate.

The most fatal flaw of all perhaps was that the analysis of the mass spectra was done manually. For the present investigator, this was the most time consuming and cumbersome part of the process. Each plate generated 192 (2 x 96) mass spectra (positive and negative ion

mode), which were then compared with the data from a pre-prepared spreadsheet, which had required calculation of combinations of 3 or 4 reagents together with possible dehydration and/or decarboxylation. Although, this gave a number of possible masses for each well, which formed the basis of the search, the task, in reality, was the equivalent of searching for the proverbial 'needle in a haystack'!

2.2.4 Isoxazolone 3-CR

Even greater frustration was occasioned on following up what appeared to be 3-component mass peaks since the reactions yielded inseparable products. In addition, once again, the crude reaction mixtures from scaled up reactions did not yield comparable mass spectra to those obtained from the polypropylene plates.

In one isolated case, before this approach was abandoned, we were able to 're-discover' an 'unusual' 3-component isoxazolone synthesis (Fig. 72). Thus, the original spectrum for the microwaved reaction of benzaldehyde (**41**), ethyl acetoacetate (**56**), hydroxylamine hydrochloride (**151**) and cytosine (**150**), had shown an interesting major peak at 328 m/z. The reaction was performed, mimicking the conditions of the combinatorially performed reaction as closely as possible (solvent, duration of microwave irradiation) on a preparative scale of 5 mmol. From the crude reaction, a voluminous yellow precipitate formed, the mass spectrum of which gave a mass of 187 m/z, a peak not observed on the original spectrum obtained from the 96-well plate. NMR, IR and microanalysis were consistent with the isoxazolone structure (**152**). This product made up 65% of the mass balance in an unoptimised reaction.

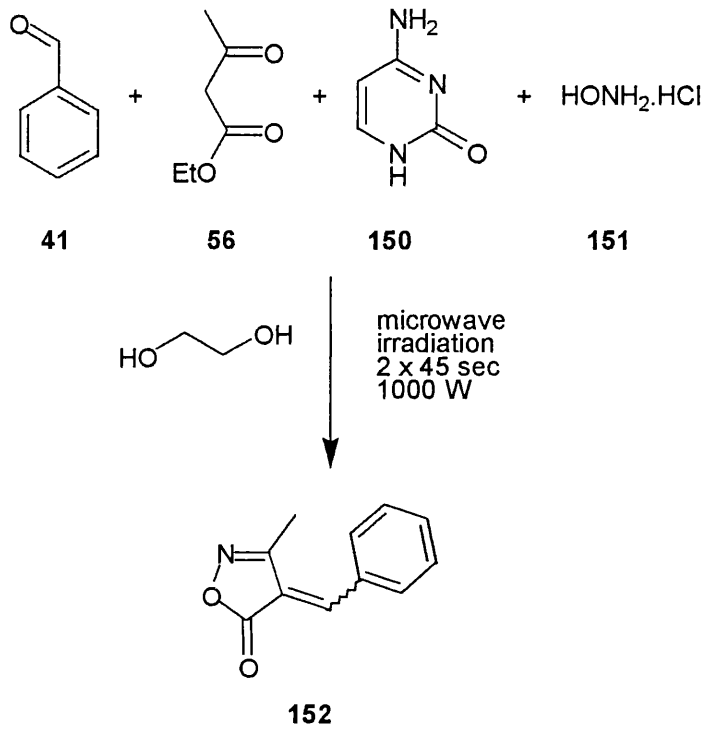
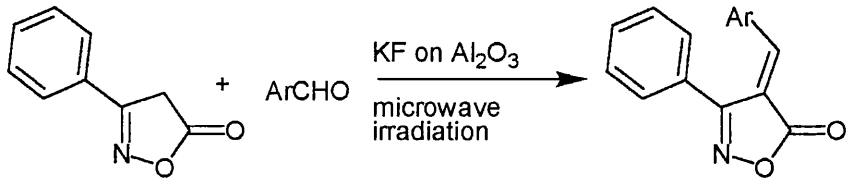


Figure 72

Indeed, leaving out cytosine (**150**) and increasing the time of irradiation to 10 min, the yields were increased to 85%. This 3-component reaction has in fact been known since the beginning of the 20th century[107]. The original literature reaction is performed by refluxing in ethanol for 2 hours, after which on cooling the product precipitates out of solution. Furthermore, the benzylidene analogue, 3-phenyl-2-isoxazolinone (**155**, Fig. 73) has been prepared more recently by the condensation of aromatic aldehydes with 3-phenyl isoxazoline-5-one (**153**) with potassium fluoride on alumina as a catalyst under microwave irradiation[108].

However, this 3-component reaction has not been previously performed under microwave conditions without the use of co-

reagents. In consequence, our method represents an 'improvement' for the preparation of these compounds.



153 **154** **155**

Figure 73

2.3 Conclusions and Perspectives for Further Work

In retrospect, given the complexity of MCRs, it was tempting to suggest that a combinatorial approach to reaction discovery is an efficient way to find and develop new reactions. However, this is critically dependent on sophisticated, efficient and accurate analytical equipment. One of the major drawbacks, as we have found to our own cost however, is that a great deal of known chemistry is simply repeated. Both simpler 2-component reactions and known 3-component reactions will simply be re-discovered. This represents a waste of both time and resources, for which the combinatorial approach is supposed to be most efficient. At least in this comparatively crude set up, such an approach is probably ill suited to the aim. A more realistic approach would certainly necessitate the inclusion of a much greater deal of sophisticated computer analysis of the reaction mixtures, *i.e.* identifying possible reactions from the spectra, but also more importantly, a mass spectral database with which to compare the reaction library data, preferably by an automatic screening method.

The use of robotics in the discovery of new reactions, although promising, requires formidable analytical and data processing resources. Therefore, this method does not lend itself well to large reagent collections, but should only be attempted with smaller collections of starting materials, generating a smaller reaction library, which can be subjected to a crude purification step on automated HPLC. In the simplest possible terms, for our original test bed Ugi reaction, we knew what to look for, but in the 'real world' situation, even if a new MCR had surfaced, it is probable that it eluded us.

In view of the unreliability and irreproducibility of this methodology, it was therefore decided to abandon the combinatorial approach and concentrate instead on a more rational approach to the design of MCRs.

CHAPTER 3

3.1 A Rational Approach to Type III MCRs

As we have seen in the introduction (*cf.* section 1.2.2) Type III MCRs, sequences of irreversible elementary reactions, are relatively rare in preparative chemistry, and are usually only observed in biochemical pathways. Very often in MCRs the irreversible step of $C^{II} \rightarrow C^{IV}$ is the final elementary reaction step in the sequence, effectively driving the reaction forward. To the best of our knowledge, no known MCR begins with the irreversible conversion of $C^{II} \rightarrow C^{IV}$ which is then followed by another reaction step.

3.1.1 Previous [1+4] and Tandem Cycloadditions

As a consequence of our interest in the utility of Ugi type multicomponent reactions, we were intrigued by the versatility and reactivity of the isocyanide moiety. In particular, we were attracted to a reaction, first discussed by Saegusa in the early seventies in which reaction of isocyanides with nitroalkenes furnished α-cyano amides[109]. A particular feature of interest to us in this work was that Saegusa's postulated mechanism proceeded, after an initial [1+4] cycloaddition of the isocyanide onto the nitroalkene (**156**), *via* an intermediate nitrile oxide (**157**, Fig. 74). We therefore speculated on the possibility of investigating the validity of the mechanism through simple trapping experiments, both in the intramolecular and in the intermolecular mode. It is interesting to note the relative acidities of H_a and H_b in (**157**), and to speculate that the timing of the elimination leading to the formation of the nitrile oxide might be favoured by proton catalysis and have E_1 character.

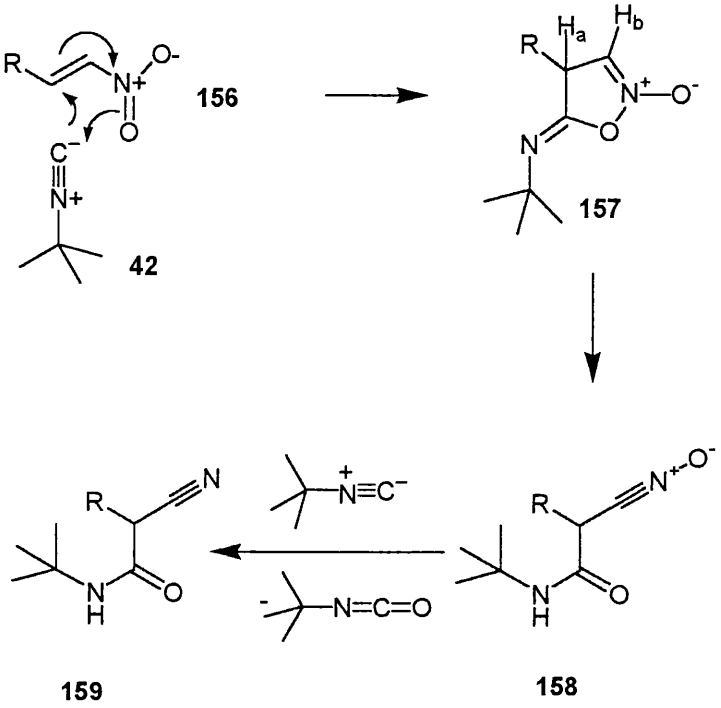
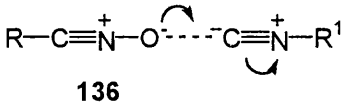


Figure 74

Saegusa's mechanism suggests that, for the quantitative formation of the α-cyano amide (**159**), at least two equivalents of isocyanide are necessary, with the second equivalent being required for the deoxygenation of the intermediate nitrile oxide (**136**, Fig. 75).



136

Figure 75

Saegusa's mechanism constitutes an unusual method for the generation of nitrile oxides. In addition, it gives rise to a functionalised nitrile oxide, which would otherwise require a multistep procedure.

Contrastingly, in related work by Foucaud's group (Fig. 76)[110], it was shown that replacement of the α-proton of the nitroalkene by an alkyl group, whilst allowing the initial [1+4] cycloaddition to proceed as far as the isoxazolone *N*-oxide intermediate (**160**), is then unable to evolve to a nitrile oxide. Instead, the authors propose the formation of a nitrosonium intermediate (**161**), presumably by a proton catalysed process, followed by an intramolecular electrophilic substitution to yield *N*-hydroxy indoles (**162**).

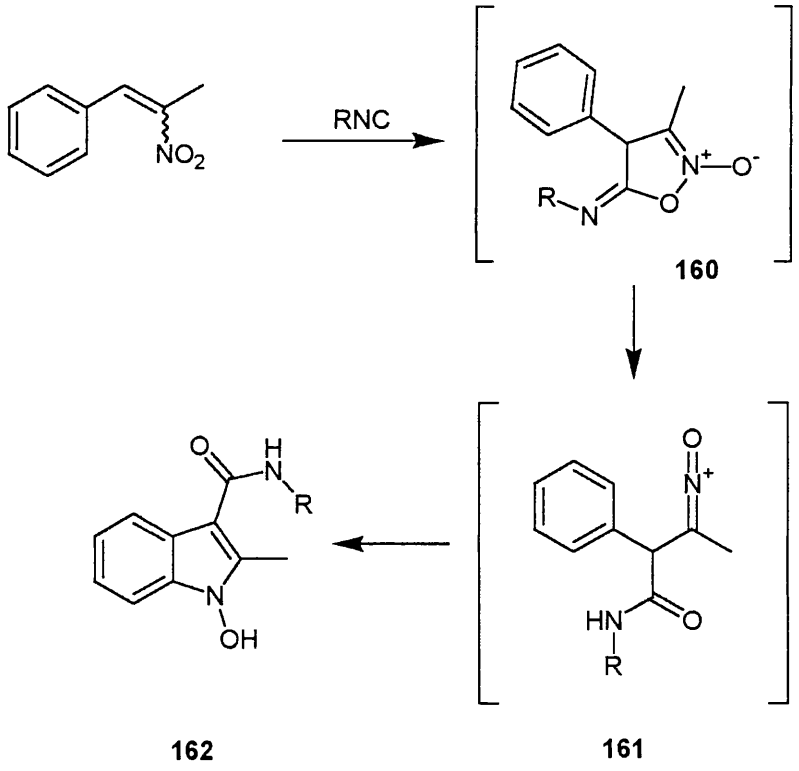


Figure 76

3.2 The Intramolecular Approach

In the first instance, we chose to trap the nitrile oxide in intramolecular fashion by tethering the alkene moiety to the nitroalkene. From our previous experience of nitroalkene synthesis, it was clear that the

condensation of an aldehyde with nitromethane was best achieved using a fully substituted aldehyde in order to block subsequent deconjugation. Additionally, we reasoned that the presence of a dialkyl unit might have a favourable effect on the conformation of the putative nitrile oxide intermediate *via* the Thorpe-Ingold effect, and thus allow for a better chance of efficient trapping. The route chosen to furnish the nitroalkadiene (**164**) proceeded *via* formation of 2,2-dimethyl-4-pentenal (**163**) utilising a highly atom efficient acid catalysed Carroll rearrangement[111]. The pentenal could then be easily condensed with nitromethane using the previously tested methodology to furnish the required 3,3-dimethyl-1-nitro-hexa-1,5-diene (**164**, Fig. 77), exclusively as the *trans* isomer as judged by the 12 Hz coupling constant of the alkene protons in the proton NMR.

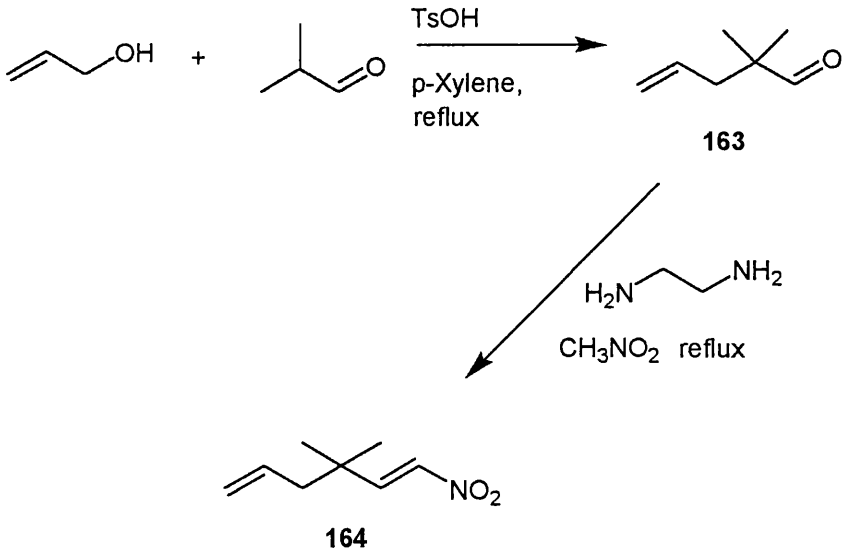


Figure 77

With the nitroalkadiene in hand, we could proceed to test the foregoing mechanistic hypothesis that an intermediate nitrile oxide was involved. Treatment of the nitroalkadiene in toluene with isocyano acetaldehyde dimethyl acetal (**165**) gave the desired bicyclic isoxazoline (**166**), albeit in

an abysmal 5.1% yield, together with the expected cyano amide (**167**) as a further 'by-product' in less than 1% yield (Fig. 78).

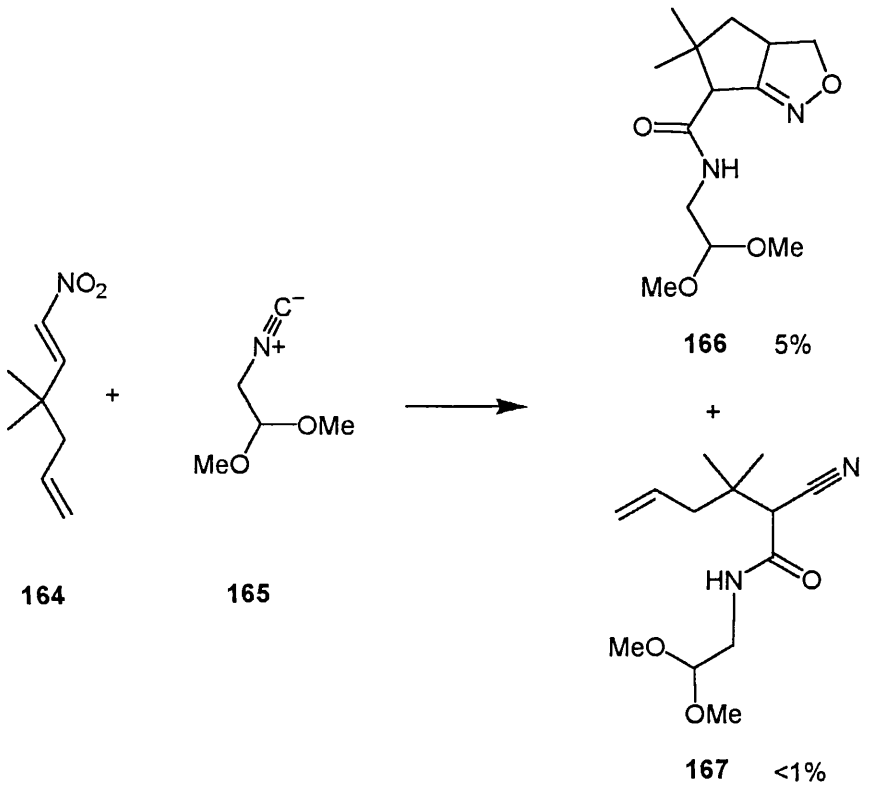
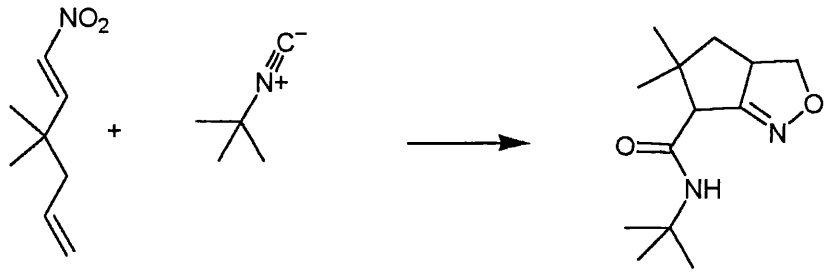


Figure 78

These results were further confirmed and the yield improved upon (Fig. 79) by selection of *tert.*-butyl isocyanide (**42**) to afford the corresponding *tert.*-butyl derivative (**168**) in 15% yield. This showed that the reaction tolerated a comparatively bulky group.

The carbon NMR spectrum displayed the typical value of 76 ppm for the CH_2O carbon of an isoxazoline ring and the *gem* dimethyl carbons could be distinguished in both the carbon and the proton spectra.



164 **42** **168**

Figure 79

In terms of stereochemistry, both diastereoisomers of **168** were formed as an inseparable mixture in a 2:1 ratio.

With this experiment, the existence of a 1,3-dipole had been verified and proof of concept had been realized.

Unfortunately, at this stage, in our enthusiasm to verify the existence of the dipolar intermediate by trapping with an alkene in a [2+3] dipolar cycloaddition, we were unaware that this very concept had been successfully demonstrated some 12 years earlier by Parsons and Knight[112] as shown in Figure 80.

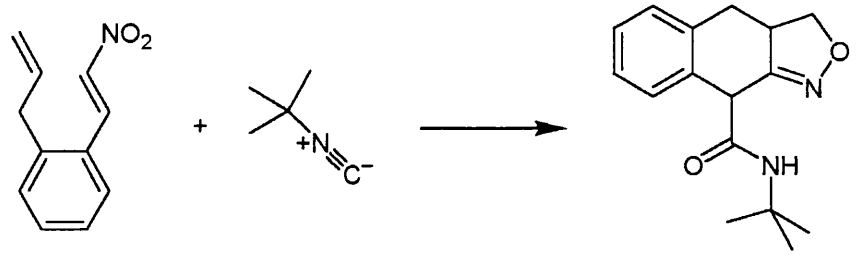


Figure 80

On making this unfortunate discovery however, we reasoned that the dipolarophilic alkene moiety could also be tethered to the isocyanide, as opposed to the nitroalkene, giving rise to a different connectivity (Fig.

81). Vinyl and allyl isocyanides especially could afford richly functionalised bicyclic derivatives.

Thus in a preliminary experiment, treatment of nitrostyrene (**144**) with readily prepared allyl isocyanide (**169**) was attempted. This should give rise to the fused isoxazoline δ-lactam (**170**). In the event however, a complex reaction ensued and only a small amount of impure material (1%) could be isolated from this reaction.

The mass spectrum exhibited a molecular ion at 217 m/z, albeit at only 5% intensity, corresponding to the formation of a 1:1 adduct and the infrared spectrum displayed a low carbonyl absorption at 1623 cm^{-1}, implying an α,β-unsaturated amide had formed. Most importantly however, in the ^1H NMR spectrum the expected benzylic proton in the theoretical adduct **170** was absent, also suggesting that the double bond had migrated into conjugation with the aromatic ring and the amide carbonyl. The data suggests structure (**171**).

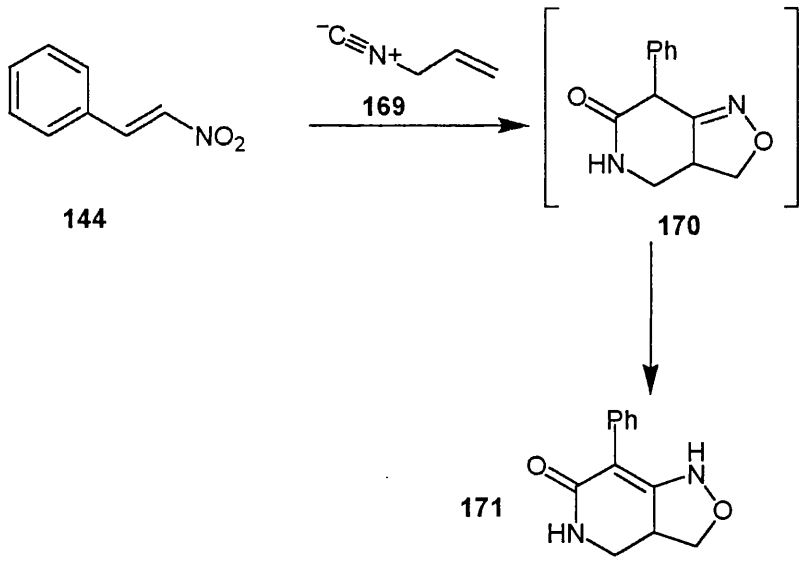


Figure 81

Since we were unable to obtain a sufficiently pure sample for microanalysis because of the low yield the low yield of the bicyclic product (**171**) in this preliminary experiment, the assignment of structure (**171**) must remain tentative.

Unfortunately, at this very moment in time, when the use of further allyl and vinyl isocyanides was being initiated, we received information that Prof. Parsons' group was also investigating this very connectivity, and this line of investigation was therefore peremptorily abandoned.

3.3 The Intermolecular Reaction

At the same time as our work on the entropically favoured intramolecular variants was underway, we had also decided to pursue the more elusive and problematic fully intermolecular 3-component reaction. From early work done on nitrile oxides (**136**), it was clear that this was a short lived and highly reactive species, liable to polymerisation (**173**) or dimerisation to form furoxans (**172**, Fig. 82).

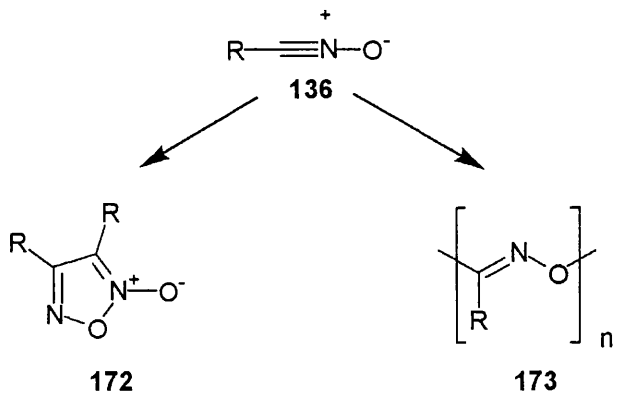


Figure 82

This meant that the dipolarophile had to be present in the reaction mixture in sufficiently high concentration to ensure an encounter with the nitrile oxide and its efficient trapping. As we have discussed earlier (*cf.* Part I, section 2.5), it was also apparent from the literature, that the reaction between a nitrile oxide and an olefin proceeds most efficiently with either an electron rich or an electron poor olefin[113], but less so with those which are electron neutral.

In the first instance, a solution of nitrostyrene in toluene was treated with 5 equivalents of methyl acrylate. The mixture was then heated and a solution of the isocyanide in toluene was added slowly. It was hoped that this experimental protocol would ensure not only a controlled slow generation of the nitrile oxide together with the efficient trapping of the dipole, but also minimise the competing oxygen atom transfer to a second molecule of isocyanide from the nitrile oxide. We were encouraged by the yield of the isoxazoline of 5% and 92% recovery of starting material and a small amount of the cyano amide by-product. This meant that under these conditions no unexpected reactions were taking place, and we assumed it was merely a matter of finding the right conditions to increase yields. The reaction appeared to tolerate bulky isocyanide groups, *tert.*-butyl and benzyl, with comparable results (Fig. 83).

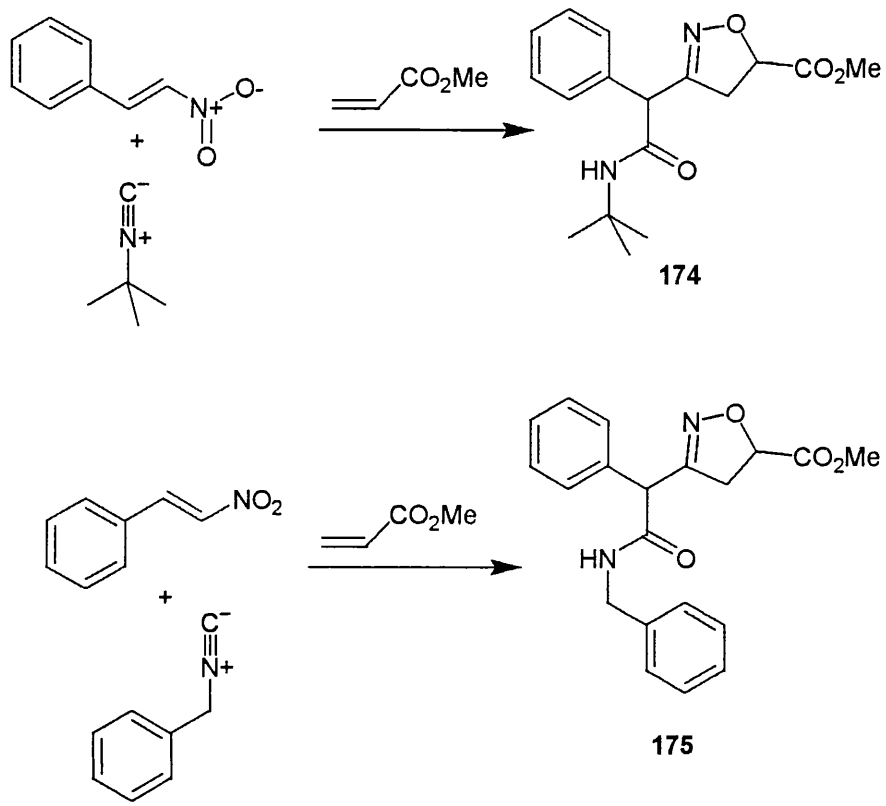


Figure 83

The same reaction carried out with ethyl vinyl ether as the dipolarophile only returned 97% of the starting material and only traces of unidentified by-products. This was especially puzzling in view of literature precedent that nitrile oxides react with vinyl ethers. However, at first this was attributed to slight differences in the reactivity of the two dipolarophiles.

