Synthesis and Chemistry of Novel Bridgehead Nitrogen Compounds

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PhD. Chemistry

The University of Edinburgh

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Declaration

I Declare that this thesis is my own composition ant that the work described has been carried out by myself, unless otherwise stated, and that it has not been submitted in any previous application for a higher degree.

The thesis describes the results of research carried out in The University of Edinburgh, chemistry Department, under the supervision of Prof. Hamish McNab since 1st October 2005, the date of my admission as a research student.

Signed:

Date: 23/2/2010

Acknowledgements

I would like to thank Prof Hamish McNab for all his support and advice throughout my PhD project, I would also like to thank all the members of the McNab research group who I have enjoyed working with.

I would also like to thank all of my friends, family and my fiancée for their support and encouragement.

Abstract

Four isomers of pyridpyrrolizinones were made by FVP of the appropriately substituted pyrrole pyridine esters. The mechanism of the cyclisation is believed to follow the cascade mechanism. The structure of two of the ismoers has been confirmed by X-ray crystallography, the NMR properties of all four ismoers is also discussed in detail. The chemistry of 9-azapyrrolo[2,1-*a*]isoindol-5-one was also investigated, it was shown to undergo ring opening with LAH the product of which can then be repyrolysed to give a pyridopyrrolizine. Ring opening also occurs in methanol to give a nicotinate and the pyrrole ring can be hydrogenated to give a tetrahydropyridopyrrolizinone.

The synthesis of pyrrolizin-1-one has been achieved by the FVP of methyl-3-(pyrrol-1-yl)-acrylate over WO3 catalyst, the reaction is believed to proceed *via* an intramolecular electrophilic substitution reaction. The chemistry of pyrrolizin-1-one was investigated, reaction with nucleophiles proceeds *via* addition across the enone double bond. When a nitrogen nucleophile is used ring opening occurs. Hydrogenation occurs at the enone bond to give a dihydrpyrrolizin-1-one.

Pyrrolinzin-1,3-dione was made by the oxidation of 1-hydroxypyrrolizin-3-one using pyridinium dichromate. The dione shows ketone properties (eg. Formation of DNP derivative) and, in common with other pyrrolizinones, the lactam unit is readily ring opened by methanol under basic conditions. The active methylene unit of pyrrolinine-1,3dione couples readily with diazonium salts to provide a hydrazone whose structure was confirmed by X-ray crystallography. It also reacts with methoxymethylene Meldrum's acid to give a Meldrumsated pyrrolizine-1,3-dione whose FVP at 700 c gives a pyronopyrrolizinine. Reaction of pyrrolizine-1,3-dione with DMF acetal gives the 2-dimethylaminomethylene derivative which exists as a mixture of rotomers at room temperature.

8-Azaindolizine was made by FVP of DBN over a WO3 catalyst. 8-Azaindolizine shows reactivity towards electrophiles in substitution reactions at the 3-position. It also reacts with methoxymethylene Meldrum's acid to give a Meldrumsated derivated whose FVP at 950 C reacts with 3-*t*-butyl-4-[1-methoxymethylene]-4*H*-isoxazol-5-one to give a isoxazolone whose FVP at 950 C gives a cyclazine.

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▪ Contents.

The Synthesis and Chemistry of Novel Bridgehead Nitrogen Compounds.

In this project the synthesis of bridgehead nitrogen compounds can be considered by separating them by the size of the fused rings. The project starts by considering 5,5,6-fused ring systems in the pyridopyrrolizinones **1,2,3 and 4** before moving onto 5,5-fused ring systems in pyrrolizin-1-one **5** and pyrrolizine-1,3-dione **6**. The project then moves away from pyrrolizinone chemistry into the 6,5-fused ring system of 8-azaindolizine 7, this then comes full circle by studying at the 5,5,6-fused ring system of 5-azacycl[3,2,2]azine **8** **(Figure 1)**.

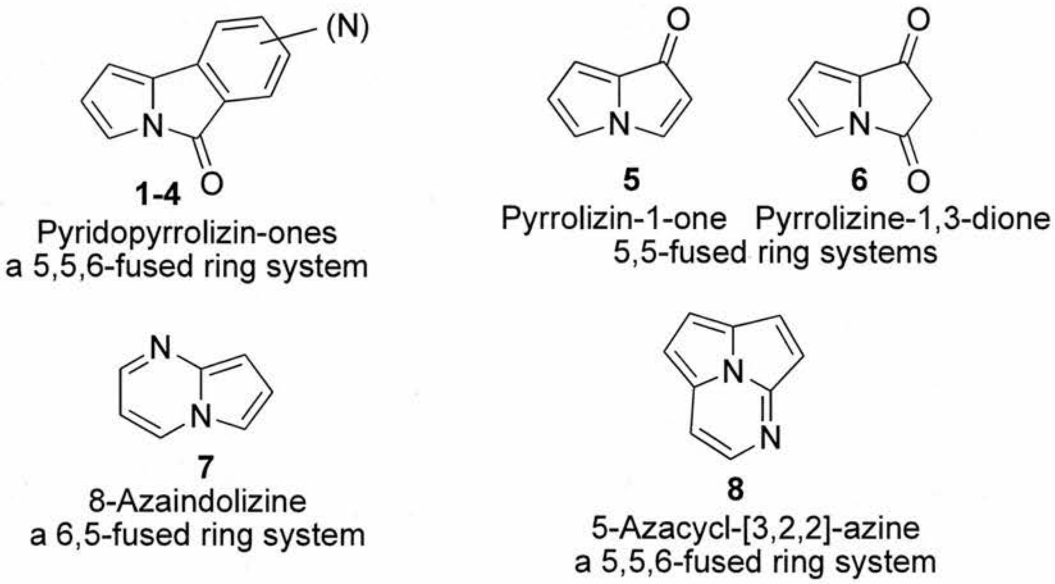
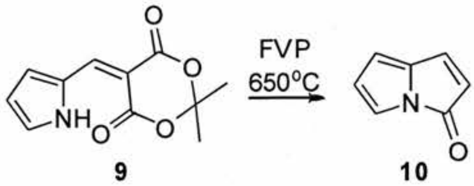


Figure 1: Ring systems that will be discussed.

The use of FVP to generate bridgehead nitrogen compounds has been well studied within the group.[1] One of the best examples is the FVP of the Meldrum's acid derivative **8** to give pyrrolizin-3-one **10** **(Scheme 1)**.[10]



Scheme 1: Synthesis of Pyrrolizin-3-one.

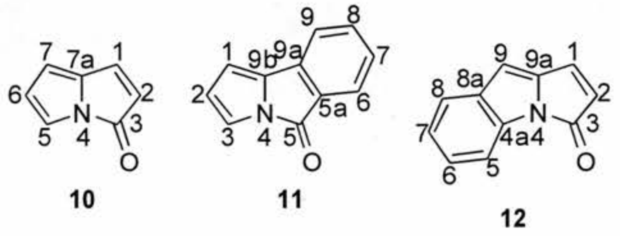
Here this is extended to the synthesis and chemistry of a series on pyridine fused analogues of pyrrolizin-3-one, **1, 2, 3** and **4.**

The used of catalysts in FVP reactions is relatively new and very few examples are known out with the group.[2] The synthesis of the little known isomer pyrrolizin-1-one has been reported in the literature however this is in very poor yield,[3] here the use of catalytic FVP is reported to produce pyrrolizin-1-one in a much improved yield enabling its chemistry to be investigated. The synthesis of the dione **6** had been reported within the group before but again with limited yield and little of its chemistry was investigated,[4] here the synthesis has been improved and the chemistry investigated.

