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The synthesis of substituted pyridines via aza-diels-alder reactions, using novel aza-dienes

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The Synthesis of Substituted Pyridines *via* Aza-Diels-Alder Reactions, using Novel Aza-Dienes.

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2.0 Abstract

Substituted pyridines are important as natural products and components of natural products and as unnatural compounds, yet their synthesis is still a challenge as there are very few general methods available. The aza-Diels-Alder method provides rapid access to highly substituted pyridines.

This research project studies the synthesis of substituted pyridines *via* aza-Diels-Alder reactions of novel aza-dienes and dienophiles. The synthesis of novel aza-dienes involved the investigation of oxime, enamine and hydrazone synthesis. Oximes were studied using ethyl acetoacetate as the starting material; this was reacted to give ethyl oximino acetoacetate. The OH group of the oxime was then reacted with trimethylsilyl chloride, ^{t}butyldimethylsilyl chloride and dimethyl sulphate to give the corresponding oxime ethers, these oximes were further reacted with pyrrolidine in an attempt to make the corresponding enamine/aza-diene, these reactions were unsuccessful and the oximes would undergo a Beckmann rearrangement.

Hydrazones were synthesised from 2,3-butanedione and *N*,*N*-dimethylhydrazine, the hydrazone was then reacted with pyrrolidine in an attempt to form an aza-diene, the reaction was repeated under various conditions but the desired product was never formed and starting materials were recovered. Various reactions were done in an attempt to react the carbonyl functional group present in the hydrazone, these reactions were also unsuccessful. The bis-hydrazone could however be formed from 2,3-butanedione but not from the mono-hydrazone.

Ethyl oximino acetoacetate was then reacted with excess trimethylsilyl chloride to form an aza-diene. This aza-diene was heated under reflux with dimethylacetylene dicarboxylate in toluene for 3 weeks to form a highly substituted pyridine, the aza-diene was then reacted with various other dienophiles but no products were isolated after 6 weeks of heating under reflux. Some of the reactions were repeated by heating in a sealed tube but these were also unsuccessful. The reaction with the aza-diene and dimethylacetylene dicarboxylate was repeated using microwave irradiation this also formed the substituted pyridine and reduced the reaction time from 3 weeks to ½ hour.

3.0 Abbreviations

The following abbreviations are used in the text:

^{t}BMP	2,6-Di-*tert*-butyl-4-methyl pyridine
Boc	*tert*-Butoxycarbonyl
CAN	Ceric ammonium nitrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DCU	*N*,*N*-Dichlorourethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarization transfer
DHP	3,4-Dihydro-2*H*-pyran
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	Methyl sulfoxide
EDG	Electron-donating group
EWG	Electron-withdrawing group
eq	Equivalents
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
IR	Infrared
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
ON	Overnight
PDC	Pyridinium dichromate
PPTS	Pyridinium *p*-toluenesulfonate
rt	Room temperature

SMP	(*S*)-(+)-2-(Methoxymethyl)pyrrolidine
TBDMS	^{t}Butyldimethylsilyl
TBDMSCl	^{t}Butyldimethylsilyl chloride
TEA	Triethanolamine
TES	Triethylsilyl
TESCl	Triethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TPA	Triethyl phosphonoacetate
Triflic	Trifluoromethanesulfonic

4.0 Contents

5.0 Introduction 1

5.1 Introduction to Pyridines and Aza-Diels-Alder Reactions 2

5.2 How Substituted Pyridines are Synthesised *via* Aza-Diels-Alder Reactions 7

5.2.1 1-Aza-Dienes 7

5.2.1.1 Summary 32

5.2.2 2-Aza-Dienes 32

5.2.2.1 Summary 36

5.2.3 Alternative Aza-Diels-Alder Reactions 36

5.2.3.1 Summary 43

5.3 General Summary 44

5.4 Synthesis of Aza-Dienes 44

5.4.1 Oximes 44

5.4.1.1 Summary 48

5.4.2 Hydrazones 48

5.4.2.1 Summary 50

5.4.3 Enamines 51

5.4.3.1 Summary 60

5.5 General Summary 60

5.6 Research Proposal 61

6.0 Results and Discussion 63

6.1 Ethyl Oximino Acetoacetate 63

6.2 Enamine of Ethyl Oximino Acetoacetate 64

6.3 Trimethylsilylation of Ethyl Oximino Acetoacetate 66

6.4 Enamine of Silylated Ethyl Oximino Acetoacetate 69

6.5 *t*-Butyldimethylsilylation of Ethyl Oximino Acetoacetate 70

6.6 Methylation of Ethyl Oximino Acetoacetate 72

6.7 Enamine of Ethyl Methoxyimino Acetoacetate 74

6.8 Enamine of Ethyl Methoxyimino Acetoacetate: Alternative Method 75

6.9 Pyrrolidine-1-Carboxylic Acid Ethyl Ester 80

6.10 3-Pyrrolidinyl-3-Buten-2-One: Attempt 1 84

6.11 3-Pyrrolidinyl-3-Buten-2-One: Attempt 2 85
6.12 3-Pyrrolidinyl-3-Buten-2-One: Attempt 3 86
6.13 2,3-Butanedione Mono-dimethylhydrazone 89
6.14 3-Pyrrolidinyl-3-Buten-2-One Mono-dimethylhydrazone: Attempt 1 90
6.15 3-Pyrrolidinyl-3-Buten-2-One Mono-dimethylhydrazone: Attempt 2 93
6.16 *N*-(Cyclohexen-1-yl) Pyrrolidine 95
6.17 3-Pyrrolidinyl-3-Buten-2-One Mono-dimethylhydrazone: Attempt 3 96
6.18 *N*-Ethoxycarbonylproline Methyl Ester 96
6.19 Reduction of *N*-Ethoxycarbonylproline Methyl Ester 97
6.20 Methylation of the Reduced *L*-Prolinol Derivative 98
6.21 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triethyl Phosphonoacetate 101
6.22 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Benzylamine 101
6.23 Bis-Hydrazone 102
6.24 Reaction of 2,3-Butanedione with Phenylhydrazine 103
6.25 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Methyl Magnesium Chloride 105
6.26 Methylation of 2,3-Butanedione Mono-dimethylhydrazone 106
6.27 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Hydroxylamine Hydrochloride 107
6.28 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triflic Anhydride 108
6.29 Exhaustive Trimethylsilylation of Ethyl Oximino Acetoacetate 110
6.30 Exhaustive Trimethylsilylation of 2,3-Butanedione Monoxime 112
6.31 ^{t}Butyl Oximino Acetoacetate 113
6.32 Exhaustive Trimethylsilylation of ^{t}Butyl Oximino Acetoacetate 114
6.33 Synthesis of a Highly Substituted Pyridine **234** 115
6.34 Attempted Synthesis of a Highly Substituted Pyridine **235** 118
6.35 Attempted Synthesis of a Highly Substituted Pyridine **240** 119
6.36 Attempted Synthesis of a Highly Substituted Pyridine **241** 121
6.37 Attempted Synthesis of a Highly Substituted Pyridine **242** 122
6.38 Attempted Synthesis of a Highly Substituted Pyridine **243** 122
6.39 Attempted Synthesis of a Highly Substituted Pyridine **244** 123

6.40 Attempted Synthesis of a Highly Substituted Pyridine **245** 124
6.41 Attempted Synthesis of a Highly Substituted Pyridine **246** 125
6.42 Attempted Synthesis of a Highly Substituted Pyridine **247** 126
6.43 Attempted Synthesis of a Highly Substituted Pyridine **248** 127
6.44 Attempted Synthesis of a Highly Substituted Pyridine **257** 127
6.45 Attempted Synthesis of a Highly Substituted Pyridine **258** 130
6.46 Attempted Synthesis of a Highly Substituted Pyridine **264** 132
6.47 Attempted Synthesis of a Highly Substituted Pyridine **271** 135
6.48 Attempted Synthesis of a Highly Substituted Pyridine **272** 138
6.49 Attempted Synthesis of a Highly Substituted Pyridine **273** 139
6.50 Attempted Synthesis of a Highly Substituted Pyridine **277** 139
6.51 Attempted Synthesis of a Highly Substituted Pyridine **288** 142
6.52 Attempted Synthesis of a Highly Substituted Pyridine **298** 145
6.53 Attempted Synthesis of a Highly Substituted Pyridine **299** 147
6.54 Attempted Synthesis of a Highly Substituted Pyridine **303** 148
6.55 Attempted Synthesis of a Highly Substituted Pyridine **303** 150
6.56 Control Study of 1-Aza-Diene Decomposition / Dimerisation 151
6.57 Synthesis of a Highly Substituted Pyridine *via* Microwave Synthesis 151

7.0 Conclusion 154

8.0 Further Work 156

9.0 Experimental Procedures 157
9.1 General Procedures 157
9.2 Preparation of Ethyl Oximino Acetoacetate 159
9.3 Attempted Preparation of the Enamine of Ethyl Oximino Acetoacetate 160
9.4 Trimethylsilylation of Ethyl Oximino Acetoacetate 161
9.5 Attempted Preparation of Enamine of Silylated Ethyl Oximino Acetoacetate 162
9.6 ^{t}Butyldimethylsilylation of Ethyl Oximino Acetoacetate 163
9.7 Methylation of Ethyl Oximino Acetoacetate 164
9.8 Attempted Enamine of Ethyl Methoxyimino Acetoacetate 164

9.9 Attempted Enamine of Ethyl Methoxyimino Acetoacetate: Alternative Method 165
9.10 Preparation of Pyrrolidine-1-Carboxylic Acid Ethyl Ester 166
9.11 Preparation of 3-Pyrrolidinyl-3-Buten-2-One: Attempt 1 167
9.12 Preparation of 3-Pyrrolidinyl-3-Buten-2-One: Attempt 2 167
9.13 Preparation of 3-Pyrrolidinyl-3-Buten-2-One: Attempt 3 168
9.14 Preparation of 2,3-Butanedione Mono-dimethylhydrazone 169
9.15 3-Pyrrolidinyl-3-Butene-2-One Mono-dimethylhydrazone: Attempt 1 169
9.16 3-Pyrrolidinyl-3-Butene-2-One Mono-dimethylhydrazone: Attempt 2 170
9.17 Preparation of *N*-(Cyclohexen-1-yl) Pyrrolidine 171
9.18 3-Pyrrolidinyl-3-Butene-2-One Mono-dimethylhydrazone: Attempt 3 172
9.19 Preparation of an *N*-Ethyloxycarbonylproline Methyl Ester 172
9.20 Reduction of the *N*-Ethyloxycarbonylproline Methyl Ester 173
9.21 Methylation of the *L*-Prolinol Derivative 174
9.22 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triethyl Phosphonoacetate 175
9.23 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Benzylamine 176
9.24 Preparation of the Bis-Hydrazone 176
9.25 Reaction of 2,3-Butanedione with Phenylhydrazine 177
9.26 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Methyl Magnesium Chloride 178
9.27 Methylation of 2,3-Butanedione Mono-dimethylhydrazone 178
9.28 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Hydroxylamine Hydrochloride 179
9.29 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triflic Anhydride 180
9.30 Exhaustive Trimethylsilylation of Ethyl Oximino Acetoacetate 181
9.31 Exhaustive Trimethylsilylation of 2,3-Butanedione Monoxime 181
9.32 Preparation of ^{t}Butyl Oximino Acetoacetate 182
9.33 Exhaustive Trimethylsilylation of ^{t}Butyl Oximino Acetoacetate 183
9.34 Synthesis of Highly Substituted Pyridine **234** 184
9.35 Attempted Synthesis of Highly Substituted Pyridine **235** 184

9.36 Attempted Synthesis of Highly Substituted Pyridine **240** 185
9.37 Attempted Synthesis of Highly Substituted Pyridine **241** 186
9.38 Attempted Synthesis of Highly Substituted Pyridine **242** 186
9.39 Attempted Synthesis of Highly Substituted Pyridine **243** 187
9.40 Attempted Synthesis of Highly Substituted Pyridine **244** 188
9.41 Attempted Synthesis of Highly Substituted Pyridine **245** 188
9.42 Attempted Synthesis of Highly Substituted Pyridine **246** 189
9.43 Attempted Synthesis of Highly Substituted Pyridine **247** 190
9.44 Attempted Synthesis of Highly Substituted Pyridine **248** 190
9.45 Attempted Synthesis of Highly Substituted Pyridine **257** 191
9.46 Attempted Synthesis of Highly Substituted Pyridine **258** 192
9.47 Attempted Synthesis of Highly Substituted Pyridine **264** 192
9.48 Attempted Synthesis of Highly Substituted Pyridine **271** 193
9.49 Attempted Synthesis of Highly Substituted Pyridine **272** 194
9.50 Attempted Synthesis of Highly Substituted Pyridine **273** 194
9.51 Attempted Synthesis of Highly Substituted Pyridine **277** 195
9.52 Attempted Synthesis of Highly Substituted Pyridine **288** 196
9.53 Attempted Synthesis of Highly Substituted Pyridine **298** 196
9.54 Attempted Synthesis of Highly Substituted Pyridine **299** 197
9.55 Attempted Synthesis of Highly Substituted Pyridine **303** 198
9.56 Attempted Synthesis of Highly Substituted Pyridine **303** 198
9.57 Control Study of 1-Aza-Diene Decomposition / Dimerisation 199
9.58 Synthesis of Highly Substituted Pyridine *via* Microwave Synthesis 200

10.0 References 201

5.0 Introduction

This research project investigated the aza-Diels-Alder reactions of aza-dienes with alkynes to form substituted pyridines. The synthesis of substituted pyridines is a significant challenge, as there are few general methods available[1-27]. Substituted pyridines are present in natural products, with a wide variety of interesting properties, *e.g.* the complex examples shown in Figure 1a and Figure 1b. Due to substituted pyridines being present in small quantities in nature a rapid, efficient and general synthesis is needed that provides easy access to them in sufficient quantities to allow further studies.

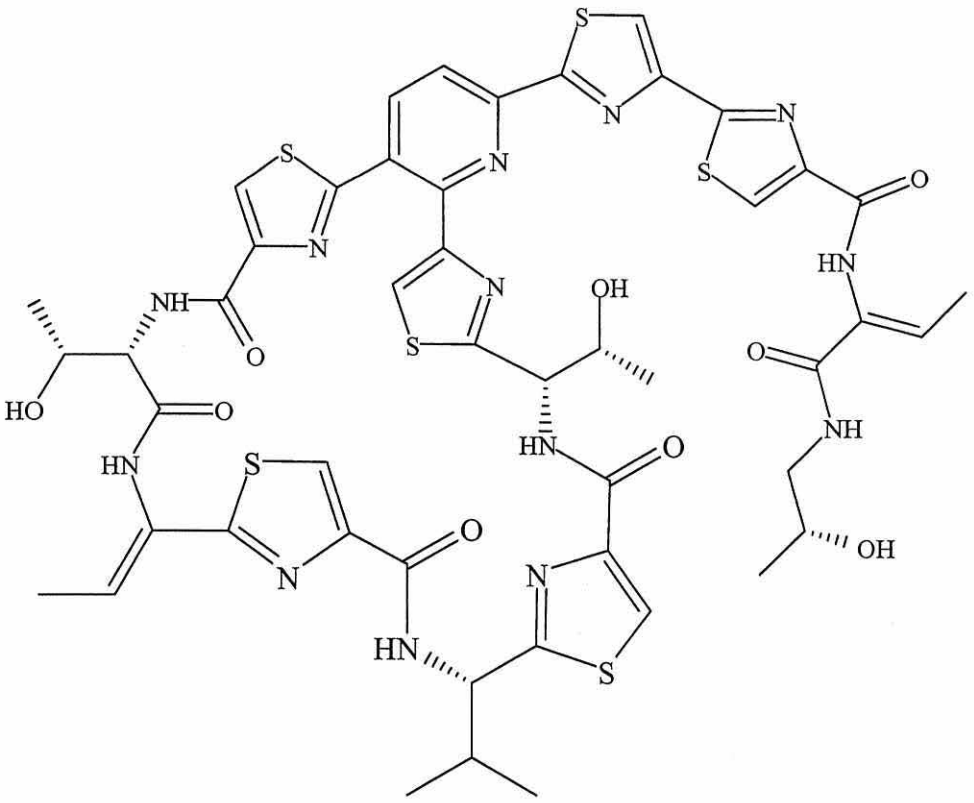


Figure 1a. Micrococcin P_1, a macrocyclic antibiotic natural product [27, 28]

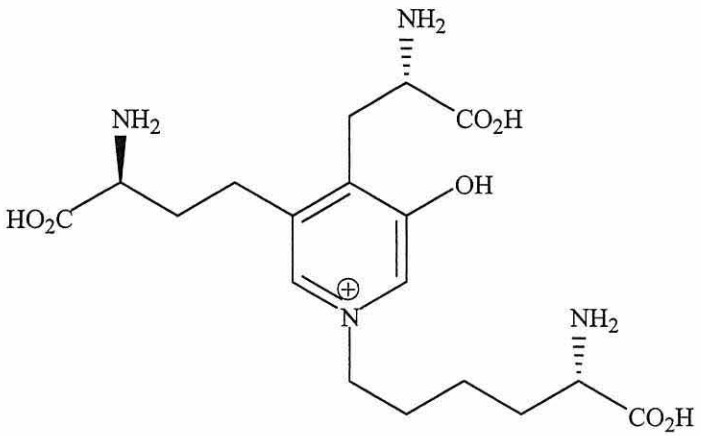


Figure 1b. (+)-Deoxypyridinoline, a biochemical marker used in th diagnosis of osteoporosis [29]

5.1 Introduction to Pyridines and Aza-Diels-Alder Reactions

Highly substituted pyridines are found as a backbone structure in many natural and unnatural compounds that are useful not only in the pharmaceutical industry[30-35] but also as antioxidants, corrosion inhibitors, dyes and agricultural chemicals[33-39]. A large range of biological activities are exhibited by various different pyridines, including, for example, interactions with DNA and peptides.

Pyridines are a type of heterocyclic base. The nitrogen atom in pyridine has a non-bonded pair of electrons, these electrons can attract protons, this makes pyridine a weak base (pKb = 8.7)[40]. Pyridines can also act as nucleophiles by using the nitrogen's lone pair of electrons; this lone pair of electrons can also promote reactions by way of nucleophilic catalysis. Pyridines can form salts with acids, and can therefore be used as a basic catalyst as well as an acid scavenger.

The electronic bonding system of pyridine is similar to that of benzene (Figure 2). It contains a delocalised π-bonding system and is a highly conjugated aromatic ring. Each of the annular atoms in pyridine has a hybridisation of sp^2 and uses one p orbital to form the delocalised π-bonding in the ring.

Figure 2. Pyridine.

The non-bonded electrons occupy one of the sp^2 hybridised orbitals in the plane of the molecule, perpendicular to the ring's π-system (Figure 3).

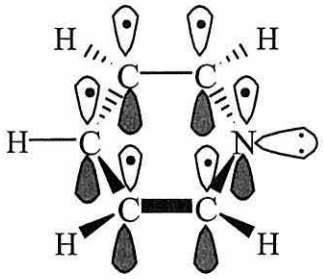
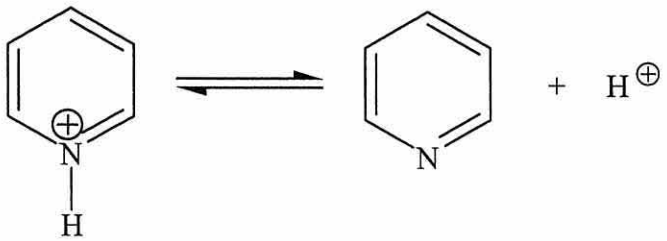


Figure 3. Bonding orbitals in pyridine.

The non-bonded electrons are not involved in the aromatic sextet and so pyridine can act as an amine, but because the basic electrons are in the sp^2 orbital[40], pyridine is 50% protonated at pH 5.2 and at pH 7 is only approximately 2% protonated (Scheme 1), *i.e.* it is a weaker base than piperidine (pKb ≈ 4).

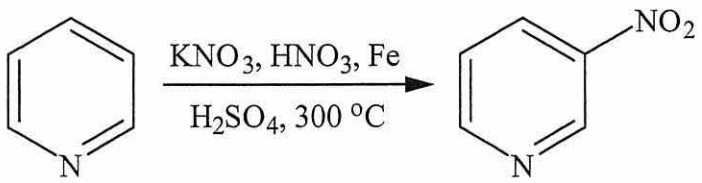


Scheme 1. Pyridine protonation.

The pyridine ring is electron deficient with respect to benzene, caused by the nitrogen atom being more electronegative than the carbon atoms.

Pyridines generally do not undergo electrophilic aromatic substitution due to the ring being electron deficient. Furthermore the nitrogen, under acidic conditions,

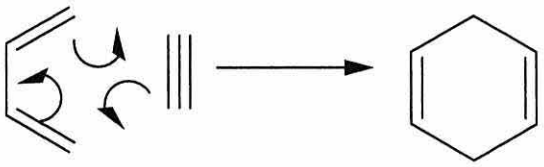
can be protonated, or complexed with a Lewis acid. Electrophilic substitution can only be achieved under drastic conditions[40] (Scheme 2).



(22%)

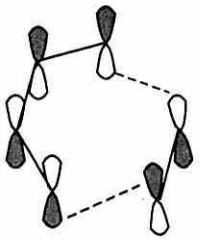
Scheme 2. 3-Nitropyridine

One powerful synthetic method for making highly substituted pyridines is *via* an aza-Diels-Alder reaction. The Diels-Alder reaction is a pericyclic reaction and is named after Otto Diels and Kurt Alder, who discovered it and won the Nobel Prize in 1950.[41-52] A Diels-Alder reaction is a thermal cycloaddition reaction between a diene and a dienophile (usually an alkene or alkyne) (Scheme 3). An aza-Diels-Alder reaction has a nitrogen atom present in either the diene or the dienophile.



Scheme 3: Diels-Alder reaction of a diene and alkyne.

The mechanism for this reaction is the σ overlap of the two unsaturated systems π-orbitals (Figure 5).



HOMO LUMO

Figure 5. Suprafacial bonding in two unsaturated systems

[4 + 2] Cycloadditions derived from $HOMO_{diene}/LUMO_{dienophile}$ controlled processes are known as normal-electron-demand Diels-Alder reactions; this cycloaddition between an electron rich diene and electron deficient dienophile account for the vast majority of synthetic applications[53]. [4 + 2] Cycloadditions can also use unactivated (neutral) substrates, for example, butadiene and ethylene, these reactions are not typical due to a greater HOMO/LUMO energy gap[53]. Inverse-electron-demand Diels-Alder reactions occur when the [4 + 2] cycloaddition is derived from a $LUMO_{diene}/HOMO_{dienophile}$ process; these cycloadditions can be achieved under milder conditions compared to normal-electron-demand Diels-Alder reactions due to a decrease in the HOMO/LUMO energy gap[53]. Figure 6 shows the different Diels-Alder reactions with their corresponding energy diagrams[53].

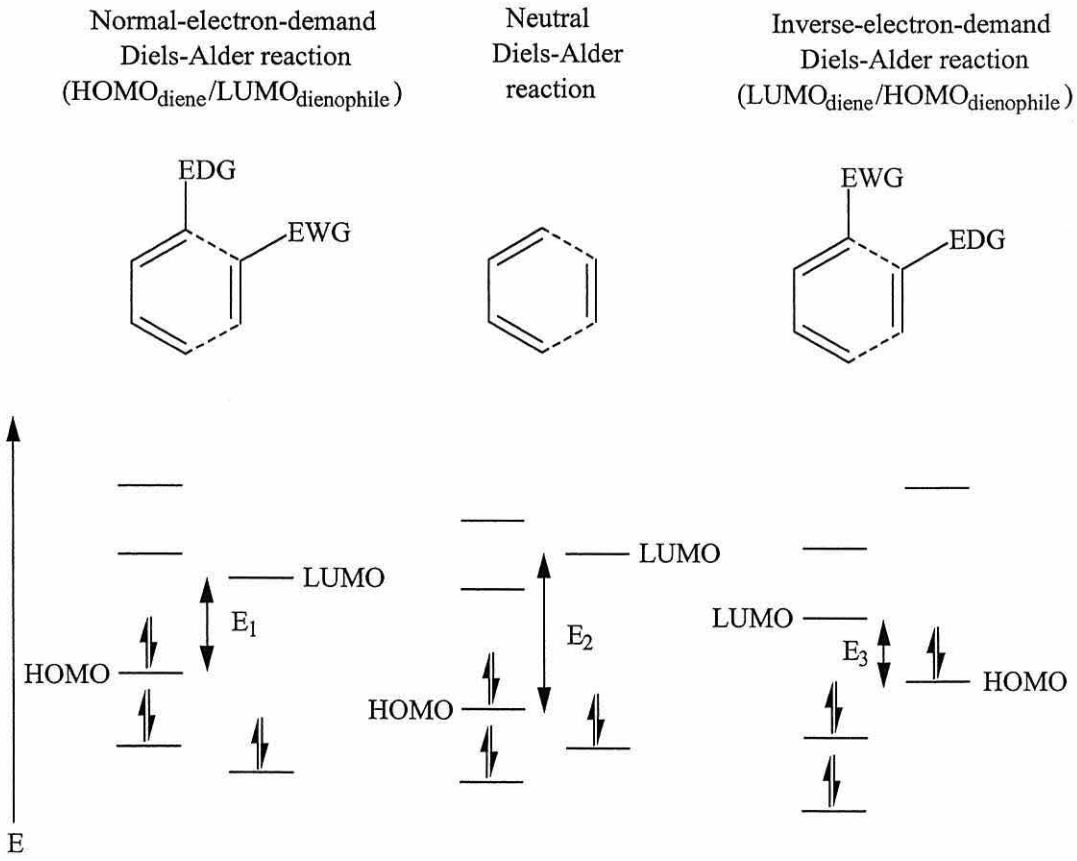


Figure 6. (EDG = electron-donating group, EWG = electron-withdrawing group)

The Diels-Alder reaction is a $[4^{\pi} + 2^{\pi}]$ cycloaddition reaction: this refers to the four π-electrons of the diene and the two π-electrons of the dienophile. This type of $[4^{\pi} + 2^{\pi}]$ cycloaddition is very common and usually proceeds *via* a *syn* addition, *i.e.* suprafacially with both the diene and the dienophile orbitals in the same phase. The diene must be in the cisoid conformation for the cycloaddition to take place[54]; the reaction is stereospecific.

The rate of the Diels-Alder reaction is controlled by the substituents on the diene and on the dienophile. In a normal-electron-demand Diels-Alder reaction, to accelerate the cycloaddition the diene needs to have electron donating substituents and the dienophile requires electron withdrawing substituents attached. For an inverse-electron-demand Diels-Alder reaction the opposite is true.

The rate of the Diels-Alder reaction is controlled by the substituents present on the diene and the dienophile. In a normal-electron-demand Diels-Alder reaction, conjugation raises the energy of the HOMO and LUMO, Figure 7 shows a general energy diagram for 1-substituted dienes[55]. Electron-withdrawing substituents on the diene to lower both the energies of the HOMO and the LUMO causing the $HOMO_{diene}/LUMO_{dienophile}$ energy gap to increase and therefore the rate of reaction is slower. Electron-donating substituents on the diene raises both the energy of the HOMO and LUMO, causing the $HOMO_{diene}/LUMO_{dienophile}$ energy gap to decrease, allowing the reaction to proceed more easily and therefore faster[55]. Simply put, in a normal-electron-demand Diels-Alder reaction, the acceleration of the cycloaddition requires the diene to have electron-donating substituents and the dienophile to have electron-withdrawing substituents attached. For a reverse-electron-demand Diels-Alder reaction the opposite is true.

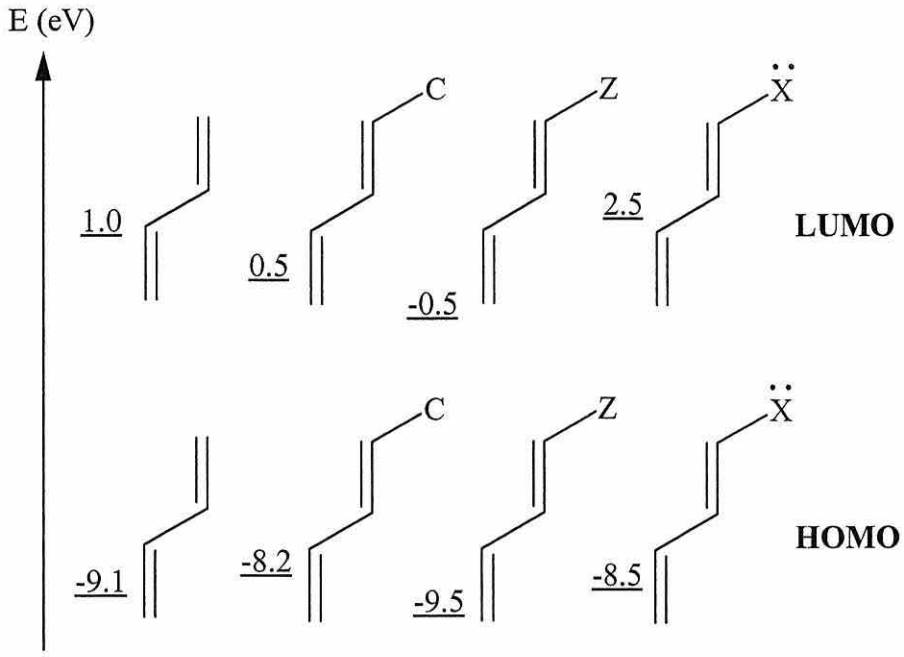


Figure 7. Typical energy values of the frontier orbitals of 1-substituted dienes. C = vinyl or phenyl; Z = CHO, CN, NO_2; X = MeO, Me_2N, Me.

Regioselectivity in Diels-Alder reactions can also be predicted by taking into consideration the frontier orbitals. In order to predict regioselectivity one needs to take into account the HOMO and LUMO energy gap of both components; using the lowest HOMO/LUMO energy gap, one estimates the relative sizes of the coefficients of the atomic orbitals on the atoms where the reaction is to take place, and matches the larger coefficients of both components[55].

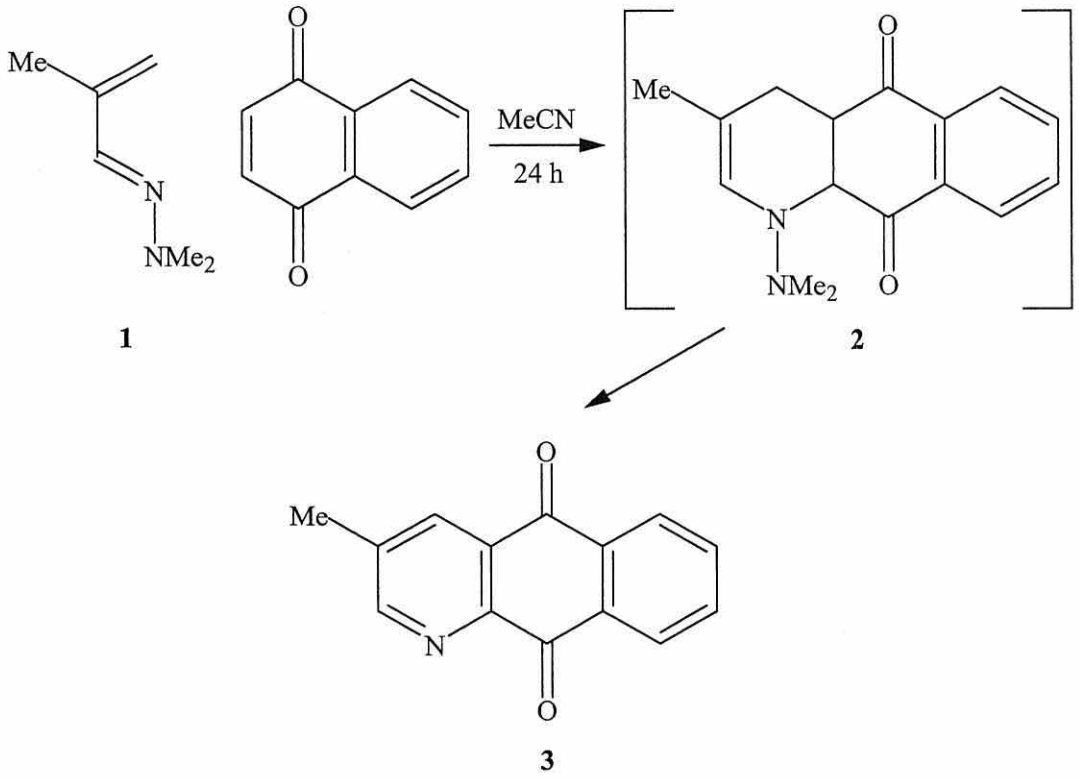
5.2 How Substituted Pyridines are Synthesised *via* Aza-Diels-Alder Reactions

Aza-Diels-Alder reactions have been the subject of numerous comprehensive reviews by Boger, Barluenga, Tietze, and Lucchi to name just a few (see references 56 – 60), therefore the following section highlights selected key results only.

5.2.1 1-Aza-Dienes

In 1982, Ghosez and co-workers[12] investigated the reaction and the regioselectivity between α,β-unsaturated hydrazones and dienophiles to give the

corresponding [4 + 2] adducts, thereof. Ghosez and co-workers used the well known capacity of hydrazones to react with electrophilic reagents at the nitrogen atom. From this they suggested an interaction between the lone pair of electrons on the nitrogen atom and the π system. They took the 1-azadiene, *N,N*-dimethylhydrazone (**1**) and reacted it with napthoquinone (2 equivalents) in acetonitrile (Scheme 4) to produce a highly substituted pyridine (**3**) in 92% yield after chromatography.



Scheme 4. Highly substituted pyridine, 92% yield.

The unstable primary adduct (**2**) was observed using NMR spectroscopy when the reaction was conducted at 20 °C in dichloromethane. The corresponding oximes (**4**, Figure 8) did not react with napthoquinone in acetonitrile after prolonged heating under reflux; the starting materials were recovered unchanged.

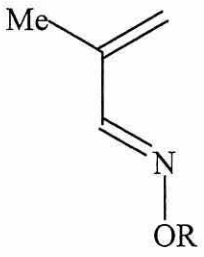


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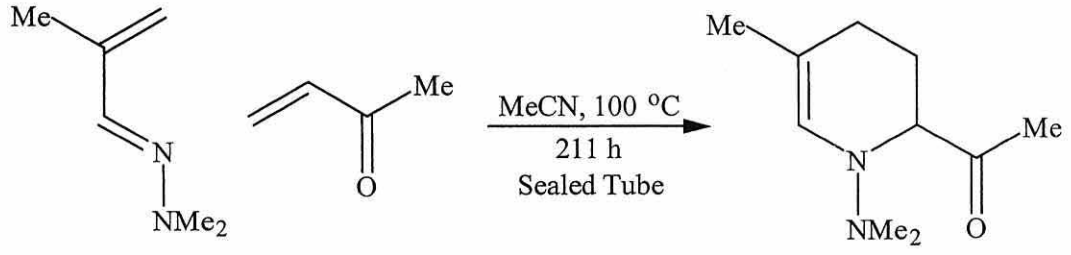
Figure 8. Oximes corresponding to **1**, R = H, Me.

They also reacted *N,N*-dimethylhydrazone (**1**) with methylvinylketone (**5**) to give the single regioisomer (**6**) (Scheme 5).



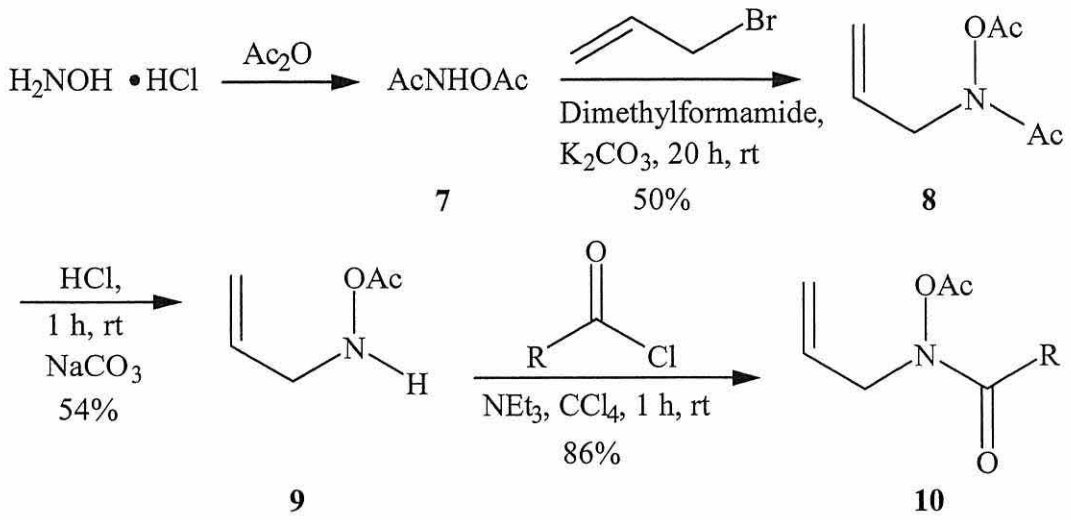
1 **5** **6**

Scheme 5. Single regioisomer in 53% yield.

Ghosez and co-workers[12] have done much further work in this area see references 61 – 70. Their main achievements were the use of chiral 1-azadienes as reagents for asymmetric [4 + 2] Diels-Alder reactions. They also did a lot of research with 2-azadienes.

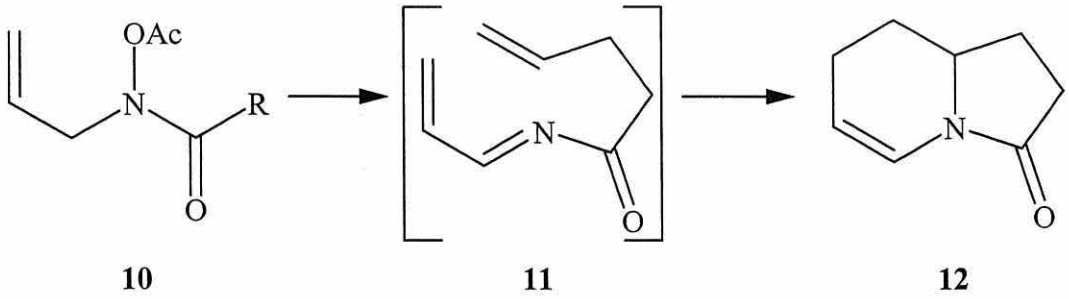
In 1983, Fowler and co-workers[71] investigated *N*-acyl-1-azadienes as possible reactants in Diels-Alder chemistry, these are however very reactive and generally not isolated but generated *in-situ* and used synthetically as intermediates; due to the unstable nature of the 1-azadiene it was studied in intramolecular Diels-Alder reactions. The group investigated *N*-acetoxy amides (**10**) as they were synthetically more accessible and could be prepared from hydroxylamine. Scheme 6 shows the reaction of *N,O*-diactylhydroxylamine (**7**) with allyl bromide to give *N*-allyl-*N,O*-diacetylhydroxylamine (**8**), followed by selective hydrolysis under acidic conditions

to give *N*-allyl-*O*-acetylhyroxylamine (**9**) with the addition of pent-4-enoyl chloride to give *O*-acetyl-*N*-allyl-*N*-pent-4-enoylhydroxylamine (**10**).



Scheme 6. R = 

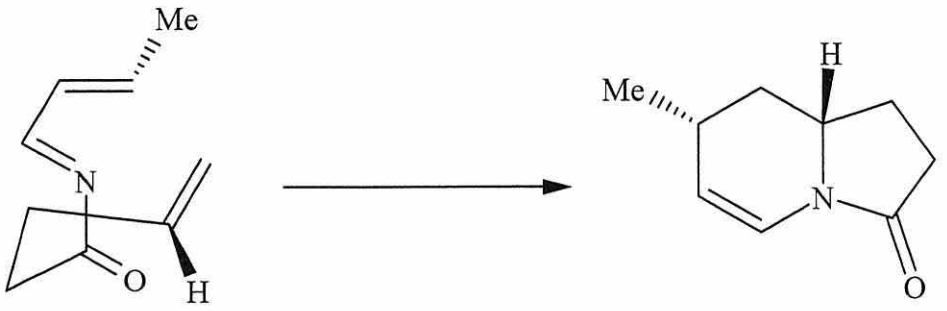
O-Acetyl-*N*-allyl-*N*-pent-4-enoylhydroxylamine (**10**) was evaporated through a hot reaction tube[72] to give the Diels-Alder adduct (**12**) (Scheme 7). This was then passed through a short column of potassium carbonate to remove the acetic acid byproduct giving a 75% yield. The 1-azadiene (**11**) is a presumed intermediate but has never been directly observed.



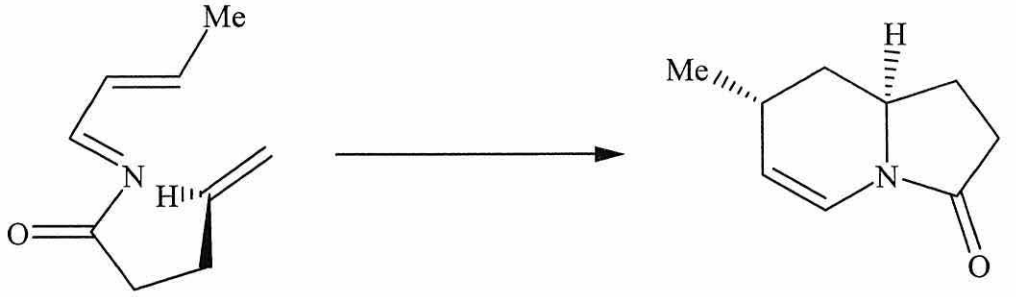
Scheme 7. Intramolecular Diels-Alder reaction, R = 

It is extremely difficult to determine the stereochemical course of the intramolecular Diels-Alder reaction, the relative importance of the two stereochemical pathways, *exo* and *endo*, are apparent from the ratio of *cis* and *trans* fused products. The group theorised that this stereochemical mystery could be answered by studying 4-

substituted azadienes (**13**). The Diels-Alder reaction of **13** gave a *trans/cis* ratio of 3:1, indicating that the reaction was proceeding predominantly but not exclusively through the *exo* transition state (Scheme 8).



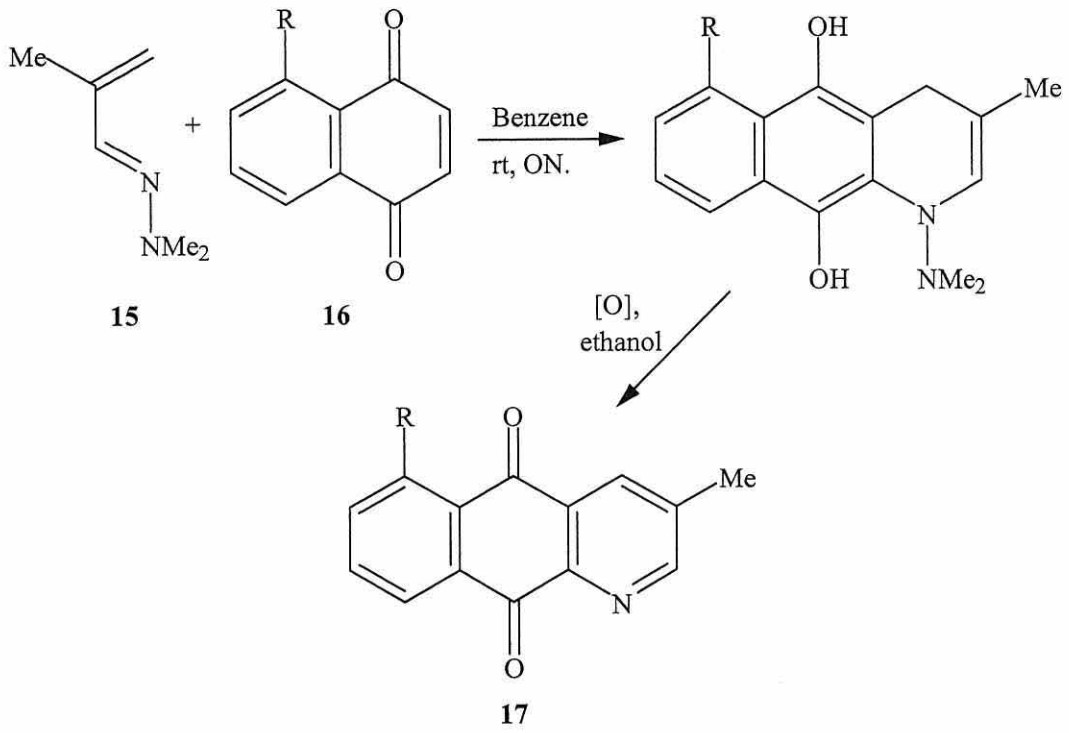
13 (*endo*) **14**



13 (*exo*) **14**

Scheme 8.

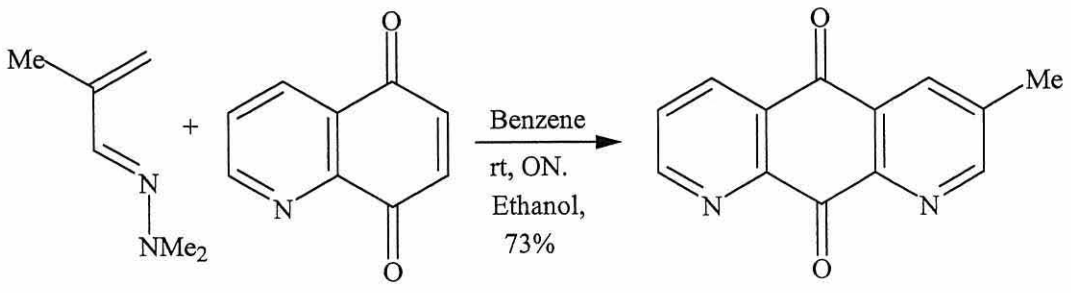
In 1984, Potts and co-workers[73] investigated a convenient route for the synthesis of a variety of substituted aza-anthraquinones. The group reacted 1-dimethylamino-3-methyl-1-azabuta-1,3-diene (**15**) with 5-hydroxynaphthoquinone (**16**, R = OH) and 5-methoxynaphthoquinone (**16**, R = OMe) to give 8-hydroxy-3-methyl-1-aza-9,10-anthraquinone (**17**, R = OH) and 8-methoxy-3-methyl-1-aza-9,10-anthraquinone (**17**, R = OMe) respectively (Scheme 9).



15 16 17

Scheme 9. R = OH, 83%; R = OMe, 62%.

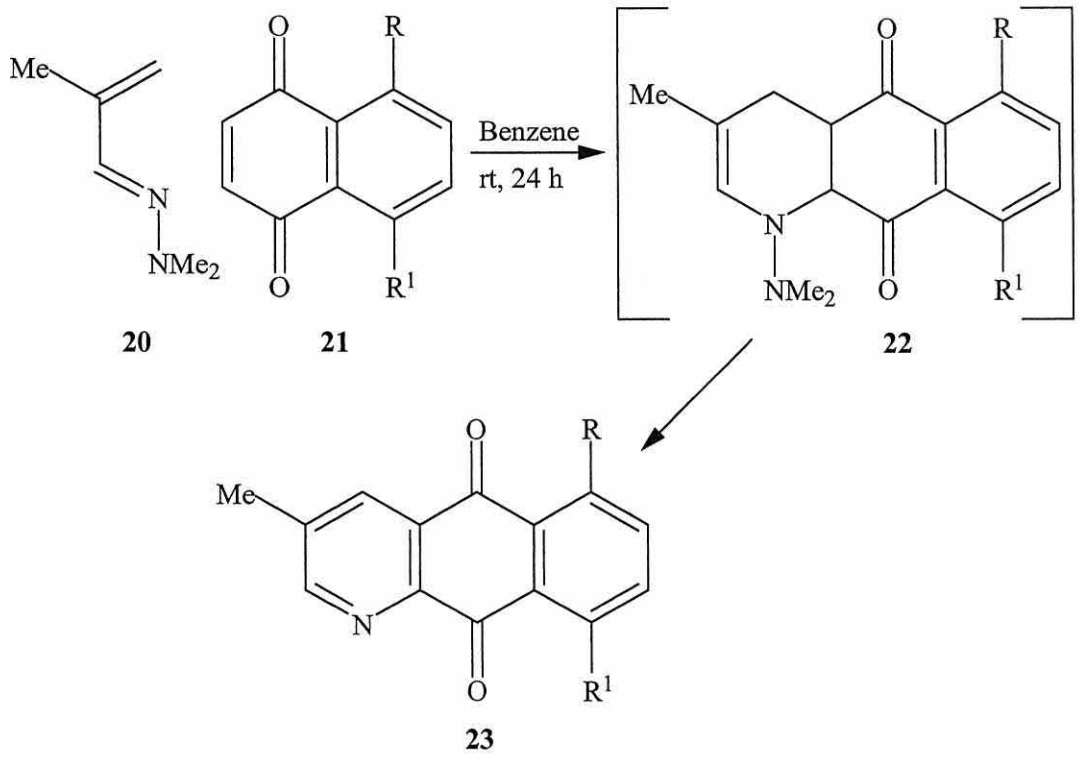
The cycloaddition of R = OMe was highly regioselective as the donor effect of the methoxy group diminishes the electron-withdrawing ability of the 4-carbonyl group causing the nucleophilic end of the diene to react at the C-3 position. The group also reacted the aza-diene (**15**) with quinoline-5,8-dione (**18**) to give 3-methyl-1,8-diaza-9,10-anthraquinone (**19**) (Scheme 10), illustrating a quick and convenient aza-Diels-Alder route, providing practical access to anthraquinone derivatives which are of current interest in cancer chemotherapy.



15 18 19

Scheme 10.

In 1987, Potts and co-workers[71] used cycloaddition reactions of aza-dienes with quinones and ring-fused azaquinones to synthesise azaanthraquinones. It was shown that methacrolein *N,N*-dimethylhydrazone (**20**) can undergo cycloaddition reactions with acetylenic and olefinic dienophiles to yield a variety of substituted pyridines and dihydropyridines. Scheme 11 shows the reaction of **20** with naphthoquinone (**21**) to give the cycloadduct intermediate (**22**) and then the fully aromatic substituted pyridine (**23**) after elimination of dimethylamine and oxidation by excess naphthoquinone (**21**). The regioselectivity for R = OMe is regiospecific. This is attributed to the 5-methoxy group in naphthoquinone (**21**, R = OMe) making the C-3 carbon more electron deficient. The reaction was also regiospecific when R = OH.

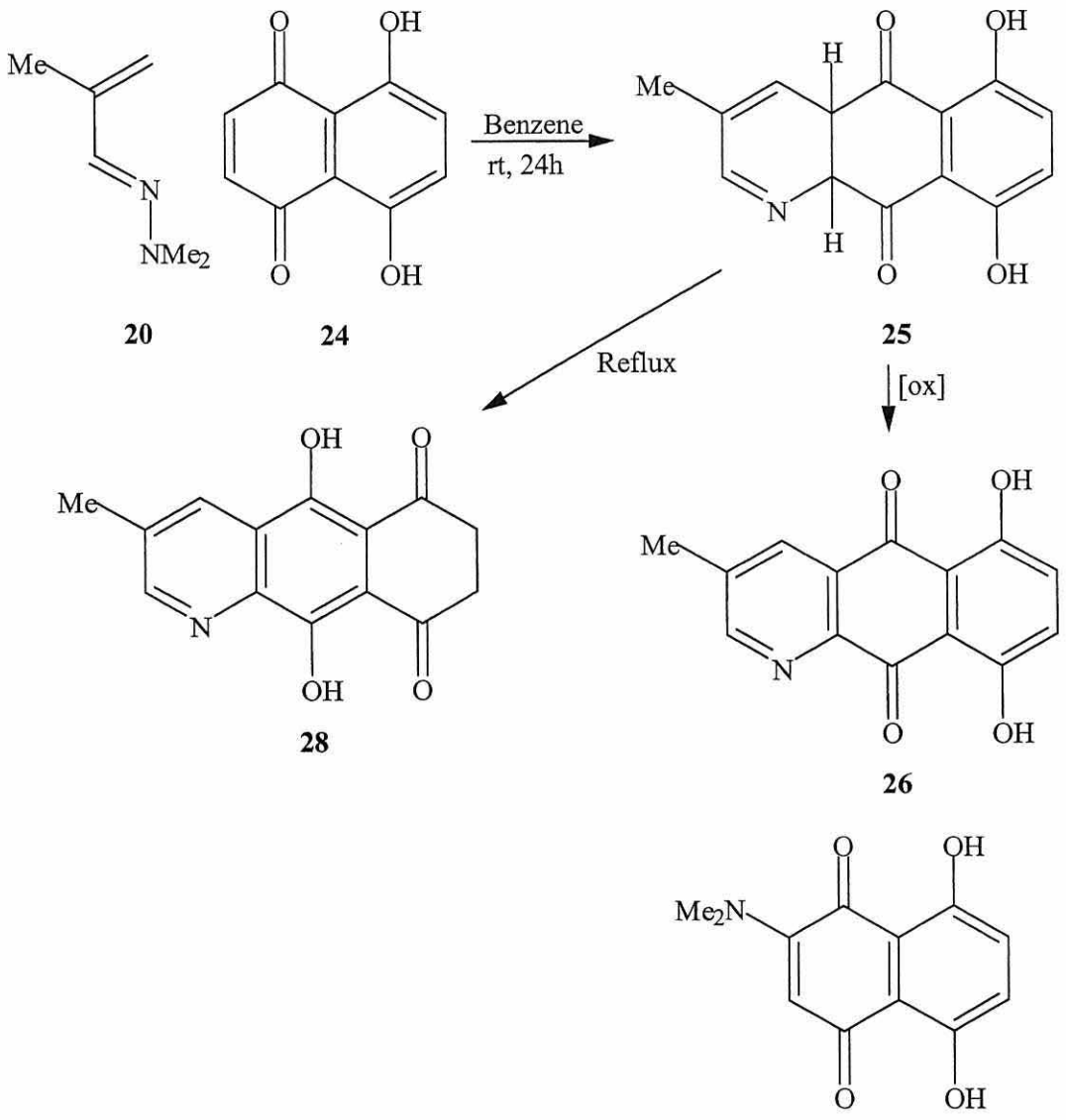


20 **21** **22** **23**

Scheme 11. R = OMe, R^1 = H, 62%; R = H, R^1 = OH, 52%; R = R^1 = H, 32%.

They also found that a competitive addition of dimethylamine occurred during the cycloaddition of 5,8-dihydroxy-1,4-naphthoquinone (**24**) with the aza-diene (**20**) (Scheme 12) in benzene at room temperature. They isolated the cycloadduct (**25**) as well as the oxidized compound (**26**). They found that bubbling argon through the mixture at 40-45 °C, stopped the formation of the byproduct (**26**), due to the

dimethylamine eliminated from the initial 1:1 cycloadduct being removed; on heating **25** oxidation was prevented and as a result 9,10-dihydroxy-3-methyl-1-azaanthracene-5,8-dione (**28**) was formed.

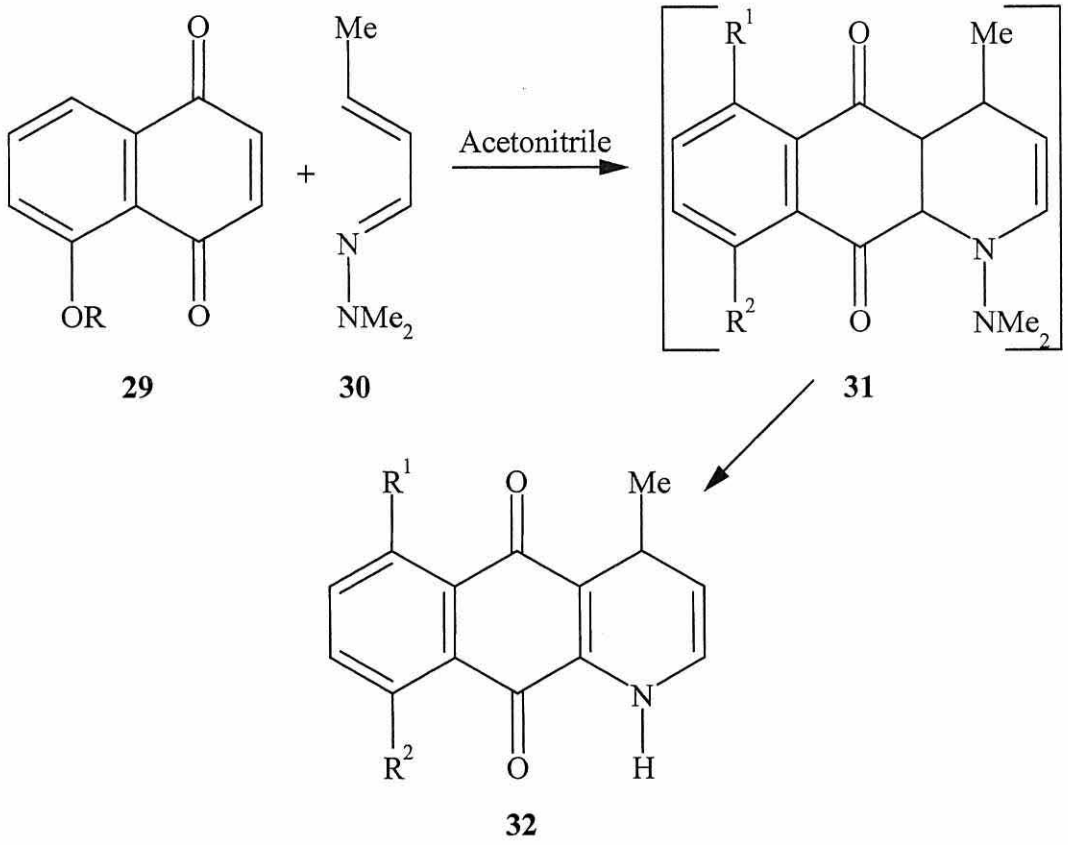


20 **24** **25** **28** **26** **27**

Scheme 12.

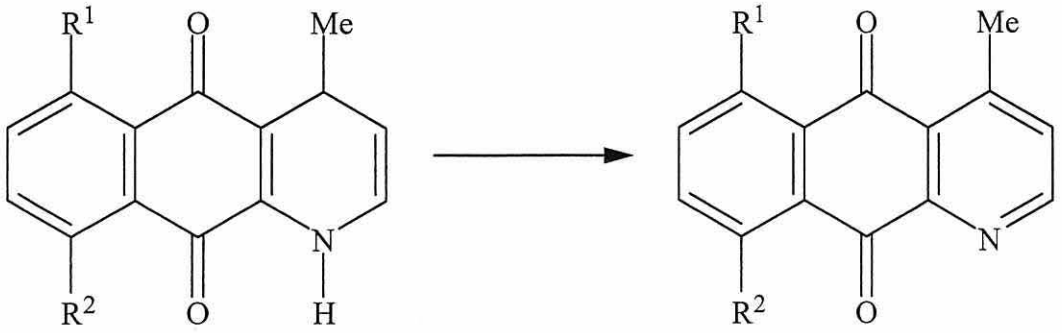
In 1988, Fillion and co-workers[75] studied the synthesis of Cleistopholine derivatives (**33**), a natural 1-aza-anthraquinone with a methyl on the C-4 position. The group reacted crotonaldehyde *N,N*-dimethylhydrazone (**30**) with naphthoquinones (**29**) to give 1,4-dihydro aza-anthraquinones (**32**) (Scheme 13). The unstable primary adducts (**31**) were not observed and products **32** were directly obtained through a

rapid elimination of dimethylamine. This was the first report of these types of structures to occur in such cycloadditions.



Scheme 13. **32a** R, R^1 = H, R^2 = OH, 24 h, rt, 50%;
32b R = Me, R^1 = OMe, R^2 = H, 18 h, 100 °C, 50%;
32c R = COMe, R^1 = H, R^2 = COMe, 30 h, rt, 70%;
32d R = COMe, R^1 = COMe, R^2 = H, 30 h, rt, 70%.

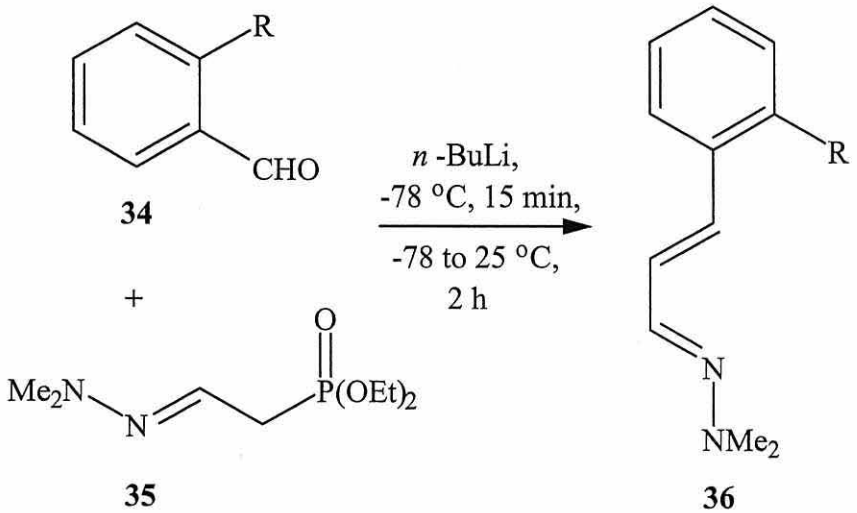
Oxidation of **32** by activated manganese dioxide gave the corresponding anthraquinones (**33**) (Scheme 14).



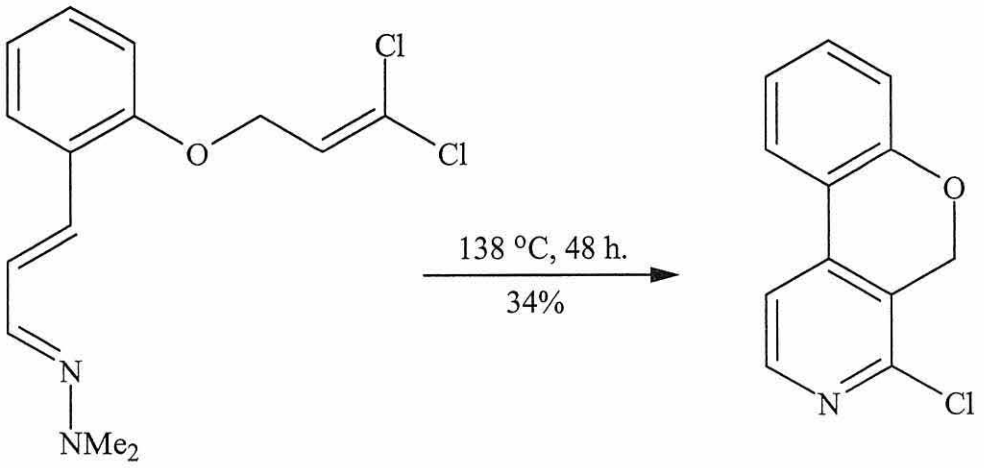
32 **33**

Scheme 14. Oxidation of **32** to give corresponding aza-anthraquinones **33**.
33a $R^1 = H$, $R^2 = OH$;
33b $R^1 = OH$, $R^2 = H$;
33c $R^1 = H$, $R^2 = OMe$;
33d $R^1 = OMe$, $R^2 = H$.

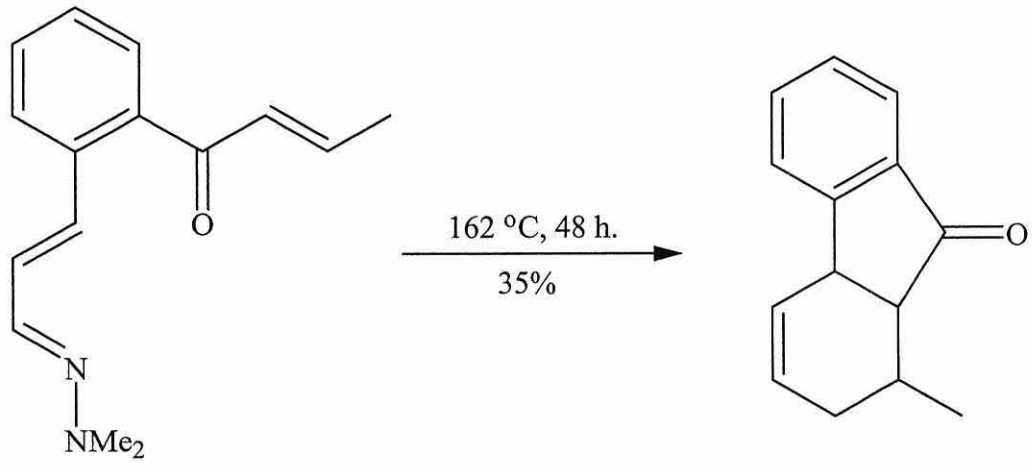
In 1988, Dolle and co-workers[76] studied the first examples of intramolecular Diels-Alder reactions of α,β-unsaturated hydrazones. The group required an efficient route to pyridine ring systems. The group studied direct Wadsworth-Emmons condensation of the aldehydes (**34**) with the lithium anion derived from phosphonate (**35**). Deprotonation of **35** with *n*-butyl lithium, with the addition of **34** gave the vinyl hydrazones (**36**) (Scheme 15). Upon heating the vinyl hydrazones intramolecular [4 + 2] cycloadditions occurred (Scheme 16).



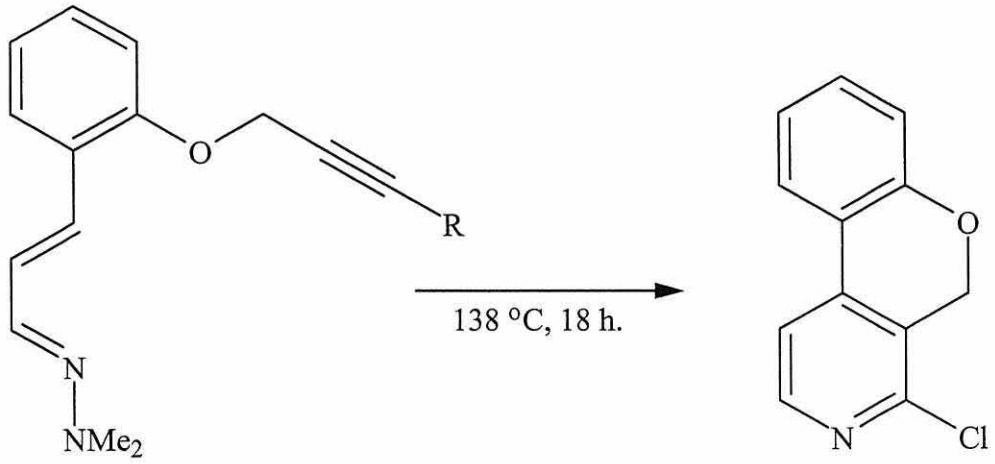
Scheme 15. Wadsworth-Emmons condensation, 50-80%.



36a **37**



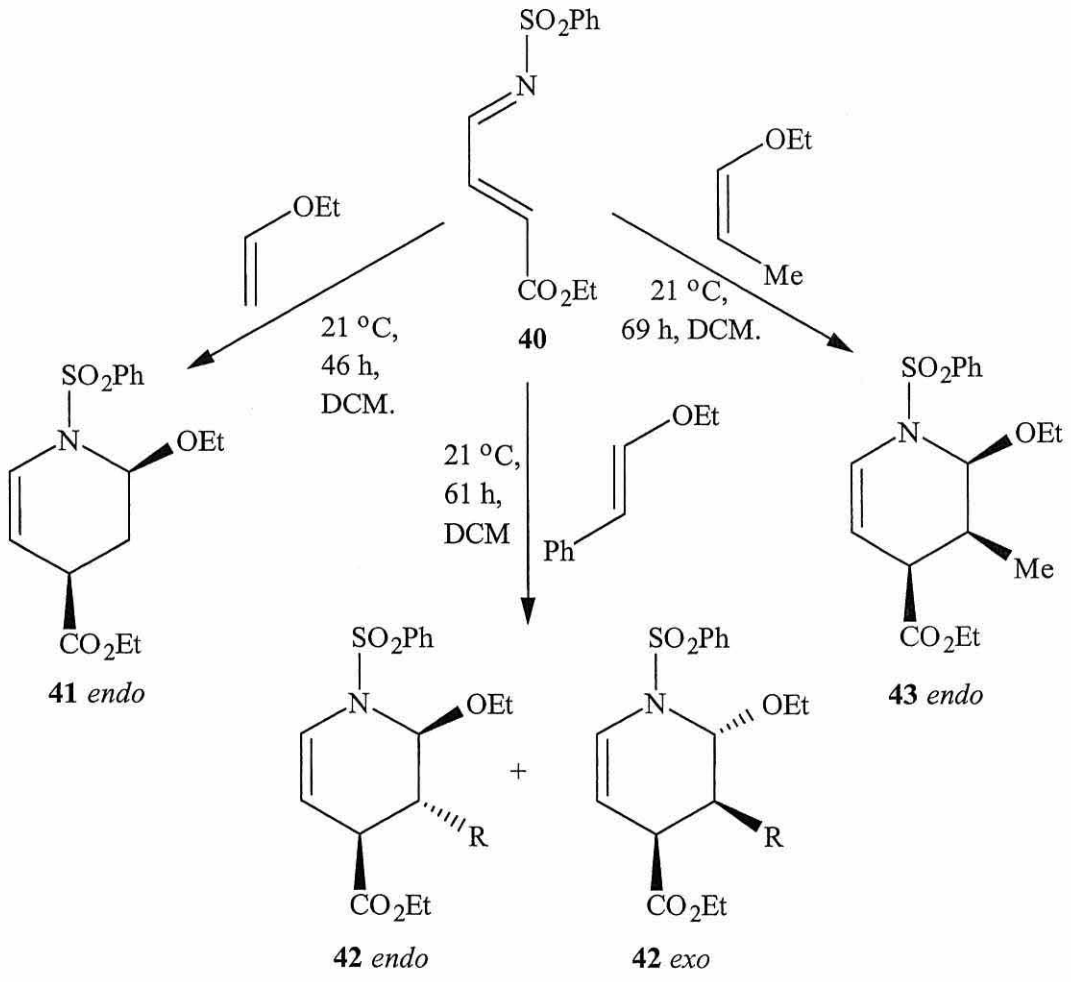
36b **38**



36c,d **39c,d**

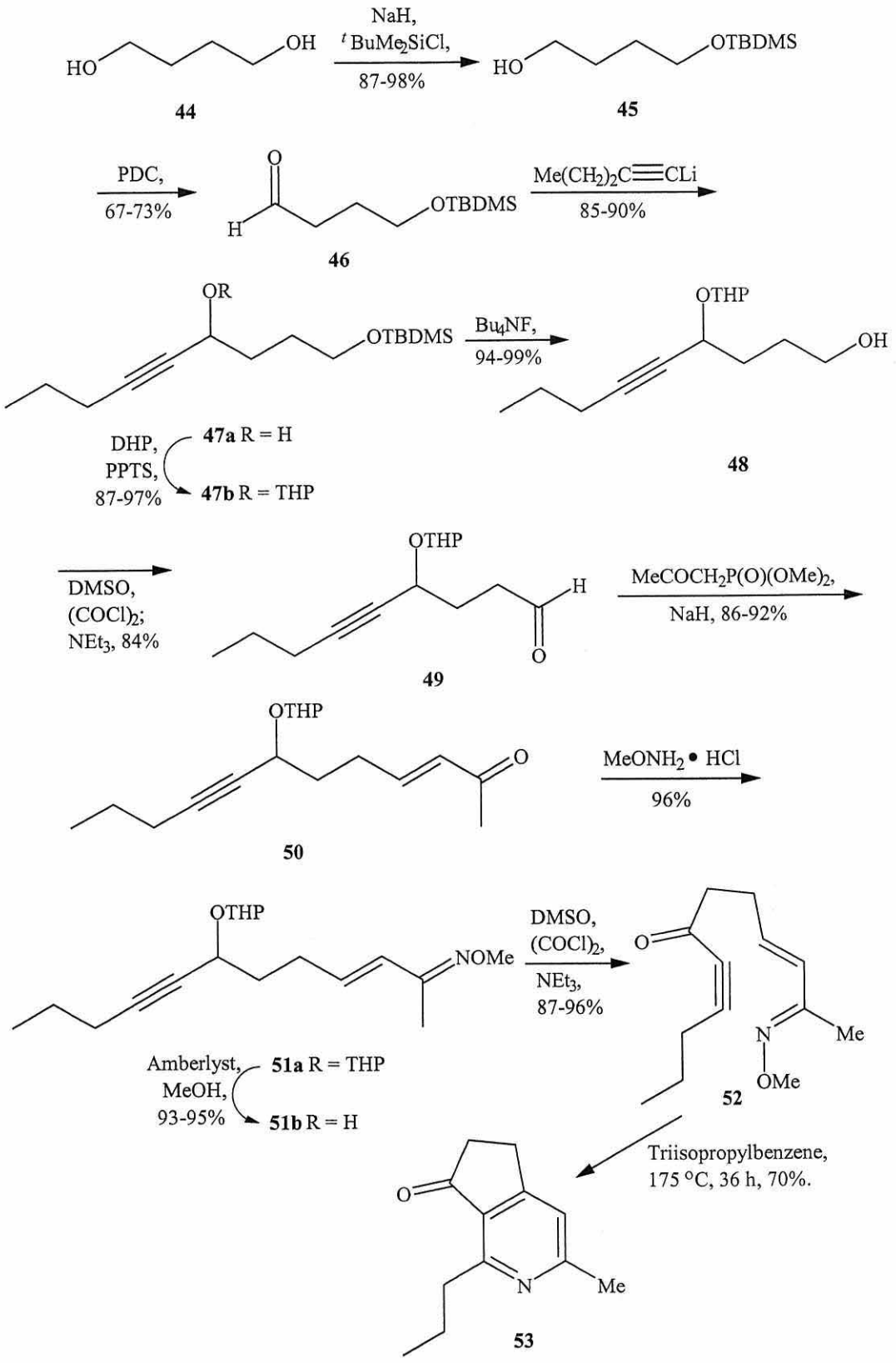
Scheme 16. **36c** R = H, 58%; **36d** R = Ph, 74%.