In similar fashion, the reaction did not proceed with acrylonitrile or with methyl vinyl ketone, and in each case, only starting material could be recovered. The reaction did however, tolerate the 1,2-disubstituted olefin, dimethyl maleate to afford the 4,4 disubstituted isoxazoline (**176**), albeit in a lower yield of 2% (Fig. 84).

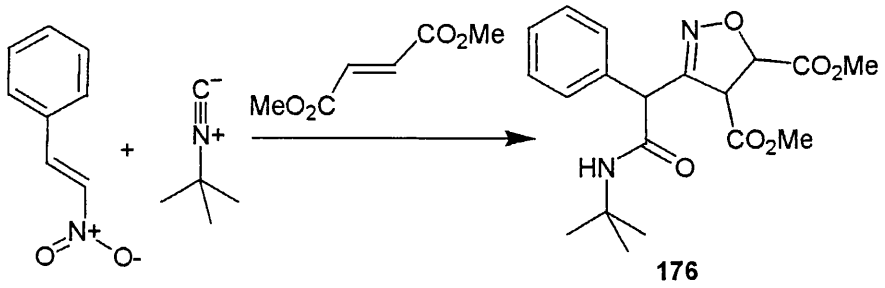


Figure 84

In terms of the overall timing and efficiency of the sequence, it was also of interest to study the electronic character of the nitroalkene acceptor in the initial [1+4] cycloaddition step.

With this thought in mind, we elected to prepare the nitroenamine derivatives (**180**) for the three component reaction and (**182**) for the tethered bimolecular variant. This was readily achieved by the reaction of a secondary amine, *e.g.* morpholine (**177**), or diallyl amine (**181**) nitromethane (**178**) and triethyl orthoformate (**179**) in a simple one-pot reaction (Fig. 85).

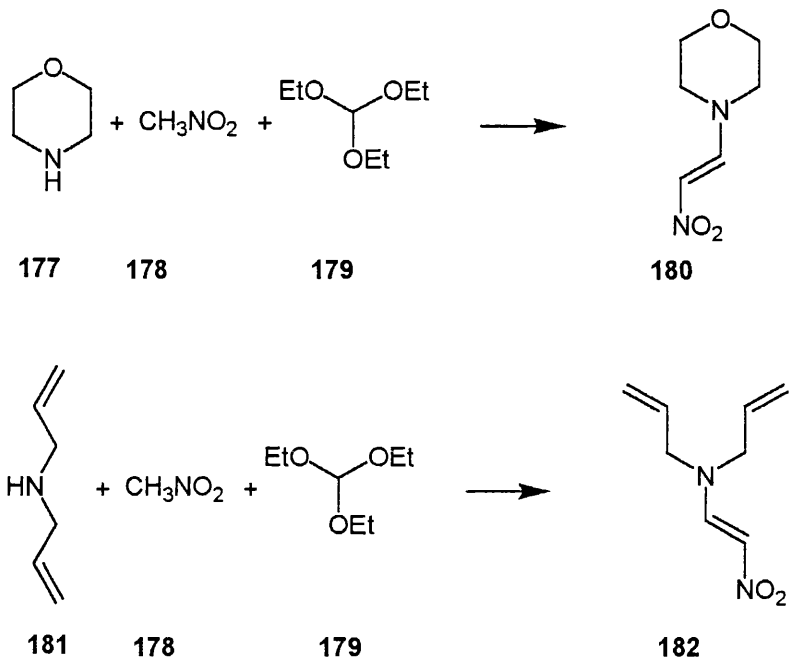


Figure 85

The behaviour of the nitroenamine was of interest to us in terms of exploring the potential asynchronicity of bond formation in the initial [1+4] cycloaddition step.

Thus, at the most simplistic level, if the isocyanide is considered to be nucleophilic in character then formation of the carbon-carbon bond can be viewed as a conjugate addition process which should be disfavoured by a more electron rich nitroenamine (Fig. 86).

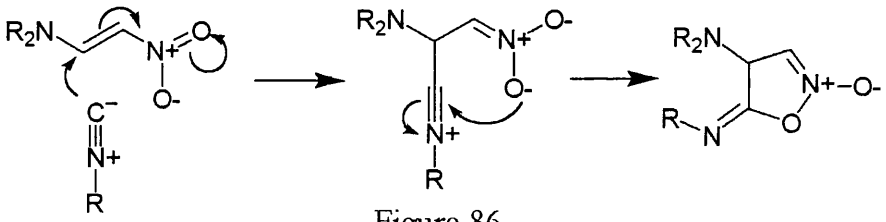


Figure 86

Contrastingly, if we consider the isocyanide as a formally electron deficient carbene, it can function to some extent as an electrophile for

an electron rich species. The scenario shown in Figure 87 can then be proposed.

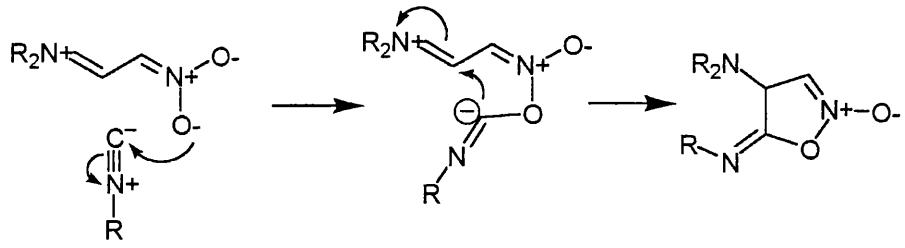


Figure 87

In the final analysis however, as we shall see later, it is the HOMO-LUMO gap of the frontier molecular orbitals, which provides the greater insight.

In the event however, in a test reaction, addition of *tert.*-butyl isocyanide to a solution of either (**180**) or (**182**) did not afford the desired isoxazolines (**183** or **184**, Fig. 88) and only returned starting material.

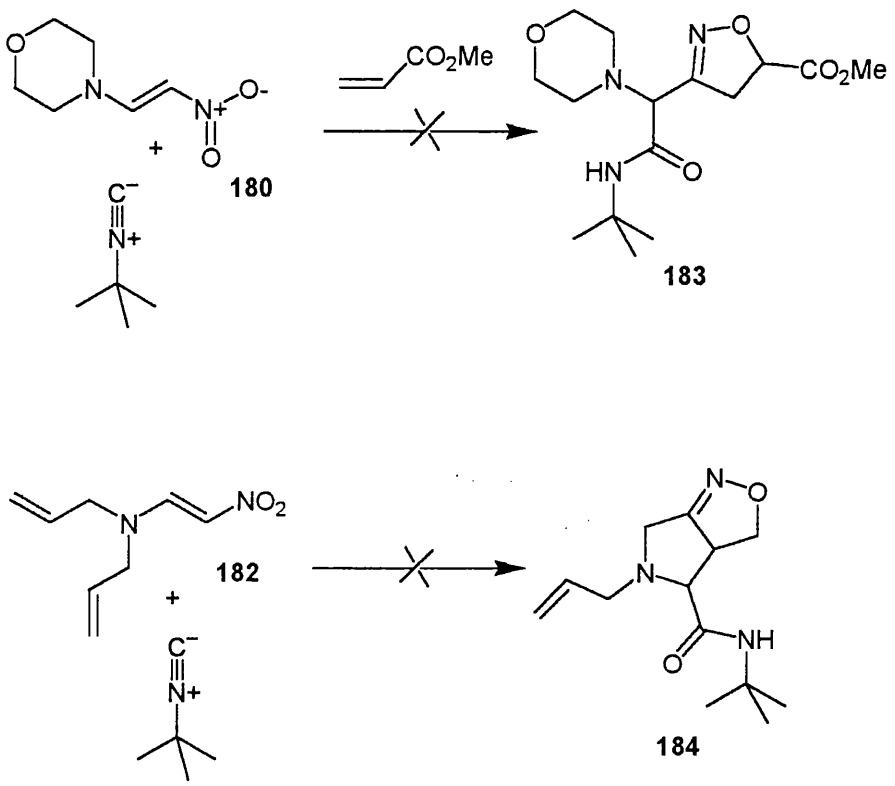


Fig. 88

Since these observations suggested that electron rich nitroalkenes might be unsuitable for this reaction, we therefore embarked on the preparation of 3-nitro methyl acrylate, but alas the following two methods were attempted, both without success:

(i) *Addition of dinitrogen tetroxide*[114]*:* Dinitrogen tetroxide was prepared by heating anhydrous lead nitrate over a Bunsen flame and capturing the resulting fumes at -20°C. The resulting liquid was used with iodine to treat ethyl acrylate and form ethyl-2-iodo-3-nitropropionate. This could not be isolated from the reaction mixture by distillation.

(ii) *Addition of nitryle chloride.* Nitryle chloride was prepared[115] by the addition of freshly distilled chloro sulphinoc acid to fuming nitric acid at 0°C. The resultant mixture was distilled to yield NO_2Cl. An

ethereal solution of ethyl acrylate was treated with nitrile chloride. The addition product, ethyl-2-chloro-3-propionate could not be isolated from the reaction mixture by distillation.

With the simplest electron poor nitroalkene eluding us, we were only able to investigate its role in the reaction theoretically (*cf.* section 3.5).

3.4 Reaction Parameter Study

In order to increase the yields of the process, a reaction parameter study was undertaken in which solvents, temperatures and reaction times were varied. From work done by Huisgen, it was clear that the solvent should have no effect on the secondary dipolar cycloaddition. Nevertheless, there is precedent for solvent dependence of the reactivity of the isocyanide[116]. Performing an Ugi Four Component Reaction in DCM or hexane yields the Passerini product, suggesting that polar solvents may increase the contribution of the dipolar form. Isocyanides are in effect stable, nucleophilic carbenes[117]. They undergo α-additions or α-insertions, reactions typical of carbenes. There is an increasing amount of literature concerning the [1+4] addition of isocyanides with electron poor heterodienes. Thus, isocyanides undergo [1+4] cycloaddition with azadienes[118], hydrazones[119], *N*-acylimines[120], enones[121] and α-halo oximes[122].

Our choice of solvents was confined to benzene, toluene, dimethylformamide and acetonitrile. From this study it was apparent that reaction times of more than 18 hours were not necessary and did not improve yields. Reaction times of 3 hours led to poorer yields throughout. The optimum appeared to be 6 hours.

The reaction was insensitive to solvent effects overall. The reaction could be carried out with similar results in a non-polar hydrocarbon solvent such as toluene or a more polar solvent such as acetonitrile. The reaction in DMF was exceptional in that it produced consistently lower yields than the other solvents.

From these results we were able to ascertain that the reaction proceeds, albeit with very low yields, with electron deficient alkenes. When the reaction was performed using ethyl vinyl ether as the dipolarophile, only starting material and a small amount of highly polar, inseparable products were obtained. At first sight, this may suggest that the presence of the α-amido functionality, which is generated on ring opening of the nitronate precursor has a profound effect on the electronic character of the nitrile oxide intermediate, thus countering the formidable body of Huisgen's studies that nitrile oxides undergo cycloaddition with both electron rich and electron poor olefins.

On further reflection however, these results can be interpreted such that the mechanism does NOT proceed *via* the commonly assumed nitrile oxide intermediate initially proposed by Saegusa.

Thus as we have discussed in the introductory overview of 1,3-dipolar cycloaddition reactions involving nitronates (*cf.* section 2.4), there is ample precedent both in the work of Denmark and Torsell that alkyl substituted nitronate esters, be they cyclic or acyclic show a preference for electron deficient alkenes as dipolarophiles. In the present case the initial [1+4] cycloaddition also produces a similar nitronate 1,3-dipole, which should also therefore react preferentially with electron poor olefins. Consequently, we currently believe that the originally proposed mechanism should be replaced by that shown in Figure 89.

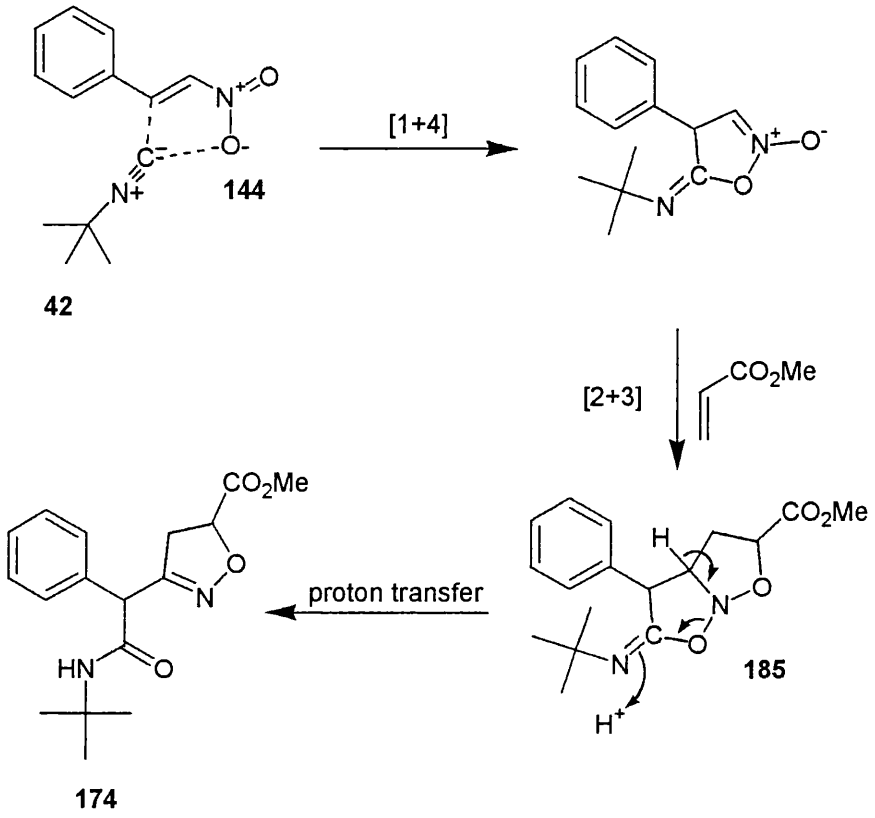


Figure 89

This alternative mechanism (Fig. 89) proceeds *via* a domino [1+4]/[2+3] cycloaddition cascade to give a putative bicyclic intermediate (**185**). This subsequently undergoes proton migration with concomitant N-O bond cleavage to afford the 3-component isoxazoline product.

Indeed, later work done in Saegusa's group[123] has shown *tert.*-butyl isocyanide (**42**) to act as a nucleophile in a conjugate addition to enones (**186**) with loss of *iso*-butene to afford the conjugate hydrocyanation product (**187**) (Fig. 90). However, the [1+4] cycloaddition product (**188**) was also produced in 15% yield.

Moreover, when Saegusa changed the catalyst from titanium tetrachloride to diethylaluminium chloride, a well known proton scavenger, the reaction afforded the iminolactone (**188**) exclusively in high yield[124].

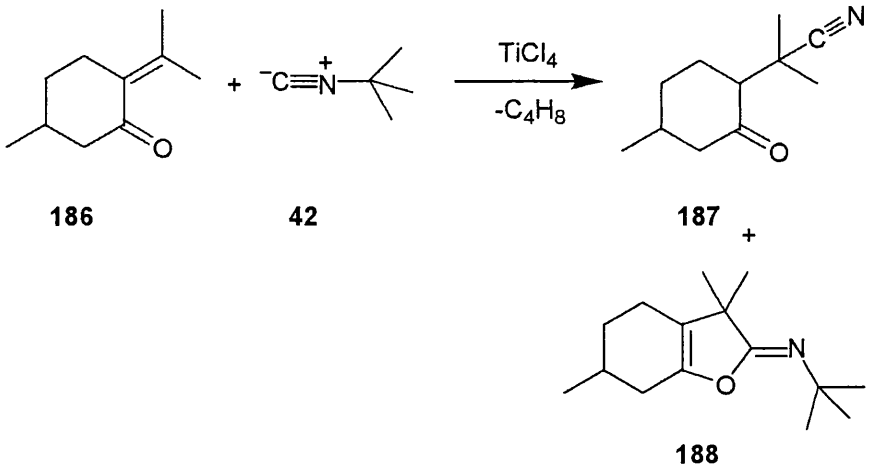


Figure 90

In possibly the earliest example of a [1+4] cycloaddition involving isocyanides, Neidlein[125] treated an ethereal solution of phenyl isocyanide (**189**) with benzoyl isocyanate (**190**) to afford the imino isoxazolone (**191**) in high yield (Fig. 91). He suggested a two-step asynchronous reaction mechanism, beginning with the nucleophilic attack of the isocyanide onto the isocyanate carbon followed by ring closure.

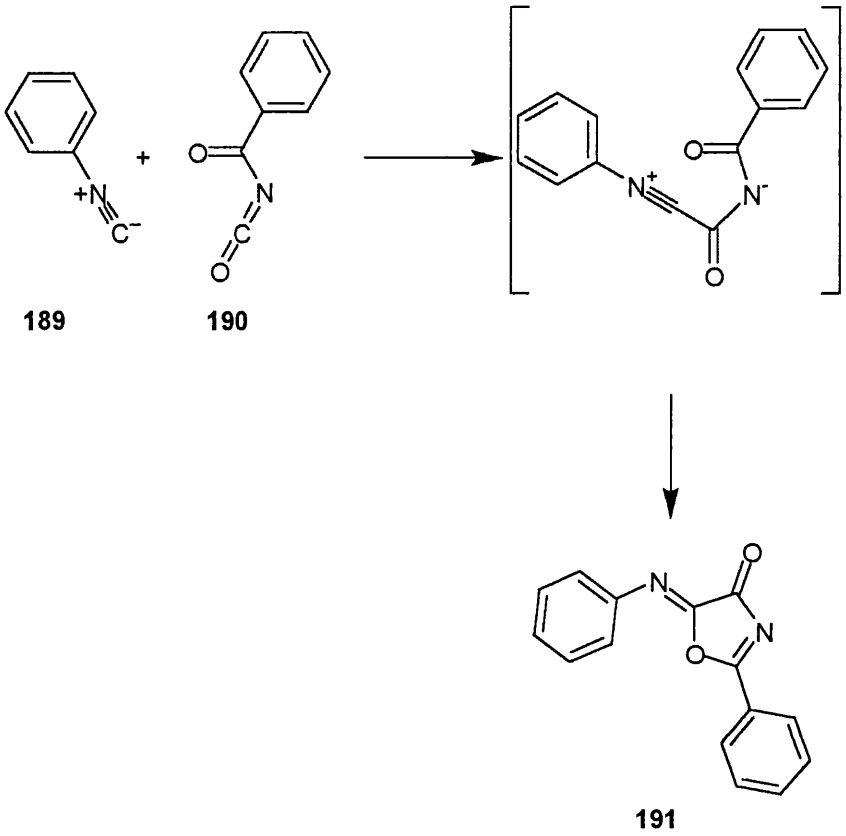
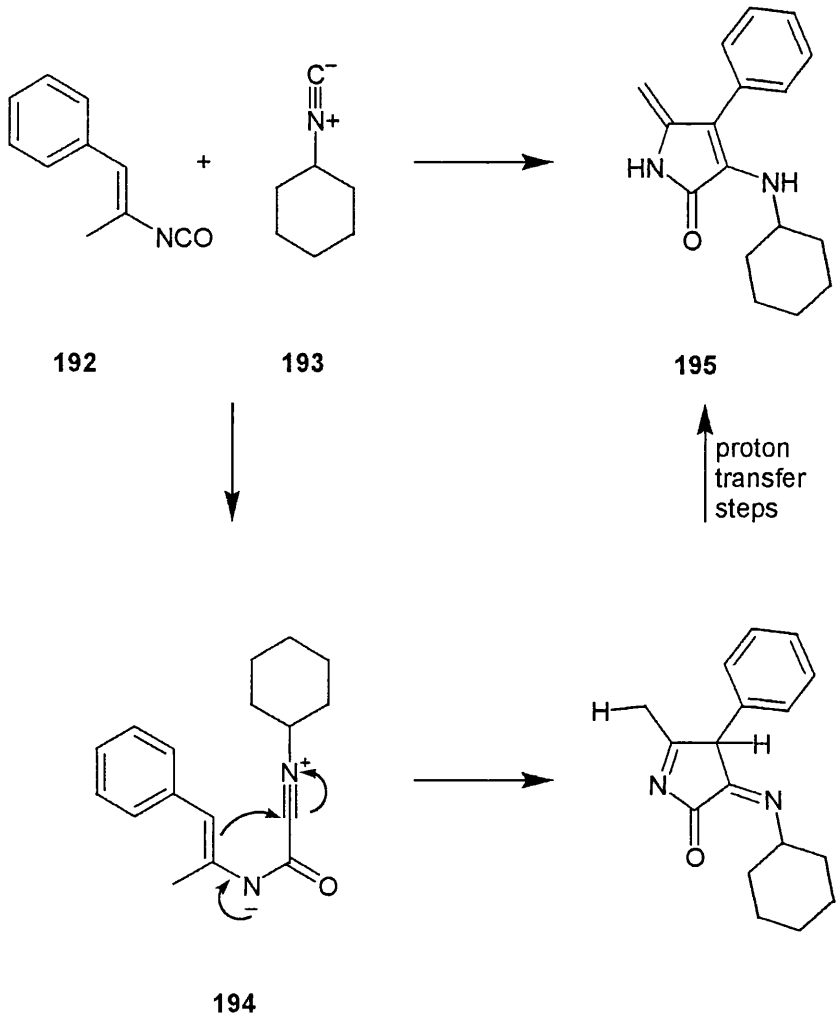


Figure 91

In the [1+4] cycloaddition of vinyl isocyanates (**192**) with isocyanides (**193**), Rigby *et al.*[126] have suggested that the mechanism of cyclisation is stepwise, proceeding *via* a nitrilium ion (**194**), generated by the nucleophilic addition of the isocyanide to the isocyanate carbon, followed by intramolecular cyclisation and imine-enamine tautomerisation to afford the pyrrolone (**195**) in excellent yield (Fig. 92).



192 193 195

194

Figure 92

The only shortcoming of this procedure appears to be the requirement for an alkyl substituent in the α-position to the isocyanate group.

The nucleophilic nature of the isocyanide group in cycloaddition reactions also has been supported by theoretical calculations[127], *i.e.* the filled *n*-orbital of the isocyanide interacts with the π*-orbital of the heterodiene, suggesting an asynchronous cyclisation process.

3.5 Computational Study

In order to help us rationalise the foregoing experimental observations we decided to calculate the HOMO-LUMO gaps involved in [1+4] cycloaddition reactions, between a number of electron rich and electron poor nitroalkenes and methyl isocyanide, vinyl isocyanide and allyl isocyanide (Fig. 93). These calculations were performed on nitrostyrene, *p*-chloro nitrostyrene, *p*-methoxy nitrostyrene, *p*-nitro nitrostyrene, *N*,-*N*-dimethyl nitroethene and 3-nitro methyl acrylate.

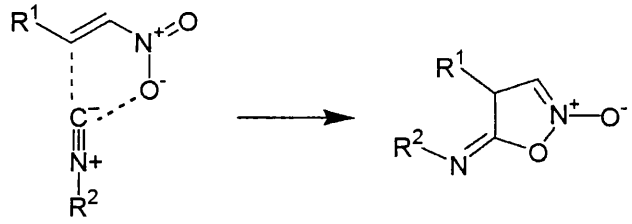


Figure 93

Δ eV	R_2=Me	R_2=vinyl	R_2=allyl
R_1=Ph	10.2535	9.21113	9.2696
R_1=*p*-ClC_6H_5	10.001	9.0580	9.1163
R_1=*p*-$MeOC_6H_5$	10.3309	9.2887	9.3470
R_1=*p*-$NO_2C_6H_5$	9.4139	8.3717	8.4300
R_1=Me_2N	10.7218	9.6796	9.7379
R_1=CO_2Me	9.9654	8.9232	8.9815

Table 2

The results of the calculations (Table 2) suggest that the 'best' reaction should be between vinyl isocyanide and *p*-nitro nitrostyrene, with a HOMO-LUMO gap of 8.3717 eV. Overall, the electron poor nitroalkenes showed smaller frontier orbital gaps with the isocyanides than the electron rich nitroalkenes.

As indicated earlier, this suggested the requirement of 3-nitro methyl acrylate for use in a 3-component coupling with methyl acrylate. However, in spite of attempting a number of different literature procedures (*cf.* section 3.3), this proved an elusive goal on several occasions.

3.6 U.V. Study

As an alternative to the construction of nitroalkenes possessing either electron donating or electron withdrawing functionality directly attached to the β-carbon atom, it was decided that a study of various *para*-substituted nitrostyrenes would also allow us to probe the electronic character of the [1+4] cycloaddition step.

The synthesis of the required nitrostyrenes proceeded analogously to that of nitrostyrene itself in good yields. These were then treated with methyl acrylate and cyclohexyl isocyanide, and the course of the reaction followed by U.V. spectroscopy, monitoring the disappearance of the λ_{max} of the nitroalkene. The results are summarised in Figure 94.

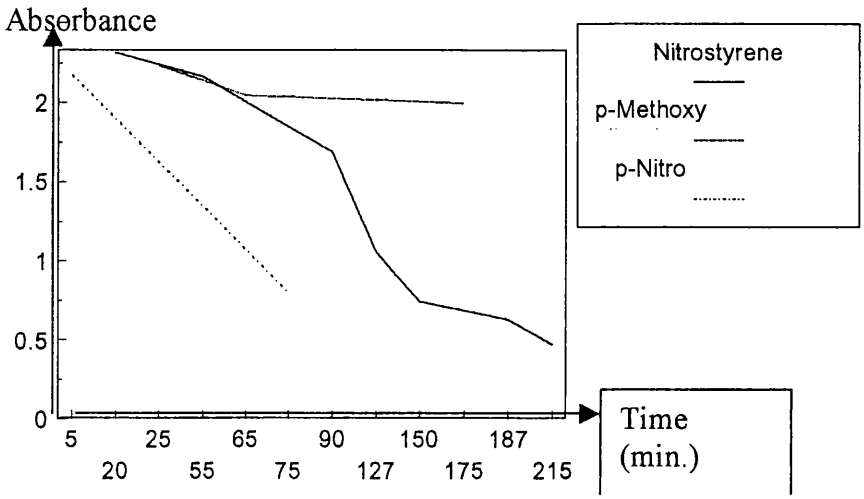


Figure 94

This qualitative study indicated that electron withdrawing groups on the phenyl ring increased the rate of reaction, whereas electron-donating groups led to virtually unreactive partners.

3.7 Co-Reagent Study

As we have seen, the initial yields of the intermolecular reaction were disappointingly low, in spite of efforts to achieve control through standard variation of solvents and relative concentrations of reagents. Accordingly, we chose to investigate the effect of a number of Lewis and Brønsted acids, and additionally DABCO on the reaction. This study also served as an additional probe for the timing of bond formation in the initial [1+4] cycloaddition.

In the first instance, we considered the use of DABCO. The reasoning behind this choice was that this base would, by analogy with the Bayliss-Hillman reaction, promote the formation of the nitronate through conjugate addition. Following this, the resulting nitronate (**196**) could then attack the isocyanide carbon (**42**) and the resultant carbanion

could then displace the base from the zwitterion in a 5-*exo* tet ring closure reaction (Fig. 95).