Here the use of WO_3 is reported as a dehydrogenation catalyst in FVP to generate 8-azaind0lizine and the use of its chemistry to produce 5-azacycl-[3,2,2]-azine, the only parent aza[3,2,2]cyclazine not previously reported in the literature.

Introduction Pyrridopyrrolizin-3-ones.

The pyrrolizinones studied can be classified by the number of rings in the system. The parent compound pyrrolizin-3-one **10**, and two benzo derivatives **11** and **12** are discussed in this introduction. The systematic numbering scheme for pyrrolizin-3-one and the two benzo derivatives is inconsistent **(Figure 2)**.



10 **11** **12**

Figure 2: The systematic numbering scheme for pyrrolizin-3-one 9 and its two benzo derivatives 10 and 11.

The core ring system can be considered to be composed of a west ring and an east ring. The position of substituents when referring to the pyrrolizinones will be specified by the appropriate points of the compass (**Figure 3**).

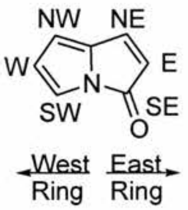


Figure 3: The description of the core ring system.

Many syntheses for pyrrolizinones exist, the first synthesis of the parent pyrrolizin-3-one being reported in 1925.[5] Since then different methods for making these compounds have been reported and these can be classified by the bond which is being formed in the ring closure step. Most of these synthesis start from a simple pyrrole.

1,2-bond formation.

This reaction, reported in 1986, works by *N*-acylation of the pyrrole followed by an intramolecular Knövenagel type condensation.[6] This procedure has been shown to be successful but yields are heavily dependent on substituents (**Scheme 2**).

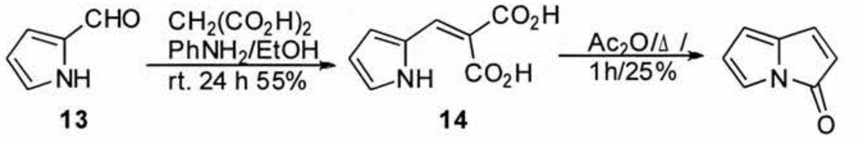
Scheme 2:

3,4-bond formation.

There are three main routes for this type of bond formation.

i. Activated amide formation.

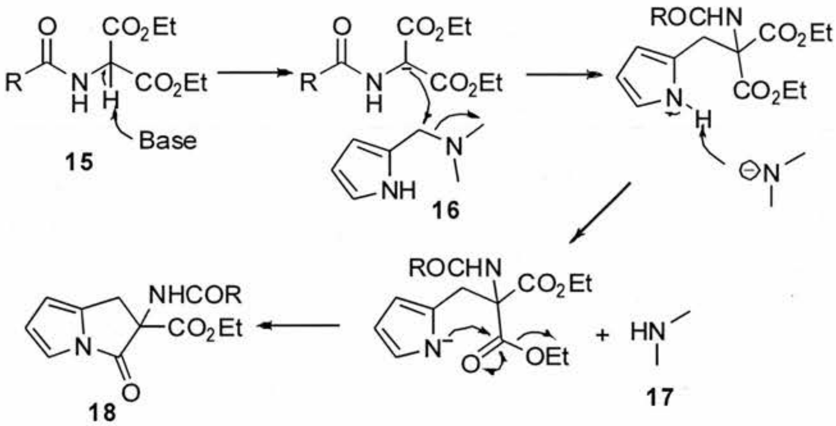
This proceeds *via* the formation of a mixed anhydride from **14** then ring closure and decarboxylation to give pyrrolizin-3-one. This reaction is very dependent on substituents and some yields are poor.[7] It has also been reported that some of the results of this process are not reproducible (**Scheme 3**).[8]



Scheme 3: Activated amide formation of pyrrolizin-3-one.

ii. Base catalysed ring closure.

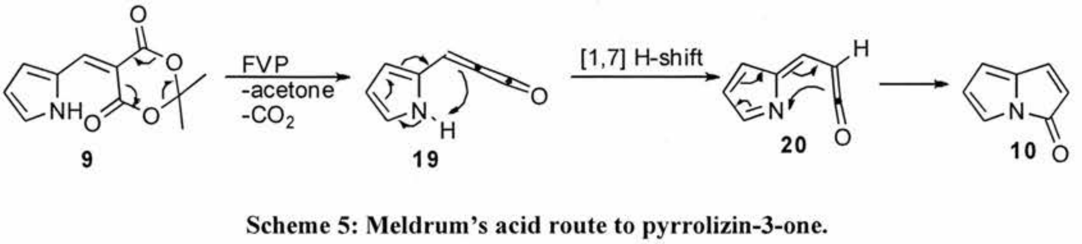
The base catalysed elimination from pyrrole propenoic acid and propenoic acid derivatives was reported in 1953.[9] It is proposed that the base removes a proton from the diester **15**; this enables the reaction with the substituted pyrrole **16** by way of loss of **17** to give **18**. Further reaction with base removes the pyrrole proton enabling attack of the carbonyl to give cyclisation *via* loss of ethoxide. This reaction is substituent dependent and only proceeds in moderate yields (**Scheme 4**). The product of this is a dihydro derivative of a pyrrolizinone but it does demonstrate the formation of this ring system.



Scheme 4: Base catalysed ring closure.

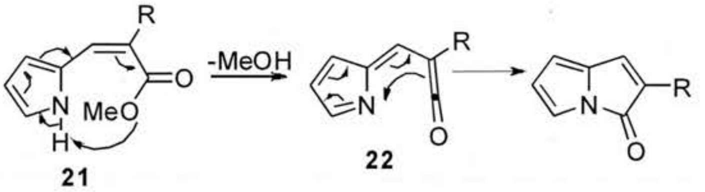
iii. Flash Vacuum Pyrolysis.

Several routes to pyrrolizinones have been reported by FVP. The first route reported was from Meldrum's acid precursors.[10] This was shown to proceed in high yields and has been carried out with many different substituents. Under FVP conditions at 600 °C the Meldrum's **acid** precursor **9** loses acetone and carbon dioxide to form an intermediate **19**, this subsequently undergoes a [1,7] H-shift to give the ketene **20** followed by cyclisation to pyrrolizin-3-one **10** (**Scheme 5**).



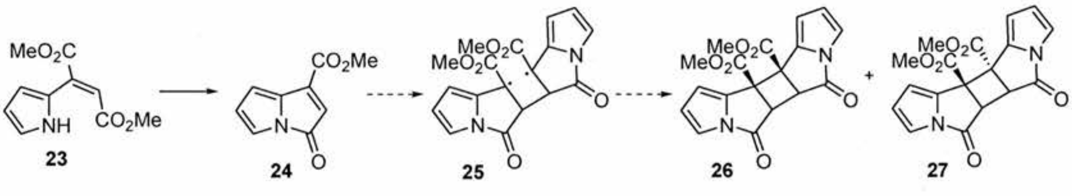
Scheme 5: Meldrum's acid route to pyrrolizin-3-one.

Due to the [1,7] H-shift in the mechanism it is not possible to introduce substitution at the 2-position of the pyrrolizinone. Due to this problem other routes were investigated which do not involve the [1,7] H-shift. Thus pyrrolizinones can be generated from pyrolysis of pyrrolepropenoic acid esters[11] **21**. This reaction proceeds *via* the loss of methanol under FVP conditions to generate the ketene **22** directly. The mechanism does not involve a [1,7] H-shift thus it is a good methodology for the formation of 2-substituted pyrrolizin-3-ones (**Scheme 6**).