In 1990, Boger and co-workers[77] investigated the *endo*-selective $LUMO_{diene}$-controlled Diels-Alder reactions of *N*-(phenylsulfonyl)-4-(ethoxycarbonyl)-1-aza-1,3-butadiene (**40**) (Scheme 17). These reactions are rarely observed, but the group demonstrated the general participation of stable *N*-(phenylsulfonyl)-1-aza-1,3-butadienes in regiospecific and *endo*-specific inverse electron-demand Diels-Alder reactions.



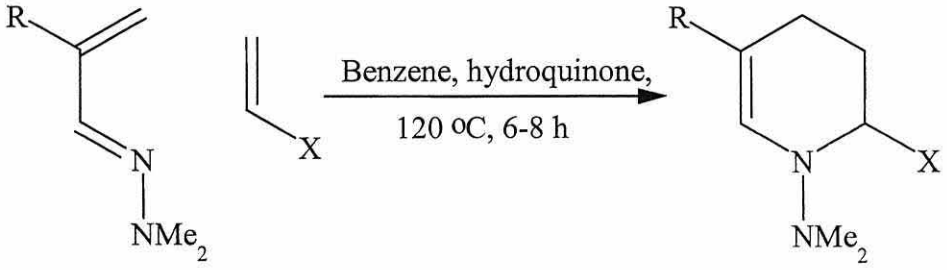
Scheme 17. **41** 82%, *endo: exo* (>20 : 1);
42 61%, *endo: exo* (5 : 1);
43 48%, *endo: exo* (>20 : 1).

In 1991, Boger and co-workers[78] investigated the participation of *O*-alkyl α,β-unsaturated oximes in intramolecular $HOMO_{diene}$-controlled Diels-Alder reactions with electron deficient alkynes in which the resulting cycloadducts undergo further oxidation to the corresponding pyridines by virtue of *in situ* elimination of alcohol (Scheme 18).


NaH,
^{t}BuMe$_2$SiCl,
87-98%
HO
OH
OTBDMS
44
45
PDC,
67-73%
O
H
OTBDMS
Me(CH$_2$)$_2$C≡CLi
85-90%
46
OR
OTBDMS
Bu$_4$NF,
94-99%
OTHP
OH
48
DHP,
PPTS,
87-97%
47a R = H
47b R = THP
DMSO,
(COCl)$_2$;
NEt$_3$, 84%
OTHP
H
O
MeCOCH$_2$P(O)(OMe)$_2$,
NaH, 86-92%
49
OTHP
O
MeONH$_2$ • HCl
96%
50
OTHP
NOMe
DMSO,
(COCl)$_2$,
NEt$_3$,
87-96%
O
N
Me
OMe
52
Amberlyst,
MeOH,
93-95%
51a R = THP
51b R = H
Triisopropylbenzene,
175 °C, 36 h, 70%.
O
N
Me
53

Scheme 18.

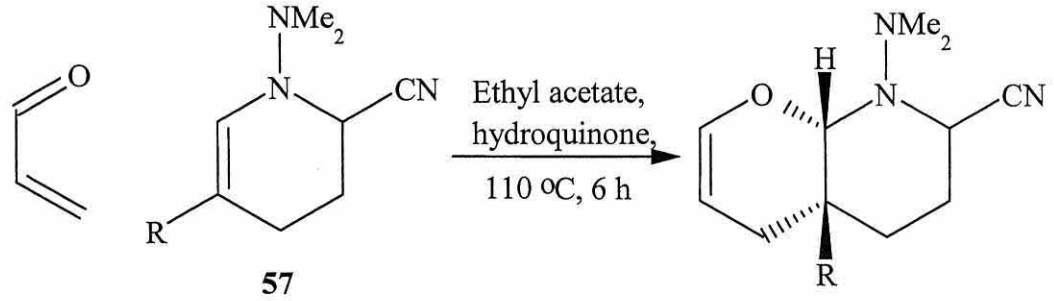
In 1992, Koldobskii and co-workers[79] studied the cycloaddition reactions of α,β-unsaturated dimethylhydrazones with various dienophiles. They took simple α,β-unsaturated dialkylhydrazones (**54**) and reacted them with various alkenes (**55**) to give the corresponding tetrahydropyridines (**56**) (Scheme 19). These reactions are regiospecific.



54 **55** **56**

Scheme 19. R = H, X = CN, 67%; R = Me, X = CO_2Me, 70%; R = C_2H_5, X = COMe, 54%.

Koldobskii and co-workers[79] conducted many cycloaddition reactions between the tetrahydropyridines (**57**) and electron-accepting olefins. For example, acrolein forms derivatives of octahydropyranopyridines and acts as an electron-deficient diene (Scheme 20). This reaction is regiospecific.

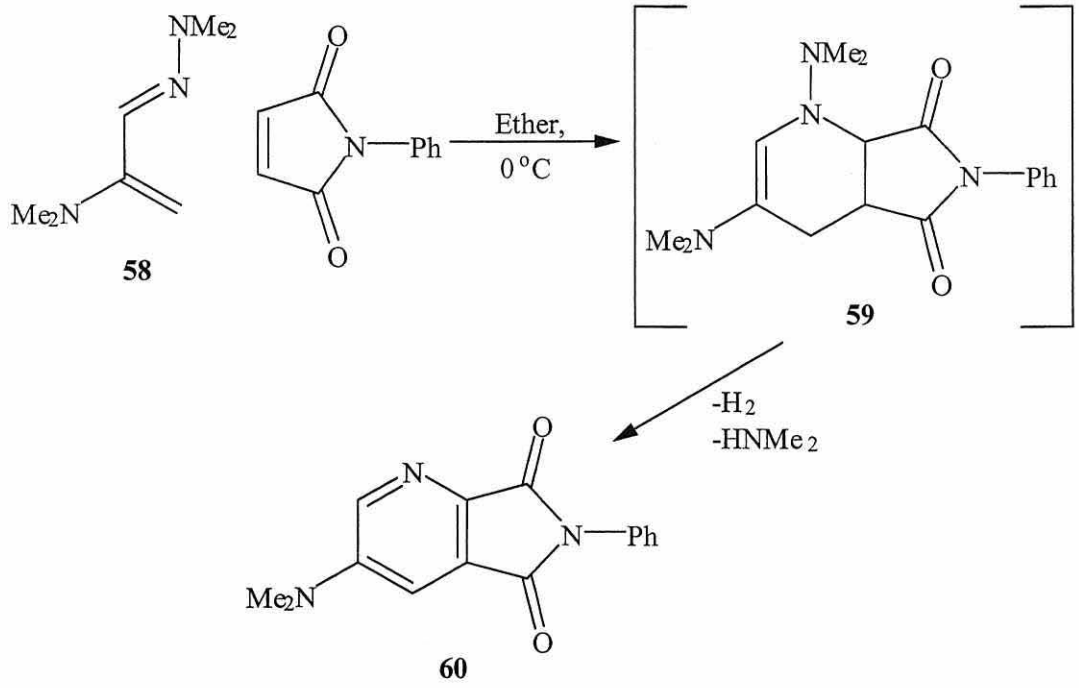


57

Scheme 20. R = H, 73%; R = Me, 49%.

After various reactions with α,β-unsaturated dimethylhydrazones the group found that the most active diene was α-dimethylaminoacrolein dimethylhydrazone (**58**) as it

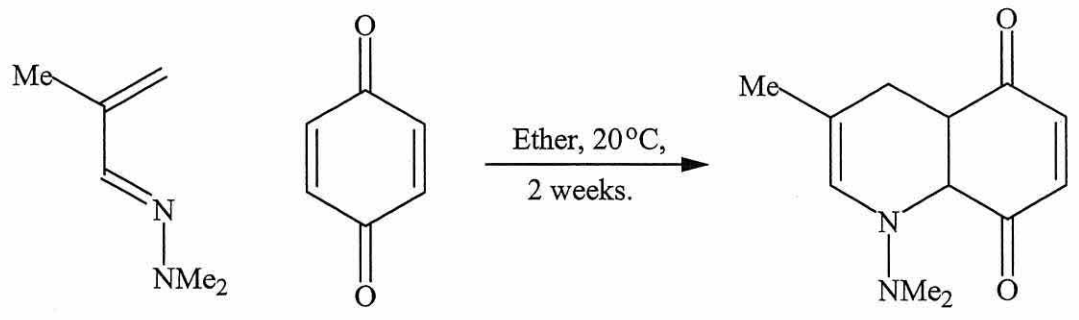
reacts instantaneously with *N*-phenylmaleimide at room temperature. The reaction is extremely exothermic (Scheme 21).



Scheme 21. 42%

The cycloaddition is accompanied by the elimination of dimethylamine and the dehydrogenation of the intermediate (**59**) by an excess of the dienophile to give the highly substituted pyridine (**60**).

They also formed an adduct of benzoquinone (**62**) *via* an aza-Diels-Alder reaction with a hydrazone (**61**) (Scheme 22). Unfortunately the benzoquinone adduct is unstable and spontaneously resinifies.



Scheme 22. 69%, decomposes at 34°C.

In 1992, Boger and co-workers[80] investigated the structure and synthesis of fredericamycin A (**63**, Figure 9), a structurally unique and potent antitumor antibiotic.

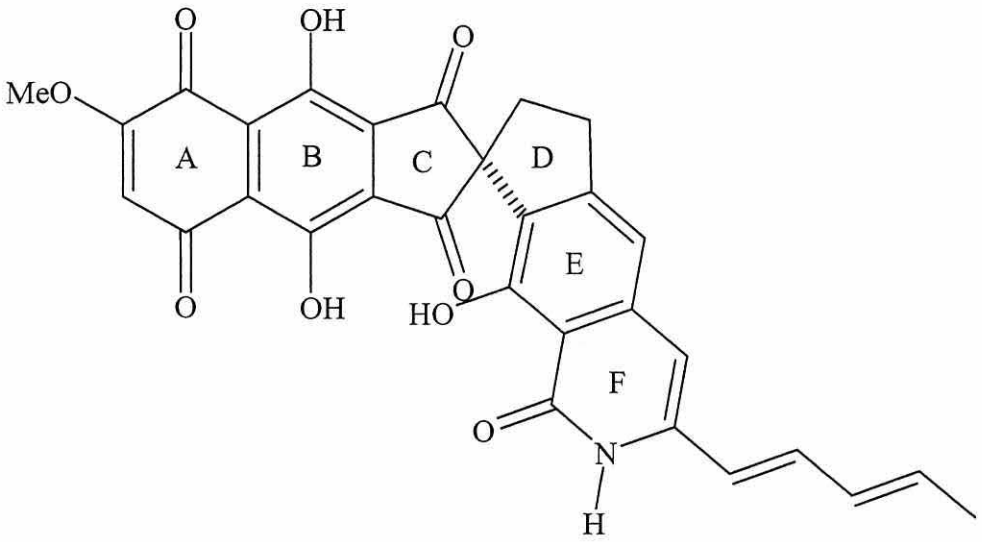
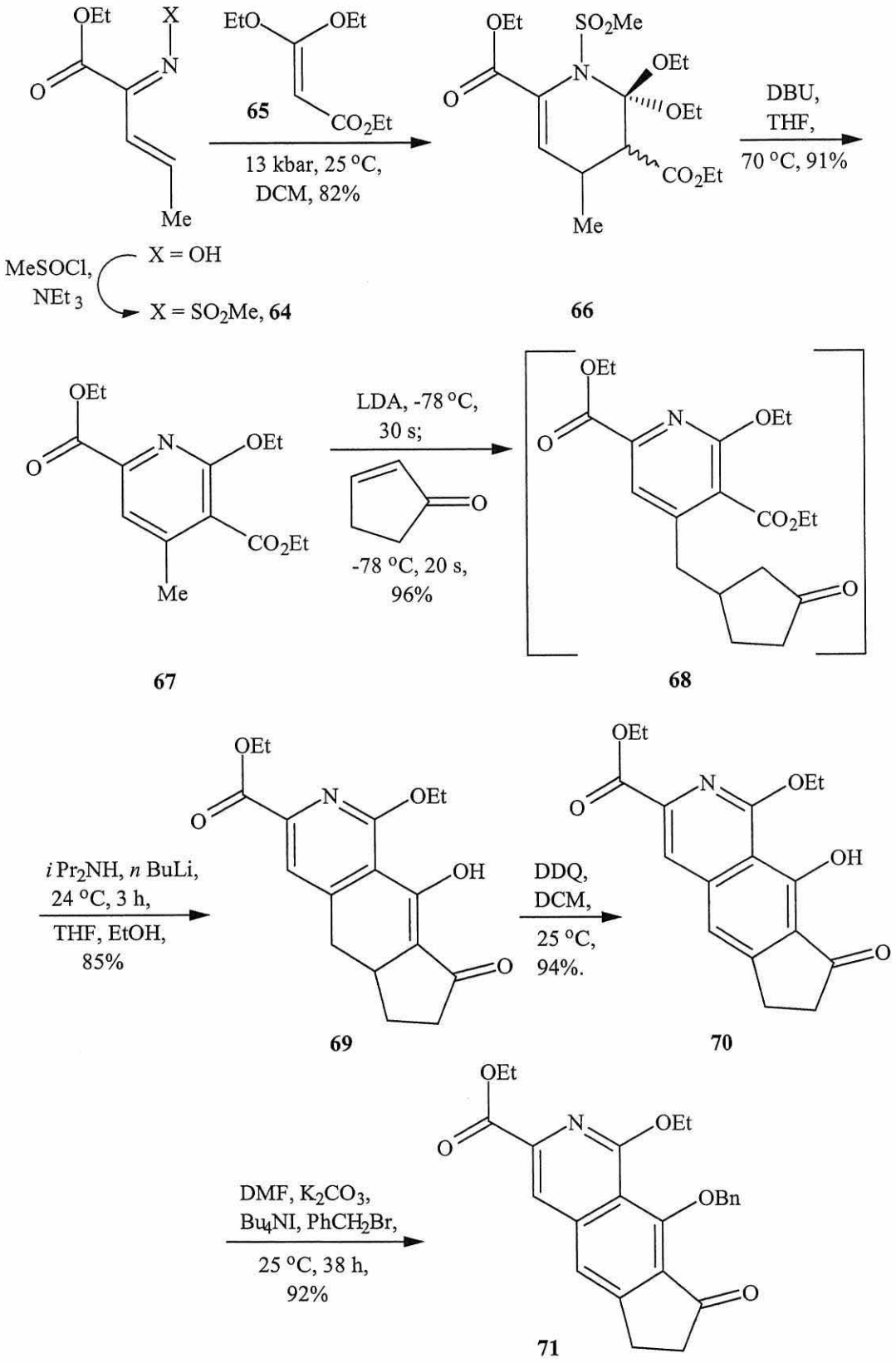


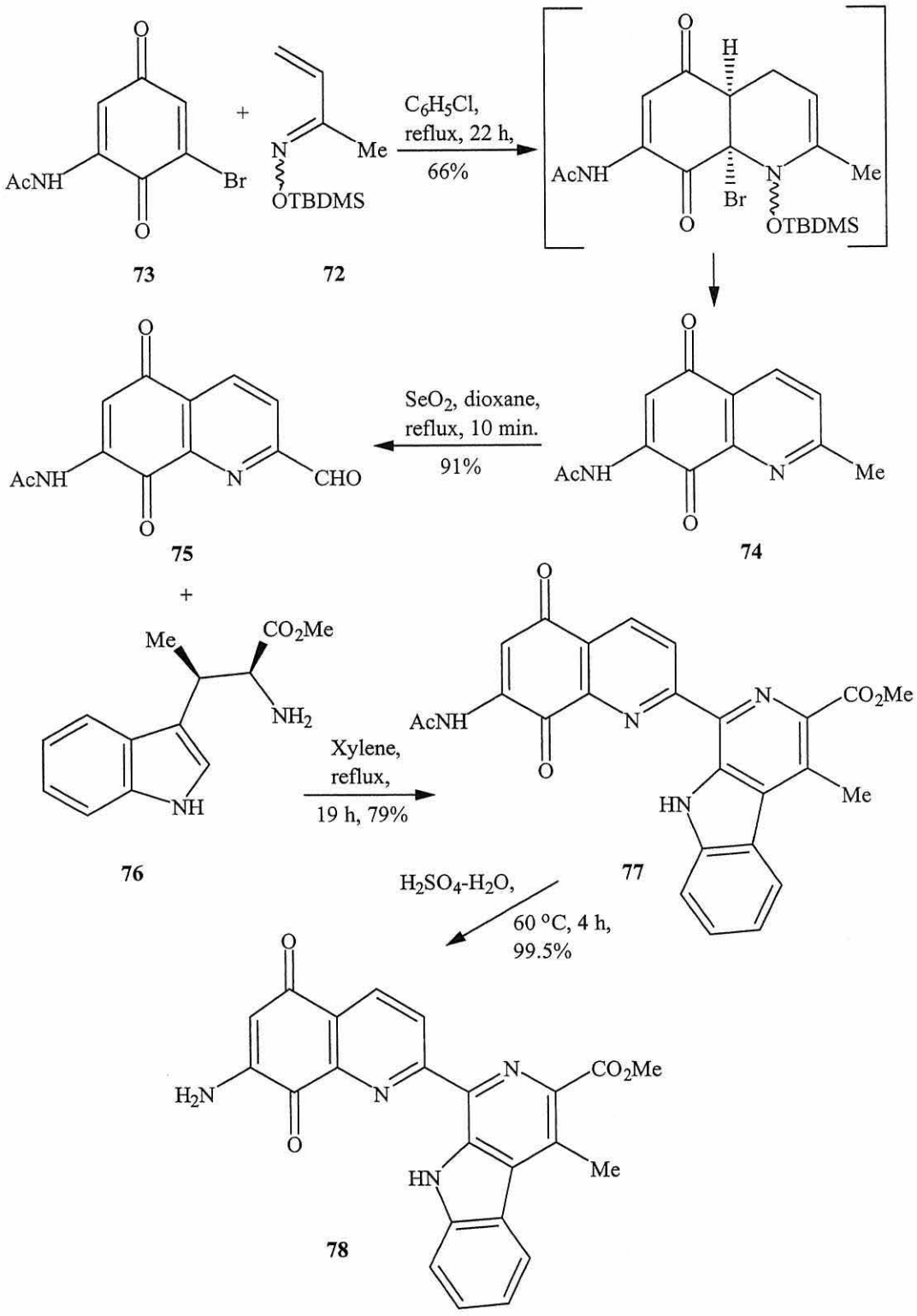
Figure 9. Fredericamycin A, (**63**)

The group investigated the synthesis of the fredericamycin A DEF ring system (**71**) using $LUMO_{diene}$-controlled Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-butadiene (**64**) (Scheme 23). Very little work had been previously done in this area.



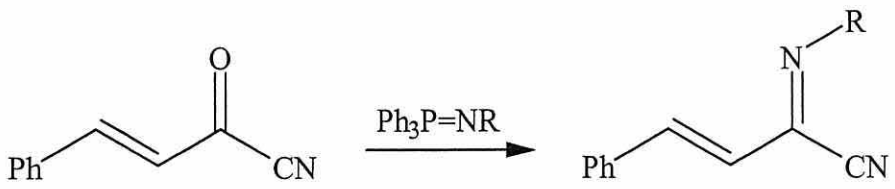
Scheme 23. Synthesis of fredericamycin a DEF ring system.

In 1993, Behforouz and co-workers[81] studied the synthesis of the highly substituted pyridine lavendamycin methyl ester (**78**), an antitumor antibiotic. The group started from a Diels-Alder reaction between a novel 1-azadiene (**72**) and bromoquinone (**73**) (Scheme 24). This is the first method where all the intermediates are stable and are obtained reproducibly in high yields. The other unique feature is the application of a novel intermolecular Diels-Alder condensation of a siloxy 1-azadiene in the synthesis of a key intermediate such as quinolinedione (**74**).



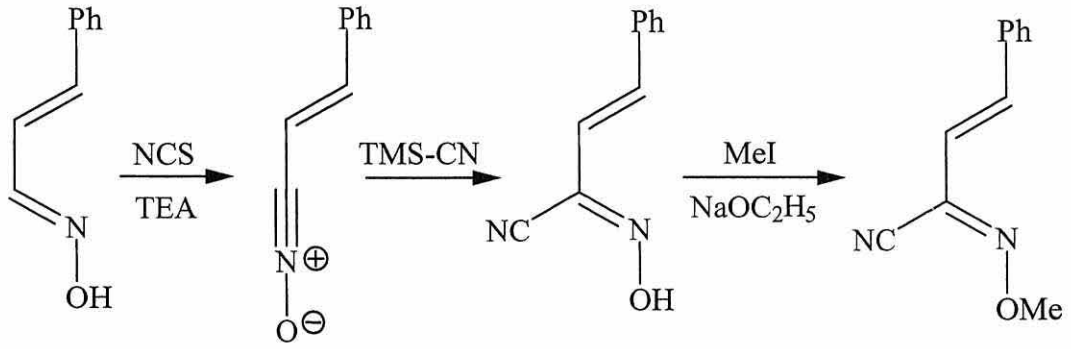
Scheme 24. Synthesis of lavendamycin methyl ester, overall yield is 33%.

In 1993, Trione, Toledo and co-workers[82] studied the aza-Diels-Alder reactions of 2-cyano-1-azadienes (**79**). The preparations of the aza-dienes (**79**) are shown in Scheme 25 and Scheme 26.



R = Ph (**79a**) 90%; R = $CO_2C_2H_5$ (**79b**) 25%.

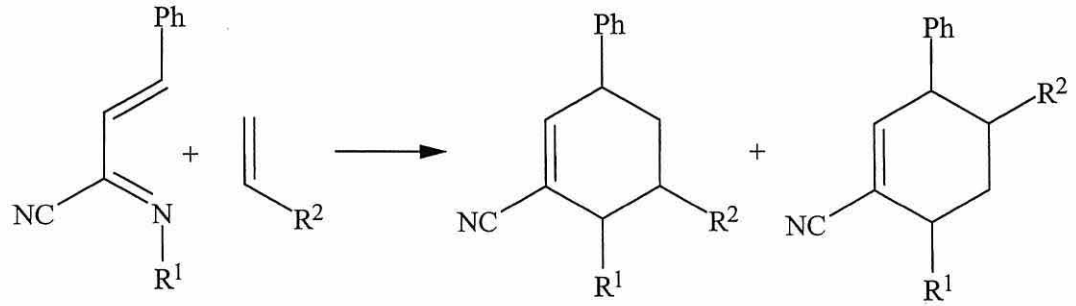
Scheme 25. Preparation of *N* -phenyl-1-azadiene (**79a**) and *N* -(ethoxycarbonyl)-1-azadiene (**79b**) using the aza-Wittig reaction.



79c

Scheme 26. Preparation of *N*-methoxy-1-azadiene, 84%.

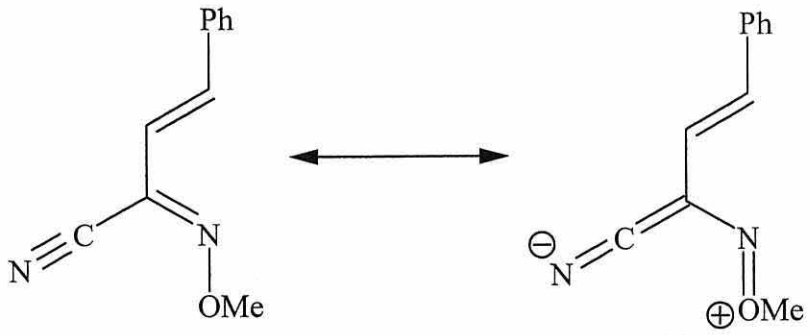
These aza-dienes (**79**) then underwent aza-Diels-Alder reactions with alkenes to produce the α-regioisomer (**80**) and/or the β-regioisomer (**81**) (Scheme 27).



79 **80** **81**

Scheme 27. $R^1 = C_6H_5$, $R^2 = C_6H_5$, 110 °C, 8 days, *cis* only, 50%;
$R^1 = C_6H_5$, $R^2 = CO_2Me$, 110 °C, 7 days, *cis:trans* = 6:1, 83%;
R^1 = C(=O)OEt, $R^2 = C_6H_5$, 90 °C, 24 h, *cis:trans* = 10:1, 92%;
R^1 = C(=O)OEt, $R^2 = CO_2Me$, 81 °C, 25 h, *cis:trans* = 10:1, 91%.

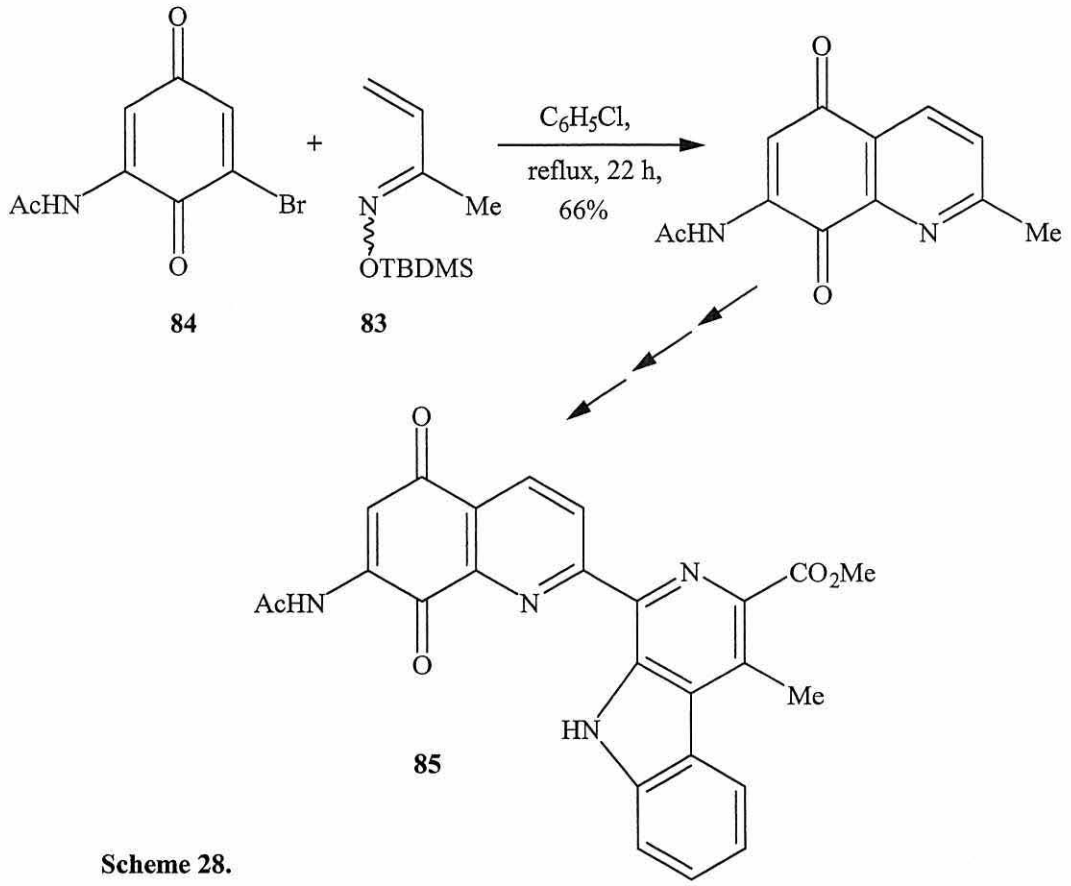
Aza-diene **79c** was unreactive with styrene, methyl acrylate and ethyl vinyl ether under the same reaction conditions that were successful for aza-dienes **79a** and **79b**. They attribute this to a significant ground-state stabilization of the 2-cyano oxime (**82**, Figure 10). This stabilising electronic interaction is destroyed during the Diels-Alder reaction and therefore increases the activation energy. A similar problem occurs with most oximes and many undergo Beckmann rearrangements/fragmentations.



79c **82**

Figure 10. Ground-state electronic stabilisation of aza-diene.

In 1997, Behforouz and co-workers[83] looked at aza-Diels-Alder reactions of *N*-silyloxy-1-azadienes (**83**). They reacted the aza-dienes with *N*-phenylmaleimide and various halobenzoquinones and napthoquinones to produce various substituted pyridines. The synthesis of lavendamycin methyl ester (an antitumor agent) (**85**), *via* an aza-Diels-Alder reaction of silyloxyazadiene (**83**) with bromoquinone (**84**), was the first reported intermolecular aza-Diels-Alder reaction of a 2-methylsubstituted 1-azadiene (Scheme 28).



Scheme 28.

Silyloxyazadiene (**83**) is free of steric interference between the methyl groups at the nitrogen and the C-2 position; this is due to the continuation of conjugation (Figure 11). It is also activated through the sharing of its oxygen non-bonding pair of electrons, allowing it to successfully undergo normal electron-demand aza-Diels-Alder reactions. This is a big advantage of oximes compared to hydrazones, as it allows the incorporation of substituents, for example, a methyl group, at the C-2 position of the pyridine ring and therefore increasing the possibility of further conversion to other functionalities. The azadiene (**86**) has steric interference between the methyl groups at the nitrogen and the C-2 position, this causes the azadiene to twist out of conjugation and therefore it is not activated (Figure 12)[81].

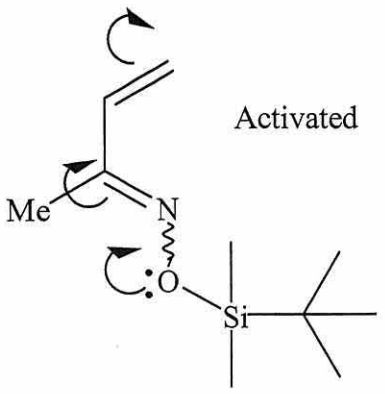


Figure 11. 83

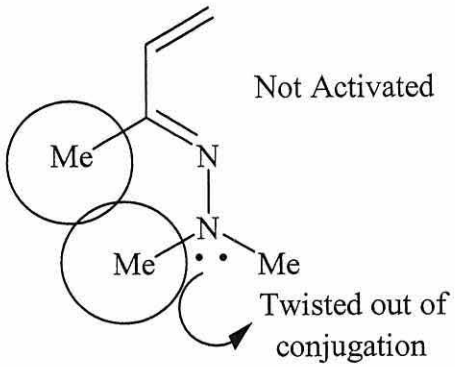
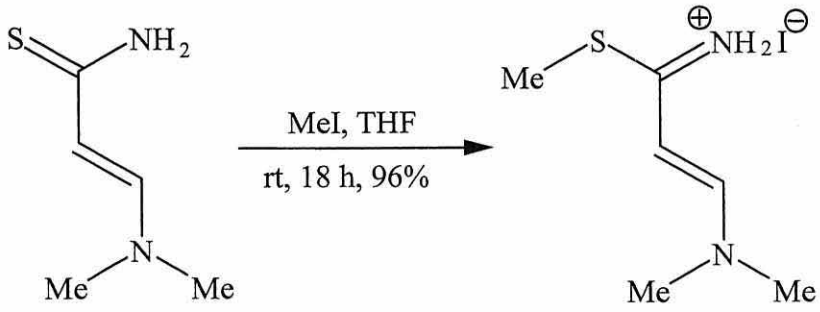


Figure 12. 86

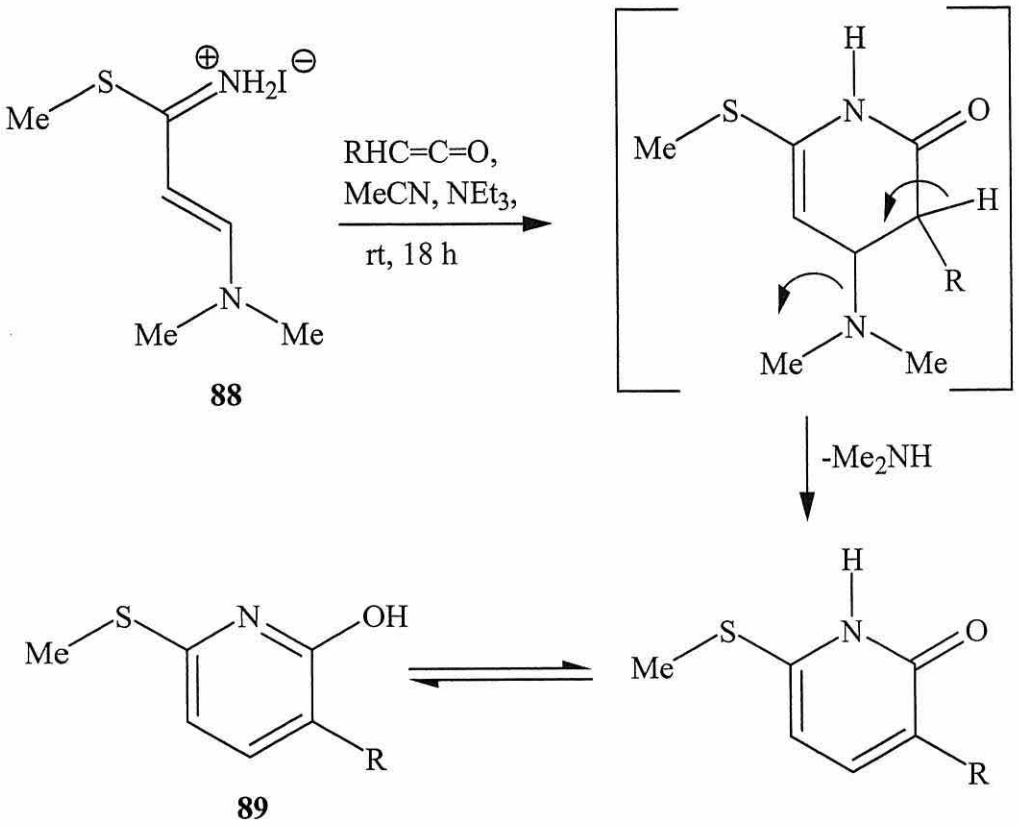
In 2004, Deniaud and co-workers[84] investigated the synthesis of di- and trisubstituted pyridines starting from an *S*-methyl salt. Vinylthioamide (**87**) was reacted with excess methyl iodide to give the corresponding *S*-methyl salt (**88**) (Scheme 29) as the sole product due to the preferential alkylation of the more nucleophilic sulphur atom.



87 **88**

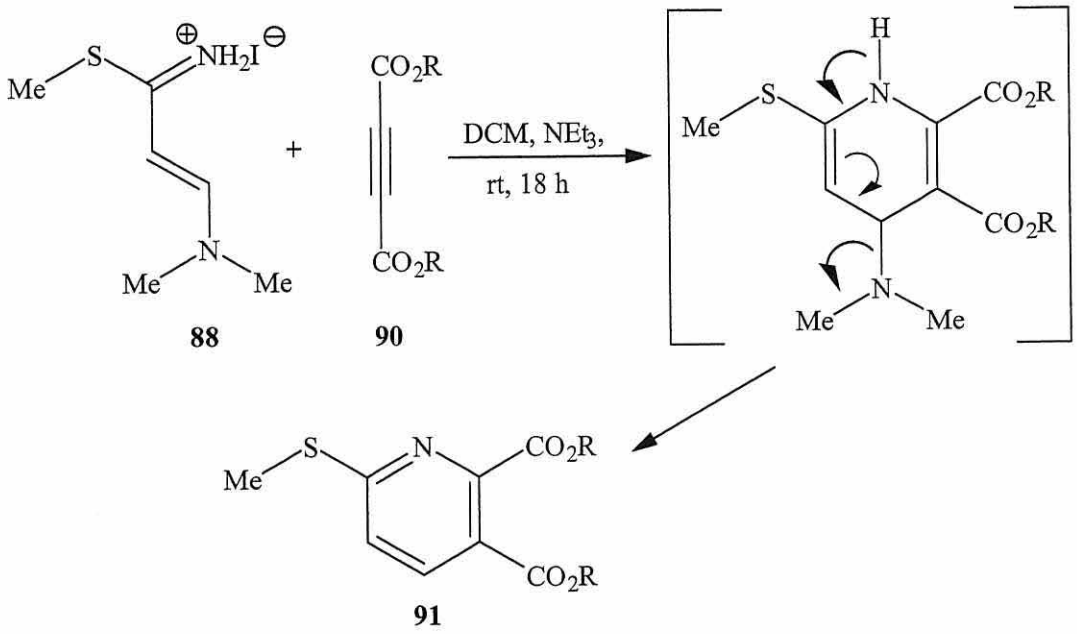
Scheme 29.

The *S*-methyl salt was then treated with a range of ketenes, obtained from the corresponding acid chlorides, leading to a [4 + 2] cyclocondensation giving 6-methylsulfanylpyridin-2(1*H*)-ones (**89**) (Scheme 30).



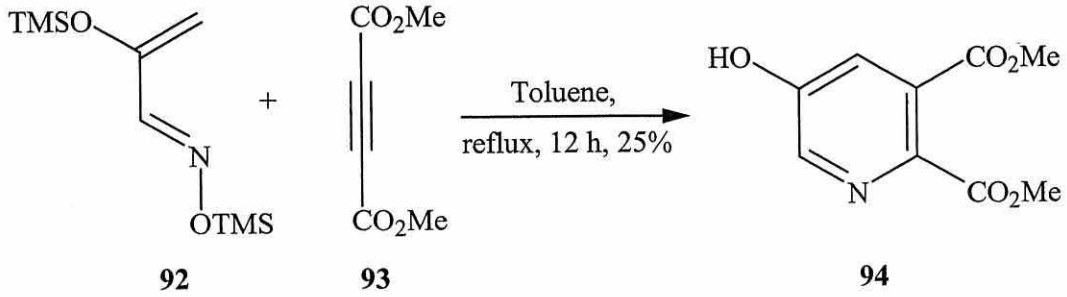
Scheme 30. **89a** R = CO_2Me, 58%;
89b R = CO_2Et, 56%;
89c R = C_6H_5, 50%.

The group performed preliminary antiviral and cytotoxic assays for compounds **89** against HSV-1 in Vero (African Green Monkey) cells. The biological tests showed that the heterocycles did not display any anti-herpes activity. The *S*-methyl salt, **88**, was also reacted with dialkyl acetylenedicarboxylate (**90**). The tandem [4 + 2] cycloaddition/deamination reaction between **88** and acetylenic dienophiles in the presence of triethylamine gave pyridines (**91**) (Scheme 31).



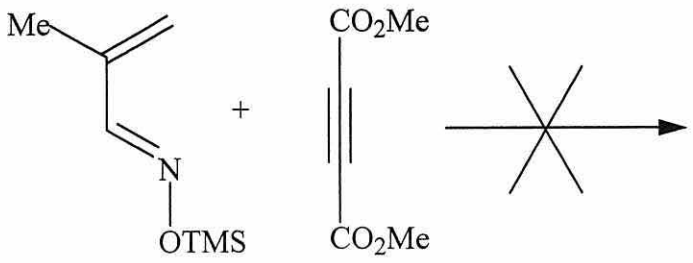
Scheme 31. **91a** R = Me, 62%;
91b R = Et, 66%.

In 1990, Igarashi and co-workers[85] investigated the Diels-Alder reactions of silylated butadiene derivatives with dimethyl acetylenedicarboxylate. The group mainly studied siloxybutadienes, with only a small amount of work done on siloxyazabutadienes (**92**). 1,3-Bis(trimethylsiloxy)-1-aza-1,3-buatdiene (**92**) was reacted with dimethyl acetylenedicarboxylate (**93**) to give the highly substituted pyridine, dimethyl 5-hydroxy-2,3-pyridinedicarboxylate (**94**) (Scheme 32).



Scheme 32. Aza-Diels-Alder reaction.

The group also tried refluxing 3-methyl-1-trimethylsiloxy-1-aza-1,3-butadiene (**95**) with **93** in toluene, but this reaction gave no cycloadduct (Scheme 33). The group were successful with numerous reactions involving siloxybutadienes and **93** to give the corresponding benzene cycloadducts.



95 **93**

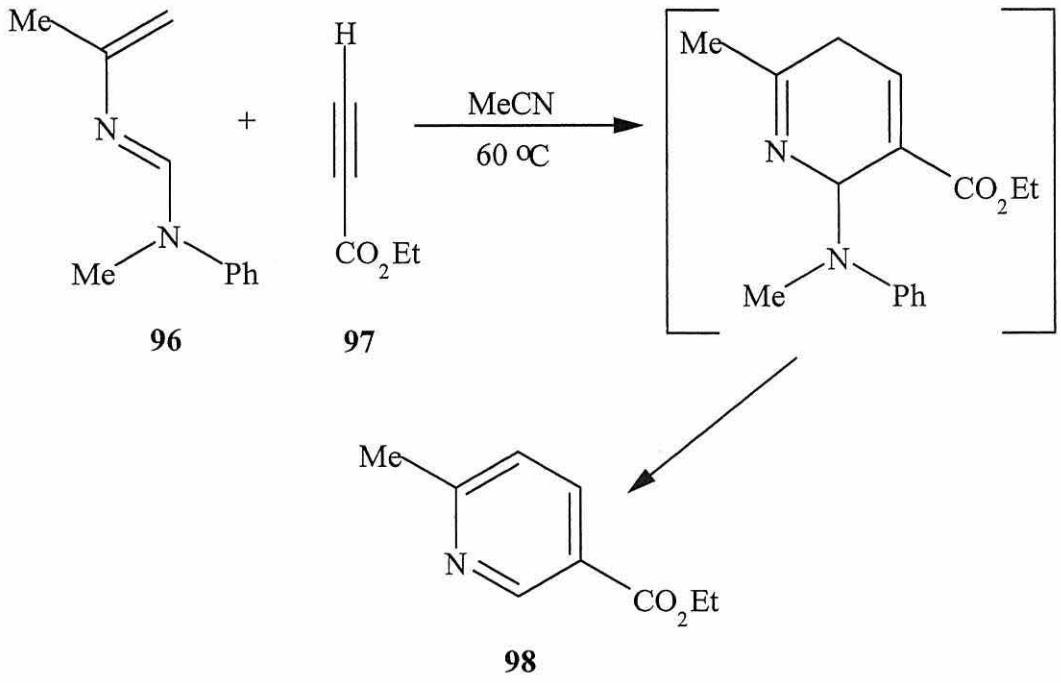
Scheme 33.

5.2.1.1 Summary

The most commonly used 1-azadienes are hydrazones, these compounds generally react relatively quickly with a wide range of dienophiles, producing highly substituted pyridines in high yield. One problem with hydrazones is that steric strain can exist, caused by substituents on the nitrogen atom. Another problem with hydrazones is that if the $^{-}NR_2$ is eliminated during the reaction it (or HNR_2) can then react with the substrates present (especially the electron-deficient dienophile) or the product. This is an insignificant problem with oximes as the eliminated ^{-}OR / HOR is less nucleophilic. Oximes are free of steric interference due to the oxygen, allowing them to readily undergo normal-electron-demand aza-Diels-Alder reactions. They do however have another problem; they readily undergo Beckmann rearrangements and Beckmann fragmentations (discussed) to form amides.

5.2.2 2-Aza-Dienes

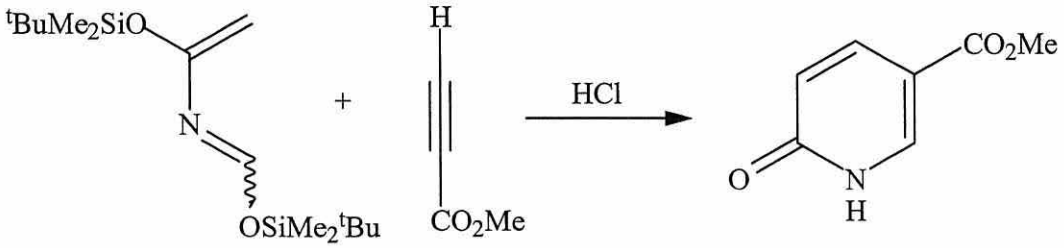
In 1982, Ghosez and co-workers[86] used 2-aza-1,3-dienes with a substituted amino group at the 1-position. This amino group's nitrogen lone pair of electrons are the driving force of the cycloaddition reaction, causing the diene to be highly reactive in a normal-electron-demand aza-Diels-Alder reaction. The 2-aza-1,3-diene (**96**) which mainly exists in the *s-cis*-conformation readily reacts with ethyl propiolate (**97**) in acetonitrile to give the disubstituted pyridine (**98**) in a 50% yield (Scheme 34).



96 **97** **98**

Scheme 34. 98, 50%.

They also investigated the reaction between the 2-aza-diene (**99**) and methyl propiolate (**100**) to give the pyridine (**101**) (Scheme 35). The regioselectivity of the cycloaddition was demonstrated by the formation of a single heterocyclic product (**101**, 64% yield).



99 **100** **101**

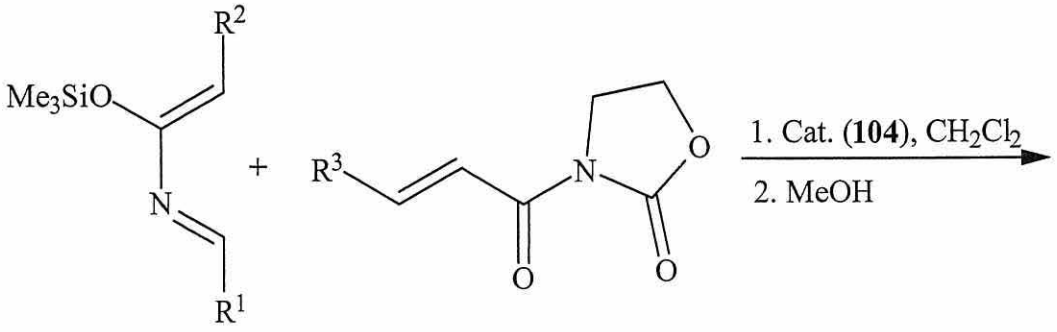
Scheme 35.

In 1999, Jnoff and Ghosez[87] researched asymmetric aza-Diels-Alder reactions of 2-azadienes that are catalysed by a chiral copper(II) complex. The success of this cycloaddition relied on finding a Lewis acid that will:

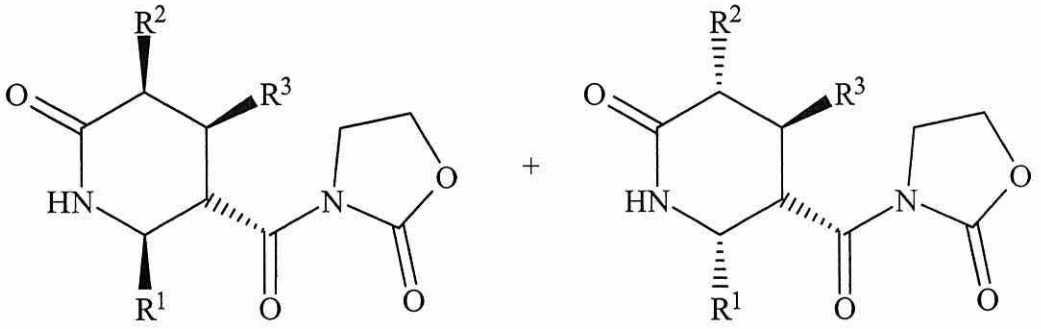
a) activate the dienophile by complexation with an appropriate functional group,

b) does not irreversibly complex the nucleophilic nitrogen atom of the azadiene.

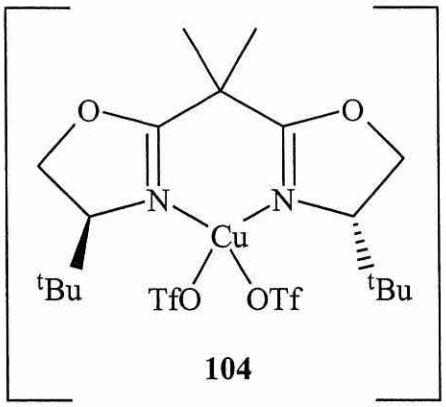
They noticed that highly nucleophilic aza-dienes were often unstable in the presence of common Lewis acids that had been successfully used in Diels-Alder reactions of carbadienes. They successfully used Evans' mild Lewis acid catalyst which is derived from copper(II) triflate and a C_2-symmetric bis(oxazoline) ligand. The Lewis acid was tolerated by the highly reactive azadiene (**102**) (Scheme 36) because it binds selectively to the bidentate imide group of the dienophile (**103**). The aza-diene was stable and did not deactivate the catalyst (**104**). The copper(II) catalyst was most effective at -45 °C, it increased the rate, diastereoselectivity and the enantioselectivity of the cycloaddition.



102 **103**



105a **105b**



104

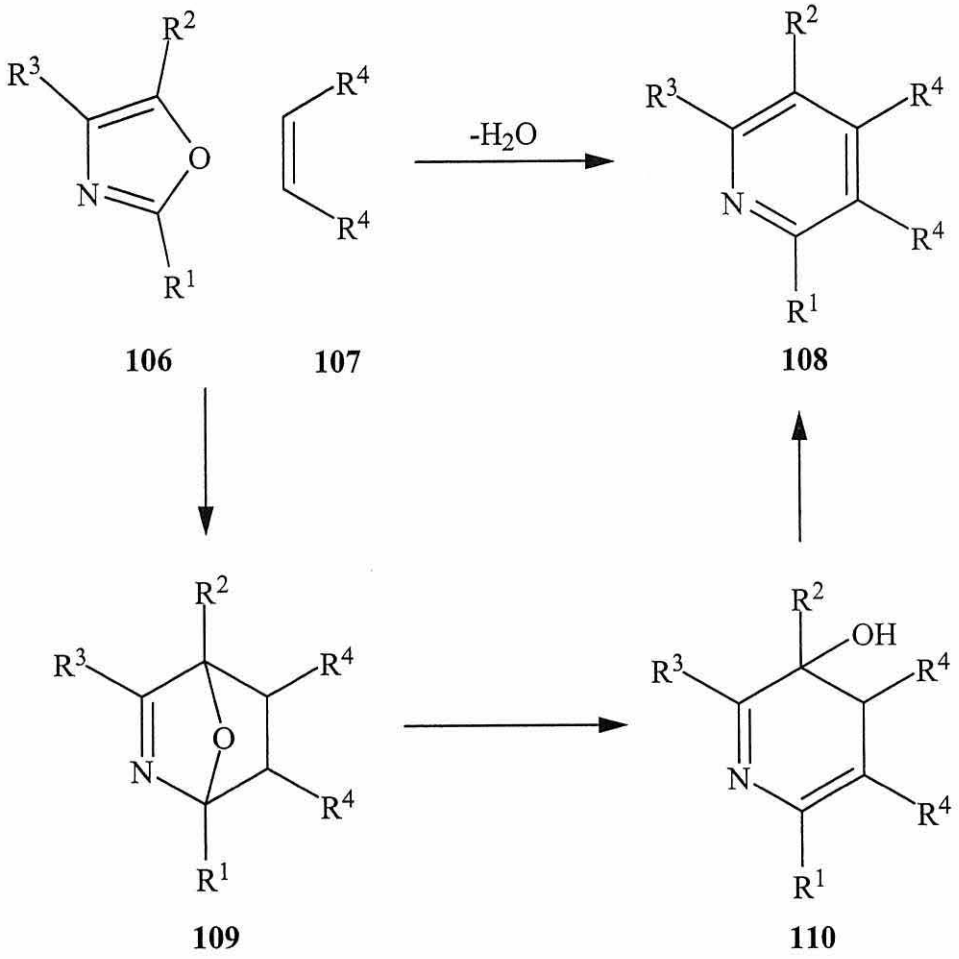
Scheme 36. **105a** = *exo* product, **105b** = *endo* product; (> 99 : 1).
(R^1 = Ph; R^2 = Me; R^3 = Me, 85%, ee = 93.4%);
(R^1 = Ph, R^2 = Me, R^3 = H, 96%, ee = 98.3%);
(R^1 = Ph, R^2 = H, R^3 = Me, 80%, ee = 93%).

5.2.2.1 Summary

2-Azadienes are highly reactive, more so with a substituted amino group in the 1-position as this is a driving force in the reaction. This area of chemistry has been studied more-so than 1-azadienes, due to their high reactivity. Ghosez and co-workers have done many investigations in this area, and there is much research still to be done.

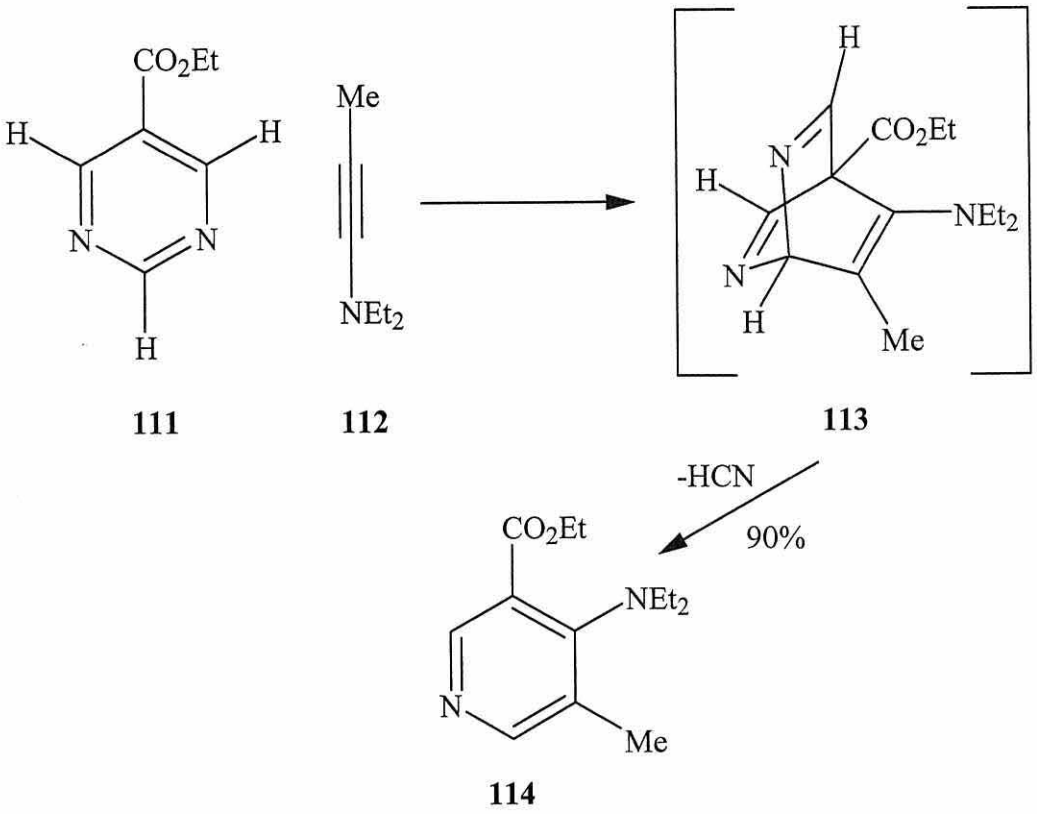
5.2.3 Alternative Aza-Diels-Alder Reactions for the Synthesis of Substituted Pyridines

In 1983, Boger[15] reported alkyloxazoles taking part in Diels-Alder reactions with maleic anhydride. From this it was observed that a $[4^{\pi} + 2^{\pi}]$ cycloaddition reaction between an oxazole (**106**) and a dienophile (**107**) resulted in the formation of a highly substituted pyridine (**108**) (Scheme 37). The aromatisation happened *via* the fragmentation of the initial $[4^{\pi} + 2^{\pi}]$ cycloadduct (**109**) to give **110** followed by elimination of water.



Scheme 37. A Diels-Alder reaction of an oxazole to form a pyridine.

Boger also investigated pyrimidines and found that on the addition of a strong electron withdrawing substituent to the pyrimidine (**111**) the rate of an inverse electron demand [$4^{\pi} + 2^{\pi}$] cycloaddition reaction is increased with an electron-rich dienophile (**112**) (Scheme 38).

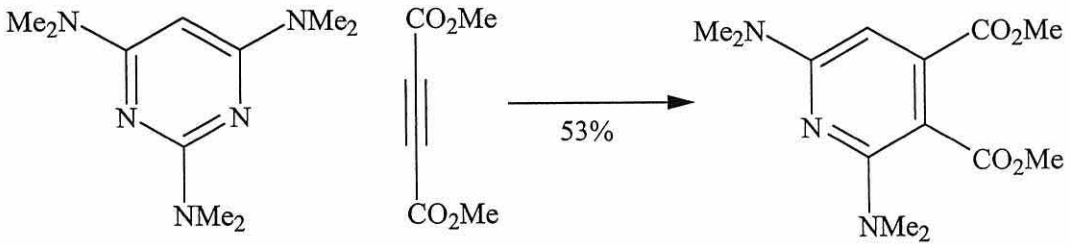


111 **112** **113**

114

Scheme 38.

The complementary substitution of pyrimidine with 2 or 3 strong electron-donating groups at the C-2, C-4 or C-6 position is sufficient for the 4π participation of the pyrimidine (**115**) in a normal electron demand Diels-Alder reaction (Scheme 39) with dimethyl acetylenedicarboxylate (**116**) to yield the highly substituted pyridine (**117**).

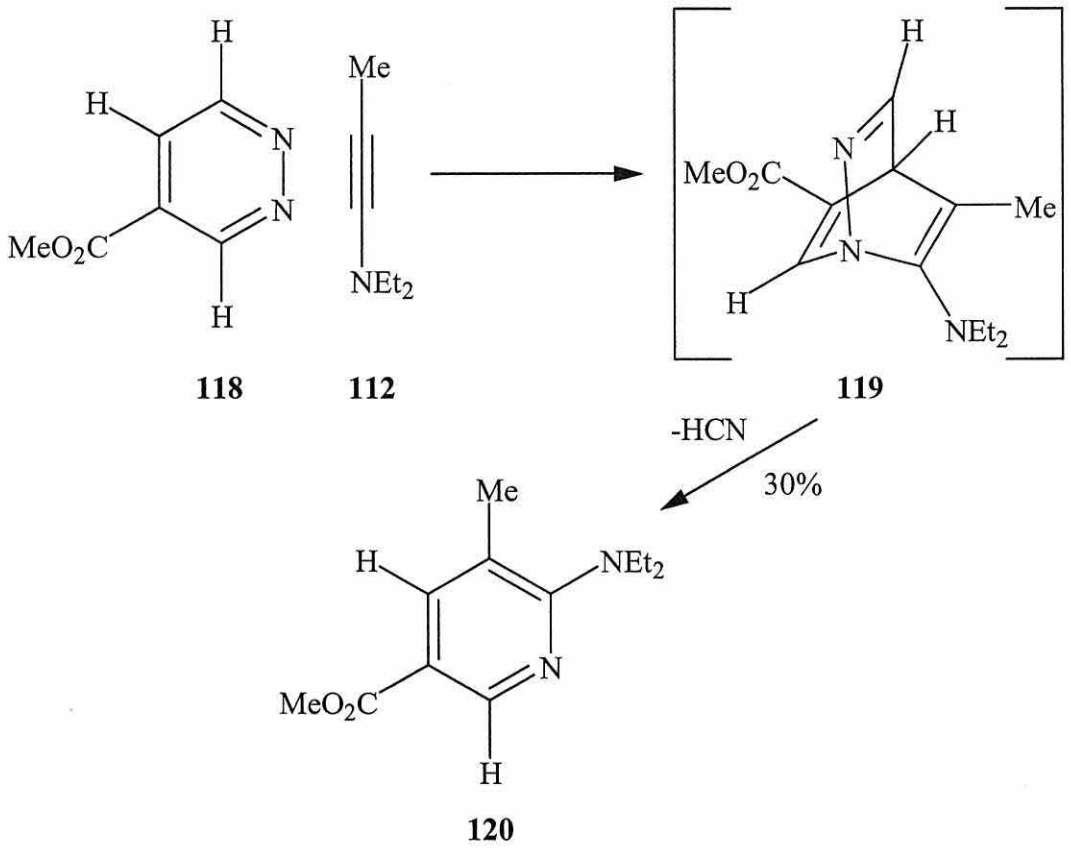


115 **116** **117**

Scheme 39.

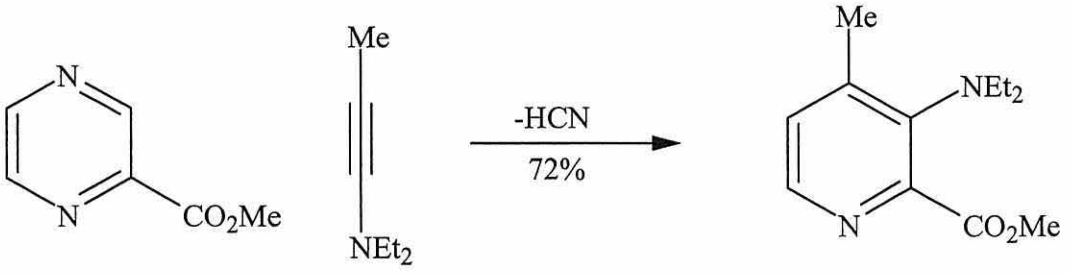
Pyridazines (1,2-diazines) (*e.g.* **118**) and pyrazines (1,4-diazines) (*e.g.* **121**) can also take part in inverse electron demand [$4^{\pi} + 2^{\pi}$] cycloadditions with an electron rich

dienophile (Schemes 40 and 41 respectively). The rate and regioselectivity of the reactions of both pyridazines and pyrazines, are controlled by the number and the position of the electron withdrawing substituents present on the 1,2-azadiene and the 1,4-azadiene respectively.



118 **112** **119** **120**

Scheme 40. Pyridazine undergoing an inverse electron-demand cycloaddition.

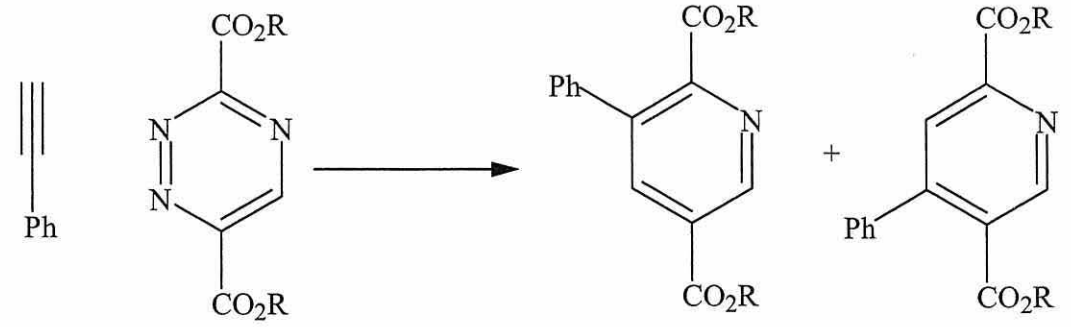


121 **112** **122**

Scheme 41. Pyrazine undergoing an inverse electron-demand cycloaddition.

In 1986, Maggiora and Mertes[88] researched aza-Diels-Alder reactions of triazines and tetrazines as a method for the preparation of substituted pyridines. They

took an alkyne (**123**) and reacted it *via* a [$4^{\pi} + 2^{\pi}$] cycloaddition reaction with 1,2,4-triazine (**124**) resulting in the formation of two substituted pyridines (**125** and **126**) with the elimination of nitrogen (Scheme 42).

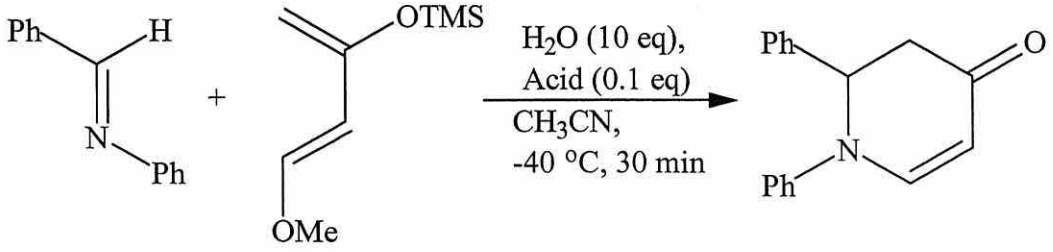


123 **124** **125** **126**

Scheme 42. 125 : 126 ratio 56 : 44

This reaction is not regioselective and so yields both the 3-phenyl (**125**) and the 4-phenyl (**126**) derivatives, with a 90 % yield overall and a ratio of 56:44 (**125**:**126**).

Imines can be used as dienophiles. In 1999 Akiyama, Takaya and Kagoshima[89] studied the aza-Diels-Alder reactions of Danishefsky's diene (**127**) and imines in aqueous media. They reported the Brønsted acid-catalysed aza-Diels-Alder reactions of aldimine and Danishefsky's diene (**127**) to produce dihydro-4-pyridone (**128**) in high yield (Scheme 43).

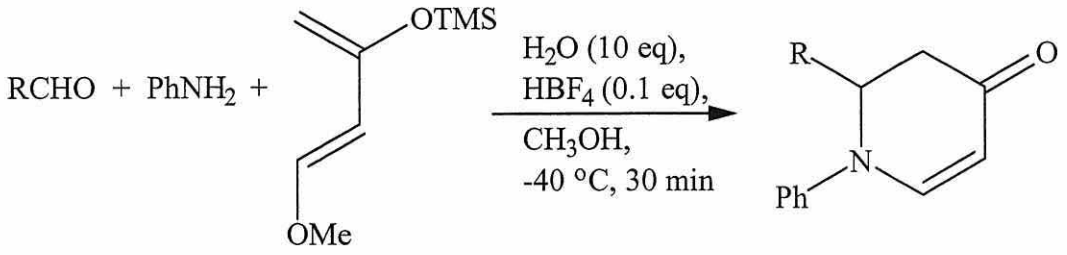


127 **128**

Scheme 43: Acid: HBF_4; 91%, *p* -TsOH; 76%, CF_3CO_2H; 89%

After screening various solvents they found that methanol was the best solvent as the Brønsted acid-catalysed aza-Diels-Alder reaction took place quickly and in high yield. The researchers then synthesised an imine that was generated *in situ* and was allowed

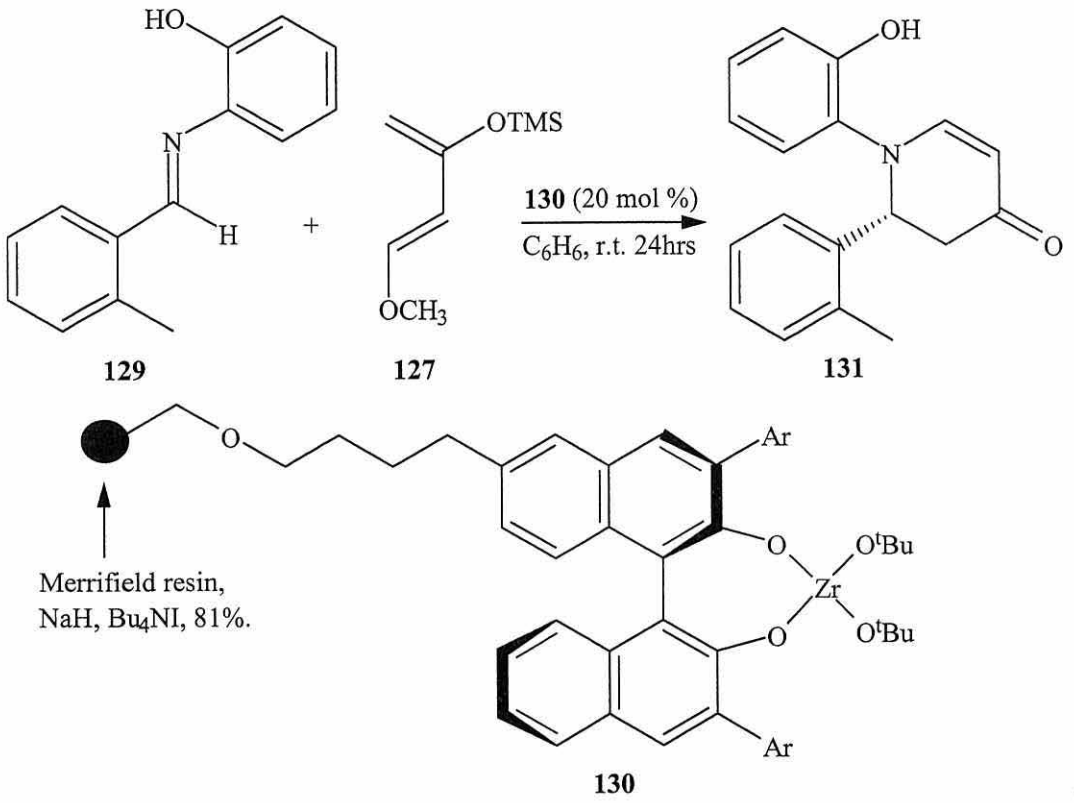
to react under one-pot reaction conditions. To achieve this they used a three component synthesis starting from an aldehyde and an amine (Scheme 44).



127

Scheme 44. R = Ph, 88 %; $PhCH_2CH_2$, 75 %; $(CH_3)_2CH$, 77 %.

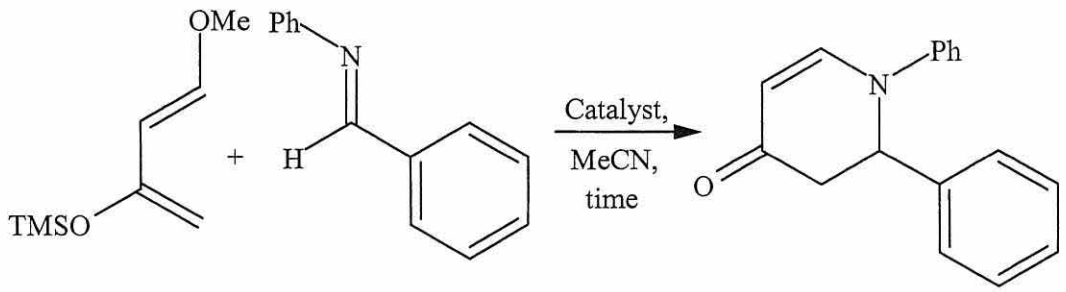
In 2000, Kobayashi and co-workers[90] looked at optimising enantioselective aza-Diels-Alder reactions by the means of a chiral catalyst in both the solid-phase and in the liquid-phase. In the presence of 20 mol % of various zirconium catalysts the aza-Diels-Alder reaction of aldimine (**129**) with Danishefsky's diene (**127**) was performed to give the substituted pyridine (**131**) (Scheme 45). The yield was dependent on the aromatic group used in the zirconium catalyst (**130**).



Scheme 45. Ar = phenyl, 61%, ee 77%; 4-biphenyl, 59%, ee 80%; 2-naphthyl, 74%, ee 74%; 4-fluorophenyl, 80%, ee 83%; 4-methoxyphenyl, 75%, ee 41%; 3,4-dimethoxyphenyl, 82%, ee 60%.

This reaction was performed using a resin to support the catalysts. The zirconium catalysts were then prepared in the liquid-phase and the reaction repeated. It was found that the reaction proceeded smoothly and gave the piperidine derivatives in high yields with good enantiomeric excess. There was very little difference between the solid- and liquid-phase reactions. There were however, higher selectivities when electron-withdrawing groups were introduced into the catalyst. The slow addition of the substrate to the catalyst (**130**) also increases the selectivity.

In 1999, Frost and co-workers[91] studied using catalysts in aza-Diels-Alder reactions. (The researchers have studied this area for many years see references 92 – 97). They looked at the efficiency of catalysis in the reaction between *N*-benzilideneaniline (**132**) and Danishefsky's diene (**127**) (Scheme 46).



127 **132** **133**

Catalyst	Time (h)	Yield (%)
None	24	<5
$Sc(OTf)_3$ (10 mol%)	20	83
$In(OTf)_3$ (10 mol%)	0.5	89
$In(OTf)_3$ (0.5 mol%)	0.5	93

Scheme 46. Catalyst efficiency in an aza-Diels-Alder reaction

In the absence of a catalyst there was only a trace amount of product (**133**) (*i.e.* <5%), after 24 hours at room temperature, but remarkably with the addition of 5 mol% indium(III) triflate, the product (**133**) was efficiently formed in 30 minutes to give an isolated yield of 93%. To prove that the reaction was indeed being promoted by the indium(III) triflate and not the triflic acid formed *in situ*, they repeated the experiment and added quantities of triflic acid, up to 30 mol%. They observed no product being formed, only the hydrolysis of Danishefsky's diene to the corresponding enone.

5.2.3.1 Summary

Highly substituted pyridines can be formed using various heterocyclic aza-dienes, for example, pyrimidines, pyridazines, pyrazines, triazines and tetrazines; these aza-dienes undergo [$4^{\pi} + 2^{\pi}$] cycloadditions with relative ease and in high yield. Electron-rich imines can under-go aza-Diels-Alder reactions with acid catalysis. Inverse electron-demand aza-Diels-Alder reactions will also occur between neutral imines and electron-deficient dienes.

5.3 General Summary

The aza-Diels-Alder reaction is a powerful synthetic method for making highly substituted pyridines. It is a thermal pericyclic cycloaddition most commonly between an aza-diene and a dienophile.

1-Azadienes are generally reacted with electron-deficient alkenes and quinines; 2-azadienes however react with a wider variety of dienophiles, such as ketones, alkenes, alkynes, aromatic alkenes and other dienes. Alternatively the nitrogen in an aza-Diels-Alder reaction may be present in the dienophile, *i.e.* imines have proven to be useful aza-dienophiles. The use of appropriate Brønsted acid catalysts and Lewis acid catalysts in aza-Diels-Alder reactions may increase the yield of the substituted pyridines produced.