Moreover, it was also argued that DABCO could facilitate the proton loss required for the generation of the nitrile oxide.

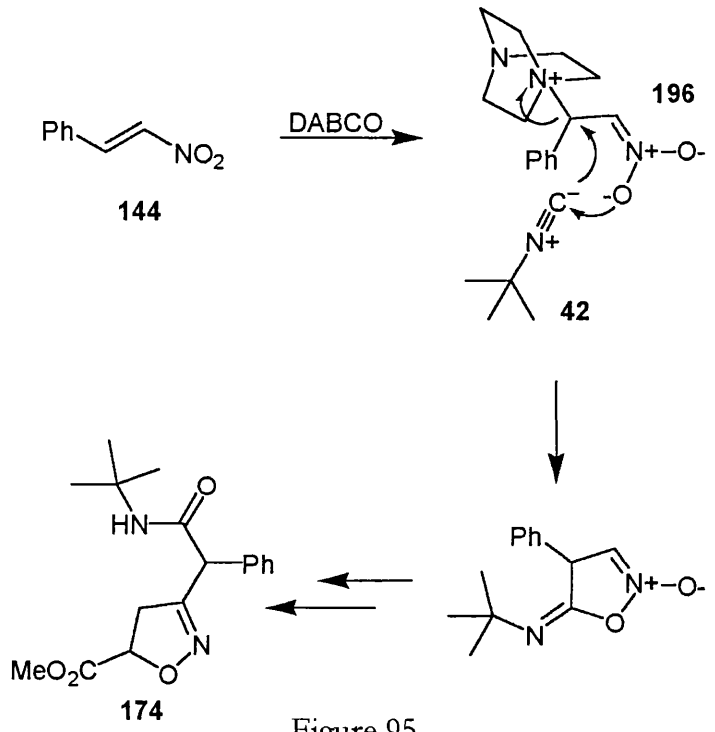


Figure 95

From the LC/MS trace the 3-component product was observed. However, when the reaction was repeated on a larger scale, the isoxazoline could not be isolated. This suggests that the tertiary amine base acts as an inhibitor to the reaction, rather than a promoter.

In the event however, the investigation of Lewis acids as promoters of the reaction proved to be much more promising. In a classical cycloaddition reaction such as the Diels-Alder reaction, Lewis acids act through coordination to the dienophile, thereby lowering the energy of the LUMO and reducing the HOMO-LUMO gap between reactants in cycloaddition reactions. For the present reaction of course, the Lewis

acid can coordinate to the isocyanide, the nitroalkene and the acrylate acceptor, and arguments can be constructed which both favour and disfavour several of the steps in the overall sequence. In our study of Lewis and Brønsted acids we chose a number of well known and comparatively hard acids: *p*-toluene sulphonic acid, zinc chloride, stannic chloride, lanthanum acetate, ceric sulphate, samarium chloride, indium chloride, dichloro titanium di-isopropoxide and lithium perchlorate. In most cases the side reaction leading to the formation of the cyano amide by-product was suppressed, at least to the extent that although it was observed in the mass spectrum in half of the cases (*p*-toluene sulphonic acid, zinc chloride, lanthanum acetate, ceric sulphate and dichloro titanium di-isopropoxide) it could not be isolated on a preparative scale. Only when samarium chloride was employed was 0.3% of this by-product isolated. In the other cases, the Lewis acids appeared to suppress the formation of the by-product completely.

Catalyst/Co-reagent	**Mol equiv.**	**Yield of isoxazoline (%)**	**Yield of nitrile (%)**
p-Toluene sulphonic acid	0.1	Not observed	Observed, not isolated
Diaza bicyclo [2.2.2]octane (DABCO)	0.1	Observed, not isolated	Not observed
$ZnCl_2$	0.1	Observed, not isolated	Observed, not isolated
$SnCl_4$	0.1	Observed, not isolated	Not observed

		not isolated	observed
$La(OAc)_3$	0.1	11%	Observed, not isolated
$Ce(SO_4)_2$	0.1	8%	Observed, not isolated
$SmCl_3$	0.1	5%	0.3%
$Sc(OTf)_3$	0.1	10%	Not observed
$Yb(OTf)_3$	0.1	10%	Not observed
$InCl_3$	0.1	8%	Not observed
$(^iPrO)_2TiCl_2$	0.1	1%	Observed, not isolated
$LiClO_4$	1	38%	Not observed
$LiClO_4$	5	36%	Not observed

Table 3

Consideration of the results in Table 3 reveals several features of interest. The isoxazoline product was not isolated when *p*-toluene sulphonic acid, zinc chloride and stannic chloride were used, although

for the latter two cases it was observed by LC/MS. In the instance when the titanium and samarium reagents were employed the yield of the 3-component product was lower than in the uncatalysed version, with 1% and 5% of the isoxazoline isolated respectively. The other Lewis acids gave yields that were comparable or identical with the uncatalysed reaction. Lithium perchlorate however, stands in isolation as the sole additive which led to a dramatic improvement in yield. Irrespective of whether one equivalent or 5 equivalents of the reagent were employed the yields increased to 38% and 36% respectively. The remainder of the mass balance being made up of nitrostyrene (58% and 54% recovery, respectively) and a small amount of highly polar unidentifiable by-products.

From El Kaim's work on [1+4] cycloadditions involving isocyanides and either nitroso alkenes[128] or α-halo hydrazones[129], it is clear that the cycloaddition favours electron deficient dienes. Although in our case the nitroalkene represents an electron deficient olefin, it does not appear to be sufficiently electron deficient to permit a facile cycloaddition to proceed. The addition of a hard Lewis acid such as the lithium cation may possibly contribute two things: lowering both the HOMO and the LUMO of the nitro alkene and also assuming that the reaction is a two-step, asynchronous process, by promoting the formation of the nitronate, thus making the nitroalkene more electrophilic (Fig. 96).

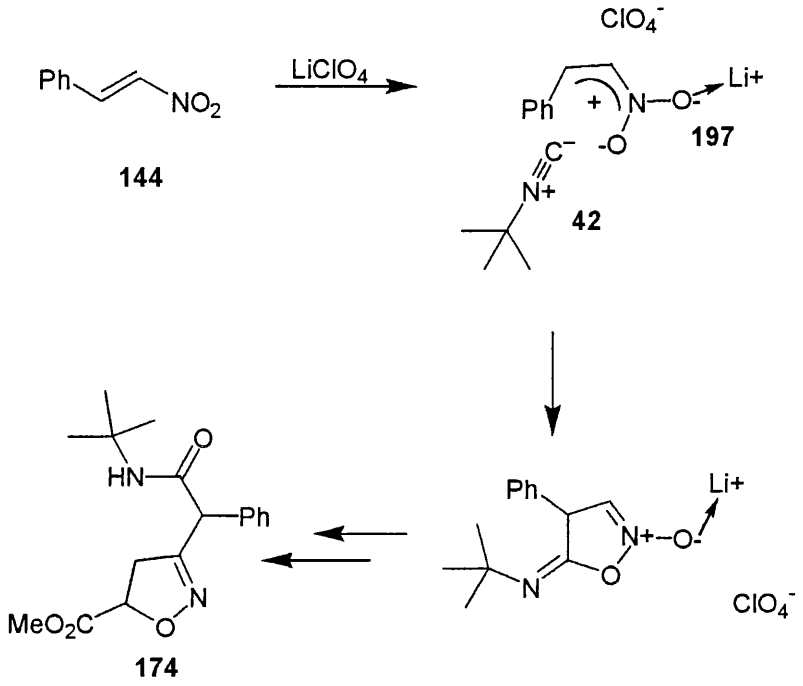


Figure 96

Grieco's original work on rate enhancement of cycloadditions[130] with lithium perchlorate was carried out in diethyl ether, and the reagent itself is often referred to as the diethyl ether complex of $LiClO_4$. The increase in reaction rate for the Diels-Alder reaction has been attributed to the effect of the Lewis acid on the HOMO-LUMO gap between the reactants. However, other Lewis acids do not appear to have the same magnitude of effect. This difference in Lewis acid catalysis has been rationalised as the result of increased ionic strength of the solution. It has been suggested that this effect is similar to the hydrophobic compression observed in the rate acceleration of the Diels-Alder reaction in water[131].

In our own case, the increase in efficiency of the reaction was not dependent on performing the reaction in diethyl ether, and reproducible results were obtained in either diethyl ether, mixtures of benzene and

diethyl ether, or neat in benzene. Moreover, the yields do not appear to be dependent on the concentration of lithium perchlorate.

CHAPTER 4

4 Addition of TMS-Phosphite to Nitrostyrene

To further our studies on the generation of 1,3-dipoles as reactive intermediates, we chose to investigate the generation of silyl nitronates by the 1,4-addition of trimethylsilyl phosphite to nitrostyrene. Silyl nitronates are comparatively recent additions to the 1,3-dipole arsenal. They were first synthesized 30 years ago by Tartakovskii's group[132]. They give comparatively good yields of the corresponding cycloadducts and the reaction exhibits strict regiospecificity. As we have seen in the introduction (p. 61-67), in contrast to alkyl nitronic esters, silyl nitronates are more versatile 1,3-dipoles, thus increasing their utility in the 1,3-dipolar cycloaddition.

Silyl nitronates are generally considered to be hydrolytically sensitive compounds and are best prepared in the presence of a dienophile. Nevertheless, Seebach and Colvin were able to isolate and characterize some simple silyl nitronates. In Seebach's work[133] the silyl nitronates were not used as 1,3-dipoles, but equally interestingly, as enolate equivalents in a fluoride catalysed Henry reaction.

Reaction of a nitronate salt (**198**, Fig. 97) with chlorotrimethylsilane results, in contrast to reaction with other electrophiles such as aldehydes or sulphenyl halides, to the formation of a silyl nitronate ester (**199**), rather than in the formation of a silicon-carbon bond. Although Tartakovskii's group postulated that the silylation reaction requires electrophilic assistance in abstraction of the leaving group from the nitronate salt[132], leading to a postulated six membered transition state

(**200**), it is probably simpler to say that as in the case of enolate anion chemistry, the hard silicon electrophile prefers the harder oxygen atom.

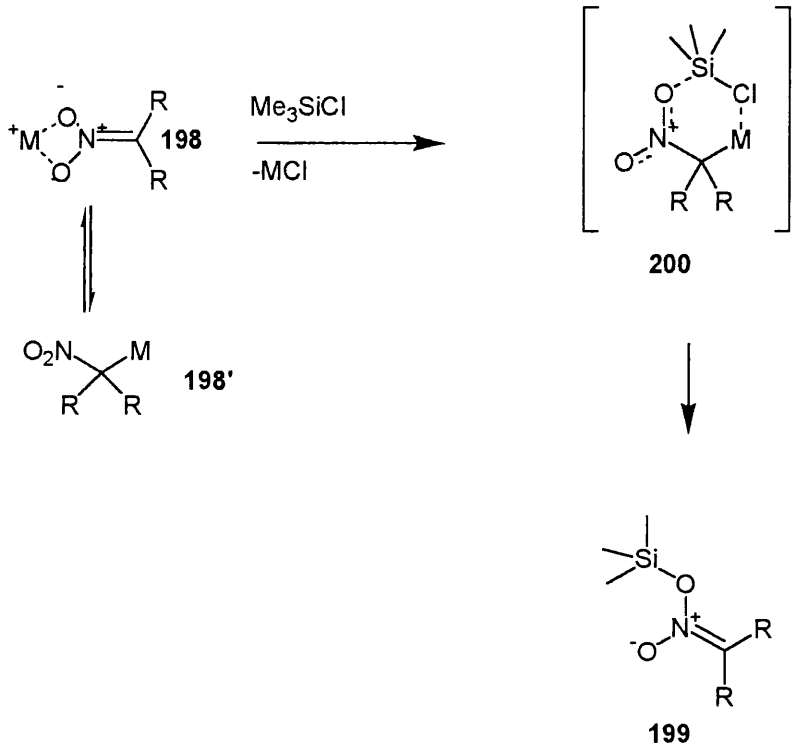


Figure 97

4.1 Sulphur and Nitrogen Silylated Nucleophiles

Work done in Hassner's group[134,135] suggested that silylated nucleophiles were capable of addition to nitroalkenes, with a subsequent dipolar cycloaddition of a tethered alkene to form isoxazolines.

In the first instance, an *S*-allyl-β-nitro thiol (**202**) was treated with triethylamine and chlorotrimethylsilane to form an intermediate silyl nitronate, which then underwent an intramolecular 1,3-dipolar cycloaddition to afford the fused isoxazoline thiophene (**203**). We were able to rediscover this result and also to improve upon it insofar as the

reaction can be performed starting from the nitroalkene (**144**) and allylmercaptan (**201**) by treatment with base and chlorotrimethylsilane to afford the product (**203**) in one step in good overall yield of 60%, with the only by-product being the *S*-allyl-β-nitro thiol (**202**, Fig. 98).

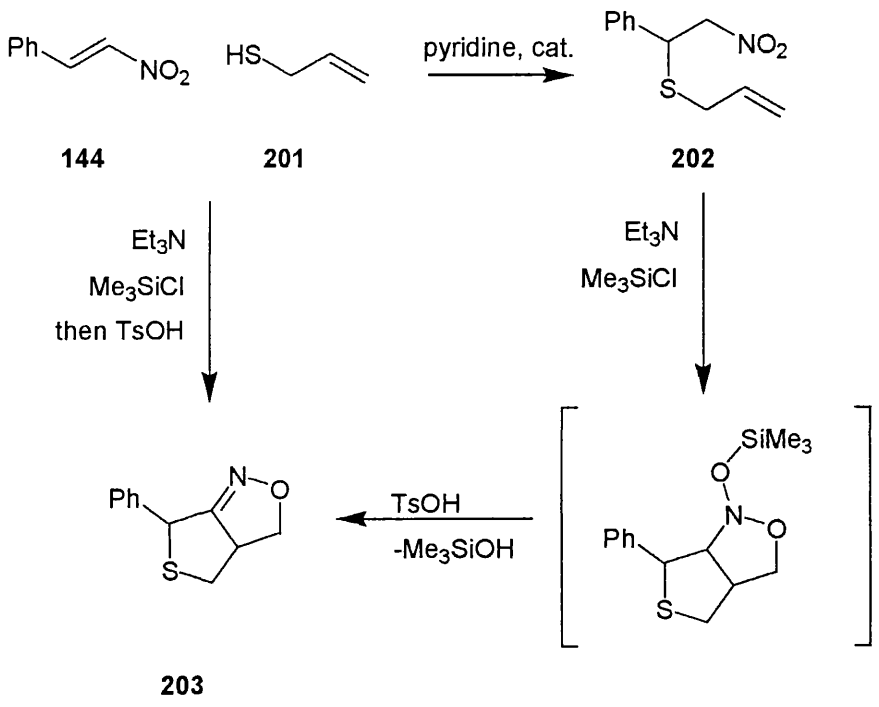
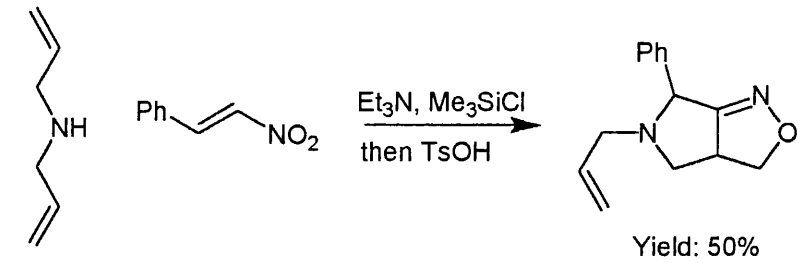


Figure 98

Similar results were also achieved using diallylamine (**182**). Indeed, in this case, as reported by Hassner[135] we were able to accomplish the Michael addition and subsequent cycloaddition in a one step, one pot procedure (Fig. 99), to afford the fused *N*-allyl pyrrole isoxazolines (**204**).



182 144 204

Figure 99

In the first instance, these results suggested not only that silylated nucleophiles are capable of performing Michael additions onto nitroalkenes to generate silyl nitronates but also that the resulting silyl nitronates were reactive enough to undergo intramolecular cycloadditions.

4.2 Silylated Phosphorus Nucleophiles

In view of Hassner's[134,135] work on sulphur and nitrogen nucleophiles, we wished to extend the concept of Michael addition followed by cycloaddition to the use of phosphorus as the nucleophilic atom. Our choice of phosphorus reagent was based on the synthesis of amino phosphonates by Afarinkia and Rees[136]. In this case, the oxophilicity of silicon provides for the formation of a trivalent phosphorus nucleophile, which can be subsequently converted into amino phosphonates (Fig. 100).

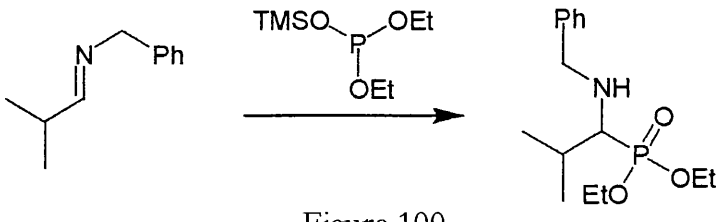


Figure 100

In fact, more recently this has been developed into a 'true' multi-component reaction[137] by reacting a dialkyl phosphite with an aldehyde and an amine to give amino phosphonates.

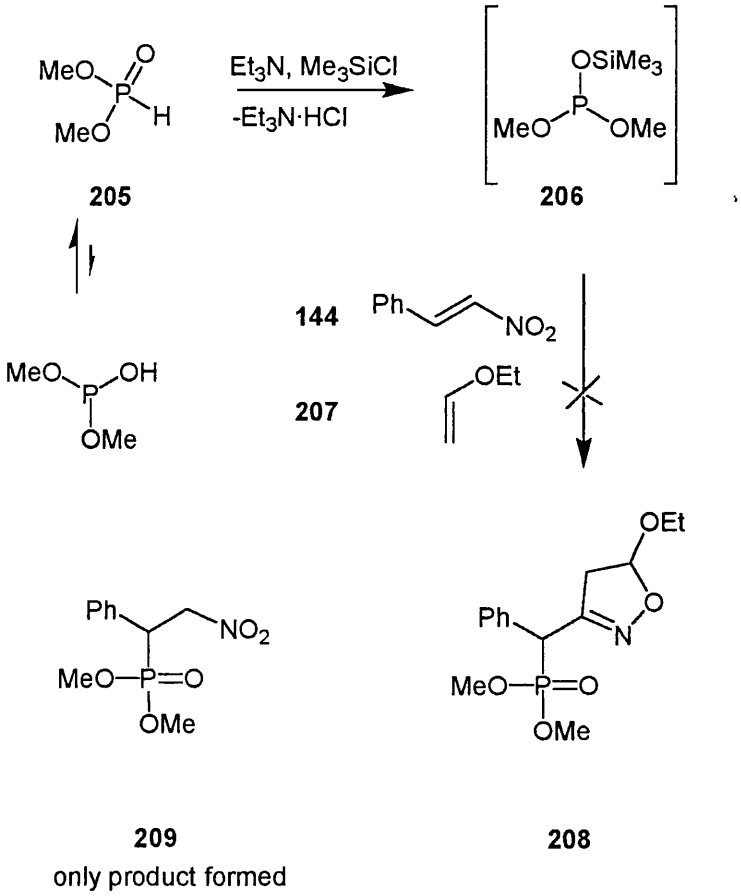


Figure 101

Initial experiments (Fig. 101) focused on the reaction of silylated dimethyl phosphite (**206**) with nitrostyrene (**144**) and ethyl vinyl ether (**207**). In the preceding discussion on the acylative cycloaddition of isocyanides, nitroalkenes and methyl acrylate, we saw that the intermolecular reaction failed with electron rich olefins. In this instance, we chose the electron rich ethyl vinyl ether to avoid

competing Michael conjugate addition of the phosphite onto the acrylate, thus allowing the addition of the phosphite to occur in the presence of the dipolarophile. Furthermore, we knew from Torsell's rich work on 1,3-dipolar cycloaddition that silyl nitronates undergo cycloaddition reactions with electron rich olefins[78].

From our first attempt, treatment of dimethyl phosphite (**205**) with triethylamine and chlorotrimethylsilane at 0°C, followed by addition of nitrostyrene (**144**) and ethyl vinyl ether (**207**) we could only isolate the conjugate addition product, the β-nitro phosphonate (**209**) in 30% yield with the remaining mass balance consisting of starting material.

Changing reaction times and intervals between addition of subsequent reagents did not meet with success. Torsell's work[78] pointed to the fact that the cycloaddition proceeds well both at room temperature, in which case the reaction takes somewhat longer to go to completion, and also in refluxing toluene, where the reaction is complete within three hours. In our case, although the cycloaddition is a thermal reaction and should be accelerated by heat, the reaction of dimethyl phosphite, nitrostyrene and ethyl vinyl ether at 120°C also did not proceed beyond the conjugate-addition product (**209**). This can be partially explained by the fact that silyl nitronates are known to be thermally unstable. However, performing the reaction at room temperature did not reward us with the 3-component product. Again, only starting material and conjugate-addition product were retrieved.

This observation showed that the phosphite does, in the first instance, undergo addition to the double bond, hence suggesting that the intermediate silyl nitronate is formed and to confirm this, we carried out a number of NMR experiments.

By treatment of a solution of dimethyl phosphite with triethylamine and chlorotrimethylsilane in $CDCl_3$ followed by addition of nitrostyrene the reaction could be followed by NMR. Attention was paid to the disappearance of the two alkene proton signals and the emergence of the nitronate proton signal at 4.40 ppm and of the α-phosphonate proton at 6.53 ppm in the ^{1}H-NMR spectrum; of nitronate carbon signal at 110 ppm in the ^{13}C-NMR spectrum and the phosphonate signal at 25 ppm in the ^{31}P-NMR spectrum.

After one hour, the reaction had gone to approximately 60% completion, based on nitrostyrene, and only a small dimethyl phosphite peak remained in the ^{31}P-NMR spectrum. Moreover, the reaction did not proceed any further. This suggests that, when the reaction is not carried out under strictly anhydrous conditions a major possible side reaction is simply hydrolysis of the silylated phosphite.

At this time, we also wished to explore the possibility of using other silylated nucleophiles which could add in conjugate fashion to the nitro alkene. Both trimethylsilyl cyanide[138] and trimethylsilyl azide[139] are known to act as nucleophiles. In addition to these reagents, *bis*-trimethylsilyl acetamide and *bis*-trimethylsilyl thio-acetamide are known as silylating agents and would be expected to react as nitrogen and sulphur nucleophiles respectively, whilst simultaneously transferring a silyl group to the nitroalkene. However, when these reactions were performed in an NMR tube no silyl nitronate was observed, even after 3 days.

With the knowledge that the silyl phosphite adds conjugatively to nitrostyrene we then tried to reason why the resulting dipole did not undergo cycloaddition chemistry.

The first interpretation was that the cycloaddition did not proceed due to electronic factors. In view of the fact that the silyl nitronate appeared to be relatively stable in solution, we reasoned that postponing addition of the dipolarophile until formation of the nitronate was complete, would allow the use of an electron deficient olefin such as methyl acrylate. Even in this case, however our efforts were unsuccessful and once again, no cycloaddition product could be isolated. Only nitro phosphonate (**209**) and nitrostyrene (**144**) were recovered.

In an alternative approach, the generation of the silyl nitronate from preformed nitro phosphonate (**209**) was also attempted, but once again this adduct did not undergo cycloaddition with either ethyl vinyl ether or with methyl acrylate (Fig. 102).

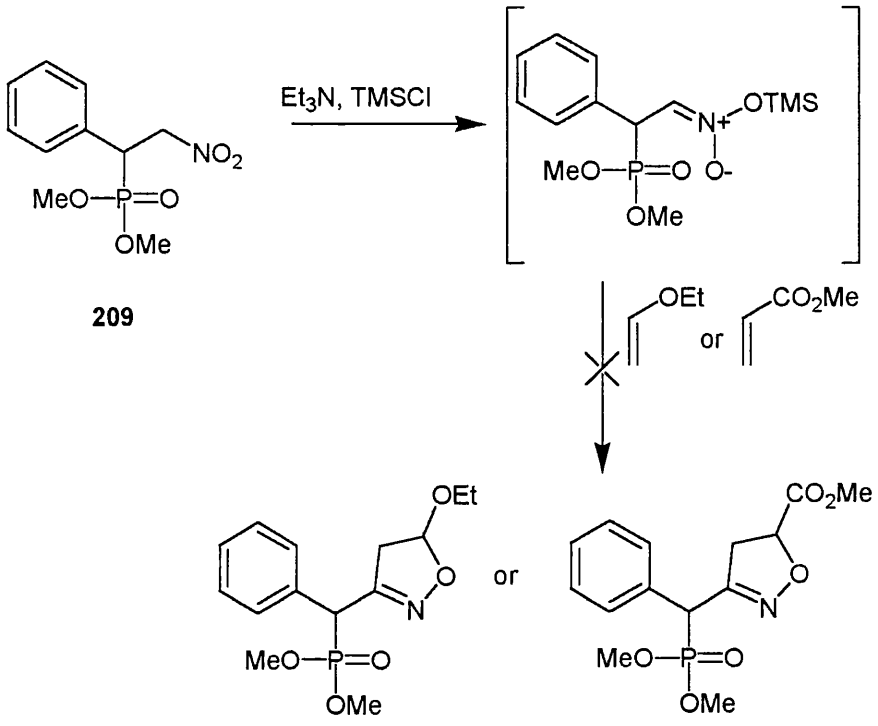
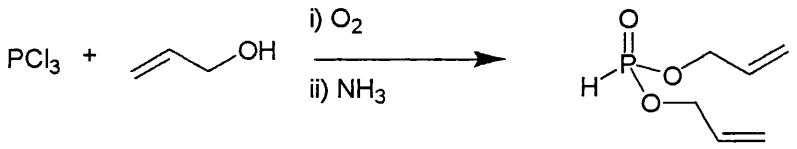


Figure 102

Additionally, by analogy with the successful cases of sulphur and nitrogen nucleophiles, we attempted the reaction of diallyl phosphite with nitrostyrene in an attempt to trap the silyl nitronate in the intramolecular mode. Diallyl phosphite (**211**) was readily synthesised from phosphorus trichloride and allyl alcohol (Fig. 103). The resulting phosphite was silylated under standard conditions and then treated with nitrostyrene. Work-up after 72 hours yielded starting material (89%) and the conjugate addition product (**212**) in a low yield of 4%. There was no evidence however for the desired cycloaddition product (**213**) (Fig. 104).