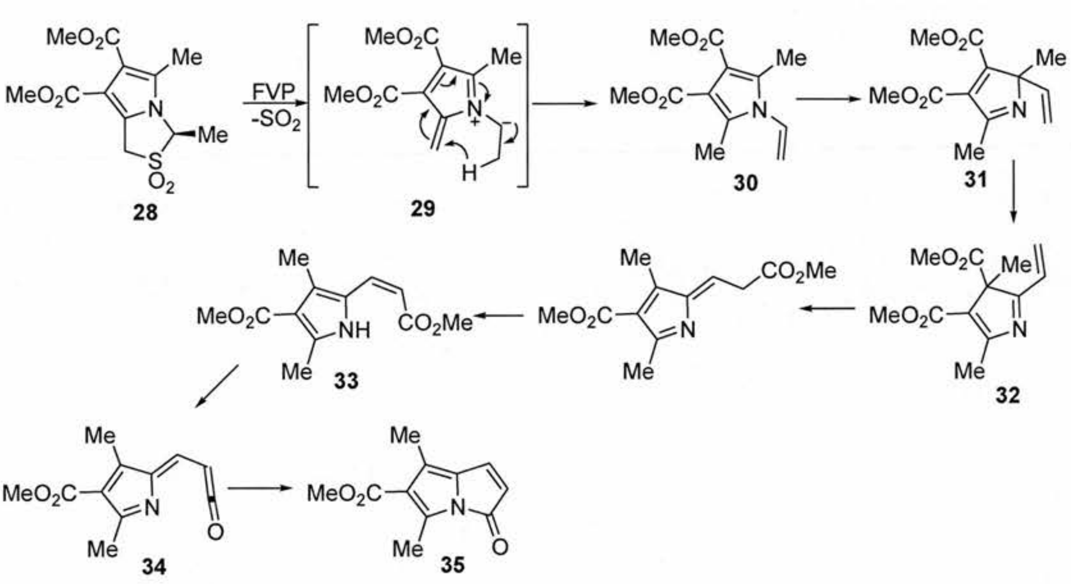
Scheme 6: Pyrrolepropenoic acid ester route to pyrrolizin-3-ones.

This has been used to produce many substituted pyrrolizinones, the propenoic acid ester precursors have the added advantage that they tend to be more volatile than their Meldrum's acid precursor counterparts. One of the reactions that has been reported is the pyrolysis of **23**.[12] It was shown that at 700 °C the pyrrolizinone **24** was formed but under normal conditions it dimerised to give two head-to-head dimers **26** and **27** (**Scheme** 7). This unusual dimerisation has been explained using previously reported phenomenon known as the captodative effect. Thus it was noted that olefins in which a single position of an alkene is substituted with both an electron withdrawing group and an electron donating group dimerise *via* an intermediate stabilised diradical.[13] In this reaction the ester and the pyrrole ring can act in this fashion generating the stabilised diradical **25**.



Scheme 7: Formation of head-to-head dimers *via* the captodative effect.

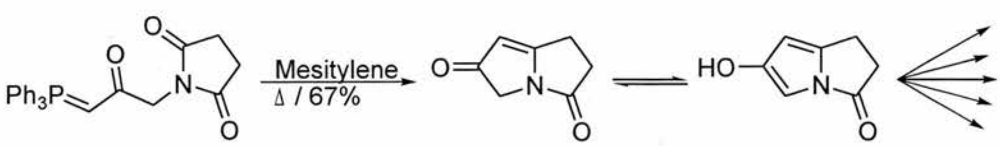
A third reaction that generates a pyrrolizinone **35** by FVP was reported in 2004. This was the pyrolysis of 3-methyl-5-methyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **28**.[14] The mechanism of this reaction proceeds by the loss of SO_2 to give the methylene pyrrole **29**, this is followed by a [1,8] H-shift in the 8π 1,7 dipolar system to give **30**, this is followed by a nitrogen to C-2 vinyl migration producing **31** and then a C-2 to C-3 methyl migration generating **32**. This then enables a carbomethoxy rearrangement to generate the pyrrole-2-propenoate **33** which facilitates the loss of methanol and electrocyclisation *via* the ketene **34** (**Scheme 8**).



Scheme 8:

7,7a bond formation.

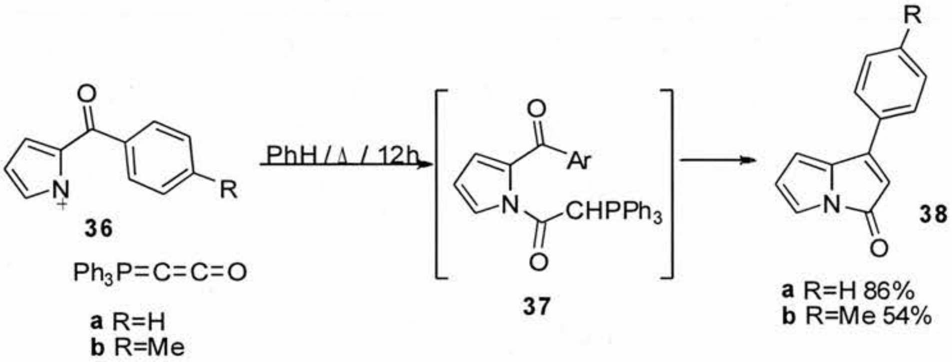
This is carried out by an intramolecular Wittig reaction as reported by Flitsch[15] and co-workers. It yielded some 6-substituted analogues in generally good yields (**Scheme 9**).



Scheme 9: Formation of 7,7a bond by intramolecular Wittig reaction.

Formation of two bonds.

Some reactions have been reported into the formation of pyrrolizinones that involve two bonds being formed in the one step. One of the better yielding reactions of this type is a reaction involving the formation of the 1,2 and 3,4 bonds.[16] This reaction proceeds by the *N*-acylation of a 2-acylpyrrole **36a** and **36b** by triphenylphosphoranylidine ketene to form the intermediate **37**, this facilitates an intramolecular Wittig reaction to give the ring closure and form the pyrrolizinone **38a** and **38b** (**Scheme 10**). The yields for this reaction are very dependent on substituents, other routes involving the formation of two bonds have been reported but only proceed in poor yields (6-30%).



Scheme 10: Formation of two bonds by intramolecular Wittig reaction.

Benzopyrrolizinones with the benzene ring attached to the "east" ring.

Another system based on the pyrrolizinone system is the benzopyrrolizinone system. This was reviewed in 1998 by E. Stevenson.[17] The third ring in this system is attached to the east ring of the pyrrolizinone (**Figure 4**). Again the synthesis of these compounds can be rationalised by which bond is formed in the ring closure step of the reaction.

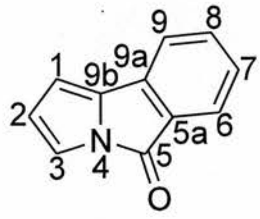
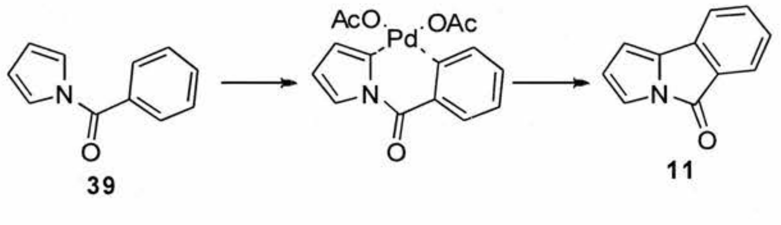


Figure 4: Numbering scheme for Benzopyrrolizin-3-ones

The majority of routes into this system are poor yielding and in some cases the formation of the pyrrolizinone is reported as a minor by product in a reaction.

9a-9b bond formation.