5.4 Synthesis of Aza-Dienes

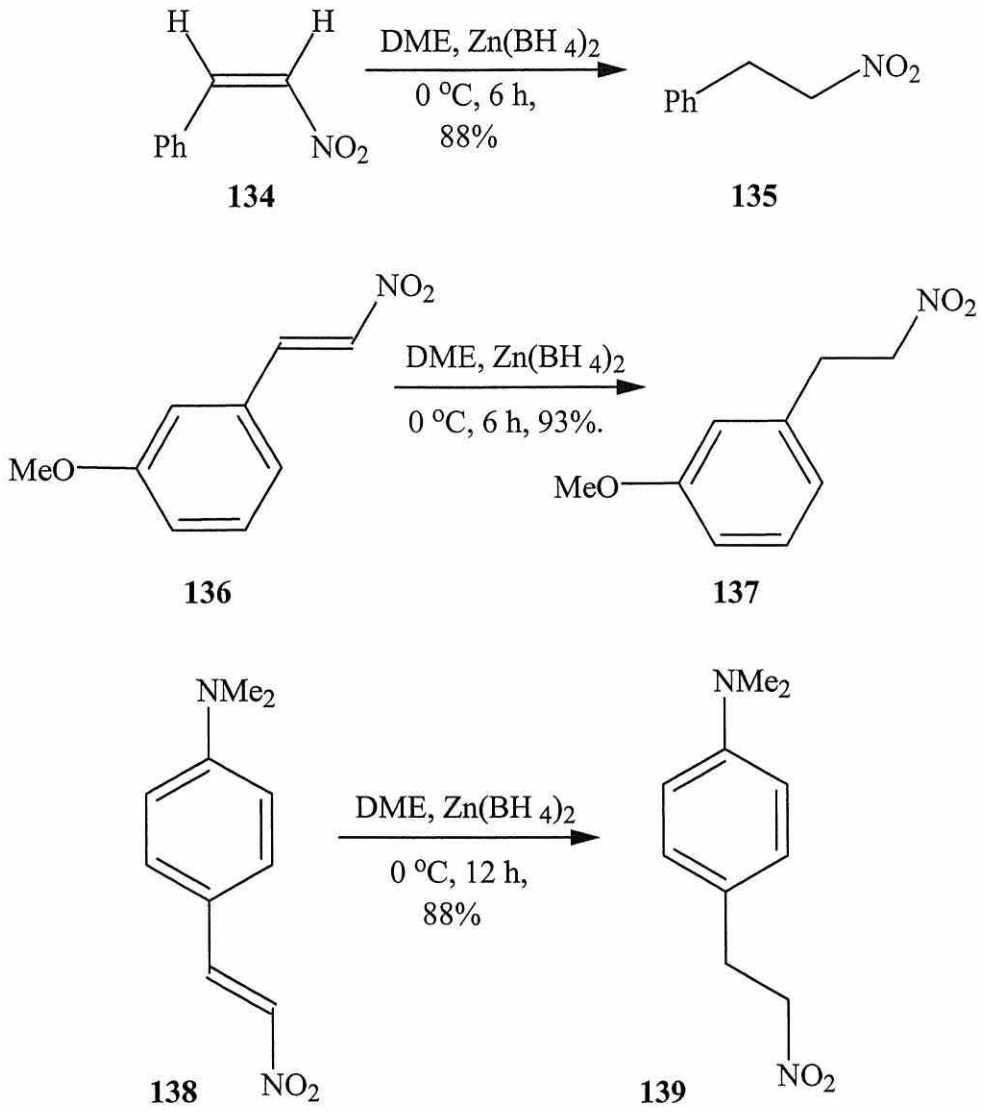
The synthesis of aza-dienes can be done from a number of different starting materials. Aza-dienes usually contain an imine, hydrazone, or oxime unit. The following section highlights the synthesis of oximes and hydrazones that are most relevant to this research, for general reviews see references 98 - 104. Enamines are also covered as they are a component of my planned work.

5.4.1 Oximes

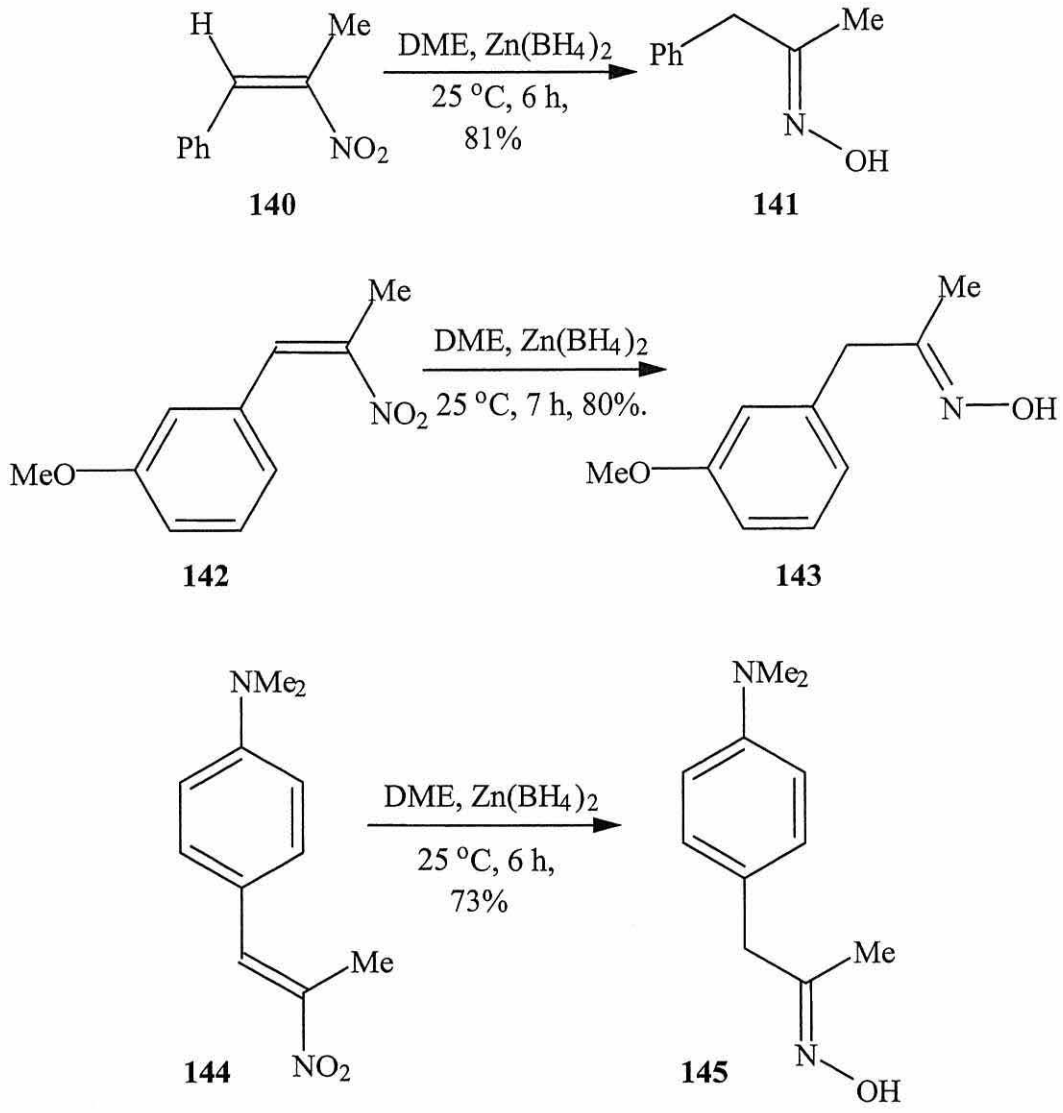
One of the most important additions to a carbonyl group is the aldol reaction. In this reaction the attacking nucleophile usually forms an enolate with the carbonyl. This may lead to a substitution reaction (for example, a Claisen condensation).

In 1992, Ranu and co-workers[105] investigated the conversion of mono- and di-substituted nitroalkenes to nitroalkanes and oximes respectively. Conjugated nitroalkenes can be reduced using a variety of reducing agents; lithium aluminium hydride gives a mixture of products containing saturated amine, nitroalkane, oxime and hydroxylamine groups. Sodium borohydride, lithium borohydride and sodium trimethoxyborohydride primarily give the corresponding nitroalkane. The researchers studied the reduction of mono-β-substituted conjugated nitroalkenes by zinc

borohydride which gave the corresponding nitroalkane (Scheme 47), whereas the disubstituted nitroalkenes produced the corresponding oximes (Scheme 48).

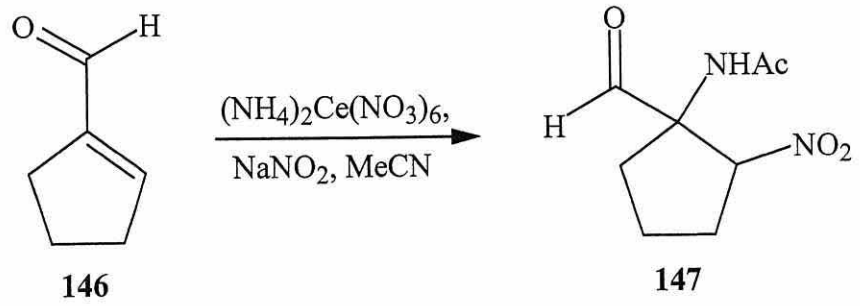


Scheme 47. Reduction of monosubstituted nitroalkenes to nitroalkanes.



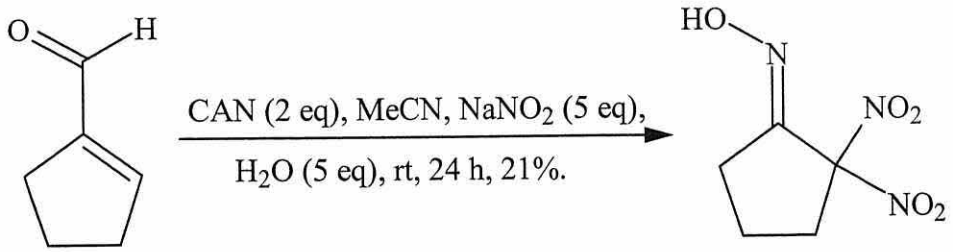
Scheme 48. Reduction of disubstituted nitroalkenes to oximes.

In 1998, Smith and co-workers[106] investigated the synthesis of 2,2-dinitrocyclopentanone oxime (**148**) during an attempted nitroacetamidation of cyclopentenecarboxaldhyde (Scheme 49). This is the first example of nitroacetamidation on α,β-unsaturated carbonyl systems. The aldehyde (**146**) was reacted with ceric ammonium nitrate (CAN) to give 2,2-dinitrocyclopentanone oxime (**148**) (Scheme 50). The reaction not only produces an α,α-dinitrooxime under mild conditions but also results in decarbonylation of the aldehyde.



146 **147**

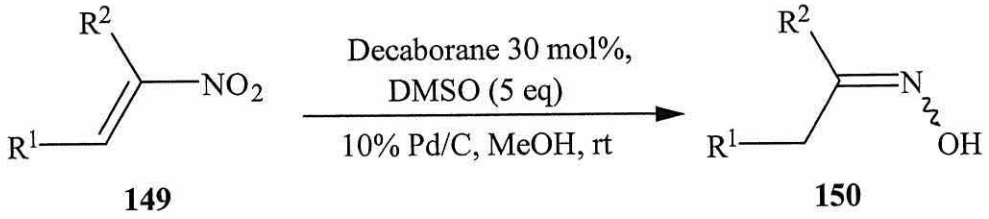
Scheme 49. Proposed nitroacetimidation of **146**.



146 **148**

Scheme 50. Formation of 2,2-dinitrocyclopentanone oxime.

In 2003, Lee, Park and Yoon[107] studied the synthesis of oximes by the reduction of nitroalkenes. They found that nitroalkenes (**149**) in methanol could be smoothly converted into oximes (**150**) using a system of decaborane and DMSO in the presence of Pd/C under nitrogen at room temperature (Scheme 51).



149 **150**

Scheme 51. 77 % isolated yield.

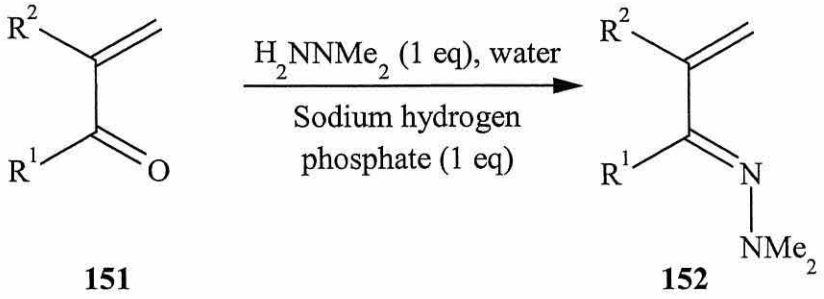
They carried out reactions in the presence and in the absence of DMSO, and each time the yield of the oximes produced was considerably higher in the presence of DMSO. During the reactions they noticed a dimethyl sulfide smell and offered the theory that the poison for the reduction of the nitroalkenes into an alkylamine may be a small amount of dimethyl sulfide generated by the reduction of dimethyl sulfoxide, although the exact role of DMSO was not yet clear.

5.4.1.1 Summary

There are very few methods available for the synthesis of oximes. The methods that are available do produce the oximes in a relatively high yield and they can generally be isolated with relative ease. Oximes are important in many aspects, *i.e.* the formation of heterocycles which can then be used for natural products, antibiotics and agonists for the treatment of diseases such as Alzeimer's disease.

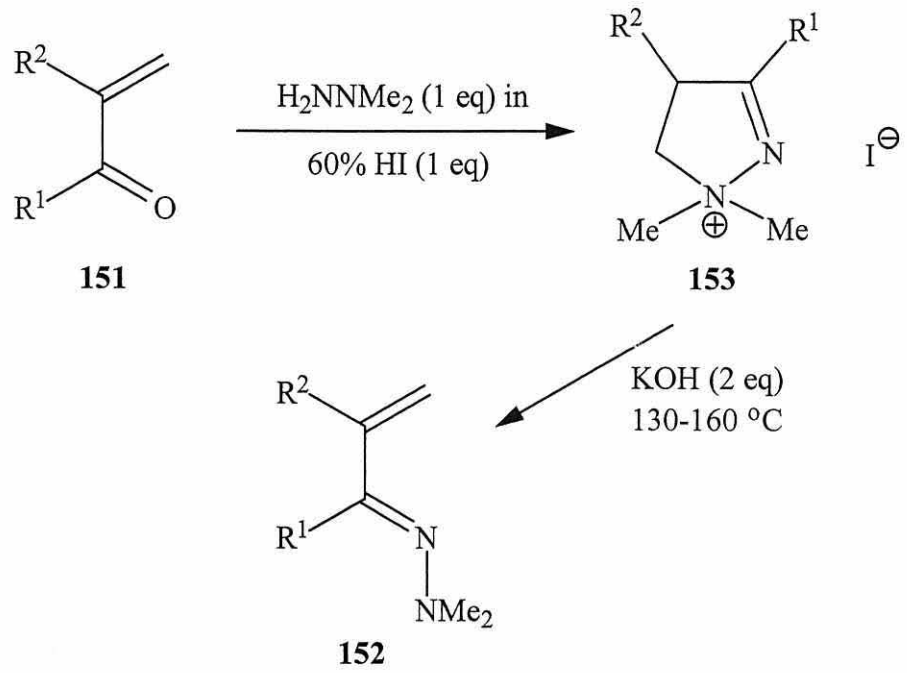
5.4.2 Hydrazones

In 1984, Tamura and co-workers[108] investigated making hydrazones as useful aza-dienes for the synthesis of pyridines. They did this by two different routes. The first was by the direct treatment of *N,N*-dimethylhydrazine with α,β-unsaturated carbonyl compounds (**151**) in a buffered solution (Scheme 52) to give the corresponding hydrazone (**152**). Care was needed with substrates like **151** as they can undergo a 1,4-addition to give **153**, therefore Hoffmann cleavage was also used (Scheme 53); both methods are successively used to convert the carbonyl into a hydrazone with relatively high yields.



151 **152**

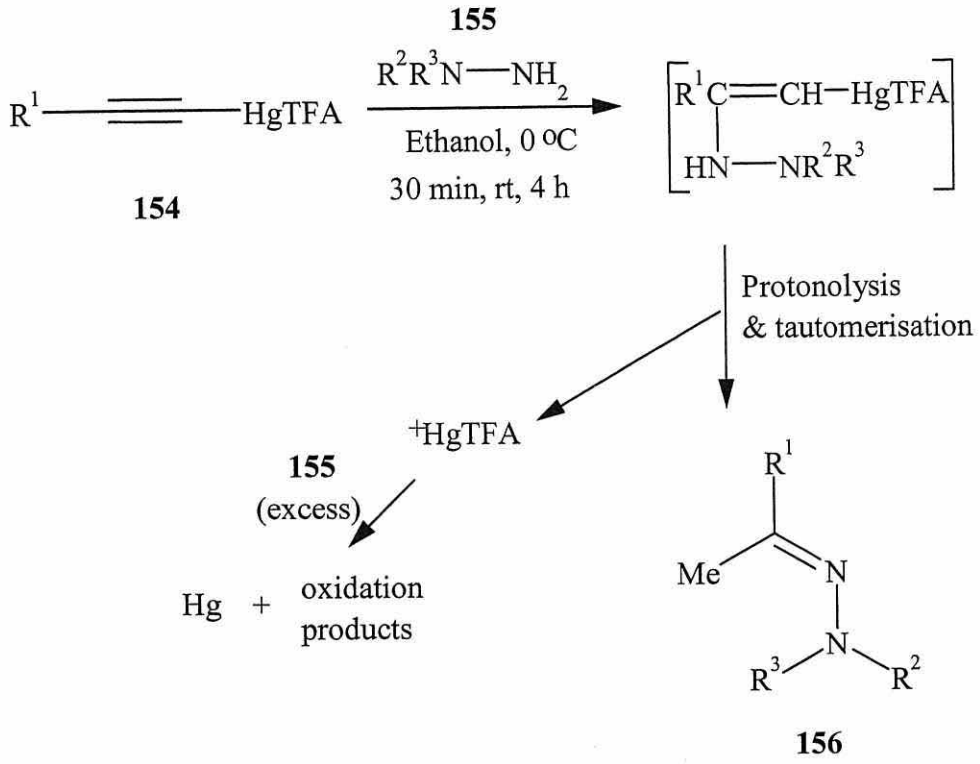
Scheme 52. Direct treatment of *N,N* -dimethylhydrazine (method A).
$R^1 = H$, $R^2 = Me$, 50%;
$R^1 = H$, $R^2 = C_2H_5$, 56%.



151 **153** **152**

Scheme 53. Hoffann cleavage (method B).
R^1 = Me, R^2 = H, 71%;
R^1 = Me, R^2 = Me, 21%;
R^1 = C_2H_5, R^2 = H, 73%.

In 1988, Barluenga and co-workers[109] looked at treating hydrazines with 1-alkynylmercury trifluoroacetates (**154**) as an easy preparation for several hydrazones and 1-amino-1-aza-1,3-dienes (**156**). They prepared several 1-alkynylmercury triflouroacetates (**154**) and reacted them with excess hydrazine (**155**) to yield the corresponding hydrazones (**156**) (Scheme 54), along with the precipitation of metallic mercury. The metallic mercury was explained as a side reaction between excess hydrazine and free mercury(II) species arising from protonolysis.



Scheme 54: Hydrazones

R^1 = Ph, R^2 = H, R^3 = H, 85%;
R^1 = Ph, R^2 = Ph, R^3 = H, 93%;
R^1 = Ph, R^2 = Ph, R^3 = Me, 66%.

1-amino-1-aza-1,3-dienes
R^1 = CH_2=CMe, R^2 = Me, R^3 = H, 51%
R^1 = CH_2=CMe, R^2 = Me, R^3 = Me, 67%.

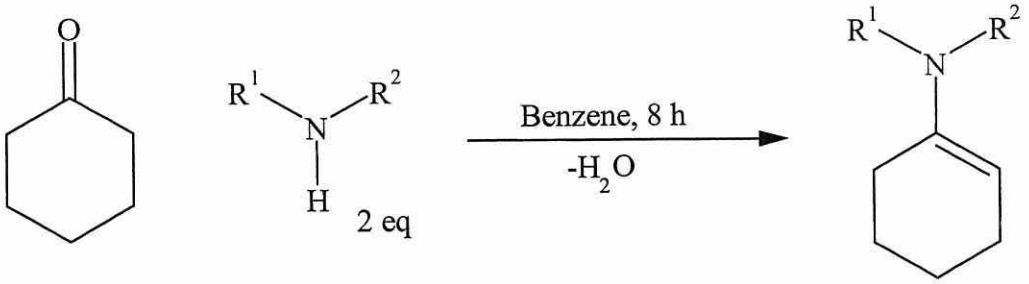
5.4.2.1 Summary

Hydrazones are relatively easy to make with respect to oximes as hydrazones do not undergo Beckmann rearrangements. They are generally made by the addition of R^1R^2N-NH_2 to a compound with a carbonyl functional group, in various different reaction conditions. Hydrazones are very useful for the formation of heterocyclic rings.

5.4.3 Enamines

For general reviews see references 100, 101, 110 – 118.

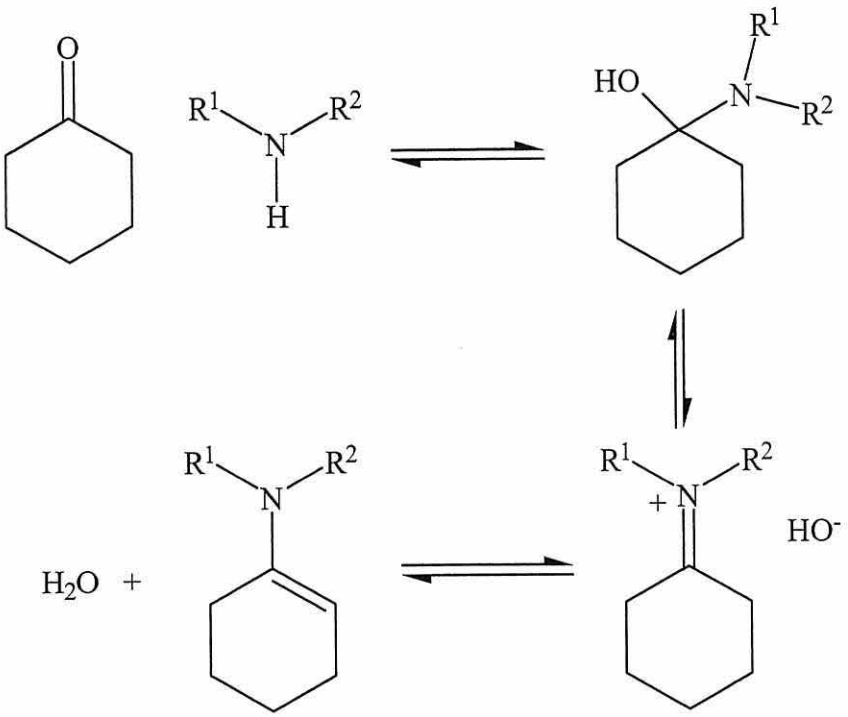
In 1963, Stork and co workers[119] studied the preparation of enamines and the rate of formation of enamines. They reacted a ketone (cyclohexanone) with a secondary amine in the presence of the dehydrating agent anhydrous potassium carbonate, to yield an enamine (**157**) (Scheme 55). They also reported that an efficient alternative method for the preparation of enamines is the removal of water *via* azeotropic distillation with benzene.



157

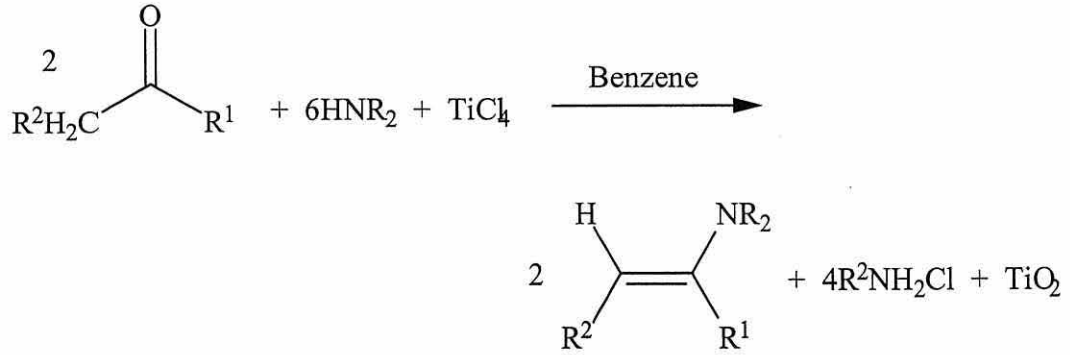
Scheme 55.

They stated that the rate of formation of enamines was affected by two main factors; the first being the basicity of the secondary amino group *e.g.* pyrrolidine is more strongly basic and has a higher rate of reaction than morpholine, and cyclic amines form enamines faster than open-chain amines. The second factor is the nature and environment of the carbonyl group. Cyclopentanone reacts faster than cyclohexanone which in return is faster than the seven-membered ketones. They deduced that the overall rate was not ascribable to any single one of the reversible steps involved in the formation of the enamine, shown in Scheme 56.



Scheme 56.

In 1967, White and Weingarten[120] looked for a general method for the synthesis of enamines and highly hindered enamines. They reported a straightforward method using titanium tetrachloride, secondary amine and either an aldehyde or ketone, leading to a direct and fast enamine formation (Scheme 57). The titanium tetrachloride acts as an efficient water scavenger, forms a Ti(IV) / HNR_2 complex and acts as a Lewis acid catalyst by polarizing the carbonyl bond.

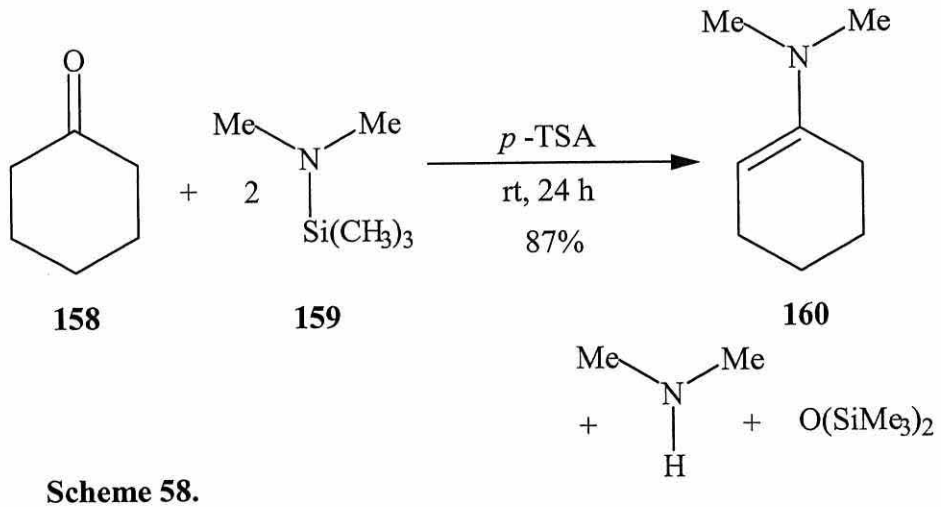


Scheme 57.

Other catalysts that they found to be active were: $AlCl_3$, $SnCl_4$, $FeCl_3$, $AsCl_3$ and $SbCl_3$, although none were reported to be better than the titanium derivative.

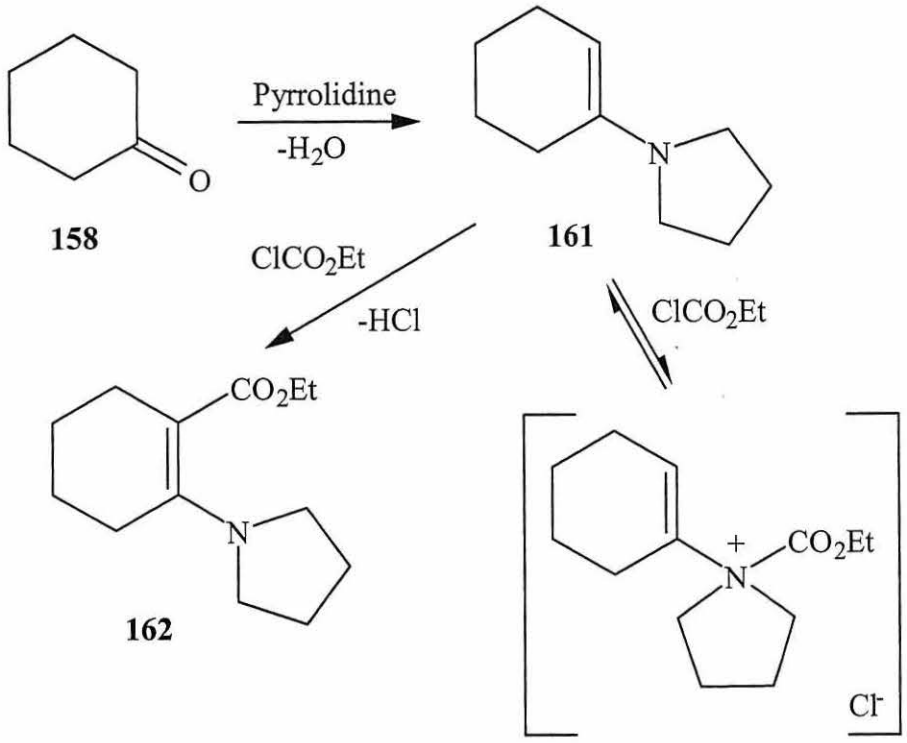
In 1971, Taguchi and Westheimer[121] studied the formation of enamines by reacting ketones and amines in the presence of molecular sieves, as a milder alternative method to titanium tetrachloride as this often causes side reactions. They report that the molecular sieves serve not only as a dehydrating agent but also as a catalyst that can be removed by the simple method of filtration at the end of the reaction.

In 1973, Comi and co-workers[122] reported that even though there were a number of methods for the synthesis of enamines available, there were still difficulties in the synthesis of dimethylaminoenamines due to the high volatility of dimethylamine. They had developed a new method which included the use of *p*-toluenesulfonic acid (*p*-TSA) in the reaction between cyclohexanone (**158**) and trimethylsilyldimethylamine (**159**) to yield 1-dimethylaminocyclohexanone (**160**) (Scheme 58) in a relatively high yield.

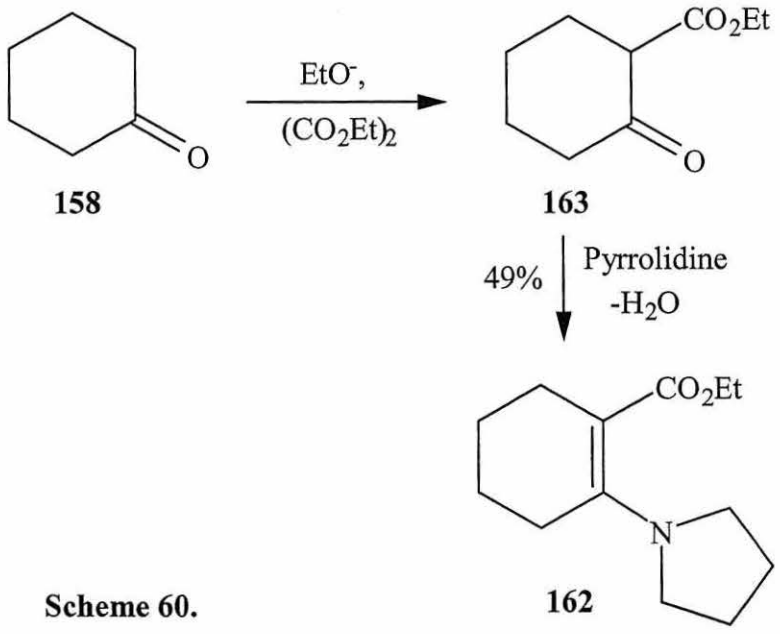


Scheme 58.

In 1982, Carlsson and Lawesson[123] looked at the formation of enaminones *via* two separate methods; the first method was acylation of the enamines derived from a ketone and secondary amines (pyrrolidine, morpholine and piperidine) by ethyl chloroformate (Scheme 59). This method of reacting the ketone with the amine and then acylation of the enamine gave the product (**162**) in trace amounts only. They reported that using two moles of the enamine (**161**) (one mole as a base instead of triethylamine) they could increase the yield to 24%. The second method was the condensation of a ketone with diethyl oxalate, giving a β-ketoester (**163**) which was then reacted with secondary amines (Scheme 60), to give the product (**162**).

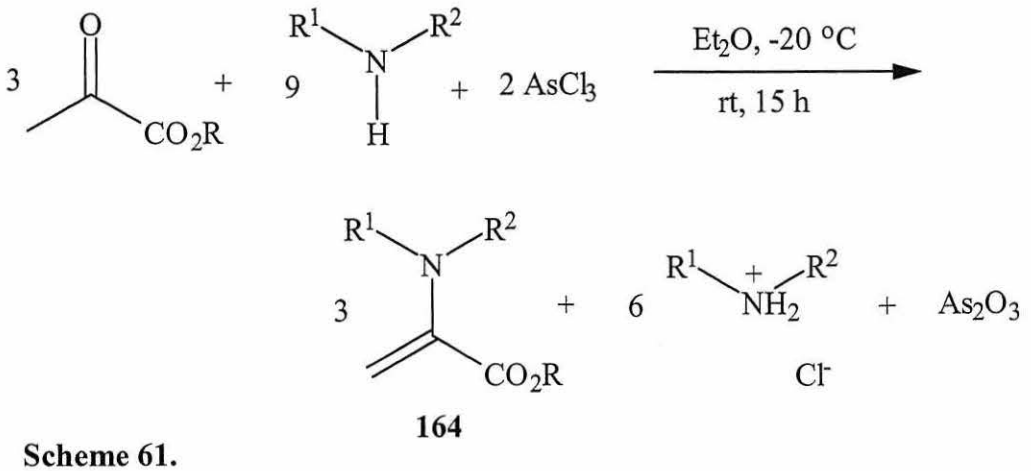


Scheme 59.



Scheme 60.

In 1990, Arnold[124] looked at the formation of enamines from the transformation of alkyl pyruvates. He specifically looked at the synthesis of 2-dialkylamino-2-propenoates (**164**) (Scheme 61).

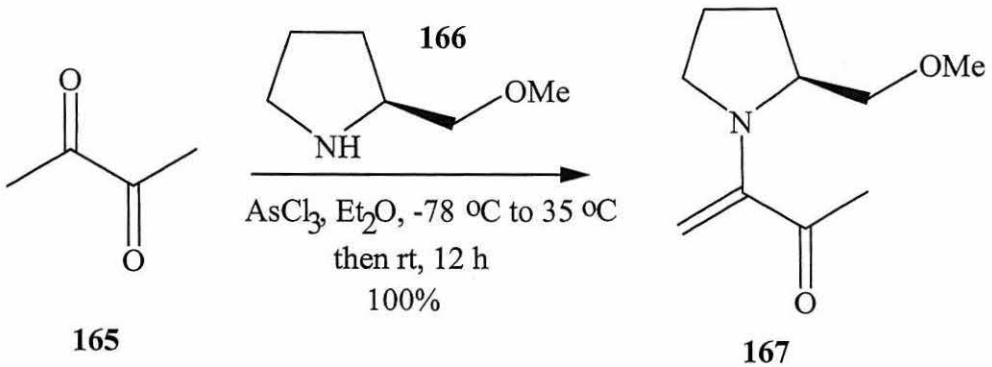


164

Scheme 61.

Arnold reported that due to the sensitivity of alkyl pyruvates towards both acidic and alkaline reagents, most current procedures of enamine synthesis could not used. Even when he used White and Weingarten[120] method, important preconditions had to be in place. The alkyl pyruvates could at no stage of the procedure be in contact with free amine. This was achieved by the stoichiometry of the reagents shown in Scheme 61, and by the preparation of the reagent by adding inorganic chloride to a solution of the amine in an inert solvent. It was also determined that arsenic(III) chloride was better than the titanium tetrachloride method, due to it being a milder reagent.

In 1992, Enders and co-workers[125] looked at an efficient synthesis for a chiral 2-aminobutadiene. They reacted 2,3-butanedione (**165**) with (*S*)-2-(methoxymethyl)pyrrolidine [SMP] (**166**) in the presence of arsenic(III) chloride (Scheme 62) to yield the enamine 3-[(*S*)-2-(methoxymethyl)pyrrolidine-1-yl]-3-buten-2-one (**167**) in excellent yield.



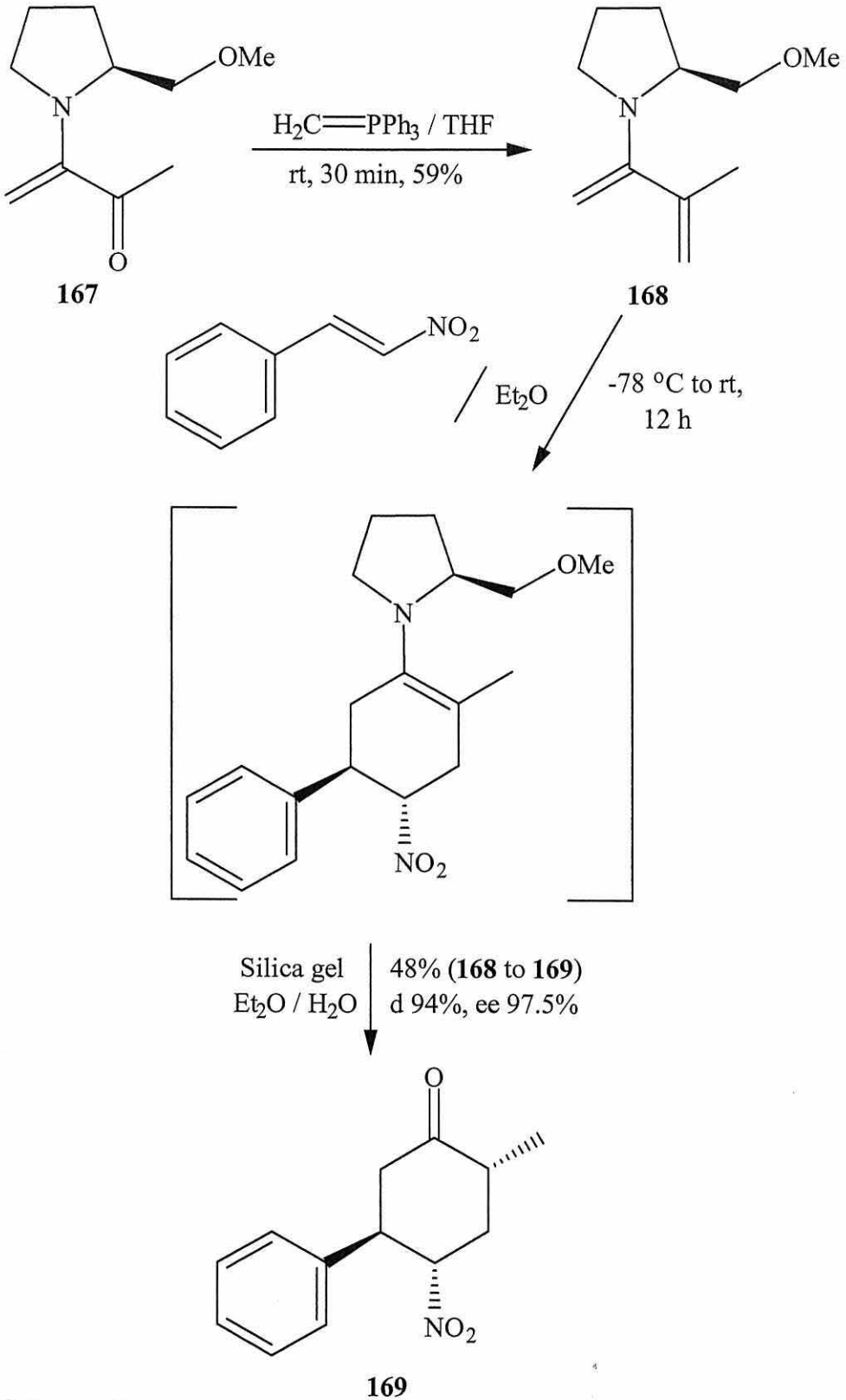
165

166

167

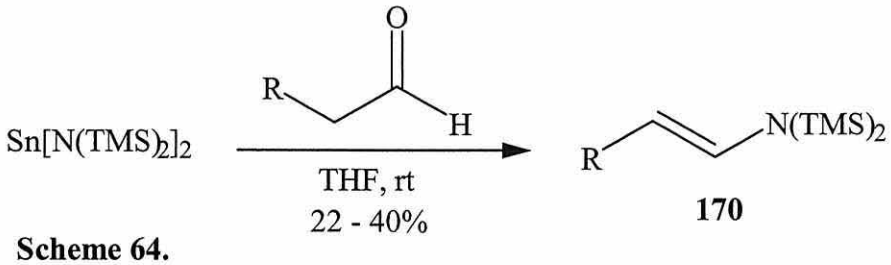
Scheme 62.

They then converted **167** into a 2-amino-1,3-butadiene (**168**) and used this as a diene in normal electron-demand Diels-Alder reactions (Scheme 63).



Scheme 63.

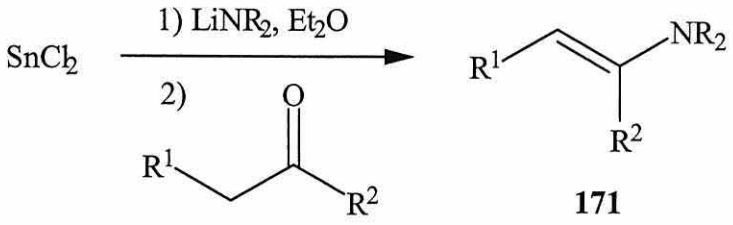
In 1993, Burnell-Curty and Roskamp[126] investigated synthesising *N,N*-dialkyl enamines by the addition of one equivalent of a secondary *N,N*-dialkylamine to bis(bistrimethylsilyl)amino tin(II), followed by treatment with either an aldehyde or ketone. They reported that *trans-N,N*-bistrimethylsilyl enamines (**170**) could be synthesised stereoselectively from primary aldehydes at room temperature using one equivalent of $Sn[N(TMS)_2]_2$ (Scheme 64).



170

Scheme 64.

They also reported that both aldehydes and ketones could be converted into *trans-N,N*-dialkyl enamines (**171**) if treated with ethereal solutions of tin(II) dialkyl amides (Scheme 65).

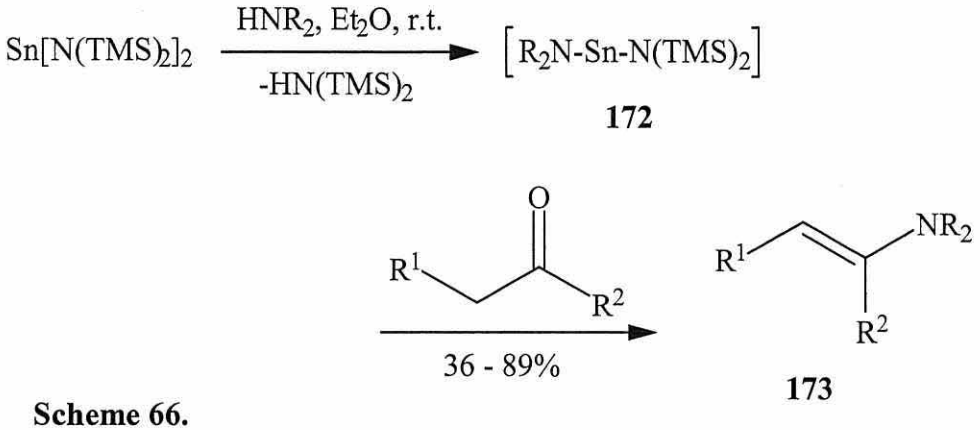


171

Scheme 65. 39 - 93%

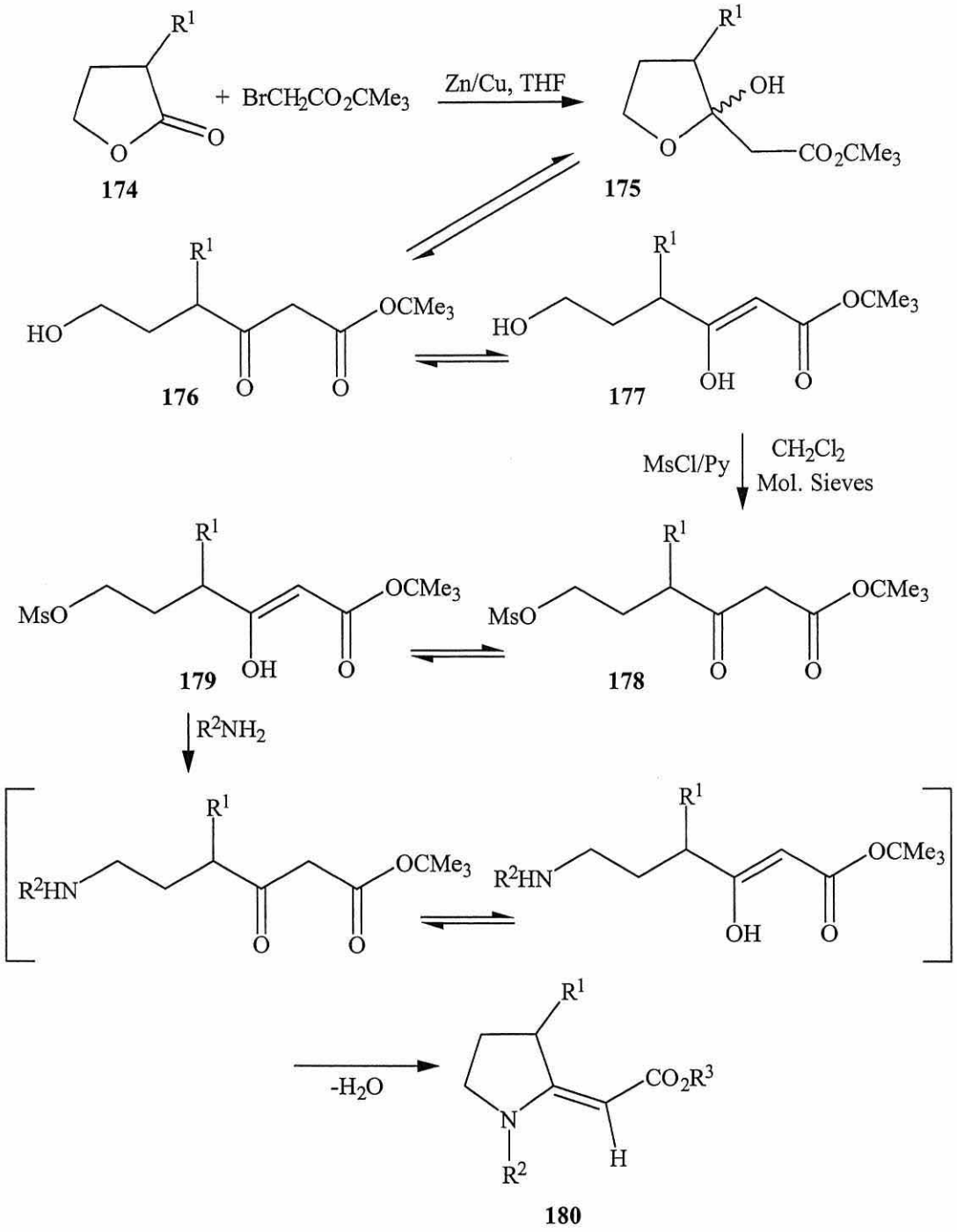
The reactions shown above were the first examples of aldehydes being used to synthesise *N,N*-bistrimethylsilyl enamines, and the first report of the transfer of a ligand from a tin(II) amide to an organic substrate. Burnell-Curty and Roskamp[126] then developed a new, faster and more convenient route for the synthesis of a larger variety of *N,N*-dialkyl enamines, using unsymmetrical tin(II) amides (**172**). This modification exploited the greater nucleophilicity of dialkylamine substituents of tin(II) compounds, compared to trimethylsilylamino substituents. They treated an ethereal solution of $Sn[N(TMS)_2]_2$ with one equivalent of dialkyl amine, to generate the unsymmetrical tin(II) amide (**172**) and one equivalent of hexamethyldisilazane.

On reacting the tin(II) amide (**172**) with either an aldehyde or a ketone, the *trans*-dialkylamino enamine (**173**) is exclusively formed (Scheme 66).



Scheme 66.

In 2003, Wang and co-workers[127] investigated the synthesis of heterocyclic enamines from the formal ring transformation reaction of lactones. Their novel synthesis comprises consecutive Reformatsky reaction of the lactone (**174**) and mesylation of the resulting ring-chain tautomers (**175**, **176** and **177**) in a one-pot synthesis, followed by the cyclocondensation reaction with a primary amine. The preparation of heterocyclic enamines (**180**) *via* this ring transformation of lactones is shown in Scheme 67. The group reported that their synthesis was based on the hemiketals (**175**) resulting from the Reformatsky reaction of lactones being in tautomeric equilibrium with their chain isomers (**176**) and (**177**). Subsequent mesylation of the ω-hydroxy group of the chain tautomers would drive the equilibrium into the side of methylsulfonate compounds (**178**) and (**179**), which are the precursors of heterocyclic enamines (**180**).



Scheme 67. $R^1 = H$, $R^2 = EtO_2CCH_2$, $R^3 = Bu^t$, 42%;
$R^1 = CH_2{=}CHCH_2O$, $R^2 = PhCH_2$, $R^3 = Bu^t$, 44%;
$R^1 = PhCH_2O$, $R^2 = PhCH_2$, $R^3 = Bu^t$, 68%;
$R^1 = PhCH_2O$, $R^2 = EtO_2CCH_2$, $R^3 = Bu^t$, 78%.

5.4.3.1 Summary

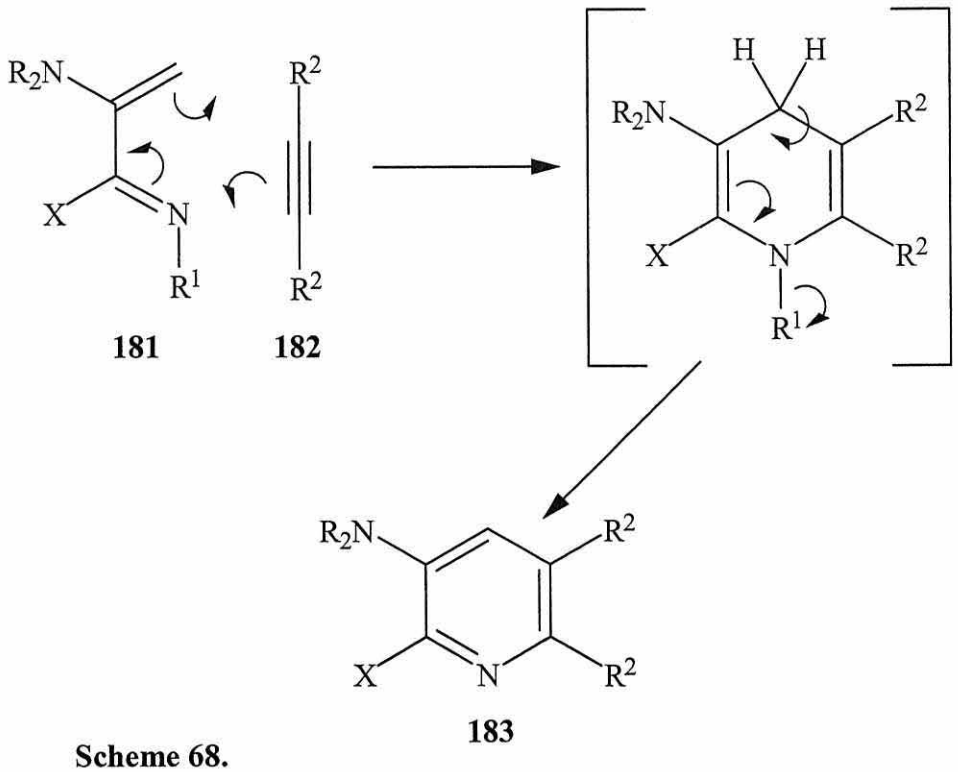
There are many methods available for the synthesis of enamines. The most commonly used method is the simple condensation of aldehyde / ketone and a secondary amine. A number of methods include the use of a catalyst, most commonly titanium tetrachloride, followed by molecular sieves and *p*-toluenesulfonic acid. In more challenging cases, arsenic(III) chloride, tin tetrachloride and bis(bistrimethylsilyl)amino tin(II) are used. All these syntheses of enamines have one thing in common, the need for anhydrous conditions and the removal of water formed during the reaction. Many enamines are formed with minor problems, for example, low yields or difficulties arise with purification.

5.5 General Summary

Enamines are common in dienes but not commonly found in aza-dienes. Oximes and hydrazones are the most common aza-dienes used for the formation of heterocycles, and react readily with dienophiles to form pyridines. Oximes and hydrazones are formed with relative ease and generally can be isolated and purified in high yield. Enamines are slightly more difficult to synthesise and problems occur with purification and isolation in high yields.

5.6 Research Proposal

The objective of the research described herein is the synthesis of an aza-diene (**181**) and the application of such aza-dienes in aza-Diels-Alder reactions with alkynes (**182**) to form highly substituted pyridines (**183**) (Scheme 68).



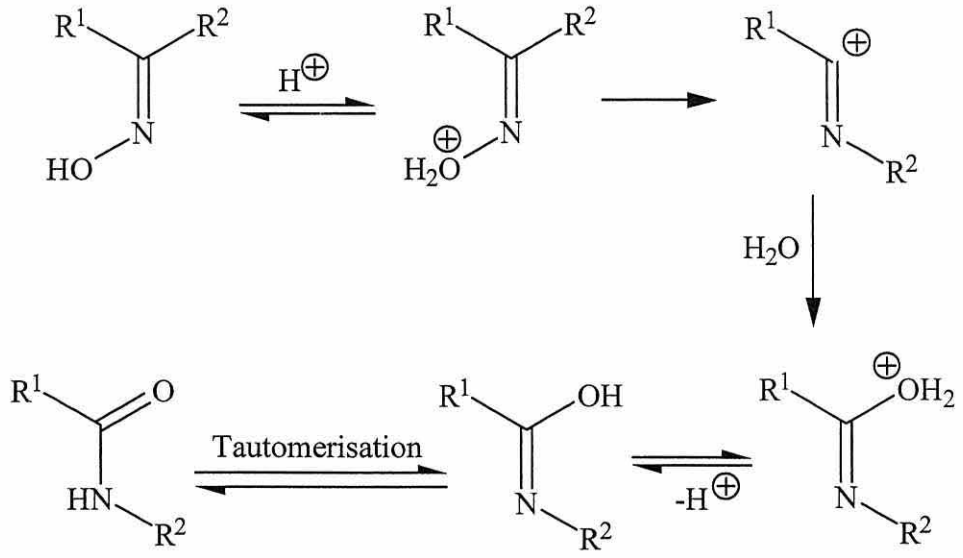
181 182

Scheme 68.

The R^1 group on the 1-position of the aza-diene will be an electron donating group, making the diene electron rich; this group needs to be stable enough for the diene to undergo the aza-Diels-Alder reaction, but not too stable as it has to eliminate, spontaneously, in order for the substituted pyridine to form. Examples of suitable R^1 groups are: trimethylsilyl ether (OTMS), ^{t}butyldimethylsilyl ether (OTBDMS), methoxy (OMe) or dimethylamino (NMe_2). A nitrogen halide (N-X) group could not be used, as it is unstable.

The main concern with the group attached to the nitrogen in the 1-position, is the possibility of a Beckmann rearrangement (Scheme 69). The most commonly used group for R^1 is NR_2 (generally R = Me). They are relatively simple groups and hydrazones do not undergo Beckmann rearrangements. The groups used in this project will be oximes (OR) which are less common. One of the main problems with

oximes is that they can undergo Beckmann rearrangements[128-143]; this will hopefully be avoided by using oxime ethers, for example, the OH functional group would be replaced with OTMS or OMe groups.



Scheme 69. Beckmann Rearrangement.

The R_2N group on the 3-position of the aza-diene will also be electron donating, increasing the electron richness of the diene. Pyrrolidine will be used in this project due to it being relatively simple, symmetrical and having a manageable boiling point (87 – 88 °C). Once a synthetic method has been established, other R_2N groups will be used as a starting point to allow access to other classes of compounds. There is also opportunity for the generation of enamines for *in situ* Diels-Alder reactions[144-145] and catalysed Diels-Alder reactions[146-151] along with the possibility of converting N to other substituents. The X group in the 2-position of the aza-diene provides a chance to make the diene highly substituted, and hence the product pyridine; the group generally used here is CO_2Et, for ease of aza-diene synthesis.

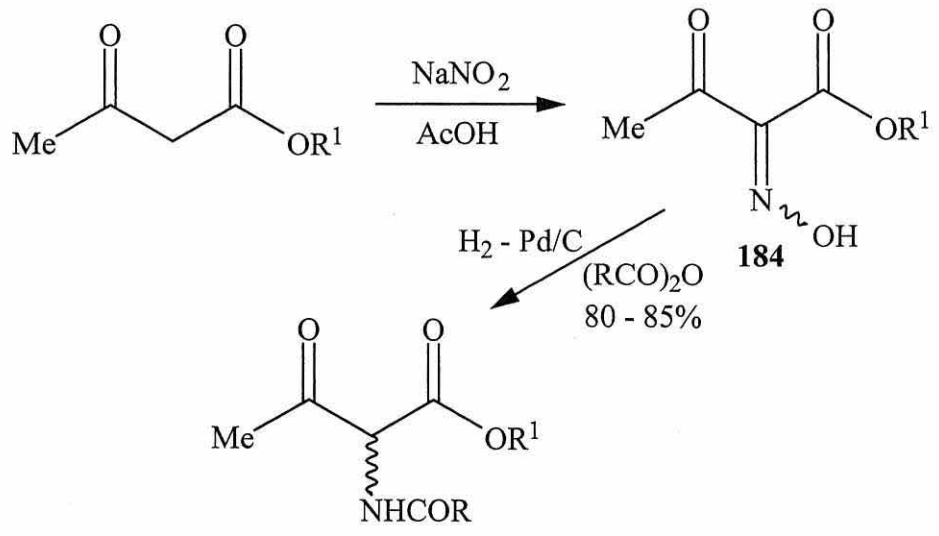
The alkyne needs to be electron deficient and therefore requires electron withdrawing groups in the R^2 position. The simplest example and starting point is dimethyl acetylenedicarboxylate (DMAD) (*i.e.* $R^2 = CO_2Me$).

6.0 Results and Discussion

The stereochemistry of the compounds described is unknown. Oximes and hydrazones are drawn as is most convenient and are further discussed below. Aza-dienes are drawn in the reactive *s-cis* conformation.

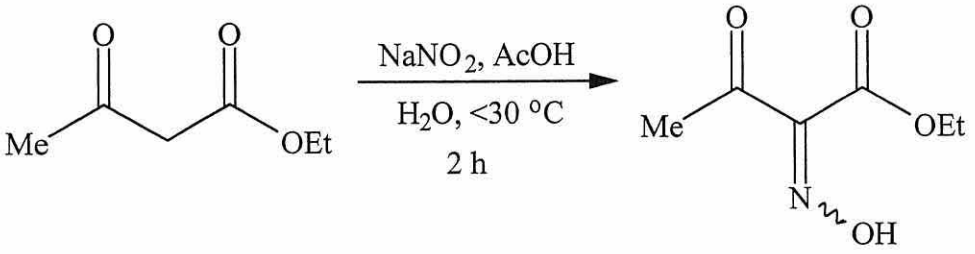
6.1 Ethyl Oximino Acetoacetate

In 1991, Genet and co-workers[152] investigated the synthesis of 2-acylamino-3-oxobutyrates *via* oximes. These were then used to make β-hydroxy-α-aminoacids, which are important in natural products in human and animal nutrition and as chiral intermediates. They used a two-step method (Scheme 70), with which to synthesise the oxime intermediate (**184**) and then reduce it to form the 2-acylamino-3-oxobutyrates (**185**) in a yield of 80-85%.



Scheme 70. R = R^1 = Me; R = Me, R^1 = C_2H_5;
R = Me, R^1 = ^tBu; R = ^iPr, R^1 = Me.

The isolation of a similar compound to **184** was attempted using their method[152] as shown in Scheme 71. Ethyl acetoacetate was reacted with sodium nitrite, acetic acid and water under a nitrogen atmosphere at <30 °C to yield ethyl oximino acetoacetate (**186**).



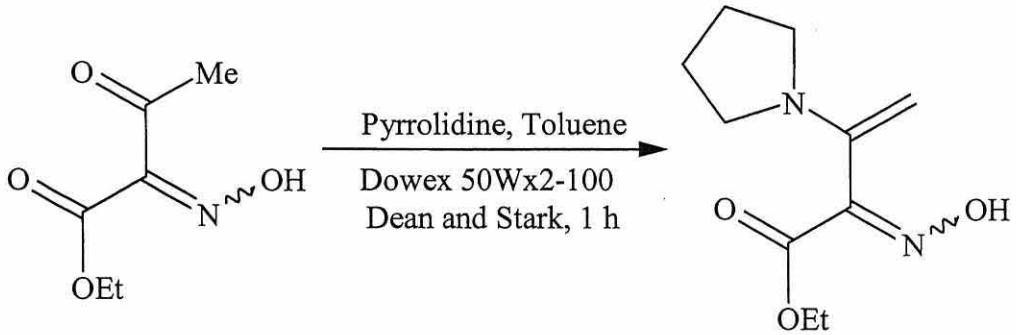
186

Scheme 70. Synthesis of ethyl oximino acetoacetate, 91%.

The ^{1}H and ^{13}C NMR spectra each contained only one set of signals implying that ethyl oximino acetoacetate exists as a single oxime diastereoisomer, or as rapidly converting $E - Z$ isomers. The stereochemistry of **186** has not been investigated further. The reaction gave the product as a colourless oil which crystallised out after 24 hours in the freezer. The reaction gave the product in high yield, 91%. The melting point of **186** was recorded at 25 – 27 °C.

6.2 Enamine of Ethyl Oximino Acetoacetate

The reaction shown in Scheme 71 was one of several attempts to synthesise the enamine of ethyl oximino acetoacetate (**188**) using an adapted general literature method.[153] Ethyl oximino acetoacetate was reacted with pyrrolidine in the presence of Dowex 50Wx2-100 under Dean and Stark conditions in toluene.



187 **188**

Scheme 71.

The IR spectrum of the product indicated that the OH group was still present, along with the ester. It also indicated that there were no unsaturated CH groups present. The ^{1}H NMR indicated that there were two ester groups present, one ethyl ester CH_3 group ($OCH_2\underline{CH_3}$) was represented as a triplet at δ_H 1.19 ppm. This belonged to an unknown compound which was later discovered to be pyrrolidine-1-carboxylic acid ethyl ester (**197**, *cf.* section 6.9). The second ethyl ester CH_3 group at δ_H 1.28 ppm was also a triplet. This represented unreacted starting material (**187**). At δ_H 1.79 ppm a multiplet with an integral of 4 H represented a CH_2 group from compound **197** ($NCH_2\underline{CH_2}$). A singlet at δ_H 2.00 ppm was unidentified but is presumably an acetyl group, though not that of the ketone group of **187**, which was also present as a singlet at δ_H 2.32 ppm. There were two triplets present at δ_H 3.27 and 3.31 ppm each with an integral of 2 H representing both CH_2 groups present in **197** ($\underline{H_2C}N\underline{CH_2}$), which are not equivalent due to restricted rotation around the amide C-N bond. A quartet with an integral of 2 H was present at δ_H 4.07 ppm indicating the CH_2 group of the ethyl ester in compound **197**; a second quartet at δ_H 4.30 ppm also with an integral of 2 H indicated the ethyl ester CH_2 group of the starting material. The C=$\underline{CH_2}$ group was expected to be at about δ_H 5.6 ppm as two doublets each with an integral of 1, by comparison to the similar enamines shown in Figure 12[154] and Figure 13[155]. Brown and Smale[154] studied versimide, a metabolite of *Aspergillus versicolor* and formulated it as methyl (+)-(*R*)-α-(methyl)succinimidoacrylate (Figure 12) from *Penicillium multicolour*. Versimide was used as an insecticide. The C=$\underline{CH_2}$ is present at δ_H 5.88 ppm as a doublet.[154] The C=$\underline{CH}$ group in figure 13 is represented by a multiplet at δ_H 5.50 ppm.[155]

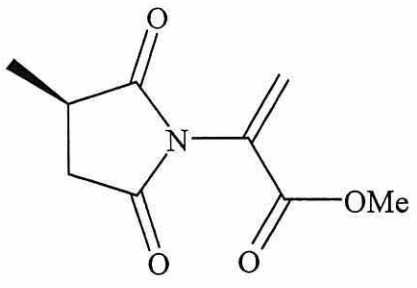


Figure 12.

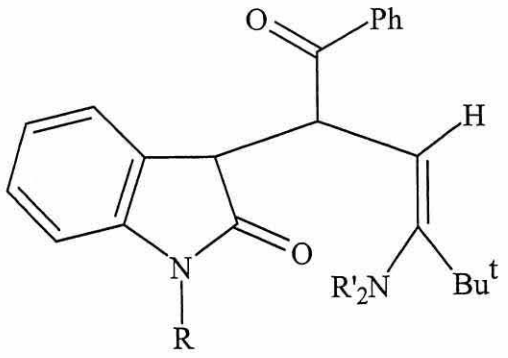


Figure 13.

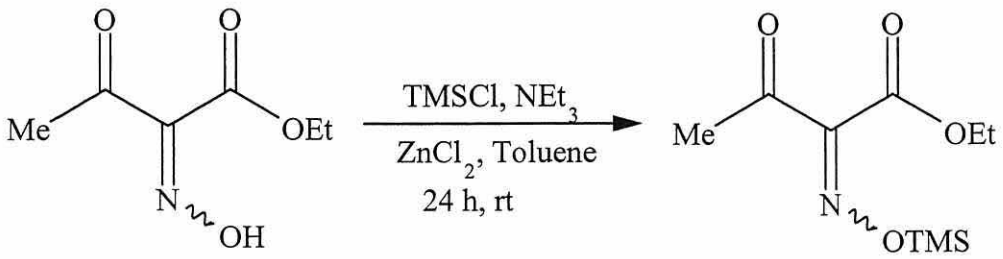
The crude data gave a good indication that the reaction had done something but had not given us the desired product. Purification was attempted: upon attempted distillation no distillate was obtained. The residue was submitted for NMR analysis and both the starting material **187** and **197** had decomposed.

Numerous variations were tried for the synthesis of **188**: the use of *p*-toluenesulfonic acid (adapted from Harwood and co-workers' method),[153] the use of titanium tetrachloride both in dichloromethane and neat, an adaptation of White and Weingarten's method[120]. Various solvents for each different reaction were studied and each time the same result was obtained. Pyrrolidine-1-carboxylic acid ethyl ester (**197**) was formed along with unreacted starting material and other unknown products, but no enamine **188**, as indicated by NMR analysis of the crude product.

The mechanism of formation of pyrrolidine-1-carboxylic acid ethyl ester suggested herein is *via* a Beckmann rearrangement, *cf.* section 6.9; therefore protection of the OH of the oxime group with a trimethylsilyl group (OTMS) was investigated to determine if it was the cause of the failure of the desired enamine formation, for example by acting as a proton source.

6.3 Trimethylsilylation of Ethyl Oximino Acetoacetate

The chemoselective incorporation of the trimethylsilyl group was done using a method adapted from Danishefsky and Kitahara[156] and Igarashi and co-workers[85]. Anhydrous triethylamine (2 eq) and trimethylsilylchloride (2 eq) were added successively to a solution of oxime **187** and anhydrous zinc(II) chloride in anhydrous toluene (Scheme 72). The reaction produced crude **189** as a yellow oil with a mass recovery of 67%, with respect to the theoretical yield of the starting material **187**. The loss was likely to have occurred during the work-up of the reaction. This method does not give any silyl enol ether in this case despite result in Danishefsky and Kitaharas[156] reactions.



187 **189**

Scheme 72. 45% (+ **187**, 22%, as determined by ^{1}H NMR spectroscopy)

The IR spectrum showed that the OH group was still present indicating that starting material **187** was present. It also showed 2 signals for the ester, ketone and oxime indicating that not only was there starting material **187** present but, a second compound which contained very similar functional groups to **187**.

The ^{1}H NMR spectrum confirmed that the OH group was still present by a single broad peak with an integral of 1 H at δ_H 11.10 ppm. At δ_H 4.29 ppm a quartet with an integral of 2 H showed the CH_2 of the ester ($O\underline{CH_2}CH_3$). This signal had shoulders present indicating a second CH_2 group present in almost the same position. At δ_H 2.35 ppm a singlet with an integral of 2 H indicated the CH_3 group next to the carbonyl ($\underline{CH_3}$-C=O). A second singlet at δ_H 2.32 ppm with an integral of 1 H represents another CH_3 group in almost the same position. This data indicates that there are two different ketone functional groups present which are most likely to be in two separate compounds in a ratio of 2:1. At δ_H 1.26 ppm a triplet with an integral of 3 H showed that the CH_3 of the ester was still present ($OCH_2\underline{CH_3}$). These peaks all have shoulders present leading one to believe that there was a second ester group present in almost the same environment but in another compound. The trimethylsilyl group was present as a singlet at δ_H 0.22 ppm with an integral of 6 H, indicating that the product **189** was present and made up 2/3^{rds} of the product, the other 1/3rd being starting material **187**.

The ^{13}C NMR spectrum backed up the ^{1}H NMR spectrum as it showed two peaks at δ_C 194.1 and 193.9 ppm for the ketone (CH_3-$\underline{C}$=O) in the trimethylsilylated product (**189**) and the starting material (**187**) respectively. The esters appeared as two resonances at δ_C 161.9 and 161.7 ppm ($\underline{C}O_2Et$) and two peaks at δ_C 154.9 and 151.3 ppm showed the carbons of the oximes ($\underline{C}$=N-OR). The two CH_2 groups in the ester

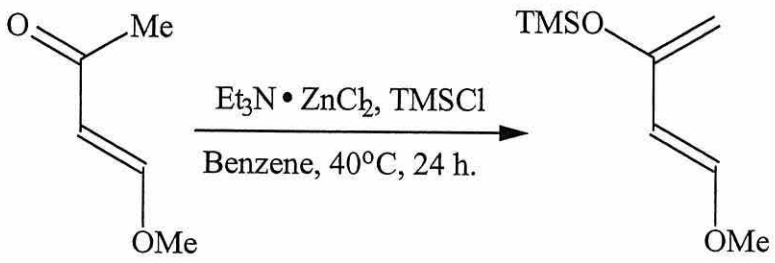
of the product **189** and the starting material **187** were represented by peaks at δ_C 62.0 and 61.9 ppm. The CH_3 groups of the ketones ($\underline{CH_3}$-C=O) were represented by two peaks, which were almost on top of each other at δ_C 45.8 ppm. The CH_3 of the ester ($OCH_2\underline{CH_3}$) in the product **189** and the starting material **187** are represented by peaks at δ_C 25.2 and 25.1 ppm, respectively. The trimethylsilyl signal occurred at δ_C –1.0 ppm.

The data suggests that the desired product (**189**) was present as 2/3rd's (45% yield) of the reaction product and that the starting material, ethyl oximino acetoacetate **187** was present as the other 1/3rd (22% yield).

The above reaction was repeated using 3 equivalents of trimethylsilylchloride and triethylamine, with 0.03 equivalents of zinc(II) chloride as the Lewis acid, but this gave the same result of 2/3rd's product and 1/3rd starting material, but in a lower yield (**189**, 36%; **187**, 18%).

The above reactions show that although it is possible to convert the OH group of the oxime to an OTMS group it is extremely difficult to do so quantitatively, probably due to the moisture sensitivity and the difficulty in isolating the product **189** from the precipitate formed during the work-up, without the hydrolysis of the product **189** back to starting material **187**. The ratio of product **189** to starting material **187** is possibly better than 2 : 1, as hydrolysis may occur during analysis.

Danishefsky and Kitahara tried a similar reaction,[156] they attempted to silylate *trans*-4-methoxybuten-2-one (**190**), and found that the triethylamine method only gave a faint indication of success. They then repeated the reaction of *trans*-4-methoxybuten-2-one with trimethylchlorosilane in the presence of triethylamine-zinc chloride complex, to give a 68% yield of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene, known as Danishefsky's diene (**191**) as shown in Scheme 73.

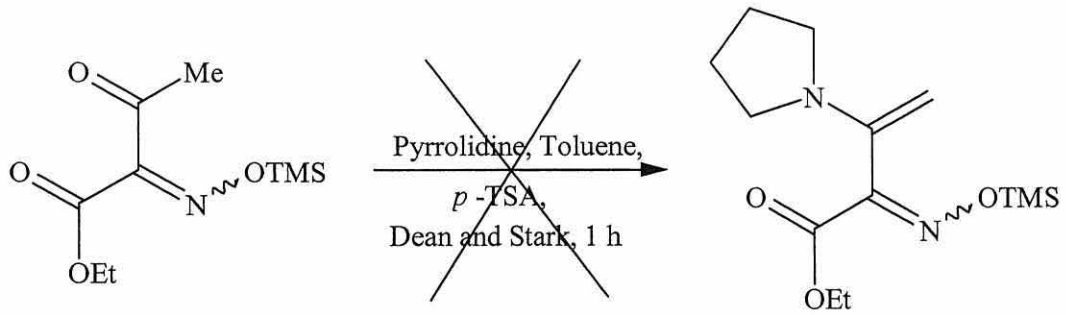


190 **191**

Scheme 73. 68%.

6.4 Enamine of Silylated Ethyl Oximino Acetoacetate[153]

The formation of the enamine (**192**) was attempted using the crude *O*-TMS ethyl oximino acetoacetate (**189**) (*i.e.* containing 1/3rd **187**), under the same conditions as Harwood and co-workers method[153]. A black oil was formed corresponding to a 77% mass recovery with respect to the theoretical yield of **192** (Scheme 74). The mass loss probably occurred during rotary evaporation.



189 **192**

Scheme 74.

The IR spectrum of the oil did not indicate that any unsaturated CH groups were present, the ester and oxime absorptions were at ν_{max} 1709.9 and 1686.2 cm^{-1} respectively. The ketone band of the starting material was now missing.

The ^1H NMR spectrum showed two doublets each with an integral of 1 H at δ_H 7.73 ppm ($CH\underline{CH}CSO_3H$) and δ_H 7.18 ppm ($\underline{CH}CHCSO_3H$), indicating that *p*-toluenesulfonic acid was present. There was a quartet present at δ_H 4.13 ppm with an integral of 2 H, which indicated the CH_2 group of the ester in a second compound (**197**, *cf.* section 6.9). A second quartet appeared at δ_H 3.85 ppm with an integral of 2 H. This peak is unidentified as the chemical shift is too low to be starting material **189**. Pyrrolidine signals ($\underline{H_2C}N\underline{CH_2}$, **197**) appeared as a triplet at δ_H 3.33 ppm with an integral of 4 H. A singlet at δ_H 2.35 ppm with an integral of 1 H indicated the CH_3 group of *p*-toluenesulfonic acid. A multiplet with an integral of 4 H at δ_H 1.85 ppm indicated the other two CH_2 groups in pyrrolidine ($NCH_2\underline{CH_2}$, **197**). A triplet was present at δ_H 1.47 ppm with an integral of 1 H which indicated that a small amount of starting material **189** was still present. At δ_H 1.23 ppm a triplet with an integral of 3

H indicated a CH_3 group of the ester to also be present in a second pyrrolidine-containing compound (**197**, *cf.* section 6.9). A trimethylsilyl signal at δ_H 0.07 ppm had an integral of only 1 H whereas it should be in the order of 9 H, indicating that the harsh conditions used in the reaction led to the partial removal of the trimethylsilyl group. The proton NMR spectrum did not have a signal present to indicate the $=CH_2$ group, which was expected to appear at approximately δ_H 5.5 ppm. The pyrrolidine peaks confirm that pyrrolidine is indeed present but not as free pyrrolidine (free pyrrolidine is represented by two multiplets at δ_H 2.80 and 1.60 ppm[157]), although it was not attached to the 3-position of the starting material **189**, see section 6.9. The trimethylsilyl group was also not present; its cleavage may be due to the nucleophilic pyrrolidine and / or the acid.