211

Figure 103

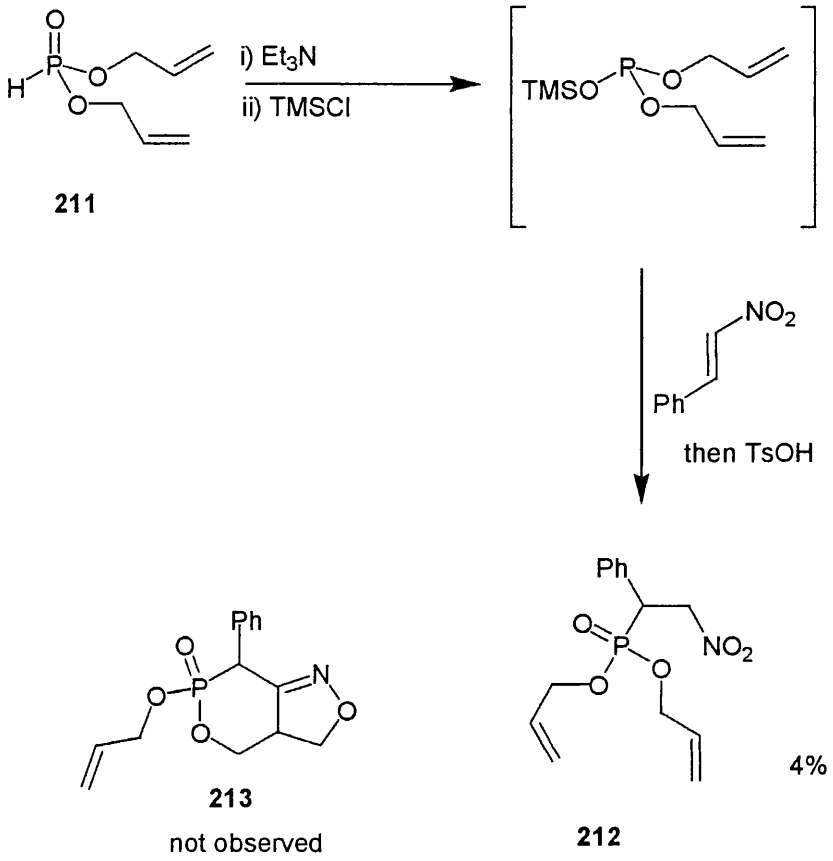


Figure 104

In conclusion, from simple, non-optimised models, it appeared that, with the silyl nitronate in a trans-configuration, both the bulky dimethyl phosphonate and the phenyl groups obscure the dipole sufficiently to hinder the dipolarophile's access, with the result that the reaction does not proceed beyond the Michael addition.

With this in mind, we reasoned that reducing the bulk of the nitroalkene would facilitate the 1,3-dipolar cycloaddition. The preparation of nitropropene (**217**)[140] was accomplished by the potassium fluoride catalysed condensation of acetaldehyde (**215**) and nitromethane (**214**) to afford the nitro alcohol (**216**). This was then dehydrated with trifluoroacetic anhydride in the presence of

triethylamine to afford the nitroalkene (**217**) in modest yield (Fig. 105). Although several attempts were made, the synthesis could not be repeated, failing each time at the dehydration step.

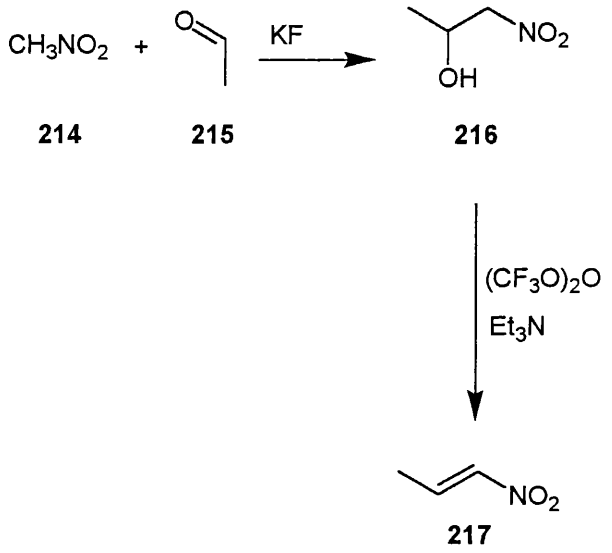


Figure 105

With a small amount of nitropropene (**217**) in hand, this was added to a solution of trimethylsilyl phosphite (**206**), stirred at room temperature for one hour and subsequently treated with methyl acrylate (Fig. 106). The reaction was worked up with toluene sulphonic acid and subjected to column chromatography. This yielded three inseparable compounds. From the NMR one of the compounds was identifiable as the conjugate-addition product (**218**); the other two could not be identified. Judging from the LC/MS trace neither of the other two peaks (219 m/z and 250 m/z) are 3-component products. One of the unknown compounds contains phosphorus, with a ^{31}P signal at 25 ppm. The other ^{31}P signal is attributable to the addition product (**218**).

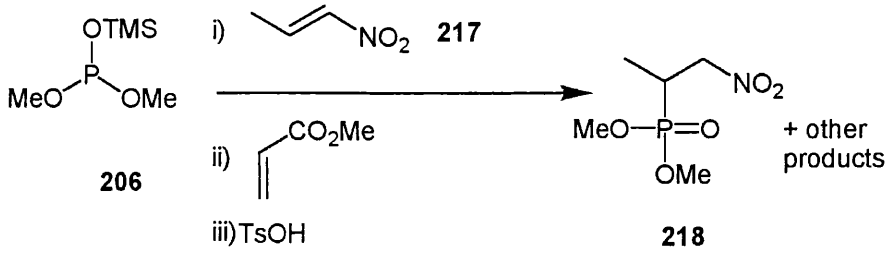


Figure 106

4.3 Silyl Mediated Anionic Cascade

The lack of evidence for a cycloaddition following the phosphite addition suggests that it is the phosphorus group, which is interfering with the reaction of the silyl nitronate and the dipolarophile.

This indicated that the site of nucleophilic attack by the phosphite, generating the nitronate has to be removed by at least one atom distance.

As noted previously, we were struck by the fact that Rees and Afarinkia had previously used silyl phosphites in the synthesis of α-amino phosphonates[136]. The reaction, they suggest, proceeds *via* a 5-membered transition state in which the silyl group migrates from oxygen to nitrogen, generating an intermediate silicon-nitrogen bond, which is hydrolysed on work-up. Bearing in mind Hassner's work on silylated nitrogen nucleophiles it appeared reasonable to attempt a cascade reaction in which a silyl phosphite reacts with an imine (**219**) to then generate an *N*-silyl amino phosphonate (**220**), which upon treatment with nitroalkene (**217**) would generate a silyl nitronate (**221**), which could be further trapped by an olefin tethered to the imine. This reaction would involve the formation of 4 bonds in one step as shown in Figure 107.

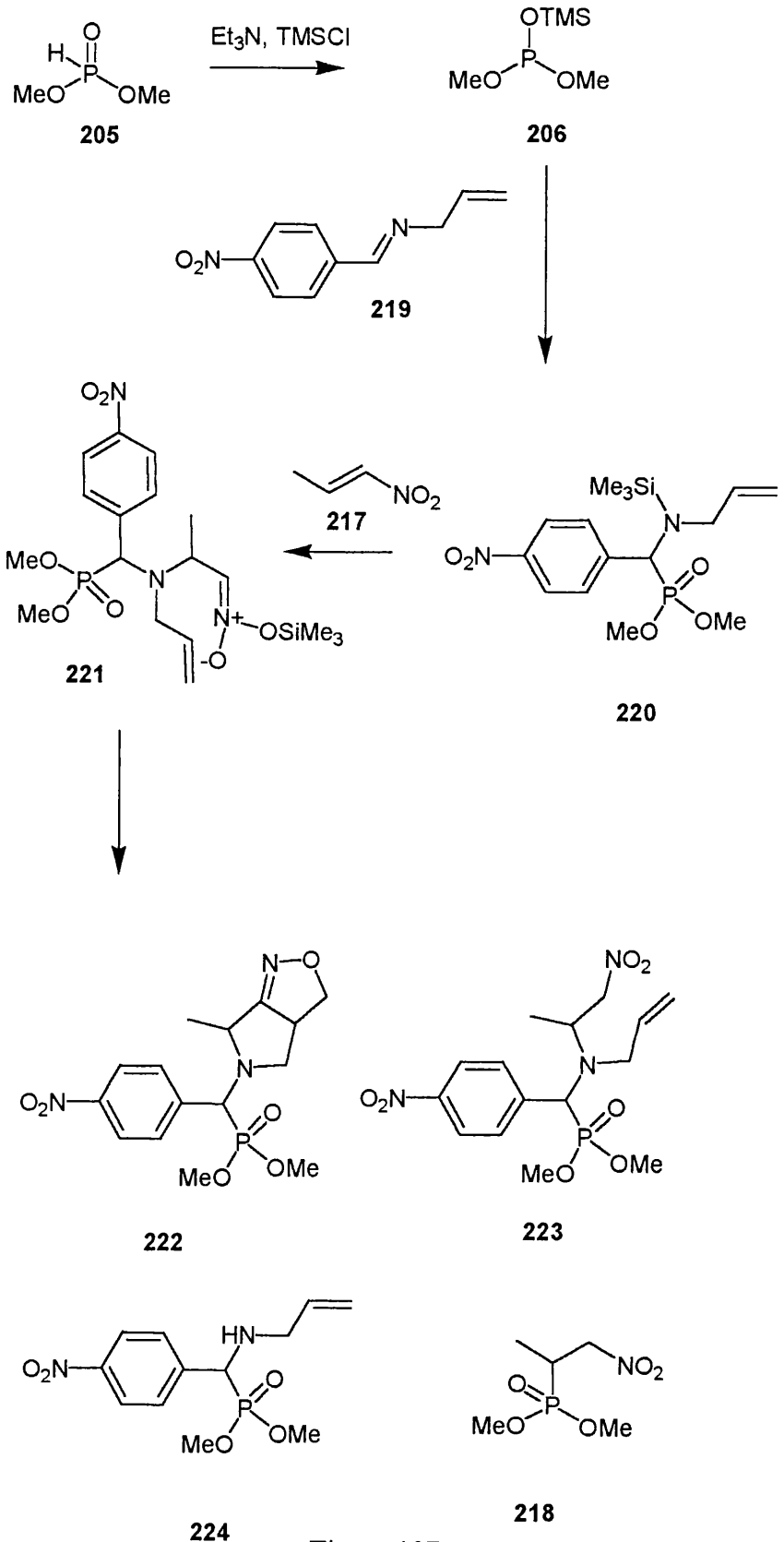

Et3N, TMSCl
OTMS
MeO
OMe
205
206
O2N
N
219
Me3Si
217
NO2
221
220
OSiMe3
222
223
HN
224
218

Figure 107

Again, we were disappointed by the absence of any 3-component product (**222** or **223**). The bulk of the recovered material was made up of the hydrolysed imine. The amino phosphonate (**224**) was isolated in low yield (15%) and intriguingly the conjugate addition product **218** of the silyl phosphite and the nitroalkene was also isolated (5%). The presence of the latter compound indicates the formation of a carbon-phosphorus bond (the amino phosphonate), which is subsequently broken with an inter-molecular migration of the phosphonate group! The most reasonable explanation is that the imine did not react to completion with the phosphite when nitropropene was added, leading to the formation of this by-product.

4.4 Conclusions

With this and the preceding chapters we have demonstrated the application of both a combinatorial and a rational approach to MCR chemistry.

The formation of isoxazolines from nitroalkenes and isocyanides, although previously performed by Parsons[112], has been extended to the intermolecular reaction. The reaction has been partially optimised. There is room for further improvements of the reaction by the use of better suited catalysts. Generating unusual atom connectivities with vinyl and allyl isocyanide components can certainly be used to increase the diversity afforded by this reaction. Moreover, our observations on the preference for electron deficient olefins have led us to propose an alternative mechanism in which a cyclic nitronate rather than a nitrile oxide is involved.

The work on silyl mediated cycloaddition and cascade reactions has been unsuccessful. However, it may be possible to employ the silyl cascade reaction intramolecularly with the alkene moiety tethered to the nitroalkene rather than the imine. This has the advantage, over a fully intermolecular version, of keeping the entropy loss of the reaction to a minimum and might allow the best chance of proof of concept. Furthermore, studies could be undertaken on the effect of transition metals on the terminal cycloaddition reaction. If the reaction does fail at the cycloaddition step then literature precedent would support the use of titanium[141], magnesium[142], palladium[143] and other transition metal catalysts in this reaction.

5 Outlook

In writing these pages and trying to come to terms with the concepts involved in multi-component chemistry, one of the questions has been a nearly trivial one: what is the difference between the Ugi reaction and the Passerini reaction? Both reactions show versatility with regard to the acid component employed (*cf.* Part I, sections 1.1.2 and 1.1.3) and in the case of the Ugi reaction even *N,N*-dialkyl aminoisocyanides have been employed[144] as an unusual isocyanide component. In the introduction (*cf.* Part I, section 1.1) the isocyanide was called an 'ambiphile' due to its ability to act both as an electrophile and as a nucleophile. Correspondingly the iminium ion in the Ugi reaction and the protonated carbonyl component in the Passerini reaction function, at least formally, as electrophiles. The counterion of the acid component might formally be classified as a nucleophile. Thus, it appears that the difference between the Ugi and Passerini reactions is in the form of the electrophile. This begs the question as to what other electrophiles can be employed in this type of isocyanide chemistry? Ugi

has provided a clue (Fig. 108) with a publication from 1964 in which water, *tert.*-butyl isocyanide (**42**) and tropylium perchlorate (**225**) were reacted to afford the corresponding amide (**226**)[163].

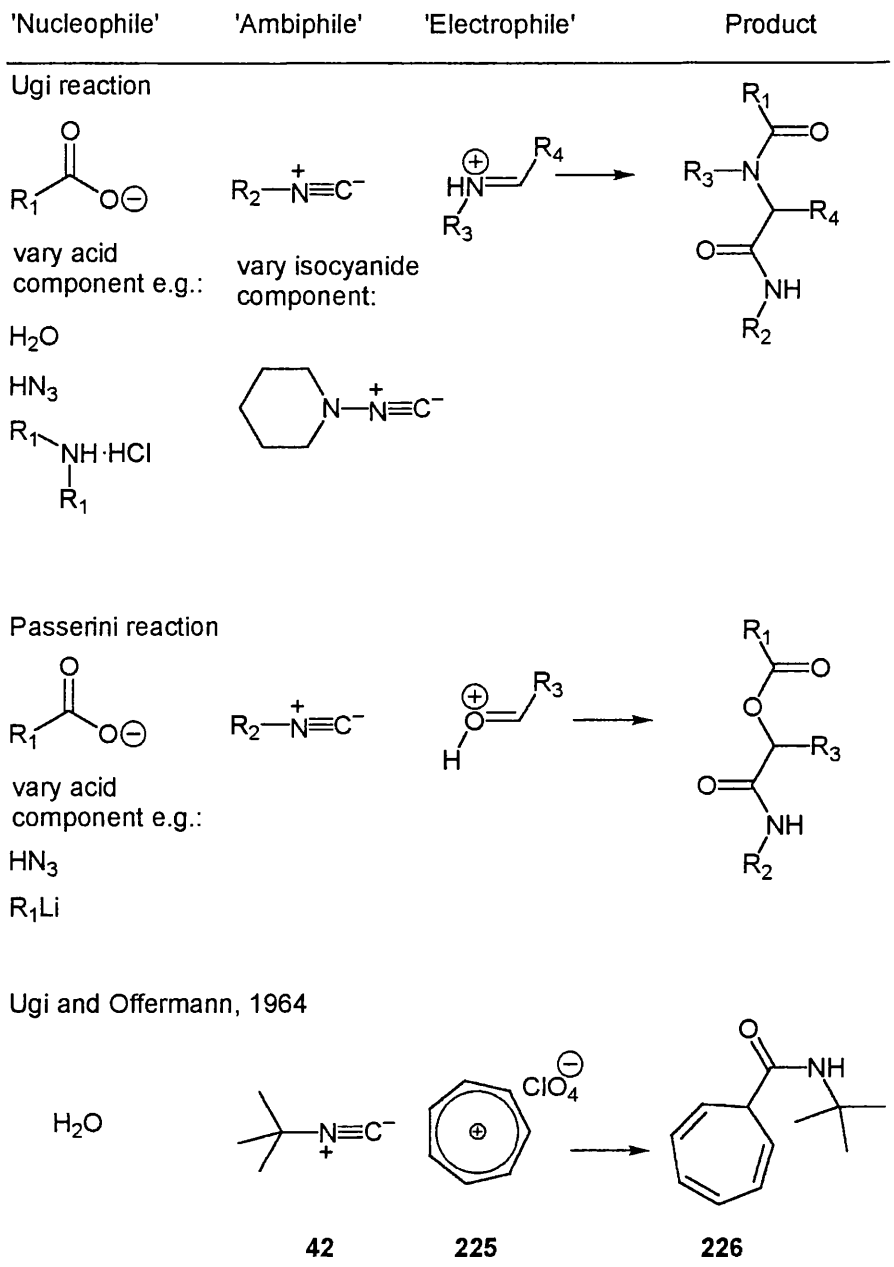


Figure 108

The final reaction of the tropylium cation immediately suggests that a reaction with other carbocations would be worth investigating. Carbocations are inherently reactive species and would have to be generated *in situ*. However, Lewis acid catalysed ring opening of epoxides can readily generate cations. Therefore, we can speculate that a carbocation (**227**) generated in such a manner might be trapped by an isocyanide and a nucleophile, such as water or an acid (Fig. 109).

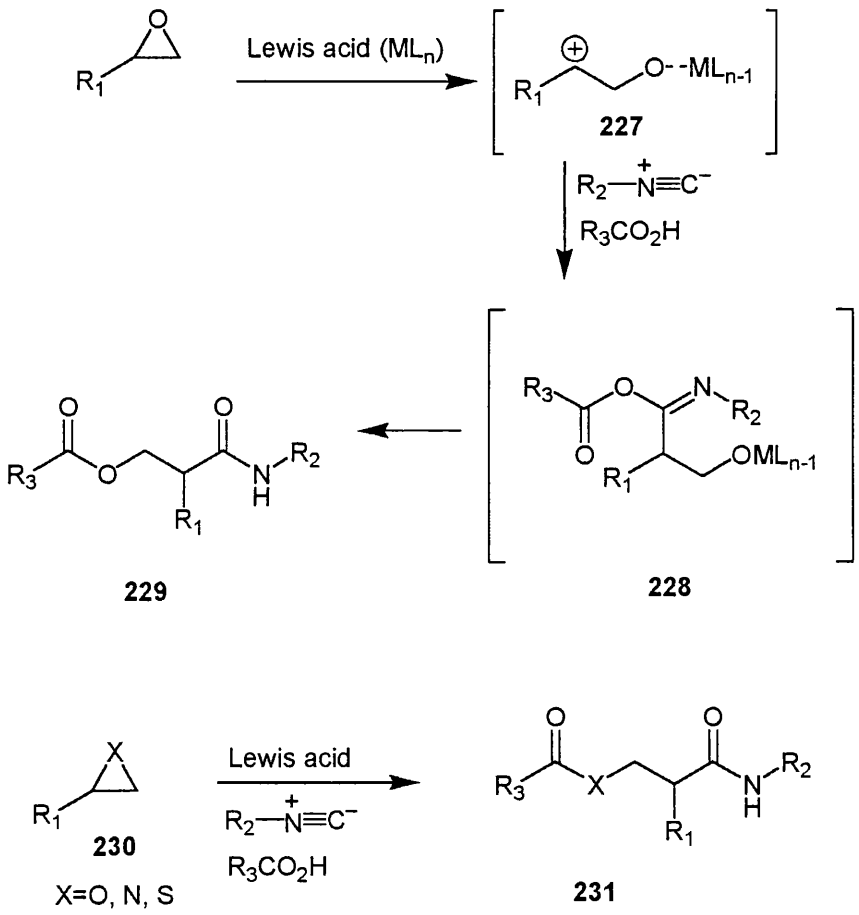
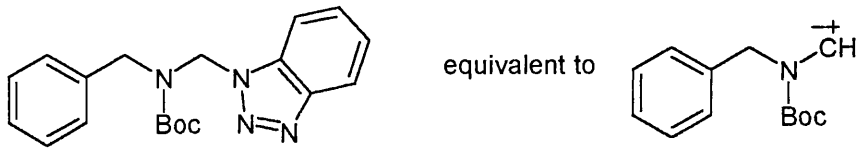


Figure 109

If the carbocation is trapped by the isocyanide and acid, the precedent supplied by the Ugi and Passerini reactions would suggest the intermediate (**228**) undergoes an acyl migration to produce a β-*O*-acyl amide (**229**), effectively a Passerini-type compound with an extra CH_2-group inserted. Similarly, use of azirines or thiiranes (**230**, X=N, S) would lead to the corresponding β-*N*-acyl amide (**231**, X=N) or β-*S*-acyl amide (**231**, X=S). The former could be seen as the corresponding Ugi product, again with a CH_2-group inserted.

Alternatively, variation of the 'ambiphile' could be envisaged. Isocyanides can be seen as stable nucleophilic carbenes. Recently, Katritzky has synthesised and characterised some unusual examples of stable nucleophilic carbenes (**231**, Fig. 110)[145]. It would therefore seem appropriate to investigate the use of these unusual carbenes in multicomponent reactions.



232

Figure 110

Unfortunately, however, time constraints did not allow us to investigate these possibilities.

Part 3:

EXPERIMENTAL

General Experimental

Proton NMR spectra were recorded on a Brucker Avance 500, Brucker AMX-400 or a Brucker AMX-300 at 500 MHz, 400 MHz or 300 MHz respectively. Carbon NMR spectra were recorded on the same machines at 125 MHz, 100 MHz and 75 MHz. Phosphorus NMR spectra were recorded on a Brucker AMX-300 at 38 MHz. Assignments were supported by DEPT editing. Proton and carbon NMR chemical shifts are reported as values in ppm from an internal standard (tetramethylsilane) or residual protic solvent. Phosphorus NMR shifts are also reported as values in ppm from an external reference. The following abbreviations are used to indicate multiplicity: s=singlet, d=doublet, t=triplet, qt=quartet, m=multiplet, dd=double doublet, dt=double triplet, br=broad. The coupling constants (*J*) are given in Hertz (Hz). Infrared spectra were recorded as thin films on KBr plates or as KBr discs on a Perkin-Elmer FT-IR 1605; abbreviations to denote peak intensity are as follows: w=weak, m=medium, s=strong, b=broad. Mass spectra were recorded under electron impact (EI), atmospheric pressure chemical ionisation (APCI) or fast atom bombardment (FAB) at the School of Pharmacy, ULIRS service or under EI conditions on a Perkin-Elmer mass spectrometer at British Biotech, Oxford. All robotic syntheses and manipulations were carried out at British Biotech using a Tecan MiniPrep or Zinnser Lizzy pipetting robot to dispense reagent solutions into Anachem Bioblock polypropylene 2 ml 96 well plates. The plates were prepared for mass spectrometry using a Zymark Rapid Plate and submitted to mass spectrometry on the above-mentioned machine at British Biotech. Melting points were taken on a Reichert hot stage and are uncorrected.

Microanalyses were performed in the University College London Chemistry Department. Organic solvents were dried over anhydrous $MgSO_4$ or Na_2SO_4. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone. Dichloromethane was pre-dried and distilled over calcium hydride. Toluene and benzene were each distilled from sodium. All reactions using dry solvents were carried out under an inert atmosphere of nitrogen. Glassware was oven dried and cooled under a stream of nitrogen. Analytical thin-layer chromatography was carried out on Merk aluminium backed plates coated with 60 F_{254} silica gel, visualised using U.V. and iodine, PMA or permanganate stain. Flash column chromatography was carried out with using the house air line in a modified procedure[146] at low positive pressure using BDH silica gel (40-60 μm).

Experimental Procedures

Generation of the reaction library and standard operating procedure for synthesis in 96 well plates:

The reactions were carried out on a 7.25 μmol scale at a concentration of 0.08 M. All reagents were used as 0.25 M stock solutions. To allow sufficient stock solution for two plates with enough 'spare capacity' to allow the pipetting needle to aspirate solution, all stock solutions were prepared as 4 ml of the 0.25 M solution of the reagents by diluting 1 mmol of reagent in 4 ml of ethylene glycol, unless otherwise stated. For a list of the reagents and amounts employed *cf.* Appendix A. The reagents were dispensed as 30 μl aliquots into each well. The reagents were divided into five sets:

Set 1, tri-functional reagents; each of the reagents (A-H) was added to each well of the appropriate row (A-H) on each plate.

Set 2, di-functional reagents; each of these reagents (1-12) was added to each well of the appropriate column (1-12) on each plate.

Set 3, mono-functional reagents (1-10); each of these reagents was added to all of the 96 wells of a plate

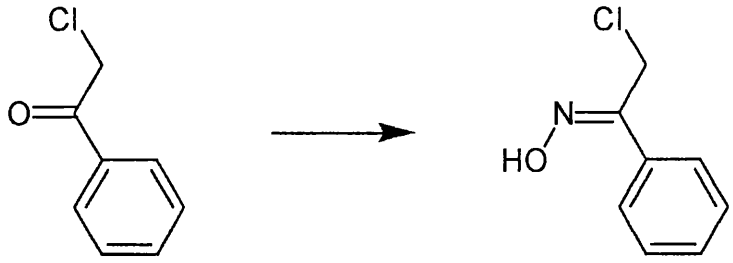
Set 4, nitrogen containing reagents (1-10); each of these reagents was added to all of the 96 wells of a plate

Set 5, catalysts (1 and 2); added in 10 mol% to each well of a plate which was to probe for catalytic activity.

Reagents A-H from set 1, and reagents 1-12 from set 2, were pipetted into the wells of the appropriate rows and columns of the plates. Following this, one reagent from each set 3 and 4 was pipetted into all 96 wells of the plates. Those plates used to probe for catalytic activity of triphenylphosphine and hydroxy pyridine were pre-loaded with the catalyst and the solvent allowed to evaporate, before the other reagents were added. The plates were labelled and left to stand for 48 hours. Those plates prepared for microwave were fitted with a lid and a few pieces of card ice distributed over the lid (to prevent the volatile components from evaporating during the microwave process) and subjected to microwaves for 90 seconds at 500 W.

All plates were diluted with methanol to 0.6 mg ml^{-1} and submitted for automated negative and positive EI-MS analysis.