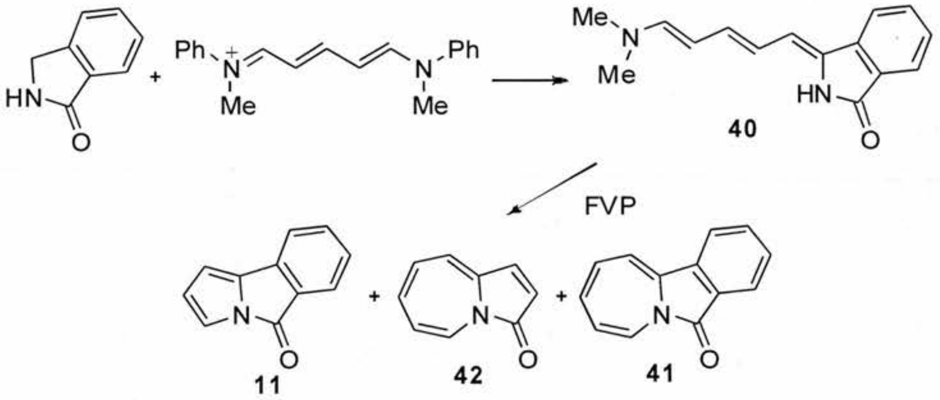
This was demonstrated by the use of Pd (II) salts (**Scheme 11**). The *N*-substituted pyrrole has been shown to undergo dehydrogenation in the presence of stoichiometric amounts of palladium acetate to give the ring closed pyrrolizinone **11**.[18] This reaction is not very synthetically useful as it requires a stoichiometric amount of palladium.



Scheme 11: Ring closure by palladium acetate.

3-4 bond formation.

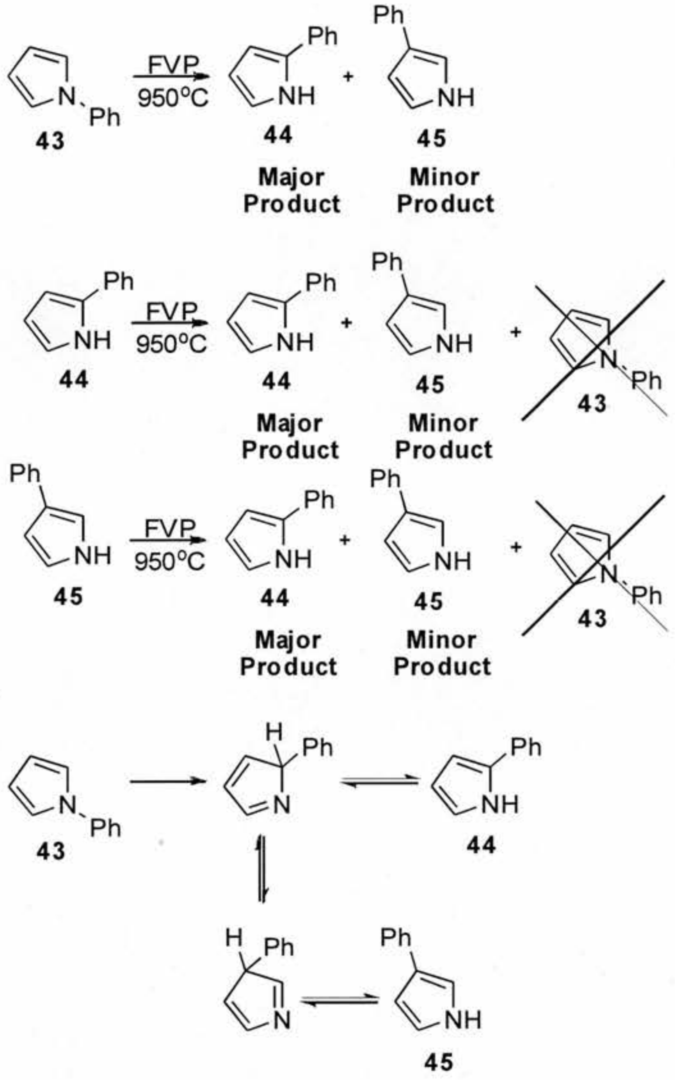
This reaction produces the pyrrolizinone in only a 9% yield but is of interest as it is a FVP example of the synthesis of this system.[19] It has been reported that the pyrolysis of **40** at 650 °C produces three products including **11**. The exact mechanism of this reaction is not clear (**Scheme 12**). The formation of **41** would be the expected product by the loss of dimethylamine and cyclisation onto the nitrogen atom forming the seven membered ring.



Scheme 12

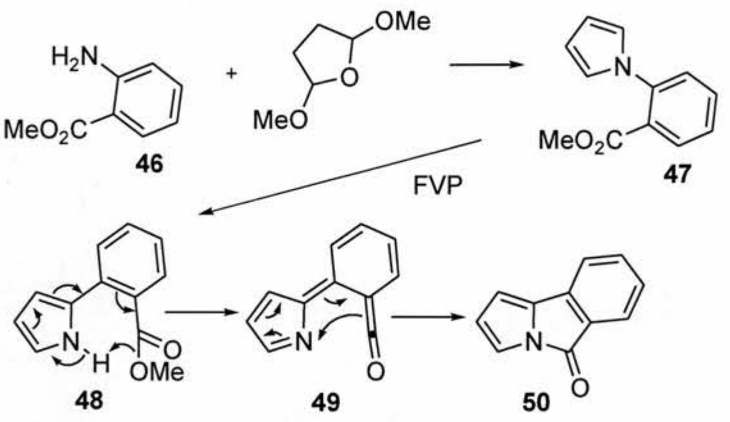
The cascade mechanism.

The cascade mechanism for the formation of this benzo-pyrrolizinone system is a combination of two well reported reactions. The first of these is the thermal isomerisation of 1-substituted pyrroles[20] **43** (**Scheme 13**), which has been reported to occur under FVP conditions. This is demonstrated by the FVP of N-phenylpyrrole, the 2-substituted pyrrole **44** was the major product with the 3-substituted isomer **45** being present as a minor product. The products were isolated and then independently pyrolysed. Pyrolysis of **44** produced a mixture of **44** and **45** with **44** being the major product and no sign of **43**. Pyrolysis of **45** again produced a mixture of **44** and **45** with **44** being the major product and no sign of **43**. This indicates that the step from the *N*-substituted pyrrole **43** to the 2-substituted pyrrole **44** is essentially irreversible. There is an equilibrium between the 2- and 3-substituted pyrroles **44** and **45** favouring the formation of the 2-substituted product **44.**



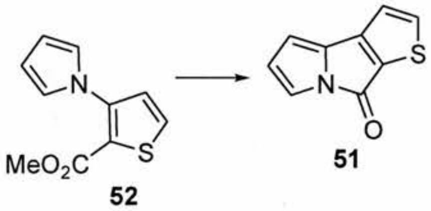
Scheme 13: Thermal rearrangement of pyrroles.

The second reaction in this series is that previously discussed (**Scheme 7)** for the formation of pyrrolizinones from pyrrole-2-propenoates. The combination of these two reactions with suitable precursor for the FVP results in a very versatile and powerful route into this system. The *N*-substituted pyrroles can be readily prepared from the appropriate amine **46** and dimethoxytetrahydrofuran. Under FVP conditions the 1-substituted pyrrole **47** undergoes isomerisation to give the 2-substituted pyrrole **48** which then loses methanol to produce the ketene **49** which subsequently cyclises to give the pyrrolizinone **50**. As **48** cannot be isolated it can be assumed that the rate determining step of this reaction is the isomerisation of the pyrrole (**Scheme 14)**.[13]



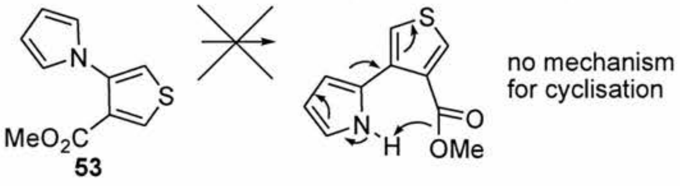
Scheme 14: The cascade mechanism.