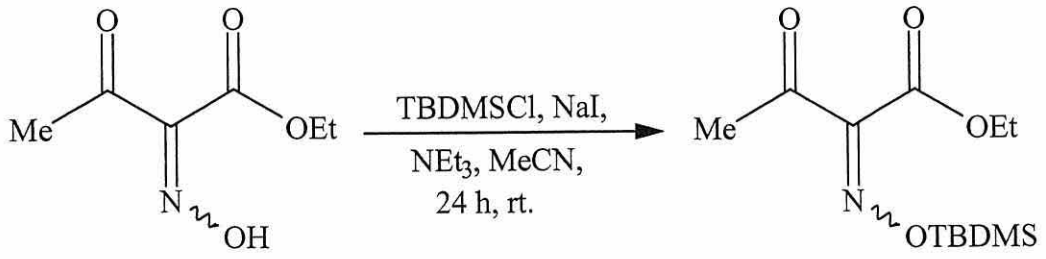
The ^{13}C NMR spectrum showed the carbonyl carbon ($\underline{C}$=O) of **197** to be present. Two carbon peaks were present at δ_C 125.8 and 128.7 ppm representing *p*-TSA. The ester appeared at δ_C 60.7 ppm ($O\underline{CH_2}CH_3$) and δ_C 14.8 ppm ($OCH_2\underline{CH_3}$) similar to the starting material. The ^{13}C NMR spectrum also contained peaks at δ_C 46.0 and 45.3 ppm ($\underline{H_2C}N\underline{CH_2}$) and δ_C 21.2 ppm ($NCH_2\underline{CH_2}$) due to the pyrrolidine ring, the $=CH_2$ group was expected to be at approximately δ_C 55.5 ppm. This attempt to synthesise the enamine lead to the formation of pyrrolidine-1-carboxylic acid ethyl ester (**197**, *cf.* section 6.9).

The above data is for the crude product. Upon attempted distillation the compound decomposed. The addition of pyrrolidine under these conditions seemed to cause the partial removal of the TMS group, so the next step was to try a bulkier group *i.e.* *t*-butyldimethylsilyl group (TBDMS).

6.5 *t*-Butyldimethylsilylation of Ethyl Oximino Acetoacetate

The *t*-butyldimethylsilyl group (TBDMS) is bulkier than the trimethylsilyl group and is more resilient as an oxygen protecting group.[158] It was introduced using 1 equivalent of *t*-butyldimethylsilylchloride (TBDMSCl), 0.25 equivalents of sodium iodide, 1 equivalent of triethylamine and acetonitrile (Scheme 75) in an attempt to synthesise the *t*-butyldimethylsilylated product **193**, as an orange oil in 70% mass recovery with respect to the theoretical yield of **193**. The mass loss occurred during the work-up of the reaction. This method was adapted from that of Igarashi and co-

workers[85], who made a number of 1-azadienes successfully and attempted aza-Diels-Alder reactions (*cf.* section 5.2.1).



187 **193**

Scheme 75. 47% (+ **187**, 23%, as determined by ^{1}H NMR spectroscopy)

The IR spectrum of the crude product showed very similar peaks as for the starting material, ethyl oximino acetoacetate **187**. The ^{1}H NMR spectrum had no OH peak present, the CH_2 signal ($O\underline{CH_2}CH_3$) was almost at the same position as that for the starting material. it also had shoulders present on the peaks indicating that there were two ester groups present. The C=O CH_3 was still present from the starting material ($\underline{CH_3}$-C=O) represented by a singlet, at δ_H 2.33 ppm with an integral of 2. A second singlet was present at δ_H 2.30 ppm with an integral of 1 H, which indicated that there were two compounds present. The CH_3 group ($OCH_2\underline{CH_3}$) was represented by a multiplet *i.e.* two overlapping triplets at δ_H 1.24 ppm with an integral of 3 H. The *t*-butyldimethylsilyl group signals were present at δ_H 0.86 ppm as a singlet with an integral of 6 H (which indicated the *t*-butyl group), and at δ_H 0.17 ppm with an integral of 4 H a singlet represented the two methyl groups attached to silicon.

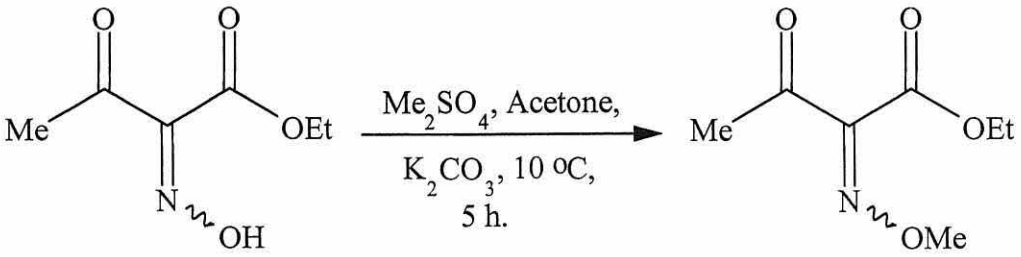
The ^{13}C NMR spectrum showed two peaks at δ_C 193.8 and 193.7 ppm for the ketone (CH_3-$\underline{C}$=O) in the product **193** and the starting material **187** respectively. Ester carbon signals ($\underline{C}O_2Et$) were present at δ_C 161.7 and 161.6 ppm, and the oxime carbon signals ($\underline{C}$=N-OR) occurred at δ_C 155.1 and 151.1 ppm for the product **193** and ethyl oximino acetoacetate **187**, respectively. The ester CH_2 carbon signals ($O\underline{CH_2}CH_3$) appeared at δ_C 62.0 and 61.8 ppm, the ketone CH_3 ($\underline{CH_3}$-C=O) signal was at δ_C 25.5 ppm, and the CH_3 of the ester ($CH_2\underline{CH_3}$) gave a peak at δ_C 13.9 ppm. The TBDMS group signals were at δ_C 18.0, –5.5 and -3.8 ppm. The above data suggests that the reaction was partially successful. The proton NMR signals for TBDMS group

should have an integral of 9 H for the *t*-butyl group, whereas the actual signal had an integral of only 6 H, the two methyl groups were expected to be a singlet with an integral of 6 H but the signal was present as a singlet with an integral of only 4 H. The ester peaks had shoulders present indicating the presence of two compounds *i.e.* 2/3rd's product **193** (47% yield) and 1/3rd starting material **187** (23% yield).

The reaction was repeated using the same number of equivalents, but this time left for 3 days to stir. The result was similar to the above reaction with 2/3rd's product **193** (44% yield) and 1/3rd starting material **187** (22% yield). The attempt to synthesise an enamine using crude **189** (*cf.* section 6.3 and 6.4) was unsuccessful possibly due to the starting material **189** not being pure (*i.e.* containing 1/3rd **187**). Due to the difficulty in synthesising pure **193**, it was not investigated further.

6.6 Methylation of Ethyl Oximino Acetoacetate

In both the above reactions the oxime protecting groups (TMS and TBDMS) were partially removed, or unsuccessfully/incompletely introduced to ethyl oximino acetoacetate **187** and so a highly stable group was required, for example, a methyl group[159]. As an oxime *O*-methyl group is considerably more stable than an *O*-silyl group it should be possible to obtain the oxime ether **194** in pure form, and ideally without the need for purification; it will also not suffer hydrolysis during the work-up of the reaction. The oxime *O*-methyl group is still suitable for aza-Diels-Alder reactions due to it being able to undergo elimination. Ethyl oximino acetoacetate **187** was reacted with 1 equivalent of dimethyl sulfate, and 1.5 equivalents of potassium carbonate in acetone, according to Burcourt and co-workers method[159] to produce ethyl methoxyimino acetoacetate **194** as a pale yellow oil in 85% yield, without the need for purification (Scheme 76).



187 **194**

Scheme 76. 194, 85%.

The ^1H and ^{13}C NMR spectra each contained only one set of signals implying that ethyl oximino acetoacetate exists as a single oxime diastereoisomer, or as rapidly converting *E* – *Z* isomers. The stereochemistry of **194** has not been investigated further. The reaction gave the product in high yield, 85%.

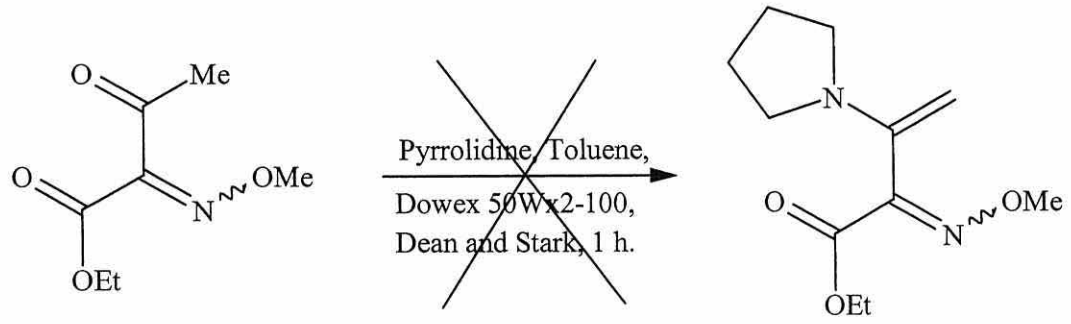
The IR spectrum showed a strong band at ν_{max} 1752.6 cm^{-1} indicating the ester to still be present. The ketone absorption appeared at ν_{max} 1703.7 cm^{-1}. The methoxy oxime group was represented by a strong band at ν_{max} 1601.9 cm^{-1}. The broad OH band which appeared in the starting material had now disappeared.

The ^1H NMR spectrum showed a quartet with an integral of 2 H at δ_H 4.33 ppm indicating the CH_2 of the ester ($O\underline{CH_2}CH_3$). At δ_H 4.08 ppm a new singlet with an integral of 3 H represented the methoxy oxime group ($N\text{-}O\underline{CH_3}$), at δ_H 2.38 ppm a singlet with an integral of 3 H represented a methyl ketone ($\underline{CH_3}\text{-}C{=}O$). At δ_H 1.32 ppm, the CH_3 of the ester ($OCH_2\underline{CH_3}$) was represented by a triplet with an integral of 3 H. The data was in good agreement with the literature[159].

The ^{13}C NMR spectrum showed the ketone carbonyl absorption to appear at δ_C 192.8 ppm ($CH_3\text{-}\underline{C}{=}O$), the ester carbon absorption ($\underline{C}O_2Et$) appeared at δ_C 161.1 ppm, and the oxime absorption at δ_C 150.0 ppm ($\underline{C}{=}N\text{-}OMe$). The methoxy oxime ($C{=}N\text{-}O\underline{Me}$) absorption appeared at δ_C 64.3 ppm. The CH_2 of the ester absorption was at δ_C 62.1 ppm ($O\underline{CH_2}CH_3$). The CH_3 next to the carbonyl ($\underline{CH_3}\text{-}C{=}O$) absorption appeared at δ_C 25.1 ppm and the ester CH_3 group absorption was at δ_C 13.9 ppm ($OCH_2\underline{CH_3}$); the data were in good agreement with those reported in the literature[159] and no unreacted starting material **187** was detected. This was backed up by TLC analysis, confirming that this reaction was successful.

6.7 Enamine of Ethyl Methoxyimino Acetoacetate[153]

One equivalent of pyrrolidine was added to ethyl methoxyimino acetoacetate (**194**), using Dowex 50Wx2-100 (10% mol) as the catalyst, in toluene, using the Dean and Stark method, in an attempt to yield the enamine (**195**) (Scheme 77). The reaction yielded an orange oil in 74% mass recovery with respect to the theoretical yield of **195**.



194 **195**

Scheme 77.

The IR spectrum of the crude product showed that the ester absorption was present at ν_{max} 1744.5 cm^{-1}. The ketone peak had not disappeared and remained at ν_{max} 1702.0 cm^{-1}. The oxime was represented by two peaks at ν_{max} 1654.1 cm^{-1} and ν_{max} 1636.7 cm^{-1}.

The ^1H NMR spectrum showed the CH_2 in the ester ($O\underline{CH_2}CH_3$) resonance as a quartet with an integral of 2 H. At δ_H 4.33 ppm, a second quartet was present with almost the same chemical shift, which showed there to be a second ester present (**197**, *cf.* section 6.9). At δ_H 4.09 ppm a singlet was present with an integral of 2 H, a second singlet with an integral of 1 H was present at δ_H 3.94 ppm. These two signals represent oxime methoxy groups (C=N-O<u>Me</u>); there were two different methoxy groups present, indicating there were two compounds present. A multiplet with an integral of 2 H was present at δ_H 3.41 ppm representing the CH_2 groups in pyrrolidine ($\underline{H_2C}N\underline{CH_2}$). Another triplet was present at δ_H 3.15 ppm with an integral of 2 H, showing there to be CH_2 groups present in a pyrrolidine ring ($\underline{H_2C}N\underline{CH_2}$) but in a different chemical environment. This indicated that there were two pyrrolidine

containing compounds present or that the pyrrolidine ring was present in only one compound and had lost its symmetry. The CH_3 group from the starting material **194** was still present as indicated by the singlet at δ_H 2.35 ppm with an integral of 2 H, showing partial consumption of the ketone group ($\underline{CH_3}$-C=O). A multiplet at δ_H 1.86 ppm represented the other two CH_2 groups in pyrrolidine ($NCH_2\underline{CH_2}$) with an integral of 4 H, (**197**, *cf.* section 6.9). The CH_3 of the esters ($OCH_2\underline{CH_3}$) were present at δ_H 1.33 ppm as two triplets with an integral of 3 H at almost the same chemical shift.

The ^{13}C NMR spectrum appeared to be almost identical to that of the starting material **194** with extra four peaks at δ_C 45.5 – 47.3 ppm and an additional 9 peaks at δ_C 21.4 – 26.1 ppm indicating the pyrrolidine CH_2 groups; this increased number of peaks has yet to be explained.

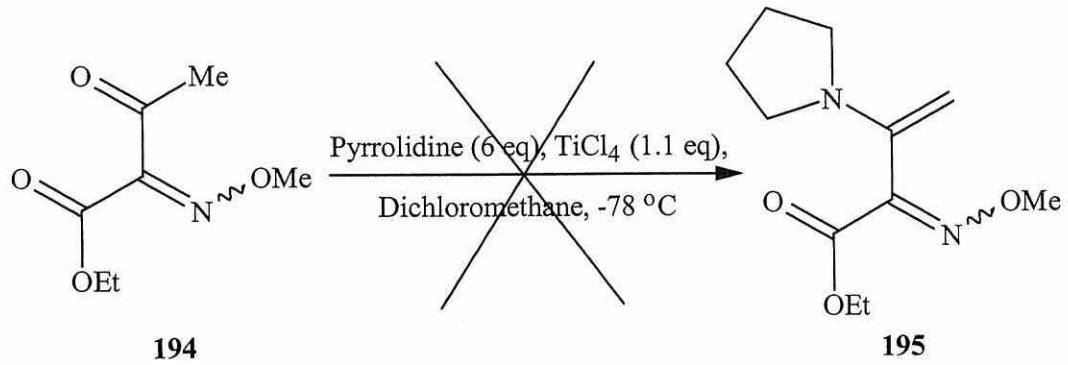
The above data suggested that ethyl methoxyimino acetoacetate (**194**) was still present, and the product (**195**) had not been formed. There appears to be at least one other compound present containing a pyrrolidine moiety. This pyrrolidine moiety is not present as free pyrrolidine, as the peaks had moved to a higher frequency compared to the ^1H and ^{13}C NMR spectra of pyrrolidine itself. One of the pyrrolidine containing compounds appeared to be pyrrolidine-1-carboxylic acid ethyl ester (**197**, *cf.* section 6.9). Distillation of the residue was attempted using a water aspirator (oil bath temperature up to 200°C) under reduced pressure (25mmHg), but no distillate was collected and the residue decomposed.

6.8 Enamine of Ethyl Methoxyimino Acetoacetate: Alternative Method

The previous attempts to form pyrrolidine enamines using the Dowex 50Wx2-100 resin as a catalyst were unsuccessful, so a different approach was needed. One approach was to use titanium tetrachloride[120, 125]; White and Weingarten[120] used titanium tetrachloride in 1967 and reported it to be a straightforward and general method, using readily available starting materials, for the synthesis of enamines. They used titanium tetrachloride as it is an effective water scavenger and secondly it can act catalytically (although is not a true catalyst as it was consumed in the reaction) in the Lewis acid sense, to polarize the carbonyl bond.

White and Weingarten's method was adapted and applied to the synthesis of **195**, thus 2 equivalents of ethyl methoxyimino acetoacetate **194** were reacted with 6

equivalents of pyrrolidine and 1.1 equivalents of titanium tetrachloride in dichloromethane at –78 °C (Scheme 65). The reaction yielded a dark red oil in 70% mass recovery with respect to the theoretical yield of **195**.



194 **195**

Scheme 78.

The IR spectrum of the crude product showed the ester to be present at ν_{max} 1740.8 cm^{-1} and the oxime at ν_{max} 1696.5 cm^{-1}. The ketone peak was now missing, a new peak was also present at ν_{max} 1629.3 cm^{-1} this could be a C=C group or a C=N group.

The ^1H NMR spectrum showed a broad peak at δ_H 4.60 ppm with an integral of 4 H. This has yet to be identified. The ester ($O\underline{CH_2}CH_3$) signal was present as a quartet with an integral of 2 H at δ_H 4.28 ppm. Shoulders were present on this peak indicating a second ester group. The methoxy group of the oxime was represented by a singlet with an integral of 3 H at δ_H 4.05 ppm. The pyrrolidine CH_2 group is represented by a triplet with an integral of 4 H at δ_H 3.14 ppm ($\underline{H_2C}N\underline{CH_2}$). The other CH_2 group signals ($NCH_2\underline{CH_2}$) were at δ_H 1.87 ppm as a multiplet with an integral of 6 H. A triplet at δ_H 1.28 ppm indicated the CH_3 of the ester ($OCH_2\underline{CH_3}$) with an integral of 3 H. There were unidentified peaks present at δ_H 3.90 and 3.67 ppm. Both were singlets with integrals of 1 H. Three multiplets were present at δ_H 2.97, 2.77 and 2.47 ppm with integrals of 1, 2 and 2 H respectively. These multiplets are too low for **197** and too high for free pyrrolidine. They remain unidentified. A singlet at δ_H 2.00 ppm with an integral of 1 H could be some kind of methyl ketone ($\underline{CH_3}C=O$) group and a multiplet with an integral of 4 H at δ_H 1.74 ppm, is unidentified. There was also another multiplet present at δ_H 1.19 ppm with an integral of 1 H, which represented

the CH_3 group of the ester in the starting material **194**. The CH_3 of the ethyl ester ($CH_2\underline{CH_3}$, **197**) absorption was represented by a triplet with an integral of 3 H at δ_H 1.28 ppm.

The ^{13}C NMR spectrum showed two ketone peaks to be present at δ_C 195.5 and 194.2 ppm. The ester appeared at δ_C 162.6 ppm and the oxime at δ_C 151.4 ppm. There was one new peak present at δ_C 116.9 ppm, which was not confirmed but was in the range for $\underline{C}=CH_2$ carbon. At δ_C 65.8 ppm the methoxy group (C=N-O$\underline{Me}$) was present. The ester CH_2 group was represented by a peak at δ_C 63.4 ppm. At δ_C 55.7 ppm a carbon peak, probably dichloromethane $\underline{CH_2}Cl_2$, was identified. Pyrrolidine units were represented by 4 resonances at about δ_C 47.0 ppm ($\underline{H_2C}N\underline{CH_2}$) and at about δ_C 26.0 ppm ($NCH_2\underline{CH_2}$), indicating that there are at least 2 pyrrolidine units present one of which is **197**. The CH_3 of the ester ($OCH_2\underline{CH_3}$) was represented by a peak at δ_C 15.4 ppm.

The above data suggested that a reaction had indeed taken place but the desired product **195** had not been formed. There were definitely two ester groups present one with the correct integrals and multiplicities. A pyrrolidine group was also shown to be present and was attached to something due to the peaks being at a higher frequency than that of free pyrrolidine. Distillation of the residue was attempted using a water aspirator (oil bath temperature up to 200°C) under reduced pressure (25mmHg), but no distillate was collected and the residue decomposed.

We tried many different approaches for the synthesis of the ethyl methoxyimino acetoacetate enamine, including: using the method from section 6.7 with an increased amount of pyrrolidine (up to 5 equivalents). We tried the above method with reflux (2 – 24 hrs), instead of stirring overnight at room temperature, with various amounts of pyrrolidine and titanium tetrachloride, along with different solvents, *i.e.* ether, toluene and benzene (Table 1). All of these reactions were however unsuccessful.

Pyrrolidine Equivalents	Catalyst / Acid (Eq)	Reaction Solvent	Reaction Method	Reaction Time (hrs)
1	*p*-TSA (10 mol%)	Toluene	Dean & Stark	5
2	*p*-TSA (10 mol%)	Toluene	Dean & Stark	5
5	*P*-TSA (10 mol%)	Toluene	Dean & Stark	5
5	*p*-TSA (10 mol%)	Toluene	Reflux	24
5	*p*-TSA (10 mol%)	Ether	Reflux	24
1	Molecular Sieves 4 Å (10 mol%)	Toluene	Dean & Stark	5
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Ether	Reflux	24
1	Dowex 50Wx2-100 (10 mol%)	Toluene	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	Ether	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	THF	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	Benzene	Dean & Stark	5
5	Dowex 50Wx2-100 (10 mol%)	Benzene	Reflux	24
1	$TiCl_4$ (1.1 eq) in CH_2Cl_2	Dichloromethane	-78 °C → rt	24
2	$TiCl_4$ (1.1 eq) in CH_2Cl_2	Dichloromethane	-78 °C → rt	24
4	$TiCl_4$ (1.1 eq) in CH_2Cl_2	Dichloromethane	-78 °C → rt	24
6	$TiCl_4$ (1.1 eq) in CH_2Cl_2	Dichloromethane	-78 °C → rt	24

6	$TiCl_4$ (1.1 eq) in CH_2Cl_2	Neat	-78 °C → rt	24
6	Neat $TiCl_4$ (1.1 eq)	Dichloromethane	-78 °C → rt	24
6	Neat $TiCl_4$ (1.1 eq)	THF	-78 °C → rt	24
6	Neat $TiCl_4$ (1.1 eq)	Toluene	-78 °C → rt	24
6	Neat $TiCl_4$ (1.1 eq)	Benzene	-78 °C → rt	24
6	Neat $TiCl_4$ (1.1 eq)	Dichloromethane	-78 °C → rt → 30 °C	24
1	None	Dichloromethane	rt	24
5	None	Dichloromethane	rt	24
5	None	Dichloromethane	Reflux	24
5	None	Toluene	rt	24
5	None	Toluene	Dean & Stark	5
5	None	Toluene	Reflux	24
5	None	Ether	rt	24
5	None	Ether	Reflux	24
5	None	THF	rt	24
5	None	THF	Reflux	24

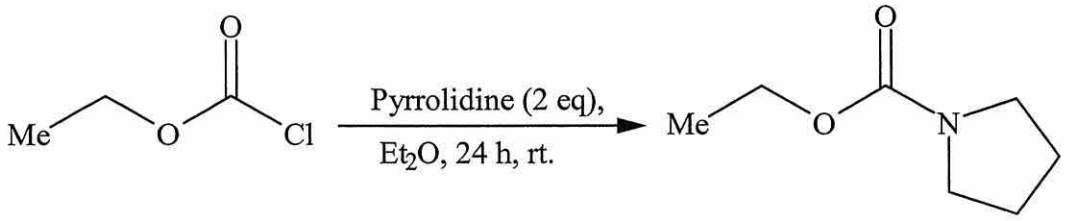
Table 1.

All the products of the above reactions for the formation of the enamines (*i.e.* sections **6.2, 6.4, 6.7, 6.8**) had similar peaks present in the ^1H NMR spectra. The ethyl ester signals were always present but at a somewhat lower frequency than those for that of the starting material – the CH_2 group of the ester ($O\underline{CH_2}CH_3$) was present at approximately δ_H 4.3 and 4.1 ppm for the starting material **194** and the products, respectively. The CH_3 of the ester group ($OCH_2\underline{CH_3}$) was present at approximately δ_H 1.3 and 1.2 ppm for the starting material and the product respectively. The acetyl group signals have disappeared to a greater or lesser extent. Multiplets corresponding to the pyrrolidine ring system were present with the $\underline{H_2C}N\underline{CH_2}$ signals shifted to a higher frequency with respect to those for free pyrrolidine. The NMR spectra

indicated the formation of the same unidentified compound in all these reactions. This compound contains an ester group and pyrrolidine; the simplest compound containing these fragments is pyrrolidine-1-carboxylic acid ethyl ester, (**141**, *cf.* section 6.9).

6.9 Pyrrolidine-1-Carboxylic Acid Ethyl Ester[160]

The compound identified as a product of the above reactions (**6.2, 6.4, 6.7, 6.8**) by the analysis of the NMR spectra their crude products was possibly pyrrolidine-1-carboxylic acid ethyl ester (**197**). No spectroscopic data was available for **197** in the literature, therefore we synthesised this compound for comparison, according to Krupinska and co-workers method.[160] One equivalent of ethyl chloroformate (**196**) was reacted with 2 equivalents of pyrrolidine in anhydrous diethyl ether (Scheme 79). The reaction yielded **197** as a colourless oil in 92% yield.



196 **197**

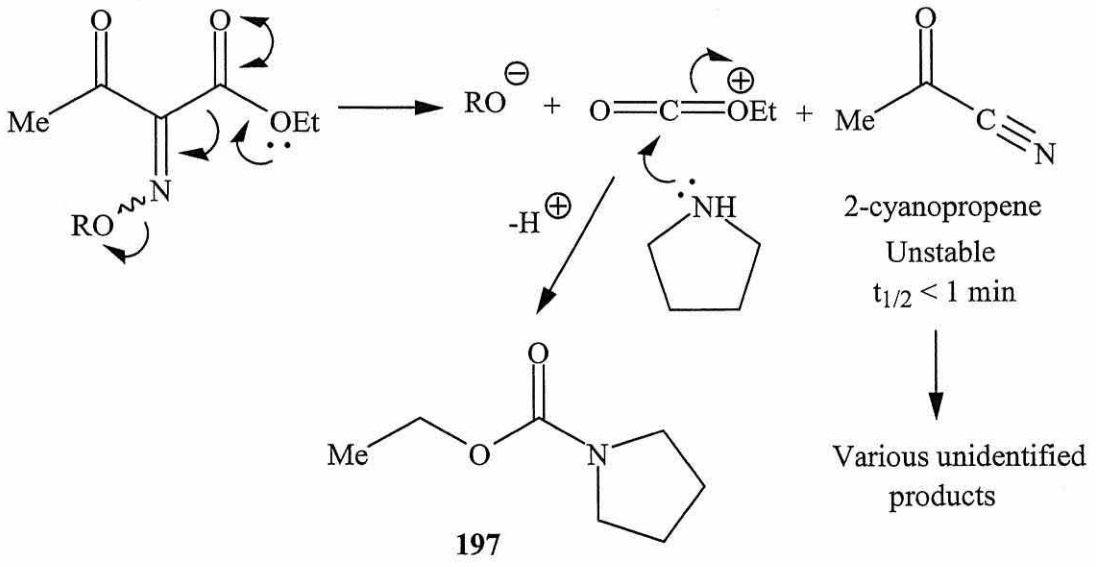
Scheme 79. 197, 92%.

The IR spectrum of the crude product showed a carbonyl peak at ν_{max} 1708.2 cm^{-1}. The ^1H NMR spectrum showed a quartet at δ_H 4.12 ppm with an integral of 2 H, which indicated the CH_2 group of the ester ($O\underline{CH_2}CH_3$). The pyrrolidine CH_2 group signals were present at δ_H 3.33 ppm ($\underline{H_2C}N\underline{CH_2}$) as two triplets overlapping to give a five lined signal with an integral of 4 H, and at δ_H 1.83 ppm ($NCH_2\underline{CH_2}$) as a multiplet with an integral of 4 H. The signal from the CH_3 group of the ester ($OCH_2\underline{CH_3}$) was present at δ_H 1.24 ppm as a triplet with an integral of 3 H.

The ^{13}C NMR spectrum showed the carbonate carbon signal at δ_C 155.2 ppm (EtO-$\underline{C}$=O), the CH_2 signal of the ester was present at δ_C 60.7 ppm ($O\underline{CH_2}CH_3$). Two CH_2 group signals of pyrrolidine ($\underline{H_2C}N\underline{CH_2}$) were present at δ_C 46.0 and 45.6 ppm. The other CH_2 group signals of pyrrolidine ($NCH_2\underline{CH_2}$) were at δ_C 25.7 and 24.9

ppm. This indicated that the pyrrolidine ring had now lost its symmetry due to the restricted rotation around the OC-N bond. The CH_3 signal of the ester was present at δ_C 14.8 ppm ($OCH_2\underline{CH_3}$).

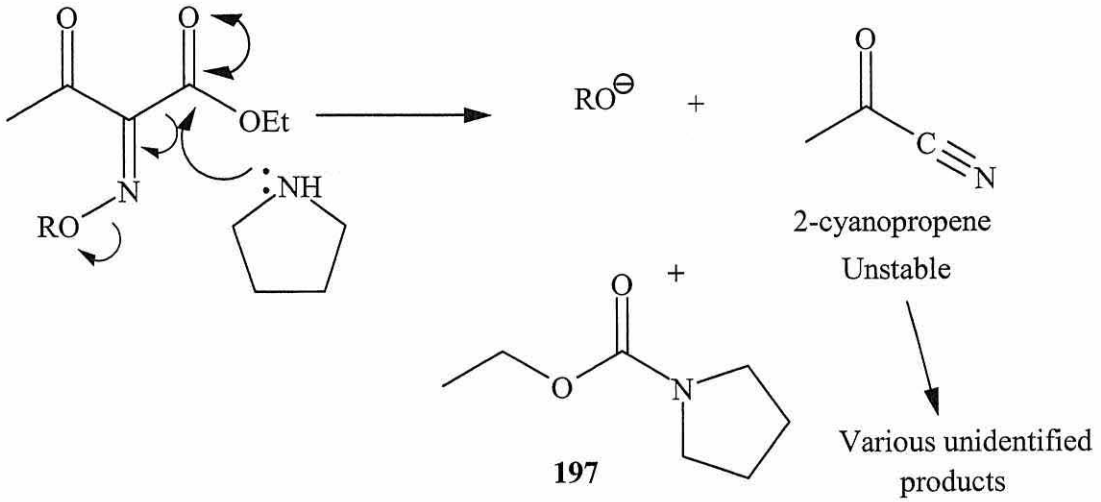
The above data showed that this reaction was successful and corresponded to that obtained for the crude products of the reactions discussed above (**6.2, 6.4, 6.7, 6.8**) and therefore confirmed that this product **197** had indeed been formed in those previous reactions. A suggested mechanism for how this product was formed in those previous reactions is shown in Scheme 80. This is a Beckmann fragmentation.[161] It is similar to a Beckmann rearrangement[162] in that the first step is acid or Lewis acid promoted loss of the oxime OR group. After this the molecule breaks apart and the nucleophile (pyrrolidine) attacks the fragment ($O=C=O^+Et$) to form pyrrolidine-1-carboxylic acid ethyl ester **197**. These two steps may be concerted as shown in Scheme 81. 2-Cyanopropene is unstable and can react/decompose further. This assumption is supported by Lobo and co-workers[163] who reacted 2-cyanopropene with PhNHOH, and found the reaction to proceed with $t_{½} < 1$ min at room temperatures. Griesbaum and co-workers[164] studied the ozonolysis of 2-cyanopropene on polyethylene and found the reaction to proceed at low temperatures of -78 °C.



Scheme 80.

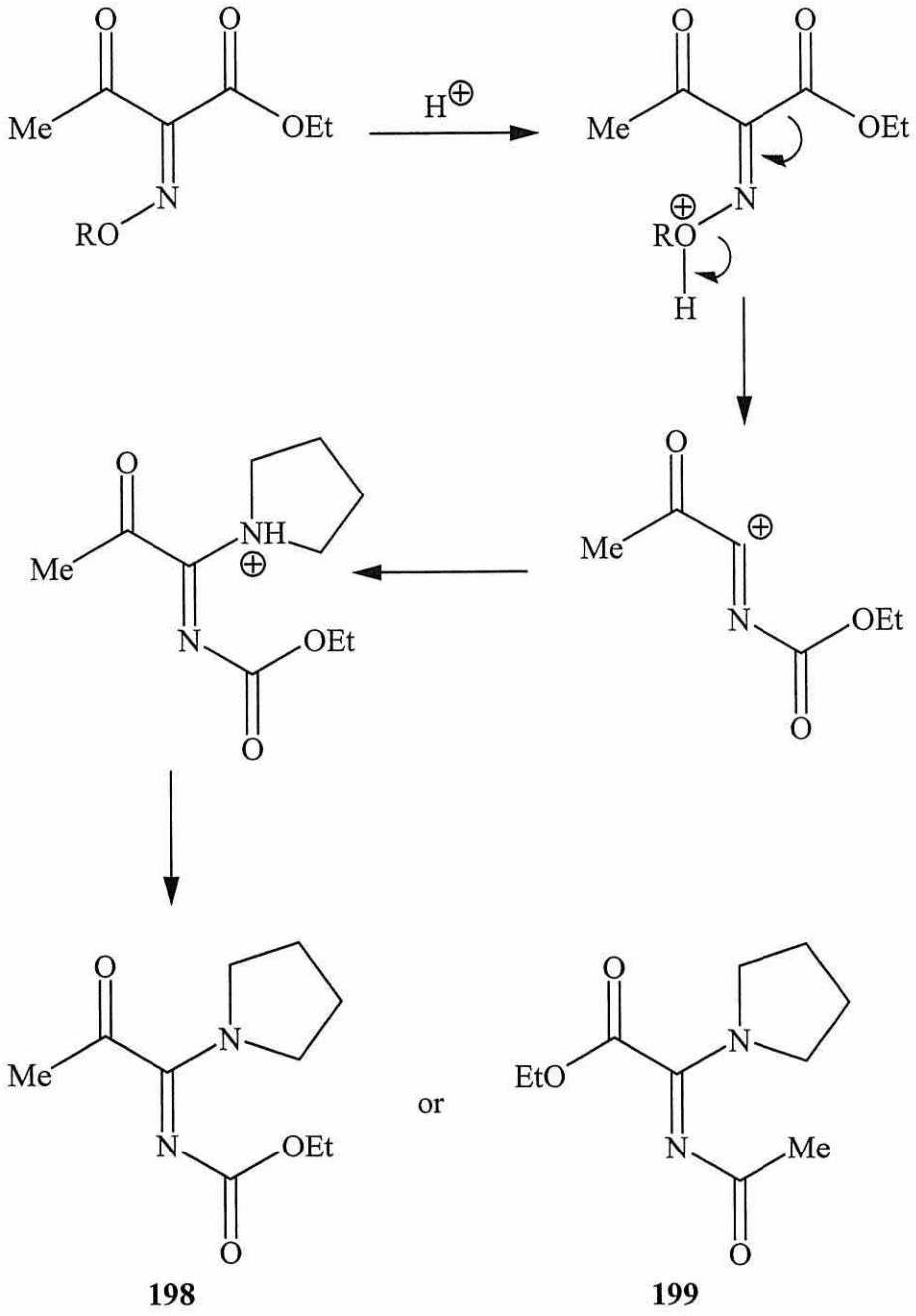
An alternative mechanism[161, 165] for the formation of carbamate **197** involves the initial attack of a nucleophile (pyrrolidine) onto the carbonyl carbon, causing a concerted fragmentation of the rest of the molecule (Scheme 81). Freeman[166]

deduced that the concerted mechanism would be operable in the presence of a good nucleophile and no hindrance at the carbonyl for attack.



Scheme 81. Addition of pyrrolidine followed by fragmentation.

A Beckmann rearrangement,[162] rather than fragmentation would also be possible (Scheme 82). An OH group on an oxime is very likely to undergo this type of rearrangement, whereas an ether is less likely although it is still possible. The NMR spectra of the crude products (*cf.* **6.2, 6.4, 6.7, 6.8**) did not show any signals expected for the Beckmann rearrangement products **198** or **199**, for which more than one carbonyl peak would be present, at least not at any significant levels. Migration is not appreciable for ester and acetyl groups therefore the reaction pathway is more likely to be *via* a Beckmann fragmentation. The Beckmann rearrangement products **198** and **199** do not look to be very stable and probably could not be isolated, therefore this pathway cannot be ruled out completely. The stereochemistry of the oxime is unknown so by the same mechanism as shown in Scheme 82 the product **199** could also be formed. This type of Beckmann fragmentation involving similar compounds to **187** and pyrrolidine has not been previously reported in the literature. The above mechanisms are just possibilities of how the reaction could occur.

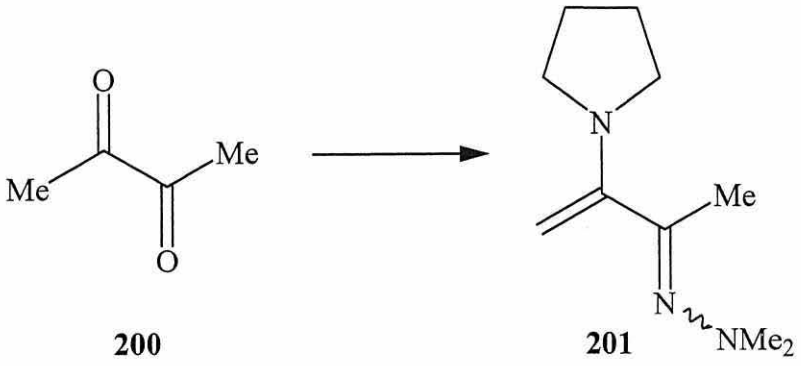


198 **199**

Scheme 82.

It is unknown, for certain, by which route the product **197** is formed, but as pyrrolidine is such a good nucleophile and in control experiments of oximes **187** and **194** (*i.e.* heating in toluene without the presence of pyrrolidine) did not lead to decomposition or formation of any new products, indicating that the presence of a nucleophile (pyrrolidine) is essential for the reactions. Due to this occurrence of Beckmann fragmentations with oximes **187** and **194**, it was decided to follow the method(s) of White and Weingarten[120] and Enders and co-workers[125] more closely

and investigate the synthesis of an enamine azadiene **201** from 2,3-butanedione, **200** (Scheme 83).

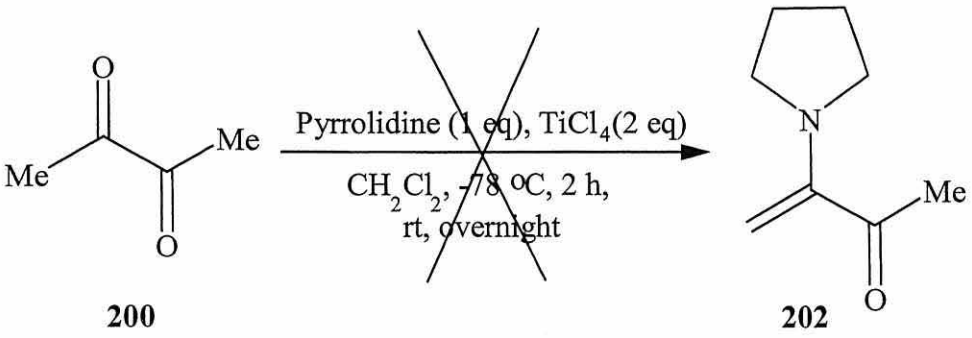


200 **201**

Scheme 83.

6.10 3-Pyrrolidinyl-3-buten-2-one Attempt 1

It was decided to try and form an enamine azadiene **201** still using pyrrolidine due to it being relatively simple, symmetrical and having a manageable boiling point (b.p. 87 – 88 °C), and so White and Weingarten's titanium tetrachloride method[120] was adapted. Titanium tetrachloride was added to pyrrolidine and left to stir at -78 °C. 2,3-Butanedione **200** was then added and the mixture left to stir overnight at room temperature (Scheme 84).



200 **202**

Scheme 84.

The IR spectrum of the crude product after work-up showed the carbonyl group to still be present by the absorption at ν_{max} 1715.5 cm^{-1}, but it also indicated that there were no unsaturated CH groups present. The ^1H NMR spectra showed only

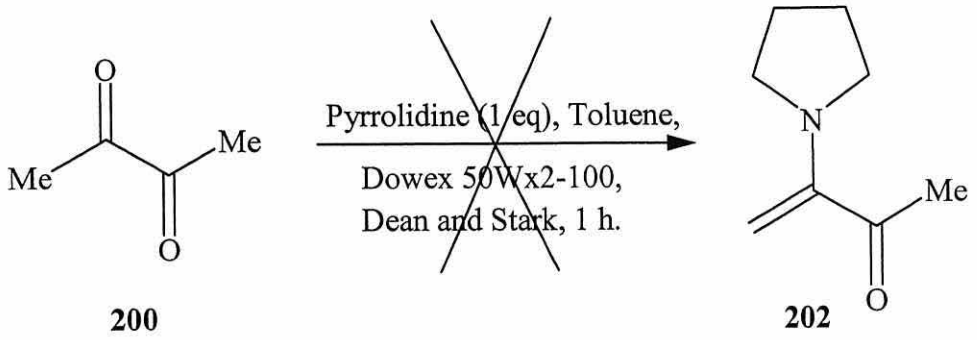
one signal at δ_H 2.30 ppm which was represented as a singlet with an integral of 6 H, correlating to the two CH_3 groups present in 2,3-butanedione **200**.

The ^{13}C NMR confirmed that the only compound present was 2,3-butanedione. There was one signal present at δ_C 23.3 ppm representing the two CH_3 groups, and one signal at δ_C 197.0 ppm representing the two carbonyl carbons (C=O). The mass recovery was 1.23 g, 85% with respect to the mass of starting material **200** used.

Enders and co-workers[125] added (*S*)-2-(methoxymethyl)pyrrolidine (SMP) to 2,3-butanedione (*cf.* section 5.5.3.) using arsenic(III) chloride instead of titanium tetrachloride, a modified method from White and Weingarten[120], and reported that this was a more efficient synthesis. An investigation into the commercial availability of arsenic(III) chloride, revealed that it is supplied only in 25 g ampoules, the scale of these reactions requires only 0.5 g, the resultant waste disposal and toxicity problems therefore ruled against the use of arsenic(III) chloride.

6.11 3-Pyrrolidinyl-3-buten-2-one Attempt 2

Pyrrolidine was added to 2,3-butanedione in the presence of Dowex 50Wx2-100 in an attempt to synthesis 3-pyrrolidinyl-3-buten-2-one *via* a general Dean and Stark reflux method[153] (Scheme 85).



200 **202**

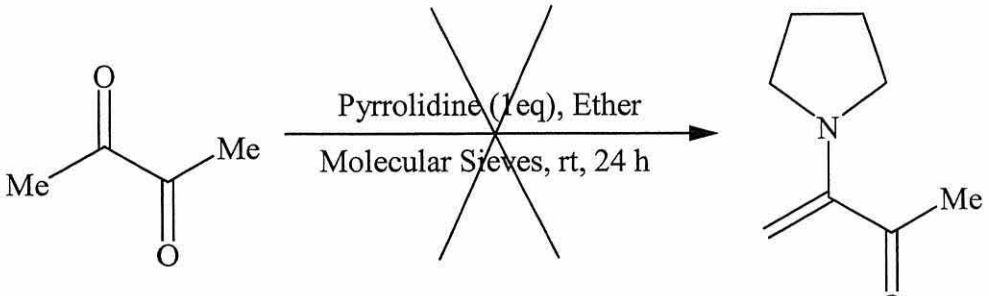
Scheme 85.

The IR, ^1H NMR and ^{13}C NMR spectra of the crude product all supported each other and showed that the only compound present was 2,3-butanedione **200**. The mass recovery was 1.99 g, 99.5% with respect to the mass of starting material **200**.

The reaction did not work and pyrrolidine was most probably lost during the work-up due to its low boiling point (compared to toluene).

6.12 3-Pyrrolidinyl-3-buten-2-one Attempt 3

Another commonly used method for the addition of an amine to a carbonyl group utilises molecular sieves as the dehydrating agent[154]; pyrrolidine was added to 2,3-butanedione **200** in the presence of powdered molecular sieves (4 Å) (Scheme 86).



200 **202**

Scheme 86.

The IR, ^{1}H NMR and ^{13}C NMR spectra of the crude product supported each other and showed that the only compound present was 2,3-butanedione **200**. The ^{13}C NMR, however, did show one extra carbon peak at δ_C 156.3 ppm, a DEPT NMR showed that this was a quaternary carbon *i.e.* had no protons attached, this peak is unassigned.

All of the above reactions in the attempt to synthesise 3-pyrrolidine-3-buten-2-one **202**, were repeated using more equivalents of pyrrolidine (up to 5 equivalent), and with the variation of solvent (toluene, pentane, ether, dichloromethane and benzene). The temperature was also varied *i.e.* stirring at -78 °C, stirring at room temperature, reflux in different solvents and the use of the Dean and Stark apparatus (Table 2). Each time the result was the same, the reaction failed and the starting material recovered, the most likely explanation for this is that no reaction takes place *i.e.* 2,3-butanedione **200** is unreactive to enamine formation. This is surprising as **200** is quite reactive. There is only one similar enamine formation reported in the

literature by Enders and co-workers[125] (*cf.* section 5.5.3), who added (*S*)-2-(methoxymethyl)pyrrolidine (SMP) to 2,3-butanedione **200**. This is the only example and no further investigations have been reported since. A less likely explanation is that pyrrolidine does react with 2,3-butanedione **200** but the product (whether enamine or not) cannot be isolated due to it being easily hydrolysed back to starting material **200** by water in the atmosphere. 2,3-Butanedione mono-dimethylhydrazone **203** is a known stable compound[167, 168] and may:

1) be reactive enough for enamine formation, but still has the possibility of no reaction occurring as discussed above;
2) lead to enamines stable enough to isolate.

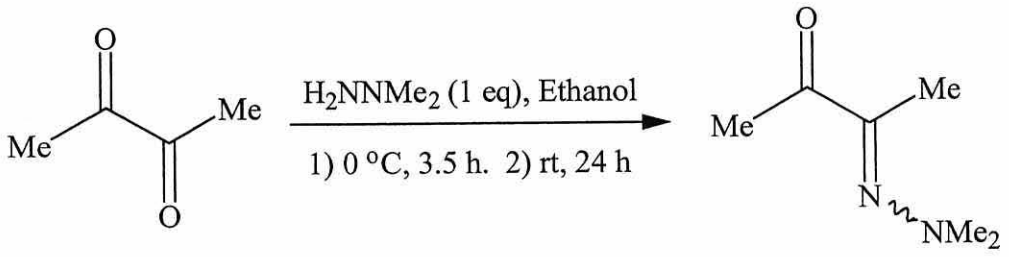
Pyrrolidine Equivalents	**Catalyst / Acid (Eq)**	**Reaction Solvent**	**Reaction Method**	**Reaction Time (hrs)**
2	$TiCl_4$ (2 eq) in CH_2Cl_2	Dichloromethane	-78 °C → rt	24
5	$TiCl_4$ (2 eq) in CH_2Cl_2	Dichloromethane	rt	24
5	Neat $TiCl_4$ (1.1 eq)	Dichloromethane	rt	24
5	Neat $TiCl_4$ (2 eq)	Dichloromethane	rt	24
5	Neat $TiCl_4$ (2 eq)	Ether	rt	24
5	Neat $TiCl_4$ (2 eq)	THF	rt	24
5	Neat $TiCl_4$ (2 eq)	Benzene	rt	24
5	Neat $TiCl_4$ (2 eq)	Toluene	rt	24
5	Neat $TiCl_4$ (2 eq)	Toluene	rt → 30 °C	8
5	Dowex 50Wx2-100 (10 mol%)	Ether	rt	24
5	Dowex 50Wx2-100 (10 mol%)	Ether	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	Dichloromethane	rt	24
5	Dowex 50Wx2-100 (10 mol%)	Dichloromethane	Reflux	24

5	Dowex 50Wx2-100 (10 mol%)	Pentane	rt	24
5	Dowex 50Wx2-100 (10 mol%)	Benzene	Dean & Stark	5
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Dean & Stark	5
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Ether	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Dichloromethane	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	THF	rt	24
5	Molecular Sieves 4 Å (10 mol%)	THF	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Pentane	rt	24
5	Molecular Sieves 4 Å (10 mol%)	Pentane	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Benzene	rt	24
5	Molecular Sieves 4 Å (10 mol%)	Benzene	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Dean & Stark	8
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Reflux	96
5	Molecular Sieves 4 Å (10 mol%)	Toluene	-78 °C → rt	24

Table 2.

6.13 2,3-Butanedione Mono-dimethylhydrazone[123, 124]

If the addition of pyrrolidine to 2,3-butanedione **200** had been successful, the next step would have been to convert the second carbonyl group into a hydrazone with the addition of *N,N*-dimethylhydrazine. It was therefore decided to try adding the components the other way round, *i.e.* the addition of *N,N*-dimethylhydrazine to 2,3-butanedione **200**, followed by the addition of pyrrolidine. 2,3-Butanedione mono-dimethylhydrazone **203** was formed in 85% yield from the addition of *N,N*-dimethylhydrazine to 2,3-butanedione **200** in ethanol (following Tödter and co-workers method[168]) (Scheme 87).



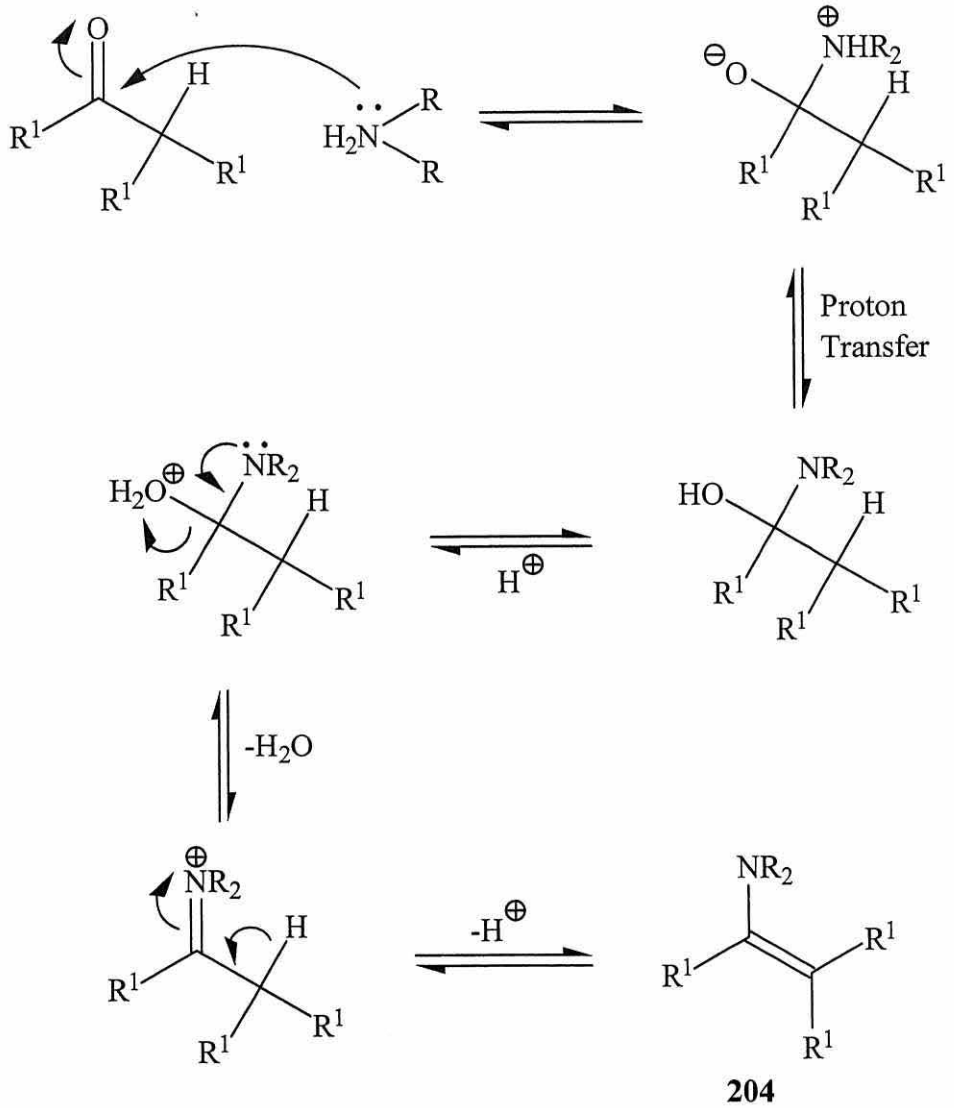
200 **203**

Scheme 87. 203, 85%.

The IR spectrum of the crude product showed one carbonyl peak at ν_{max} 1678.6 cm^{-1}. This is rather low for a carbonyl peak (~ 1715 cm^{-1}) which may indicate the carbonyl to be unreactive. The ^1H NMR spectrum of the crude product had a singlet with an integral of 3 H present at δ_H 1.96 ppm representing a CH_3 group ($\underline{CH_3}$-C=N), and a singlet with an integral of 3 H at δ_H 2.28 ppm showing a second CH_3 group which was in a slightly different environment ($\underline{CH_3}$-C=O). The NMe_2 group of the hydrazone was represented by a singlet with an integral of 6 H at δ_H 2.93 ppm. The ^{13}C NMR spectrum of the crude product showed the two CH_3 group signals ($\underline{CH_3}$-C=N) and ($\underline{CH_3}$-C=O) at δ_C 12.7 and 24.4 ppm respectively, the NMe_2 group signal of the hydrazone appeared at δ_C 46.8 ppm. The carbon signal of the hydrazone (CH_3-$\underline{C}$=N) appeared at δ_C 147.0 ppm and the carbonyl carbon (CH_3-$\underline{C}$=O) was represented by a signal at δ_C 198.9 ppm. This data was in agreement with the literature,[167, 168] showing that the reaction was successful.

6.14 3-Pyrrolidine-3-Buten-2-one Mono-dimethylhydrazone Attempt 1

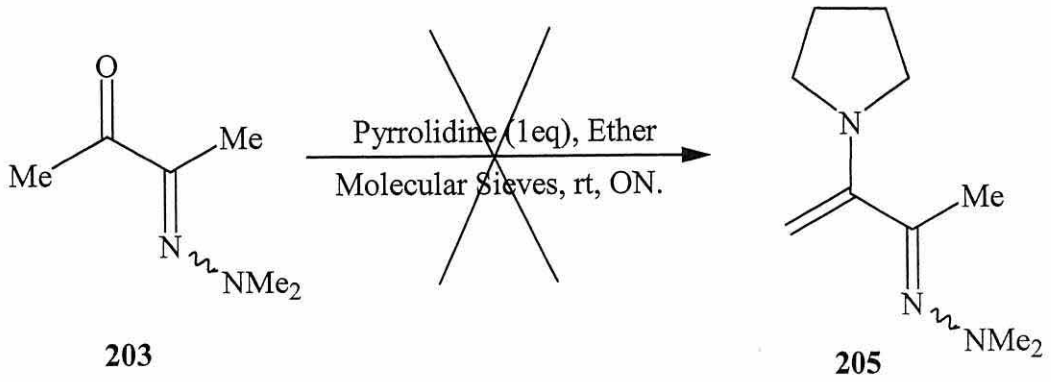
Enamines are prepared from either a ketone or aldehyde with a secondary amine. Scheme 88 shows a suggested mechanism for the general formation of enamines (**204**).



204

Scheme 88. A general mechanism for the formation of enamines.

Pyrrolidine (a secondary amine) was added to 2,3-butanedione mono-dimethylhydrazone **203** in the presence of molecular sieves (4 Å) in ether (Scheme 89), in an attempt to form the 1-azadiene **205**.



203 **205**

Scheme 89.

The IR spectrum of the crude product indicated that the carbonyl group was still present by the absorption at ν_{max} 1685.3 cm^{-1}. The ^1H NMR spectrum showed a multiplet present at δ_H 1.68 ppm with an integral of 2 H representing the two CH_2 groups present in pyrrolidine ($NCH_2\underline{CH_2}$). A singlet with an integral of 3 H at δ_H 2.00 ppm showed the methyl group next to the hydrazone ($\underline{CH_3}$-C=N) to still be present. The chemical shift of this methyl group correlates to the methyl group present in the starting material, **203**. The methyl group next to the carbonyl ($\underline{CH_3}$-C=O) was represented by a singlet at δ_H 2.32 ppm with an integral of 3 H. This also correlates to the starting material, **203**. At δ_H 2.86 ppm a multiplet with an integral of 2 H represents the other two CH_2 groups present in pyrrolidine ($N\underline{CH_2}CH_2$). The two methyl groups of the hydrazone ($N\underline{Me_2}$) were represented by a singlet at δ_H 2.96 ppm with integral of 6 H. The NH group in pyrrolidine was represented by a broad singlet with an integral of 1 H at δ_H 3.70 ppm. The ^1H NMR spectrum therefore showed that the reaction did not work and that only the starting materials (2,3-butanedione mono-dimethylhydrazone, **203** and free pyrrolidine) were present.

The ^{13}C NMR data supported the ^1H NMR and IR spectra indicating that the reaction was indeed unsuccessful and that starting materials only were present. The reactions were repeated using molecular sieves in various solvents at room temperature *i.e.* toluene, benzene, ether, dichloromethane and THF. These reaction were also refluxed for a varied length of time (1 hr – 24 hrs) in the various solvents, and Dowex 50Wx2-100 was also used as a catalyst in toluene and benzene for varied lengths of time (Table 3), all without success.

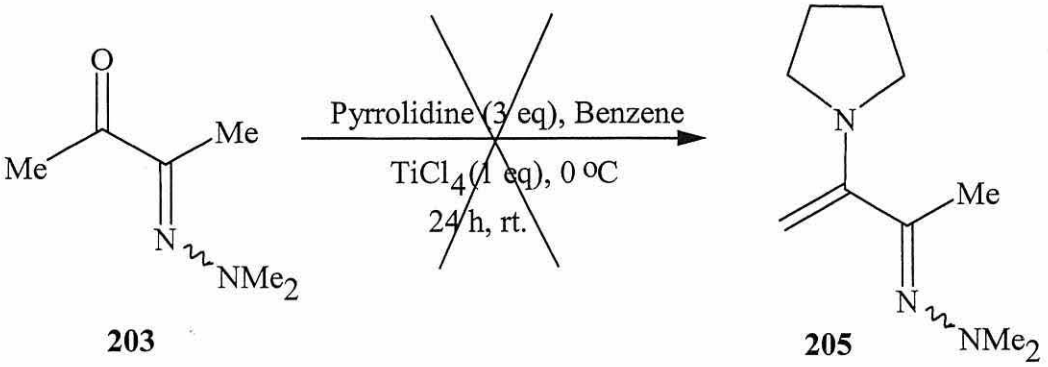
Pyrrolidine Equivalents	Catalyst / Acid (Eq)	Reaction Solvent	Reaction Method	Reaction Time (hrs)
1	Molecular Sieves 4 Å (10 mol%)	Ether	Reflux	24
3	Molecular Sieves 4 Å (10 mol%)	Ether	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Ether	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Dichloromethane	rt	24
5	Molecular Sieves 4 Å (10 mol%)	Dichloromethane	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	THF	rt	24
5	Molecular Sieves 4 Å (10 mol%)	THF	Reflux	8
5	Molecular Sieves 4 Å (10 mol%)	THF	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Benzene	rt	24
5	Molecular Sieves 4 Å (10 mol%)	Benzene	Reflux	24
5	Molecular Sieves 4 Å (10 mol%)	Toluene	rt	24
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Dean & Stark	5
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Dean & Stark	12
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Dean & Stark	24
5	Molecular Sieves 4 Å (10 mol%)	Toluene	Reflux	24

5	Dowex 50Wx2-100 (10 mol%)	Benzene	rt	24
5	Dowex 50Wx2-100 (10 mol%)	Benzene	Reflux	12
5	Dowex 50Wx2-100 (10 mol%)	Benzene	Reflux	24
5	Dowex 50Wx2-100 (10 mol%)	Toluene	rt	24
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Dean & Stark	8
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Dean & Stark	24
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Reflux	12
5	Dowex 50Wx2-100 (10 mol%)	Toluene	Relfux	24

Table 3.

6.15 3-Pyrrolidine-3-Buten-2-One Mono-dimethylhydrazone[101, 106] Attempt 2

The synthesis of enamine **205** by the addition of pyrrolidine to ketone **203** using a modified method of White and Weingarten[120] was attempted. Three equivalents of pyrrolidine were added to 2,3-butanedione mono-dimethylhydrazone, **203** (2 equivalents) in the presence of 1 equivalent of titanium tetrachloride in benzene (Scheme 90).



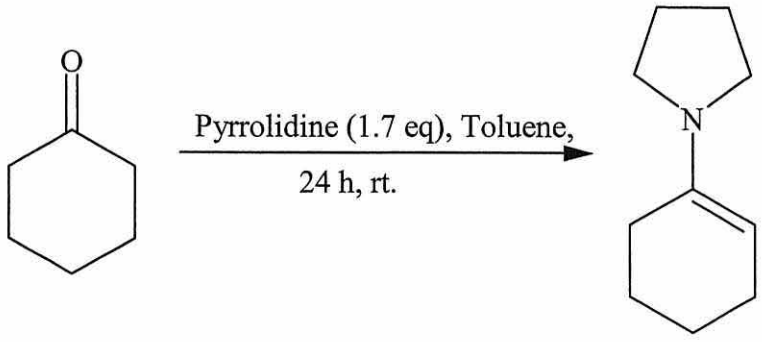
203 **205**

Scheme 90.

The IR spectrum of the crude product showed there to be a carbonyl group still present with a strong absorption at ν_{max} 1684.8 cm^{-1}. The ^{1}H NMR showed a singlet with an integral of 3 H at δ_H 2.04 ppm representing a methyl group. A second singlet at δ_H 2.34 ppm with an integral of 3 H showed there to be a second methyl group present in a similar environment to the other methyl group, but not identical. A singlet with an integral of 6 H was present at δ_H 2.98 ppm representing two methyl groups. This data corresponds to the starting material, **203**. The ^{13}C NMR data supported the ^{1}H NMR spectrum and confirmed that the reaction was unsuccessful. The reaction above was repeated in benzene, but still gave only starting material **203**. Lanthanum triflate was tried as an alternative Lewis acid catalyst in ether; this method was modified from that of Aspinall and co-workers[169, 170] who used lanthanum triflate in combination with benzoic acid catalyses for the allylation of aldehydes and for the *in situ* formation and allylation of various imines from aldehydes. Itoh and co-workers[171] used scandium triflate as a catalyst for the synthesis of secondary and tertiary amines from aldehydes and ketones. A sealed tube was also used for the attempted synthesis of 3-pyrrolidine-3-buten-2-one mono-dimethylhydrazone, **205**: pyrrolidine and **203** were heated in toluene to 150 °C for up to 8 h; this reaction was also repeated with *p*-toluenesulfonic acid added to the tube. All of these reactions gave the same result *i.e.* no reaction between pyrrolidine and the starting material.

6.16 *N*-(Cyclohexen-1-yl) Pyrrolidine

After numerous attempts to synthesise the enamines **188**, **202** and **205** had failed, it was decided to investigate the synthesis of a simpler carbonyl compound and obtain an easy method for its conversion to an enamine. McLean and co-workers[172] investigated the synthesis of *N*-(cyclohexen-1-yl)pyrrolidine to use as a heterocyclic diene in an "inverse electron-demand" Diels-Alder reaction and the reactions were done *in situ*. Their method[172] to synthesise *N*-(cyclohexen-1-yl)pyrrolidine, **207** was followed and the reaction gave **207** as a yellow oil in 78% yield. On the addition of pyrrolidine to cyclohexanone a colour change took place. The reaction was repeated with the addition of pyrrolidine to cyclohexanone in toluene and observed by ^{1}H NMR analysis and TLC. After the reaction mixture had been stirred for 24 hours at room temperature the data indicated that the reaction had gone to completion (Scheme 77).



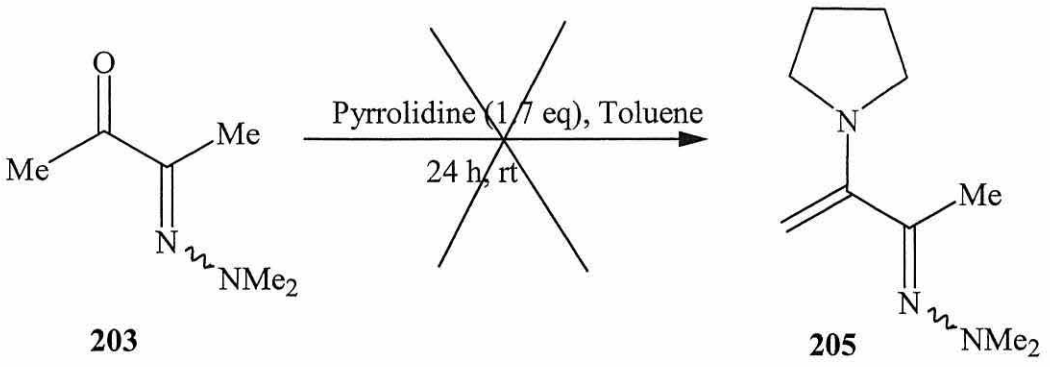
206 **207**

Scheme 91. **207**, 99% (crude).

The IR, ^{1}H NMR and ^{13}C NMR spectra were all in fair agreement with the literature.[172] Although the IR spectrum showed the crude product, **207** to have a small amount of cyclohexanone, **206** still present, this could have been caused by hydrolysis of **207** by the atmosphere whilst the sample was being run. A simple method for the formation of enamines had now been established, and so this method was applied to 2,3-butanedione mono-dimethylhydrazone, **203** and pyrrolidine.

6.17 3-Pyrrolidine-3-Buten-2-one Mono-dimethylhydrazone Attempt 3

2,3-Butanedione mono-dimethylhydrazone and pyrrolidine were left to stir for 24 hours (Scheme 92) under the same conditions used for the synthesis of *N*-(cyclohexen-1-yl) pyrrolidine (**207**, *cf.* section 6.16) to see if a simple general method for the formation of enamines could be applied to **203**.



203 **205**

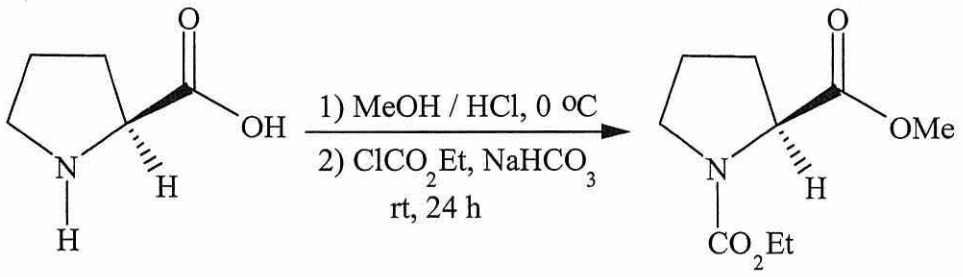
Scheme 92.

After 24 hours of monitoring the reaction by IR and ^{1}H NMR analysis there was no indication of any product being present and only starting materials were recovered. The method that McLean and co-workers[172] had devised and that worked well on simpler ketones *e.g.* cyclohexanone, proved to be too simple for the hydrazone **203**, confirming that either the ketone of **203** is unreactive towards enamine formation or, the less likely scenario, that enamine **205** cannot be isolated and reverts back to **203** on any attempt to do so (and / or the position of the equilibria between **203** and **205** lies far towards **203**).

6.18 *N*-Ethyloxycarbonylproline Methyl Ester[173]

Enders and co-workers[125] have reported the synthesis of 3-[(*S*)-2-(methoxymethyl)pyrrolidine-1-yl]-3-buten-2-one **167** *via* the addition of (*S*)-2-(methoxymethyl)pyrrolidine (SMP) **166** to 2,3-butanedione **165** using arsenic(III) chloride, Scheme 62 a method that they adapted from White and Weingarten's titanium tetrachloride method[120] section 5.5.3. Therefore the next approach towards the target enamine aza-diene was to make some SMP as the oxygen atom present may

make a difference to the success of enamine synthesis by coordinating to titanium / arsenic. An attempt to make 3-[(*S*)-2-(methoxymethyl)pyrrolidine-1-yl]-3-buten-2-one (**209**), was done *via* the addition of acetyl chloride followed by the addition of ethyl chloroformate to L-proline (**208**) (Scheme 93) a modified method to that of Lewis and co-workers.[173]



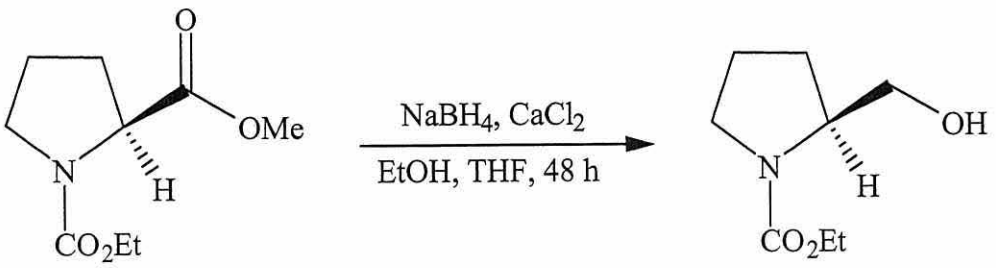
208 **209**

Scheme 93. 209, 50%.

The ^{1}H and ^{13}C NMR spectrum were in agreement with the literature[173], indicating that the reaction was a success.

6.19 Reduction of *N*-Ethyloxycarbonylproline Methyl Ester 153

The next step was to reduce the methyl ester of **209**, with the addition of "calcium borohydride" (formed *in situ* from calcium chloride and sodium borohydride) (Scheme 94). "Calcium borohydride" was used instead of sodium borohydride or lithium aluminium hydride as these reducing agents are too strong and would also reduce the ethyl ester carboxyl group.



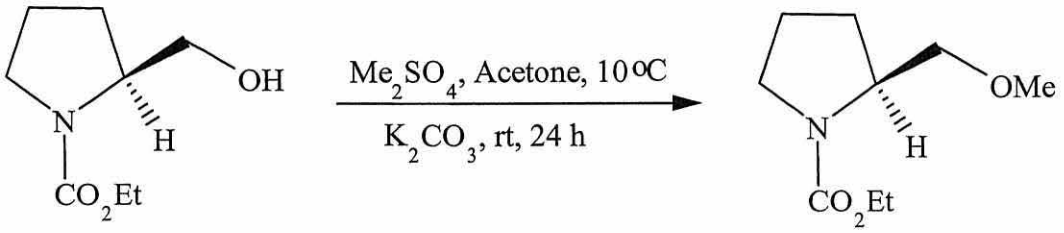
209 **210**

Scheme 94. 210, 94%.

The IR, ^{1}H NMR and ^{13}C NMR spectrum were in agreement with the literature[173] and confirmed that the reaction was successful.

6.20 Methylation of the *L*-Prolinol Derivative

N-Ethoxycarbonylprolinol **210** was treated with dimethyl sulfate in an attempt to methylate the alcohol group (Scheme 95).



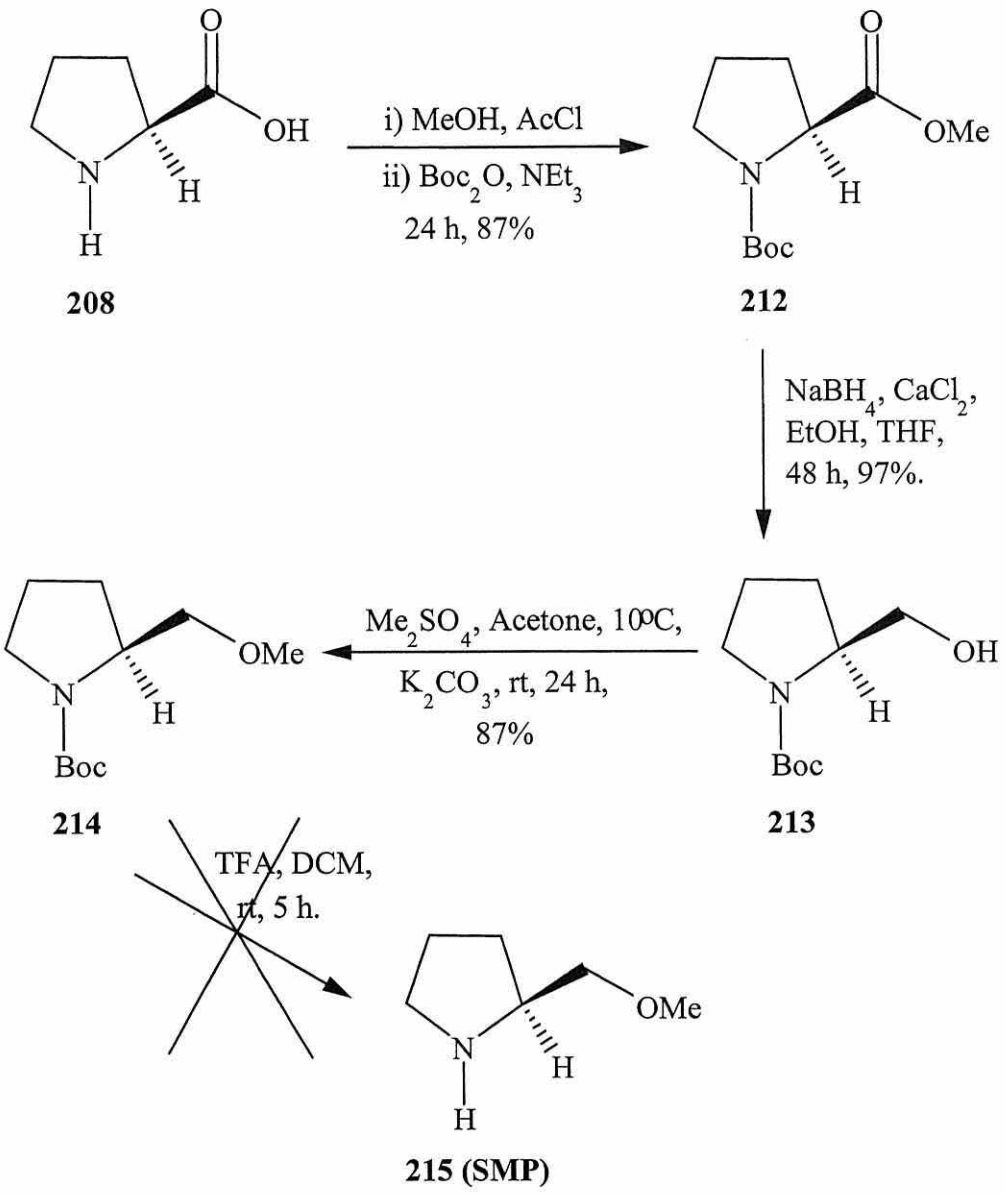
210 **211**

Scheme 95. 211, 83%.