Synthesis of α-chloro acetophenone oxime[97]



An aqueous solution of hydroxylamine hydrochloride (2.9 g, 55 mmol) in water (20 ml) was cooled to 0°C on an ice bath and treated with a solution of sodium hydroxide (3.2 g, 80 mmol) in water (15 ml). To this solution 2-chloroacetophenone (6.13 g, 40 mmol) was added slowly and the cold reaction mixture stirred for 90 min. After this time a white precipitate formed. The product was extracted with ether (5 x 10 ml)

and ethyl acetate (5 x 10 ml). The organics were combined and dried over Na_2SO_4 and the solvents removed to yield the title compound as a pale pink solid. Yield 80%.

m.p.: 91°C (lit.[97]: 89°C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 9.11 (1H, br, O***H***), 7.35-7.70 (5H, m, Ar***H***), 4.61 (2H, s, C***H***$_2$Cl)

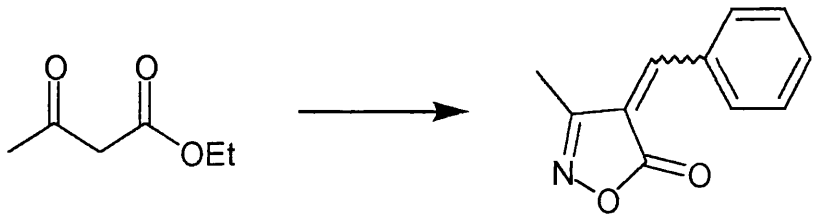
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 158 (***C***=N), 129-134 (***C***$_{Aryl}$), 45 (***C***H_2Cl)

IR (nujol) ν_{max}/cm^{-1}: 3293 (br, O-H), 3063 (s, Ar-H), 2927 (m, C-H, nujol), 1617 (m, C=N), 1501 (m, Ar-H)

LRMS (EI) m/z: 169 (M^+, 80%), 152 (30%), 120 (90%), 103 (100%), 91 (75%), 77 (90%), 65 (35%)

HRMS: Found: 169.0281 (required: 169.0294)

Synthesis of 4-benzylidene-3-methyl-4*H*-isoxazol-5-one[147]



A solution of ethyl acetoacetate (1.3 ml, 10 mmol), hydroxylamine hydrochloride (690 mg, 10 mmol) and benzaldehyde (1 ml, 10 mmol) in ethylene glycol (10 ml) was placed in a microwave oven fitted with a reflux condenser and microwaved for 10 min. at 1000W. The solution was poured onto ice/$NaHCO_3$, filtered and the solid dissolved in DCM, dried over $MgSO_4$ and purified by column chromatography (DCM 100%) to yield the title compound in 1.6 g yield (85%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.21-7.45 (5H, m, Ar***H***), 6.15 (1H, s, C=C***H***), 2.83 (3H, s, C***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 168 (***C***=O), 161 (***C***=N), 134-128 (***C***$_{Aryl}$), 119 (Ph***C***H=C), 64 (PhCH=***C***), 12 (***C***H$_3$)

LRMS (FAB) m/z: 188 (95%, M+1), 115 (10%), 89 (50%), 70 (100%), 63 (60%), 51 (70%), 39 (55%), 31 (25%)

Synthesis of nitrostyrene[148,149]

Method 1:

Benzaldehyde (26 g, 0.25 mol) was dissolved in nitromethane (25 ml, 0.25 mol) and cooled in an ice bath. Sodium hydroxide solution (11 g, 0.25 mol in 5 ml water) was added slowly. The resulting paste was dissolved with water and methanol and left to stand for 15 min. After this time ice-water (~200 ml) was added to make a clear solution, followed by addition of HCl/water (1:1.5, 200 ml) to form a yellow precipitate. The solid was filtered and washed with water. The yellow crystals were melted on a water bath. The freed water was decanted and the product re-crystallised from ethanol to yield nitrostyrene (30 g, 80%).

Method 2:

Benzaldehyde (26 g, 0.25 mol) was dissolved in nitromethane (60 ml). The solution was treated with ethylene diamine (0.5 ml, 7 mmol) and refluxed for 2 hours. The reaction mixture was allowed to cool and was passed through a 2 cm pad of silica gel. The pad was washed with DCM (~30 ml) and then the solvents were removed from the filtrate to yield a tan coloured oil. This was dissolved in the smallest possible volume of hot ethanol, from which on cooling the product crystallised as yellow needles. Yield 27 g (74 %).

m.p.: 57-59°C (lit.[150]: 63°C)

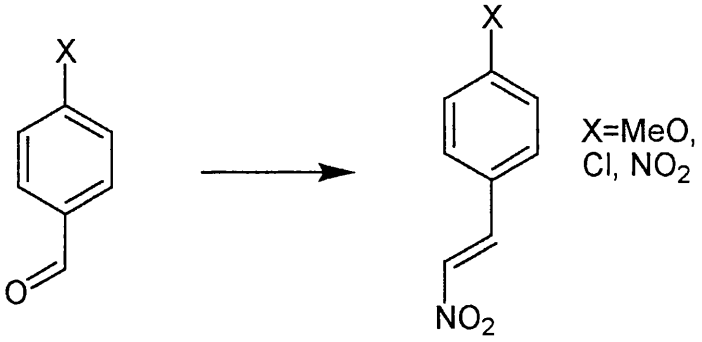
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 8.00 (1H, d, *J*=13.6 Hz, C***H***), 7.60 (1H, d, *J*=13.6 Hz, C***H***), 7.40-7.50 (5H, m, Ar***H***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 139 (NO_2***C***H=CH), 132 (CH=***C***HPh), 129-132 (***C***$_{Aryl}$)

IR (nujol) ν_{max}/cm^{-1}: 3109 (w, Ar-H), 1632 (s, C=C), 1514 (s, N=O), 1343 (s, N=O), 966 (s, CH=CH)

LRMS (FAB) m/z: 150 (100%, M+1), 137 (45%), 91 (25%, $PhCH_2^+$), 77 (25%), 51 (15%), 39 (15%)

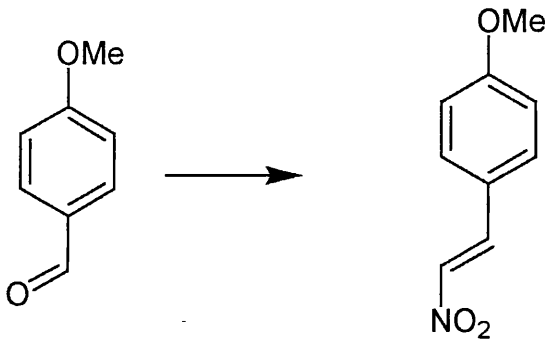
General method for the synthesis of para-substituted nitrostyrenes



The aldehyde (0.20 mol) was dissolved in nitromethane (60 ml). The solution was treated with ethylene diamine (0.2 ml) and refluxed for 3 hours. The reaction mixture was allowed to cool and was passed through a 2 cm pad of silica gel. The pad was washed with DCM (~30 ml) and then the solvents were removed from the filtrate to yield a tan

coloured oil. This was dissolved in the smallest possible volume of hot methanol, from which on cooling the product crystallised.

Data for 1-Methoxy-4-(2-nitro vinyl)-benzene



Yield 20 g, 60 %.

m.p.: 82-84°C (lit.[151]: 86°C)

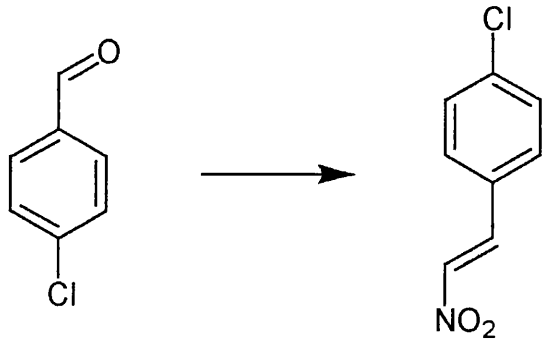
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.80 (1H, d, *J*=13 Hz, CH=C***H***NO_2), 7.30 (1H, d, *J*=13 Hz, C***H***=CHNO_2), 7.25 (2H, d, Ar***H***), 6.85 (2H, d, Ar***H***), 3.65 (3H, s, OC***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 139 (CH=***C***HNO_2), 129-137 (***C***$_{Aryl}$), 115 (***C***H=CHNO_2), 55 (O***C***H_3)

IR (KBr) ν_{max}/cm^{-1}: 3112 (w, C-H), 3040 (s, C-H), 2959 (C-H), 1497 (s, N-O), 1341 (m, N-O)

LRMS (APCI) m/z: 180 (38%, M+1), 163 (10%, M-O), 137 (100%, M-HCNO), 109 (20%, p-Me$OC_6H_4^+$)

Data for 1-chloro-4-(2-nitro vinyl)-benzene



Yield 23 g, 65 %.

m.p.: 108-109°C (lit.[152]: 111-112°C)

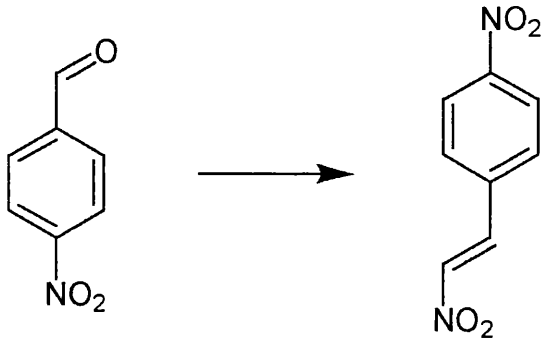
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.98 (1H, d, *J*=13 Hz, CH=C***H***NO_2), 7.55 (1H, d, *J*=13 Hz, C***H***=CHNO_2), 7.45-7.53 (4H, m, Ar***H***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 138 (NO_2***C***H=CH), 137 (NO_2CH=***C***H), 129-130 (***C***$_{Aryl}$)

IR (KBr) ν_{max}/cm^{-1}: 3111 (w, C-H), 3054 (m, C-H), 2985 (w, C-H), 1492 (m, N-O), 1342 (s, N-O)

LRMS (APCI) m/z: 184 (30%, M+1), 168 (10%, M-O), 141 (40%, M-HCNO)

Data for 1-nitro-4-(2-nitro vinyl)-benzene



Yield 20 g, 60 %.

m.p.: 212°C (lit.[153]: 199-202°C)

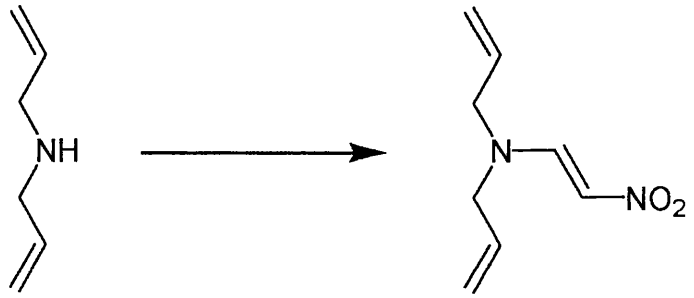
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 8.25 (2H, d, Ar***H***), 7.96 (1H, d, *J*=12 Hz, CH=C***H***NO_2), 7.65 (2H,d, Ar***H***), 7.61(1H, d, *J*=12 Hz, C***H***=CHNO_2)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 139 (NO_2***C***H=CH), 136 NO_2CH=***C***H), 124-130 (***C***$_{Aryl}$)

IR (KBr) ν_{max}/cm^{-1}: 3111 (w, Ar-H), 3054 (w, CH=C-H), 1535 (s, C-NO_2), 1344 (s, C-NO_2),

LRMS (EI) m/z: 194 (55%, M+1), 178 (10%, M-O), 147 (75%), 118 (50%), 102 (100%)

Synthesis of diallyl-(2-nitro-vinyl)-amine[154]



A solution of diallylamine (53 ml, 430 mmol), triethyl orthoformate (128 g, 860 mmol) and *p*-toluene sulphonic acid (2 g, 11 mmol) was refluxed in nitromethane (120 ml, 2.2 mol) for 3 hours. The volatile components were removed *in vacuo* to yield the title compound as a dark oil (110 g, 60%).

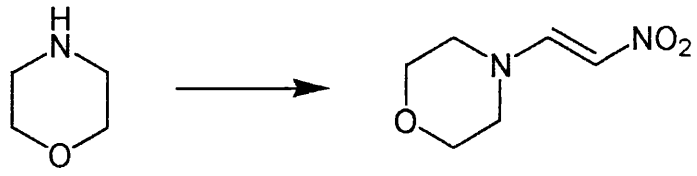
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 8.06 (1H, d, *J*=11 Hz, CH=C***H***NO_2), 6.55 (1H, d, *J*=11 Hz, C***H***=CHNO_2), 5.53-5.86 (2H, m, CH_2=C***H***), 5.04-5.18 (4H, m, C***H$_2$***=CH), 3.75 (4H, dd, CH_2=CHC***H$_2$***N)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 150 (NCH=***C***HNO_2), 133 (CH_2=***C***H), 118 (***C***H_2=CH), 112 (N***C***H=CHNO_2), 59 (N***C***H_2)

IR (nujol) ν_{max}/cm^{-1}: 3085 (m, CH_2=C), 2977 (s, CH_2), 1531 (m, C-NO_2), 1310 (s, C-NO_2)

LRMS (EI) m/z: 205 (100%), 169 (50%, M+1), 153 (25%), 68 (30%), 41 (90%)

Synthesis of 4-(2-nitro-vinyl)-morpholine[154]



A solution of morpholine (8.7 ml, 100 mmol), triethyl orthoformate (27 ml, 200 mmol) and *p*-toluensulphonic acid (0.5 g, 11 mmol) were refluxed in nitromethane (28 ml, 500 mmol) for 1 hour. The solvent were removed *in vacuo* and the product recrystallised from EtOH as brick coloured needles. Yield 10.7g (68%).

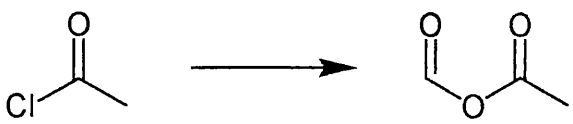
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm 8.08 (1H, d, J=12 Hz, CH=C***H***NO_2), 6.70 (1H, d, J=12 Hz, C***H***=$CHNO_2$), 3.76 (4H, m, OC***H***$_2$), 3.36 (4H, br, NC***H***$_2$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm 149 (O_2N***C***H=CH), 113 (***C***$HCHNO_2$), 77 (O***C***H_2), 66 (N***C***H_2)

IR (neat) ν_{max}/cm^{-1}: 2854 (s, C-H), 1631 (m, CH=C-H), 1376 (s, N-O)

LRMS (FAB) m/z: 159 (100%, M+1), 142 (30%, M-OH)

Synthesis of formyl acetic anhydride[155]



In a dried round bottom flask, equipped with a thermometer, acetyl chloride (9 ml, 120 mmol) was dissolved in diethyl ether (10 ml) under a

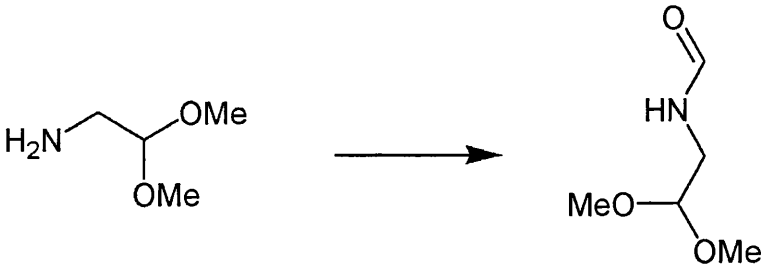
stream of nitrogen. Sodium formate (8.2 g,120 mmol) was added in small portions, such that the internal temperature did not exceed 27°C. The salt was filtered off and the solvent removed under reduced pressure to give the title compound (5 g, 55%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 9.10 (1H, s, (CO)***H***), 2.30 (3H, C***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 167 (CH_3***C***O_2), 156 (H***C***O_2), 21 (***C***H_3)

IR (neat) ν_{max}/cm^{-1}: 1769(CO), 1044 (COC)

Synthesis of *N*-formyl amino acetaldehyde dimethylacetal[155]



In a dried round bottom flask a solution of aminoacetaldehyde dimethyl acetal (105 mg, 1 mmol) was dissolved in formic acid (5 ml) at 0°C. At this temperature formyl acetic anhydride (265 mg, 3 mmol) was added slowly. The reaction mixture was stirred at 0°C for 40 min after which the ice bath was removed and stirring continued at room temperature for a further 1.5 hours. The solvent was removed under reduced pressure to yield the title compound (190 mg, 70%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 9.61 (1H, br, N***H***), 4.72 (1H, tr, C***H***), 3.40 (6H, s, OC***H$_3$***), 3.1 (2H, d, C***H$_2$***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 166 (H(***C***O)N), 100 (***C***$(OMe)_2$), 40 (***C***H_2)

IR (neat) ν_{max}/cm^{-1}: 3381 s, NH), 2831 (s, OMe), 1599 (m, CO), 1462 (m, N-H), 1072 (m, C-N)

LRMS (EI) m/z: 134 (70%, M+1), 102 (100%, M-OMe)

Synthesis of isocyano acetaldehyde dimethyl acetal[156]

In a dry round bottom flask *N*-formyl aminoacetaldehyde dimethyl acetal (1.9 g, 15 mmol) was dissolved in DCM (2 ml), under a stream of nitrogen. To this solution, carbon tetrachloride (1.45 ml, 15 mmol) and triethylamine (2 ml, 30 mmol) were added. The reaction mixture was then treated with triphenylphosphine (3.9 g, 15 mmol). The solution was stirred for 48 hours after which time the solution was passed through a pad of silica, the solvent removed under reduced pressure and the resulting tan coloured paste purified by kugelrohr distillation to afford the title compound (0.5 g, 26%).

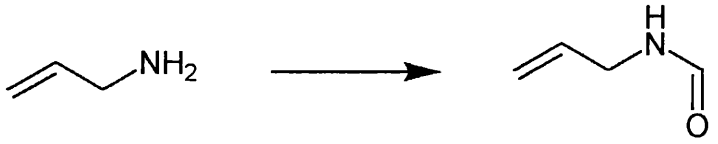
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 4.41 (1H, tr, *J*=5 Hz, C***H***$(OMe)_2$), 3.41 (2H, d, *J*=5 Hz, C***H$_2$***NC), 3.35 (6H, s, OC***H$_3$***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 153 (***C***N-), 100 (***C***H$(OMe)_2$), 54 (O***C***H_3), 43 (***C***H_2NC)

IR (neat) ν_{max}/cm^{-1}: 2940 (s, C-H), 2838 (s, OMe), 2156 (s, -NC)

LRMS (FAB) m/z: 116 (50%, M+1), 84 (100%, M-OMe)

Synthesis of allyl formamide[157]



Allylamine (57 g, 1.1 mol) was refluxed in ethyl formate (450 ml, 3.5 mol) for 4 hours. The volatile components were removed under reduced pressure to afford a crude red oil which was purified by distillation to yield the title compound (95 g, 98%).

b.p.: 122°C (17 torr)[157]

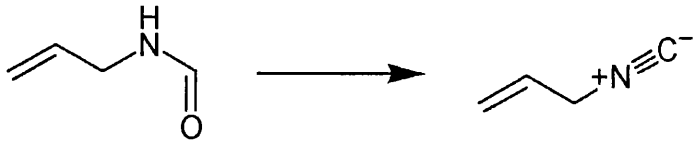
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 8.08 (1H, s, HNC(O)***H***), 7.13 (1H, br, N***H***), 5.77-5.88 (1H, m, CH_2=C***H***), 5.12-5.26 (2H, m, C***H***$_2$=CH), 3.88-3.99 (2H, d, NHC***H***$_2$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 161 (HN***C***O), 134 (H_2***C***=CH), 117 (H_2C=***C***H), 40 (***C***H_2NH)

IR (neat) ν_{max}/cm^{-1}: 3288 (s, N-H), 3051 (m, C-H), 2919 (m, C-H), 1666 (s, C=O, amide I), 1533 (s, N-H, amide II), 1425 (s, C-H), 992 (s, CH=CH_2), 922 (s, CH=CH_2)

LRMS (FAB) m/z: 86 (20%, M+1), 41 (100%, $C_3H_5^+$)

Synthesis of allyl isocyanide[158]



Method 1:

Allylformamide (32 g, 1.13 mol) and triethylamine (83 ml, 0.31 mol) were dissolved in DCM (100 ml) and cooled to 0°C. The solution was treated with phosphorus oxychloride (35 g, 376 mmol) over a period of 30 min. The reaction was stirred at 0°C for 2 hours and then allowed to reach room temperature. The reaction mixture was poured onto aq. sodium bicarbonate solution (100 ml) and extracted with DCM (3 x 100 ml). The solution was distilled to yield a colourless solution of allyl isocyanide in DCM (0.5% yield).

Method 2:

In a two necked flask equipped with a dropping funnel, charged with allyl formamide (65 g, 785 mmol), and a distillation condenser, tosyl chloride (216 g, 1.13 mol) and freshly distilled quinoline (380 ml, 3.02 mol) were heated to 90°C. The allyl formamide was slowly added to the solution over a period of 20 min and the resulting allyl isocyanide distilled out as a clear liquid.

b.p.: 109-117°C (lit.: 122°C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 5.76-5.85 (1H, m, CH_2=C***H***), 5.12-5.33 (2H, m, C***H$_2$***=CH), 4.07-4.09 (2H, m, NHC***H$_2$***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 149 (CH_2N***C***), 136 (H_2***C***=CH), 118 (H_2C=***C***H), 44 (***C***H_2NC)

IR (neat) ν_{max}/cm^{-1}: 3094 (m, C-H), 2975 (m, C-H), 2152 (s, -NC), 1425 (s, C-H), 993 (m, CH=CH_2), 930 (m, CH=CH_2)

LRMS (FAB) m/z: 68 (10%, M+1), 41 (100%, $C_3H_5^+$)

Synthesis of 2,2-dimethyl-pentenal[111]

A solution of allylalcohol (10 ml, 150 mmol) in *p*-cymene (30 ml) was treated with isobutyraldehyde (20 ml, 225 mmol) and a catalytic amount of *p*-toluenesulphonic acid (0.05 g, 0.5 mmol). The reaction mixture was refluxed under Dean-Stark conditions for 48 hours. The crude reaction mixture was distilled at ambient pressure to yield the title compound (3.3 g, 20 %) as a solution in *p*-cymene.

b.p.: 126-127°C[111]

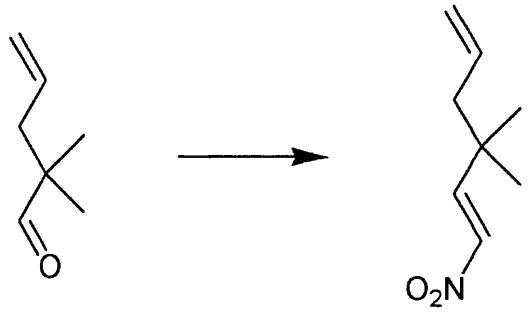
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 9.47 (1H, s, C***H***O), 5.7-5.8 (1H, m, CH_2=C***H***), 5.01-5.10 (2H, m, C***H$_2$***=CH), 2.15 (2H, d, *J*=7.5 Hz, C***H$_2$***CMe_2), 1.02 (6H, s, C***H$_3$***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 206 (***C***HO), 133 (***C***H_2=CH), 118 (CH_2=***C***H), 42 (CH***C***H_2), 34 (***C***Me_2), 24 (***C***H_3)

IR (neat) ν_{max}/cm^{-1}: 2965 (w, C-H), 1708 (s, CHO), 1455 (m, C-H), 1378 (m, CH_3), 960 (m, CH=CH_2)

LRMS (EI) m/z: 113 (2%, M+1), 97 (25%, M-CH_3), 94 (45%, M-H_2O), 83 (70%, M-COH), 70 (70%, M-C_3H_6), 56 (90%, 97-C_3H_5), 55 (100%), 41 (80%, $C_3H_5^+$)

Synthesis of 3,3-dimethyl-1-nitro-1,5-hexadiene



2,2-Dimethyl pentenal (3.3 g, 30 mmol) was dissolved in nitromethane (30 ml) and treated with a catalytic amount of ethylene diamine (50µl). The solution was refluxed for two hours, after which time the reaction mixture was passed through a pad of silica and then washed through with a small amount of DCM. The solvents were removed under reduced pressure to yield the nitroalkene as a yellow oil (2.14 g, 65%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.24 (1H, d, *J*=12 Hz, CH=C***H***NO_2), 6.88(1H, d, *J*=12 Hz, C***H***=$CHNO_2$), 5.7-5.8 (1H, m,

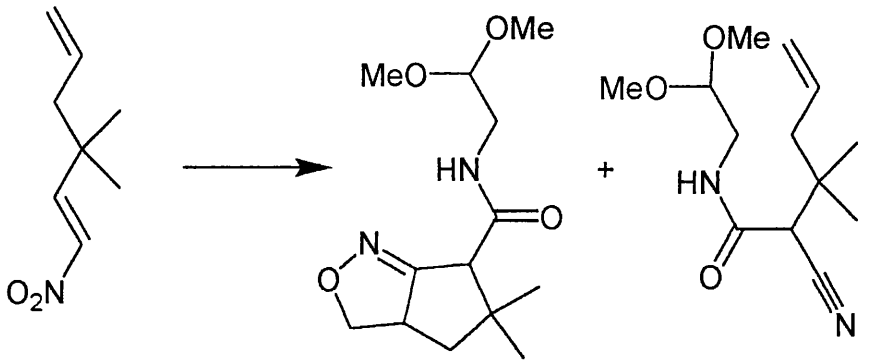
CH_2=C***H***), 5.01-5.10 (2H, m, C***H***$_2$=CH), 2.15 (2H, d, *J*=7.5 Hz, C***H***$_2$CMe$_2$), 1.02 (6H, s, C***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 151 (***C***HNO_2), 138 (***C***H=CHNO_2) 133 (***C***H_2=CH), 119(CH_2=***C***H), 46 (CH***C***H_2), 36 (***C***Me_2), 26 (***C***H_3)

IR (neat) ν_{max}/cm^{-1}: 3078 (m, C=CH_2), 2968, 2931, 2874 (s, C-H),1643 (s, C=C), 1529 (m, N=O), 1469 (m, C-H), 1351 (m, N-O), 995 (s, C-$CHCH_2$), 968 (s, NO_2CH=CH), 920 (s, C-$CHCH_2$)

LRMS (FAB) m/z: 156 (1%, M+1), 138 (5%), 124 (5%), 75 (100%)

Synthesis of 5,5-dimethyl-3a,4,5,6-tetrahydro-3H-cyclopenta[*c*] isoxazole-6-carboxylicacid-dimethylacetaldehyde-amide



A solution of 3,3-dimethyl-1-nitro-1,5-hexadiene (2.14 g, 13.8 mmol) in *p*-cymene (3 ml) was heated to 70°C under nitrogen. To this a solution of isocyano acetaldehyde dimethyl acetal (1.58 g, 13.8 mmol) in *p*-cymene (2 ml) was added drop-wise over 1 hour. The reaction

mixture was kept at 70°C for a further 3 hours. The solution was purified by column chromatography (EtOAc:Hex=1:1 then EtOAc) to give the title compound (192 mg, 5.1%) as an inseparable mixture of both diastereoisomers in a 2:1 ratio.