This methodology was extended to the generation of the thiophene derivative **51** which was also produced successfully in high yield from the appropriately substituted pyrrole **52** (**Scheme 15**).[13]



Scheme 15

Support for this mechanism is demonstrated by reaction of the thiophene compound **53.** In this compound the sulfur atom is in such a place in the molecule that this concerted process cannot take place. It has been shown that the FVP of this compound does not produce any cyclised product **(scheme 16).**



Scheme 16:

Benzopyrrolizinones with the benzene ring attached to the "west" ring.

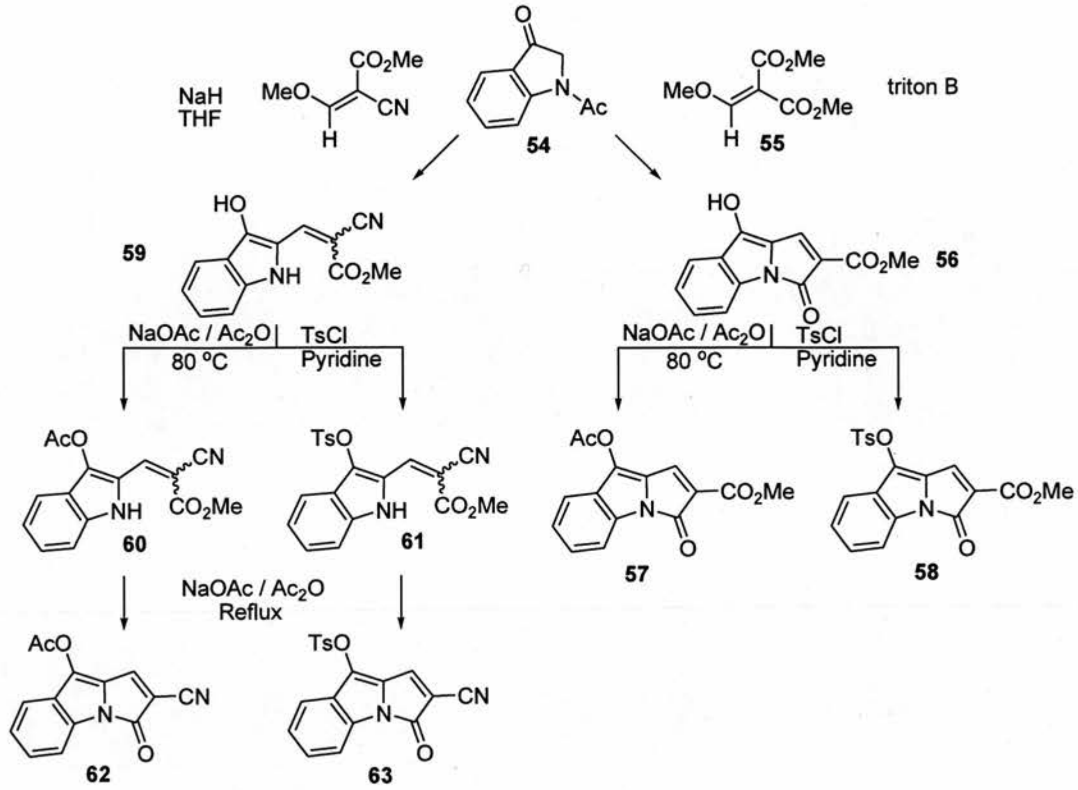
The synthesis of benzopyrrolizinones with the benzene ring fused onto the west ring of the pyrrolizinone has also been studied. Again there are many different ways to generate these compounds but they usually begin with an indole.

3,4 bond formation.

This appears to be the most popular bond formation in the ring closure step to form the pyrrolizinone. The yields in these reactions vary and many different strategies have been used.

Ring closure by base.

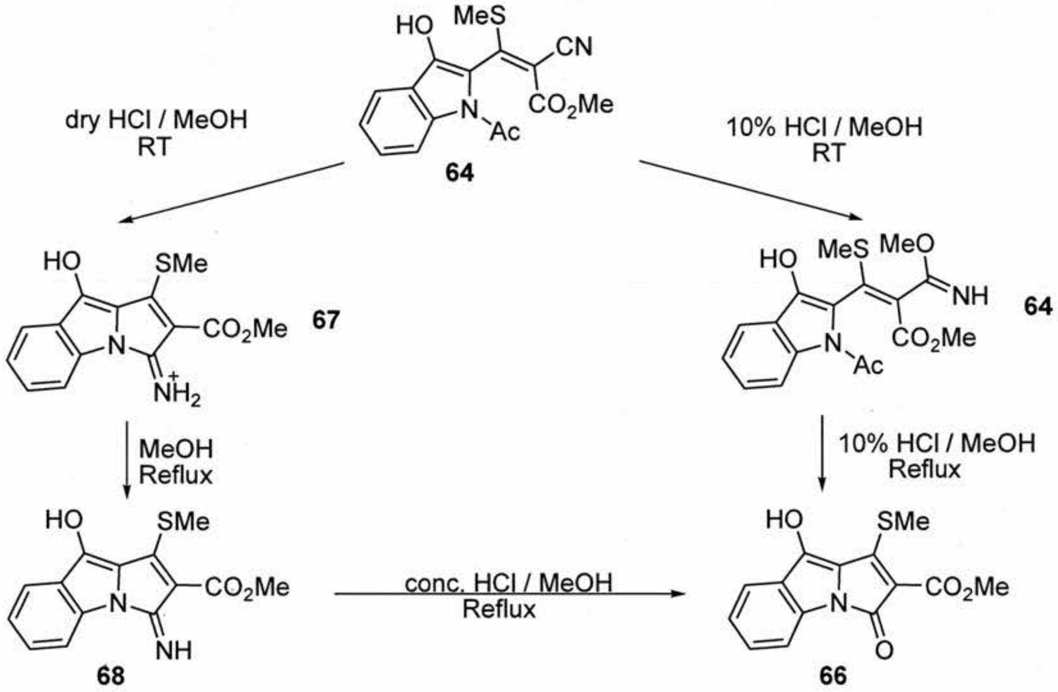
Two sets of experimental conditions have been reported both yielding benzopyrrolizin-3-ones **(scheme 17)**.[21] When **54** is treated with triton B and the ester **55** cyclisation occurs and the cyclised product **56** can be treated with either NaOAc / Ac_2O or TsCl in pyridine allowing the two cyclised products **57** and **58** to be obtained. When the reaction is carried out with NaH as the base in THF the 2-acylated product **59** is formed. This can then be treated with either NaOAc / Ac_2O or TsCl to give **60** and **61** followed by reflux in NaOAc /Ac_2O to induce cyclisation generating **62** and **63**.



Scheme 17: Ring closure by base

Ring closure by acid.