The ^{1}H and ^{13}C NMR spectra of the crude product was similar to the starting material, which is what was expected, but the integrals were not exactly right and there were numerous peaks present so the crude product was run through a silica column using ethyl acetate : methanol (95 : 5) as the eluent, but no product or starting material could be recovered, presumably it absorbed too strongly onto the silica or decomposed.

The above reactions were repeated with Boc as the protecting group instead of ethoxycarbonyl. The *L*-prolinol derivative was methylated *via* the same route as above. The addition of the Boc protecting group was done following a standard

procedure and gave the product **212** in 87% yield. The reduction of **212** was done following the procedure used in Scheme 94 *cf.* section 6.19 to give the product **213** in 97% yield. The methylation of **213** was done using the same procedure as Scheme 95 to give the methylated product **214** in 87% yield (Scheme 96); the ^{1}H and ^{13}C NMR spectra for the crude products **212**, **213** and **214** showed not only the products to be present but also contained numerous unidentified peaks. An attempt to purify the crude products by distillation resulted in the products decomposing. The crude products were run through a silica column using ethyl acetate : methanol (95 : 5) as the eluent on each occasion but no product was recovered. Presumably they either decomposed or were absorbed to strongly on the silica. On trying to remove the Boc protecting group from the crude product **214** using trifluoroacetic acid (TFA), the compound again decomposed.

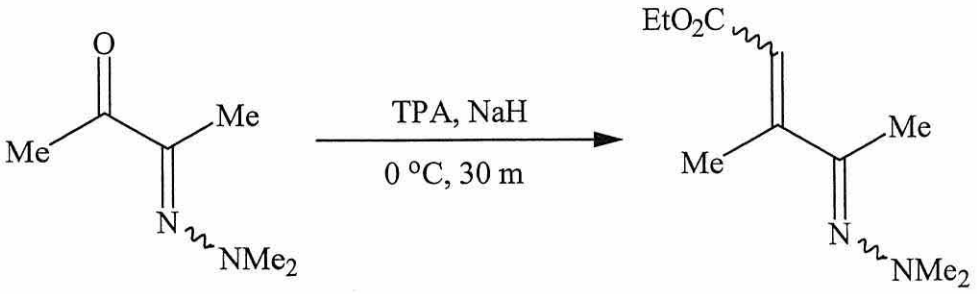


Scheme 96. Attempted synthesis of SMP using Boc as the protecting group.

Therefore some SMP was purchased from Aldrich and used in an attempt to repeat the procedure of White and Weigarten[101] and Enders and co-workers[106]. Unfortunately, due to SMP being very expensive, this reaction could only be attempted once and it failed (*cf.* Scheme 84, section 6.10), 2,3-butanedione was recovered in 92% yield as was a little SMP-hydrochloride (5% yield) as an orange precipitate.

6.21 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triethyl Phosphonoacetate

2,3-Butanedione mono-dimethylhydrazone **203** was treated with a solution of the phosphonate anion in ether (Scheme 97). This type of reaction is known as a Horner-Wadsworth-Emmons olefination or a Horner-Wadsworth-Emmons modification of the Wittig reaction[174]; this reaction was investigated to determine if an aza-Wittig type route to enamines[175] was worth developing.



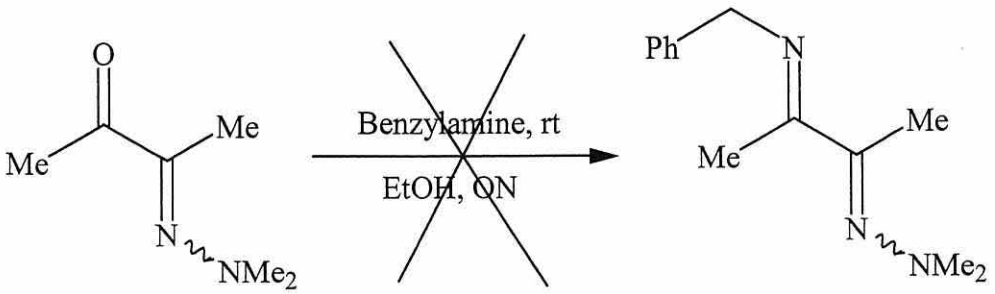
203 **217**

Scheme 97.

The IR, ^{1}H and ^{13}C NMR spectra of the crude product all indicated that the only compound present was crude 2,3-butanedione mono-dimethylhydrazone **203** recovered in 96% yield after being run through a silica column using petrol : ether (70 : 30) and that no reaction had taken place.

6.22 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Benzylamine

Benzylamine was reacted with **203** in ethanol (Scheme 98) to synthesise the imine **218**; the synthesis of enamines with secondary amines mechanism proceeds *via* an iminium ion, so now an attempt was made to synthesise an imine with a primary amine.



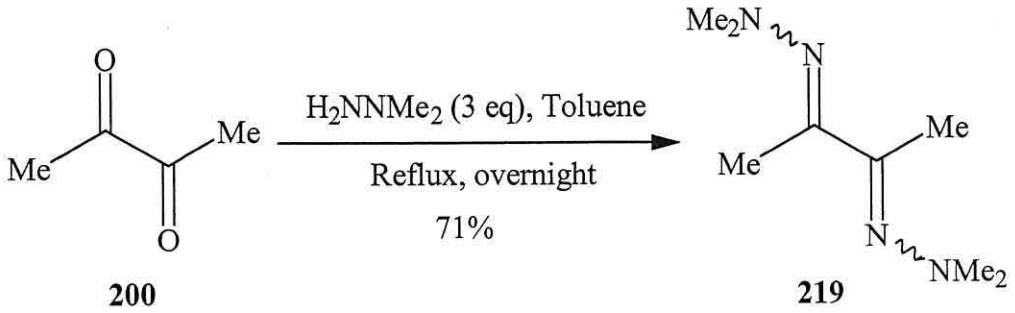
203 **218**

Scheme 98.

The IR spectrum of the crude product indicated that the carbonyl group was still present by a peak at ν_{max} 1679.6 cm^{-1}. The ^{1}H NMR spectrum showed a methyl group to be present at δ_H 1.90 ppm represented by a singlet with an integral of 3 H ($\underline{CH_3}C{=}N$). The other methyl group was represented by a singlet at δ_H 2.21 ppm also with an integral of 3 H ($\underline{CH_3}C{=}O$). The two hydrazone methyls were indicated by a singlet with an integral of 6 H at δ_H 2.87 ppm. The spectrum showed many unidentified signals each having an integral of 1 H between δ_H 1.09 and 3.63 ppm. The ^{13}C NMR spectrum showed the two methyl groups in similar environments ($\underline{CH_3}C{=}N$) and ($\underline{CH_3}C{=}O$) to be present at δ_C 12.6 and 24.3 ppm respectively. The hydrazone methyl groups were represented by a signal at δ_C 46.7 ppm ($N\underline{Me_2}$). The hydrazone carbon ($CH_3\underline{C}{=}N$) and carbonyl carbon ($CH_3\underline{C}{=}O$) were represented by peaks at δ_C 146.6 and 198.9 ppm respectively. There are also a number of unidentified peaks present. Although both the ^{1}H and ^{13}C NMR spectra have unidentified peaks present it was clear that the reaction was either unsuccessful or there was a reaction but the product was not formed in appreciable quantities due to the low reactivity of the carbonyl group.

6.23 Bis-Hydrazone[176], 219

N,N-Dimethylhydrazine was heated under reflux with 2,3-butanedione **200** in toluene in an attempt to synthesise the bis-hydrazone, **219** (Scheme 99), following Bock and tom Dieck's method.[176]



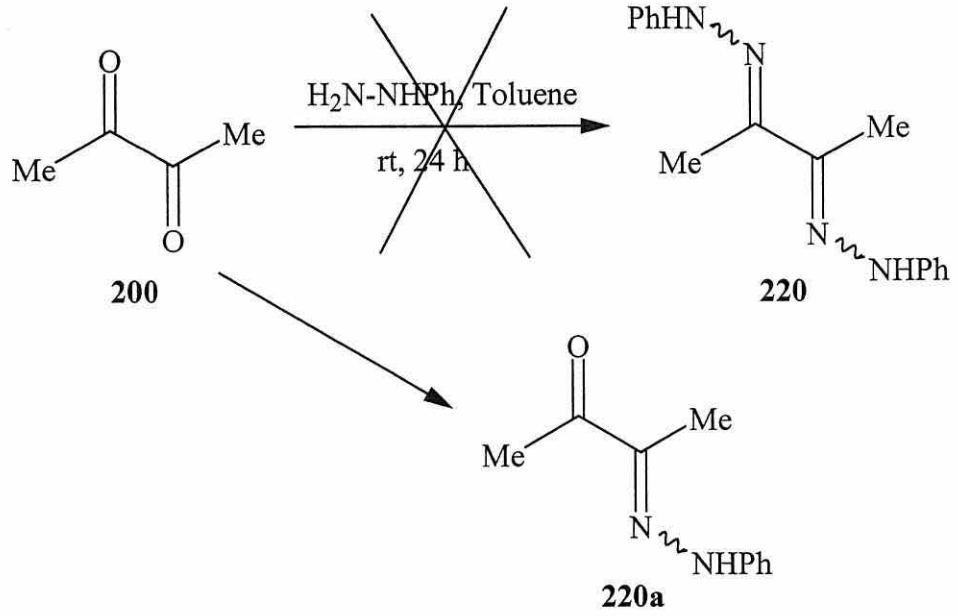
200 **219**

Scheme 99.

The IR spectrum of the distilled product showed a C=N functional group to be present by a peak at ν_{max} 1687.1 cm^{-1}. The ^1H NMR spectrum, provided by Awen Haf Jones (a third year undergraduate student) who repeated the reaction under the same conditions and purified by distillation, showed a singlet to be present at δ_H 2.07 ppm with an integral of 3 H representing the methyl group next to the hydrazone ($\underline{CH_3}C=N$, **219**) and the methyl groups present in the hydrazone were represented by a singlet with an integral of 6 H at δ_H 2.55 ppm ($N\underline{Me_2}$, **219**). The bis-hydrazone is a well known compound and the data agrees with the literature.

6.24 Reaction of 2,3-Butanedione with Phenylhydrazine

Phenylhydrazine (3 equivalents) was added to 2,3-butanedione **200** and toluene and stirred for 24 hours (Scheme 100).



Scheme 100. Formation of the mono-hydrazone, **220a** and not the bis-hydrazone, **220**.

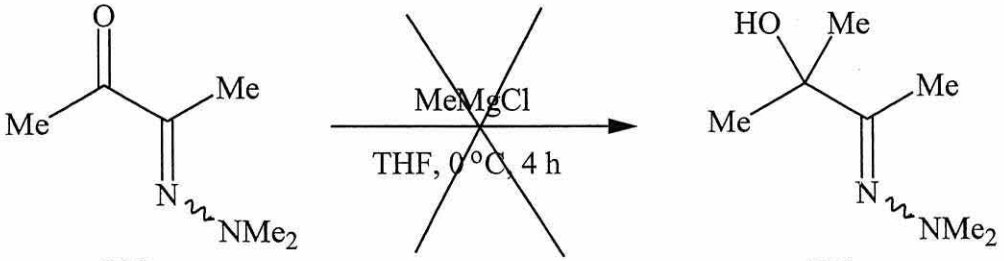
The IR spectrum of the crude product had a very weak carbonyl peak at ν_{max} 1688.3 cm^{-1}. There was also a peak at ν_{max} 1600.3 cm^{-1} representing a C=N functional group. The ^1H NMR spectrum had a singlet present at δ_H 1.29 ppm representing a methyl group next to a hydrazone ($\underline{CH_3}C=N$). A singlet at δ_H 2.24 ppm represented the methyl group in the starting material **200** ($\underline{CH_3}C=O$). The integrals for these two methyl groups were only 1 H but the signals are at the correct chemical shift for the mono-hydrazone. The NH group was shown by a broad singlet at δ_H 3.66 ppm with an integral of 1 H; a multiplet at δ_H 6.85 ppm with an integral of 4 H indicated that the two CH groups in the phenyl of the hydrazone (Ph 3-$\underline{CH}$) are present. The other two CH groups in the same environment (Ph 2-$\underline{CH}$) are represented by a multiplet at δ_H 7.27 ppm with an integral of 4 H, the CH group in the 4 position of the phenyl (Ph 4-$\underline{CH}$) was represented by a multiplet with an integral of 2 H at δ_H 7.39 ppm. The mono-hydrazone and starting material **200** were present in a 3 : 1 ratio as determined by ^1H NMR spectroscopy.

The ^{13}C NMR spectrum showed the two different methyl group signals ($\underline{CH_3}C=N$, **220a**) and ($\underline{CH_3}C=O$, **200**) to be present at δ_C 9.2 and 31.2 ppm respectively. The CH group in the 4 position of the phenyl group was represented by a signal at δ_C 112.1 ppm, the two CH groups present at the 3 and 5 position of the

phenyl group (Ph 3-CH) were represented by a signal at δ_C 119.4 ppm. The CH groups at the 2 and 6 position of the phenyl (Ph 2-CH) were indicated by a signal at δ_C 129.3 ppm. The carbon in the 1 position attached to the nitrogen (N-CCHCHCH) appeared at δ_C 151.3 ppm. The carbon attached to the hydrazone (CH_3C=N, mono-hydrazone) and the carbonyl carbon (CH_3C=O, **200**) were represented by signals present at δ_C 156.3 and 189.4 ppm, respectively. The data suggests that a reaction did occur but that the mono-hydrazone was formed and not the bis-hydrazone. There was also some starting material **200** still present. The two compounds could not be separated by distillation and the products decomposed as determined by ^{1}H NMR spectroscopy. There are very few bis-hydrazones discussed in the literature and since their synthesis was not the main aim of this research project no further investigation was undertaken.

6.25 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Methyl Magnesium Chloride

The addition of a methyl group to the carbonyl carbon by adding methyl magnesium chloride to 2,3-butanedione mono-dimethylhydrazone **203** (Scheme 101) was attempted to investigate whether the carbonyl would react with a good nucleophile.



203 **221**

Scheme 101.

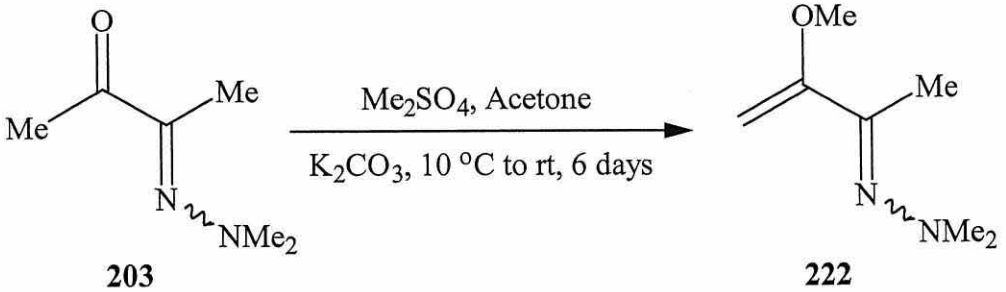
The IR spectrum of the crude product showed a strong carbonyl peak at ν_{max} 1678.4 cm^{-1}. The ^{1}H NMR spectra indicated that the starting material **203** was the main compound present. The methyl group next to the hydrazone (CH_3C=N) was represented by a multiplet at δ_H 1.93 ppm, the methyl next to the carbonyl (CH_3C=O)

was also a multiplet at δ_H 2.25 ppm both having an integral of 3 H. The hydrazone ($N\underline{Me_2}$) was represented by a multiplet with an integral of 6 H at δ_H 2.90 ppm. The ^{13}C NMR supported the ^1H NMR indicating that the desired reaction had not taken place. There were however a number of unidentified peaks present in the ^1H and ^{13}C NMR spectra of the crude product. The crude product was put on to a silica column with petrol : ether (70 : 30) as the eluent. The starting material **203** was the only compound recovered in 76% yield.

The above reaction was repeated using methyllithium instead of methylmagnesium chloride.[167] Here the "Me⁻" acts as a base; stirring at -78 °C for 1 hour followed by stirring at room temperature for 4 days, this reaction was also unsuccessful. The NMR spectra of the crude product showed there to be 2,3-butanedione mono-dimethylhydrazone, **203** present along with a number of unidentified peaks; **203** was recovered in a 16% yield after being passed through a silica column with the eluent as petrol : ether (70 : 30). It is possible that a reaction did occur and that the product **221** is not stable and decomposed or that **221** was not formed in appreciable quantities due to the low reactivity of the carbonyl group.

6.26 Methylation of 2,3-Butanedione Mono-dimethylhydrazone

An attempt to methylate the oxygen of the carbonyl group of **203** using a method adapted from Burcourt and co-workers[159] who made ethyl methoxyimino acetoacetate **194** (*cf.* Scheme 76, section 6.6), dimethyl sulfate was added to a mixture of **203** and potassium carbonate in acetone (Scheme 102).



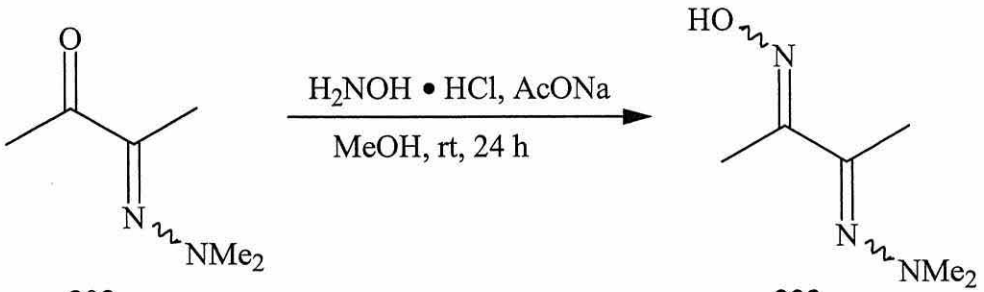
203 **222**

Scheme 102.

The IR, ^{1}H and ^{13}C NMR spectra all indicated that the reaction was unsuccessful and only starting material **203** was recovered, in 57% yield, after work-up.

6.27 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Hydroxylamine Hydrochloride

Moody and co-workers[177] investigated the synthesis of oxime-hydrazones. Scheme 103 shows the synthesis of the oxime of 2,3-butanedione mono-dimethylhydrazone **223** following Moody and co-workers' method.



203 **223**

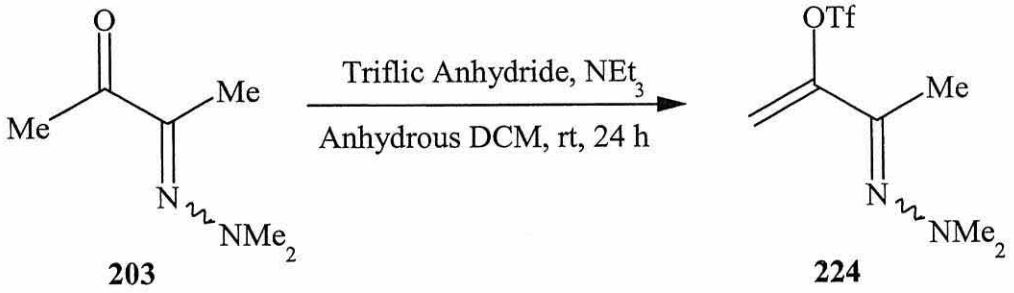
Scheme 103. 223, 97%.

The IR spectrum of the crude product showed an OH group absorption present at ν_{max} 3225.8 cm^{-1}, but a very weak carbonyl peak absorption remained at ν_{max} 1712.5 cm^{-1} *i.e.* some unreacted **203**. The ^{1}H NMR spectrum of the crude product showed a methyl group to be present represented by a singlet at δ_H 2.07 ppm with an integral of 3 H ($\underline{CH_3}C{=}N\text{-}NMe_2$). A second methyl group in a similar environment ($\underline{CH_3}C{=}N\text{-}OH$) was represented as a singlet with an integral of 3 H at δ_H 2.11 ppm. A singlet at δ_H 2.60 ppm with an integral of 3 H indicated the methyl group of the hydrazone ($N\underline{Me_2}$) to still be present, although the integral is small the signal is at the correct chemical shift; an OH group was present at δ_H 7.45 ppm as a broad singlet with an integral of 1 H. The ^{13}C NMR spectrum of the crude product showed the two methyl groups ($\underline{CH_3}C{=}N\text{-}NMe_2$) and ($\underline{CH_3}C{=}N\text{-}OH$) represented by peaks at δ_C 13.9 and 21.3 ppm respectively; the hydrazone methyls ($N\underline{Me_2}$) were represented by a signal at δ_C 47.2 ppm. The carbon of the hydrazone ($CH_3\underline{C}{=}N\text{-}NMe_2$) was

represented by a peak at δ_C 156.3 ppm. The carbon of the oxime group ($CH_3\underline{C}$=N-OH) was present at a lower chemical shift than the carbonyl group and appeared at δ_C 176.2 ppm. The data was in agreement with the literature,[178] using a slightly different method.

6.28 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triflic Anhydride[179, 180]

The carbonyl group of 2,3-butanedione mono-dimethylhydrazone was proving to be very unreactive, so it was decided to try and react it with various electrophiles to see if the carbonyl group would do anything. The carbonyl group was reacted with triflic anhydride (Scheme 104).



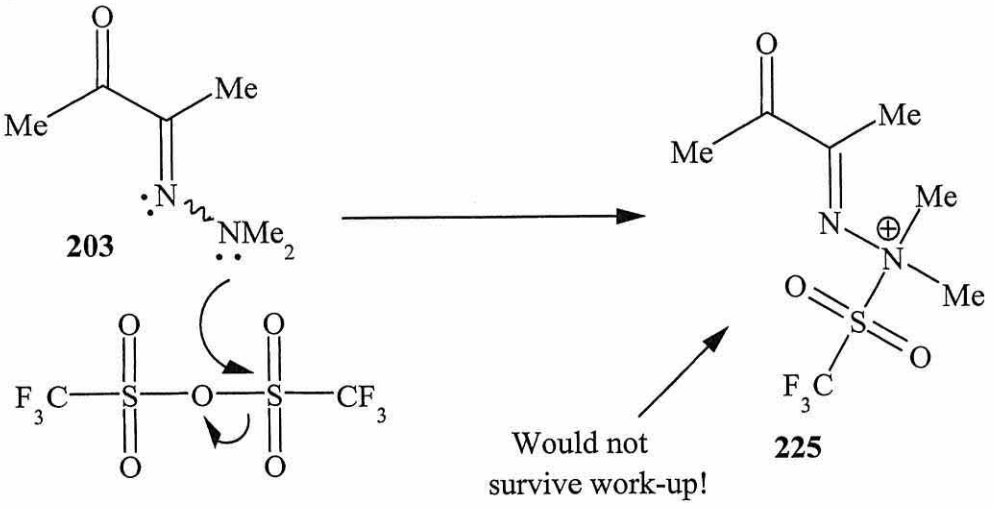
203 **224**

Scheme 104.

The IR spectrum of the crude product showed a carbonyl group to still be present at ν_{max} 1686.6 cm^{-1}. The ^1H NMR showed the starting material **203** to still be present with two singlets present at δ_H 1.87 and 2.19 ppm each with an integral of 3 H representing two different methyl groups in similar environments ($\underline{CH_3}$-C=N) and ($\underline{CH_3}$-C=O) respectively. The two methyl groups forming part of the hydrazone functional group were represented by a singlet at δ_H 2.85 ppm with an integral of 6 H. The ^{13}C NMR confirmed that the starting material **203** was present; both the ^1H and ^{13}C NMR have extra signals present in the crude product that remain unexplained, but do not correspond with the expected resonance's of enol triflate **224**.

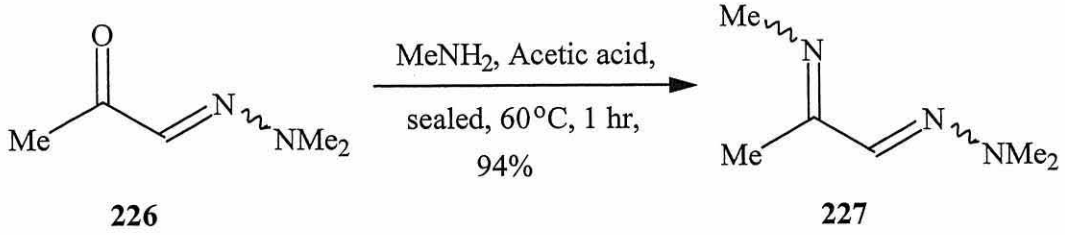
This reaction was repeated using triflic anhydride and 2,6-di-*t*-butyl-4-methyl pyridine.[181] This also gave unreacted 2,3-butanedione mono-dimethylhydrazone **203**

(8% recovered, so most was destroyed), therefore, either enol triflate **224** is too unstable to isolate from the reaction, or, more probably, it was not formed in appreciable quantities due to the low reactivity of the carbonyl group of **203**; it is also possible that an unproductive reaction occurred at the hydrazone group (Scheme 105). This could also occur at the other more nucleophilic nitrogen atom, but the literature suggests that both are unlikely and the product **225** would not survive the work-up.



Scheme 105

Koldobskii and co-workers[110] studied the synthesis of dimethylhydrazone of α-dimethylaminoacrolein from the 1-dimethylhydrazone of methylglyoxal. The first stage of this reaction was to form 1-dimethylhydrazono-2-(*N*-methylimino) propane **227** from 1-dimethylhydrazone of methylglyoxal **226** (Scheme 106) by the reaction of the hydrazone carbonyl group with methylamine.

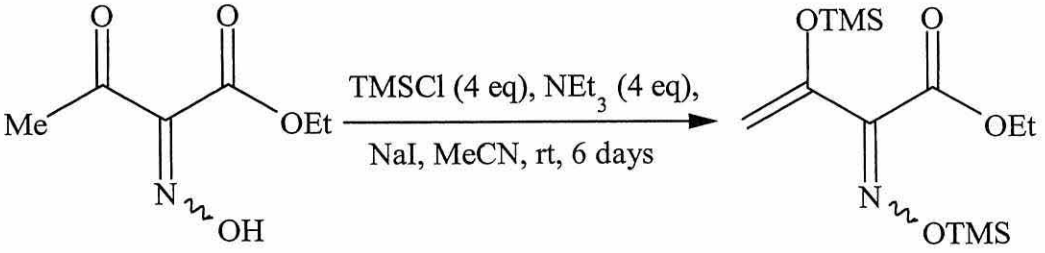


Scheme 106. Reaction on the carbonyl group of the hydrazone.

There are very few other examples of reactions of the carbonyl group of α-ketohydrazones in the literature, in particular ones similar to 2,3-butanedione mono-dimethylhydrazone **203**. 2,3-Butanedione can be reacted to form the mono-hydrazone (*cf.* section 6.23 and 6.24) and the bis-hydrazone **219**. Unfortunately the carbonyl group present in the mono-hydrazone **203** is generally unreactive. **203** would only react with very strong nucleophiles at room temperature over a minimum of 24 hours and were not clean reactions.

6.29 Exhaustive Trimethylsilylation of Ethyl Oximino Acetoacetate[85]

In 1974, Danishefsky and Kitahara[156] investigated the synthesis of silyl enol ethers (*cf.* section 6.3) and in 1990, Igarashi and co-workers[85] investigated oxime-silyl enol ether aza-dienes (*e.g.* **228**) similar to the targets of this work, **192**, **195** and **205**. Due to the difficulties in synthesising enamine-aza-dienes such as **192** and **205**, it was decided to study the scope of aza-dienes such as **228** in pyridine synthesis. As described in section 5.2.1, aza-dienes such as **228** have been used successfully in some previous pyridine syntheses. Aza-diene **228** was prepared by exhaustive trimethylsilylation of ethyl oximino acetoacetate **187** (Scheme 107)[85].



187 **228**

Scheme 107. 228, 47%.

The literature method[85] stirred the reaction for 12 hours at room temperature. After 12 hours a small quantity of the reaction mixture above was removed and analysed by ^{1}H NMR spectroscopy. It showed the reaction had not gone to completion. The reaction was left to stir at room temperature and monitored by ^{1}H NMR analysis. After 4 days the reaction had gone to completion (*i.e.* no starting material **187** remained) but the yield was only 21%. Upon leaving the reaction 6 days

the yield was improved to 47% giving the product **228** as a brown oil. Increasing the reaction time beyond 6 days made no difference to the overall yield. 47% yield was the highest yield obtained with product being lost in the work-up washings. This was a relatively low yield compared to the literature which achieved a yield of 81%.

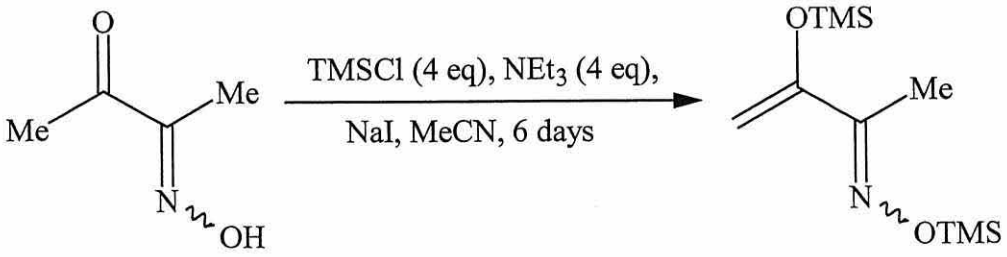
The IR spectrum of the crude product still showed the presence of an OH group, with a peak at ν_{max} 3363.5 cm^{-1}. A carbonyl group was also still present represented by a peak at ν_{max} 1750.2 cm^{-1}. Additionally a double bond was now present, indicated by a peak at ν_{max} 1701.1 cm^{-1}. The ^1H NMR spectrum showed the two trimethylsilyl groups (OTMS) to be present at δ_H 0.22 ppm as a singlet with an integral of 18 H. The CH_3 group of the ethyl ester ($OCH_2\underline{CH_3}$) was represented by a triplet with an integral of 3 H at δ_H 1.32 ppm. The CH_2 group of the ethyl ester ($O\underline{CH_2}CH_3$) was a quartet at δ_H 4.33 ppm with an integral of 2 H. At δ_H 4.69 and 4.71 ppm were two doublets each with an integral of 1 H indicating that the $C=\underline{CH_2}$ group was now present. The methyl group in the starting material ($\underline{CH_3}C=O$) which appears at δ_H 2.36 ppm had now disappeared. The ^{13}C NMR spectra showed the trimethylsilyl group (OTMS) represented by a signal at δ_C -0.5 ppm. The CH_3 group ($OCH_2\underline{CH_3}$) and the CH_2 group ($O\underline{CH_2}CH_3$) of the ethyl ester were represented by signals at δ_C 14.1 and 61.5 ppm respectively. The CH_2 double bond ($C=\underline{CH_2}$) was represented by a signal at δ_C 100.9 ppm and the carbon of the double bond ($\underline{C}=CH_2$) at δ_C 163.3 ppm. The oxime carbon ($\underline{C}$=N-OTMS) and the ester carbon ($\underline{C}O_2Et$) were represented by signals at δ_C 148.4 and 155.1 ppm.

The ^1H and ^{13}C NMR spectra were very clean and showed that the reaction was successful with no residual starting material **187** or monosilylated product **189**. The IR spectrum showed an OH peak. This can be explained by the product **228** being hydrolysed during the preparation and process of IR analysis; due to previous work done on similar compounds[85] the aza-diene was expected to be colourless so purification by Kugelrohr distillation was attempted on the product (oil bath temperature up to 200°C, 25 mmHg). A colourless oil was collected. Upon ^1H NMR analysis this proved to be the precursor **187.** When stored in the freezer a white solid proceeded to form characteristic of **187**. The residual mixture was a brown oil. A ^1H NMR spectrum indicated that the product **228** still remained along with an unidentified contaminant represented by a broad signal at δ_H 3.25 ppm. Precursor **187** was also present. Purification by column chromatography was attempted, petrol :

ethyl acetate (30 : 70), but this removed the silyl groups and destroyed the aza-diene **228**, leading only to the isolation of precursor **187**. A second purification by column chromatography was attempted with all glassware and silica being washed with triethylamine before use in an attempt to stop the product from decomposing due to it being acid sensitive. Again the only compound collected was the precursor using petrol : ethyl acetate (30 : 70) as the eluent; a possibility for the product **228** being a brown oil instead of a colourless oil could be due to I^- / I_2 being present. The product **228** could not be put through our GC-MS machine as it would not have survived the process and any product that had would probably of stuck to the GC column. As the crude compound looked very pure by NMR it was used in aza-Diels-Alder reactions without further purification.

6.30 Exhaustive Trimethylsilylation of 2,3-Butanedione Monoxime[85]

The synthesis of a second aza-diene using the same method as above, adapted from Igarashi and co-workers[85] who synthesised a very similar aza-diene to **230** (3 carbon chain instead of a 4 carbon chain). Triethylamine and chlorotrimethylsilane were added to a solution of 2,3-butadione monoxime **229** and sodium iodide in acetonitrile (Scheme 108).



229 **230**

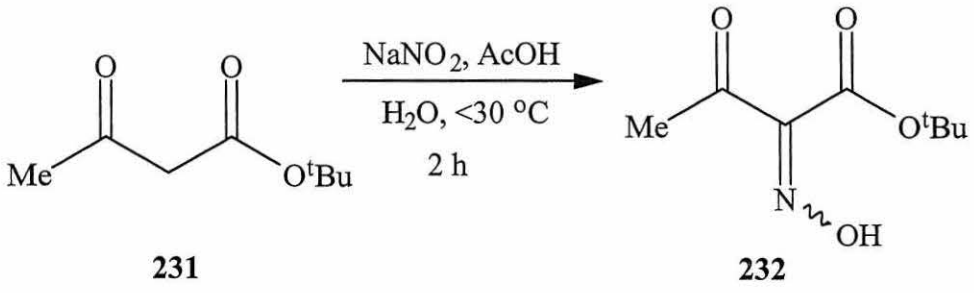
Scheme 108. 230, 49%.

The reaction was monitored by ^{1}H NMR analysis. After 4 days the ^{1}H NMR spectrum indicated that the starting material had been consumed. The reaction mixture was left to stir for a further two days in order to optimise the yield as in the reaction shown in Scheme 107.

The IR spectrum of the crude product showed that there was still an OH group, present at ν_{max} 3366.6 cm^{-1}. A carbonyl group was also still present represented by a peak at ν_{max} 1749.3 cm^{-1}. The double bond was now present indicated by a peak at ν_{max} 1702.0 cm^{-1}. The ^1H NMR spectrum showed the trimethylsilyl group (TMS) as a singlet with an integral of 18 H at δ_H 0.22 ppm. The methyl group next to the oxime ($\underline{CH_3}$-C=N) was represented by a singlet at δ_H 1.97 ppm with an integral of 3 H. Two doublets present at δ_H 4.55 and 4.82 ppm each with an integral of 1 H indicated that the double bond was now present (C=$\underline{CH_2}$). The ^{13}C NMR spectrum showed the trimethylsilyl group to be present at δ_C -0.6 ppm. The methyl group ($\underline{CH_3}$-C=N) was at δ_C 11.0 ppm. The carbon of the oxime was represented by a signal at δ_C 153.3 ppm. The double bond was represented by two signals at δ_C 97.3 and 157.4 ppm (C=$\underline{CH_2}$) and ($\underline{C}$=CH_2) respectively. The NMR spectra again looked very pure, so the aza-diene **230** was used in aza-Diels-Alder reactions without further purification.

6.31 ^{t}Butyl Oximino Acetoacetate[152]

^{t}Butyl oximino acetoacetate, **232** differs from ethyl oximino acetoacetate, **186** only in the ester group and was synthesised successfully in the same way in 92% yield (Scheme 109).



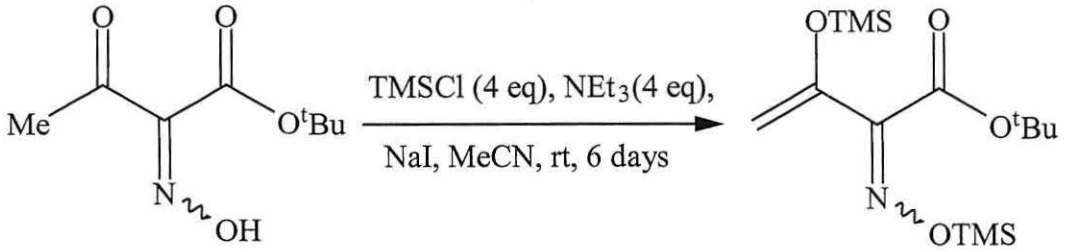
231 **232**

Scheme 109. 232, 92%.

The spectroscopic data agreed with the structure and the literature[152].

6.32 Exhaustive Trimethylsilylation of ^{t}Butyl Oximino Acetoacetate[85]

The exhaustive trimethylsilylation of ^{t}butyl oximino acetoacetate, **232** (Scheme 110) was achieved using the same method as for ethyl oximino acetoacetate *cf.* section 6.29 and 6.30.



232 **233**

Scheme 110. 233, 37%.

This reaction was done following the same method used in Scheme 107. The reaction was monitored by ^{1}H NMR analysis. After 6 days the reaction gave the aza-diene **233** in 37% yield, with most of the product being lost during the work-up washings. All glassware was washed with triethylamine before use in an attempt to remove any acidity on the glass. The product **233** was not a colourless oil as expected but a brown oil. This possible impurity could be due to I^{-} / I_2 still being present.

The IR spectrum of the crude product showed there to be no OH group present. The ester carbonyl was represented by a peak at ν_{max} 1730.1 cm^{-1} and the oxime by a peak at ν_{max} 1615.1 cm^{-1}. The ^{1}H NMR spectrum showed a singlet at δ_H 0.20 ppm representing the trimethylsilyl groups with an integral of 18 H. The tertiary butyl group was represented by a singlet with an integral of 9 H at δ_H 1.50 ppm. There were now 2 doublets present each with an integral of 1 H at δ_H 4.69 ppm indicating the double bond (C=$\underline{C}H_2$). The ^{13}C NMR spectrum showed the trimethylsilyl group at δ_C -0.1 ppm and the three methyl groups present in ^{t}butyl at δ_C 27.9 ppm. The carbon in tertiary butyl ($\underline{C}Me_3$) was represented by a signal at δ_C 65.8 ppm. The double bond was represented by two signals at δ_C 100.8 and 162.5 ppm (C=$\underline{C}H_2$) and ($\underline{C}$=CH_2) respectively; the oxime carbon ($\underline{C}$=N-OTMS) was present at δ_C 148.6 ppm and the ^{t}butyl ester carbon ($\underline{C}O_2{}^{t}Bu$) at δ_C 155.5 ppm.

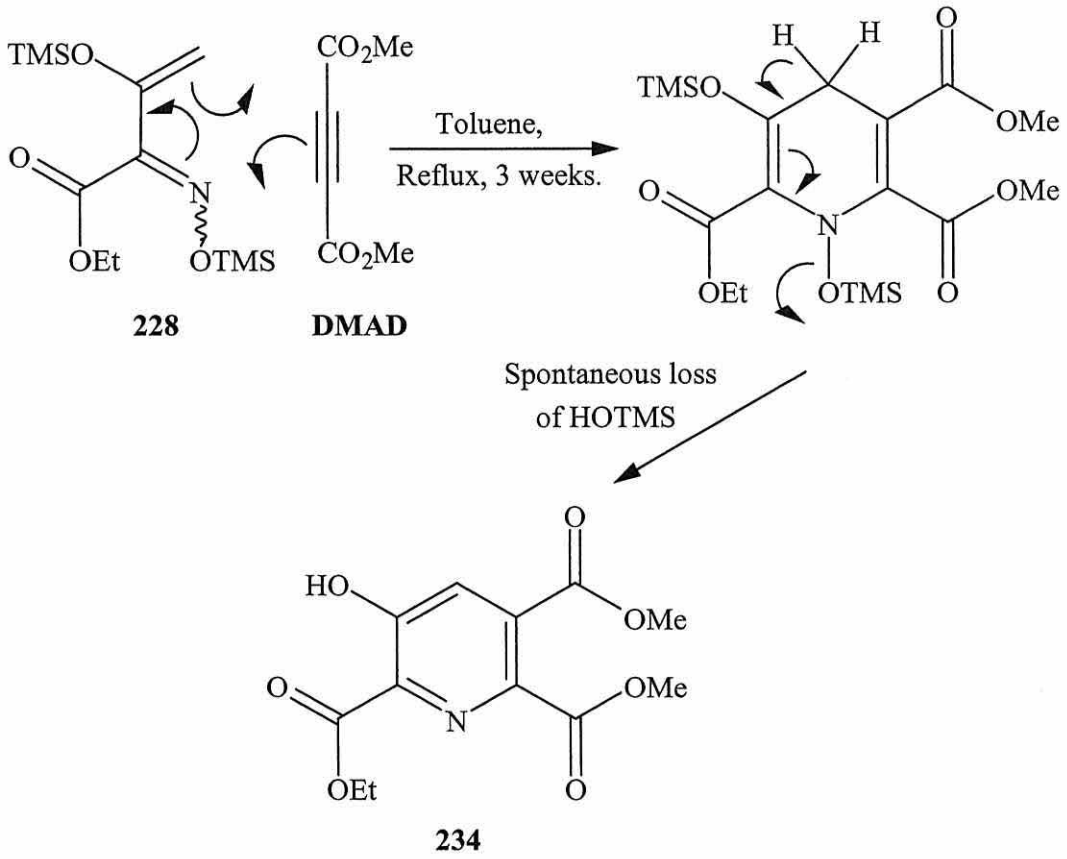
The spectroscopic data looked very pure and proved that the reaction was successful. The aza-diene **233** was used without further purification.

6.33 Synthesis of a Highly Substituted Pyridine[85]

The next step was to attempt aza-Diels-Alder reactions with the aza-dienes **228**, **230** and **233**. The following reactions require 2 molecules to come together and will vary in rate with concentration. The aza-Diels-Alder reactions were done with similar molar concentrations, *i.e.* 30 mmol and variation of concentration was not investigated. Similarly no detailed investigations of temperature of reaction or solvent variations were done; 4 others solvents were tried for the aza-Diels-Alder reaction as shown in Scheme 111 (discussed later). Previous studies with aza-dienes similar to **228** showed that the best reaction conditions were heating under reflux in tolune[182]. The first reaction to try used dimethyl acetylenedicarboxylate (DMAD) as the dienophile, due to it being electron deficient, relatively simple, cheap and readily available and an excellent dienophile in normal electron-demand Diels-Alder reactions (*cf.* section 5.0, 5.2.1, 5.2.2 and 5.2.3). Similar aza-Diels-Alder reactions are studied by Igarashi and co-workers.[85] These sort of substituted pyridines are very useful and are, for example, used for the synthesis of thiopeptide antibiotics such as nosiheptide and glycothiohexide[27] and other pharmaceutical uses if chemistry can be done at the hydroxy group.

The aza-diene, **228** was heated under reflux with DMAD (1 eq) in toluene (Scheme 111) for three weeks. Igarashi and co-workers[85] did a similar aza-Diels-Alder reaction using DMAD (*cf.* section 5.2.1. Scheme 32) which required being heated to reflux for 12 hours. The same conditions were used on aza-diene **228** and the reaction mixture analysed by ^{1}H NMR spectroscopy. The data showed the aza-diene **228** C=$\underline{CH_2}$ group signal to still be present. The reaction was repeated and heated under reflux in toluene; the reaction could not be monitored by TLC analysis due to the silyl groups on the starting material **228** being removed by the silica leading to the decomposition of **228** so the reaction was monitored by ^{1}H NMR spectroscopy. After 2 weeks of heating under reflux the ^{1}H NMR spectrum indicated that the aza-diene **228** C=$\underline{CH_2}$ group signal was beginning to disappear. After 3 weeks the C=$\underline{CH_2}$ group had completely disappeared indicating that all the starting material **228** had been consumed. The reaction was repeated in 4 different solvents

(*i.e.* benzene, chloroform, ether and THF). These attempts were monitored by ^{1}H NMR spectroscopy. After 3 weeks of heating under reflux the ^{1}H NMR spectrum still had the C=$\underline{CH_2}$ group signal. The reaction mixtures were heated under reflux for a further 3 weeks whilst being monitored by ^{1}H NMR spectroscopy. After a total of 6 weeks heating under reflux the ^{1}H NMR spectrum showed that the aza-diene **228** had reverted back to its original precursor **187**. A microwave assisted synthesis of **234** was also attempted *cf.* section 6.59.



228 **DMAD**

234

Scheme 111. 234, 37%.

The ^{1}H and ^{13}C NMR spectra of the crude product showed the pyridine **234** to be present but the spectra also contained numerous unidentified signals, so the crude product was run through a silica column eluting with chloroform : methanol (99.5 : 0.5) to give the pure pyridine **234** as a yellow oil in 37% yield and the precursor **187** in 51% yield. The ^{1}H NMR spectrum showed evidence of an OTMS group present which may have been attached to something, but this was never recovered from the column.

The IR spectrum of **234** showed there to be a carbonyl functional group still present by a peak at ν_{max} 1738.0 cm^{-1}. There was now a peak at ν_{max} 1681.7 cm^{-1} indicating an aromatic ring (C=C) to be present. The ^1H NMR spectrum had a triplet present at δ_H 1.50 ppm with an integral of 3 H representing the CH_3 group in the ethyl ester ($OCH_2\underline{CH_3}$). The CH_2 group of the ethyl ester ($O\underline{CH_2}CH_3$) was represented by a quartet with an integral of 2 H at δ_H 4.56 ppm. This was slightly higher than in the starting material **228** which was represented by a peak at δ_H 4.33 ppm giving another diagnostic position to look for in crude spectra. The two methoxy methyl groups (C=C-$CO_2\underline{Me}$) and (N=C-$CO_2\underline{Me}$) were represented by two singlets at δ_H 3.96 and 3.97 ppm respectively each with an integral of 3 H; these could not be unreacted dimethyl acetylenedicarboxylate as this has just a singlet at δ_H 3.73 ppm in its ^1H NMR spectrum, which was not present in the spectrum of purified pyridine **234**. Again the change of the DMAD signals was useful for hunting product in other spectra. The aromatic hydrogen (C=C-$\underline{H}$) was represented by a singlet at δ_H 7.67 ppm and the OH group was represented by a singlet at δ_H 11.17 ppm, each with an integral of 1 H which were also useful diagnostic signals.

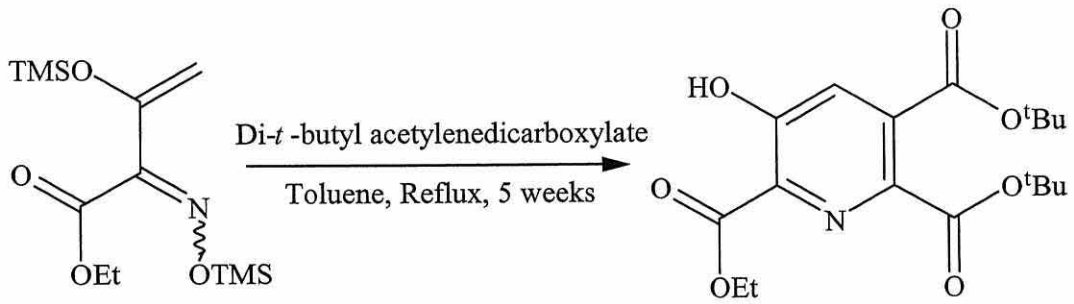
The ^{13}C NMR spectrum showed the CH_3 and the CH_2 of the ethoxy group ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) represented by signals at δ_C 14.0 and 63.4 ppm, respectively; the two CH_3 groups ($CO_2\underline{Me}$) were represented by a single peak at δ_C 53.3 ppm. The carbon with the aromatic hydrogen (C=$\underline{C}$-H) was represented at δ_C 127.0 ppm. The carbon next to the OH group (C=$\underline{C}$-OH) was represented by a signal at δ_C 129.4 ppm. The (C=$\underline{C}$-CO_2Me) carbon was represented by a signal at δ_C 131.2 ppm; the (N=$\underline{C}$-CO_2Me) and (N=$\underline{C}$-CO_2Et) carbons were represented by one signal at δ_C 135.8 ppm, as they are in very similar environments. The carbonyl carbons (C=C-$\underline{C}O_2$Me), (N=C-$\underline{C}O_2$Et) and (N=C-$\underline{C}O_2$Me) are represented by signals at δ_C 159.5, 165.1 and 168.3 ppm. There was no data in the literature for this compound so a small quantity of the pure product was sent to the EPSRC national mass spectrometry service centre at the University of Wales Swansea, for an accurate mass measurement (electrospray). The calculated mass $[M + H]^+$ was 284.0765 and the measured mass $[M + H]^+$ was 284.0769 confirming that the highly substituted pyridine **234** was present.

With a general reaction method for the synthesis of substituted pyridines from aza-diene **288** in hand other aza-Diels-Alder reactions using the same aza-diene **228**

but different dienophiles were undertaken to investigate the synthetic scope of this strategy.

6.34 Attempted Synthesis of a Highly Substituted Pyridine, 235

Di-*t*-butyl acetylenedicarboxylate was chosen next as it is very similar to dimethyl acetylenedicarboxylate and so should behave like DMAD. Due to it being more sterically hindered it would require a longer reaction time and probably have lower yields, but the pyridine would have orthogonal ester protecting groups. Di-*t*-butyl acetylenedicarboxylate (1 eq) was heated under reflux in toluene with 1-aza-diene, **228** for 5 weeks (Scheme 112). The reaction was monitored by ^{1}H NMR analysis. After 5 weeks the ^{1}H NMR spectrum showed the starting material to have been consumed.



228 **235**

Scheme 112.

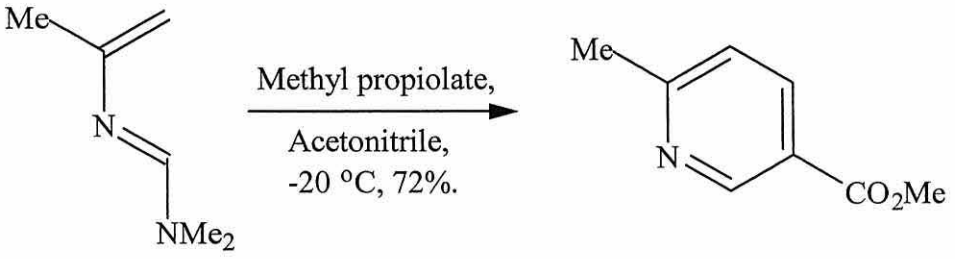
The spectra of the crude product no longer showed the aza-diene **228** C=$\underline{CH_2}$ signal to be present and indicated that the aza-diene **228** had reverted back to precursor **187**. The crude product was purified by column chromatography with ethyl acetate as the eluent.

The IR spectrum of the purified compound showed an OH group at ν_{max} 3285.4 cm^{-1}. There were two carbonyl peaks at ν_{max} 1728.9 and 1681.2 cm^{-1}. The ^{1}H NMR spectra showed an ethyl ester to be present at δ_H 1.28 and 4.31 ppm represented by a triplet with an integral of 3 H and a quartet with an integral of 2 H, confirming the presence of (OCH$_2\underline{CH_3}$) and (O$\underline{CH_2}$CH$_3$), respectively. A singlet at δ_H 2.35 ppm with an integral of 3 H represented the methyl group next to the ketone ($\underline{CH_3}$C=O).

The ^{13}C NMR spectra confirmed that the only compound present was the precursor, **187**, to the starting material recovered in 98% yield.

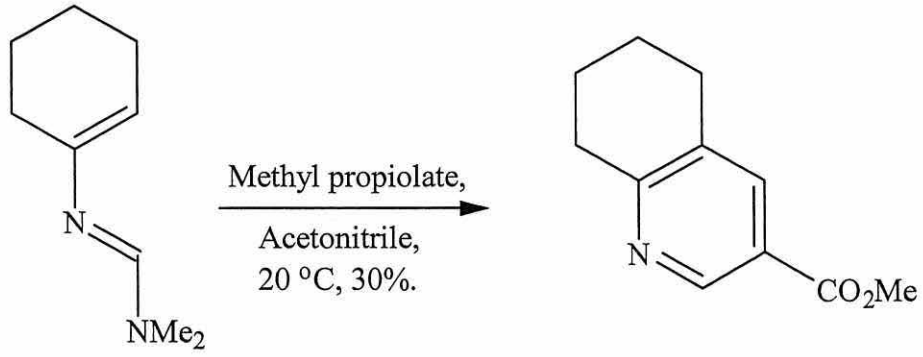
6.35 Attempted Synthesis of a Highly Substituted Pyridine, 240

In 1975, Demoulin and co-workers[183] and in 1980, Gompper and co-workers[184] published two of the many examples of the use of methyl propiolate as a dienophile in aza-Diels-Alder reactions. Demoulin and co-workers[183] investigated the synthesis of substituted pyridines with the cycloadditions of 1-amino-2-aza-dienes and methyl propiolate (Scheme 113 and 114). Methyl propiolate is similar to dimethyl acetylenedicarboxylate, which was used as a dienophile and produced the highly substituted pyridine **234** *cf.* section 6.33, so it was decided to try employing methyl propiolate under those same conditions (Scheme 115).



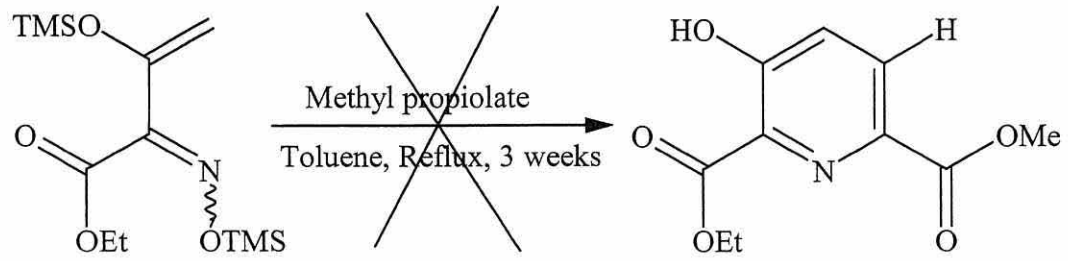
236 **237**

Scheme 113.



238 **239**

Scheme 114.



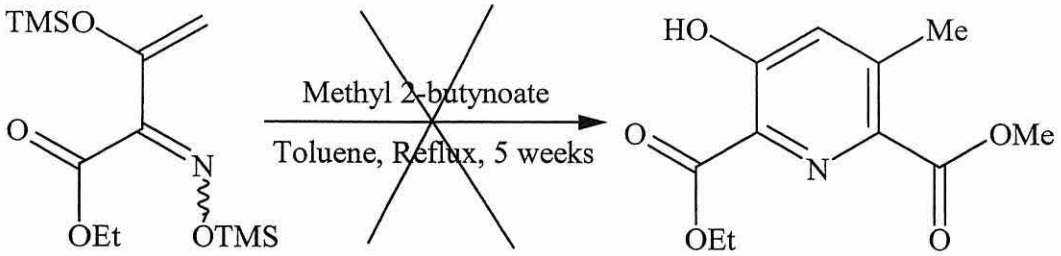
228 **240**

Scheme 115.

The ^{1}H and ^{13}C NMR spectra of the crude product for this reaction were extremely messy. The reaction was repeated under the same conditions but heated in a sealed tube (temperature of oil bath up to 200 °C) instead of heating under reflux (methyl propiolate b.p. 103-105 °C therefore may have boiled off). This however gave the same unidentifiable ^{1}H and ^{13}C NMR spectra; there are numerous aromatic signals present. The unexplainable data does not correspond to any of the previous reactions where the starting material only reverted back to its precursor, **187**, *cf.* section 6.29. The data also showed that the desired product **240** was not present when compared to the data for the similar substituted pyridine **234** described in section 6.33. A reaction does seem to have taken place as the aza-diene **228** has been consumed. One possibility is that the aza-diene **228** (or decomposition product thereof) has acted as a nucleophile instead of an aza-diene and reacted with methyl propiolate to form some unknown product; a second possibility is that an aza-Diels-Alder reaction took place and methyl propiolate further reacted with the aza-Diels-Alder product and either formed another unknown compound or decomposed. The substituted pyridine **240** may have formed its intermediate and then decomposed before it had chance to eliminate or the methyl propiolate may have reacted with itself to form an unknown compound. All of these options are possible and it remains unknown as to which of these, if any, happened. Purification by column chromatography was attempted. A trace amount of **187** was collected (0.04 g, 2%) and no other identifiable compounds were found.

6.36 Attempted Synthesis of a Highly Substituted Pyridine, 241

Methyl 2-butynoate is very similar to methyl propiolate; it has a slightly lower boiling point (76-77 °C) than methyl propiolate (b.p. 103-105 °C). Methyl 2-butynoate was heated under reflux with **228** in toluene (Scheme 113) with monitoring by ^{1}H NMR analysis, in the hope that the methyl 2-butynoate product, *e.g.* **241**, was more stable than that of methyl propiolate **240**, once the substituted pyridine had formed.



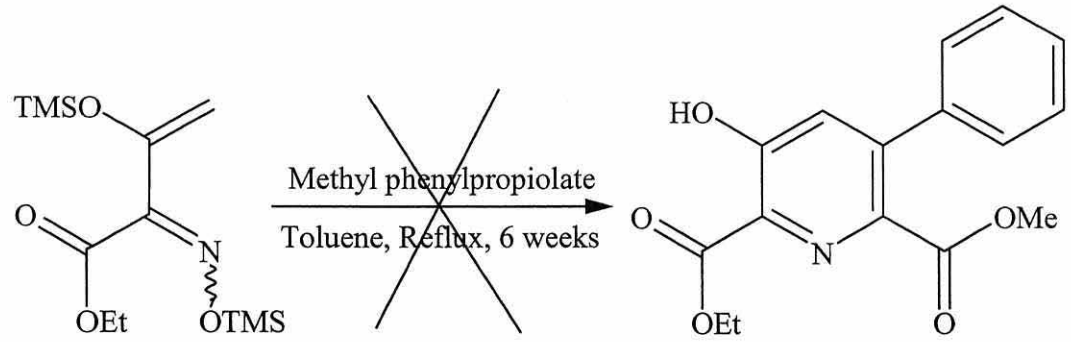
228 **241**

Scheme 116.

This, unfortunately, was not the case, a ^{1}H NMR spectrum of the crude product indicated that the starting material had been consumed after 5 weeks of heating under reflux and was purified by column chromatography with ethyl acetate as the eluent. The ^{1}H NMR spectrum of the purified product showed the ethyl ester ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) to be present at δ_H 1.31 and 4.33 ppm as a triplet and a quartet with integrals of 3 H and 2 H, respectively. The methyl ketone ($\underline{CH_3}C{=}O$) was represented by a singlet at δ_H 2.36 ppm with an integral of 3 H. The ^{13}C NMR spectrum supported the ^{1}H NMR and showed the only compound to be present was precursor **187** recovered in 41% yield. This reaction was repeated in a sealed tube which unfortunately, gave the same outcome of the starting material **228** being reverted back to precursor **187.** The next step was to try something that was even bulkier in an attempt to make the pyridine more stable once formed.

6.37 Attempted Synthesis of a Highly Substituted Pyridine, 242

A similar but bulkier dienophile was methyl phenylpropiolate. This dienophile differs in its electronics from the previous two, due to a phenyl group being present. Methyl phenylpropiolate was heated to reflux with **228** in toluene for 6 weeks (Scheme 117) with monitoring for the consumption of starting material by ^{1}H NMR analysis.



228 **242**

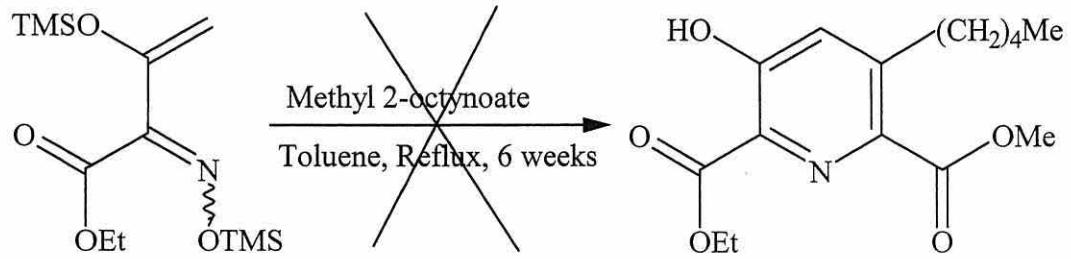
Scheme 117.

As in section 6.36, the crude product indicated that the starting material **228** had been consumed and the diagnostic characteristics of pyridine (discussed earlier) were not present. There were no signals representing the dienophile, unreacted methyl phenylpropiolate (b.p. 109-110°C) which presumably was lost during the removal of toluene as they have similar boiling points. The crude product was purified by column chromatography with ethyl acetate as the eluent. The ^{1}H and ^{13}C NMR spectra suggested that the reaction was unsuccessful and that the starting material **228** had reverted back to its precursor **187**, which was recovered as a colourless oil in 89% yield.

6.38 Attempted Synthesis of a Highly Substituted Pyridine, 243

Methyl 2-octynoate is similar to methyl 2-butynoate but has a much higher boiling point (217-220 °C and 76-77 °C, respectively) eliminating the problem of the dienophile being boiled off. Methyl 2-octynoate was heated to reflux in toluene with

our aza-diene, **228** for 6 weeks (Scheme 118), until ^{1}H NMR analysis showed the consumption of the starting material **228**.



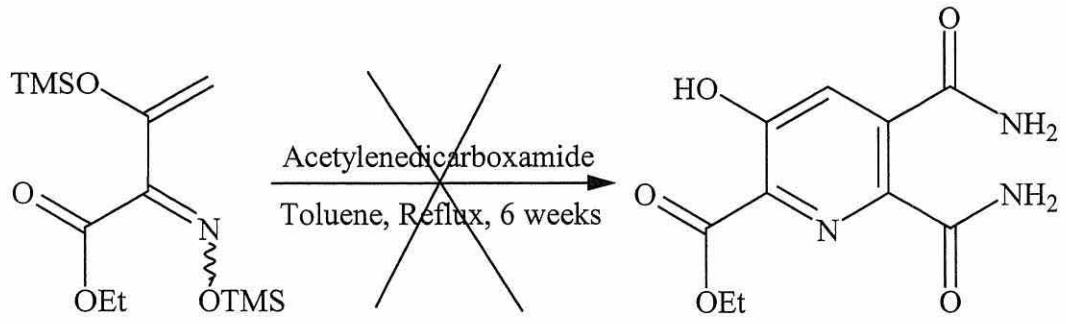
228 **243**

Scheme 118.

After being heated to reflux for 6 weeks the reaction mixture turned to a thick brown oil. The crude mixture was run through a silica column with ethyl acetate as the eluent and a colourless oil was collected. A ^{1}H NMR spectrum of the colourless oil indicated that the reaction was unsuccessful and the only compound to be present was the precursor **187** of the starting material **228**; the ^{13}C NMR spectrum supported the ^{1}H NMR data confirming that the starting material **228** had indeed reverted back to its precursor **187**, however there were also signals present corresponding to methyl 2-octynoate which could not be seen in the ^{1}H NMR spectrum. The dienophile and the precursor **187** could not be separated by distillation (oil bath temperature up to 180 °C, 25 mmHg).

6.39 Attempted Synthesis of a Highly Substituted Pyridine, 244

Acetylenedicarboxamide is very similar to dimethyl acetylenedicarboxylate (DMAD). The NH_2 groups may make the triple bond slightly less electron deficient than the methoxy groups present in DMAD, but the aza-Diels-Alder reaction should still be able to take place. Thus acetylenedicarboxamide was subjected to the same reaction conditions as DMAD (Scheme 111) *cf.* section 6.33.



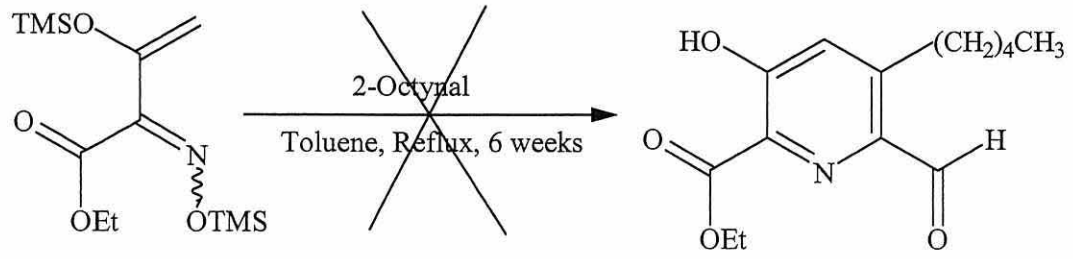
228 **244**

Scheme 119.

After 3 weeks of heating the reaction mixture under reflux, a small quantity was removed and analysed by ^{1}H NMR spectroscopy. The data indicated that the starting material **228** was still present so the reaction mixture was heated under reflux for a further 3 weeks and monitored by ^{1}H NMR spectroscopy. After a total of 6 weeks the starting material **228** had been consumed as determined by the disappearance of the diagnostic C=$\underline{CH_2}$ group signal at ~ δ_H 4.70 ppm. The crude product (an orange oil) was purified by column chromatography with ethyl acetate as the eluent. A ^{1}H NMR spectrum of the colourless oil collected showed the starting material **228** had reverted back to precursor **187**; the ^{13}C NMR spectrum supported the ^{1}H NMR data and also showed the dienophile acetylenedicarboxamide (high m.p. 179-240°C) to still be present, confirming that the desired reaction had not taken place. The amido groups of acetylenedicarboxamide are nucleophilic and may therefore cause a problem of trimethylsilyl group transfer accelerating the decomposition of **228**.

6.40 Attempted Synthesis of a Highly Substituted Pyridine, 245

2-Octynal was tried as a dienophile as it had electron-withdrawing groups and was cheap and readily available from Aldrich; 2-octynal was heated under reflux with **228** in the presence of toluene (Scheme 120), until the ^{1}H NMR showed that all the starting material **228** had been consumed.



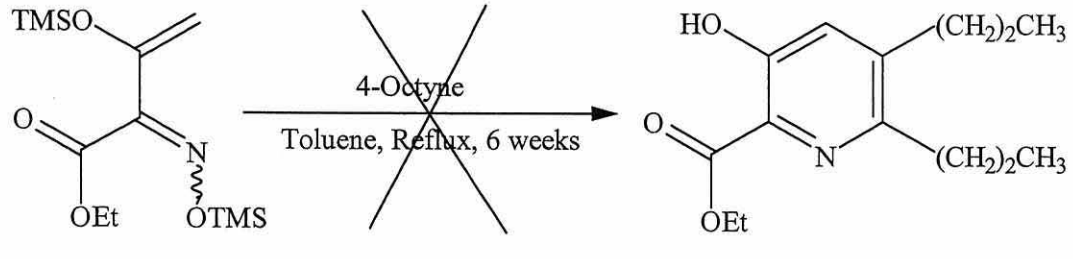
228 **245**

Scheme 120.

In common with the previous reactions, the ^{1}H NMR spectrum of the purified oil (crude product, a red oil, run through a silica column with ethyl acetate as the eluent) showed the reaction to be unsuccessful and the starting material, **228** to have reverted back to its precursor, **187** (recovered in 68% yield). The ^{13}C NMR spectrum confirmed that the precursor **187** was present. There were no signals representing the dienophile in the ^{1}H and ^{13}C NMR spectra. This was probably due to it having a relatively low boiling point (b.p. 74-76°C) and therefore decomposing during the reaction.

6.41 Attempted Synthesis of a Highly Substituted Pyridine, 246

The next dienophile that was tried was 4-octyne; this was also obtained from Aldrich and is symmetrical so there are no regiochemical issues. 4-Octyne was heated under reflux for 6 weeks in toluene with the 1-aza-diene, **228** (Scheme 121) until ^{1}H NMR analysis indicated that all the starting material **228** had been consumed.



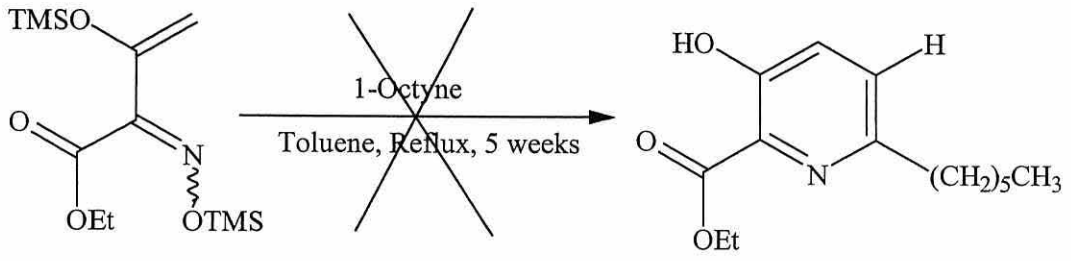
228 **246**

Scheme 121.

As in the above reactions, the crude product (a brown oil) was purified by column chromatography with ethyl acetate as the eluent. The IR, ^{1}H and ^{13}C NMR data of the purified colourless oil confirmed that the reaction was unsuccessful and that the starting material, **228** had reverted back to its precursor, **187** with 95% of precursor recovered. There was no indication of the dienophile being present in any of the fractions collected from the column; 4-octyne has a relatively high boiling point (b.p. 131-132°C) therefore it is unlikely to have been lost during the reaction (oil bath temperature up to 137°C). The dienophile was probably removed along with the solvent when the reaction mixture was concentrated by rotary evaporation under reduced pressure.

6.42 Attempted Synthesis of a Highly Substituted Pyridine, 247

The next alkyne to try was 1-octyne readily available from Aldrich; 1-octyne was reacted with **228** in the usual method of heating under reflux in toluene for 5 weeks monitored by ^{1}H NMR analysis for the disappearance of the starting material **228** (Scheme 122).



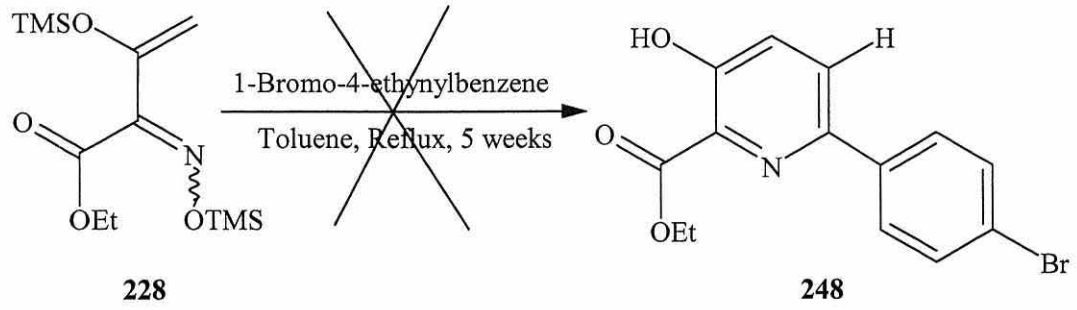
228 **247**

Scheme 122.

The IR, ^{1}H and ^{13}C NMR spectra of the crude product all confirmed that the reaction was unsuccessful and that the starting material **228** had started to revert back to its precursor **187**. There was <1/3rd starting material **228** and >2/3rd's precursor **187** present as determined by ^{1}H NMR spectroscopy. The 1-octyne signals were not present in the ^{1}H and ^{13}C NMR spectra. The boiling point of 1-octyne (b.p. 123-126 °C) is relatively close to toluene (b.p. 110-111 °C) and therefore was probably lost with the removal of the solvent.

6.43 Attempted Synthesis of a Highly Substituted Pyridine, 248

The alkyne 1-bromo-4-ethynylbenzene is readily available from Aldrich and the triple bond is slightly electron deficient, so was heated under reflux with the aza-diene, **228** in toluene for 5 weeks (Scheme 99) during which time the progress of the reaction was monitored by ^{1}H NMR analysis.



228 **248**

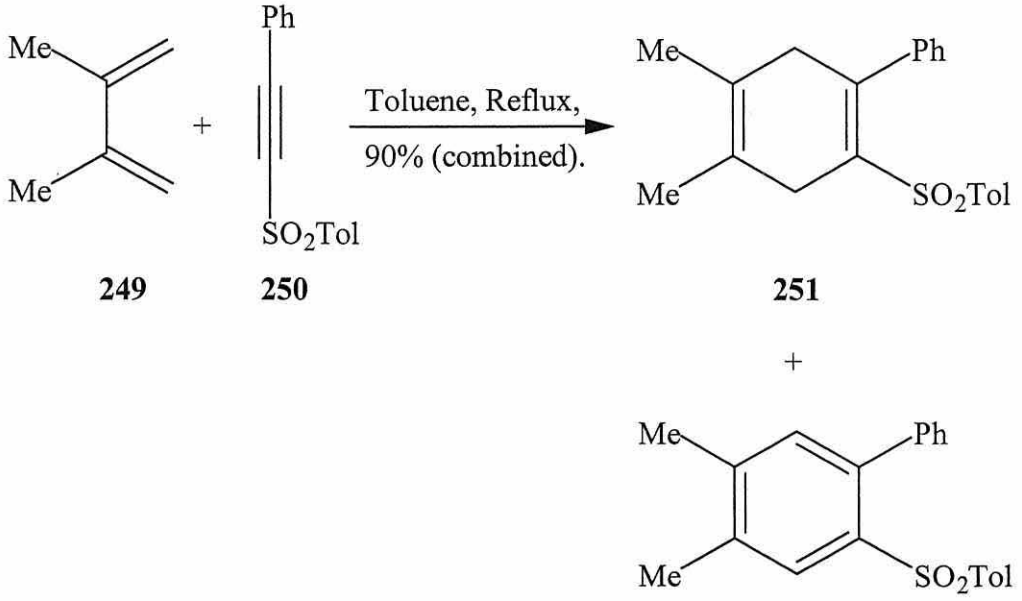
Scheme 123.