^{1}H NMR data for the minor diastereoisomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.34 (0.3H, br, N***H***), 4.57-4.63 (1H, m, CH***H***$_{ax}$O), 4.38-4.42 (1H, m, C***H***$(OMe)_2$), 4.12 (1H, m, CH_2C***H***CH_2), 3.79-3.84 (1H, m, CH***H***$_{eq}$O), 3.30-3.44 (2H, m, C***H***$_2$CH$(OMe)_2$), 3.28 (0.3H, s, C***H***C=N), 1.95-2.01 (1H, m, $C(Me)_2CH$***H***$_{ax}$), 1.40-1.44 (1H, m, $C(Me)_2CH$***H***$_{eq}$), 1.15-1.30 (6H, s x2, $C(C$***H***$_3)_2$)

^{1}H NMR data for the major diastereoisomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 6.49 (0.7H, br, N***H***), 4.57-4.63 (1H, m, CH***H***$_{ax}$O), 4.38-4.42 (1H, m, C***H***$(OMe)_2$), 4.12 (1H, m, CH_2C***H***CH_2), 3.79-3.84 (1H, m, CH***H***$_{eq}$O), 3.30-3.44 (2H, m, C***H***$_2$CH$(OMe)_2$), 3.14 (0.7H, s, C***H***C=N), 1.95-2.01 (1H, m, $C(Me)_2CH$***H***$_{ax}$), 1.40-1.44 (1H, m, $C(Me)_2CH$***H***$_{eq}$), 1.15-1.30 (6H, s x2, $C(C$***H***$_3)_2$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 170 (NH***C***O), 168 (***C***=N), 102 (***C***H$(OMe)_2$), 76 (***C***H_2O), 54 (O***C***H_3), 52 (Me_2C***C***H), 50 (CH_2***C***HCH_2), 48 (***C***Me_2), 42 ($(Me)_2C$***C***H_2), 41 (***C***$H_2CH(OMe)_2$), 30 (***C***H_3), 25 (***C***H_3)

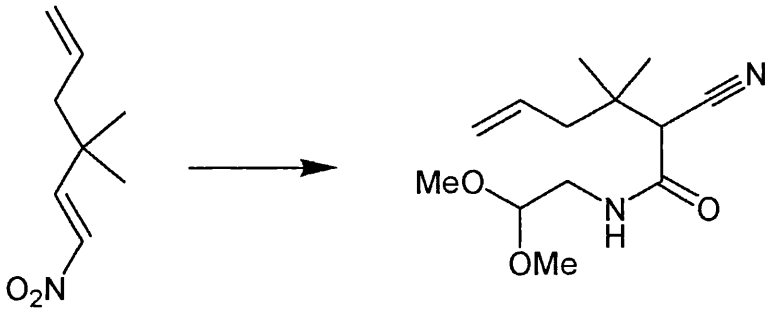
IR (neat) ν_{max}/cm^{-1}: 3331 (br, N-H), 3057 (w), 2958 (s, C-H), 1665 (s, C=O), 1543 (s, N-H), 1462 (m, C=N) 1369 (m, N-O), 1270 (m), 1200 (m), 1130 (s), 1062 (s)

LRMS (FAB) m/z: 271 (10%, M+1), 239 (100%, M-MeO), 207 (5%, M-2xMeOH), 166 (8%), 138 (9%)

HRMS m/z: 271.1643 (M+H), calculated 271.1658 (M+H)

Microanalysis: Found C 57.01%, H 8.30%, N 10.35%, (required: C 57.70%, H 8.20%, N 10.36%)

Data for 2-cyano-*N*-(2,2-dimethoxy-ethyl)-3,3-dimethyl-hex-5-enoic amide



Yield: 35 mg, 0.1%

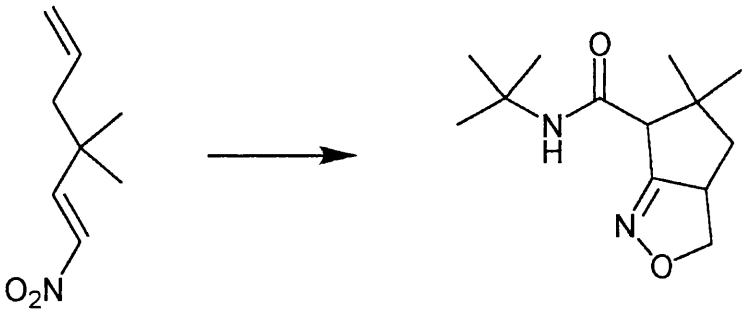
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 6.2 (1H, br, N***H***), 5.7-5.9 (1H, m, CH_2=C***H***), 5.15 (2H, dd, C***H$_2$***=CH), 4.10 (1H, tr, C***H***$(OMe)_2$), 3.45 (2H, d, C***H$_2$*** $CH(OMe)_2$), 3.40 (6H, s, $CH(OCH_3)_2$), 3.25 (1H, s, C***H***CN), 2.24 (2H, d, CH_2=CH-C***H$_2$***), 1.17 (3H, s, C***H$_3$***), 1.13 (3H, s, C***H$_3$***)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 164 (***C***ONH), 133 (***C***H_2=CH), 120 (CH_2=***C***H), 117 (***C***N), 102 (***C***H$(OMe)_2$), 54 (O***C***H_3), 48 (***C***CN), 45 (CH_2=CH-***C***H_2), 37 (NH***C***H_2), 26 (***C***H_3), 25 (***C***H_3)

IR (neat) ν_{max}/cm^{-1} : 3323 (br, N-H), 3077 (w, C=CH_2), 2969, 2951, 2895 (s, C-H), 2845 (s, OMe), 2245 (m, -CN), 1643 (s, C=O), 1556 (s, N-H), 973 (s, C-$CHCH_2$), 899 (s, C-$CHCH_2$),

LRMS (FAB) m/z: 273 (100%, CN→CO_2H), 255 (10%, M+1), 223 (90%, M-OMe), 124 (10%), 100 (20%), 75 (85%), 41 (15%, $C_3H_5^+$)

Synthesis of 5,5-dimethyl-3a,4,5,6-tetrahydro-3H-cyclopenta[*c*] isoxazole-6-carboxylicacid-*tert.*-butyl amide



A solution of 3,3-dimethyl-1-nitro-1,5-hexadiene (560 mg, 3.6 mmol) in benzene (5 ml) was refluxed under nitrogen. Over a period of two hours a solution of *tert.*-butyl isocyanide (410 µl, 3.6 mmol) in benzene (2 ml) was added to the refluxing solution. The reaction was kept under reflux for a further 5 hours, after which time the reaction was allowed to cool down, the solvent was removed under reduced pressure, and the crude purified by column chromatography (EtOAc:Hex=1:1 then EtOAc) to yield the title compound (129 mg, 15%).

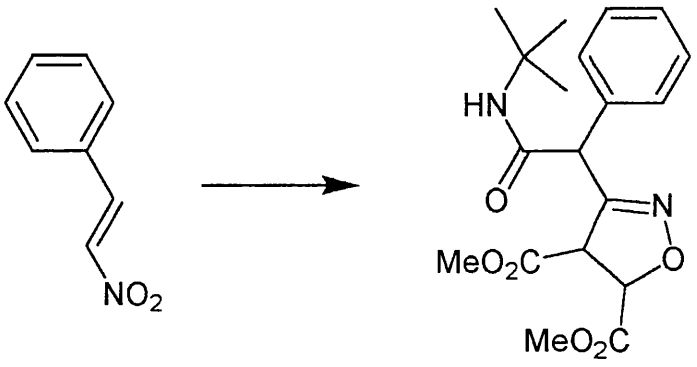
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 5.86 (1H, br, N***H***), 4.56-4.62 (1H, m, OCH***H***$_{eq}$), 4.04-4.12 (1H, m, CH_2CHCH_2), 3.76-3.83 (1H, m, CHC***H***$_{ax}$), 3.02 (1H, s, $C(Me)_2CH$), 1.91-2.00 (1H, m, $C(Me)_2CHH_{eq}$), 1.37-1.43 (1H, m, $C(Me)_2CHH_{ax}$), 1.31 (9H, s, $C(CH_3)_3$), 1.26 (3H, s, $C(CH_3)_{eq}(CH_3)_{ax}$), 1.17(3H, s, $C(CH_3)_{ax}(CH_3)_{eq}$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 171 (***C***ONH), 167 (***C***=N), 76 (***C***H_2O), 54 (CH_2***C***HCH_2), 53 (***C***$HC(Me)_2$), 52 (N***C***$(Me)_3$), 49 (***C***$(Me)_2$), 42 ($C(Me)_2$***C***H_2CH), 30 ($C($***C***$H_3)_{eq}(CH_3)_{ax}$), 29 ($C($***C***$H_3)_3$), 24 ($C($***C***$H_3)_{ax}(CH_3)_{eq}$)

IR (KBr) ν_{max}/cm^{-1}: 3297 (br, N-H), 3070 (s, C-H), 2966(s, C-H), 2867 (s, CH_2), 1635 (s, C=O), 1459 (s, C=N), 1362 (s, N-O)

LRMS (FAB) m/z: 239 (100%, M+1), 183 (100%, M-C_4H_5), 166 (70%), 138 (35%), 83 (20%), 57 (100%, $C_4H_6^+$), 41 (55%)

Synthesis of 3-(2',2'-phenylacetic acid-*tert.*-butyl amide)-4,5-dimethyl carboxylate-2-isoxazolidine



Nitrostyrene (745 mg, 5 mmol) and dimethyl maleate (2.5 ml, 20 mmol) were dissolved in toluene (10 ml) and heated to 70°C. To this was

added a solution of *tert.*-butyl isocyanide (565 μl, 5 mmol) in toluene (5 ml) over a period of two hours. The reaction mixture was kept at 70°C for a further 15 hours. The solvent was removed *in vacuo* and the crude material subjected to column chromatography (hexane then EtOAc:Hex=2:1) to yield the title compound (40 mg, 2%) as a mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.27-7.51 (10H, m, Ar***H***), 6.51 (1H, br, N***H***), 6.36 (1H, br, N***H***), 5.37 (1H, d, *J*=6.6Hz, OC***H***CO_2Me), 5.35 (1H, d, *J*=6.4Hz, OC***H***CO_2Me), 4.72 (1H, s, PhC***H***), 4.71 (1H, s, PhC***H***), 4.52 (1H, d, *J*=6.4 Hz, C***H***CO_2Me), 4.31 (1H, d, *J*=6.6 Hz, C***H***CO_2Me), 3.81 (3H, s, CO_2C***H*****$_3$**), 3.78 (3H, s, CO_2C***H*****$_3$**), 3.65 (3H, s, CO_2C***H*****$_3$**), 3.53 (3H, s, CO_2C***H*****$_3$**), 1.31 (9H, s, $C(C$***H*****$_3)_3$**), 1.28 (9H, s, $C(C$***H*****$_3)_3$**)

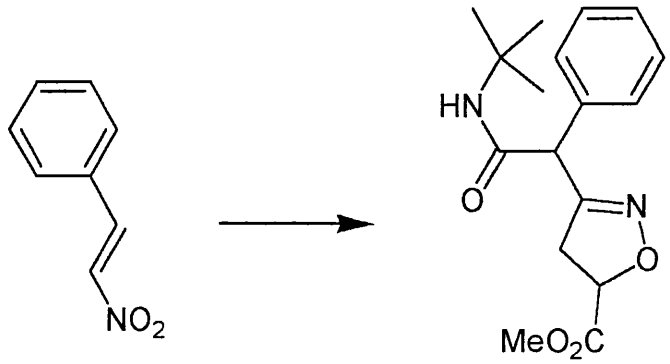
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 169 (***C***O_2Me), 167 (***C***ONH), 154 (***C***=N), 135 (***C*****$_{ipso}$**), 129-128 (**C$_{aryl}$**), 80 (O***C***HCO_2Me), 58 (***C***HCO_2Me), 53 (CO_2***C***H_3), 52 (Ph***C***H), 28 ($C($***C***$H_3)_3$)

IR (neat) ν_{max}/cm^{-1}: 3290 (br, N-H), 3065 (s, C-H), 2947 (s, C-H), 1651 (C=O), 1461 (C=N), 1348 (s, N-O)

LRMS (FAB) m/z: 377 (100%, M+1), 321 (24%, M-C_4H_8), 270 (16%), 214 (35%), 188 (25%)

HRMS m/z: 377.1697 (M+1), calculated 376.1618 (M)

Synthesis of 3-(2',2'-phenylacetic acid-*tert.*-butyl amide)-5-methyl carboxylate-2-isoxazolidine



A solution of nitrostyrene (820 mg, 5.5 mmol) and methyl acrylate (2.25 ml, 25 mmol) in toluene (5 ml) was heated to 100°C. *Tert.*-butyl isocyanide (565 µl, 5 mmol) in toluene (5 ml) was added slowly. The reaction mixture was heated at 100°C for a further 6 hours after which the solvent was removed *in vacuo* and the crude purified by column chromatography to yield the title compound as a yellow solid (190 mg, 15%), rf=0.56 (EtOAc:Hex=1:1).

m.p.: 188°C

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.30-7.38 (5H, m, Ar***H***), 6.17 (1H, br, N***H***), 4.91-5.01 (1H, dd, J_{cis}=7Hz, J_{trans}=12Hz, C***H***CO_2CH_3), 4.68 (1H, s, PhC***H***), 3.74 (3H, s, CO_2C***H***$_3$), 3.42-3.62 (1H, m, J_{cis}=7Hz, J_{trans}=12Hz, CH***H***$_{eq}$CHCO$_2$Me), 2.97-3.18 (1H, m, J_{cis}=7Hz, J_{trans}=12Hz, CH***H***$_{ax}$CHCO$_2$Me), 1.32 (9H, s, C(C***H***$_3$)$_3$)

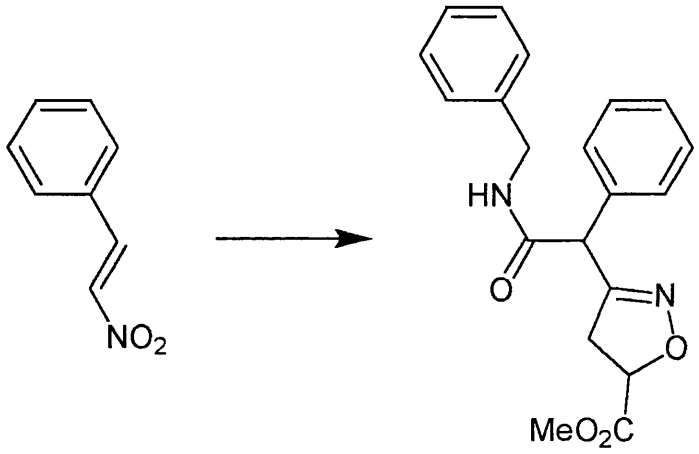
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 171 (***C***O$_2$Me), 168 (***C***ONH), 158 (***C***=N), 135, 129, 128, 77 (CH_2***C***HCO$_2$Me), 53 (O***C***H$_3$), 52 (Ph***C***H), 40 (***C***H$_2$CHCO$_2$Me), 28 (C(***C***H$_3$)$_3$)

IR (neat) ν_{max}/cm^{-1}: 3281 (br, N-H), 3057 (s, C-H), 2973 (s, C-H), 1638 (C=O), 1461 (C=N), 1332 (s, N-O)

LRMS (FAB) m/z: 319 (100%, M+1), 303 (3%, M-CH_3) 263 (30%, M-C_4H_8), 219 (10%, M- CO_2Me), 154 (25%), 130 (27%)

HRMS m/z: 319.1658 (M+1), calculated 318.1580 (M^+)

Synthesis of 3-(2',2'-phenylacetic acid benzyl amide)-5-methyl carboxylate-2-isoxazolidine



Nitrostyrene (745 mg, 5 mmol) and methyl acrylate (2.7 ml, 30 mmol) were dissolved in toluene (7 ml) and heated to reflux. A solution of benzyl isocyanide (610µl, 5 mmol) in toluene (5 ml) was added to the reaction over 30 min. The reaction was refluxed for 18 hours. The solvent was removed under reduced pressure and the crude material purified by column chromatography (EtOAc:Hex=1:1 then EtOAc) to yield the title compound (32 mg, 1.7%) as an inseperable mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H/ppm: 7.28-7.50 (20H, m, Ar***H***), 6.51 (2H, br, N***H***), 5.01-5.05 (1H, dd, J_{cis}=7.1 Hz, J_{trans}=12.1 Hz, C***H***CO_2Me), 5.03-4.99 (1H, dd, J_{cis}=6.3 Hz, J_{trans}=11.7 Hz, C***H***CO_2Me), 4.75 (2H, s, PhC***H***), 4.47 (4H, d, PhC***H***$_2$), 3.78 (3H, s, OC***H***$_3$), 3.75 (3H, s, OC***H***$_3$), 3.58-3.62 (1H, dd, CH***H***$_{ax}$$CHCO_2Me$), 3.44-3.49 (1H, dd, CH***H***$_{ax}$$CHCO_2Me$), 3.17-3.23 (1H, dd, CH***H***$_{eq}$$CHCO_2Me$), 3.11-3.16 (1H, dd, CH***H***$_{eq}$$CHCO_2Me$)

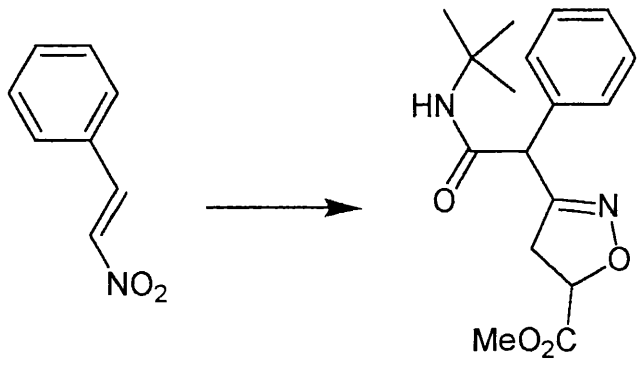
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 170 (***C***O_2Me), 169 (***C***ONH), 157 (***C***=N), 128-135 (***C***$_{Aryl}$), 77 (CH_2***C***HCO_2Me), 60 (Ph***C***HNH) 53 (O***C***H_3), 52 (Ph***C***H), 40 (***C***H_2CHCO_2Me)

IR (neat) ν_{max}/cm^{-1}: 3430 (br, N-H), 3032 (w, C-H), 2927 (s, C-H), 1743 (s, MeOC=O), 1676 (s, amide I, C=O), 1519 (s, amide II, N-H), 1458 (m, C=N) 1382 (m, N-O), 1265 (m), 1219 (m), 1096 (m)

LRMS (FAB) m/z: 353 (70%, M+1), 327 (10%), 276 (5%, M-C_6H_5), 130 (15%), 91 (100%, $PhCH_2^+$)

HRMS m/z: 377.1697 (M+1), calculated 376.1618 (M)

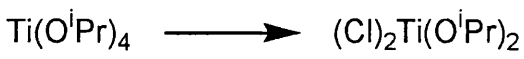
Reaction parameter study



A solution of nitrostyrene (820 mg, 5.5 mmol), methyl acrylate (2.25 ml, 25 mmol) and *tert.*-butyl isocyanide (565 μl, 5 mmol) in the appropriate solvent (5 ml) was heated to the temperature indicated in the table. After the time indicated the solvent was removed *in vacuo* and the crude purified by column chromatography to yield the title compound.

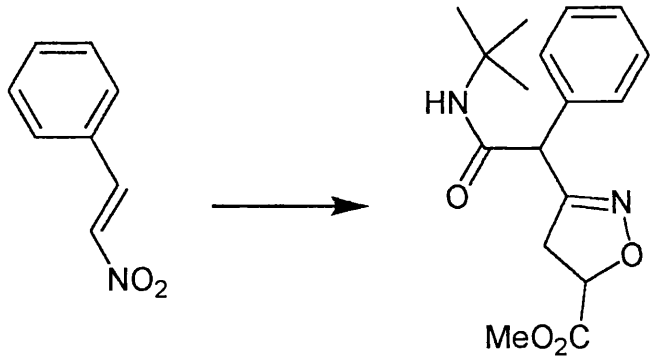
Solvent	Temperature (°C)	Reaction time (hours)	Yield (%)
Benzene	60	3	7
		6	10
		18	9
Toluene	60	6	11
		18	10
	120	6	11
		18	9
DMF	60	6	2
	120	6	3
MeCN	60	6	9
		18	9

Synthesis of dichloro diisopropoxy titanium[159]



Under nitrogen a solution of titanium tetraisopropoxide (7.37 ml, 25 mmol) in dry DCM (35 ml) was treated with titanium tetrachloride (2.73 ml, 25 mmol) at 0°C. The solution was stirred for 1 hour and DCM (4.9 ml) added to make a total of 50 ml, equivalent to a 1 M solution. The reagent was kept in the fridge and used as a 1 M stock solution.

Catalyst and co-reagent study



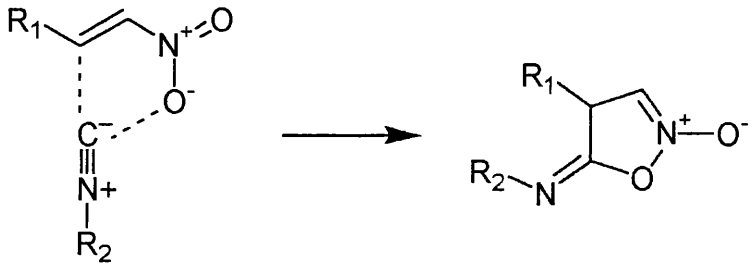
A solution of nitrostyrene (145 mg, 1 mmol), methyl acrylate (500 µl, 5.5 mmol) and *tert.*-butyl isocyanide-(220 µl, 2 mmol) in acetonitrile (3 ml) was treated with the appropriate catalyst/co-reagent (0.1 eq. – 5 eq.) and heated to 60°C under nitrogen for 20 hours. The reaction was quenched with water (15 ml) and extracted with DCM (3 x 10 ml), dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude was subjected to LC/MS and those reactions which showed a mass peak of 319 m/z with a retention time of 3.02 min. (indicating isoxazoline formation) were purified by column chromatography, and yields

determined. Isolated compounds were spectroscopically identical to previously synthesised samples.

Catalyst/Co-reagent	**Amount**	**Yield of isoxazoline (%)**	**Yield of nitrile (%)**
p-Toluene sulphonic acid	0.1	Not observed	Observed, not isolated
Diaza bicyclo [2.2.2]octane (DABCO)	0.1	Observed, not isolated	Not observed
$ZnCl_2$	0.1	Observed, not isolated	Observed, not isolated
$SnCl_4$	0.1	Observed, not isolated	Not observed
$La(OAc)_3$	0.1	11%	Observed, not isolated
$Ce(SO_4)_2$	0.1	8%	Observed, not isolated
$SmCl_2$	0.1	5%	0.3%
$Sc(OTf)_3$	0.1	10%	Not observed
$Yb(OTf)_3$	0.1	10%	Not observed

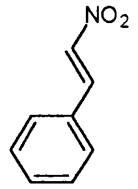
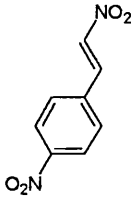
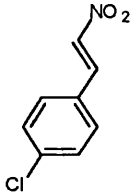
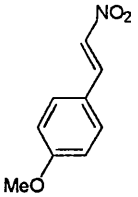
			observed
$InCl_3$	0.1	8%	Not observed
$(^iPrO)_2TiCl_2$	0.1	1%	Observed, not isolated
$LiClO_4$	1	38%	Not observed
$LiClO_4$	5	36%	Not observed

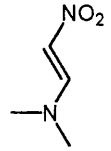
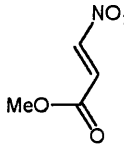
Computational study: The effect of electron rich and electron poor nitroalkenes on the HOMO-LUMO gap in the 1+4 cycloaddition



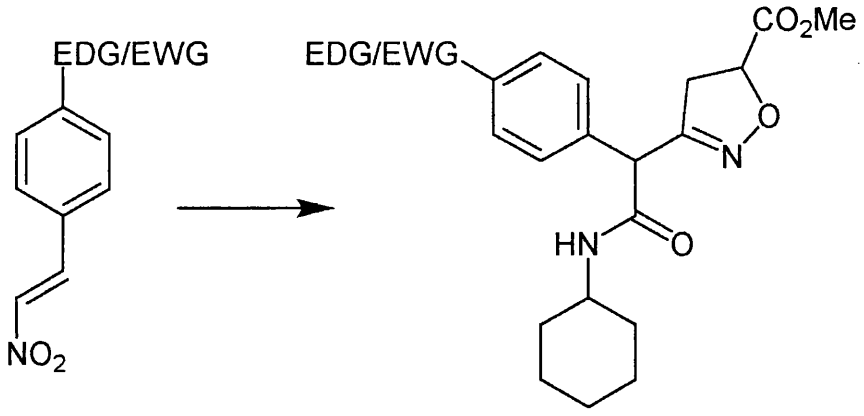
Calculations of HOMO-LUMO gaps were performed using the PM3 semi-empirical molecular orbital calculation method, in the MOPAC package. The programme was used to assess the orbital interactions for the first [1+4] addition of the isocyanide onto the nitroalkene to form the putative intermediate isoxazolone *N*-oxide. For the calculations, each molecule was 'built' and its geometry optimised and steric energy minimized. The structure was then submitted for the frontier orbital energies of the molecule to be calculated. The results were collected and the HOMO-LUMO gaps for the reagents determined.

The calculations were carried out for the following substituted nitroalkenes and isocyanides: *p*-nitro nitrostyrene, *p*-methoxy nitrostyrene, *p*-chloro nitrostyrene, *N,N*-dimethyl nitroenamine, methylester nitroethene, methyl isocyanide, vinyl isocyanide and allyl isocyanide.

		Methyl isocyanide		Vinyl isocyanide		Allyl isocyanide	
		HOMO – 11.9678 eV	**LUMO** 1.5324 eV	**HOMO** – 10.6556 eV	**LUMO** –0.0693 eV	**HOMO** – 10.7139 eV	**LUMO** 0.4695 eV
	**HOMO** -10.0476 eV		11.5800 eV		9.9783 eV		10.5171 eV
	LUMO –1.4443 eV	**10.2535 eV**		**9.2113 eV**		**9.2696 eV**	
	**HOMO** –10.8940 eV		12.4264 eV		10.8247 eV		11.3635 eV
	LUMO -2.2839 eV	**9.4139 eV**		**8.3717 eV**		**8.4300 eV**	
	**HOMO** –9.7501 eV		11.2815 eV		9.6808 eV		10.2196 eV
	LUMO –1.5976 eV	**10.1002 eV**		**9.0580 eV**		**9.1163 eV**	
	**HOMO** –9.5164 eV		11.0488 eV		9.4471 eV		9.9859 eV
	LUMO –1.3669 eV	**10.3309 eV**		**9.2887 eV**		**9.3470 eV**	

	**HOMO** –10.0380 eV		11.5704 eV		9.9687 eV		10.5075 eV
	LUMO –0.9760 eV	**10.7218 eV**		**9.6796 eV**		**9.7379 eV**	
	**HOMO** –12.0004 eV		13.5328 eV		11.9311 eV		12.4699 eV
	LUMO –1.7324 eV	**9.9654 eV**		**8.9232 eV**		**8.9815 eV**	

U.V. absorption study



Nitroalkene (5 mmol), methyl acrylate (0.27 ml, 3 mmol) and cyclohexyl isocyanide (65 μl, 5 mmol) were dissolved in toluene (1 ml) to give a 246.3 mM solution of the nitroalkene. The solution was refluxed under nitrogen and the reaction monitored by U.V. At intervals, an aliquot

(0.15 ml) was removed from the reaction and diluted to 5 ml with methanol. A 0.25 ml aliquot was removed from the dilute solution and diluted further to 25 ml with methanol to give a concentration of the nitroalkene of 0.103 mmol. The U.V. spectrum of this solution was measured and λ_{max} recorded. The study was performed using nitrostyrene, 2-(4-nitro phenyl)-nitro ethene and 2-(4-methoxy phenyl)-nitro ethene.