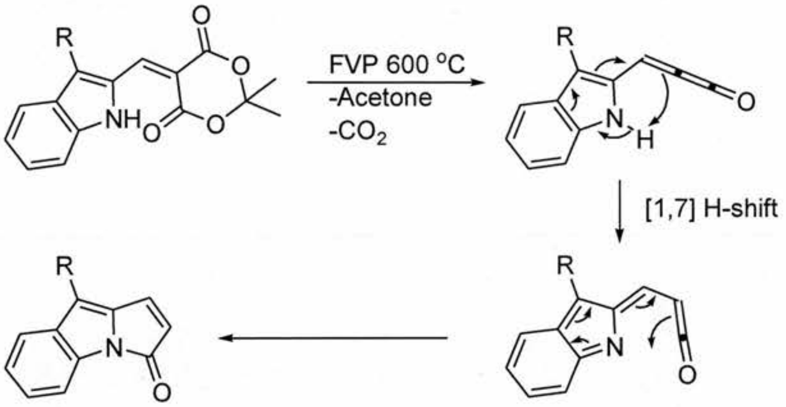
Reported ring closure under acidic conditions follows one of two possible routes dependent upon conditions. In the first route dry HCl is used for the ring closure followed by reflux with conc. HCl in MeOH to generate the pyrrolizinone. The second route involves the use of 10% HCl in MeOH to generate the intermediate which can then be heated under reflux to give the pyrrolizinone (**Scheme 18**).



Scheme 18: Ring closure by acid.

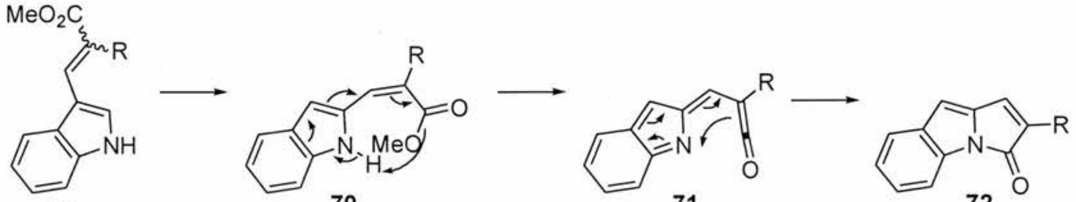
FVP to generate the desired ring closure.

A number of routes into this benzopyrrolizinone system are known to occur by FVP. Firstly the Meldrum's acid route to pyrrolizinones can be applied to this system (**Scheme 19**). This synthesis works well but again due to the [1,7] H-shift it is not possible through this route to attain substitution at the 2-position. In addition to these problems indole-2-carboxaldehydes that are required as precursors are often not readily available.



Scheme 19: Meldrum's acid route to benzopyrrolizinones.

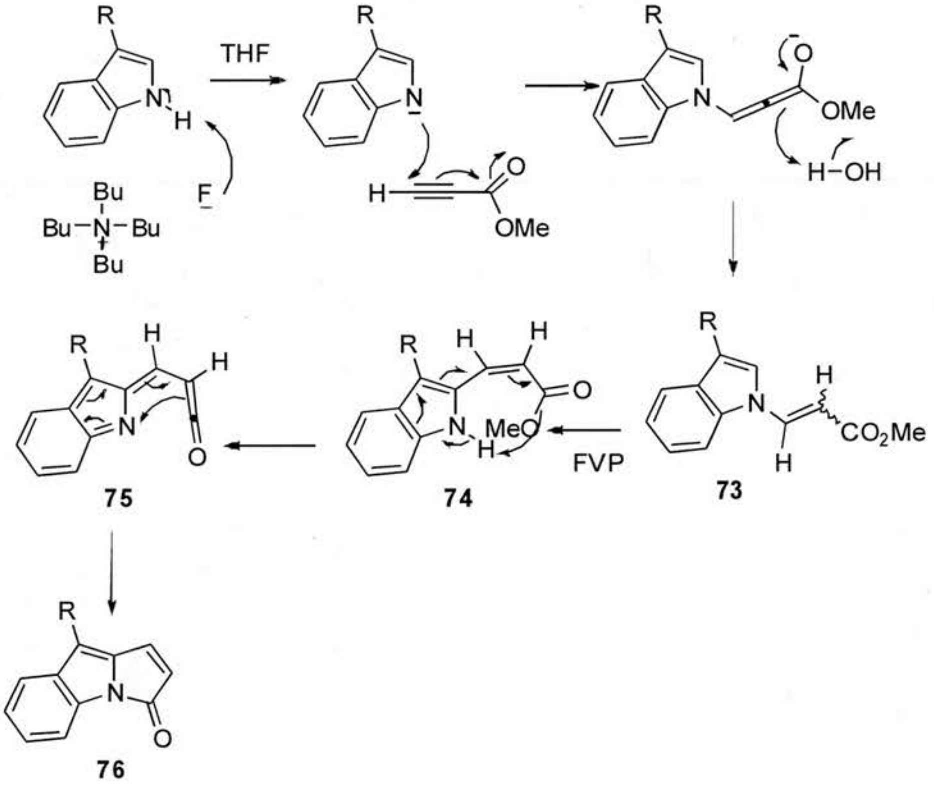
Other precursors have been used for the generation of these benzopyrrolizin-3-ones.[22] The use of indole 3-propenoates as precursors has been reported as they have the advantage of being readily made *via* Wittig / Knövenagel type reactions with indole 3-carboxaldehyde with an active methylene compound. The precursor **69** then undergoes isomerisation under FVP conditions to form the indole 2-propenoate **70** which subsequently loses methanol to give the ketene **71**. This then rapidly cyclises onto the nitrogen to give the pyrrolizinone **72**. Due to the isomerisation this route cannot be used to generate pyrrolizinones with substitution at the NE position of the central pyrrolizinone ring (**Scheme 20**).



69 **70** **71** **72**

Scheme 20: FVP of indole 3-propenoates.

Another reaction reported was the preparation and pyrolysis of *N*-propenoate precursors **73**.[18] These precursors also isomerise to give the 2-propenoate **74** before forming the ketene **75** and cyclising to form the pyrrolizinone **76**. The advantage of this route is that substitution is now viable at the NE position of the pyrrolizinone (**Scheme 21**). Also the generation of the *N*-substituted indoles is easily achieved and tend to be more volatile and thus pyrolyse easier.



Scheme 21: FVP of *N*-substituted indoles.

Other ring closing reactions have been reported including an intramolecular Wittig reaction and a [3+2]-cycloaddition reactions; these all proceeded in poor yields.

The use of TBAF as a base to deprotonate indole has been demonstrated to work well.[23] Many different vinyl indole derivatives were prepared in this way. As such this has been adopted by our group as a method and used successfully for deprotonating indoles and has been. Some experimental evidence shows that F$^-$ is abstracting the proton as glassware used in these reactions becomes etched, presumably by the HF generated in *situ* by the reaction.