After 5 weeks of heating under reflux the ^{1}H NMR spectrum of the crude reaction mixture showed the starting material **228** had started to revert back to its precursor **187**, <1/3rd of **228** and >2/3rd's of **187** as determined by ^{1}H NMR spectroscopy. The data of the crude reaction mixture also showed the dienophile to still be present. The reaction was stopped and the solvent removed. A ^{1}H NMR spectrum of the concentrated mixture showed **187** and **228** to still be present but the 1-bromo-4-ethynylbenzene signals were no longer present. The dienophile (m.p. 64-67 °C) had probably decomposed during the reaction. The crude mixture was purified by column chromatography with ethyl acetate as the eluent. **187** was the only compound recovered in 93% yield. **228** was not expected to be recovered as the TMS groups are removed by the silica causing the decomposition of **228**.

6.44 Attempted Synthesis of a Highly Substituted Pyridine, 257

A type of dienophile which has been successful in numerous aza-Diels-Alder reactions are acetylenic sulfones.[185-187] In 1988, De lucchi and co-workers[187] investigated the behaviour of phenyl(tolylsulfonyl)acetylene in cycloaddition reactions. The group reacted phenyl(tolylsulfonyl)acetylene **250** with the acyclic

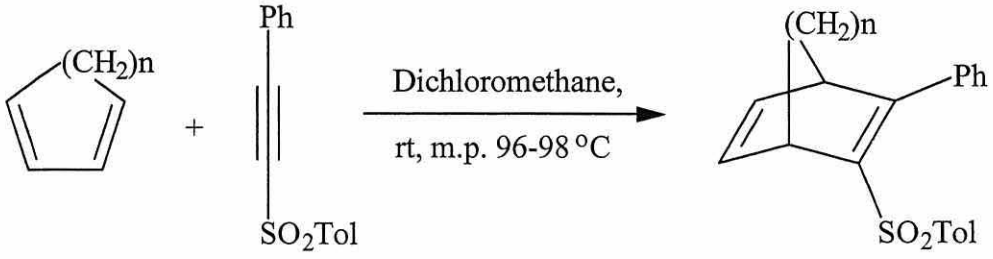
diene, 2,3-dimethyl-1,3-butadiene **249** in refluxing toluene to afford the cycloadduct **251** and **252** in 90% combined yield (Scheme 124). Biphenyl **252** was accounted for by air oxidation of the primary cycloadduct **251** under the reaction conditions.



249 **250** **251** + **252**

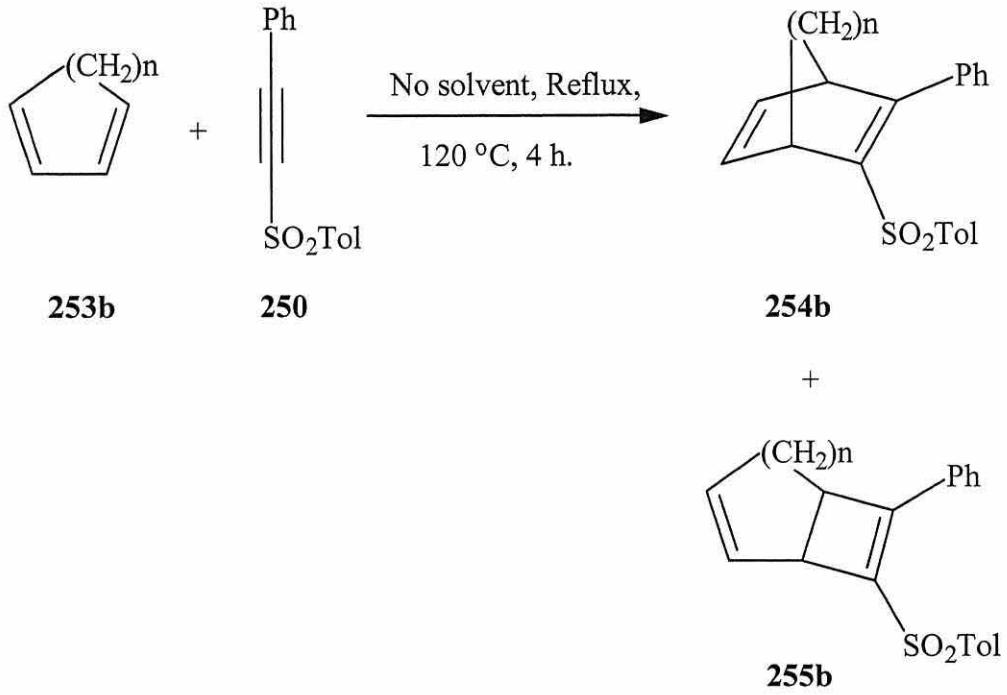
Scheme 124.

De lucchi and co-workers[187] also reacted phenyl(tolylsulfonyl)acetylene **250** with cyclopentadiene **253a** to give the expected Diels-Alder adduct **254a** (Scheme 125) and 1,3-cyclohexadiene **253b** to give the (4 + 2) cycloadduct **254b** and the (2 + 2) cycloadduct **255a** (Scheme 126).



253a **250** **254a**

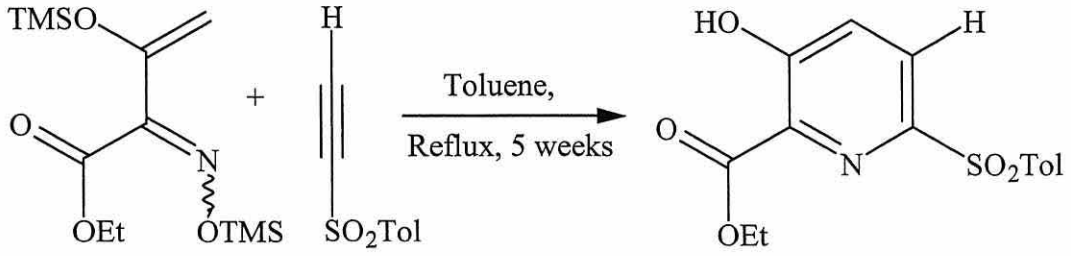
Scheme 125. n = 1.



253b **250** **254b** **255b**

Scheme 126. n = 2;
254b, 35%, (4 + 2) cycloadduct;
255b, 20%, (2 + 2) cycloadduct.

Phenyl(tolylsulfonyl)acetylene **250** is not readily available; ethynyl *p*-tolyl sulfone **256** is similar to **250** and readily available from Aldrich so was heated under reflux with **228** in toluene for 5 weeks and the progress of the reaction monitored by ^{1}H NMR analysis (Scheme 127).



228 **256** **257**

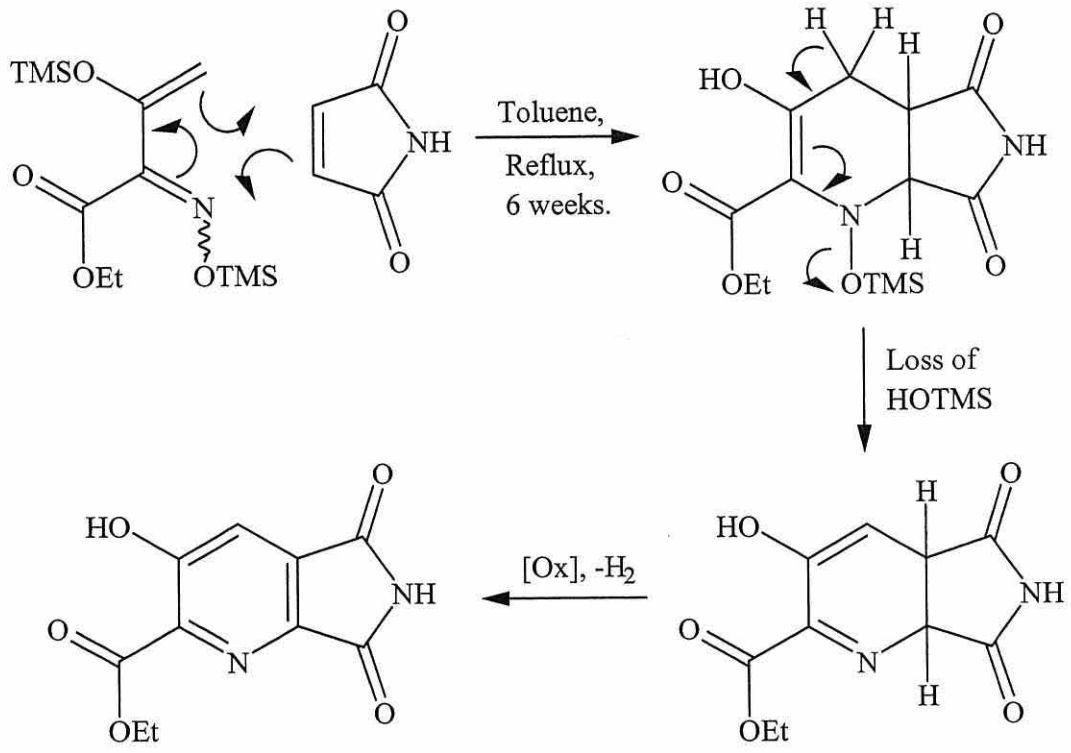
Scheme 127.

After 1 week of being heated under reflux the reaction mixture turned from a light brown colour to a dark brown/black colour. A ^{1}H NMR analysis showed no reaction to have taken place and the starting material **228** and the dienophile **256** were

present and unchanged. The reaction was heated under reflux for a further 4 weeks after which a ^{1}H NMR spectrum of the crude reaction mixture showed the starting material **228** to be decomposing. The IR, ^{1}H and ^{13}C NMR spectra of the concentrated crude product all confirmed that the reaction was unsuccessful and that the starting material **228** had started to revert back to its precursor, **187** (2 : 1 ratio of **187** : **228**). The dienophile **256** was no longer present and probably decomposed during the reaction (m.p. 73-74 °C). **187** was recovered in 42% yield by column chromatography with ethyl acetate as the eluent. A more common sulfone dienophile is phenyl vinyl sulfone *cf.* section 6.51.

6.45 Attempted Synthesis of a Highly Substituted Pyridine, 258

The next dienophile used was maleimide. This is also electron deficient, cheap and readily available from Aldrich; for this alkene to form a pyridine the loss of a further hydrogen molecule (H_2) *i.e.* oxidation is required. There were very few examples of maleimide being used as a dienophile in aza-Diels-Alder reactions in the literature. It was however used as a dienophile in a stereoselective Diels-Alder reaction with a exocyclic diene for the synthesis of cyclohexannulated [5.3.1]propellane as a precursor of an ABC ring analogue of palitaxel (Taxol^{TM})[188]. The aza-diene, **228** and maleimide were heated under reflux in toluene and the progress of the reaction monitored by ^{1}H NMR analysis; the reaction was stopped after 6 weeks (Scheme 128).



Scheme 128.

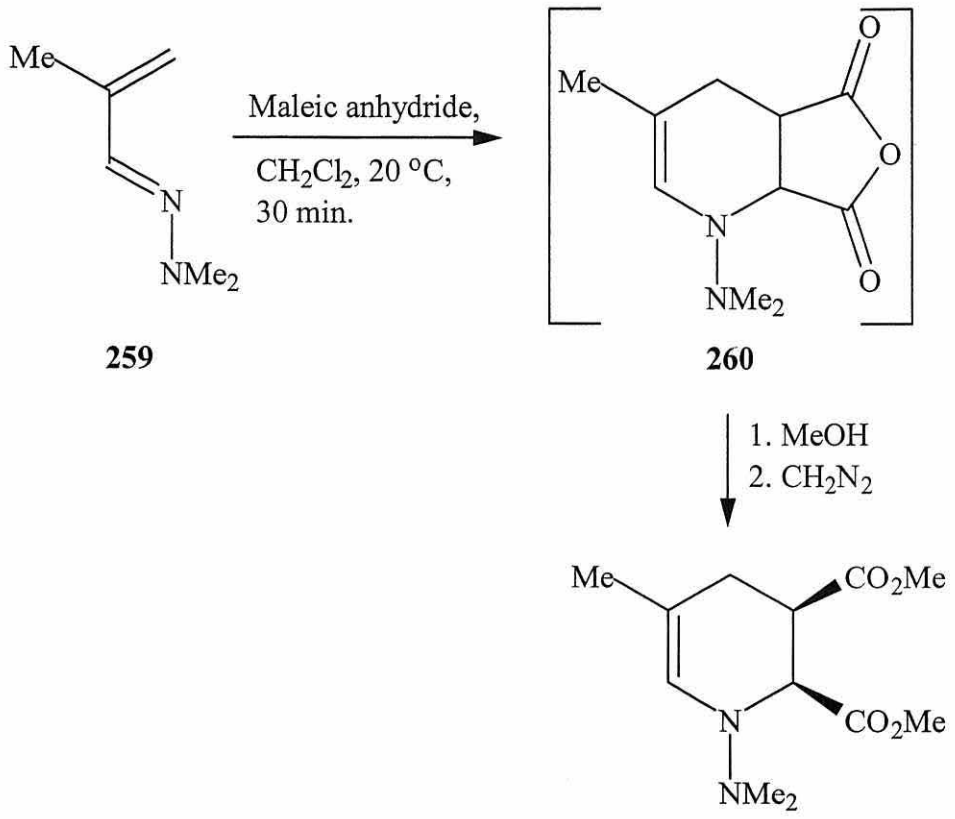
The reaction mixture was a brown colour before heating under reflux began. After 2 weeks the colour changed to orange. The ^{1}H NMR spectrum of the orange reaction mixture showed the starting material **228** to still be present along with unreacted maleimide represented by a singlet at δ_H 6.72 ppm with an integral of 2 H (HC=CH) and a broad singlet at δ_H 8.22 ppm with an integral of 1 H (NH). Further heating under reflux of the reaction mixture was done with the progress of the reaction monitored by ^{1}H NMR spectroscopy. After 5 weeks the reaction mixture had turned a dark brown. The ^{1}H NMR spectrum of the crude product showed no sign of the dienophile, which had probably decomposed during the reaction (m.p. 92-94°C) and showed the precursor **187** to be present. The brown oil was purified by column chromatography with ethyl acetate as the eluent to give a colourless oil.

The IR spectrum of the pure colourless oil showed that an OH group was represented by a peak at ν_{max} 3333.1 cm^{-1}; the ester was represented by a peak at ν_{max} 1724.8 cm^{-1} and a carbonyl at ν_{max} 1701.2 cm^{-1}. The ^{1}H NMR spectrum of the pure oil showed a triplet present at δ_H 1.32 ppm with an integral of 3 H, corresponding to a methyl group ($OCH_2\underline{CH_3}$). A singlet at δ_H 2.38 ppm had an integral of 3 H and

represented a methyl group next to a carbonyl ($\underline{CH_3}$-C=O); the CH_2 group of the ester was represented by a quartet with an integral of 2 H at δ_H 4.35 ppm. The ^{1}H NMR data indicated that the colourless oil was in fact the precursor **187**. The ^{13}C NMR spectrum supported the ^{1}H NMR and showed ethyl oximino acetoacetate **187** to be present; the CH_3 and CH_2 group of the ester was represented by signals at δ_C 13.9 and 62.4 ppm, respectively. The methyl group next to the carbonyl was present at δ_C 25.2 ppm. The oxime ($\underline{C}$=N-OH), ester ($\underline{C}O_2Et$) and carbonyl ($CH_3\underline{C}$=O) were present at δ_C 151.0, 162.1 and 194.4 ppm, respectively. The precursor was recovered in 93% yield.

6.46 Attempted Synthesis of a Highly Substituted Pyridine, 264

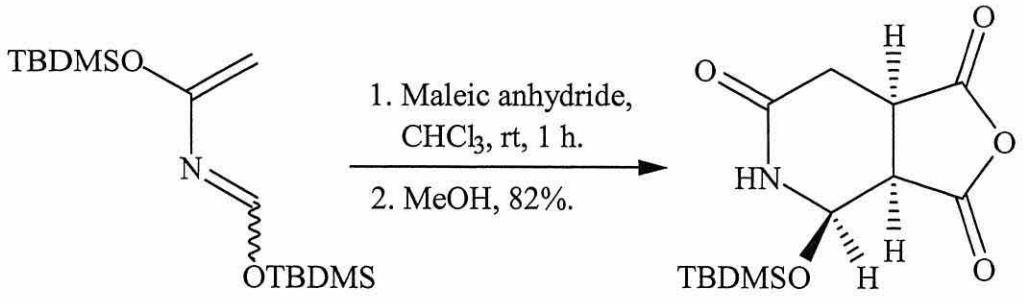
Maleic anhydride has been used successfully as a dienophile for numerous aza-Diels-Alder reactions[12, 86, 189]. In 1982, Ghosez and co-workers[12] investigated the synthesis of **261** by reacting the *N*-dimethylhydrazone **259** with maleic anhydride followed by methanolysis of the adduct **260** and esterification with diazomethane (Scheme 129).



259 **260** **261**

Scheme 129. 261, 56% (from**259**)

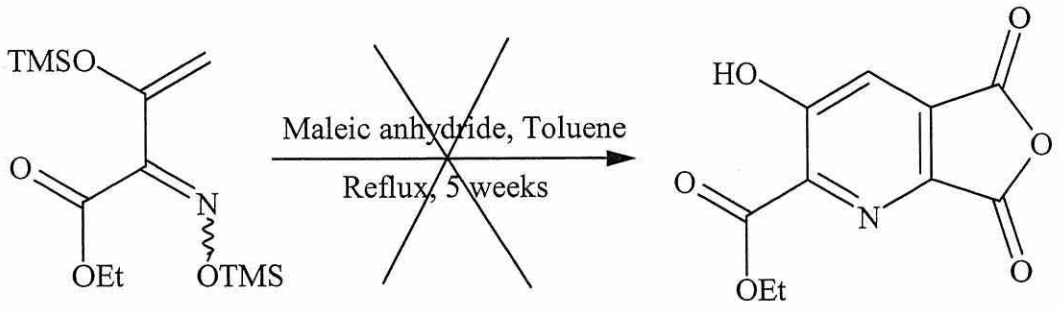
In 1982, Ghosez and co-workers[86] investigated the synthesis of pyridone and piperidone derivatives *via* aza-Diels-Alder chemistry (*cf.* section 5.2.1). The group reacted maleic anhydride and the diene **262** to form a 1 : 1 adduct after 1 hour in chloroform, followed by the addition of methanol for monoprotodesilylation (Scheme 130).



262 **263**

Scheme 130.

The reaction of aza-diene, **228** with maleic anhydride was attempted, by heating under reflux in toluene for 5 weeks (Scheme 131).



228 **264**

Scheme 131.

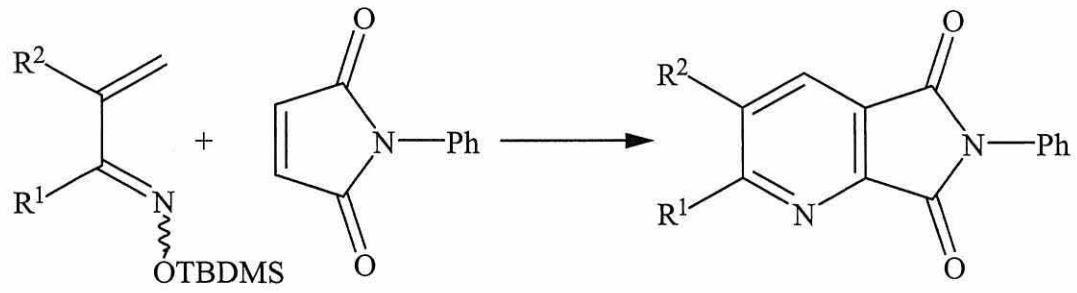
The reaction mixture turned dark brown from light brown within 24 hours. The ^{1}H NMR spectrum however showed both the aza-diene **228** and maleic anhydride to be unreacted. The reaction was heated under reflux for a total of 5 weeks.

The IR spectrum of the crude product showed an OH group peak at ν_{max} 3246.1 cm^{-1}, an ester carbonyl at ν_{max} 1731.6 cm^{-1} and the ketone carbonyl at ν_{max} 1715.2 cm^{-1}. The ^{1}H NMR spectrum showed there to be trimethylsilyl groups still present at δ_H 0.07, 0.17, 0.30 and 0.43 ppm each represented by a singlet with an integral of 10, 3, 5 and 2, respectively. The presence of more than 1 signal representing OTMS indicates that the starting material **228** is decomposing. A multiplet at δ_H 1.34 ppm with an integral of 6 H represented the methyl group of the ester ($OCH_2\underline{CH_3}$, **187**) and an unknown methyl ester group. A peak at δ_H 1.49 ppm with an integral of 2 H indicated the methyl group of the ester ($OCH_2\underline{CH_3}$) of **228** to still be present, but the small integral indicated decomposition; the methyl group next to the carbonyl was represented by a multiplet at δ_H 2.44 ppm with an integral of 3 H. The two CH_2 groups of the ester ($O\underline{CH_2}CH_3$, **187**, **228**) were represented by a multiplet at δ_H 4.37 ppm with an integral of 3 H; the carbon-carbon double bond ($C=\underline{CH_2}$) in the starting material was represented by a multiplet at δ_H 4.54 ppm, but only has an integral of 1 H. Maleic anhydride ($\underline{HC}=\underline{CH}$) was represented by a singlet at δ_H 7.03 ppm with an integral of 1 H indicating this was also decomposing (m.p. 51-56°C). There were two signals at δ_H 8.02 and 8.87 ppm both as 2 doublets each with

an integral of <1 H. These signals are unidentified. The ^{13}C NMR spectrum supported the ^{1}H NMR and confirmed that the reaction was unsuccessful and the desired product **264** was not present and that **187**, **228** and maleic anhydride were present in a ratio of 2 : 1 : 1 respectively. The ^{1}H NMR spectrum also had some unidentified signals present; this could mean that although there was no sign of the desired product **264**, a Diels-Alder reaction may have taken place and the cycloadduct was not stable, or a different and unknown reaction had taken place, or simply that the starting material **228** and maleic anhydride had decomposed. It is unknown which, if any, of the above happened.

6.47 Attempted Synthesis of a Highly Substituted Pyridine[114], 271

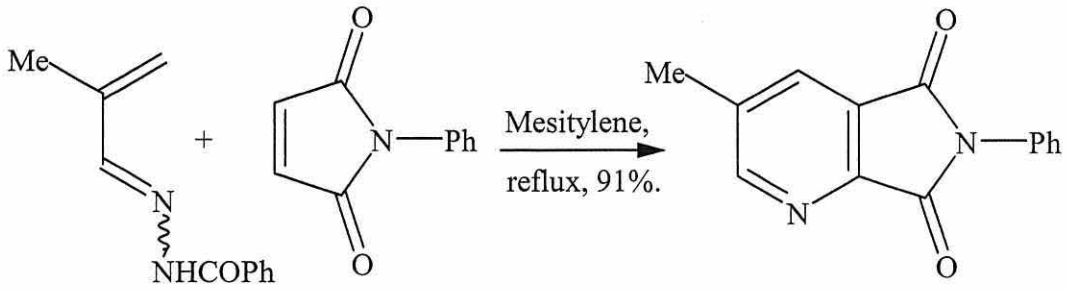
In the above reactions, both maleimide and maleic anhydride were unsuccessful as dienophiles in the synthesis of the highly substituted pyridines **258** and **264**; *N*-phenylmaleimide was employed here as this has been used for aza-Diels-Alder reactions[83, 190, 191] with success. In 1997, Behforouz and co-workers[83] studied the synthesis of substituted pyridines (*cf.* section 5.2.1). The group reacted *N*-phenylmaleimide with the aza-diene **265a** and **265b** to form the pyridine heterocycles **266a** and **266b** (Scheme 132).



265a, b **266a, b**

Scheme 132. **266a**, R^1 = Me, R^2 = H; C_6H_5Cl, reflux, 48 h, 25%;
266b, R^1 = H, R^2 = Me; neat, reflux, 36 h, 52%.

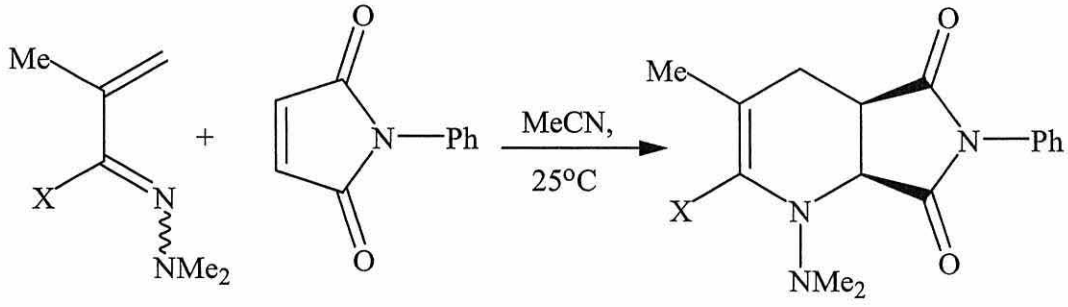
In 1991, Allcock and co-workers[190] investigated the reaction of *N*-phenylmaleimide with aza-diene **267** in mesitylene (b.p. 162 °C) to give the substituted pyridine **268** in 91% yield (Scheme 133).



267 **268**

Scheme 133.

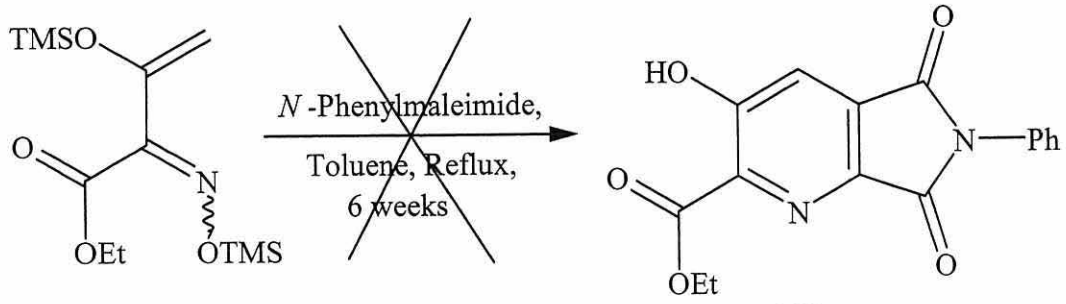
In 1995, Ghosez and co-workers[191] investigated the reactions of α,β-unsaturated hydrazones with electron-poor dienophiles. The group reacted aza-dienes **269a-c** with *N*-phenylmaleimide in acetonitrile at room temperature to give adducts **270a-c** in high yields (Scheme 134) ($LiNTf_2$ = lithium trifluromethanesulfonimide).



269a-c **270a-c**

Scheme 134. **270a**, X = CO_2Me; 3 days, 76%;
270b, X = CN; 14 days, 91%;
270b, X = CN; 2.5 M $LiNTf_2$-acetonitrile, 3 h, 82%;
270c, X = H; 1 day, 95%.

N-Phenylmaleimide is more common dienophile in the literature than maleimide. This suggests that the NH group in maleimide is a problem and the phenyl group (NPh) makes the cycloadduct more stable once formed. *N*-Phenylmaleimide was heated under reflux with aza-diene **228** in toluene for 6 weeks (Scheme 135).



228 **271**

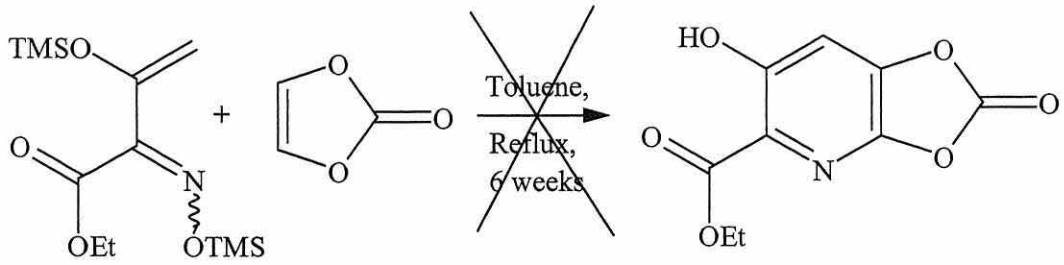
Scheme 135.

The reaction mixture changed colour from brown to orange. After 3 days a small quantity of reaction mixture was removed and the ^{1}H NMR spectrum showed the unreacted *N*-phenylmaleimide represented by a singlet at δ_H 7.85 ppm with an integral of 2 H (HC=CH) and a multiplet at δ_H 7.36 and 7.47 ppm each with an integral of 2 H representing the phenyl group. Unreacted **228** was also still present. The reaction was heated under reflux for a total of 6 weeks and the progress of the reaction monitored by ^{1}H NMR spectroscopy by which time the reaction mixture had turned dark brown and the ^{1}H NMR data showed all the starting material **228** to have been consumed. The concentrated brown oil was purified by column chromatography with ethyl acetate as the eluent. A colourless oil was the only compound collected.

The IR spectrum of the colourless oil indicated that the reaction had not worked. A peak at ν_{max} 3355.5 cm^{-1} indicated the presence of an OH group, an ester carbonyl at ν_{max} 1730.5 cm^{-1}, a ketone carbonyl at ν_{max} 1698.7 cm^{-1} and a C=N resonance at ν_{max} 1622.3 cm^{-1}. The ^{1}H NMR spectrum showed the ester group at δ_H 1.35 and 4.38 ppm as a triplet with an integral of 3 H and a quartet with an integral of 2 H, representing ($OCH_2\underline{CH_3}$, **187**) and ($O\underline{CH_2}CH_3$, **187**), respectively; the methyl group next to the carbonyl ($\underline{CH_3}C=O$) was represented by a singlet at δ_H 2.41 ppm with an integral of 3 H. The ^{13}C NMR spectrum supported the ^{1}H NMR spectrum and confirmed that the reaction was unsuccessful and the starting material **228** had reverted back to its precursor, **187**. There was no sign of the dienophile in the ^{1}H NMR spectrum of the crude brown oil or in the fractions collected from the column. *N*-Phenylmaleimide has a melting point of 85-87 °C and therefore probably decomposed during the harsh conditions of the reaction.

6.48 Attempted Synthesis of a Highly Substituted Pyridine, 272

Vinylene carbonate was readily available from Aldrich and so was heated under reflux in toluene with the aza-diene, **228** and the progress of the reaction monitored by ^{1}H NMR analysis (Scheme 136). The reaction was stopped after 6 weeks of heating under reflux as the ^{1}H NMR spectrum showed only the starting material **228** to be decomposing back to its precursor **187**.



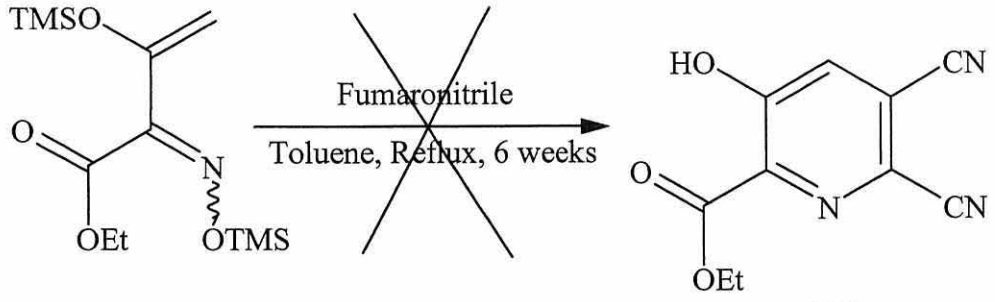
228 **272**

Scheme 136.

The IR, ^{1}H and ^{13}C NMR spectra confirmed that like the previous reactions there was no product present and the starting material **228** was decomposing. The ^{1}H NMR spectrum had a singlet at δ_H 0.03, 0.20 and 0.25 ppm with integrals of 1, 4 and 4 H, respectively, indicating that the trimethylsilyl group was still present but **228** was decomposing. At δ_H 1.30 ppm there were two triplets overlapping each other with a combined integral of 3 H, representing two methyl groups that were in very similar environments ($OCH_2\underline{CH_3}$, **187**, **228**). There were two unidentified singlets present at δ_H 1.98 and 2.36 ppm each with an integral of <1 H. The methyl group next to the ketone ($\underline{CH_3}C{=}O$, **187**) was represented by a singlet with an integral of 2 H at δ_H 2.38 ppm. The CH_2 group of the ethyl ester ($O\underline{CH_2}CH_3$, **187**, **228**) were represented by 2 overlapping quartets at δ_H 4.32 ppm; the $C{=}\underline{CH_2}$ group was present at δ_H 4.68 ppm as two doublets with a combined integral of 1 H. This data indicated that the starting material **228** and precursor **187** were present in a ratio of < 1 : 2. There were no signs of vinylene carbonate in the ^{1}H and ^{13}C NMR spectra; it has a relatively high boiling point (b.p. 162°C) so is not likely (although not impossible) to have been lost during the removal of toluene.

6.49 Attempted Synthesis of a Highly Substituted Pyridine, 273

In 1970, Caglioti and co-workers[192] used tetracyanoethylene successfully as an electron deficient dienophile. Fumaronitrile is very similar to both tetracyanoethylene and the common fumarate ester dienophiles; fumaronitrile was heated under reflux with the aza-diene, **228** for 6 weeks in toluene (Scheme 137) and the progress of the reaction monitored by ^{1}H NMR analysis.



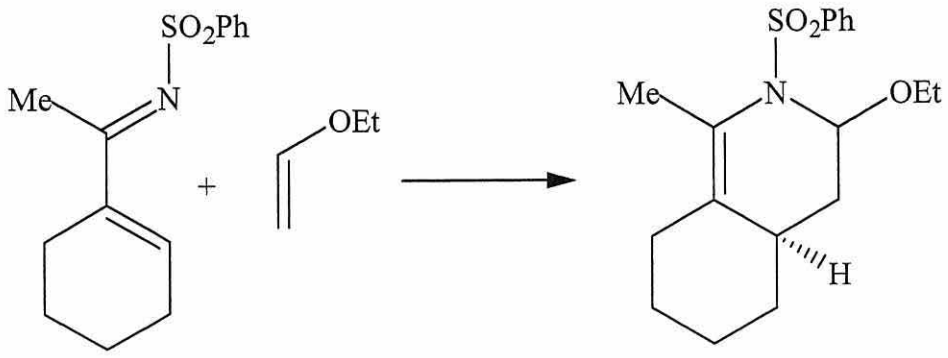
228 **273**

Scheme 137.

No colour change was noted over the 6 weeks, and the ^{1}H NMR spectrum of the crude product showed that the desired reaction had not taken place, and that the starting material **228** had reverted back to its precursor, **187**. The crude brown oil was purified by column chromatography with ethyl acetate as the eluent. There were no signs of fumaronitrile (m.p. 96-99°C) in any of the fractions collected. The only compound collected was pure **187** as a colourless oil, 41% recovered. No other fumarates were tried with aza-diene **228**.

6.50 Attempted Synthesis of a Highly Substituted Pyridine, 277

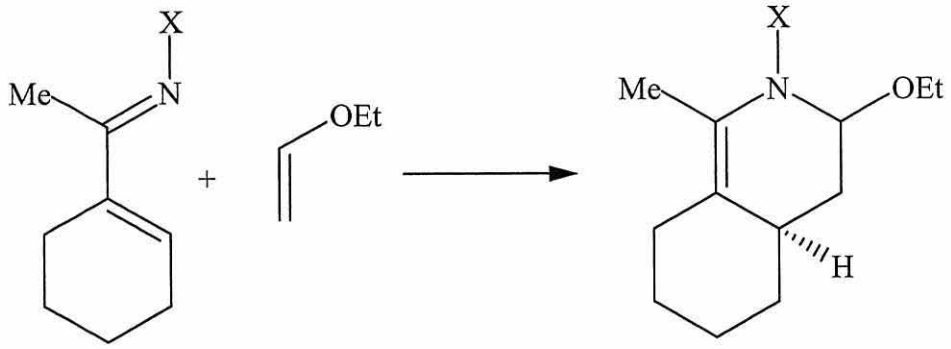
Ethyl vinyl ether has been used successfully as an electron-rich dienophile in inverse electron-demand aza-Diels-Alder reactions[82, 193-197]. In 1989, Boger and Kasper[193] investigated the reactions of α,β-unsaturated *N*-benzenesulfonyl imines with various electron-rich dienophiles. Ethyl vinyl ether **275** was reacted with the 1-aza-1,3-butadiene **274** to cleanly produce the [4 + 2] cycloadduct **276** (Scheme 138).



274a **275** **276a**

Scheme 138. 1. **275**, 5 eq; CH_2Cl_2, 12 kbar, 87 h, 89%;
2. **275**, 5 eq; Toluene, 110°C, 48 h, 79%.

The group demonstrated that *N*-substitution of the 1-aza-1,3-butadiene **274** with an electron-withdrawing substituent facilitates its participation in $LUMO_{diene}$-controlled Diels-Alder reactions: *N*-benzenesulfonyl imine, **274a** = *N*-diphenylphosphinyl imine, **274b** >> oxime, **274c** = *O*-methyl oxime, **274d** (Scheme 139).

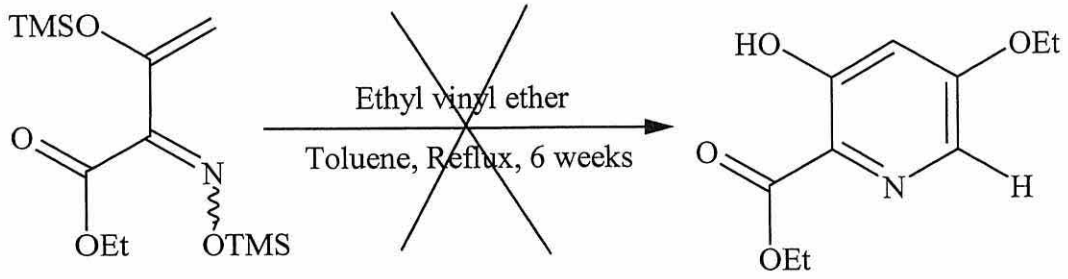


274a-d **275** **276a-d**

Scheme 139. **276a.** X = SO_2Ph, **275**, 5 eq; CH_2Cl_2, 12 kbar, 87 h, 89%;
276a. X = SO_2Ph, **275**, 5 eq; Toluene, 110°C, 48 h, 79%;
276b. X = $P(O)Ph_2$, **275**, 5 eq; CH_2Cl_2, 12 kbar, 135 h, 75%;
276c. X = OH, **275**, 5 eq; CH_2Cl_2, 12 kbar, 72 h, no reaction;
276d. X = OMe, **275**, 5 eq; CH_2Cl_2, 12 kbar, 72 h, no reaction.

It was decided to try heating under reflux ethyl vinyl ether with the aza-diene, **228** in toluene for 6 weeks (Scheme 140). The reaction was stopped when all the

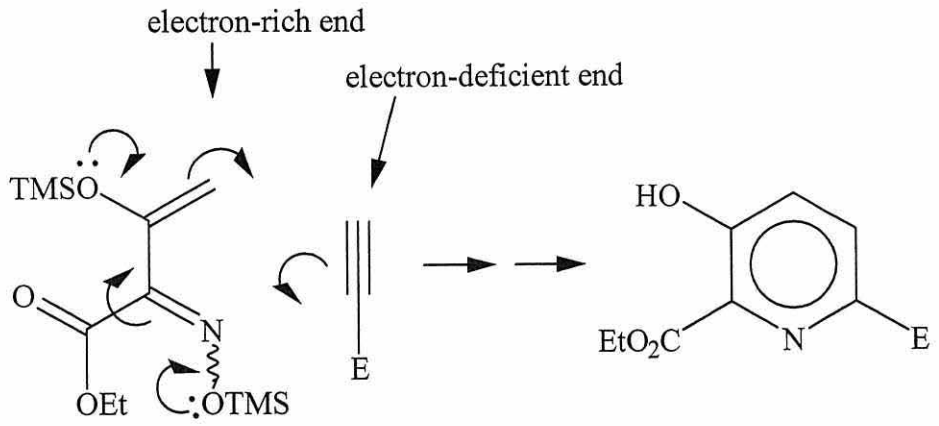
starting material **228** had been used up, as determined by ^{1}H NMR analysis. It was unknown as to whether the ester of the otherwise electron-rich aza-diene **228** was electron-withdrawing enough to allow it to react as an electron-deficient aza-diene with ethyl vinyl ether **275**. This reaction was also a "model" for the potential of the aza-diene **228** reacting with itself; the silyl enol ether of **228** is similar to ethyl vinyl ether and is therefore probably electron-donating enough to act as an electron-rich dienophile (*cf.* section 6.56).



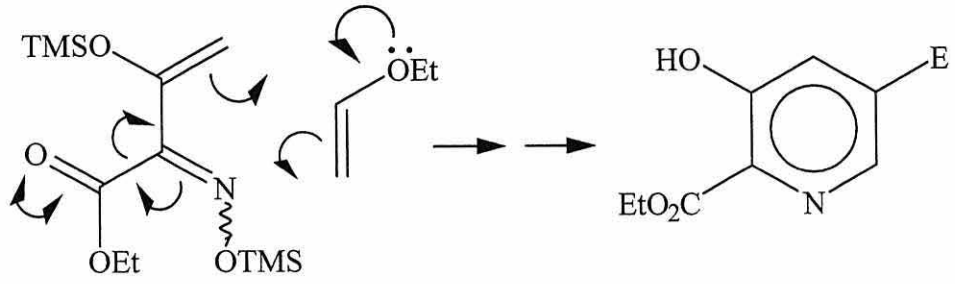
228 **277**

Scheme 140.

There was no colour change during the reaction. After 6 weeks of heating under reflux the IR, ^{1}H and ^{13}C NMR spectrum of the crude product supported each other and confirmed that all the starting material **228** had disappeared and reverted back to precursor **187**. Not surprisingly ethyl vinyl ether signals were not present the dienophile had probably decomposed during the reaction or been removed along with the solvent (b.p. 33-34 °C). There was no indication of any products or that any other reactions had taken place; due to the low boiling point of ethyl vinyl ether the reaction was repeated in a sealed tube. This however produced the same results with the starting material **228** reverting back to precursor **187**. The regiochemistry of **277** shown in Scheme 140 was expected because in a normal-electron-demand aza-Diels-Alder reaction the electron-rich diene (*e.g.* **228**) attacks the electron-deficient dienophile (Scheme 141) promoted by the oxime; but when the dienophile is electron-rich (*e.g.* **275**) this attacks the more electron-deficient nitrogen in the aza-diene (*e.g.* **228**) (Scheme 142).



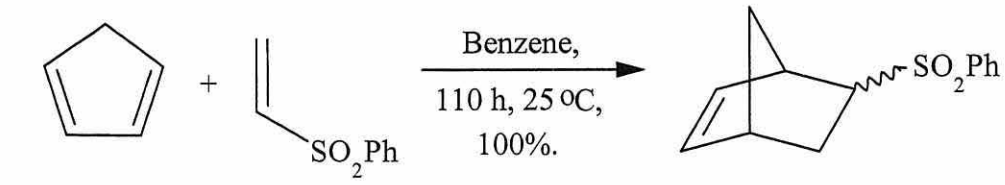
Scheme 141. Normal-electron-demand aza-Diels-Alder reaction.



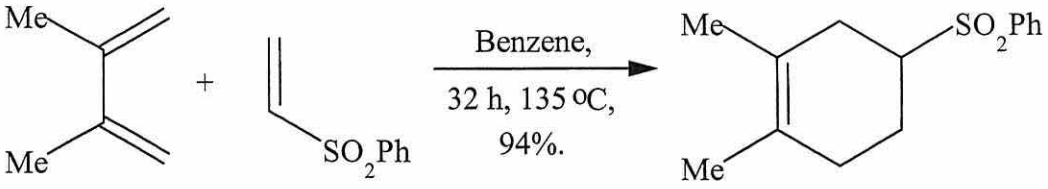
Scheme 142. Inverse-electron-demand aza-Diels-Alder reaction.

6.51 Attempted Synthesis of a Highly Substituted Pyridine, 288

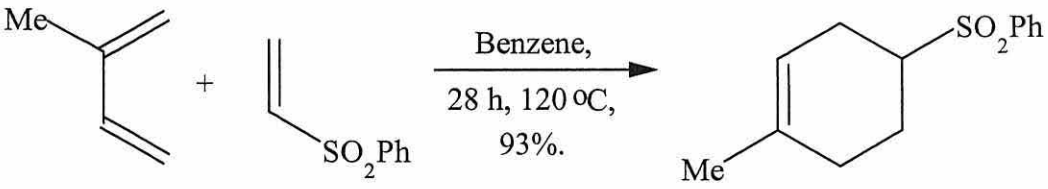
Phenyl vinyl sulfone has been used successfully as a dienophile for many different Diels-Alder reactions [198-210]. In 1980, Paquette and co-workers[210] studied the general synthetic application of phenyl vinyl sulfone for the construction of functionalised six-membered rings. The group successfully reacted phenyl vinyl sulfone with numerous dienes in high yields (Scheme 143). Once isolated and purified the group proceeded to do either reductive desulfonylation or alkylation-desulfonylation on the adducts.



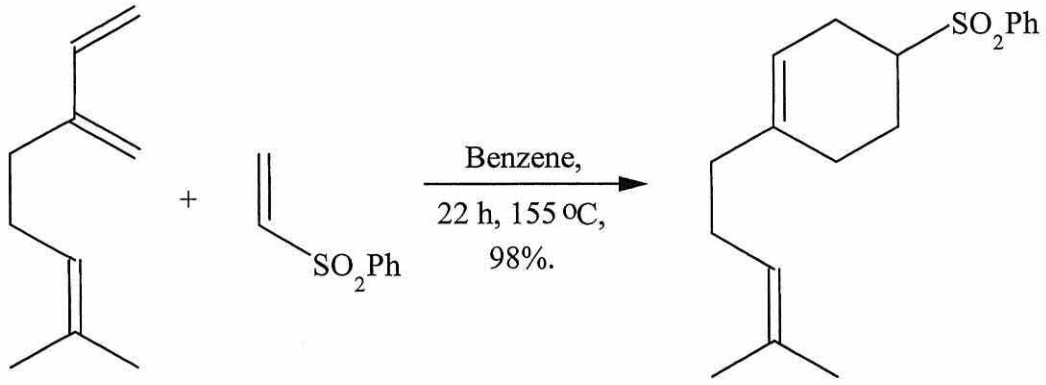
278 **279**



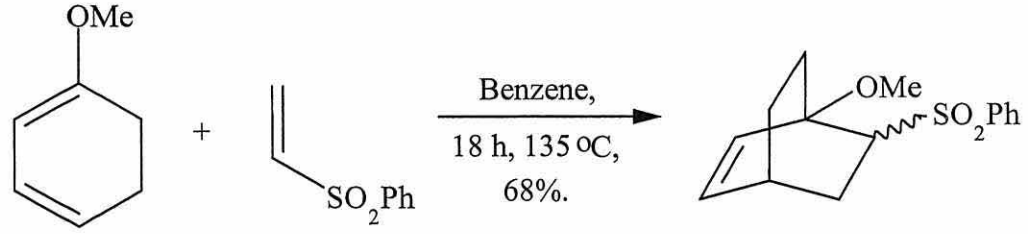
280 **281**



282 **283**



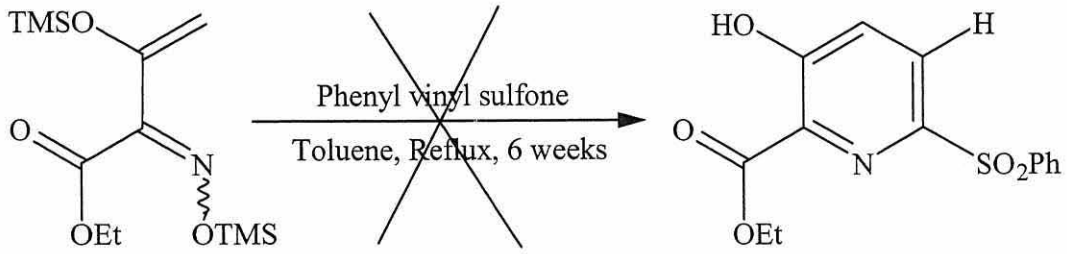
284 **285**



286 **287**

Scheme 143. Cycloaddition of phenyl vinyl sulfone to various dienes.
279, 22% *exo*, 78% *endo*;
287, 18% *exo*, 82% *endo*.

Phenyl vinyl sulfone was therefore heated under reflux with the aza-diene, **228** in toluene (Scheme 144). The reaction was stopped after 6 weeks, when a ^{1}H NMR spectrum indicated that all the starting material **228** had been consumed.



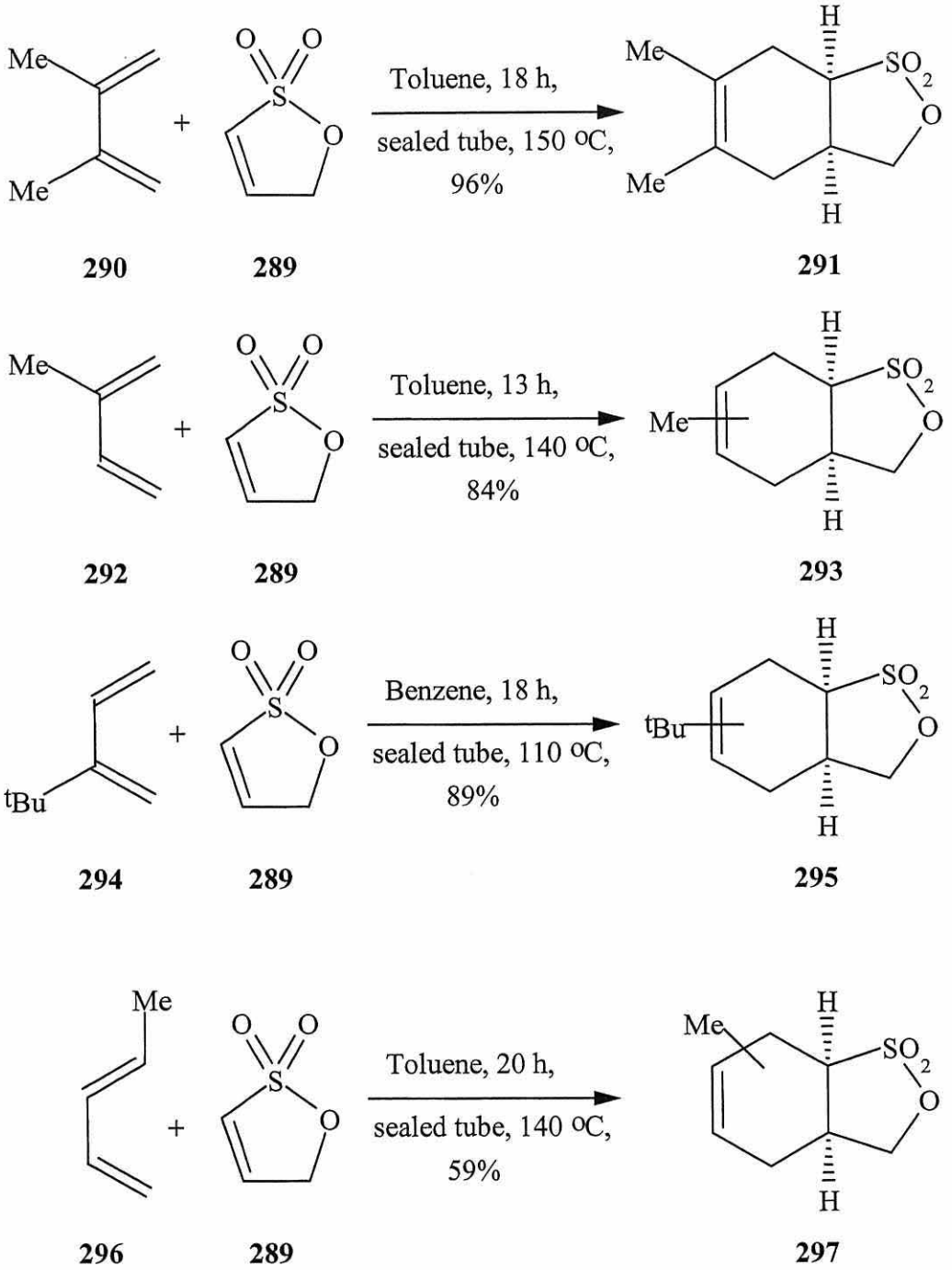
228 **288**

Scheme 144.

The reaction mixture turned a slightly darker brown after 3 weeks but the ^{1}H NMR spectrum showed the starting material **228** to still be present. The reaction was heated under reflux for a further 3 weeks and the reaction monitored by ^{1}H NMR analysis; after a total of 6 weeks the ^{1}H NMR spectrum of the reaction mixture showed **228** to have been consumed. The IR spectrum of the crude product showed an OH peak at ν_{max} 3315.7 cm^{-1}, an ester carbonyl at ν_{max} 1732.3 cm^{-1} and a ketone carbonyl at ν_{max} 1676.6 cm^{-1}. The ^{1}H NMR spectrum showed there to be a triplet at δ_H 1.30 ppm with an integral of 3 H indicating that the ethyl ester ($OCH_2\underline{CH_3}$) was still present; a singlet with an integral of 3 H represented a methyl ketone ($\underline{CH_3}C=O$) at δ_H 2.36 ppm. The CH_2 group of the ethyl ester ($O\underline{CH_2}CH_3$) was represented by a quartet with an integral of 2 H at δ_H 4.33 ppm. The ^{13}C NMR spectrum showed the ethyl ester ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) to be present with signals at δ_C 13.9 and 62.3 ppm and the methyl ketone ($\underline{CH_3}C=O$) signal at δ_C 25.1 ppm. The oxime ($\underline{C}$=N-OH), ester ($\underline{C}O_2Et$) and ketone ($CH_3\underline{C}=O$) were represented by signals at δ_C 151.0, 162.1 and 194.3 ppm. All the above data support each other and confirm that the reaction was unsuccessful and the starting material **228** had reverted back to its precursor **187**. As in the previous reactions there was no sign of the dienophile in the ^{1}H or ^{13}C NMR spectra. Phenyl vinyl sulfone was probably decomposed during the reaction (m.p. 68-69 °C).

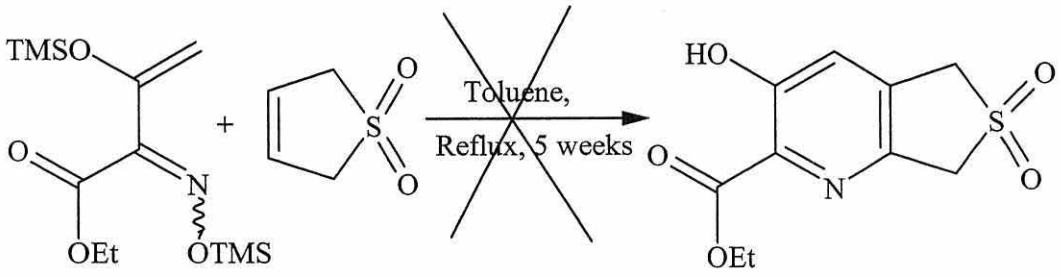
6.52 Attempted Synthesis of a Highly Substituted Pyridine, 298

In 1999, Chan and co-workers[211] synthesised prop-1-ene-1,3-sultone **289** and reported the first Diels-Alder reactions with various dienophiles (Scheme 145).



Scheme 145. 293, 295 and **297** were formed as a mixture of inseparable isomers.

Prop-1-ene-1,3-sulfone **289** was not readily available. Several attempts were tried to synthesise **289** following literature method.[211] These were however, unsuccessful. Butadiene sulfone is similar to **289**, though not electron deficient, and is cheap and readily available from Aldrich and so was the next choice for a dienophile (Scheme 146).



228 **298**

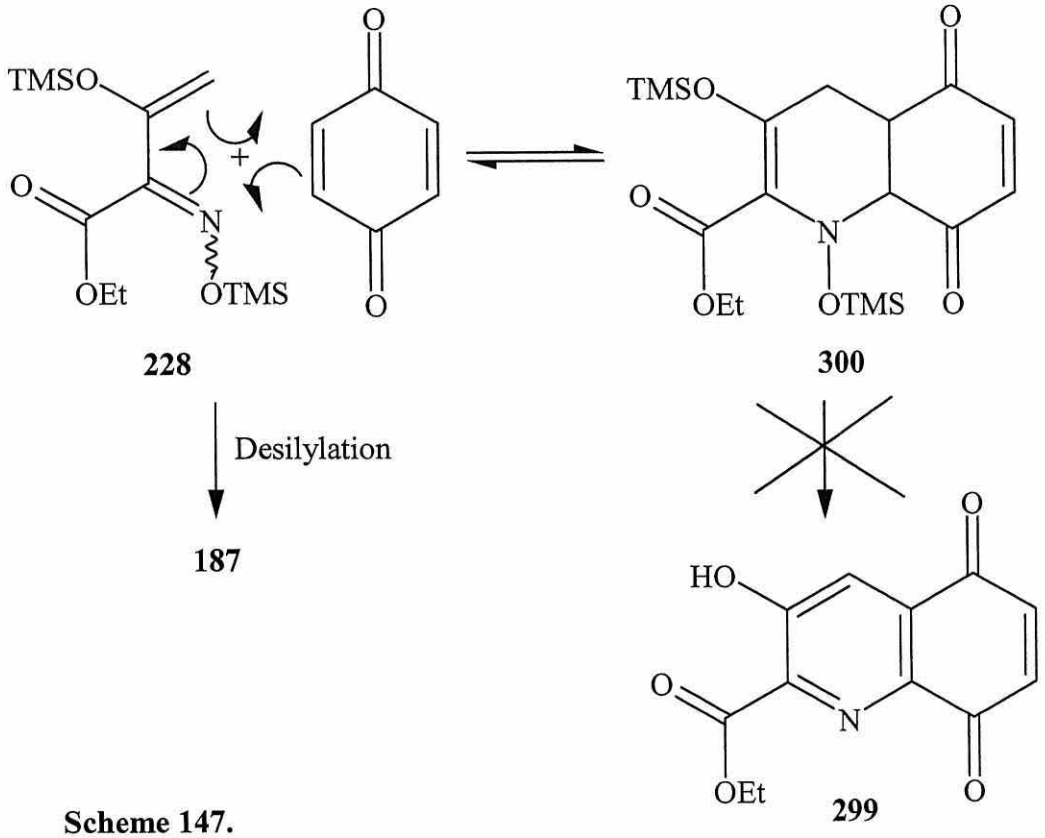
Scheme 146.

The reaction was monitored by ^{1}H NMR analysis. After 5 weeks of heating under reflux the reaction mixture had turned black and the ^{1}H NMR spectrum no longer showed the butadiene sulfone signals at δ_H 3.74 and 6.06 ppm, so the reaction was stopped and the reaction mixture concentrated with the removal of toluene. The IR spectrum of the crude product showed an OH peak at ν_{max} 3316.1 cm^{-1}, an ester carbonyl at ν_{max} 1733.7 cm^{-1}. The ketone carbonyl group (C=O) and oxime (C=N) group were represented by peaks at ν_{max} 1677.8 and 1629.3 cm^{-1} respectively. The ^{1}H NMR spectrum showed small trimethylsilyl signals at δ_H 0.21, 0.26 and 0.28 ppm as singlets with integral of 2, 2 and 6, respectively. The ethyl ester group ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) were represented by two multiplets at δ_H 1.31 and 4.33 ppm with integrals of 4 H and 2 H respectively. Each multiplet represented both precursor **187** and starting material **228** in a ratio of > 2: 1. The methyl group next to the ketone ($\underline{CH_3}C$=O, **187**) was represented by a singlet at δ_H 2.39 ppm with an integral of 2 H; there were also two broad doublets present at δ_H 4.69 ppm which had a combined integral of less than 1 H, indicating that the C=$\underline{CH_2}$ group was still present but in the process of disappearing. The ^{13}C NMR spectrum confirmed that the reaction was unsuccessful and that precursor **187** was present. There was no sign of the dienophile

(m.p. 65-66 °C) in the ^{1}H and ^{13}C NMR spectra of the crude product, indicating that it decomposed whilst being heated under reflux.

6.53 Attempted Synthesis of a Highly Substituted Pyridine, 299

There are few examples of 1,4-benzoquinone being used as a dienophile in aza-Diels-Alder reactions with dienes similar to **228**. 1,4-Benzoquinone is however a good dienophile therefore the reaction of this dienophile with aza-diene **228** was attempted by heating under reflux in toluene (Scheme 147). Scheme 147 shows that the Diels-Alder reaction was reversible although goes forwards more often than backwards; the intermediate **300** was expected to eliminate quickly followed by oxidation to form the pyridine **299**.



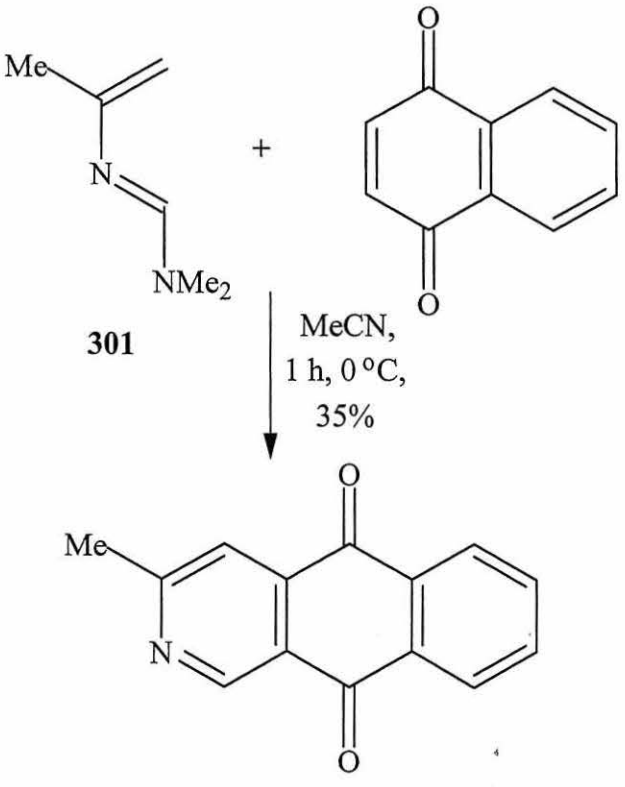
Scheme 147.

The reaction slowly turned black after 3 weeks. Reaction was monitored by ^{1}H NMR spectroscopy for a total of 6 weeks, after which the ^{1}H NMR spectrum showed the starting material **228** to have been consumed. The solvent was removed to give a thick black oil. This was purified by column chromatography with ethyl

acetate as the eluent. The IR, ^{1}H and ^{13}C NMR spectra showed that the reaction was unsuccessful and that the starting material **228** had reverted back to its precursor **187**. There was no indication of any product **229** forming at all. As the Diels-Alder reaction is reversible it is possible that if the intermediate **300** does not eliminate then the equilibrium can be pulled to the left hand side towards **228** which then decomposes – this is unlikely but not impossible. There were no signs of 1,4-benzoquinone in the ^{1}H NMR spectrum of the crude product, indicating the likely decomposition of the dienophile during the reation (m.p. 113-115 °C).

6.54 Attempted Synthesis of a Highly Substituted Pyridine, 303

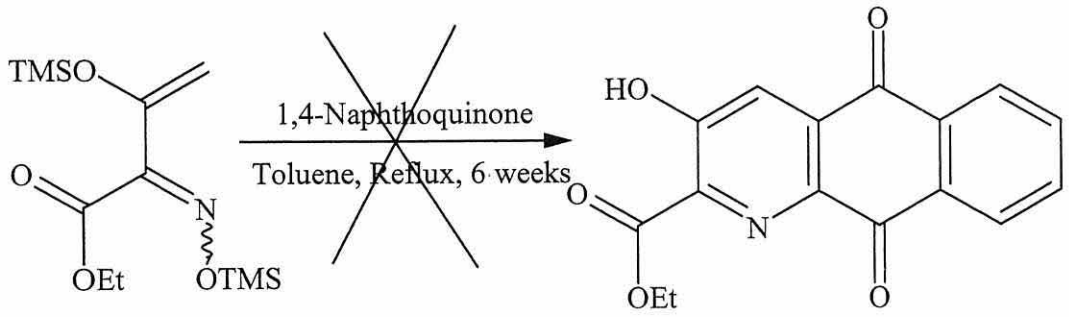
The next logical dienophile to try was 1,4-naphthoquinone as this is bulkier than 1,4-benzoquinone and hopefully more stable once the pyridine has formed. One side is also blocked so the stoichiometry can only be 1 : 1. 1,4-Naphthoquinone has been used as a dienophile in aza-Diels-Alder reactions successfully[183, 212-214]. In 1975, Ghosez and co-workers[183] reacted the 1-amino-2-aza-diene **301** with 1,4-naphthoquinone to give the highly substituted pyridine **302** (Scheme148).



301 **302**

Scheme 148.

1,4-Naphthoquinone was heated under reflux for 6 weeks and the progress of the reaction monitored by ^{1}H NMR analysis (Scheme 149).



228 **303**

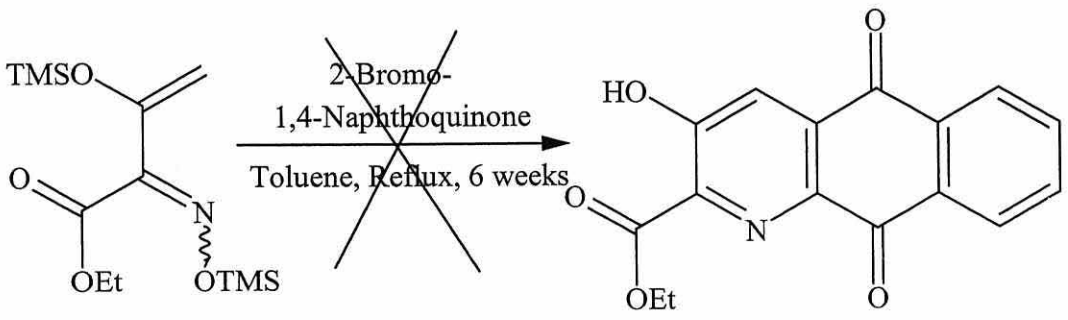
Scheme 149.

After being heated under reflux for 6 weeks the reaction mixture had not undergone any colour change. The ^{1}H NMR spectrum showed the starting material **228** to have been consumed, so the reaction mixture was concentrated by the removal of toluene under reduced pressure to give a brown solid. A TLC (eluent: ethyl acetate) of the brown solid showed only one spot corresponding to precursor **187**. The brown solid was purified by column chromatography to give a colourless oil. The IR spectrum of the colourless oil showed there to be an OH group represented by a peak at ν_{max} 3322.2 cm^{-1}, an ester carbonyl at ν_{max} 1729.8 cm^{-1}. The ketone carbonyl group and oxime (C=N) group were represented by peaks at ν_{max} 1689.7 and 1629.3 cm^{-1} respectively. The ^{1}H NMR spectrum showed there to be no aromatic signals present and no starting material **228** signal to represent the C=$\underline{CH_2}$ group. There was a triplet at δ_H 1.27 ppm with an integral of 3 H representing a CH_3 group ($OCH_2\underline{CH_3}$). A singlet with an integral of 3 H at δ_H 2.34 ppm indicated the CH_3 next to a carbonyl ($\underline{CH_3}C=O$). The CH_2 group of the ethyl ester ($O\underline{CH_2}CH_3$) was represented by a quartet at δ_H 4.30 ppm with an integral of 2 H. The ^{13}C NMR spectrum showed the ethyl ester ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) at δ_C 13.8 and 62.4 ppm, respectively. A signal at δ_C 25.1 ppm indicated the methyl group next to the carbonyl ($\underline{CH_3}C=O$). The oxime ($\underline{C}$=N-OH), ester ($\underline{C}O_2Et$) and carbonyl ($CH_3\underline{C}$=O) were represented by signals at δ_C 150.9, 162.3 and 194.8 ppm, respectively; the above data confirmed that the reaction was unsuccessful and that the starting material **228**

had reverted back to precursor **187**. The dienophile signals were not present in the ^{1}H NMR spectrum, 1,4-naphthoquinone has a relatively high melting point (m.p. 118-122 °C) so was unlikely to have been removed along with toluene, suggesting that it was lost during purification.

6.55 Attempted Synthesis of a Highly Substituted Pyridine, 303

2-Bromo-1,4-naphthoquinone is very similar to 1,4-naphthoquinone with a bromine atom in the 2-position instead of a hydrogen atom. The bromine group helps drive the reaction due to it being a better leaving group than hydrogen. It also solves the oxidation problem faced in the previous two reactions. So the general procedure was followed and the aza-diene **228** was heated under reflux with 2-bromo-1,4-naphthoquinone in toluene for 6 weeks (Scheme 150), with the progress of the reaction monitored by ^{1}H NMR analysis.



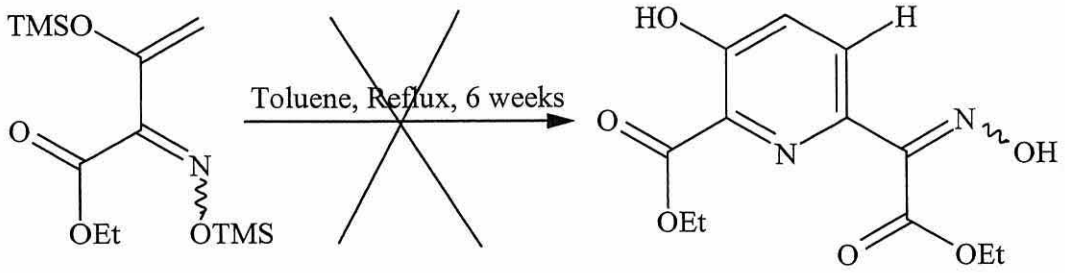
228 **303**

Scheme 150.

As in the above reaction (Scheme 149) there was no colour change during the 6 weeks of heating under reflux. The ^{1}H NMR spectrum of the crude product was very messy. There were a lot of multiplets present in the ethyl ester region and the diagnostic C=$\underline{CH_2}$ signal of the starting material **228** had disappeared. The crude product (a brown solid) was therefore run through a silica column with toluene : methanol (98 : 2) as the eluent, but the only fraction to elute from the column was the precursor **187** (0.61 g, 61%). The column had turned black and nothing else came off, leading to the conclusion that this reaction was unsuccessful.

6.56 Control Study of 1-Aza-Diene 228 Decomposition / Dimerisation

The 1-aza-diene, **228** was heated under reflux on its own in toluene (Scheme 151) for 6 weeks and the progress of the reaction monitored by ^{1}H NMR analysis, to see if the aza-diene **228** would react with itself to form a substituted pyridine *via* an aza-Diels-Alder reaction (*cf.* section 6.50) and to find out if this is a side reaction in any of the above and to see if any other decomposition pathways are obvious.



228 **304**

Scheme 151.

After 5 weeks of heating under reflux the ^{1}H NMR spectrum showed clear signs of the starting material **228** decomposing and reverting back to precursor **187**; the reaction was stopped after 6 weeks because the ^{1}H NMR spectrum showed that over half of the starting material **228** had been consumed. The IR, ^{1}H and ^{13}C NMR spectra all supported the conclusion that the starting material **228** was reverting back to its precursor **187**. There was also the possibility that a Diels-Alder reaction had taken place and that the product **304** had then decomposed, although the ^{1}H NMR spectrum did not indicate that anything else had formed or decomposed.

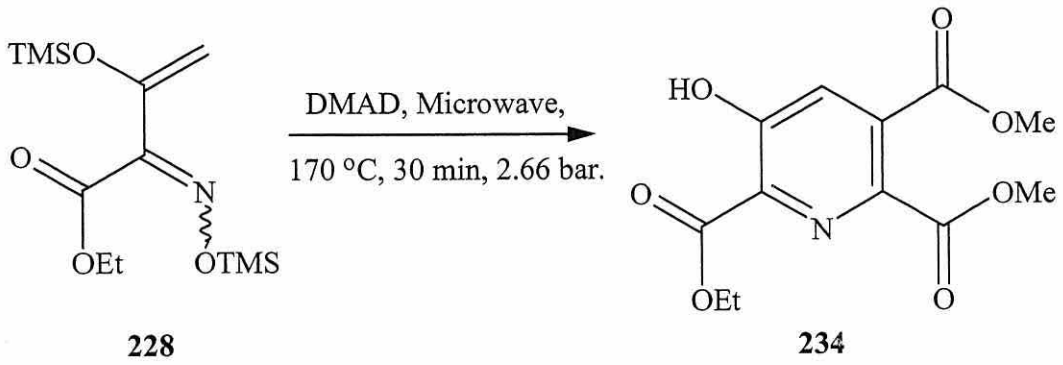
6.57 Synthesis of a Highly Substituted Pyridine, 234 *via* Microwave Synthesis

The above reactions (except DMAD, section 6.33) were all unsuccessful (*cf.* sections 6.34-6.56) probably for a range of different reasons. Unfortunately it took 5-6 weeks for each reaction to determine its outcome; this is a very long reaction time. The aza-Diels-Alder reaction that was successful (DMAD, *cf.* section 6.33) also took 3 weeks for completion; a faster and more efficient reaction procedure is obviously

required which can avoid subjecting the starting materials to the harsh conditions in our general procedure.

There have been many reports on the promotion of various reactions, including cycloadditions, by microwave irradiation.[215-231] Microwave irradiation is commonly used instead of conventional heating and microwave synthesis generally results in faster, cleaner, higher yielding reactions. The next step was therefore to investigate the potential of this approach in the aza-Diels-Alder reaction described herein, which required collaboration with StylaCats to use their microwave equipment.