Nitrostyrene: λmax=308.5 nm, ε=0.103 mM

Time/min	20	55	90	127	150	183	215
Absorbance	2.315	2.165	1.689	1.06	0.742	0.626	0.472

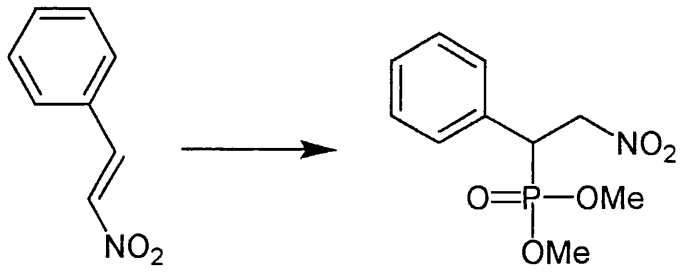
2-(4-nitro phenyl)-nitro ethene: λmax=304.0 nm, ε=0.103 mM

Time/min	5	75
Absorbance	2.176	0.8

2-(4-methoxy phenyl)-nitro ethene: λmax=347.5 nm, ε=0.103 mM

Time/min	25	65	175	405
Absorbance	2.231	2.048	1.998	2.064

Synthesis of (1-phenyl-2-nitro-ethyl)-phosphonic acid dimethyl ester[160]



A dry flask was charged with a solution of dimethyl phosphite (458 µl, 5 mmol) and triethylamine (800 µl, 5.5 mmol) in toluene (20 ml). The solution was cooled to 0°C and treated with chlorotrimethylsilane (700 µl, 5.5 mmol). After 10 min a solution of nitrostyrene (745 mg, 5 mmol) in toluene (7 ml) was added. The reaction was allowed to reach room temperature and stirred for a further 30 min. After addition of methyl acrylate (5 ml, 25 mmol) and heating at reflux for 3 hours, the solvents were removed under reduced pressure and the crude purified by column chromatography (DCM, then DCM/MeOH 30%) to yield the title compound (260 mg, 20%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.36-7.30 (5H, m, Ar***H***), 4.95 (2H, dd, $J^3_{P\text{-}H}$= 7.6 Hz, $J_{H\text{-}H}$=7.8 Hz, C***H***$_2NO_2$), 4.05 (1H, dt, $J^2_{P\text{-}H}$=24 Hz, $J_{H\text{-}H}$=7.8 Hz, PhC***H***), 3.70 (3H, d, $J^3_{P\text{-}H}$=10.9 Hz, OC***H***$_3$), 3.49 (3H, d, $J^3_{P\text{-}H}$=10.9 Hz, OC***H***$_3$)

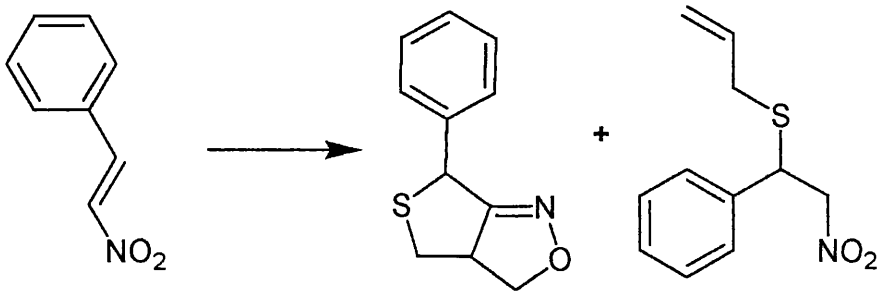
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 128-131 (Aryl), 75 (***C***H_2NO_2), 54 (O***C***H_3), 53 (O***C***H_3), 43-42 (d, $J_{P\text{-}C}$=138 Hz, Ph***C***H)

^{31}P NMR ($CDCl_3$, 121 MHz) δ_P/ppm: 25 (***P***(O)(OMe)$_2$)

IR (neat) ν_{max}/cm^{-1}: 3059 (m, Ar-H), 2959, 2925, 2852 (m, C-H), 1550 (s, N-O), 1456 (m, C-H), 1439 (w, P-OMe), 1377 (m, N-O), 1185 (m, P-OMe),

LRMS (FAB) m/z: 260 (100%, M+1), 213 (70%, M-HNO_2), 137 (25%), 109 (30%), 91 (30%)

Synthesis of 6-phenyl-3,3a,4,6-tetrahydrothiopheno[3,4-c] isoxazole[136] and (1-allylsulphanyl-nitro-ethyl)-benzene[136]



A solution of technical grade allyl mercaptan (70%, 590 µl, 5 mmol) in benzene (5 ml) was treated with triethylamine (765 µl, 5.5 mmol) and trimethylchlorosilane (630 µl, 5.5 mmol); the resulting suspension was stirred at room temperature for 10 min. To the suspension, a solution of nitrostyrene (745 mg, 5 mmol) in benzene (5 ml) was added. The reaction mixture was stirred overnight at room temperature. The reaction was worked up by refluxing with *p*-toluenesulphonic acid (0.3 g, 1.5 mmol) for 30 min. The mixture was washed with saturated $NaHCO_3$ (aq.), then water. The aqueous extracts were washed with ether (2 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to afford the title

compound as a yellow oil (615 mg, 60%) after purification by column chromatography (EtOAc:Hex=2:1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.44-7.26 (5H, m, Ar***H***), 5.18 (1H, s, PhC***H***), 4.44-4.50 (1H, dd, *J*=10 Hz, *J*=8.5 Hz, OCHH_{ax}), 4.15-4.27 (1H, qt, *J*=9.6 Hz, CH_2CHCH_2), 3.99-4.05 (1H, dd, *J*=10.2 Hz, *J*=8.2 Hz, OCHH_{eq}), 3.06-3.13 (1H, dd, *J*=8.5 Hz, SCHH_{ax}), 2.75-2.81 (1H, dd, *J*=9.6 Hz, SCHH_{eq})

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 168 (***C***=N), 127-129 (C_{aryl}), 75 (OCH_2), 55 (Ph***C***H), 43 (CH_2CHCH_2), 31 (SCH_2)

IR (neat) ν_{max}/cm^{-1}: 3060 (m, Ar-H), 2938 (s, C-H), 1555 (s, C=N), 1313 (s, N-O)

LRMS (FAB) m/z: 206 (100%, M+1), 188 (15%), 175 (75%), 121 (30%), 91 (45%, $PhCH_2^+$), 73 (15%), 41 (15%)

Data for (1-allylsulphanyl-nitro-ethyl)-benzene:

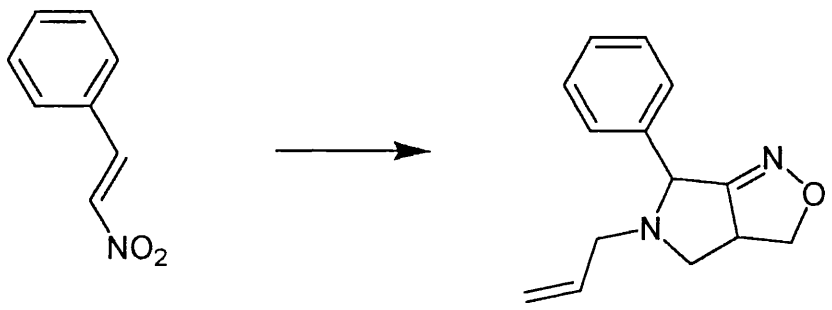
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm 7.46-7.59 (5H, m, Ar***H***), 5.95-6.08 (1H, m, CH_2=C***H***), 5.39-5.49 (2H, dd, CH_2=CH), 4.99 (2H, d, CH_2=CHCH_2), 4.75-4.80 (1H, tr, SC***H***), 3.24-3.30 (2H, m, CH_2NO_2)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm 134 (H***C***=CH_2) 120-129 (C_{Aryl}), 117 (CH=***C***H_2), 82 (***C***H_2NO_2), 56 (Ph***C***H), 44 (SCH_2),

IR (neat) ν_{max}/cm^{-1}: 3064 (m, Ar-H), 2978 (s, C-H), 1316 (s, NO_2)

LRMS (FAB) m/z: 224 (15%, M+1), 200 (30%), 188 (40%), 177 (20%), 163 (65%), 121 (30%), 104 (100%, M- NO_2- C_3H_5S), 91 (25%, $PhCH_2^+$), 73 (40%, C_3H_5S), 41 (45%, $C_3H_5^+$)

Synthesis of 5-allyl-6-phenyl-3a,4,5,6-tetrahydro-*3H*-pyrrolo[3,4-c] isoxazole[137]



Diallylamine (615 µl, 5 mmol) in benzene (5 ml) was treated successively with triethylamine (765 µl, 5.5 mmol) and trimethylchlorosilane (630 µl, 5 mmol) and stirred for 30 min. After this time nitrostyrene (750 mg, 5 mmol) was added and the solution was stirred at room temperature over night. The reaction was worked up with a catalytic amount of *p*-toluene sulphonic acid (0.5 g). The reaction mixture was then washed with saturated $NaHCO_3$ (aq.), followed by water. The organic layer was dried over Na_2SO4 , the solvents removed and the crude purified by column chromatography to yield the title compound as an oil (575 mg, 50 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.18-7.33 (5H, m, Ar***H***), 5.62-5.72 (1H, m, CH_2=C***H***), 5.02-5.12 (2H, dd, J_{trans}=13.1 Hz, J_{cis}=7.6 Hz,

C***H***$_2$=CH), 4.20 (1H, s, PhC***H***), 3.68 (2H, d, *J*=11.2 Hz, CH_2=CHC***H***$_2$N), 3.12-3.21 (3H, m, NCH***H***$_{eq}$, CH_2C***H***CH_2, OCH***H***$_{eq}$), 2.78-2.83 (1H, dd, *J*= 5.9 Hz, *J*=10 Hz, OCH***H***$_{ax}$), 2.25-2.29 (1H, dd, *J*=6.8 Hz, NCH***H***$_{ax}$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 165 (***C***=N), 139 (*ipso*-***C***$_{aryl}$), 134 (CH_2=***C***H), 127-129 (***C***$_{aryl}$), 118 (***C***H_2=CH), 68 (Ph***C***H), 62 (CH_2=CH***C***H_2), 56 (O***C***H_2), 54 (N***C***H_2), 44 (CH_2***C***HCH_2)

IR (neat) ν_{max}/cm^{-1}: 30430 (m, Ar-H), 2938 (s, C-H), 1455 (s, C=N), 1353 (s, N-O)

LRMS (EI) m/z: 229 (35%, M+1), 197 (100%, M-HNO), 188 (10%, M-C_3H_5), 41 (35%, $C_3H_5^+$)

Synthesis of nitropropanol[142]

A solution of nitromethane (10 ml, 760 mmol) and acetaldehyde (10 ml, 180 mmol) in *iso*-propanol (50 ml) was cooled on an ice bath to 0°C and treated with a catalytic amount of potassium fluoride (0.7 g, 40 mmol). The reaction was stirred at 0°C for two hours, the ice bath removed and stirring continued for a further 15 hours. Water (50 ml) was then added and the solution extracted with diethyl ether (2 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvents removed *in vacuo* to afford the intermediate nitropropanol (17 g, 90%). This was subjected without further purification to dehydration.

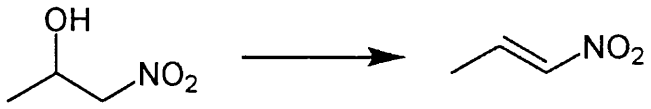
^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm 4.59-4.83 (1H, m, C***H***OH), 4.45-4.50 (2H, m, C***H***$_2NO_2$), 3.12 (1H, br, O***H***), 1.28 (3H, d, C***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm 81 (***C***H_2NO_2), 65 (***C***HOH), 19 (***C***H_3)

IR (neat) ν_{max}/cm^{-1}: 3408 (br, OH), 2936 (s, C-H), 1558 (s, NO_2), 1455, 1384 (s, NO_2), 1137 (s)

LRMS (FAB) m/z: 105 (1%, M^+), 83 (65%), 69 (40%), 55 (100%), 41 (80%)

Synthesis of nitropropene [142]



Nitropropanol (1.7 g, 16 mmol) and trifluoroacetic anhydride (9 ml, 16 mmol) were dissolved in DCM (10 ml). Triethylamine (4.8 ml, 35 mmol) was added slowly to the reaction mixture over a period of 15 min. The reaction was stirred at room temperature for 3 hours, after which time the reaction was washed with saturated $NaHCO_3$ (aq.) (3 x 15 ml) followed by water (10 ml). The organic layers were dried over $MgSO_4$ and distilled under reduced pressure to yield nitropropene (730 mg, 50%).

CAUTION: This compound is an intense lachrymator and should only be handled in a fumehood.

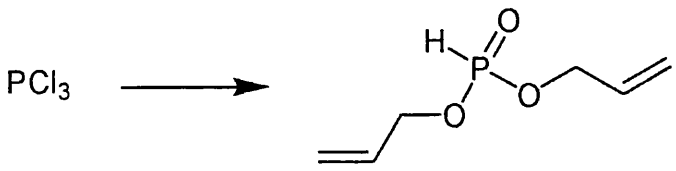
b.p.: 40-47°C, 16 torr (lit.: 70°C at 20 torr)

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.17-7.31 (1H, dq, *J*=13.2 Hz, *J*=7.2 Hz, C***H***=CHNO$_2$), 6.98-7.03 (1H, d, *J*=13.3 Hz, CH=C***H***NO$_2$), 1.93-1.96 (3H, d, *J*=7.2 Hz, C***H***$_3$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 140 (CH=***C***HNO$_2$), 138 (***C***H=CHNO$_2$), 14 (***C***H$_3$)

LRMS (EI) m/z: 87 (100%, M^+), 46 (20%, NO_2), 41 (30%, $C_3H_5^+$)

Synthesis of diallyl phosphite[161]



A two necked round bottomed flask fitted with a pressure equalising dropping funnel containing allyl alcohol (80 ml, 1.7 mol) and an air inlet tube connected to the house air line, was charged with a solution of phosphorus trichloride (40 ml, 460 mmol) in diethyl ether (150 ml) and cooled on an ice bath. The ally alcohol was added slowly with air bubbling through the solution. After the addition was complete, the ice bath was removed and air bubbled through the solution for a further 1 hour. This was followed by bubbling ammonia gas through the solution to precipitate NH_4Cl. The precipitate was filtered off and

the resulting clear liquid was distilled to afford the title compound. Yield 24 g (32 %)

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm 6.87 (1H, d, $J_{P\text{-}H}$=702 Hz, P***H***), 5.89-5.95 (2H, m, CH_2=C***H***), 5.24-5.40 (4H, m, C***H$_2$***=CH), 4.54-.459 (4H, m, CHC***H$_2$***O)

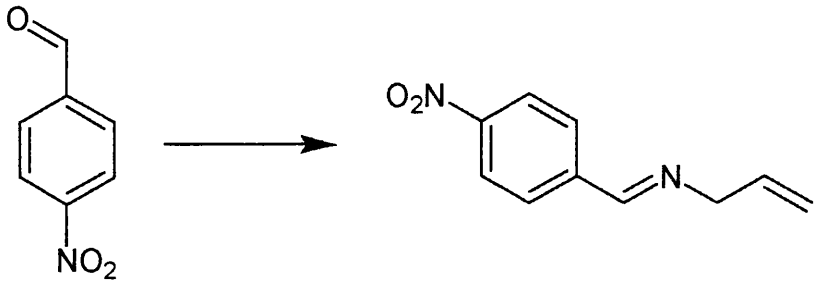
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm 132 (***C***H_2=CH), 118 (CH_2=***C***H), 66 (***C***H_2O-P)

^{31}P NMR ($CDCl_3$, 121 MHz) δ_P/ppm 8.5 (P=O)

IR (neat) ν_{max}/cm^{-1}: 3086 (m, C-H), 2947 (w, C-H), 2887 (m, C-O), 2434 (s, P-H), 1460 (s, C-H), 1363 (w), 1260 (P=O)

LRMS (EI) m/z: 162 (100%, M^+), 121 (25%, M-C_3H_5), 41 (30%, $C_3H_5^+$)

Synthesis of *N*-allyl-*p*-nitro-benzaldimine[138]



A solution of *p*-nitrobenzaldehyde (930 mg, 6 mmol) in DCM (4 ml) was treated with allylamine (1 ml, 13 mmol) and stirred for 1 hour. The reaction was dried over $MgSO_4$ and the solvents removed *in vacuo* to yield the title compound (1g, 87%).

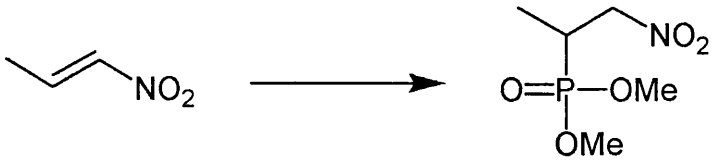
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H/ppm: 8.39 (1H, s, C***H***=N), 8.27 (2H, Ar***H***), 7.92 (2H, d, Ar***H***), 6.03-6.12 (1H, m, CH_2=C***H***), 5.18-5.23 (2H, m, C***H$_2$***=CH), 4.31-4.34 (2H, m, CHC***H$_2$***N)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 159 (H***C***=N), 149 (***C$_{aryl}$***NO_2), 142 (***C$_{aryl}$***C=N), 135 (***C***H=CH_2), 124-129 (***C$_{aryl}$***), 117 (CH=***C***H_2), 63 (CH***C***H_2N)

IR (neat) ν_{max}/cm^{-1}: 3076 (m, CH=CH_2), 2839 (w, C-H), 1642 (w, C=N), 1598 (m, C=C), 1519 (s, N-O), 1344 (s, N-O)

LRMS (FAB) m/z: 191 (20%, M+1), 96 (30%), 84 (45%), 70 (40%), 41 (100%)

Synthesis of dimethyl-(1-methyl-2-nitro-ethyl) phosphonate[162]



A solution of dimethyl phosphite (180 µl, 2 mmol) in DCM (3 ml) was cooled to 0°C and treated with triethylamine (300 µl, 2.1 mmol) and trimethylchlorosilane (260 µl, 2.1 mmol), stirred for 15 min, after which time nitropropene (180 mg, 2 mmol) was added and the reaction was stirred for a further 2 hours. Water (5 ml) was then added to the reaction mixture, the layers separated and the organic layer dried over $MgSO_4$. The solvent was removed *in vacuo* and the resultant oil

subjected to column chromatography (DCM/5% MeOH – DCM/10% MeOH) to yield the title compound as a viscous oil. Yield 3.5 mmol (30%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H/ppm: 4.66-4.73 (1H, m, CH***H***NO_2), 4.30-4.38 (1H, m, CH***H***NO_2), 3.79 (6H, d, POC***H***$_3$), 281-2.90 (1H, m, PC***H***), 1.22-1.34 (3H, dd, C***H***$_3$)

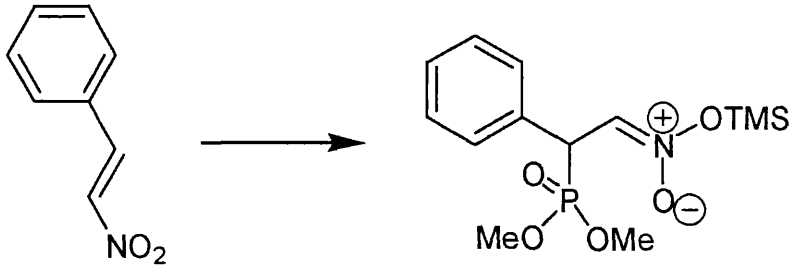
^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 76 (***C***H_2NO_2), 53 (O***C***H_3), 30 (P***C***H), 12 (***C***H_3)

^{31}P NMR ($CDCl_3$, 121 MHz) δ_P/ppm: 30 (***P***(O)(OMe)$_2$)

IR (neat) ν_{max}/cm^{-1}: 2959 (s, C-H), 1558 (s, C-NO_2), 1374 (s, C-NO_2), 1261 (s, P=O), 830 (m, P-O-Me)

LRMS (FAB) m/z: 395 (45%, 2M+1), 198 (90%, M+1), 151 (95%, M-NO_2), 110 (85%, P(O)(OMe)$_2$+1), 93 (50%, P(OMe)$_2$), 41 (25%, C_3H_5)

Formation of phosphono nitronate



A dry NMR tube was charged with a solution of nitrostyrene (45 mg, 0.3 mmol) and dimethyl phosphite (30 µl, 0.3 mmol) in $CDCl_3$ (0.6 ml), and flushed with nitrogen. The solution was treated with

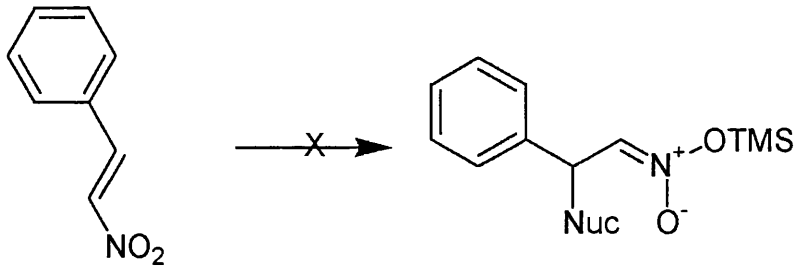
hexamethyldisilazane (80 µl, 0.3 mmol) and chlorotrimethylsilane (15 µl, 0.15 mmol). The reaction was monitored by NMR and shown to have reached 60% conversion of nitrosytrene after 2 hours, with no further dimethyl phosphite observed.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 7.92 (1H, d, $NO_2C\boldsymbol{H}$=CH), 7.60 (1H, d, NO_2CH=C$\boldsymbol{H}$), 7.22-7.50 (5H, m, Ar$\boldsymbol{H}$), 6.53 (1H, dd, P(O)$(OMe)_2C\boldsymbol{H}$CH), 4.40 (1H, dd, P(O)$(OMe)_2$CHC$\boldsymbol{H}$=N(O)OTMS), 3.45 (6H, dd, P(O)$(OC\boldsymbol{H_3})_2$)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 135, 130, 125-128 ($\boldsymbol{C_{aryl}}$), 110 ($\boldsymbol{C}$H=N(O)OTMS), 51 (O$\boldsymbol{C}H_3$), 40 (P(O)$(OMe)_2\boldsymbol{C}$H)

^{31}P NMR ($CDCl_3$, 121 MHz) δ_P/ppm: 129 ($\boldsymbol{P}$OTMS$(OMe)_2$), 25 ($\boldsymbol{P}$(O)$(OMe)_2$)

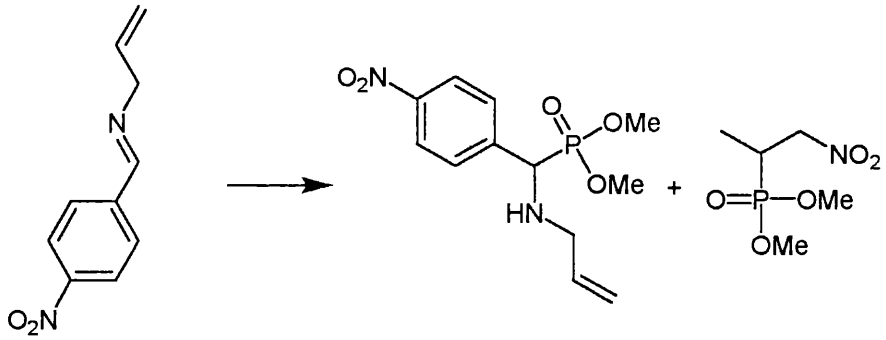
Attempted formation of nitronates using other silylated nucleophiles:



A dry NMR tube was charged with a solution of nitrostyrene (45 mg, 0.3 mmol) in $CDCl_3$ (0.6 ml) and treated with the silylated nucleophile (1 eq.). The reaction was monitored by NMR over a period of 26 hours.

TMS-Nuc reagent	$TMS-N_3$	TMS-CN	Bis-silyl acetamide	Bis-silyl thio-acetamide
Formation of nitronate	None observed	None observed	None observed	None observed

Attempted synthesis of *N*-*p*-nitro benzyl dimethyl phosphonate-6-methyl-3a,4,5,6-tetrahydro-*3H*-pyrrolo[3,4-c] isoxazole



A solution of dimethyl phosphite (92 µl, 1 mmol) in DCM (5 ml) was cooled on an ice bath and treated successively with triethylamine (140 µl, 1.1 mmol) and chlorotrimethylsilane (130 µl, 1.1 mmol). The resulting suspension was stirred for 15 min and *N*-allyl-*p*-nitro-benxaldimine (190 mg, 1 mmol) was added. The reaction was allowed to reach room temperature and stirred for 20 hours. After this time nitropropene (91 mg, 1 mmol) was added and the reaction stirred for a further 24 hours. *p*-Toluene sulphonic acid (0.2 g) was added and the reaction heated to reflux for 30 min. The mixture was washed with

$NaHCO_3$ (aq.) solution (3 x 10 ml) and brine (3 x 10 ml). The organic layer was dried over $MgSO_4$, the solvents removed *in vacuo* and the crude subjected to column chromatography to yield the aminophosphonate and dimethyl-(1-methyl-2-nitro-ethyl) phosphonate in 15% and 5% respectively.

Data for the aminophosphonate.