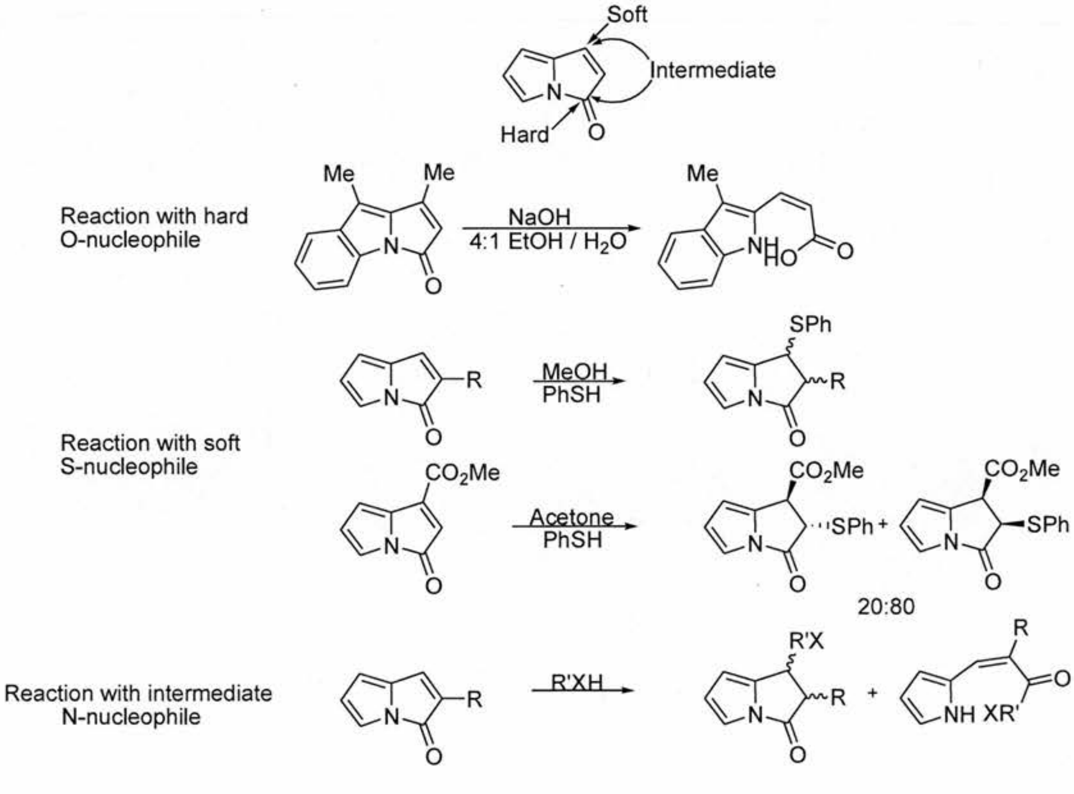
Chemical properties of pyrrolizin-3-ones.

Pyrrolizinones possess certain substructures that show particular properties in pyrrolizin-3-one and its benzoanalogues. Reactions in the "east" ring are almost independent of the presence of the fused benzene ring on the "west" ring of the pyrrolizinone. Similarly reactions on the "west" ring are independent of a fused benzene ring on the "east" ring.

Pyrrolizinones can be considered to react at three different positions, the 1,2-bond is open to electrophilic addition across the bond, nucleophilic addition with soft nucleophiles, hydrogenation and pericyclic reactions where the 1,2-bond acts as a dieneophile. The pyrrole ring is open to electrophilic aromatic substitution at the 5-position and hydrogenation. The carbonyl centre is open to attack by hard nucleophiles where the pyrrole ring then acts as a good leaving group forming ring opened products, as demonstrated by the reaction with LAH and methoxide.

Reactions with nucleophiles.

The reaction of pyrrolizinones with nucleophiles is most easily described by considering them as either hard or soft nucleophiles. It therefore follows that hard nucleophiles react at the hard carbonyl position, soft nucleophiles react at the soft C-1 position and intermediate nucleophiles give the potential for attack at either of the electrophilic centres. This is demonstrated by the reactions of *O*-, *S*-, and *N*-nucleophiles with pyrrolizinones (**Scheme 22**). One of the most important of the *O*-nucleophiles studied is methoxide. It has been noted that pyrrolizinones undergo ring opening in the presence of methanol. This reaction has been shown to be a base catalysed reaction and proceeds very rapidly in the presence of one drop of Hünig's base.

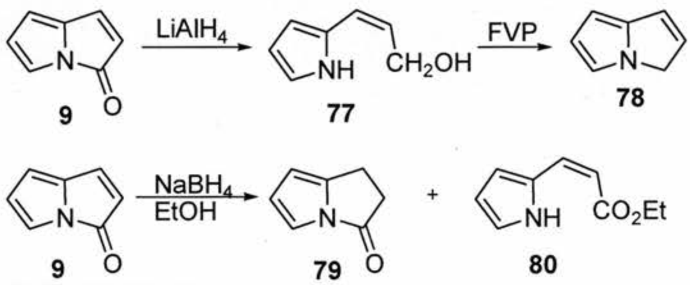


Scheme 22: Reactions with nucleophiles.

This demonstrates reaction at the 1,2-bond in the case with soft and intermediate nucleophiles. It is also clear that the presence of a fused benzene ring on the "east" ring stops this reaction. Also demonstrated here is the reaction at the carbonyl when reaction is carried out with hard nucleophiles. This reaction is unaffected by the presence of a fused benzene ring on the "east" or "west" ring.

Reactions with H-nucleophiles.

The reaction of pyrrolizin-3-ones with H-nucleophiles has also been reported. The reaction with LAH produces the ring opened product **77** which can in turn be repyrolysed to give a pyrrolizine **78**. Softer H-nucleophiles such as sodium borohydride give **79** but a competitive ethanolysis forms **80**.[24] (**Scheme 23**).

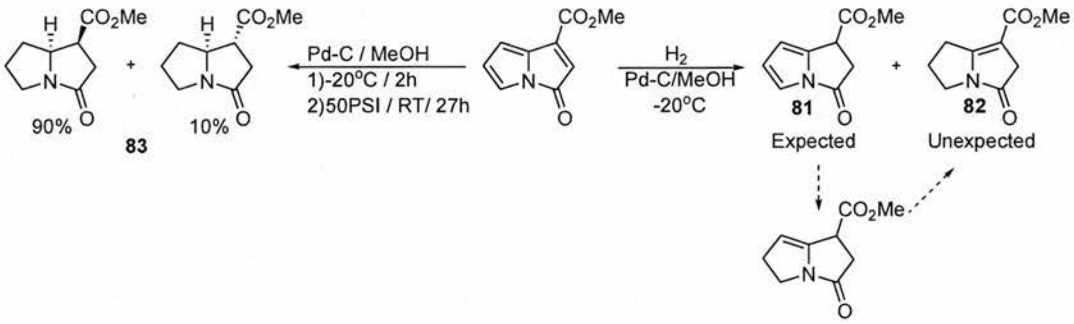


Scheme 23: Reaction with H-nucleophiles.

The reaction with LAH demonstrates the classic reaction at the carbonyl centre of pyrrolizinones. It is believed that the LAH reacts at the carbonyl forming the aldehyde in so doing it expels the pyrrole ring as a leaving group. The aldehyde is then further reduced to the alcohol. This reaction is unaffected by the presence of a fused benzene ring on either the "east" or "west" rings of the pyrrolizinone. The reaction with the softer sodium borohydride nucleophile gives reaction at the 1,2-bond this would clearly be prevented by the presence of a fused benzene ring on the "east" ring of the pyrrole.

Hydrogenation reactions of pyrrolizinones.

The partial and full hydrogenation of pyrrolizinones is known to occur. The hydrogenation of the 1,2-bond occurs first to produce the expected 1,2-dihydro product in the particular case of the 1-ester **81**. Also even under mild conditions an unexpected product **82** is formed, which is the product of the hydrogenation of two double bonds (**Scheme 24**). The formation of the unexpected product is produced by the hydrogenation of the 5,6-bond of **81**, then isomerisation occurs on the catalyst surface driven by the stability of the enamido-type ester formed. This type of double bond migration is common in olefin hydrogenation. The fully hydrogenated product **83** is also attainable by the use of more forcing conditions, producing mainly the *cis*-isomer.[24]

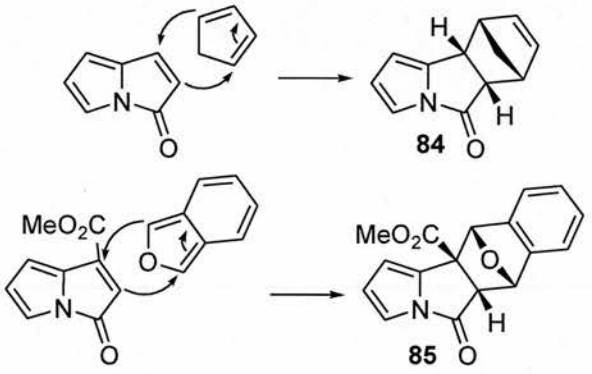


Scheme 24: Hydrogenation of pyrrolizinones.