After microwave irradiation of the 1-aza-diene, **228** with DMAD in toluene at 140 °C for 30 mins (initial power 100 W, 0.9 Bar), the ^{1}H NMR spectrum of the crude product showed the starting material **228** and DMAD to still be present and no product to have formed. Therefore the reaction was repeated using trifluorotoluene as the reaction could be taken to a higher temperature than toluene. The reaction was heated to 180 °C for 30 min (initial power 150 W, 4.5 Bar). This also gave only starting materials and no product. Microwave irradiation without any solvent present was then tried, so **228** and DMAD were irradiated at 200 °C for 30 min (initial power 100 W, 7.3 Bar). This approach worked and gave the substituted pyridine **234**, but the ^{1}H NMR spectrum of the crude product also showed a number of unidentified by-products present, so these conditions were a little too harsh for this pyridine synthesis. The reaction was repeated, heating only to 150 °C for 30 min (initial power 50 W, 1.32 Bar). The ^{1}H NMR spectrum of the crude product showed there to be product **234** and starting materials present, but no sign of any by-products, therefore the optimum conditions were somewhere in the middle. Finally irradiation at 170 °C for 30 min (initial power 70 W, 2.66 Bar) was tried (Scheme 152) and the ^{1}H NMR spectrum of the crude product indicated that all the starting materials had been consumed and that product **234** was present.



228 **234**

Scheme 152. 234, 10%.

The crude product, a thick brown oil, was purified by column chromatography to yield the pure product **234** as a pale yellow oil in 10% yield. The ^{1}H NMR spectrum showed the ethyl ester ($OCH_2\underline{CH_3}$) and ($O\underline{CH_2}CH_3$) to be present as a triplet and a quartet with integrals of 3 H and 2 H at δ_H 1.49 and 4.55 ppm, respectively. The two methyl esters (C=C-$CO_2\underline{Me}$) and (N=C-$CO_2\underline{Me}$) were represented by two singlets each with an integral of 3 H at δ_H 3.95 and 3.96 ppm respectively. The aromatic hydrogen (C=$\underline{CH}$) was represented by a singlet with an integral of 1 H at δ_H 7.67 ppm and the OH group was present as a singlet at δ_H 11.16 ppm with an integral of 1 H. A mass spectrum confirmed the mass of the substituted pyridine, **234** to be 283 (M^+), and the ^{1}H NMR data was almost identical to the substituted pyridine formed *via* conventional methods, *i.e.* heating under reflux.

Microwave synthesis had cut the reaction time down from 3 weeks to 30 mins and without the need for solvent. Unfortunately the yield was compromised. The conditions used may not have been the optimum conditions and with a small amount of optimisation the yield may be increased.

Other approaches to improving these aza-Diels-Alder reactions were investigated. The 1-aza-diene, **234** / DMAD mixture was sent to Reading University to undergo a high pressure reaction done in dichloromethane (due to their requirements) at 19 Kbar, 22 ^{0}C for 24 hour, for comparison with conventional heating under reflux, sealed tube conditions and microwave irradiation; this unfortunately caused the starting materials to decompose and no product was formed.

7.0 Conclusion

Ethyl oximino acetoacetate **187** was formed with relative ease, however on the addition of pyrrolidine instead of an aza-diene being formed, a Beckmann fragmentation occurred; therefore the starting material was made more stable by silylating the oxime with both chlorotrimethylsilane and ^{t}butyldimethylsilyl chloride, but these products **189** and **193** also underwent Beckmann fragmentations. The oxime was then methylated **194** to increase stability but this too underwent a Beckmann fragmentation with the addition of pyrrolidine to form pyrrolidine-1-carboxylic acid ethyl ester **197**.

2,3-Butanedione was converted easily into 2,3-butanedione mono-dimethylhydrazone **203**, to which the addition of pyrrolidine to give an aza-diene was studied, unfortunately the carbonyl group of the mono-hydrazone was extremely unreactive and despite the widely varied methods tried, from gentle stirring to the harsh conditions of titanium tetrachloride, the general outcome was no product being formed and no reaction taking place at all with the recovery of the mono-hydrazone **203**. The mono-hydrazone **203** was reacted with various nucleophiles to see if the carbonyl group was at all reactive, the outcome was the same – starting material recovered. The mono-hydrazone carbonyl did react with hydroxylamine hydrochloride to turn the generally unreactive carbonyl into an oxime functional group. It seemes that 2,3-butanedione mono-hydrazone **203** will only react with excellent nucleophiles and is therefore not ideal for enamine aza-diene formation.

Therefore ethyl oximino acetoacetate **187** was reinvestigated and converted to an aza-diene; Igarashi and co-workers[85] achieved this with similar oximes, for example, ^{t}butyl oximino acetoacetate by exhaustive trimethylsilylation, with success.

The next stage was to try aza-Diels-Alder reactions with these aza-dienes. The first aza-diene **228** was heated under reflux with dimethyl acetylenedicarboxylate in toluene, the reaction was monitored by removing a small amount of the reaction mixture, concentrating the sample and subjecting it to ^{1}H NMR analysis, after 3 weeks the ^{1}H NMR spectrum showed all the starting material **228** was consumed and indicated that a substituted pyridine had formed, the reaction was stopped and the mixture concentrated and purified to give the pure highly substituted pyridine **234**, in 39% yield.

The scope of this general procedure was then investigated with a vast number of dienophiles and the same aza-diene **228**, using ^{1}H NMR analysis to monitor the reaction; the reaction time varied from 5-6 weeks at heating under reflux and the reactions were stopped when the ^{1}H NMR spectrum indicated that all the starting material **228** had been consumed. The general outcome was for the starting material to revert back to its precursor, **187**. One reaction where the dienophile was methyl propiolate gave an unknown product *via* an unknown reaction pathway, the ^{1}H NMR spectrum was too messy and had too many multiplet signals for product identification. The concentration of the reaction mixture has no effect on the outcome of the reaction, as when the reaction was repeated using a larger molar quantity in the same amount of solvent the reaction still took 3 weeks for completion and gave a very similar yield. The solvent used does however have an effect on the reaction, when the aza-Diels-Alder reaction was repeated in different solvents (chloroform, dichloromethane, THF, ether and benzene), no product was formed and the starting material **228** reverted back to its precursor **187**. Synthesis of a highly substituted pyridine using this 1-aza-diene **228** is extremely difficult and when it is successful long reaction times under harsh reaction conditions are needed, **228** will only react with highly electron-deficient alkyne dienophiles.

Microwave irradiation is one promising way forward: the substituted pyridine, **234** was formed in a microwave reactor without the need for any solvent at 170 °C in just 30 minutes, the down side was that the product yield after purification was less than the conventional method, with a small amount of optimisation the yield could possibly have been increased once optimum conditions had been found. Microwave synthesis would however allow the rapid determination of the success of these aza-Diels-Alder reactions with different dienophiles allowing up to 14 reactions in one day rather than one reaction in 3-6 weeks, not only is this more time efficient but is also less wasteful in solvent. A control reaction of 1-aza-diene **228** with DMAD was carried out in a sealed tube this however caused **228** to revert back to its precursor **187**. A high pressure reaction had been performed on the same starting materials (**228** and DMAD), this unfortunately was unsuccessful showing that this synthesis substituted pyridines requires specific conditions.

8.0 Further Work

There are a number of alternative dienophiles that can still be tried, for example, alkynes and alkenes containing CN groups and nitroso- groups (NO_2), carbenes (=C=) can also be used. Similar dienophiles are (R_2C=C=O), (PhN=C=S), (PhN=C=O) and (O_2S=COPh) all of which are worth trying.

All of the aza-Diels-Alder reactions that were tried using the conventional reflux technique could be repeated using microwave irradiation, to see if this method would be enough to drive the reaction. The most promising dienophiles to try are 2-bromo-1,4-naphthoquinone, maleic anhydride, *N*-phenylmaleimide and methyl propiolate. The other two 1-aza-dienes can also undergo aza-Diels-Alder chemistry to see if the bulkier ^{t}butyl group or the methyl group causing less steric hindrance makes a difference with the dienophiles already tried.

The 2,3-butanedione mono-dimethylhydrazone could undergo microwave irradiation in the presence of pyrrolidine to see if this method allows for a reaction to occur. Compounds similar to 2,3-butanedione with longer carbon chains either side of the carbonyl groups, for example, 3,4-hexanedione could be made into mono-hydrazones, and then subjected to pyrrolidine under various reaction conditions to see if the chain length makes a difference to the reactivity. 2,3-Butanedione mono-dimethylhydrazone can also be reacted with pyrrolidine using the arsenic trichloride method in the hope that the severe reaction conditions would cause the carbonyl to react.

It would also be interesting to look at the highly substituted pyridine **234** to see if we could react it further. This could be done in two main places on our substituted pyridine; the first is the hydroxy group – can this undergo a substitution reaction allowing us to add to the pyridine and form more complex compounds and a route to the synthesis of pyridine containing natural products. Secondly does, for example, the nitrogen lone pair of electrons in the pyridine further react with dienophiles to allow the addition onto the nitrogen and is this what happened when our 1-aza-diene, **228** was reacted with methyl propiolate.

The next thing that is of interest is can either the general method or the microwave irradiation method be applied to the synthesis of natural and medicinal products, allowing us to synthesise large quantities, efficiently *via* aza-Diels-Alder chemistry, which is of benefit to both medicine and industry.

9.0 Experimental Procedures

All reactions were carried out in oven-dried glassware.

The NMR chemical shifts are reported as δ values in ppm, which are referenced to chloroform at δ_H 7.26 ppm and δ_C 77.0 ppm for the ^1H and ^{13}C NMR spectra respectively. The proton and carbon NMR spectra were recorded on a Bruker AC250 NMR spectrometer or a Bruker AC500 NMR spectrometer where indicated, using deuterochloroform as the solvent; coupling constants (*J*) are given in Hz. The assignments of the ^{13}C NMR spectra were assisted by DEPT experiments. (*NB.* Where the assignment is unknown, the compound is unidentified as well as the peak assignment).

Infrared (IR) spectra were recorded as Nujol mulls between sodium chloride plates on a Perkin Elmer 1600 series FTIR spectrophotometer.

Mass spectra were performed by the EPSRC National service at the University of Wales, Swansea.

Column chromatography was performed using matrix silica 60 (partial size 100 microns). TLC eluents are as stated for each reaction.

9.1 General Procedures

9.1.1 Anhydrous Triethylamine

Triethylamine was distilled from calcium hydride (88 – 90 °C) [232].

9.1.2 Anhydrous Toluene

Anhydrous toluene was supplied by Aldrich.

9.1.3 Anhydrous Acetonitrile

Acetonitrile was distilled from potassium carbonate (81 – 84 °C) [232].

9.1.4 Anhydrous Diethyl Ether

Diethyl ether (ether) was distilled from sodium/benzophenone ketyl (35 – 37 °C) [232].

9.1.5 Anhydrous Dichloromethane

Dichloromethane was distilled from calcium hydride (38 – 41 °C) [232].

9.1.6 Anhydrous Acetone

Anhydrous acetone was supplied by Aldrich.

9.1.7 Deuteriochloroform

Deuteriochloroform was passed through a column of basic alumina before use[232].

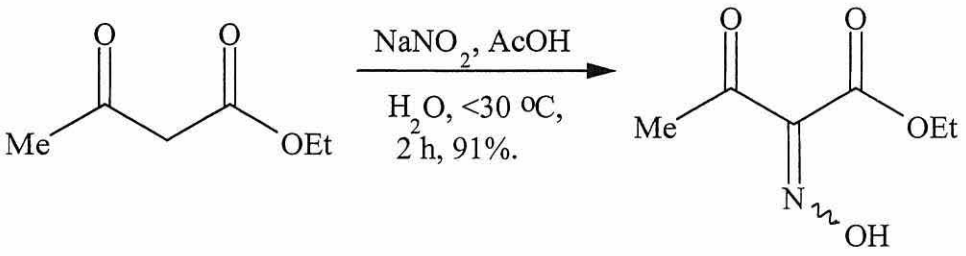
9.1.8 Anhydrous Ethanol

Anhydrous ethanol was supplied by Aldrich.

9.1.9 Brine

Brine refers to saturated aqueous sodium chloride

9.2 Preparation of Ethyl Oximino Acetoacetate[152]



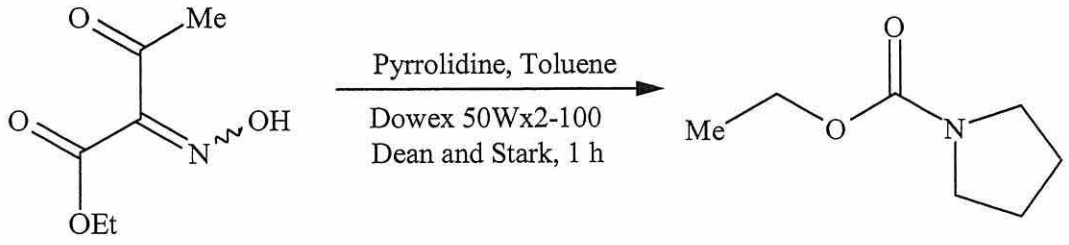
187

A solution of sodium nitrite (23.46 g, 0.34 mol) in water (50 mL) was added slowly to a solution of ethyl acetoacetate (40.00 g, 0.31 mol) in acetic acid (45 mL) cooled in a salt-ice bath. The temperature was maintained below 30 °C during the addition. The orange solution was stirred at room temperature for a further 30 minutes, then water (150 mL) was added and the mixture stirred for a further 2 hours.

The reaction mixture was extracted with ether (3 x 50 mL); the combined extracts were washed successively with water (25 mL), saturated $NaHCO_3$ (4 x 25 mL), and water (25 mL), then dried over sodium sulfate. The mixture was then evaporated to give a colourless residue, ethyl oximino acetoacetate (44.71 g, 91%); ν_{max}/cm^{-1} 3314.2br (OH), 1726.0s (CO_2Et), 1684.0s ($CH_3C=O$), 1625.2s (C=N); δ_H(250MHz, $CDCl_3$), 1.29 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$), 2.36 (3 H, s, $\underline{CH_3}C=O$), 4.32 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$); δ_C(62.5MHz, $CDCl_3$), 13.5 ($OCH_2\underline{CH_3}$), 24.8 ($\underline{CH_3}C=O$), 62.3 ($O\underline{CH_2}CH_3$), 150.6 ($\underline{C}$=N-OH), 162.1 ($\underline{C}O_2Et$), 194.9 ($CH_3\underline{C}=O$); *m/z* 159 (M^+), 131 ($-C_2H_4$), 113 (-OEt), 86 (-CO).

The data was in fair agreement with the literature[152]. After 6 weeks storage in the freezer crystallisation occurred to give colourless needles; m.p. 18-20 °C (literature[152] m.p. 47-48 °C)

9.3 Attempted Preparation of the Enamine of Ethyl Oximino Acetoacetate



187 **197**

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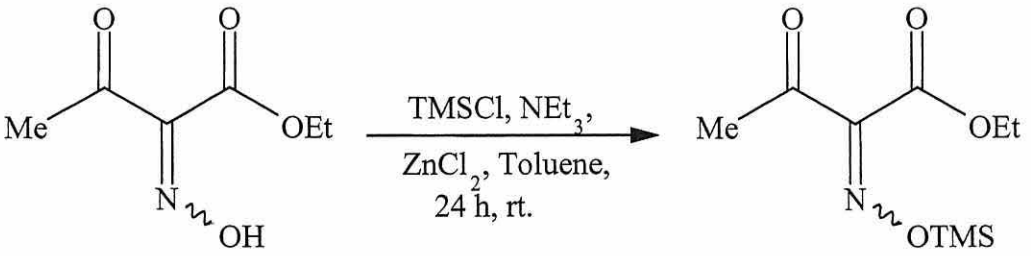
Unknowns

Ethyl oximino acetoacetate (4.0 g, 0.025 mol), pyrrolidine (1.78 g, 0.025 mol) and Dowex 50Wx2-100 (0.5 g, 10 mol %) was added to toluene (40 mL). A Dean and Stark apparatus was connected to the flask with a reflux condenser, protected with a calcium chloride drying tube. The reaction mixture was heated under reflux for 1 hour, during which time water collected in the trap, then the mixture was allowed to cool, the Dowex beads filtered off and washed with anhydrous toluene, and the filtrate evaporated under reduced pressure to yield a black tar (3.70 g, 75%); ν_{max}/cm^{-1} 3189.8br (OH), 1707.1s (CO_2Et), 1641.6s (C=N); δ_H(500MHz, $CDCl_3$), 1.19 (3 H, t, *J* 3.5, $OCH_2\underline{CH_3}$, **197**), 1.28 (3 H, t, *J* 7.1, $OCH_2\underline{CH_3}$, **187**), 1.79 (4 H, m, $NCH_2\underline{CH_2}$, **197**), 2.00 (1 H, s, unknown), 2.32 (1 H, s, $\underline{CH_3}C=O$, **187**), 3.27 (2 H, t, *J* 6.3, $\underline{H_2C}NCH_2$, **197**), 3.31 (2 H, t, *J* 6.0, $H_2CN\underline{CH_2}$, **197**), 4.07 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **197**), 4.30 (1 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**), 7.21 (1 H, s, OH, **187**); δ_C(62.5MHz, $CDCl_3$), 15.0 ($OCH_2\underline{CH_3}$, **197**), 25.5 ($NCH_2\underline{CH_2}$, **197**), 45.6 ($N\underline{CH_2}CH_2$, **197**), 60.8 ($O\underline{CH_2}CH_3$, **197**), 113.1 (unknown), 155.3 ($\underline{C}$=O, **197**).

Distillation of the residue was attempted using a water aspirator (oil bath temperature up to 180 °C), but no distillate was collected and the residue decomposed.

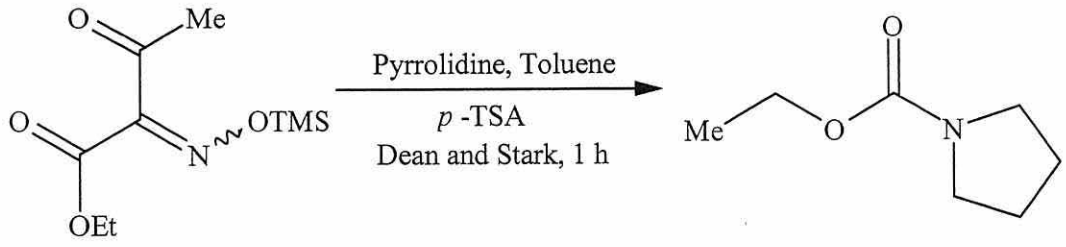
9.4 Trimethylsilylation of Ethyl Oximino Acetoacetate, 187



187 **189**

Ethyl oximino acetoacetate (3.0 g, 19 mmol) and anhydrous zinc(II) chloride (0.05 g, 0.38 mmol) were added to anhydrous toluene (25 mL). Anhydrous triethylamine (3.85 g, 38 mmol) was then added slowly, followed by trimethylsilylchloride (4.12 g, 38 mmol) dropwise. The mixture was then stirred at room temperature overnight. The white precipitate was then filtered off and washed with anhydrous ether and the filtrate evaporated, anhydrous ether was added to the resultant residue, which was filtered again, to remove further white precipitate. The precipitate was washed with anhydrous ether (total 80 mL), the filtrates combined and evaporated to give the product as a yellow oil (3.0 g, **187**, 22%, **189**, 45%, as determined by ^{1}H NMR spectroscopy); ν_{max}/cm^{-1} 3312.1br (OH), 1749.0s (CO_2Et), 1700.5s (CO_2Et), 1627.9w ($CH_3C=O$), 1598.3w ($CH_3C=O$), 1558.1w (C=N), 1540.1w (C=N); δ_H(250MHz, $CDCl_3$), 0.22 (6 H, s, OTMS), 1.26 (3 H, 2 x t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**, **189**), 2.32 (1 H, s, $\underline{CH_3}C=O$, **187**), 2.35 (2 H, s, $\underline{CH_3}C=O$, **189**), 4.29 (2 H, 2 x q, *J* 7.0, $O\underline{CH_2}CH_3$, **187**, **189**), 11.10 (1 H, s, OH, **187**); δ_C(62.5MHz, $CDCl_3$), -1.0 (OTMS), 25.1 ($OCH_2\underline{CH_3}$, **187**), 25.2 ($OCH_2\underline{CH_3}$, **189**), 45.8 ($\underline{CH_3}C=O$, **187**, **189**), 61.9 ($O\underline{CH_2}CH_3$, **187**), 62.0 ($O\underline{CH_2}CH_3$, **189**), 151.3 ($\underline{C}$=N-OH), 154.9 ($\underline{C}$=N-OTMS), 161.7 ($\underline{C}O_2Et$, **187**), 161.9 ($\underline{C}O_2Et$, **189**), 193.9 ($CH_3\underline{C}=O$, **187**), 194.1 ($CH_3\underline{C}=O$, **189**).

9.5 Preparation of the Enamine of Silylated Ethyl Oximino Acetoacetate[153]

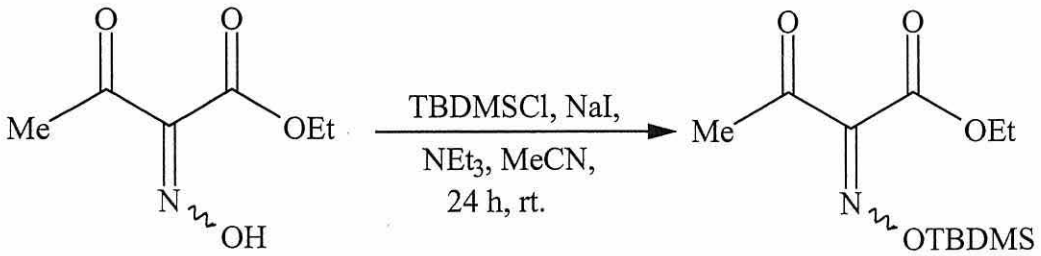


189 **197** + Unknowns

Crude silylated ethyl oximino acetoacetate (1.5 g, 6.5 mmol), pyrrolidine (0.46 g, 6.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.075 g, 0.39 mmol) were dissolved in toluene (15 mL). A Dean and Stark apparatus was connected to the flask with a water condenser, protected with a calcium chloride drying tube. The reaction mixture was heated under reflux for 1 hour, during which time water collected in the trap, then the mixture was allowed to cool and the solvent evaporated under reduced pressure to yield a black oil (1.42 g, 77%); ν_{max}/cm^{-1} 3427.8br (OH), 1709.9s (CO_2Et), 1686.2s (C=N); δ_H(250MHz, $CDCl_3$), 0.07 (1 H, s, OTMS), 1.23 (3 H, t, *J* 7.4, $OCH_2\underline{CH_3}$, **197**), 1.85 (4 H, m, 2 x $\underline{CH_2}$, **197**), 2.35 (1 H, s, *p*TsOH), 3.33 (4 H, t, *J* 6.5, 2 x $\underline{CH_2}$, **197**), 3.85 (2 H, q, *J* 7.0, $O\underline{CH_2}CH_3$, unknown), 4.13 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **197**), 7.18 (1 H, d, *J* 7.6, *p*TsOH), 7.73 (1 H, d, *J* 7.6, *p*TsOH); δ_C(62.5MHz, $CDCl_3$), 14.8 ($OCH_2\underline{CH_3}$ **197**), 21.2 ($NCH_2\underline{CH_2}$, **197**), 45.3 (*p*TsOH), 46.0 ($\underline{H_2C}N\underline{CH_2}$, **197**), 60.7 ($O\underline{CH_2}CH_3$, **197**), 125.8 (*p*TsOH), 128.7 (*p*TsOH), 139.7 (C=O, **197**).

Distillation of the residue was attempted using a water aspirator (oil bath temperature up to 180°C) under reduced pressure (25mmHg), but no distillate was collected and the residue decomposed.

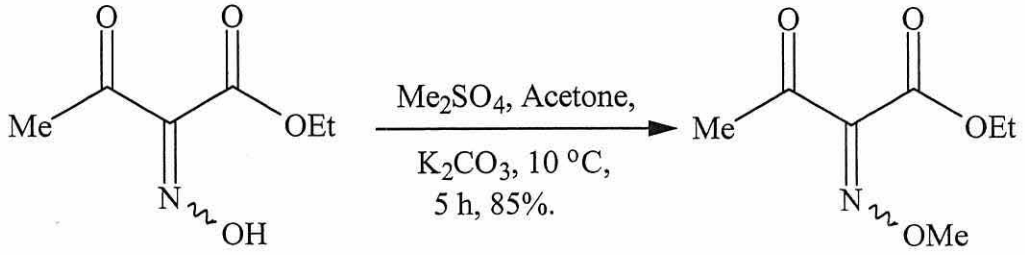
9.6 ^{t}Butyldimethylsilylation of Ethyl Oximino Acetoacetate[85]



187 **193**

Triethylamine (1.32 g, 13 mmol) was added to a stirred solution of ethyl oximino acetoacetate (2.0 g, 13 mmol), sodium iodide (0.49 g, 3.3 mmol) and TBDMSCl (1.96 g, 13 mmol) in anhydrous acetonitrile (20 mL). The resultant mixture was then stirred overnight at room temperature. The resultant orange solution was then evaporated to dryness, anhydrous ether (30 mL) was added and the mixture filtered to remove the white precipitate. The orange filtrate was evaporated to yield an orange oil (2.48 g; **193**, 47%; **187**, 23%, as determined by ^{1}H NMR spectroscopy); ν_{max}/cm^{-1} 3373.9br (OH), 1750.3s (CO_2Et), 1702.8s ($CH_3C=O$), 1598.2s (C=N); δ_H(250MHz, $CDCl_3$), 0.17 (4 H, s, TBDMS, **193**), 0.86 (6 H, s, $C\underline{Me}_3$, **187**), 1.24 (3 H, 2 x t, *J* 7.2, $OCH_2\underline{CH}_3$, **187**, **193**), 2.30 (1 H, s, $\underline{H}_3C$-C=O, **187**), 2.33 (2 H, s, $\underline{CH}_3$-C=O, **193**), 4.25 (2 H, 2 x q, *J* 7.2, $O\underline{CH}_2CH_3$, **187**, **193**); δ_C(62.5MHz, $CDCl_3$), -5.5 (TBDMS, **193**), -3.8 (TBDMS, **193**), 13.9 ($OCH_2\underline{CH}_3$, **187**, **193**), 18.0 ($C\underline{Me}_3$, **193**), 25.5 ($\underline{H}_3C$-C=O, **187**, **193**), 61.8 ($O\underline{CH}_2CH_3$, **187**), 62.0 ($O\underline{CH}_2CH_3$, **193**), 151.0 ($\underline{C}$=N-OH), 155.1 ($\underline{C}$=N-OTBDMS), 161.6 ($\underline{C}O_2Et$, **187**), 161.7 ($\underline{C}O_2Et$, **193**), 193.7 ($CH_3\underline{C}$=O, **187**), 193.8 ($CH_3\underline{C}$=O, **193**).

9.7 Methylation of Ethyl Oximino Acetoacetate[159]

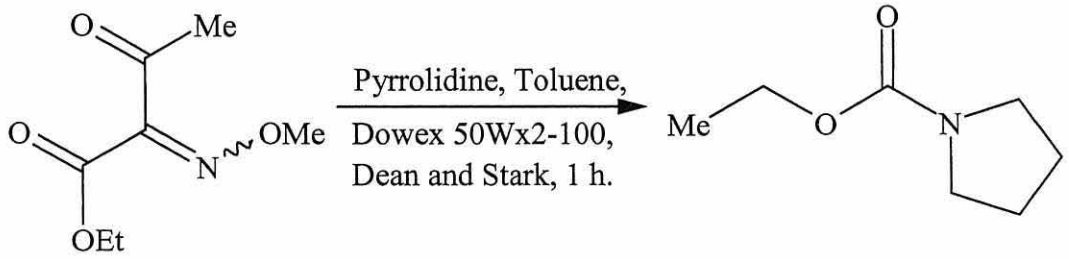


187 **194**

Dimethyl sulphate (1.64 g, 130 mmol) was added slowly to a mixture of ethyl oximino acetoacetate (2.0 g, 13 mmol) and potassium carbonate (2.76 g, 20 mmol), in acetone (12 mL) at 10 °C. The mixture was stirred for 5 hours. The mixture was then poured into ice/water (45 mL) and stirred for 30 mins, the resultant mixture was then extracted with dichloromethane (4 x 50 mL), the combined extracts dried over Na_2SO_4, filtered and evaporated to yield a pale yellow oil (1.91 g, 85%); ν_{max}/cm^{-1} 1752.6s (CO_2Et), 1703.7s, ($CH_3C=O$), 1601.9s (C=N); δ_H(250MHz, $CDCl_3$), 1.32 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$), 2.38 (3 H, s, $\underline{CH_3}$-C=O), 4.08 (3 H, s, N-O$\underline{CH_3}$), 4.33 (2 H, q, *J* 7.1, O$\underline{CH_2}CH_3$); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$), 25.1 ($\underline{CH_3}$-C=O), 62.1 (O$\underline{CH_2}CH_3$), 64.3 (=N-O$\underline{CH_3}$), 150.0 (<u>C</u>=N-OMe), 161.1 ($\underline{C}O_2Et$), 192.8 (Me-<u>C</u>=O).

The data was in good agreement with literature[159].

9.8 Enamine of Ethyl Methoxyimino Acetoacetate[153]



194 **197**

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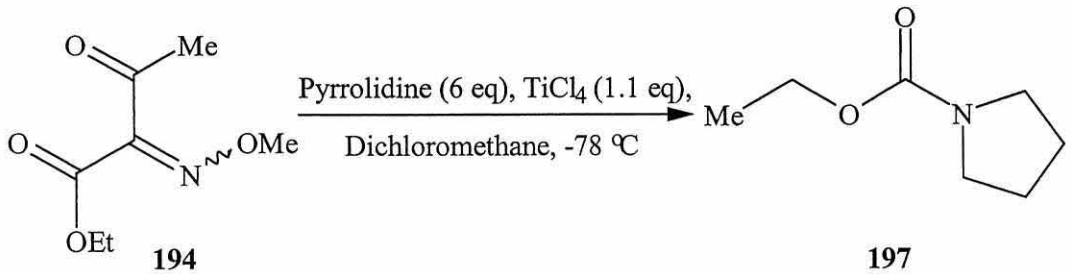
Unknowns

Ethyl methoxyimino acetoacetate (0.50 g, 2.9 mmol), pyrrolidine (0.21 g, 2.9 mmol) and Dowex 50Wx2-100 (0.06 g, 10 mol %) were added to toluene (5mL). A Dean and Stark apparatus was connected to the flask with a reflux condenser, protected with a calcium chloride drying tube. The reaction mixture was heated under reflux for 1 hour, during which time water collected in the trap, then the mixture was allowed to cool, the Dowex beads filtered off and washed with anhydrous toluene. The filtrate was evaporated under reduced pressure, to yield an orange oil (0.49 g, 74%); ν_{max}/cm^{-1} 1744.5m (CO_2Et), 1702.0w (CH_3-C=O), 1654.1m (C=N), 1636.7m (C=N); δ_H(250MHz, $CDCl_3$), 1.25 (1 H, t, $OCH_2\underline{CH_3}$, **194**), 1.33 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **197**), 1.86 (4 H, m, $NCH_2\underline{CH_2}$, **197**), 2.35 (2 H, s, $\underline{CH_3}$-C=O, **194**), 3.15 (2 H, t, *J* 6.7, $\underline{H_2C}NCH_2$, **197**), 3.41 (2 H, m, $H_2CN\underline{CH_2}$, **197**), 3.94 (1 H, s, O<u>Me</u>, **194**) 4.09 (2 H, s, O<u>Me</u>, **194**), 4.32 (2 H, 2 x q, *J* 7.2, $O\underline{CH_2}CH_3$, **194**, **197**); δ_C(62.5MHz, $CDCl_3$), 14.0 ($OCH_2\underline{CH_3}$, **194**, **197**), 25.2 ($\underline{CH_3}$-C=O, **194**), 26.0 ($NCH_2\underline{CH_2}$, **197**), 48.8 ($\underline{H_2C}N\underline{CH_2}$, **197**), 62.1 ($O\underline{CH_2}CH_3$, **194**, **197**), 64.3 (N-O<u>Me</u>, **194**), 128.2 (unknown), 150.0 (<u>C</u>=N-OMe), 161.2 ($\underline{C}O_2Et$), 192.8 (CH_3-<u>C</u>=O).

9.9 Enamine of Ethyl Methoxyimino Acetoacetate: Alternative Method[120, 125]



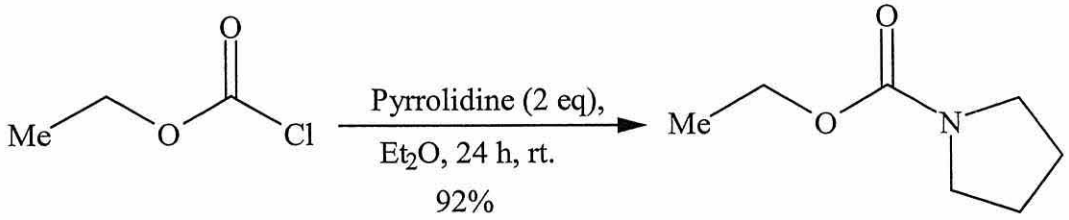
194 **197** + Unknowns

Ethyl oximino acetoacetate (2.89 g, 17 mmol) in CH_2Cl_2 (84 mL) was placed into a 250 mL flask, to this was added a solution of pyrrolidine (3.63 g, 51 mmol) in CH_2Cl_2 (17 mL) under an inert nitrogen atmosphere. To the resultant solution, over a 20 minute period, a solution of titanium tetrachloride in dichloromethane (1.0 M, 1.78 g, 9.4 mmol) diluted with additional CH_2Cl_2 (17 mL) was added, the temperature of the

reaction mixture was kept at -78 °C during the addition, and then stirred overnight at room temperature.

The resultant white precipitate was filtered off and washed with CH_2Cl_2, the filtrate was evaporated under reduced pressure to yield a dark red oil (3.15 g, 70%); ν_{max}/cm^{-1} 1740.8m (CO_2Et), 1696.5m (C=N) 1629.3w (C=N or C=C); δ_H(250MHz, $CDCl_3$), 1.19 (1 H, m, $OCH_2\underline{CH_3}$, **194**), 1.28 (3 H, t, *J* 7.1, $OCH_2\underline{CH_3}$, **197**), 1.74 (4 H, m, unknown), 1.87 (6 H, m, $NCH_2\underline{CH_2}$, **197**), 2.00 (1 H, s, unknown), 2.35 (1 H, s, $\underline{CH_3}$-C=O, **194**), 2.47 (2 H, m, unknown), 2.77 (2 H, m, unknown), 2.97 (1 H, m, unknown), 3.14 (4 H, 2 x t, *J* 6.9, $\underline{H_2C}N\underline{CH_2}$, **197**), 3.67 (1 H, s, unknown), 3.90 (1 H, s, unknown), 4.05 (3 H, s, O<u>Me</u>, **194**), 4.28 (2 H, q, *J* 7.0, $O\underline{CH_2}CH_3$, **197**), 4.60 (4 H, s, broad, unknown); δ_C(62.5MHz, $CDCl_3$), 15.4 ($OCH_2\underline{CH_3}$, **197**), 26.0 ($NCH_2\underline{CH_2}$, **197**), 47.0 ($\underline{H_2C}N\underline{CH_2}$, **197**), 55.7 (unknown), 63.4 ($O\underline{CH_2}CH_3$, **197**), 65.8 ($O\underline{CH_2}CH_3$, **194**), 116.9 (<u>C</u>=N, **194**), 151.4 ($\underline{C}O_2Et$, **197**), 162.6 ($\underline{C}O_2Et$, **194**), 194.2 (CH_3-<u>C</u>=O, **194**), 195.5 (CH_3-<u>C</u>=O, **194**).

9.10 Preparation of Pyrrolidine-1-Carboxylic Acid Ethyl Ester[160]

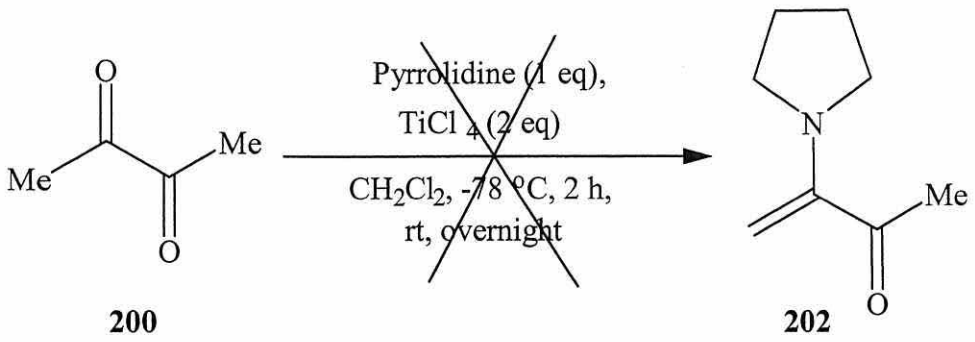


196 **197**

Ethyl chloroformate (1.0 g, 9.2 mmol) and pyrrolidine (1.28 g, 18 mmol) were stirred in anhydrous diethyl ether (10 mL) overnight. The resultant white precipitate was filtered off and washed with anhydrous ether (20 mL). The filtrate was washed successively with 1M hydrochloric acid (15 mL), water (15 mL), 10% $NaHCO_3$ (15 mL) and brine (15 mL), and dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a colourless oil (1.22 g, 92%); ν_{max}/cm^{-1} 1708.2 (C=O); δ_H(250MHz, $CDCl_3$), 1.24 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **197**), 1.83 (4 H, m, $NCH_2\underline{CH_2}$, **197**), 3.33 (2 H, t, *J* 6.1, $\underline{H_2C}NCH_2$, **197**), 3.33 (2 H, t, *J* 6.5, $H_2CN\underline{CH_2}$, **197**), 4.12 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **197**); δ_C(62.5MHz, $CDCl_3$), 14.8 ($OCH_2\underline{CH_3}$,

197), 24.9 ($NCH_2\underline{CH_2}$, **197**), 25.7 ($NCH_2\underline{CH_2}$, **197**), 45.6 ($\underline{H_2C}NCH_2$, **197**), 46.0 ($H_2CN\underline{CH_2}$, **197**), 60.7 ($O\underline{CH_2}CH_3$, **197**), 155.2 (C=O, **197**).

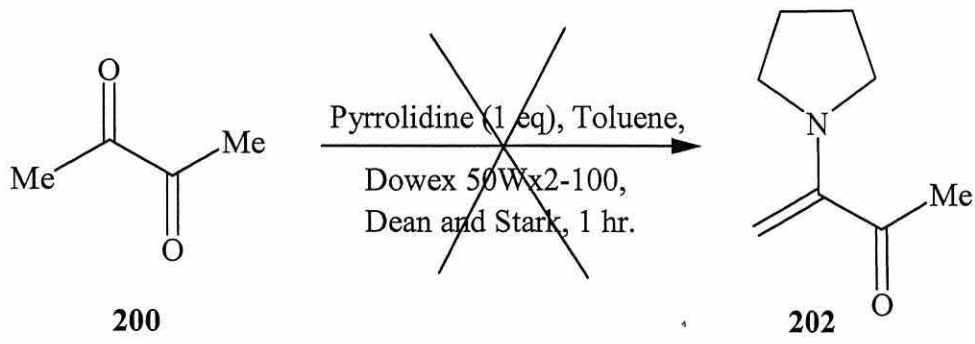
9.11 Preparation of 3-Pyrrolidine-3-Buten-2-one[120, 125] Attempt 1



200 **202**

A solution of titanium tetrachloride in dichloromethane (1.0 M, 2.12 g, 11.2 mmol) diluted with additional CH_2Cl_2 (15 mL) was added with stirring to a solution of pyrrolidine (0.40 g, 5.6 mmol) in CH_2Cl_2 (15 mL) at –78 °C, under a nitrogen atmosphere. Stirring was continued at this temperature for 2 hours. 2,3-Butanedione **200** (1.45 g, 16.8 mmol) as a solid was then added in one batch. The cooling bath was removed and the mixture was then stirred overnight at room temperature. The white precipitate was filtered off and washed with CH_2Cl_2 (3 x 50 mL). The filtrate was then evaporated under reduced pressure to yield 2,3-butanedione **200** as a black oil (1.23 g, 53%); ν_{max}/cm^{-1} 1715.5 (C=O); δ_H(250MHz, $CDCl_3$), 2.30 (6 H, s, $\underline{CH_3}$-C=O); δ_C(62.5MHz, $CDCl_3$), 23.3 ($\underline{CH_3}$-C=O), 197.0 ($\underline{C}$=O).

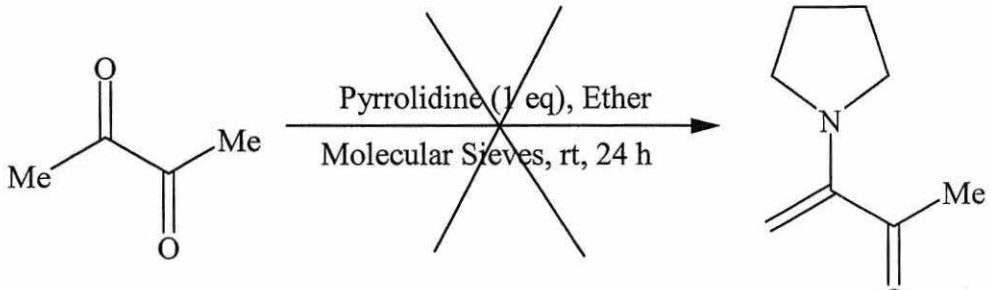
9.12 Preparation of 3-Pyrrolidine-3-Buten-2-one[153] Attempt 2



200 **202**

2,3-Butanedione **200** (2.00 g, 23.0 mmol), pyrrolidine (1.64 g, 23.0 mmol) and Dowex 50Wx2-100 (0.24 g, 10 mol %) were added to anhydrous toluene (30 mL). A Dean and Stark apparatus was connected to the flask with a reflux condenser, protected with a calcium chloride drying tube. The reaction mixture was heated under reflux for 1 hour, during which time water collected in the trap, then the mixture was allowed to cool, the Dowex beads filtered off and washed with anhydrous toluene. The filtrate was evaporated under reduced pressure, to yield 2,3-butanedione **200** as a black oil (1.99 g, 62%); ν_{max}/cm^{-1} 1679.8 (C=O); δ_H(250MHz, $CDCl_3$), 2.31 (6 H, s, $\underline{CH_3}$-C=O); δ_C(62.5MHz, $CDCl_3$), 23.3 ($\underline{CH_3}$-C=O), 197.1 ($\underline{C}$=O).

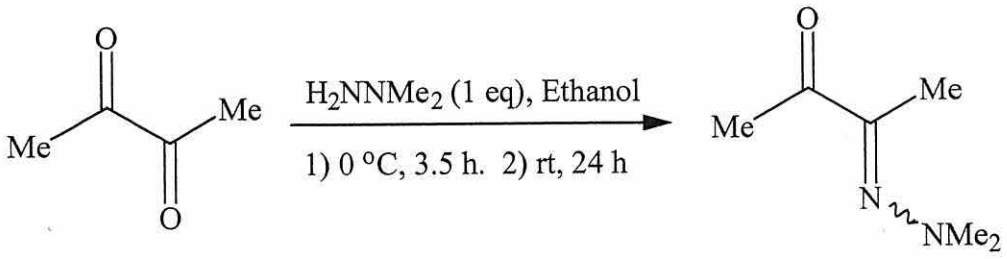
9.13 Preparation of 3-Pyrrolidine-3-Buten-2-one[154] Attempt 3



200 **202**

Pyrrolidine (1.64 g, 23.0 mmol) and 2,3-butanedione **200** were placed into a 100mL round bottom flask containing anhydrous ether (50 mL). Molecular sieves (4Å, 0.36 g, 10% mass) were added and the resultant mixture stired overnight. The resultant white precipitate was filtered off and washed with ether, the filtrate was evaporated under reduced pressure to yield 2,3-butanedione **200** as a yellow/orange oil (2.99 g, 93%); ν_{max}/cm^{-1} 1718.7 (C=O); δ_H(250MHz, $CDCl_3$), 2.30 (6 H, s, $\underline{CH_3}$-C=O); δ_C(62.5MHz, $CDCl_3$), 23.3 ($\underline{CH_3}$-C=O), 156.3 (unknown), 197.0 ($\underline{C}$=O).

9.14 Preparation of 2,3-Butanedione Mono-dimethylhydrazone[123, 124]



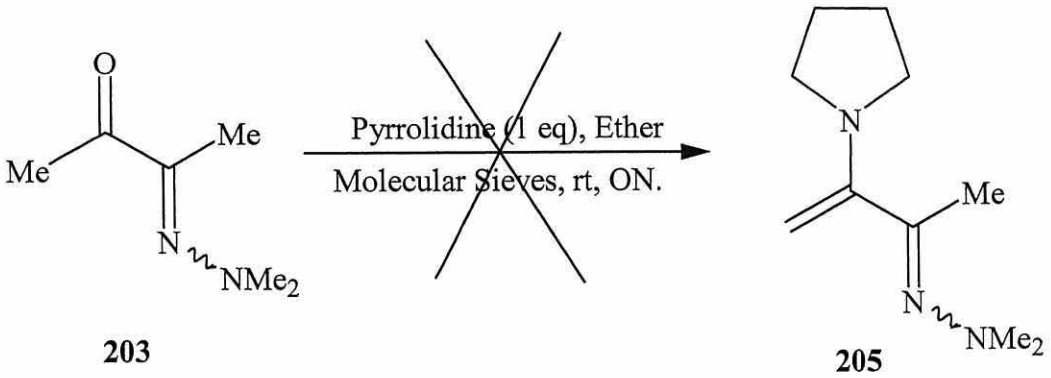
200 **203**

N,N-Dimethylhydrazine (17.47 mL, 230 mmol) was added to a solution of 2,3-butanedione **200** (20.0 g, 230 mmol) in anhydrous ethanol (80 mL) at 0°C under a nitrogen atmosphere. The mixture was then stirred at 0°C for 3.5 hours, the resultant mixture was allowed to warm slowly to room temperature and stirred for 24 hours. The mixture was then dried over magnesium sulfate and filtered, the filtrate was then concentrated to yield the crude product **203** as a yellow liquid (24.92 g, 85%); ν_{max}/cm^{-1} 1678.6 (C=O) 1574.3 (C=N); δ_H(250MHz, $CDCl_3$), 1.96 (3 H, s, $\underline{CH_3}$-C=N-), 2.28 (3 H, s, $\underline{CH_3}$-C=O), 2.93 (6 H, s, $N\underline{Me_2}$); δ_C(62.5MHz, $CDCl_3$), 12.7 ($\underline{CH_3}$-C=N-), 24.4 ($\underline{CH_3}$-C=O), 46.8 ($N\underline{Me_2}$), 147.0 (CH_3-$\underline{C}$=N-), 198.9 (CH_3-$\underline{C}$=O).

The data was in agreement with the literature[167, 168].

9.15 Preparation of 3-Pyrrolidinyl-3-Butene-2-one Mono-dimethylhydrazone

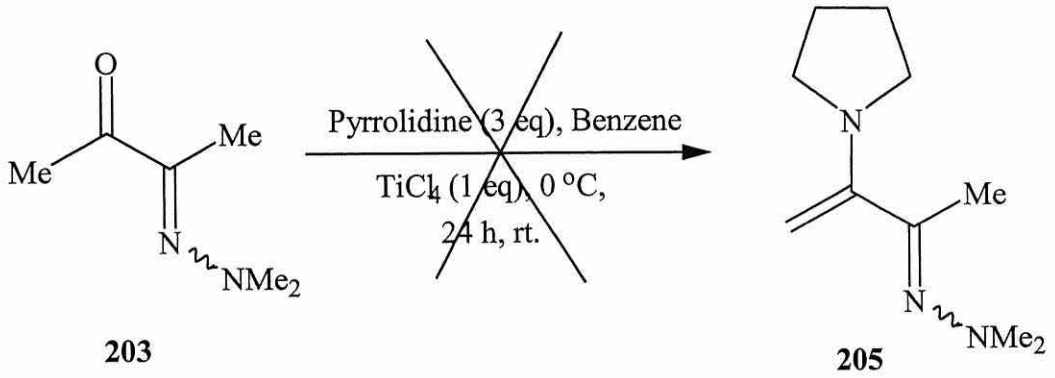
Attempt 1



203 **205**

Pyrrolidine (1.11 g, 15.6 mmol) was added to a flask containing anhydrous ether (20 mL). To this was added 2,3-butanedione mono-dimethylhydrazone, **203** (2.0 g, 15.6 mmol). Molecular sieves (4Å, 0.31 g, 10 mol%) were then added as a slurry in additional anhydrous ether (25 mL). The resultant mixture was then stirred under a nitrogen atmosphere overnight at room temperature. The mixture was then filtered and the solvent removed from the filtrate under reduced pressure, to yield an orange oil (2.05 g, 73%); ν_{max}/cm^{-1} 1685.3 (C=O), 1582.1 (C=N); δ_H(250MHz, $CDCl_3$), 1.68 (2 H, m, $NCH_2\underline{CH_2}$, pyrrolidine), 2.00 (3 H, s, $\underline{CH_3}$-C=N-, **203**), 2.32 (3 H, s, $\underline{CH_3}$-C=O, **203**), 2.86 (2 H, m, $N\underline{CH_2}CH_2$, pyrrolidine), 2.96 (6 H, s, $N\underline{Me_2}$, **203**), 3.70 (1 H, s, NH, pyrrolidine); δ_C(62.5MHz, $CDCl_3$), 24.4 ($NCH_2\underline{CH_2}$, pyrrolidine), 25.5 ($\underline{CH_3}$-C=N-, **203**), 45.9 ($N\underline{CH_2}CH_2$, pyrrolidine), 46.6 ($\underline{CH_3}$-C=O, **203**), 67.1 ($N\underline{Me_2}$, **203**), 147.2 (CH_3-$\underline{C}$=N-, **203**), 199.0 (CH_3-$\underline{C}$=O, **203**).

9.16 Preparation of 3-Pyrrolidinyl-3-Butene-2-One Mono-dimethylhydrazone[120] Attempt 2

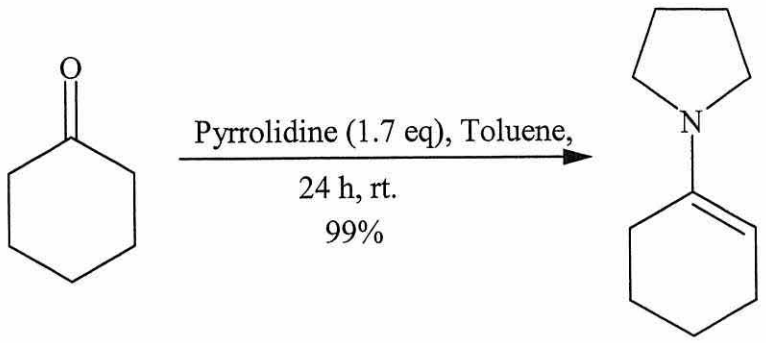


203 **205**

2,3-Butanedione mono-dimethylhydrazone, **203** (1.00 g, 7.8 mmol) was placed into a 250 mL flask containing anhydrous benzene (100 mL), to this was added a solution of pyrrolidine (0.83 g, 11.7 mmol) in anhydrous benzene (15 mL) in an inert nitrogen atmosphere. To the resultant solution, over a 20-60 minute period, titanium tetrachloride (0.74 g, 3.9 mmol) dissolved in benzene (15 mL) was added, the temperature of the reaction mixture was kept between 0 – 10 °C during the addition. The resultant reaction mixture was stirred overnight at room temperature. The resultant white precipitate was filtered off and washed with pentane, the filtrate was evaporated under reduced pressure to yield 2,3-butanedione mono-dimethylhydrazone

203 as a yellow oil (0.56 g, 40%); ν_{max}/cm^{-1} 1684.8 (C=O), 1581.5 (C=N); δ_H(250MHz, $CDCl_3$), 2.04 (3 H, s, $\underline{CH_3}$-C=N-), 2.34 (3 H, s, $\underline{CH_3}$-C=O), 2.98 (6 H, s, N$\underline{Me_2}$); δ_C(62.5MHz, $CDCl_3$), 24.5 ($\underline{CH_3}$-C=N-), 46.8 ($\underline{CH_3}$-C=O), 67.4 (N$\underline{Me_2}$), 147.5 (CH_3-$\underline{C}$=N-), 198.6 (CH_3-$\underline{C}$=O).

9.17 Preparation of *N*-(Cyclohexen-1-yl)Pyrrolidine[172]

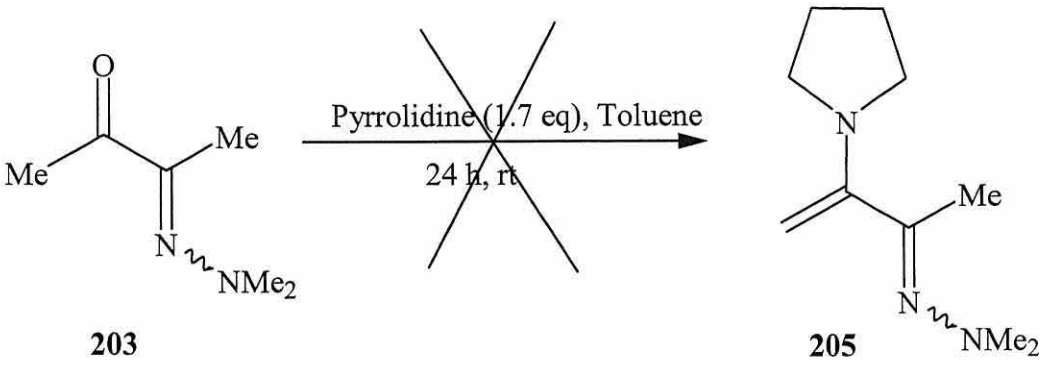


206 **207**

Cyclohexanone (10.00 g, 100 mmol) and pyrrolidine (12.00 g, 170 mmol) were added to anhydrous toluene (150 mL) and stirred at room temperature overnight. The resultant mixture was concentrated under reduced pressure to yield the crude product as a yellow oil (15.02 g, 99%); ν_{max}/cm^{-1} 1719.0 (C=O, **206**), 1642.0 (C=C); δ_H(250MHz, $CDCl_3$), 1.58 (4 H, m, $\underline{CH_2}CH_2$-C=CH-$CH_2\underline{CH_2}$), 1.78 (4 H, m, $NCH_2\underline{CH_2}$), 2.31 (4 H, m, $CH_2\underline{CH_2}$-C=CH-$\underline{CH_2}CH_2$), 3.00 (4 H, m, N$\underline{CH_2}CH_2$), 4.29 (1 H, m, N-C=$\underline{CH}$); δ_C(250Hz, $CDCl_3$), 23.3 ($\underline{CH_2}CH_2$-C=CH-$CH_2\underline{CH_2}$), 23.4 ($\underline{CH_2}CH_2$-C=CH-$CH_2\underline{CH_2}$), 24.5 ($NCH_2\underline{CH_2}$), 25.4 ($CH_2\underline{CH_2}$-C=CH-$\underline{CH_2}CH_2$), 27.5 ($CH_2\underline{CH_2}$-C=CH-$\underline{CH_2}CH_2$), 47.4 (N$\underline{CH_2}CH_2$), 93.5 (N-C=$\underline{C}$H), 143.4 (N-$\underline{C}$=CH).

The data was in agreement with the literature[172].

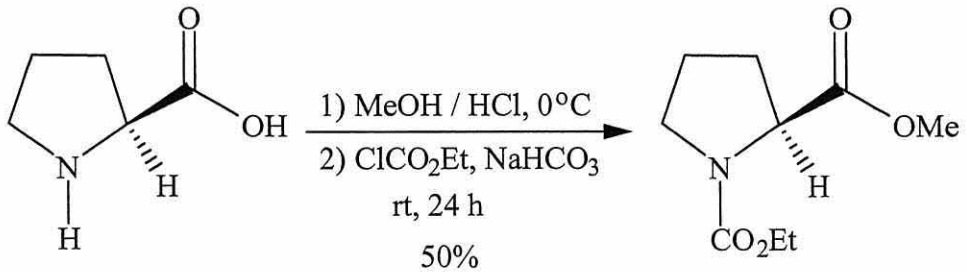
9.18 Preparation of 3-Pyrrolidinyl-3-Butene-2-one Mono-dimethylhydrazone Attempt 3



203 **205**

2,3-Butanedione mono-dimethylhydrazone **203** (1.00 g, 7.8 mmol) and pyrrolidine (0.71 g, 10 mmol) were added to anhydrous toluene (20 mL) and stirred at room temperature overnight. The resultant mixture was concentrated under reduced pressure to yield a green/brown oil (1.03 g, 73%); ν_{max}/cm^{-1} 1683.1 (C=O), 1580.5 (C=N); δ_H(250MHz, $CDCl_3$), 1.99 (4 H, m, $NCH_2\underline{CH_2}$, pyrrolidine), 2.16 (3 H, s, $\underline{CH_3}$-C=N-, **203**), 2.32 (4 H, m, $N\underline{CH_2}CH_2$, pyrrolidine), 2.35 (3 H, s, $\underline{CH_3}$-C=O, **203**), 2.95 (6 H, s, $N\underline{Me_2}$, **147**); δ_C(62.5MHz, $CDCl_3$), 24.4 ($NCH_2\underline{CH_2}$, pyrrolidine), 27.0 ($\underline{CH_3}$-C=N-, **203**), 46.8 ($N\underline{CH_2}CH_2$, pyrrolidine), 47.1 ($\underline{CH_3}$-C=O, **203**), 65.4 ($N\underline{Me_2}$, **203**), 147.1 (CH_3-$\underline{C}$=N), 198.9 (CH_3-$\underline{C}$=O).

9.19 Preparation of an *N*-Ethyloxycarbonylproline Methyl Ester[173]



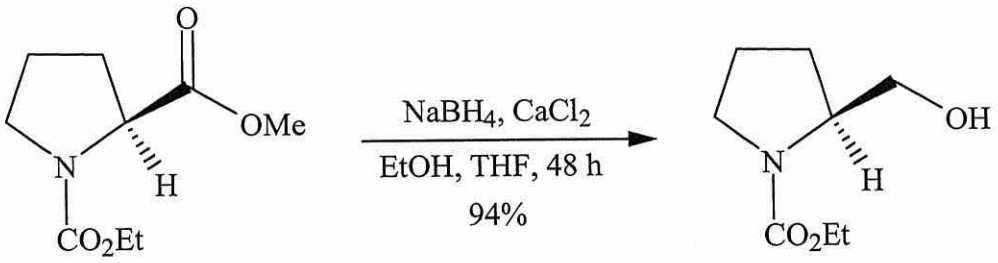
208 **209**

Acetyl chloride (7.50 mL, 105 mmol) was added drop-wise to ice-cooled methanol (40 mL) over 15 mins. L-Proline (5.00 g, 43.4 mmol) was added and the solution

stirred overnight. The solvent was removed *In – vacuo* to yield crude praline methyl ester as a yellow oil, theis compound was then dissolved in water (110 mL) and sodium hydrocarbonate (18.48 g, 220 mmol) added portion-wise. Ethylchloroformate (4.97 mL, 52 mmol) was added cautiously drop-wise and the solution stirred vigorously for 24 hrs. The solution was then filtered. The product was extracted from the filtrate with dichloromethane (3 x 30 mL), the solvent was removed under reduced pressure to yield the crude product **209** as a colourless oil (6.44 g, 50%); ν_{max}/cm^{-1} 1757.2 (C=O), 1713.4 (C=O); δ_H(250MHz, $CDCl_3$), 1.14 (3 H, m, $CO_2CH_2\underline{CH_3}$), 1.87 (2 H, m, $NCH_2\underline{CH_2}$), 2.13 (2 H, m, $NCH\underline{CH_2}$), 3.39 (2 H, m, $N\underline{CH_2}CH_2$), 3.64 (1 H, m, $N\underline{CH}$), 4.05 (3 H, m, $CO_2\underline{CH_3}$), 4.25 (2 H, m, $CO_2\underline{CH_2}CH_3$); δ_C(62.5MHz, $CDCl_3$), 14.5 ($CO_2CH_2\underline{C}H_3$), 24.2 ($NCH_2\underline{C}H_2$), 30.7 ($NCH\underline{C}H_2$), 46.2 ($N\underline{C}H_2CH_2$), 51.9 ($CO_2\underline{C}H_3$), 53.4 ($CO_2\underline{C}H_2CH_3$), 58.6 ($N\underline{C}H$), 173.1 ($\underline{C}O_2CH_3$), 173.3 ($\underline{C}O_2CH_2CH_3$).

The data was in agreement with the literature[173].

9.20 Reduction of *N*-Ethyloxycarbonylproline Methyl Ester 153[173]



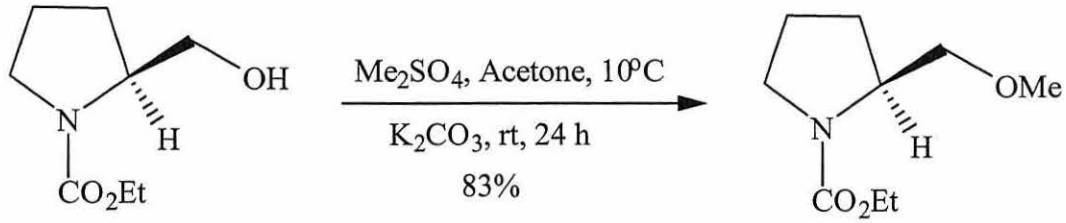
209 **210**

Calcium chloride (2.33 g, 21 mmol) and sodium borohydride (1.63 g, 43 mmol) were added successively to a solution of (*S*)-*N*-ethyloxycarbonylproline methyl ester, **209** (2.00 g, 9.9 mmol) in ethanol (20 mL) and THF (10 mL). The suspension was stirred for 48 hrs. The mixture was poured cautiously into aqueous conc citric acid (35 mL) and then filtered. The product was extracted from the filtrate with ethyl acetate (2 x 20 mL), and the combined organic extracts washed with brine (10 mL). The solvent was removed under reduced pressure to yield the product **210** as a white solid (1.60 g, 94%); ν_{max}/cm^{-1} 3385.5br (OH), 1679.2 (C=O); δ_H(250MHz, $CDCl_3$), 1.24 (3 H, m, $CO_2CH_2\underline{CH_3}$), 1.86 (2 H, m, $NCH_2\underline{CH_2}$), 2.06 (2 H, m, $NCH\underline{CH_2}$), 3.37 (2 H, m,

$N\underline{CH_2}CH_2$), 3.63 (1 H, m, $N\underline{CH}$), 4.07 (2 H, m, $\underline{CH_2}OH$), 4.19 (2 H, m, $CO_2\underline{CH_2}CH_3$), 4.60 (1 H, s, br, OH); δ_C(62.5MHz, $CDCl_3$), 14.6 ($CO_2CH_2\underline{C}H_3$), 24.0 ($NCH_2\underline{C}H_2$), 38.6 ($NCH\underline{C}H_2$), 47.2 ($N\underline{C}H_2CH_2$), 53.8 ($CO_2\underline{C}H_2CH_3$), 60.5 ($N\underline{C}H$), 67.2 ($\underline{C}H_2OH$), 173.4 ($\underline{C}O_2CH_2CH_3$); m.p. 42-45 °C

The data was in agreement with the literature.[173]

9.21 Methylation of the *L*-Prolinol Derivative[159]

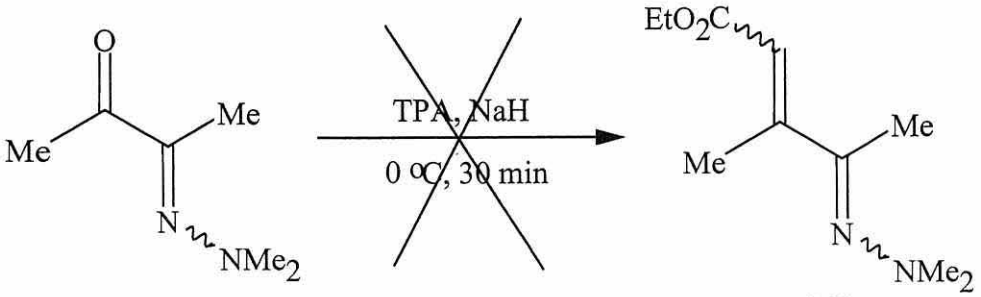


210 **211**

Dimethyl sulfate (0.87 g, 6.9 mmol) was added slowly to a mixture of *L*-prolinol derivative, **210** (1.20 g, 6.9 mmol) and potassium carbonate (1.44 g, 10.4 mmol), in acetone (10 mL) at 10°C. The mixture was stirred for 5 hours at this temperature, then allowed slowly to warm to room temperature and stirred overnight. The mixture was then poured into ice/water (25 mL) and stirred for 30 mins, the resultant mixture was then extracted with dichloromethane (4 x 25 mL), the combined extracts dried over sodium sulfate, filtered and evaporated to yield the crude product **211** as a colourless oil (1.07 g, 83%); ν_{max}/cm^{-1} 3431.8 (OH), 1755.3 (C=O); δ_H(250MHz, $CDCl_3$), 1.21 (3 H, t, *J* 7.0, $CO_2CH_2\underline{CH_3}$, **211**), 1.85 (2 H, m, $NCH_2\underline{CH_2}$, **211**), 2.02 (2 H, m, $NCH\underline{CH_2}$, **211**), 3.38 (2 H, m, $N\underline{CH_2}CH_2$, **211**), 3.56 (1 H, m, $N\underline{CH}$, **211**), 3.72 (2 H, m, $\underline{CH_2}OMe$, **211**), 3.90 (2 H, m, $CH_2O\underline{Me}$, **211**), 4.09 (2 H, q, *J* 7.0, $CO_2\underline{CH_2}CH_3$, **211**); δ_C(62.5MHz, $CDCl_3$), 14.6 ($CO_2CH_2\underline{C}H_3$, **211**), 23.9 ($NCH_2\underline{C}H_2$, **211**), 30.8 ($NCH\underline{C}H_2$, **211**), 47.0 ($N\underline{C}H_2CH_2$, **211**), 53.4 ($CO_2\underline{C}H_2CH_3$, **211**), 60.3 ($N\underline{C}H$, **211**), 63.9 ($\underline{C}H_2OMe$, **211**), 66.5 ($CH_2O\underline{Me}$, **211**), 173.7 ($\underline{C}O_2CH_2CH_3$, **211**).

The residue was put onto a silica column, eluent was ethyl acetate : methanol (95 : 5), the compound decomposed but no starting material or product was recovered.

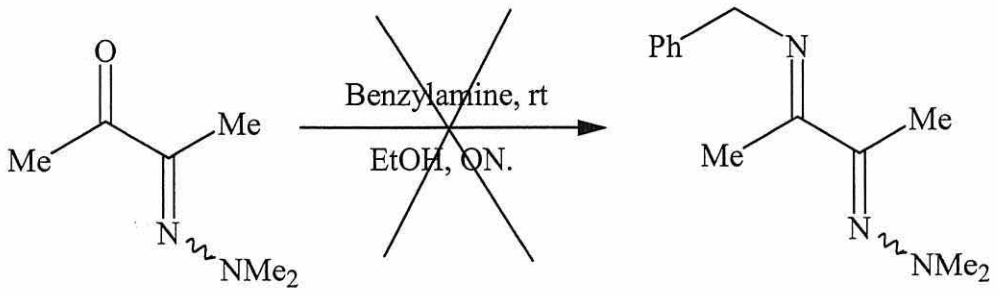
9.22 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triethyl Phosphonoacetate



203 **217**

Sodium hydride (60% dispersion in mineral oil, 0.75 g, 31.2 mmol) was washed with anhydrous petrol and suspended in anhydrous ether (30 mL). To the sodium hydride/ether suspension was added drop-wise a solution of triethyl phosphonoacetate (6.19 mL, 31.2 mmol) in anhydrous ether (10 mL) at 0°C over 10 mins and the resultant solution stirred for 30 mins under nitrogen. A solution of 2,3-butanedione mono-dimethylhydrazone, **203** (2.00 g, 15.6 mmol) in anhydrous ether (10 mL) was added drop-wise under nitrogen at 0°C over 5 mins. Water (30 mL) and ether (30 mL) were added, and the layers separated, the aqueous layer was further extracted with ether (30 mL). The combined organic layers were washed with water (10 mL), dried over magnesium sulfate and filtered. The solvent was remover under reduced pressure to yield a yellow oil (2.74 g, 89%); ν_{max}/cm^{-1} 1687.8 (C=O); δ_H(250MHz, $CDCl_3$), 1.28 (3 H, m, $\underline{CH_3}$-C=N-, **203**), 1.95 (3 H, m, $\underline{CH_3}$-C=O, **203**), 2.92 (6 H, m, N$\underline{Me_2}$, **203**); δ_C(62.5MHz, $CDCl_3$), 12.6 ($\underline{CH_3}$-C=N-, **203**), 24.4 ($\underline{CH_3}$-C=O, **203**), 46.8 (N$\underline{Me_2}$, **203**), 146.9 (CH_3-$\underline{C}$=N-, **203**), 198.9 (CH_3-$\underline{C}$=O, **203**).

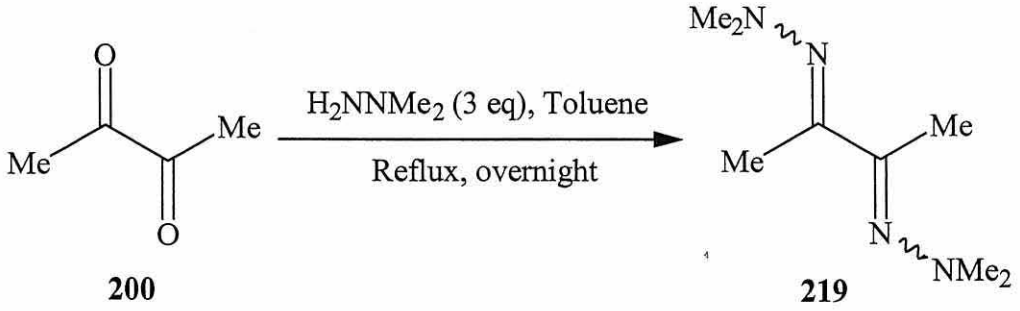
9.23 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Benzylamine



203 **218**

Benzylamine (1.70 mL, 15.6 mmol) was added to a solution of 2,3-butanedione mono-dimethylhydrazone **203** (2.00 g, 15.6 mmol) in anhydrous ethanol (20 mL) and stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to yield a yellow oil (2.70 g, 80%); ν_{max}/cm^{-1} 1679.6 (C=O); δ_H(250MHz, $CDCl_3$), 1.12 (1 H, m, unknown), 1.20 (1 H, m, unknown), 1.45 (1 H, m, unknown), 1.90 (3 H, s, $\underline{CH_3}$-C=N-, **203**), 2.14 (1 H, s, unknown), 2.17 (1 H, s, unknown), 2.21 (3 H, s, $\underline{CH_3}$-C=O, **203**), 2.29 (1 H, s, unknown), 2.36 (1 H, m, unknown), 2.50 (1 H, m, unknown), 2.87 (6 H, s, N$\underline{Me_2}$, **203**) 3.10 (1 H, s, unknown), 3.14 (1 H, s, unknown); δ_C(62.5MHz, $CDCl_3$), 12.6 ($\underline{CH_3}$-C=N-, **203**), 18.2 (unknown), 24.3 ($\underline{CH_3}$-C=O, **203**), 24.4 (unknown), 24.5 (unknown), 24.6 (unknown), 25.5 (unknown), 26.9 (unknown), 34.1 (unknown), 34.3 (unknown), 46.7 (N$\underline{Me_2}$, **203**), 57.8 (unknown), 74.6 (unknown), 102.4 (unknown), 118.7 (unknown), 138.1 (unknown), 138.5 (unknown), 146.6 (CH_3-$\underline{C}$=N-, **203**), 167.2 (unknown), 168.7 (unknown), 198.8 (CH_3-$\underline{C}$=O, **203**) 200.2 (unknown).

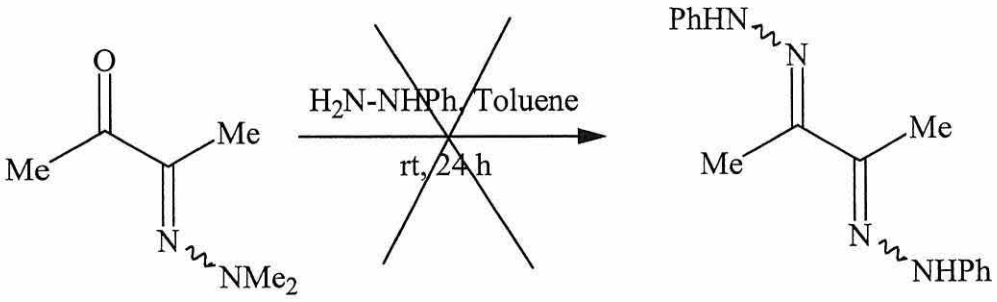
9.24 Preparation of the Bis-Hydrazone[176], 219



200 **219**

N,N-Dimethylhydrazine (5.25 mL, 69 mmol) was added to a solution of 2,3-butanedione, **200** (2.00 g, 23 mmol) in anhydrous toluene (30 mL) and heated to reflux overnight. Once cooled, the solvent was removed under reduced pressure to yield the crude product as a yellow oil (2.79 g, 71%); ν_{max}/cm^{-1} 1687.1 (C=O); δ_H(250MHz, $CDCl_3$), 2.05 (3 H, s, $\underline{CH_3}$-C=N-, **219**), 2.55 (6 H, s, N$\underline{Me_2}$, **219**).