^{1}H NMR ($CDCl_3$, 300 MHz) δ_H/ppm: 8.25 (2H, d, *J*=8 Hz, Ar***H***), 7.75 (2H, d, *J*=8 Hz, Ar***H***), 6.1-6.7 (1H, br, N***H***), 5.7-5.8 (1H, m, C***H***=CH_2), 5.1-5.15 (1H, m, CH=C***H$_2$***), 4.24 (1H, d, $J_{H\text{-}P}$=20 Hz, C***H***), 3.65 (6H, d, POC***H$_3$***) 3.00-3.12 (2H, m, C***H$_2$***),

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C/ppm: 146 (***C$_{aryl}$***NO_2), 135 (***C***H=CH_2), 125-128 (***C$_{aryl}$***), 114 (CH=***C***H_2), 67 (***C***HP), 61 (CH***C***H_2N), 52 (O***C***H_3)

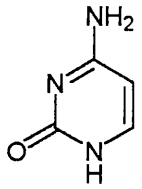
IR (KBr) ν_{max}/cm^{-1}: 3111 (w, Ar-H), 3054 (w, CH=C-H), 1535 (s, C-NO_2), 1344 (s, C-NO_2),

APPENDIX A

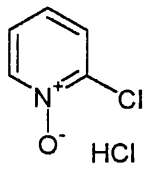
List of reagents used in the reaction library:

Group 1 Trifunctional Reagents:

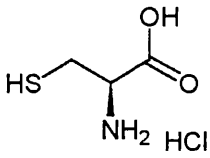
A: Cytosine, 111 mg



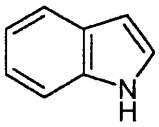
B: 2-Chloropyridin-N-oxide.HCl 129 mg



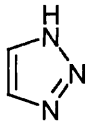
C: L-Cysteine.HCl 157 mg



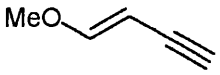
D: Indole 117 mg



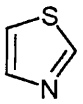
E: Triazole 58 μl



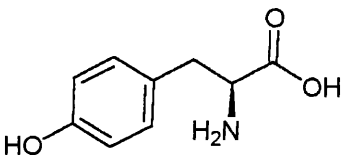
F: 1-Methoxy-but-1-ene-3-yne 82 mg in MeOH



G: Thiazole 85 mg

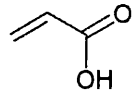


H: 4-Hydroxy phenylglycine 167 mg

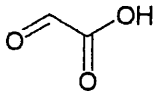


Group 2 Difunctional Reagents:

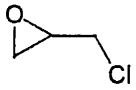
1: Acrylic acid 70μl



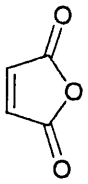
2: Glyoxylic acid 70 mg



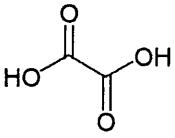
3: Epichlorohydrin 78 μl



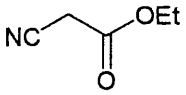
4: Maleic anhydride 54 mg



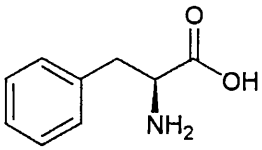
5: Oxalic acid 68 mg



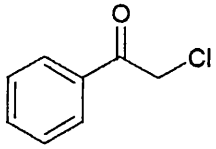
6: Ethylcyano acetate 113 mg



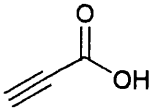
7: L-Phenylalanine 164 mg



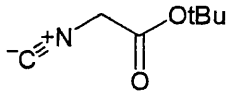
8: Chloroacetophenone 154 mg



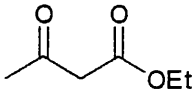
9: Propionic acid 63 μl



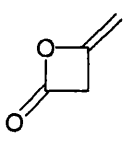
10: tert-Butylisocyanoacetate 150 μl



11: Ethylacetoacetate 127 μl

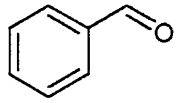


12: Diketene 77 μl in DMF

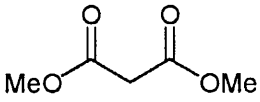


Group 3 Monofunctional Reagents:

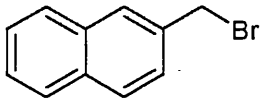
1: Benzaldehyde 101μl



2: Dimethylmalonate 132 mg



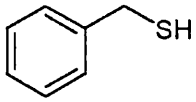
3: 2-Bromonaphthalene 221 mg



4: 3-Hexyne 82 mg

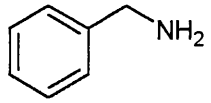
5: trans Hexene 84 mg

6: Benzylmercaptan 124 mg

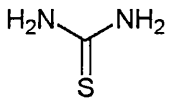


Group 4 *N*-functional Reagents:

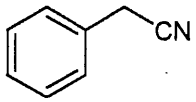
1: Benzylamine 109 µl



2: Thiourea 76 mg



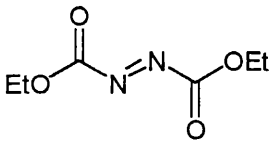
3: Benzylcyanide 117 mg



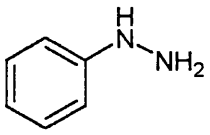
4: Hydroxylamine 33 mg

NH_2OH

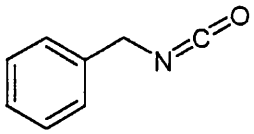
5: Diethylazodicarboxylate 174 mg



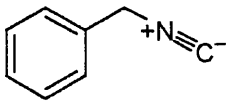
6: Phenylhydrazine 108 mg



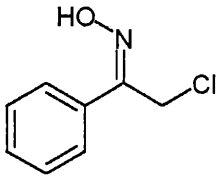
7: Benzylisocyanate 133 mg



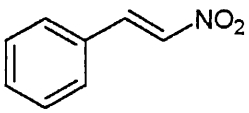
8: Benzylisocyanide 117 mg



9: Chloromethylphenoxime 196 mg

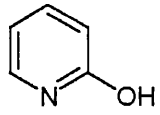


10: Nitrostyrene 149 mg

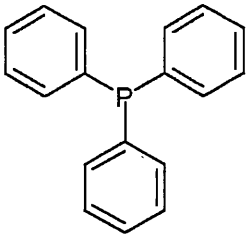


Group 5 Catalysts:

1: 2-Hydroxypyridine 95 mg



2: Triphenylphosphine 262 mg
in ether



REFERENCES

[1] (a) O. Roelen; *Angew. Chem.*; **1948**; *60*; 62

(b) O. Roelen; *Angew. Chem.*; **1948**; *60*; 213

[2] (a) W. Reppe; *Neue Entwicklungen auf dem Gebiet der Chemie des Acetylens und Kohlenmonoxyd*; **1949**; Springer, Berlin

(b) W. A. Hermann, B. Cornis, C. Kohlpaintner; *Nachr. Chem. Technol. Lab.*; **1993**; 41; 544

[3] G. H. Posner, *Chem. Rev.*; **1986**; *86*; 831

[4] L. F. Tietze, U. Beifuss; *Angew. Chem. Int. Ed. Engl.*; **1993**; *32(2)*; 131

[5] T. L. Ho; *Tandem Organic Reactions*; Wiley; **1992**

[6] B. M. Trost; *Angew. Chem. Int. Edn. Engl.*; **1995**; *34*; 259

[7] I. Ugi, C. Steinbrückner; *Chem. Ber.*; **1961**; *94*; 734

[8] I. Ugi; *J. Prakt. Chem.*; **1997**; *339*; 499

[9] (a) A. Strecker; *Ann. Chem. Pharm.*; **1850**; *75*; 27

(b) R. M. Williams, J. A. Hendrix; *Chem Rev.*; **1992**; *92*; 889

[10] J. E. Baldwin, R. C. Whitehead; *Tetrahedron Lett*; **1992**; *33*; 2059

[11] R. Robinson ;*J.Chem. Soc.*; **1917**; 762

[12] C. Schöpf, G. Lehmann; *Liebigs Ann. Chem.*; **1935**; *518*; 1

[13] A. Dömling, I. Ugi; *Angew. Chem. Int. Ed. Engl.*; **2000**; *39*; 3169

[14] A. M. van Leusen, H. Siderius, B. E. Hoogenboom, D. van Leusen; *Tetrahedron Lett.*; **1972**; *13*; 5337

[15] A. M. van Leusen; *Synthesis*; **1991**; 531

[16] R. Schröder, U. Schöllkopf, E. Blume, I. Hoppe; *Ann.*; **1975**; 533

[17] A. M. van Leusen, J. Wildeman, O. H. Oldenziel; *J. Org. Chem.*; **1977**; *42*; 1153

[18] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, H. Yoshioka; *Tetrahedron. Lett.*; **1966**; 6121

[19] T. Saegusa, Y. Ito, S. Kobayashi; *Tetrahedron. Lett.*; **1968**; 935

[20] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota; *Tetetrahedron. Lett*; **1968**; 521

[21] T. Saegusa, S. Kobayashi, K. Hirota, Y. Okumura, Y. Ito; *Bull. Chem. Soc. Jpn*; **1968**; *41*; 1638

[22] J.U. Nef; *Justus Liebigs Ann. Chem.*: **1894**; *280*; 291

[23] W. L. Jorgensen, L. Salem; *The Organic Chemist's Book of Orbitals*; Academic Press; **1973**

[24] K. Tamao, K. Kobayashi, Y. Ito; *J. Am. Chem. Soc.*; **1988**; *110*; 1286

[25] M. Passerini, G. Ragni; *Gazz. Chim. Ital.*; **1931**; *61*; 964

[26] (a) I. Hagedorn, U. Eholzer, H. D. Winkelmann; *Angew. Chem.*; **1964**; *76*; 583

(b) B. Zeeh, E. Müller; *Justus, Liebigs, Ann. Chem.*; **1968**; *715*; 47

[27] M. Murakami, H. Ito, Y. Ito; *Bull. Chem. Soc. Jpn.*; **1996**; *69*; 25

[28] I. Ugi, F. K. Rosendahl; *Chem. Ber.*; **1961**; *94*; 2233

[29] I. K. Ugi; personal communication

[30] H. Gross, J. Gloede, I. Keitel, D. Kunath; *J. Prakt. Chem.*; **1968**; *37*; 192

[31] (a) I. Ugi, R. Obrecht, S. Tourré; *Heterocycles*; **1984**; *21*; 271

(b) I. Ugi; *Angew. Chem. Int. Ed. Engl.*; **1982**; 94; 826

(c) I. Ugi, E. Wischhöfer; *Chem. Ber.*; **1961**; *95*; 136

[32] A. Dömling, I. Ugi; *Angew. Chem. Int. Ed. Engl.*; **2000**; *39*; 3168

[33] I. Hagedorn; *Angew. Chem.*; **1963** ; *75*; 305

[34] I. Ugi. D. Marquarding, R. Urban; *Chemistry and Biology of Amino Acids, Peptides and Proteins*; Ed.: B. Weinstein; Marcel Dekker; **1982**

[35] I. Ugi, G. Kaufhold; *Liebigs Ann. Chem.*; **1967**; *407*; 11

[36] (a) I. Ugi, C. Steinbrückner; *Chem. Ber.*; **1961**; *94*; 734

(b) I. Ugi, *Isonitrile Chemistry*; Ed. I. Ugi, Academic Press; **1971**, p. 149

[37] I. Ugi, C. Steinbrückner; Patent: *Deutsche Offenlegungschrift* DE-B 1,103,337; **1959**

[38] J. Pitlik, C. A. Townsend; *Bioorg. Med. Chem. Letts.*; **1997**; *7(31)*; 3129

[39] (a) C. D. Floyd, M. Whittaker; Patent WO9626918; **1996**

(b) C. D. Floyd, C. N. Lewis, Patent WO9626223; **1996**

[40] (a) H. T. Bucherer; W. Steiner; *J. Prakt. Chem.*; **1934**; *140*; 291

(b) H. Bergs, *Chem. Abs.*; **1933**; *27*; 1001

(c) H. Bergs, Patent: *Deutsches Reichspatent* 566094; **1929**

[41] (a) K. Groebke, L. Weber, F. Mehlin; *Synlett*; **1998**; 661

(b) C. Blackburn, B. Guan, K. Shiosaki, S. Tsai; *Tetrahedron. Lett.*; **1998**; *39*; 3635

(c) H. Bienaymé, K. Bouzid; *Angew. Chem. Int. Ed. Engl.*; **1998**; *39*; 2234

[42] O. Lack, L. Weber; *Chimia*; **1996**; *50*; 445

[43] H. Hellman, G. Opitz; *α-Amino Alkylierung*; Verlag Chemie GmbH; Weinheim; **1960**

[44] R. V. Stevens, A. W. M. Lee; *J. Am. Chem. Soc.*; **1979**; *101*; 7032

[45] (a) P. Biginelli; *Gazz. Chim. Ital.*; **1893**; *23*; 360

(b) C. O. Kappe; *Tetrahedron*; **1993**; *49*; 6937

[46] T. Godfraind, R. Miller, M. Wibo; *Pharmacol. Rev.*; **1986**; *38*; 321

[47] E. H. Hu, D. R. Sidler, U.-H. Dolling; *J. Org. Chem.*; **1998**; *63*; 3454

[48] B. C. O'Reilly, K. S. Atwal; *Heterocycles*; **1987**; *26*; 1185

[49] A. Hantzsch; *Ber. Dtsch. Chem. Ges.*; **1890**; *23*; 1474

[50] U. Eisner; *Chem. Rev.*; **1972**; *72*; 1

[51] R. A. Jones (Ed.); *Pyrroles – The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring – Part I; Heterocyclic Compounds*; **1990**; *48*; 135

[52] Y. Satoh, M. Ichihashi, K. Okumura; *Chem. Pharm. Bull.*; **1992**; *40*; 912

[53] T. L. Ho; *Tandem Organic Reactions*; John Wiley and Sons Inc.; **1992**

[54] L. F. Tietze, T. Hippe, A. Steinmetz; *Synlett*; **1996**; 1043

[55] (a) L. F. Tietze, A. Steinmetz; *Angew. Chem. Int. Ed. Engl.*; **1996**; *108*; 682

(b) L. F. Tietze, A. Steinmetz; *Synlett*; **1996**; 667

[56] W. S. Johnson, T. K. Schaaf, *J.Chem.Soc., Chem. Commun*, **1969**, 611

[57] R. Grigg, R. Rasal, V. Savic; *Tetrahedron Lett.*; **1997**; *38*; 1825

[58] (a) O. Tsuge, S. Kanemasa, S. Takenaka; *Bull. Chem. Soc. Jpn.*; **1986**; *59*; 3631

(b) A. J. Bicknell, N. W. Hird, S. A. Readshaw; *Tetrahedron Lett.*; **1998**; *39*; 5869

[59] D. Fokas, W. J. Ryan, D. S. Casebier, D. L. Coffen; *Tetrahedron Lett.*; **1998**; *39*; 2235

[60] (a) P. Grieco, A. Bahas; *Tetrahedron Lett.*; **1988**; *29*; 5855

(b) A. S. Kislyov, L. Smith II, R. W. Armstrong; *Tetrahedron*; **1998**; *54*; 5089

[61] (a) K. Rossen, J. Sager, L. DiMichele; *Tetrahedron Lett.*; **1997**; *38*; 3183

(b) I. Ugi, W. Hörl, C. Hanusch-Compa, T. Schmid, E. Herdtweck; *Heterocycles*; **1998**; *47*; 965

[62] T. A. Keating, R. W. Armstrong; *J. Am. Chem. Soc.*; **1996**; *118*; 2574

[63] I. Ugi, A. Dömling, W. Hörl; *Endeavour*; **1994**; *18*; 115

[64] A. Dömling, I. Ugi; *Angew, Chem. Int. Ed. Engl.*; **1993**; *32*; 563

[65] Dr A. Dömling, Morphochem, Munich, *personal communication*

[66] I. Ugi, S. Lohberger, R. Karl; in *Comprehensive Organic Synthesis – Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Eds.: B. M. Trost, I. Fleming; Volume 2, Part 2; page 1083; Pergamon Press; **1991**

[67] I. Fleming; *Frontier Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons; **1976**

[68] R. A. Firestone; *J. Org. Chem.*; **1968**; *33*; 2285

[69] B. Kast, M. Christl, R. Huisgen, W. Mack; *Chem. Ber.*; **1973**; *106*; 3312

[70] R. Huisgen; *J. Org. Chem.*; **1968**; *33*; 2291

[71] K. N. Houk, R. A. Firestone, L. l. Munchausen, P. H. Mueller, B. H. Arison, L. A. Garcia; *J. Am. Chem. Soc.*; **1985**; *107*; 7227

[72] (a) R. B. Woodward, R. Hoffmann; *Angew. Chem.*; **1969**; *81*; 797

(b) K. Fukui; *Acc. Chem. Res.*; **1971**; *57*; 4

[73] (a) R. Sustmann; *Tetrahedron. Lett.*; **1971**; 2717

(b) R. Sustmann, H. Trill; *Angew. Chem. Int. Ed. Engl.*; **1972**; *11*; 838

[74] E. W. Colvin, D. Seebach; *J. Chem. Soc., Chem. Commun.*; **1978**; 689

[75] I. S. Levina, E. I. Mortikova, A. V. Kamernitzky; *Synthesis*; **1974**; 562

[76] (a) S. E. Denmark, J. A. Dixon; *J. Org. Chem.*; **1997**; *62*; 7086

(b) S. E. Denmark, L. R. Marcin; *J. Org. Chem.*; **1997**; *62*; 1675

[77] J. Sauer, R. Sustmann; *Angew. Chem. Int. Edn. Engl.*; **1980**; *19*; 779

[78] (a) K. E. Larsen, K. B. Torssell; *Tetrahedron*; **1984**; *40*; 2985

(b) S. H. Anderson, K. K. Sharma, K. B. G. Torssell; *Tetrahedron*; **1983**; *39*; 2241

[79] E. W, Colvin, A. K. Beck, D. Seebach; *Helv. Chim. Acta.*; **1981**; *64*; 2264

[80] A. Quilico, G. Stagno d'Alcontres, P. Grünanger; *Nature*; **1950**;*166*; 226

[81] S. Gabriel, M. Koppe; *Ber.*; **1886**; *19*; 1145

[82] T. Wieland, F. Turba; in *Houben-Weyl – Methoden der Organischen Chemie*; (Ed.: E. Müller); **1953**; Vol 2 *Analytische Methoden*; 876

[83] K. B. G. Torssell; *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH, **1988**

[84] M. T. Reetz; *Angew. Chem. Int. Ed. Engl.*; **2001**; *40*; 284

[85] L. Weber, K. Illgen, M. Almstetter; *Synlett*, **1999**, *3*, 366

[86] H. Ishitani, S. Komiyama, Y. Hasegawa, S. Kobayashi; *J. Am. Chem. Soc.*; **2000**; *122*, 762

[87] M. Broy; *Informatik – Teil IV. Theoretische Informatik, Algorithmen und Datenstrukturen, Logikprogrammierung, Objektorientierung*; Springer Verlag; **1991**

[88] M. Deweß; in *Teubner Taschenbuch der Mathmatik Teil II*; Eds.: G. Grosche, V. Ziegler, D. Ziegler, E. Zeidler; *B. G. Teubner – Stuttgart, Leipzig*; **1995**, 217

[89] D. E. Goldberg, *Genetic Algorithms in Search, Optimization and Machine Learning*, Addison-Wesely Inc, **1989**

[90] L. Weber, S. Wallbaum, C. Broger, K. Grubernator; *Angew. Chem. Int. Ed. Engl.*; **1996**; *34*; 2280

[91] (a) I. Ugi, *Proc. Estonian Acad. Sci. Chem.*; **1995**; *44*; 237

(b) P. A. Tempest, S. D. Brown, R. W. Armstrong; *Angew. Chem. Int. Ed. Engl.*; **1996**; *35*; 640

(c) S. Kobayshi,, S. Komiyama, H. Ishitani; *Biotech. & Bioeng. (Combinatorial Chemistry);* **1998**; *61*; 23

(d) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop; *J. Med. Chem.*; **1994**; *37*; 1233

(e) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop; *J. Med. Chem.*; **1994**; *37*; 1385

[92] P. Göthner; in *Teubner Taschenbuch der Mathmatik*; Eds.: G. Grosche,

V. Ziegler, D. Ziegler, E. Zeidler; *B. G. Teubner – Stuttgart, Leipzig*; **1991**, 111

[93] A. R. Katritzky, J. S. Kiely, N. Hébert, C. Chassaing; *J. Comb. Chem.*; **2000**; *2*; 2

[94] C. E. Griffin, R. N. Hazeldine, *J. Chem. Soc.*; **1960**; 1398

[95] A. G. M. Barret, G. G. Grabosky; *Chem. Rev.*; **1986**; *86*; 751

[96] J. McNulty, R. Mo; *J. Chem. Soc. Chem. Commun.*; **1998**; 933

[97] H. Korten, R. Scholl; *Chem. Ber.*; **1901**; 1901

[98] D. H. R. Barton, W. B. Motherwell, S. Z. Zard; *Bull. Soc. Chem. Fr.*; **1983**; 61

[99] D. E. Worral; *Org. Synth.*; Vol 1 (2nd edn.); 413

[100] (a) C. D. Floyd, C. N. Lewis, M. Whittaker; *Chem. Brit.*; **1996**; 31

(b) A. W. Czarnik, S. Hobbs DeWitt; *Chem. Brit.*; **1996**; 43

(c) Dr M. Whittaker, British Biotech, Oxford, *personal communication*

(d) Dr A. Dömling, Morphochem, Munich, *personal communication*

[101] S. Hobbs DeWitt, J. S. Kiely, C. J. Stankocic, M.C. Schroeder, D. M. Cody, M. R. Pavia; *Proc. Nat. Acad. Sci. USA*; **1993**; *90*; 6909

[102] (a) M. Passerini; *Gazz. Chim. Ital.*; **1921**; *51*; 126

(b) M. Passerini; *Gazz. Chim. Ital.*; **1921**; *51*; 181

(c) M. Passerini; *Gazz. Chim. Ital.*; **1926**; *56*; 826

(d) M. Passerini, G. Ragni; *Gazz. Chim. Ital.*; **1931**; *61*; 964

[103] P. Biginelli; *Gazz. Chim. Ital.*; **1893**; *23*; 360

[104] (a) P. Grieco, A. Bahas; *Tetrahedron. Lett.*; **1988**; *29*; 5855

(b) A. S. Kislyov, L. Smith II, R. W. Armstrong; *Tetrahedron*; **1998**; *54*; 5089

[105] (a) S. Caddick; *Tetrahedron*; **1995**; *51*; 10403

(b) S. Deshayes, M. Liagre, A. Loupy, J.-L. Luche, A. Petit;

Tetrahedron; **1999**; *55*; 10851

[106] R. J. Giguere, T. L. Bray, S. M. Duncan; *Tetrahedron Lett.*; **1986**; *26*; 4945

[107] F. B. Dains, E. L. Griffith; *J. Am. Chem. Soc.*; **1913**; *35*; 962

[108] D. Villemin, B. Martin, B. Garriges; *Synth. Commun.*; **1993**; *23(16)*; 2251

[109] T. Saegusa, S. Kobayashi, Y. Ito, I. Marino; *Tetrahedron*; **1972**; *28*; 3389

[110] A. Foucaud, C. Razolrilanarabearivony, E. Loukakou, H. Person; *J.Org.Chem.*; **1983**; *48*; 3639

[111] P. D. Magnus, M. S. Knobbs; *Synth. Commun.*; **1980**; *10(4)*; 273

[112] (a) J. Knight, P. J. Parsons; *J. Chem. Soc., Chem. Commun.*; **1987**, 189

(b) J. Knight, P. J. Parsons; *J. Chem. Soc., Perkin Trans. II.*; **1989**, 979

[113] (a) P. Grünager, P. Vita-Finzi; *Isoxazoles – Part I*; in: *The Chemistry of Heterocyclic Compounds*; Ed.: E. C. Taylor, A. Weissberger; *Vol. 49*; p. 491

(b) B. Kast, M. Christl, R. Huisgen, W. Mack; *Chem. Ber.*; **1973**; *106*; 3312

[114] N. Levy, C. W. Scaife; *J. Am. Chem. Soc.*; **1946**; *68*; 1093

[115] G. Kaplan, H. Schechter, *Inorg. Synth.*; **1952**; *4*; 52

[116] M. Waki, J. Meienhofer; *J. Am. Chem. Soc.*; **1977**; *99*; 6075

[117] R. W. Hoffmann, K. Steinbach, W. Lilienblum; *Chem. Ber.*; **1976**; *109*; 1759

[118] G. Morel, E. Marchand, A. Foucaud; *J. Org. Chem.*; **1989**; *54*; 1185

[119] V. Atlan, C. Buron, L. El. Kaim; *Synlett*; **2000**; *4*; 489

[120] J. A. Deyrup, K. K. Killion; *J. Heterocycl. Chem.*; **1972**; *9*; 1045

[121] Y. Ito, H. Kato, T. Saegusa; *J. Org. Chem.*; **1982**; *47*; 741

[122] C. Buron, L. El Kaim, A. Uslu; *Tetrahedron Lett.*; **1997**; 8027

[123] Y. Ito, H. Kato, H. Imai, T. Saegusa; *J. Am. Chem. Soc.*; **1982**; *104*; 6449

[124] Y. Ito, H. Kato, T. Saegusa; *J. Org. Chem.*; **1982**; *47*; 741

[125] R. Neidlein, *Chem. Ber.*; **1964**; *97*; 3476

[126] J. H. Rigby, M. Qabar, G. Ahmed, R. C. Hughes; *Tetrahedron*; **1993**; *49(45)*; 10219

[127] A. K. Chandra, P. Geerlings, M. T. Nguyen; *J. Org. Chem.*; **1997**; *62*; 6417

[128] C. Buron, L. El Kaim, A. Uslu; *Tetrahedron. Lett*; **1997**; *38*; 8027

[129] V. Atlan, C. Buron, L. El Kaim; *Synlett*; **2000**; *4*; 489

[130] P. A. Grieco, J. J. Nunes, M. D. Gaul; *J. Am. Chem. Soc.*; **1990**; *112*; 4594

[131] S. D. Larsen, P. A. Grieco; *J. Am. Chem. Soc.*; **1985**; *107*; 1768

[132] S. L. Ioffe, M. V. Kashutina, V. M. Shitkin, A. Z. Yankelevich, A. A. Levin, A. A. Tartakovskii; *Izv. Akad. Nauk. SSSR*; **1972**; 1341

[133] E. W, Colvin, A. K. Beck, D. Seebach; *Helv. Chim. Acta.*; **1981**; *64*; 2264

[134] A. Hassner, W. Dahaen; *J. Org. Chem.*; **1990**; *55(20)*; 5505

[135] A. Hassner, R. Maurya, E. Meske; *Tetrahedron. Lett.*; **1988**; *29(41)*; 5313

[136] K. Afarinkia, C. W. Rees, J. I. G. Cadogan; *Tetrahedron*; **1990**; *46*; 7175

[137] B. Ranu, A. Hajra, U. Jana; *Org. Lett.;* **1999**; *1*; 1141

[138] A. E. Williamson; *J. Prakt. Chem.*; **1854**; *61*; 60

[139] U. Schmidt, P. Gleich; *Angew. Chem. Int. Ed. Engl.*; **1985**; *24*; 569

[140] D. Lucet, S. Saballe, O. Kostelitz, T. Le Gall, C. Mioskowski; *Eur. J. Org. Chem.*; **1999**; 2583

[141] (a) D. Seebach, B. Weidmann, L. Wilder; *Modern Synthetic Methods*; Ed.: R. Scheffold; New York; **1983**

(b) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakshima, J. Sugimori; *J. Am. Chem. Soc.*; **1989**; *111*; 5340

[142] (a) S. Kanesama, T. Tsurukora; *Chem. Lett.*, **1995**; 49

(b) S. Kanesama, M. Nishiuchi, A. Kamimura, K. Hori; *J. Amer. Chem. Soc.*; **1994**; *116*; 2324

[143] K. Hori, H. Kodama, T. Ohta, I. Furukawa; *Tetrahedron Lett.*; **1996**; *37*; 5947

[144] E. Müller, R. Beutler, B. Zeeh; *Liebigs Ann.*; **1968**; *72*; 719

[145] A. R. Katritzky, Z. Luo, Y. Fang, P. J. Steel; *J. Org. Chem.*; **2001**; *66*; 2858

[146] T. Wieland, F. Turba; in *Houben-Weyl – Methoden der Organischen Chemie*; (Ed.: E. Müller); **1953**; Vol 2 *Analytische Methoden*; 876

[147] F.B Dains, E. L. Griffith; *J. Am. Chem. Soc.*; **1913**; *35*; 962

[148] D. H. R. Barton, W. B. Motherwell, S. Z. Zard; *Bull. Soc. Chem. Fr.*; **1983**; 61

[149] D. E. Worral; *Org. Synth.*; Vol 1 (2nd edn.); 413

[150] S. E. Denamrk, B. S. Keseler, Y.-C. Moon; *J. Org. Chem.*; **1992**; *57(18)*; 2912

[151] E. Knoevenagel, L. Walter; *Chem. Ber.*; **1904**; *37*; 4505

[152] R. Menicagli, S. Samaritani; *Tetrahedron*; **1996**; *52*; 1425

[153] P. Pfeiffer; *Chem. Ber.*; **1914**; *47*; 1762

[154] M. Faulques, L. Rene, R. Royer; *Synthesis*; **1982**; 260

[155] I. Muramatsu, M. Murakami, T. Yoneda. A. Hagitani; *Bull. Chem. Soc. Jpn.*; **1965**; *38(2)*; 244

[156] R. Appel, R. Kleistück, K. D. Ziehn; *Angew. Chem. Int. Ed. Engl.*; **1971**; *10*; 132

[157] U. Schöllkopf, R. Jentsch, K. Madawinata, R. Harms; *Liebigs Ann. Chem.*; **1976**; 2105

[158] U. Schöllkopf, R. Jentsch, K. Madawinata, R. Harms; *Liebigs Ann. Chem.*; **1976**; 2105

[159] (a) M.T. Reetz, 'Titanium in Organic Synthesis', in *Organometallics in Synthesis – A Manual*, Ed.: M. Schlosser, p.258, John Wiley & Sons, **1994**

(b) M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek, S. Maus; *Chem. Ber.*, **1985**, *118*, 1421

[160] W. E. Krueger; *J. Org. Chem.*; **1978**; *43*; 2877

[161] K. Sasse, *Phosphorverbindungern II*; Houben-Weyl, Volume 12 part II, p. 23

[162] M. Yamashita, M. Sugiura, T. Oshikawa, S. Inokawa; *Synthesis*; **1987**; *1*; 62

[163] I. Ugi, W. Betz; *Chem. Ber.*; **1964**; *97*; 3008