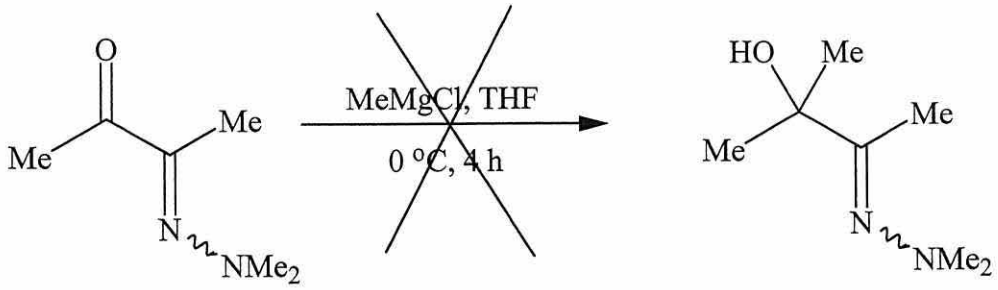
9.25 Reaction of 2,3-Butanedione with Phenylhydrazine



203 **220**

Phenylhydrazine (6.79 mL, 69.0 mmol) was added to a solution of 2,3-butanedione **200** (2.00 g, 23.0 mmol) in anhydrous toluene (30 mL) and stirred for 24 hours. The resulting solution was filtered and the precipitate washed with anhydrous toluene (5 mL). The solvent was removed under reduced pressure to yield a yellow solid (4.21 g, **200**, 17%; mono-hydrazone, 50%); ν_{max}/cm^{-1} 1600.3 (C=N); δ_H(250MHz, $CDCl_3$), 1.29 (1 H, s, $\underline{CH_3}$-C=N-, mono-hydrazone), 2.24 (1 H, s, $\underline{CH_3}$-C=O, **200**), 3.66 (1 H, br, N$\underline{H}$, mono-hydrazone), 6.85 (4 H, m, Ph 3-$\underline{CH}$, mono-hydrazone), 7.27 (4 H, m, Ph 2-$\underline{CH}$, mono-hydrazone), 7.39 (2 H, m, Ph 4-$\underline{CH}$, mono-hydrazone); δ_C(62.5MHz, $CDCl_3$), 9.2 ($\underline{CH_3}$-C=N-, mono-hydrazone), 31.2 ($\underline{CH_3}$-C=O, **200**), 112.1 (Ph 4-$\underline{CH}$, mono-hydrazone), 119.4 (Ph 3-$\underline{CH}$, mono-hydrazone), 129.3 (Ph 2-$\underline{CH}$, mono-hydrazone), 151.3 (Ph 1-$\underline{C}$, mono-hydrazone), 156.3 (CH_3-$\underline{C}$=N-, mono-hydrazone), 189.4 (CH_3-$\underline{C}$=O, **200**).

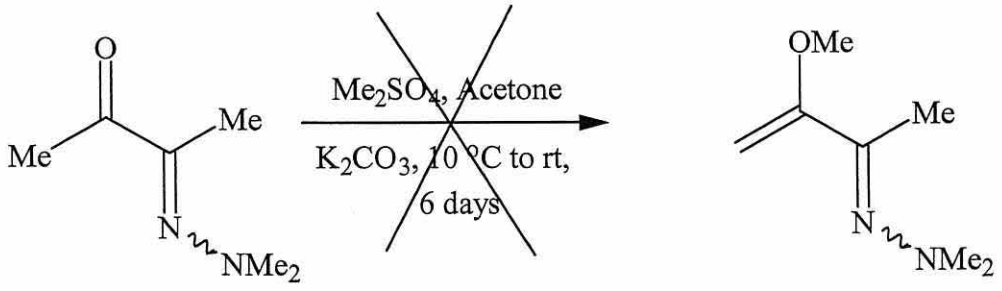
9.26 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Methyl Magnesium Chloride



203 **221**

Methylmagnesium chloride (3.0 M in THF, 1.15 mL, 15.6 mmol) was added to a solution of 2,3-butanedione mono-dimethylhydrazone, **203** (2.00 g, 15.6 mmol) in anhydrous THF (20 mL) at 0°C and stirred for 4 hours. The resultant solution was filtered and the solvent removed under reduced pressure to yield an orange oil (2.22 g, 99%); ν_{max}/cm^{-1} 1678.4 (C=O); δ_H(250MHz, $CDCl_3$), 1.17 (2 H, m, unknown), 1.93 (3 H, m, $\underline{CH_3}$-C=N-, **203**), 2.11 (1 H, m, unknown), 2.25 (3 H, m, $\underline{CH_3}$-C=O, **203**), 2.42 (1 H, m, unknown), 2.53 (2 H, m, unknown), 2.90 (6 H, m, N$\underline{Me_2}$, **203**), 3.69 (2 H, m, unknown); δ_C(62.5MHz, $CDCl_3$), 12.5 ($\underline{CH_3}$-C=N-, **203**), 12.6 (unknown), 20.3 (unknown), 24.2 ($\underline{CH_3}$-C=O, **203**), 24.4 (unknown), 24.5 (unknown), 25.5 (unknown), 27.8 (unknown), 46.7 (N$\underline{Me_2}$, **203**), 67.5 (unknown), 67.9 (unknown), 68.0 (unknown), 88.4 (unknown), 146.8 (CH_3-$\underline{C}$=N-, **203**), 198.8 (CH_3-$\underline{C}$=O, **203**).

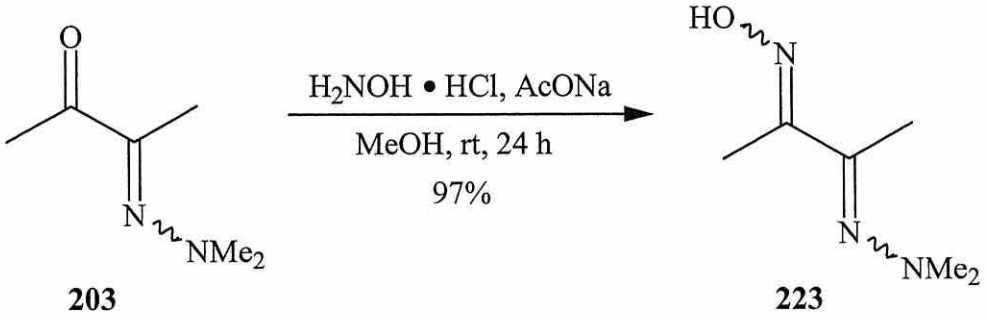
9.27 Methylation of 2,3-Butanedione Mono-dimethylhydrazone



203 **222**

Dimethyl sulfate (1.48 mL, 15.6 mmol) was added slowly to a mixture of 2,3-butanedione mono-dimethylhydrazone, **203** (2.00 g, 15.6 mmol) and potassium carbonate (3.23 g, 23.4 mmol) in acetone (15 mL) at 10°C, under nitrogen. The mixture was left to warm slowly to room temperature and stirred for 6 days. The red mixture was poured into ice-water (45 mL) and stirred for 30 mins. The resultant mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic extracts dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield a dark yellow oil (1.27 g, 57%); ν_{max}/cm^{-1} 1687.3 (C=O); δ_H(250MHz, $CDCl_3$), 1.92 (3 H, m, $\underline{CH_3}$-C=N-, **203**), 2.23 (3 H, m, $\underline{CH_3}$-C=O, **203**), 2.89 (6 H, m, N$\underline{Me_2}$, **203**); δ_C(62.5MHz, $CDCl_3$), 12.6 ($\underline{CH_3}$-C=N-, **203**), 24.3 ($\underline{CH_3}$-C=O, **203**), 46.7 (N$\underline{Me_2}$, **203**), 146.8 (CH_3-$\underline{C}$=N-, **203**), 198.8 (CH_3-$\underline{C}$=O, **203**).

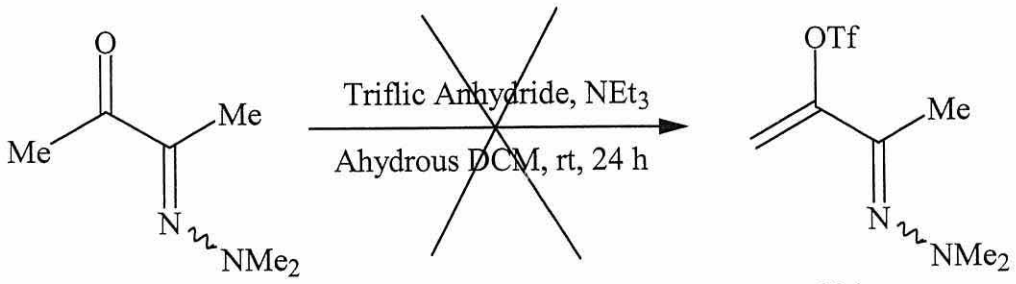
9.28 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Hydroxylamine Hydrochloride



203 **223**

Sodium acetate (1.28 g, 15.6 mmol) and hydroxylamine hydrochloride (1.08 g, 15.6 mmol) were added successively to a solution of 2,3-butanedione mono-dimethylhydrazone **203** (2.00 g, 15.6 mmol) in methanol (25 mL) at room temperature and stirred for 24 hours. The resultant solution was filtered and the solvent removed under reduced pressure to yield the crude product **223** as an orange oil, (2.16 g, 97%); ν_{max}/cm^{-1} 3225.8br (OH); δ_H(250MHz, $CDCl_3$), 2.07 (3 H, s, $\underline{CH_3}$-C=N-NMe_2), 2.11 (3 H, s, $\underline{CH_3}$-C=N-OH), 2.60 (3 H, s, N$\underline{Me_2}$) 7.45 (1 H, br, OH); δ_C(62.5MHz, $CDCl_3$), 13.9 ($\underline{CH_3}$-C=N-NMe_2), 21.3 ($\underline{CH_3}$-C=N-OH), 47.2 (N$\underline{Me_2}$), 156.3 (CH_3-$\underline{C}$=N-NMe_2), 176.2 (CH_3-$\underline{C}$=N-OH). The data was in good agreement with the literature[178].

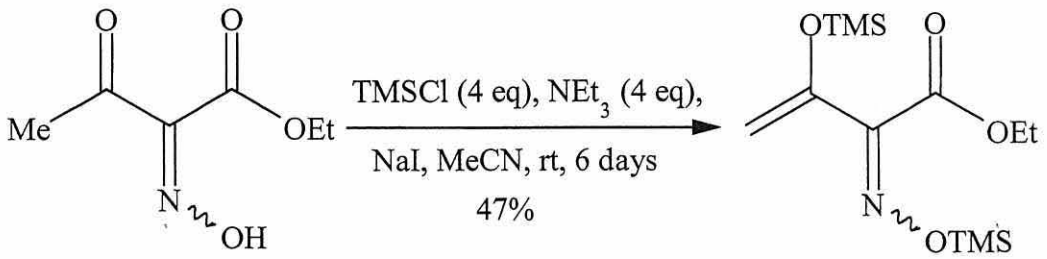
9.29 Reaction of 2,3-Butanedione Mono-dimethylhydrazone with Triflic Anhydride



203 **224**

Triflic anhydride (1.45 mL, 8.6 mmol) was added cautiously to a stirred solution of 2,3-butanedione mono-dimethylhydrazone, **203** (1.00 g, 7.8 mmol) and triethylamine (1.20 mL, 8.6 mmol) in anhydrous dichloromethane (20 mL) at room temperature and stirred for 24 hours. The resulting solution was poured into water (10 mL) and extracted with ether (4 x 20 mL). The combined ether extracts were washed with water (20 mL), 10% aqueous hydrochloric acid (20 mL), water (20 mL) and brine (20 mL). The organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a dark brown oil (0.16 g); ν_{max}/cm^{-1} 1686.6 (C=O); δ_H(250MHz, $CDCl_3$), 1.10 (1 H, m, unknown), 1.19 (1 H, m, unknown), 1.40 (1 H, m, unknown), 1.87 (3 H, s, $\underline{CH_3}$-C=N-, **203**), 2.11 (1 H, s, unknown), 2.15 (1 H, s, unknown), 2.19 (3 H, s, $\underline{CH_3}$-C=O, **203**), 2.27 (1 H, s, unknown), 2.34 (1 H, m, unknown), 2.46 (1 H, m, unknown), 2.85 (6 H, m, N$\underline{Me_2}$, **203**), 3.08 (1 H, s, unknown), 3.12 (1 H, s, unknown); δ_C(62.5MHz, $CDCl_3$), 12.5 ($\underline{CH_3}$-C=N-, **203**), 18.2 (unknown), 24.2 ($\underline{CH_3}$-C=O, **203**), 24.4 (unknown), 24.5 (unknown), 24.6 (unknown), 25.5 (unknown), 26.9 (unknown), 34.1 (unknown), 34.3 (unknown), 46.7 (N$\underline{Me_2}$, **203**), 138.1 (unknown), 146.6 (CH_3-$\underline{C}$=N-, **203**), 168.7 (unknown), 198.7 (CH_3-$\underline{C}$=O, **203**) 199.0 (unknown), 200.2 (unknown), 212.7 (unknown).

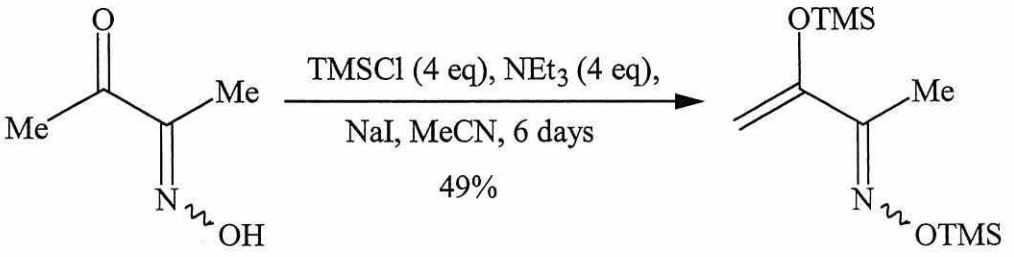
9.30 Exhaustive Trimethylsilylation of Ethyl Oximino Acetoacetate[85]



187 **228**

Triethylamine (35.1 mL, 252 mmol) and chlorotrimethylsilane (32.0 mL, 252 mmol) were added successively to a solution of ethyl oximino acetoacetate, **187** (10.00 g, 63 mmol) and sodium iodide (9.44 g, 63 mmol) in anhydrous acetonitrile (205 mL) at room temperature, under nitrogen and stirred for 6 days. The resultant solution was filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield a brown solid. Anhydrous ether (80 mL) was added to the solid, the solution filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield the crude product as a black oil (9.08 g, 47%); ν_{max}/cm^{-1} 3363.5br (OH), 1750.2 (C=O), 1701.1 (C=C); δ_H(250MHz, $CDCl_3$), 0.22 (18 H, s, OTMS), 1.32 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$), 4.33 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$), 4.69 (2 x 1 H, d, *J* 1.8, $C=\underline{CH_2}$), 4.71 (1 H, d, *J* 1.8, $C=\underline{CH_2}$); δ_C(62.5MHz, $CDCl_3$), -0.5 (OTMS), 14.1 ($OCH_2\underline{CH_3}$), 61.5 ($O\underline{CH_2}CH_3$), 100.9 ($C=\underline{CH_2}$), 148.4 ($\underline{C}$=N-OTMS), 155.1 ($\underline{C}O_2Et$), 163.3 ($\underline{C}=CH_2$).

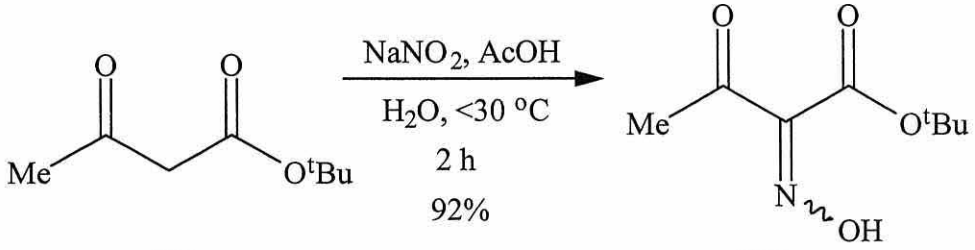
9.31 Exhaustive Trimethylsilylation of 2,3-Butanedione Monoxime[85]



229 **230**

Triethylamine (55.2 mL, 396 mmol) and chlorotrimethylsilane (50.3 mL, 396 mmol) were added successively to a solution of 2,3-butanedione monoxime, **229** (10.00 g, 98.9 mmol) and sodium iodide (14.82 g, 98.9 mmol) in anhydrous acetonitrile (330 mL) at room temperature, under nitrogen and stirred for 6 days. The resultant solution was filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield a brown solid. Anhydrous ether (80 mL) was added to the solid, the solution filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield the crude product as an orange oil (9.20 g, 49%); ν_{max}/cm^{-1} 3366.6br (OH), 1749.3 (C=O), 1702.0 (C=C); δ_H(250MHz, $CDCl_3$), 0.22 (18 H, s, OTMS), 1.97 (3 H, s, $\underline{CH_3}$-C=N), 4.55 (1 H, d, *J* 1.0, C=$\underline{CH_2}$), 4.82 (1 H, d, *J* 1.0, C=$\underline{CH_2}$); δ_C(62.5MHz, $CDCl_3$), -0.6 (OTMS), 11.0 ($\underline{CH_3}$-C=N), 97.3 (C=$\underline{CH_2}$), 153.3 (CH_3-$\underline{C}$=N), 157.4 ($\underline{C}$=CH_2).

9.32 Preparation of ^{t}Butyl Oximino Acetoacetate[152]

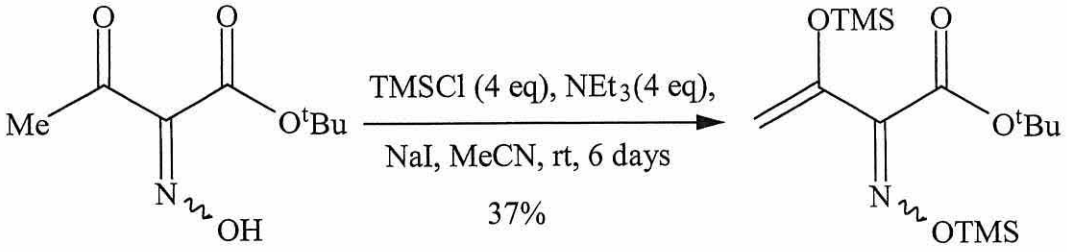


231 **232**

A solution of sodium nitrite (19.18 g, 278 mmol) in water (50 mL) was added slowly to a solution of ^{t}butyl acetoacetate (40.00 g, 253 mmol) in acetic acid (36 mL), cooled in a salt-ice bath. The temperature of the reaction mixture was maintained below 30°C during the addition. The orange solution was stirred at room temperature for a further 30 minutes, then water (150 mL) was added and the mixture stirred for a further 2 hours. The reaction mixture was extracted with ether (3 x 50 mL); the combined extracts were washed successively with water (25 mL), saturated $NaHCO_3$ (4 x 25 mL), and water (25 mL), then dried over sodium sulfate. The mixture was then evaporated to yield the crude product as a colourless oil, ethyl oximino acetoacetate **232** (43.76 g, 92%); ν_{max}/cm^{-1} 3300.4br (OH), 1729.5s ($CO_2{}^t$Bu), 1695.1s

(CH_3C=O), 1629.5s (C=N); δ_H(250MHz, $CDCl_3$), 1.53 (9 H, s, 3 x $\underline{CH_3}$, ^{t}Bu), 2.36 (3 H, s, $\underline{CH_3}$C=O), 10.74 (1 H, br, OH); δ_C(62.5MHz, $CDCl_3$), 14.8 ($\underline{CH_3}$C=O), 28.0 (3 x $\underline{CH_3}$, ^{t}Bu), 66.1 ($\underline{C}Me_3$, ^{t}Bu), 151.4 ($\underline{C}$=N-OH), 161.3 ($\underline{CO_2}^t$Bu), 194.5 ($CH_3\underline{C}$=O).

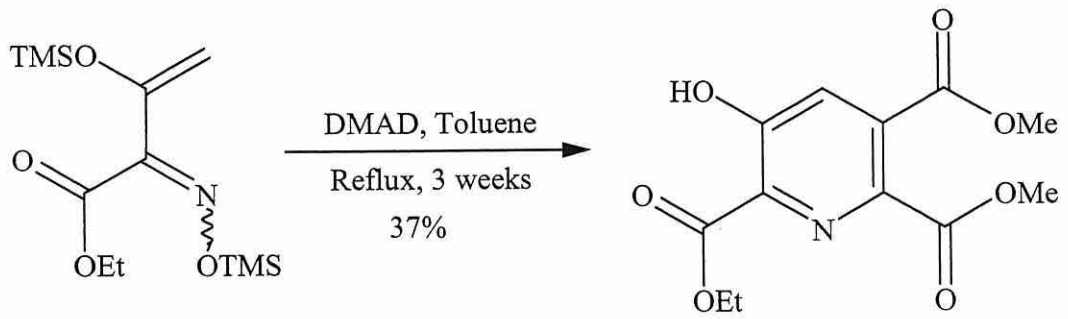
9.33 Exhaustive Trimethylsilylation of ^{t}Butyl Oximino Acetoacetate[85]



232 **233**

Triethylamine (29.8 mL, 214 mmol) and chlorotrimethylsilane (27.2 mL, 214 mmol) were added successively to a solution of ^{t}butyl oximino acetoacetate, **232** (10.00 g, 534 mmol) and sodium iodide (8.00 g, 534 mmol) in anhydrous acetonitrile (173 mL) at room temperature, under nitrogen and stirred for 6 days. The resultant solution was filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield a brown solid. Anhydrous ether (80 mL) was added to the solid, the solution filtered (under nitrogen) and the solvent removed under reduced pressure (calcium chloride drying tube used to release vacuum) to yield the crude product as a brown oil (6.56 g, 37%); ν_{max}/cm^{-1} 1730.1s ($CO_2{}^t$Bu), 1615.1s (C=N); δ_H(250MHz, $CDCl_3$), 0.20 (18 H, s, TMS), 1.50 (9 H, s, 3 x $\underline{CH_3}$, ^{t}Bu), 4.69 (2 x 1 H, d, C=$\underline{CH_2}$); δ_C(62.5MHz, $CDCl_3$), -0.1 (TMS), 27.9 (3 x $\underline{CH_3}$, ^{t}Bu), 65.8 ($\underline{C}Me_3$, ^{t}Bu), 100.8 (C=$\underline{CH_2}$), 148.6 ($\underline{C}$=N-OH), 155.5 ($\underline{CO_2}{}^t$Bu), 162.5 ($\underline{C}$=CH_2).

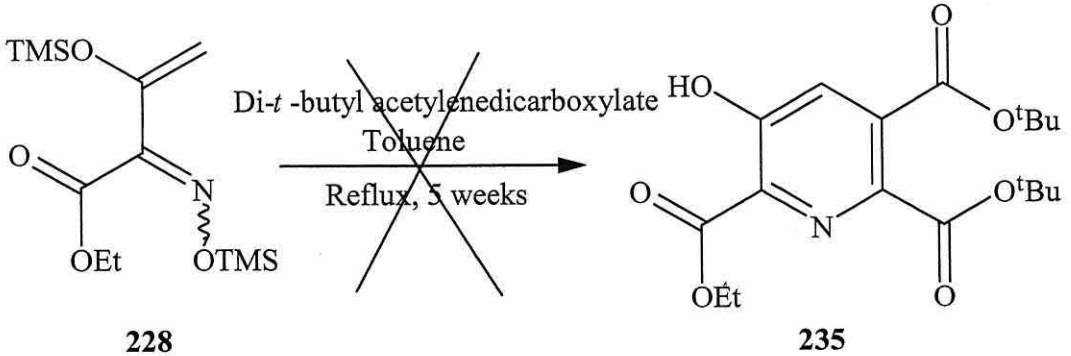
9.34 Synthesis of Highly Substituted Pyridine[85], 234



228 **234**

Dimethylacetylene dicarboxylate (0.70 g, 4.9 mmol) was added to a solution of the 1-aza-diene, **228** (1.50 g, 4.9 mmol) in anhydrous toluene (30 mL) and the mixture heated under reflux for 3 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a red oil, (1.34 g), which was purified by column chromatography with chloroform : methanol (99.5 : 0.5) as eluent to yield the pure product **234** as an orange oil (0.52 g, 39%); ν_{max}/cm^{-1} 1738.0s (C=O), 1681.7m (C=C); δ_H(250MHz, $CDCl_3$), 1.50 (3 H, t, *J* 7.1, $OCH_2\underline{CH_3}$), 3.96 (3 H, s, C=C-$CO_2\underline{Me}$), 3.97 (3 H, s, N=C-$CO_2\underline{Me}$), 4.56 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$), 7.67 (1 H, s, C=C-$\underline{H}$), 11.17 (1 H, s, $\underline{OH}$); δ_C(62.5MHz, $CDCl_3$), 14.0 ($OCH_2\underline{CH_3}$), 53.3 ($O\underline{Me}$), 63.4 ($O\underline{CH_2}CH_3$), 127.0 (C=$\underline{C}$-H), 129.4 (C=$\underline{C}$-OH), 131.2 (C=$\underline{C}$-CO_2Me), 135.8 (N=$\underline{C}$-CO_2Me & Et), 159.5 (C=C-$\underline{C}O_2$Me), 165.1 (N=C-$\underline{C}O_2$Et), 168.3 (N=C-$\underline{C}O_2$Me); *m/z* 284 $(M + H)^+$, calculated: 284.0765, measured: 284.0769, 226 (CO_2Me).

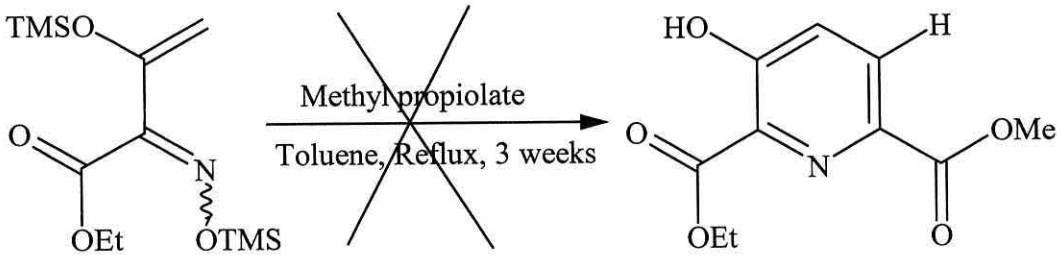
9.35 Attempted Synthesis of Highly Substituted Pyridine, 235



228 **235**

Di-*tert*-butyl acetylenedicarboxylate (0.75 g, 3.3 mmol) was added to a solution of the 1-aza-diene, **164** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown oil (1.33 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (0.98 g, 98%); ν_{max}/cm^{-1} 3285.4br (OH), 1728.9w (CO_2Et), 1681.2w ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.28 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**), 2.35 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.31 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 25.1 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 150.9 ($\underline{C}$=N-OH, **187**), 162.2 ($\underline{C}O_2Et$, **187**), 194.4 ($CH_3\underline{C}=O$, **187**).

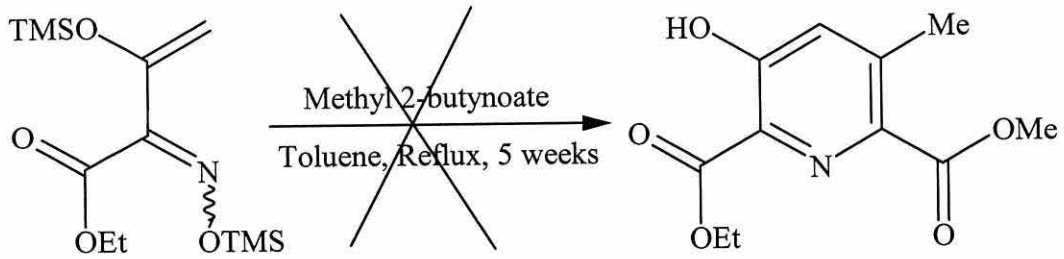
9.36 Attempted Synthesis of Highly Substituted Pyridine, 240



228 **240**

Methyl propiolate (0.55 g, 6.6 mmol) was added to a solution of the 1-aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (50 mL) and heated under reflux for 3 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a yellow oil (2.79 g); ν_{max}/cm^{-1} 3353.7br (OH), 1702.9s, br (CO_2Et), 1599.5w (C=C); δ_H(250MHz, $CDCl_3$), 0.13 (1 H, m, TMS), 1.42 (2 H, m, $OCH_2\underline{CH_3}$, **187**), 2.37 (2 H, m, $\underline{CH_3}C=O$, **187**), 3.86 (2 H, m, unknown), 4.36 (2 H, m, $O\underline{CH_2}CH_3$, **187**), 4.71 (1 H, s, unknown), 5.28 (3 H, m, unknown) 7.44 (20 H, m, unknown), 7.90 (2 H, m, unknown), 8.12 (3 H, m, unknown); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 65.3 ($O\underline{CH_2}CH_3$, **187**), 125.3 (unknown), 127.0 (unknown), 127.4 (unknown), 127.6 (unknown), 128.2 (unknown), 128.4 (unknown), 128.5 (unknown), 128.8 (unknown), 129.0 (unknown), 129.6 (unknown), 129.8 (unknown), 130.1 (unknown), 132.3 (unknown), 133.5 (unknown), 134.5 (unknown), 156.3 ($\underline{C}$=N-OH, **187**), 192.3 ($CH_3\underline{C}=O$, **187**).

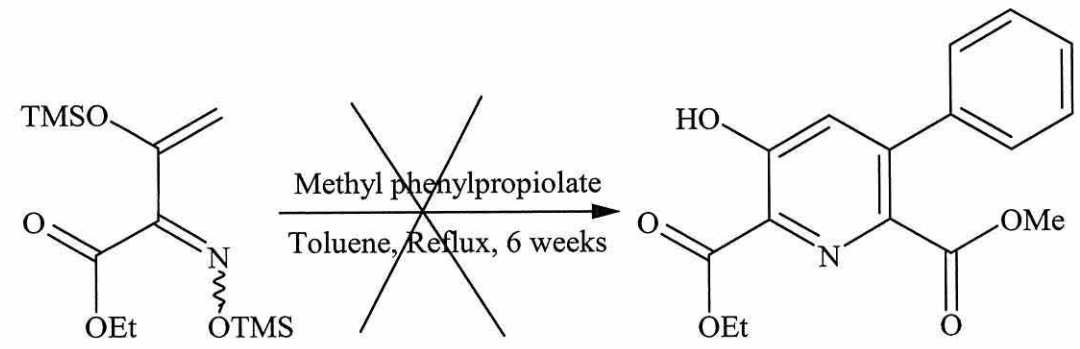
9.37 Attempted Synthesis of Highly Substituted Pyridine, 241



228 **241**

Methyl 2-butynoate (0.36 mLs, 3.6 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as an orange oil (1.52 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (0.41 g, 41%); ν_{max}/cm^{-1} 3314.7br (OH), 1733.1m (CO_2Et), 1675.6m ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.31 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.36 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.33 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 25.1 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 194.3 ($CH_3\underline{C}=O$, **187**).

9.38 Attempted Synthesis of Highly Substituted Pyridine, 242

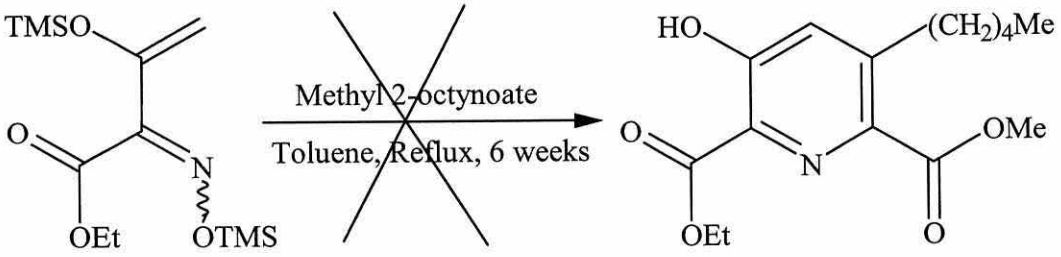


228 **242**

Methyl phenylpropiolate (0.86 g, 5.4 mmol) was added to a solution of the 1-aza-diene, **228** (1.50 g, 4.9 mmol) in anhydrous toluene (50 mL) and heated to reflux for 6

weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as an orange oil (1.93 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.33 g, 89%); ν_{max}/cm^{-1} 3315.6br (OH), 1732.8m (CO_2Et), 1676.7m ($CH_3C=O$), 1629.3w (C=N); δ_H(250MHz, $CDCl_3$), 1.31 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.37 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.34 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 25.2 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 194.3 ($CH_3\underline{C}=O$, **187**).

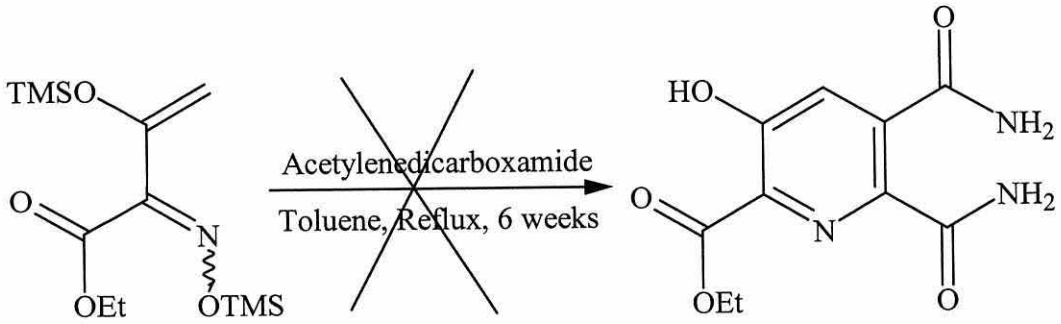
9.39 Attempted Synthesis of Highly Substituted Pyridine, 243



228 **243**

Methyl 2-octynoate (0.61 mLs, 3.6 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and refluxed for 6 weeks. The solvent was removed under reduced pressure to yield the crude product as a brown oil (1.52 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (0.67 g, 67%); ν_{max}/cm^{-1} 3317.8br (OH), 1729.3m (CO_2Et), 1673.4m ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.30 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.36 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.33 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 13.9 ($[CH_2]_4\underline{Me}$, dienophile), 14.8 ($[\underline{CH_2}]_4Me$, dienophile), 17.6 ($[\underline{CH_2}]_4Me$, dienophile), 20.6 ($[\underline{CH_2}]_4Me$, dienophile), 25.1 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 66.1 ($O\underline{Me}$, dienophile), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 176.4 (C≡C, dienophile), 194.4 ($CH_3\underline{C}=O$, **187**), 197.8 (C=O, dienophile).

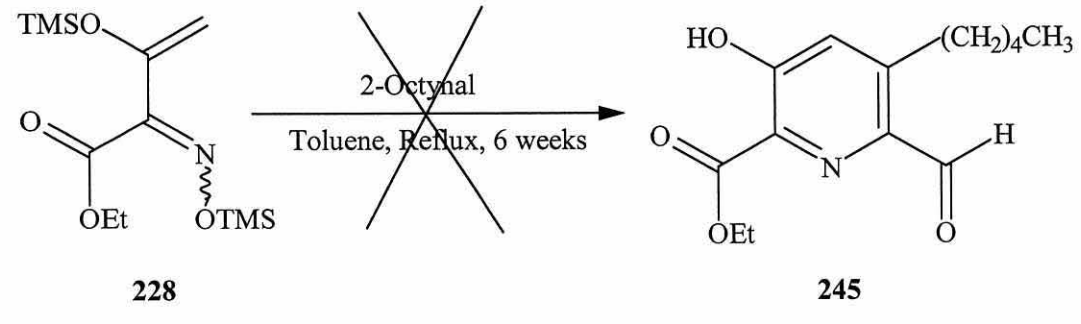
9.40 Attempted Synthesis of Highly Substituted Pyridine, 244



228 **244**

Acetylenedicarboxamide (0.61 g, 5.4 mmol) was added to a solution of the 1-aza-diene, **164** (1.50 g, 4.9 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as an orange oil (1.52 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.29 g, 86%); ν_{max}/cm^{-1} 3314.8br (OH), 1729.4m (CO_2Et), 1682.8m ($CH_3C=O$), 1629.0w (C=N); δ_H(250MHz, $CDCl_3$), 1.28 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.34 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.30 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.7 ($OCH_2\underline{CH_3}$, **187**), 13.8 (unknown), 14.7 (unknown), 20.6 (unknown), 25.1 ($\underline{CH_3}C=O$, **187**), 30.1 (unknown), 62.2 ($O\underline{CH_2}CH_3$, **187**), 66.1 (unknown), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 176.3 (C≡C, dienophile), 194.5 ($CH_3\underline{C}=O$, **187**), 197.9 (C=O, dienophile).

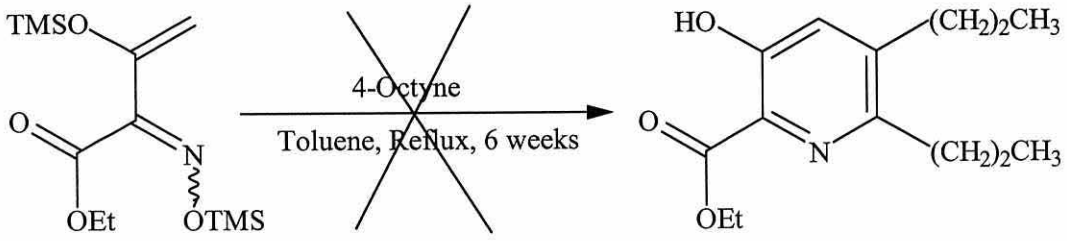
9.41 Attempted Synthesis of Highly Substituted Pyridine, 245



228 **245**

2-Octynal (0.67 g, 5.4 mmol) was added to a solution of the 1-aza-diene, **228** (1.50 g, 4.9 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a red oil (1.85 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.02 g, 68%); ν_{max}/cm^{-1} 3315.1br (OH), 1728.4m (CO_2Et), 1682.4m ($CH_3C=O$), 1628.7 (C=N); δ_H(250MHz, $CDCl_3$), 1.29 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.35 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.31 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 14.7 (solvent), 20.6 (solvent), 25.1 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 66.1 (unknown), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 176.3 (solvent), 194.4 ($CH_3\underline{C}=O$, **187**), 197.9 (unknown).

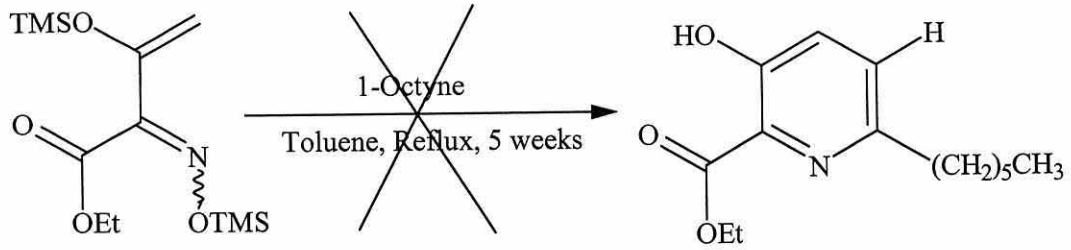
9.42 Attempted Synthesis of Highly Substituted Pyridine, 246



228 **246**

4-Octyne (0.48 mls, 3.3 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown oil (1.37 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil, (0.95 g, 95%); ν_{max}/cm^{-1} 3316.3br (OH), 1729.8m (CO_2Et), 1628.8 (C=N); δ_H(250MHz, $CDCl_3$), 1.32 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.36 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.33 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 14.8 (solvent), 20.6 (solvent), 25.1 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**), 66.1 (unknown), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 176.4 (solvent), 194.3 ($CH_3\underline{C}=O$, **187**).

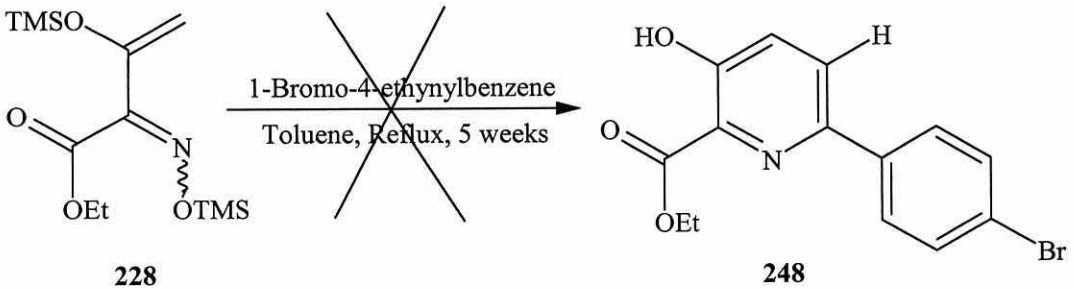
9.43 Attempted Synthesis of Highly Substituted Pyridine, 246



228 **247**

1-Octyne (0.48 mls, 3.3 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as an orange/brown oil (0.79 g, **187**, 67%, **228**, 33%, as determined by ^{1}H NMR spectroscopy); ν_{max}/cm^{-1} 3333.2br (OH), 1750.4m (CO_2Et), 1701.3m ($CH_3C=O$), 1630.1w (C=N); δ_H(250MHz, $CDCl_3$), 0.16 (6 H, s, OTMS, **228**), 1.26 (3 H, 2 x t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**, **228**), 2.33 (1 H, s, $\underline{CH_3}C=O$, **187**), 4.27 (2 H, 2 x q, *J* 7.0, $O\underline{CH_2}CH_3$, **187**, **228**), 4.63 (1 H, 2 x d, *J* 1.7, $C=\underline{CH_2}$, **228**); δ_C(62.5MHz, $CDCl_3$), -0.2 (OTMS), 13.9 ($OCH_2\underline{CH_3}$, **187**, **228**), 25.1 ($\underline{CH_3}C=O$, **187**), 61.2 ($O\underline{CH_2}CH_3$, **187**, **228**), 100.8 ($C=\underline{CH_2}$, **228**), 148.4 (C=N-OR, **187**, **228**), 155.1 ($\underline{C}O_2Et$, **187**, **228**), 163.2 ($\underline{C}=CH_2$, **228**), 193.2 ($CH_3\underline{C}=O$, **187**).

9.44 Attempted Synthesis of Highly Substituted Pyridine, 248

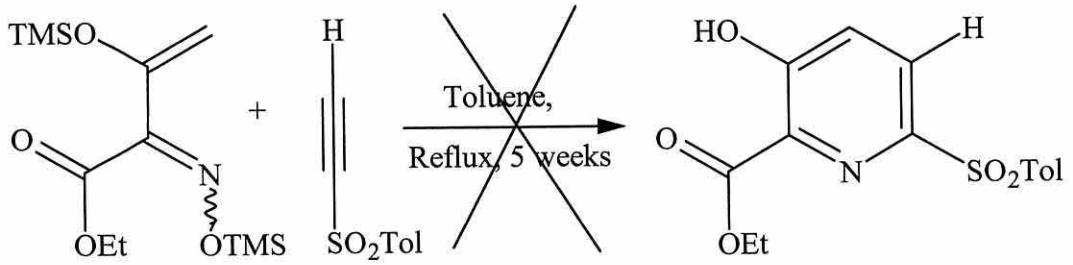


228 **248**

1-Bromo-4-ethynylbenzene (0.50 g, 2.8 mmol) was added to a solution of the 1-aza-diene, **228** (0.85 g, 2.8 mmol) in anhydrous toluene (30 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield a

brown oil (1.19 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (0.79 g, 93%); ν_{max}/cm^{-1} 3319.6br (OH), 1732.0m (CO_2Et), 1679.8m ($CH_3C=O$), 1629.3w (C=N); δ_H(250MHz, $CDCl_3$), 1.33 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.40 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.36 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 25.2 ($\underline{CH_3}C=O$, **187**), 62.5 ($O\underline{CH_2}CH_3$, **187**), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 194.5 ($CH_3\underline{C}=O$, **187**).

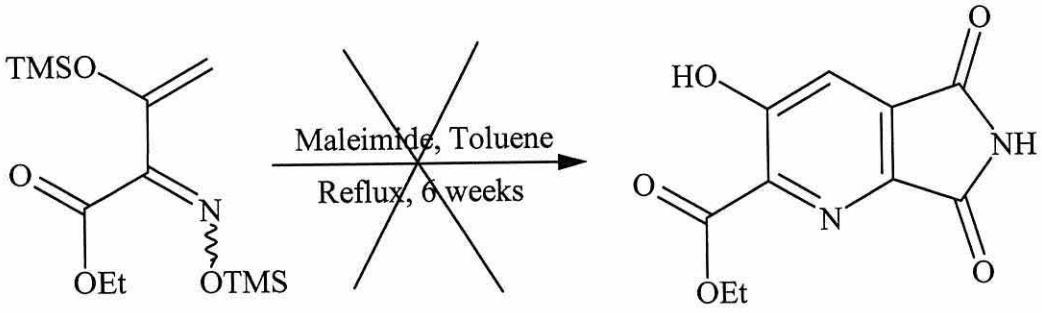
9.45 Attempted Synthesis of Highly Substituted Pyridine, 257



228 **256** **257**

Ethynyl *p*-tolyl sulfone (0.59 g, 3.3 mmol) was added to a solution of 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a dark brown oil (1.06 g, **187**, 67%, **228**, 33%, as determined by ^1H NMR spectroscopy); ν_{max}/cm^{-1} 3362.3br (OH), 1749.6s (CO_2Et), 1702.4s ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 0.17 (6 H, s, OTMS, **228**), 1.27 (3 H, 2 x t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**, **228**), 2.34 (1 H, s, $\underline{CH_3}C=O$, **187**), 4.27 (2 H, 2 x q, *J* 7.0, $O\underline{CH_2}CH_3$, **187**, **228**), 4.65 (1 H, 2 x d, *J* 1.8, $C=\underline{CH_2}$, **228**); δ_C(62.5MHz, $CDCl_3$), -0.2 (OTMS), 14.0 ($OCH_2\underline{CH_3}$, **187**, **228**), 25.1 ($\underline{CH_3}C=O$, **187**), 61.2 ($O\underline{CH_2}CH_3$, **187**, **228**), 100.8 ($C=\underline{CH_2}$, **228**), 148.4 ($\underline{C}$=N-OR, **187**, **228**), 154.8 ($\underline{C}O_2Et$, **187**, **228**), 163.2 ($\underline{C}=CH_2$, **228**), 193.2 ($CH_3\underline{C}=O$, **187**).

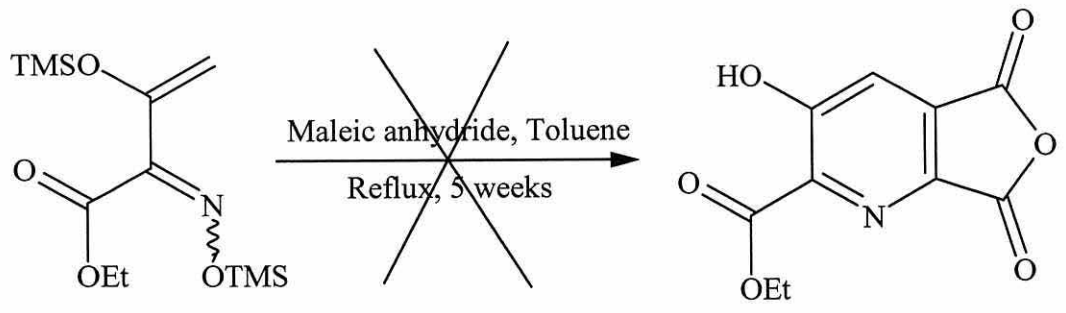
9.46 Attempted Synthesis of Highly Substituted Pyridine, 258



228 **258**

Maleimide (0.48 g, 4.9 mmol) was added to a solution of 1-aza-diene, **228** (1.50 g, 4.9 mmol) in anhydrous toluene (30 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield a brown oil (1.89 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.40 g, 93%); ν_{max}/cm^{-1} 3333.1br (OH), 1724.8s (CO_2Et), 1701.2s ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.32 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.38 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.35 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 25.2 ($\underline{CH_3}C=O$, **187**), 62.4 ($O\underline{CH_2}CH_3$, **187**), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 194.4 ($CH_3\underline{C}=O$, **187**).

9.47 Attempted Synthesis of Highly Substituted Pyridine, 264

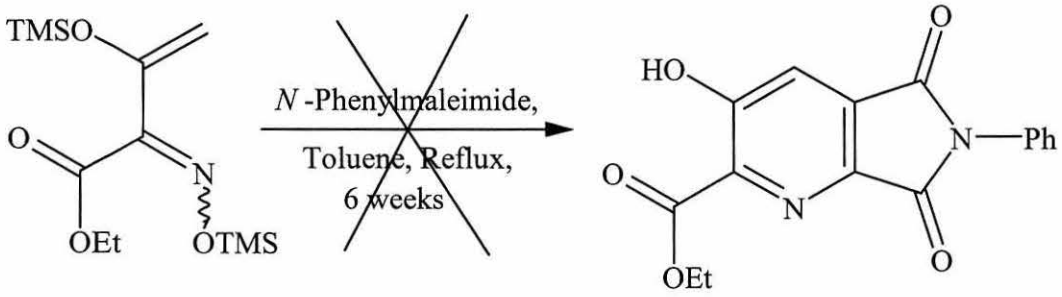


228 **264**

Maleic anhydride (0.65 g, 6.6 mmol) was added to a solution of 1-aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (40 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield a brown oil

(1.49 g); ν_{max}/cm^{-1} 3246.1br (OH), 1731.6s (CO_2Et), 1715.2 (C=O); δ_H(250MHz, $CDCl_3$), 0.07 (10 H, s, OTMS), 0.17 (3 H, s, OTMS), 0.30 (5 H, s, OTMS), 0.43 (2 H, s, OTMS), 1.34 (6 H, m, $OCH_2\underline{CH_3}$, **187**, unknown), 1.49 (2 H, m, $OCH_2\underline{CH_3}$, **228**), 2.36 (5 H, s, toluene), 2.44 (3 H, m, $\underline{CH_3}C=O$, **187**), 4.37 (3 H, m, $O\underline{CH_2}CH_3$, **187**, **228**), 4.54 (1 H, m, $C=\underline{CH_2}$, **228**), 7.03 (1 H, s, $\underline{HC}=\underline{CH}$, maleic anhydride), 7.19 (5 H, m, toluene), 7.26 (4 H, m, toluene), 8.02 (<1 H, 2 x d, unknown), 8.87 (<1 H, 2 x d, unknown), 10.81 (<1 H, br, OH); δ_C(62.5MHz, $CDCl_3$), -0.9 (OTMS), 1.3 (OTMS), 1.9 (OTMS), 14.1 ($OCH_2\underline{CH_3}$, **187**, **228**), 25.4 ($\underline{CH_3}C=O$, **187**), 62.3 ($O\underline{CH_2}CH_3$, **187**, **228**), 128.2 (C=N-OR), 129.0 (C=N-OR), 156.3 ($\underline{C}O_2Et$, **187**, **228**).

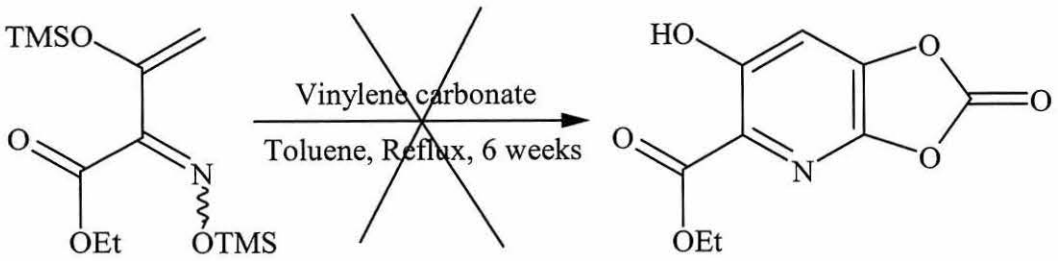
9.48 Attempted Synthesis of Highly Substituted Pyridine, 271



228 **271**

N-Phenylmaleimide (1.14 g, 6.6 mmol) was added to a solution of 1-aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (40 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield an orange oil, (2.01 g) which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.68 g, 84%); ν_{max}/cm^{-1} 3355.5br (OH), 1730.5w (CO_2Et), 1698.7w ($CH_3C=O$), 1622.3w (C=N); δ_H(250MHz, $CDCl_3$), 1.35 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.41 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.38 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 14.0 ($OCH_2\underline{CH_3}$, **187**), 25.3 ($\underline{CH_3}C=O$, **187**), 62.5 ($O\underline{CH_2}CH_3$, **187**), 151.1 (C=N-OH, **187**), 156.3 ($\underline{C}O_2Et$, **187**), 194.1 ($CH_3\underline{C}=O$, **187**).

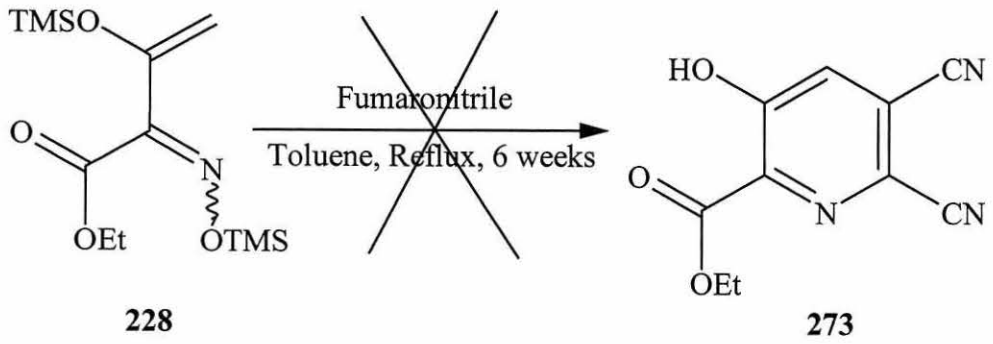
9.49 Attempted Synthesis of Highly Substituted Pyridine, 272



228 **272**

Vinylene carbonate (0.21 mLs, 3.3 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown oil (0.66 g, **187**, 67%, **228**, 33%, as determined by ^{1}H NMR spectroscopy); ν_{max}/cm^{-1} 3333.2br (OH), 1750.1m (CO_2Et), 1702.2m ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 0.03 (1 H, s, OTMS), 0.20 (4 H, s, OTMS), 0.25 (4 H, s, OTMS), 1.30 (3 H, 2 x t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**, **228**), 1.98 (<1 H, s, unknown), 2.36 (<1 H, s, unknown), 2.38 (1 H, s, $\underline{CH_3}C=O$, **187**), 4.32 (2 H, 2 x q, *J* 7.0, $O\underline{CH_2}CH_3$, **187**, **228**), 4.68 (1 H, 2 x d, *J* 1.8, $C=\underline{CH_2}$, **228**); δ_C(62.5MHz, $CDCl_3$), -1.0 (OTMS), -0.9 (OTMS), -0.1 (OTMS), 1.8(OTMS), 14.0 ($OCH_2\underline{CH_3}$, **187**, **228**), 25.2 ($\underline{CH_3}C=O$, **187**), 61.4 (unknown), 61.8 ($O\underline{CH_2}CH_3$, **187**, **228**), 61.9 ($O\underline{CH_2}CH_3$, **187**, **228**), 101.0 ($C=\underline{CH_2}$, **228**), 148.4 (<u>C</u>=N-OR, **187**, **228**), 151.1 (unknown), 154.8 (unknown), 155.0 ($\underline{C}O_2Et$, **187**, **228**), 156.3 ($\underline{C}O_2Et$, **187**, **228**), 161.6 (unknown), 163.4 ($\underline{C}=CH_2$, **228**), 193.6 ($CH_3\underline{C}=O$, **187**).

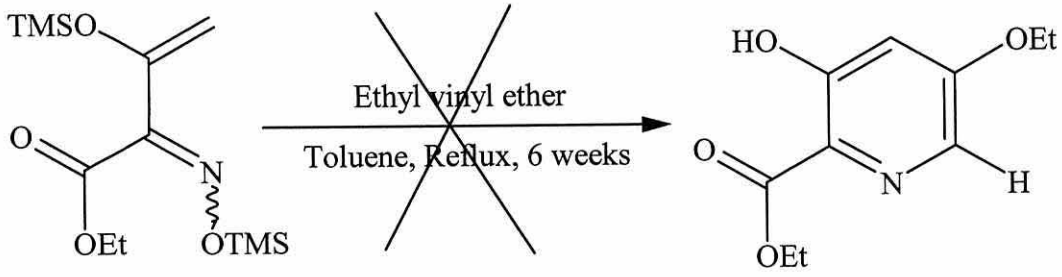
9.50 Attempted Synthesis of Highly Substituted Pyridine, 273



228 **273**

Fumaronitrile (0.38 g, 4.9 mmol) was added to a solution of the 1-aza-diene, **228** (1.50 g, 4.9 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown oil (1.43 g) which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (0.62 g, 41%); ν_{max}/cm^{-1} 3325.7br (OH), 1727.9m (CO_2Et), 1687.3m ($CH_3C=O$), 1629.2w (C=N); δ_H(250MHz, $CDCl_3$), 1.32 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.38 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.35 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 25.1 ($\underline{CH_3}C=O$, **187**), 62.4 ($O\underline{CH_2}CH_3$, **187**), 150.9 ($\underline{C}$=N-OH, **187**), 162.3 ($\underline{C}O_2Et$, **187**), 194.7 ($CH_3\underline{C}=O$, **187**).

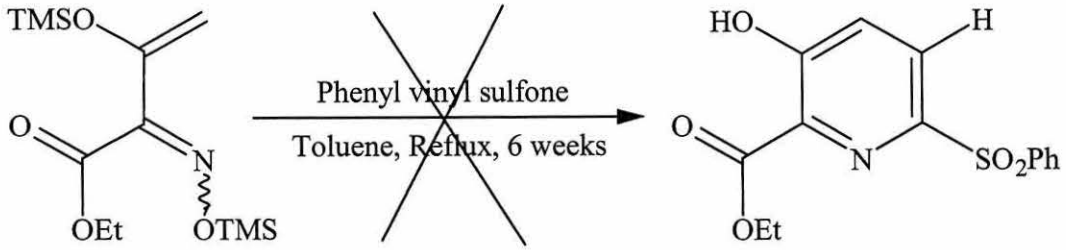
9.51 Attempted Synthesis of Highly Substituted Pyridine, 277



228 **277**

Ethyl vinyl ether (0.32 mLs, 3.3 mmol) was added to a solution of the 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled ether was added to aid solvent removal under reduced pressure to yield the crude product as a light brown oil (0.60 g); ν_{max}/cm^{-1} 3316.8br (OH), 1728.3w (CO_2Et), 1681.9w ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.15 (3 H, t, *J* 7.0, ether), 1.25 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**), 2.32 (3 H, s, $\underline{CH_3}C=O$, **187**), 3.47 (2 H, q, *J* 7.0, ether), 4.27 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**) 4.81 (<1 H, br, unknown); δ_C(62.5MHz, $CDCl_3$), 13.7 ($OCH_2\underline{CH_3}$, **187**), 13.8 (unknown), 14.7 (ether), 17.5 (unknown), 20.5 (unknown), 25.0 ($\underline{CH_3}C=O$, **187**), 30.1 (unknown), 62.2 ($O\underline{CH_2}CH_3$, **187**), 62.5 (unknown), 66.0 (ether), 149.6 (unknown), 150.9 ($\underline{C}$=N-OH, **187**), 160.8 (unknown), 162.2 ($\underline{C}O_2Et$, **187**), 194.5 ($CH_3\underline{C}=O$, **187**), 198.0 (unknown).

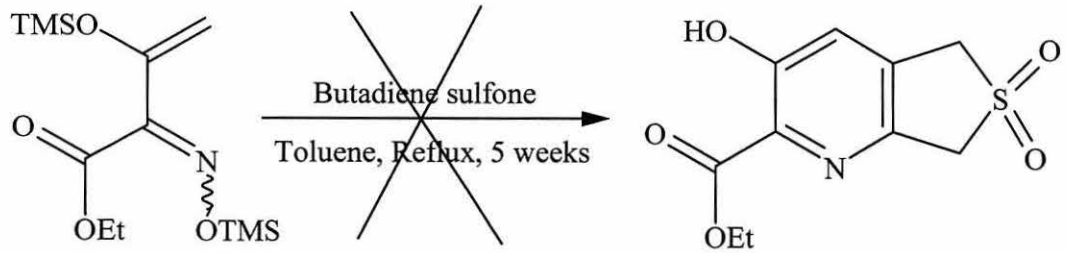
9.52 Attempted Synthesis of Highly Substituted Pyridine, 288



228 **288**

Phenyl vinyl sulfone (0.56 g, 3.3 mmol) was added to a solution of 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled ether was added to aid solvent removal under reduced pressure to yield the crude product as a brown oil (0.76 g); ν_{max}/cm^{-1} 3315.7br (OH), 1732.3w (CO_2Et), 1676.6w ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.20 (3 H, t, *J* 7.0, ether), 1.30 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**), 2.36 (3 H, s, $\underline{CH_3}C=O$, **187**), 3.53 (2 H, q, *J* 7.0, ether), 4.34 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.9 ($OCH_2\underline{CH_3}$, **187**), 14.8 (ether), 17.6 (unknown), 20.6 (unknown), 25.1 ($\underline{CH_3}C=O$, **187**), 30.1 (unknown), 62.3 ($O\underline{CH_2}CH_3$, **187**), 62.6 (unknown), 66.1 (ether), 149.6 (unknown), 151.0 ($\underline{C}$=N-OH, **187**), 162.1 ($\underline{C}O_2Et$, **187**), 176.4 (unknown), 194.3 ($CH_3\underline{C}=O$, **187**).

9.53 Attempted Synthesis of Highly Substituted Pyridine, 298

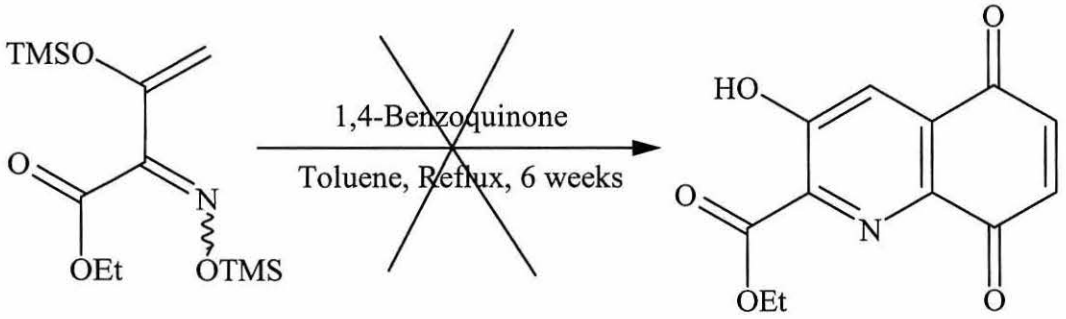


228 **298**

Butadiene sulfone (0.78 g, 6.6 mmol) was added to a solution of 1-aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (50 mL) and heated under reflux for 5 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a black oil (1.56 g); ν_{max}/cm^{-1} 3316.1br (OH), 1733.7m (CO_2Et), 1677.8m

(CH_3C=O), 1629.3w (C=N); δ_H(250MHz, $CDCl_3$), 0.21 (2 H, s, OTMS), 0.26 (2 H, s, OTMS), 0.28 (6 H, s, OTMS), 1.31 (4 H, m, $OCH_2\underline{CH_3}$, **187**, **228**), 2.15 (<1 H, s toluene), 2.36 (<1 H, s, unknown), 2.39 (2 H, s, $\underline{CH_3}C$=O, **187**), 4.32 (2 H, m, $O\underline{CH_2}CH_3$, **187**, **228**), 4.69 (<1 H, 2 x d, br, C=$\underline{CH_2}$, **228**), 7.13-7.37 (<1 H, m, toluene); δ_C(62.5MHz, $CDCl_3$), -11.7 (OTMS), -9.8 (OTMS), 13.8 ($OCH_2\underline{CH_3}$, **187**, **228**), 14.7 (unkown), 20.5 (uknown), 25.1 ($\underline{CH_3}C$=O, **187**), 30.1 (unknown) 62.4 ($O\underline{CH_2}CH_3$, **187**, **228**), 66.2 (unknown), 149.6 ($\underline{C}$=N-OTMS, **228**), 150.9 ($\underline{C}$=N-OH, **187**), 156.3 (unknown), 160.8 ($\underline{C}O_2Et$, **228**), 162.2 ($\underline{C}O_2Et$, **187**), 176.1 (unknown), 194.7 ($CH_3\underline{C}$=O, **187**) 198.2 (unknown).

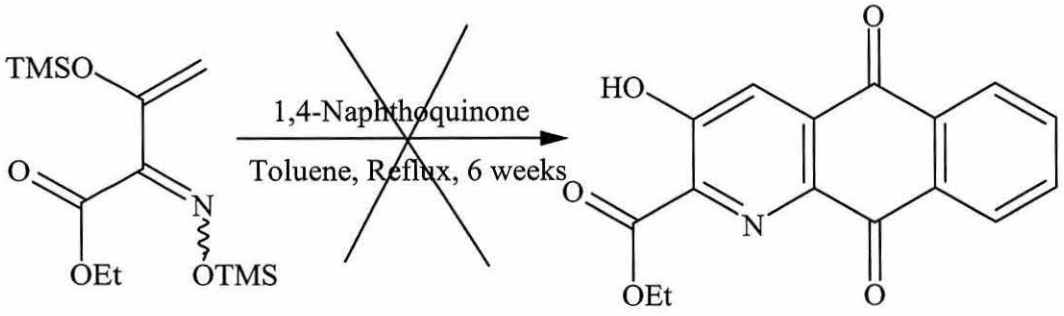
9.54 Attempted Synthesis of Highly Substituted Pyridine, 299



228 **299**

1,4-Benzoquinone (0.71 g, 6.6 mmol) was added to a solution of 1-aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a black oil, (2.38 g) which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.43g, 72%); ν_{max}/cm^{-1} 3313.9br (OH), 1734.9m (CO_2Et), 1675.0m (CH_3C=O), 1600.7w (C=N); δ_H(250MHz, $CDCl_3$), 1.34 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$, **187**), 2.40 (3 H, s, $\underline{CH_3}C$=O, **187**), 4.37 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$, **187**), 6.68 (<1 H, s, unknown), 10.73 (1 H, br, OH); δ_C(62.5MHz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 14.7 (unknown), 20.5 (unknown), 25.2 ($\underline{CH_3}C$=O, **187**), 30.2 (unknown), 62.5 ($O\underline{CH_2}CH_3$, **187**), 66.2 (unknown), 149.6 (unknown), 150.9 ($\underline{C}$=N-OH, **187**), 160.8 (unknown), 162.2 ($\underline{C}O_2Et$, **187**), 176.1 (unknown), 194.6 ($CH_3\underline{C}$=O, **187**), 198.1 (unknown).

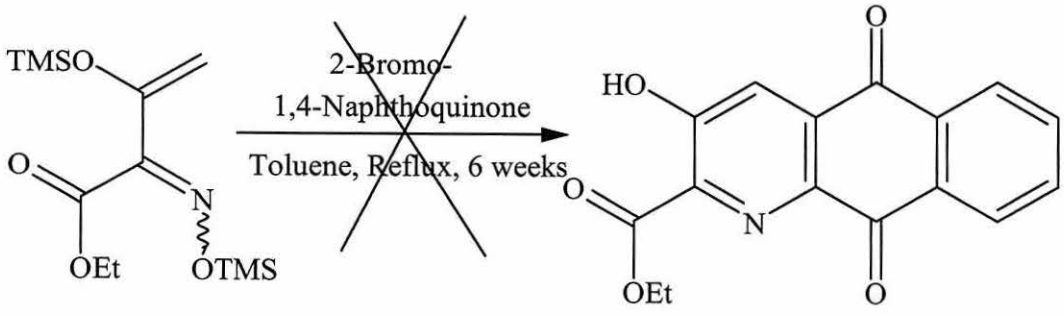
9.55 Attempted Synthesis of Highly Substituted Pyridine, 303



228 **303**

1,4-Naphthoquinone (1.04 g, 6.6 mmol) was added to a solution of the aza-diene, **228** (2.00 g, 6.6 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown solid (1.29 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil (1.32g, 66%); ν_{max}/cm^{-1} 3322.2br (OH), 1729.8m (CO_2Et), 1689.7m ($CH_3C=O$), 1629.3w (C=N); δ_H(250MHz, $CDCl_3$), 1.27 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**), 2.34 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.30 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(250Hz, $CDCl_3$), 13.8 ($OCH_2\underline{CH_3}$, **187**), 14.7 (unknown), 20.5 (unknown), 25.1 ($\underline{CH_3}C=O$, **187**), 30.1 (unknown), 62.4 ($O\underline{CH_2}CH_3$, **187**), 62.7 (unknown), 66.2 (unknown), 149.6 (unknown), 150.9 (C=N-OH, **187**), 160.8 (unknown), 162.3 ($\underline{C}O_2Et$, **187**), 176.0 (unknown), 194.8 ($CH_3\underline{C}=O$, **187**) 198.3 (unknown).

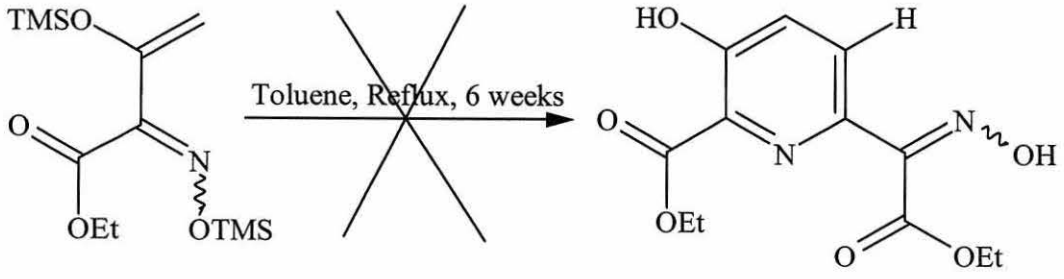
9.56 Attempted Synthesis of Highly Substituted Pyridine, 303



228 **303**

2-Bromo-1,4-naphthoquinone (0.85 g, 3.6 mmol) was added to a solution of 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) and heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown solid (1.76 g), which was purified by column chromatography with ethyl acetate as eluent to yield the precursor **187** as a colourless oil, (0.61 g, 61%); ν_{max}/cm^{-1} 3314.9br (OH), 1733.1w (CO_2Et), 1675.8w ($CH_3C=O$); δ_H(250MHz, $CDCl_3$), 1.27 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**), 2.34 (3 H, s, $\underline{CH_3}C=O$, **187**), 4.29 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$, **187**); δ_C(62.5MHz, $CDCl_3$), 13.7 ($OCH_2\underline{CH_3}$, **187**), 20.6 (unknown), 25.1 ($\underline{CH_3}C=O$, **187**), 62.2 ($O\underline{CH_2}CH_3$, **187**), 66.1 (unknown), 150.9 ($\underline{C}$=N-OH, **187**), 162.2 ($\underline{C}O_2Et$, **187**), 176.2 20.6 (unknown), 194.5 ($CH_3\underline{C}=O$, **187**).

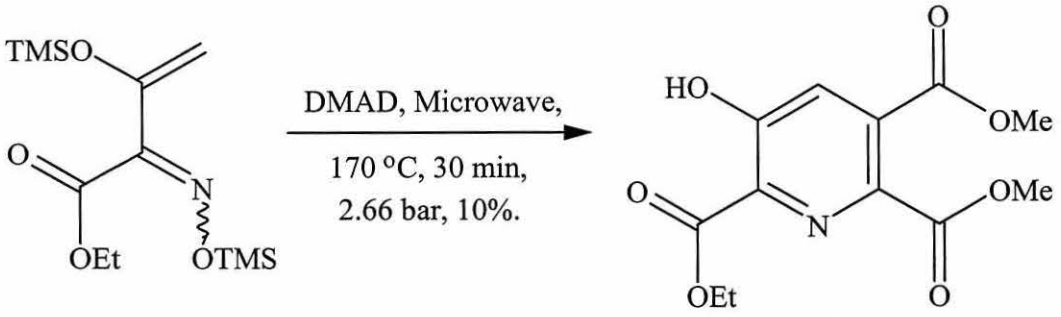
9.57 Control Study of 1-Aza-Diene 228 Decomposition / Dimerisation



228 **304**

The 1-aza-diene, **228** (1.00 g, 3.3 mmol) in anhydrous toluene (50 mL) was heated under reflux for 6 weeks. Once cooled the solvent was removed under reduced pressure to yield the crude product as a brown oil (0.87 g); ν_{max}/cm^{-1} 3363.1br (OH), 1749.0m (CO_2Et), 1701.6m ($CH_3C=O$), 1627.5w (C=N); δ_H(250MHz, $CDCl_3$), 0.04 (1 H, s, OTMS), 0.20 (9 H, s, OTMS), 0.27 (3 H, s, OTMS), 1.30 (3 H, t, *J* 7.0, $OCH_2\underline{CH_3}$, **187**, **228**), 2.38 (1 H, s, $\underline{CH_3}C=O$, **187**), 4.31 (2 H, 2 x q, *J* 7.0, $O\underline{CH_2}CH_3$, **187**, **228**), 4.68 (1 H, 2 x d, *J* 1.8, $C=\underline{CH_2}$, **228**); δ_C(62.5MHz, $CDCl_3$), -0.9 (OTMS), -0.1 (OTMS), 1.8 (OTMS), 14.0 ($OCH_2\underline{CH_3}$, **187**, **228**), 14.1 ($OCH_2\underline{CH_3}$, **187**, **228**), 25.2 ($\underline{CH_3}C=O$, **187**), 61.3 ($O\underline{CH_2}CH_3$, **187**, **228**), 61.7 ($O\underline{CH_2}CH_3$, **187**, **228**), 100.9 ($C=\underline{CH_2}$, **228**), 148.4 ($\underline{C}$=N-OR, **187**, **228**), 154.8 ($\underline{C}O_2Et$, **187**, **228**), 155.1 ($\underline{C}O_2Et$, **187**, **228**), 163.4 ($\underline{C}=CH_2$, **228**), 193.4 ($CH_3\underline{C}=O$, **187**).

9.58 Synthesis of a Highly Substituted Pyridine, 234 *via* Microwave Synthesis



228 **234**

1-Aza-diene, **228** (1.20 g, 3.95 mmol) and DMAD (0.62 g, 4.35 mmol) were sealed in the reaction vessel, and the mixture placed into the microwave machine (CEM Voyager stop-flow batch reactor). The machine was set to run for 30 min at 170 °C with the initial output at 70 W, the pressure rose to 2.66 bar, to yield the crude product as a brown oil, (1.20 g); a portion of which was purified by column chromatography eluting with chloroform : methanol (99.5 : 0.5) to yield pure material as a pale yellow oil (0.10 g, 10%); δ_H(250MHz, $CDCl_3$), 1.49 (3 H, t, *J* 7.2, $OCH_2\underline{CH_3}$), 3.95 (3 H, s, C=C-$CO_2\underline{Me}$), 3.96 (3 H, s, N=C-$CO_2\underline{Me}$), 4.55 (2 H, q, *J* 7.1, $O\underline{CH_2}CH_3$), 7.67 (1 H, s, C=C-$\underline{H}$), 11.16 (1 H, s, $\underline{OH}$); *m/z* 283 (M^+). Data as before.

10.0 References

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