This demonstrates both reaction at the 1,2-bond and reaction at the pyrrole ring. The presence of a fused benzene ring on the “east” ring of the molecule stops the hydrogenation of the 1,2-bond. The presence of a fused benzene on the “west” ring affects the hydrogenation on the pyrrole ring. The hydrogenation of pyrrolizin-3-one is discussed later **(page 97)**.

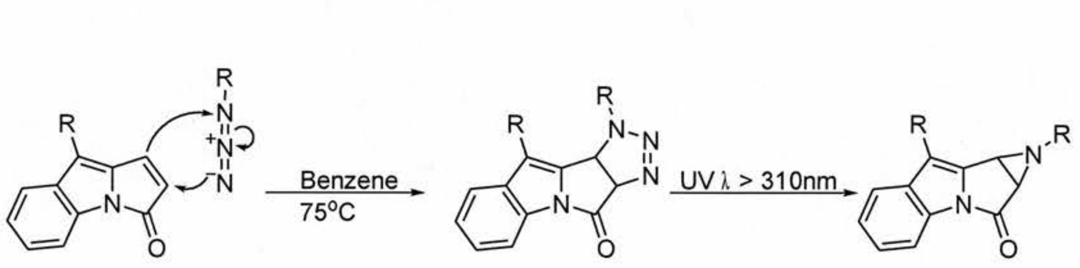
Pericyclic reactions.

The high reactivity of the enone moiety makes pyrrolizinones suitable as a dieneophile in a Diels Alder reaction. This has been shown to take place with both cyclopentadiene[25] and isobenzofuran[7] giving the adducts in primarily the *endo*-isomeric form **84** and **85** **(Scheme 25)**.



Scheme 25: Diels Alder cycloaddition reactions.

1,3-Dipolar cycloadditions of azides are also known to occur to dipolarophilic double bonds conjugated with carbonyls **(Scheme 26)**.[26]

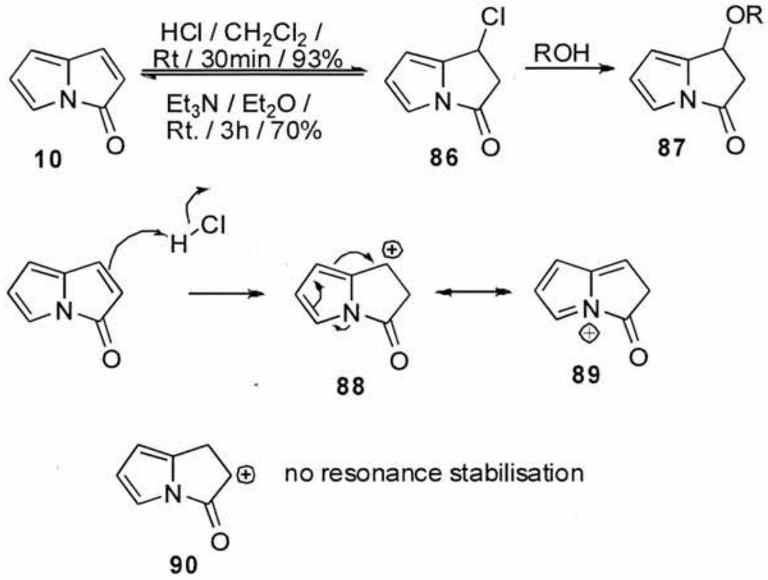


Scheme 26

This is one of the reactions of the 1,2-bond, these pericyclic reactions are unaffected by the presence of the fused benzene ring on the "west" ring of the pyrrolizinone but these reactions cannot proceed in the presence of a fused benzene ring on the "east" ring of the pyrrolizinone, due to blocking of the 1,2-bond.

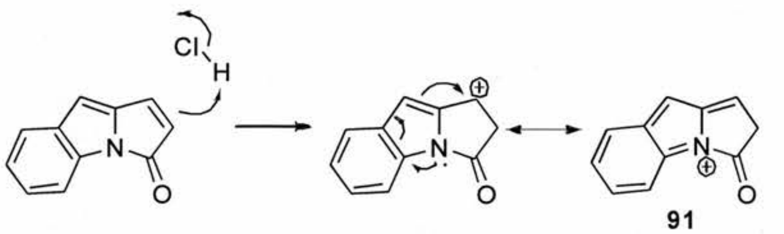
Reaction with electrophiles.

Reaction with HCl produces addition across the 1,2-double bond of the ring; the lability of the Cl substituent can then be demonstrated by its displacement with O-nucleophiles (**Scheme 27**).[20] The stabilisation of the cationic intermediate **88** is an important feature of this reaction, it is the delocalisation of the negative charge onto the bridgehead nitrogen **89** that enables this reaction to proceed and also directs the Cl onto the 1-position. No resonance stabilisation is available for the possible cationic intermediate **90**.



Scheme 27

This is a reaction of the 1,2-double bond therefore the presence of a fused benzene ring on the "east" ring of the pyrrole would block this reaction. The presence of the benzene ring in the "west" ring of the pyrrole would also affect this reaction as the carbocation intermediate requires stabilisation from donation of the nitrogen lone pair. The presence of a fused benzene ring would block this stabilisation as this would require the aromaticity of the benzene ring to be broken **91 (scheme 28)**.



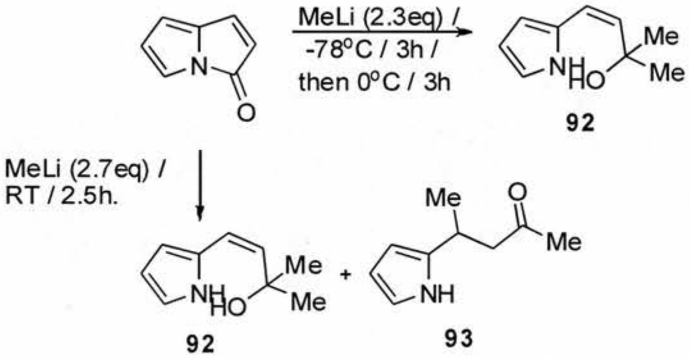
91

resonance form breaks aromaticity of benzene ring

Scheme 28: Resonance form of 91

Reaction with organometallics.

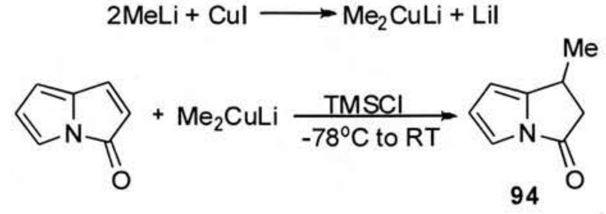
The reaction of two equivalents of methyl lithium with pyrrolizin-3-one has been shown to be a temperature dependent reaction.[8] At low temperatures the addition of the two equivalents occurs at the carbonyl centre to give **92**. At RT the reaction proceeds in addition by the addition of one methyl lithium at the carbonyl centre to give **92** and 1-position in a Michael type manner to give **93** (**Scheme 29**).



92 **92** **93**

Scheme 29

The reaction of pyrrolizin-3-one with dimethylcuprate in the presence of TMSCl has been shown to give the 1,4-Michael type addition product **94** as the sole product **(Scheme 30)**.

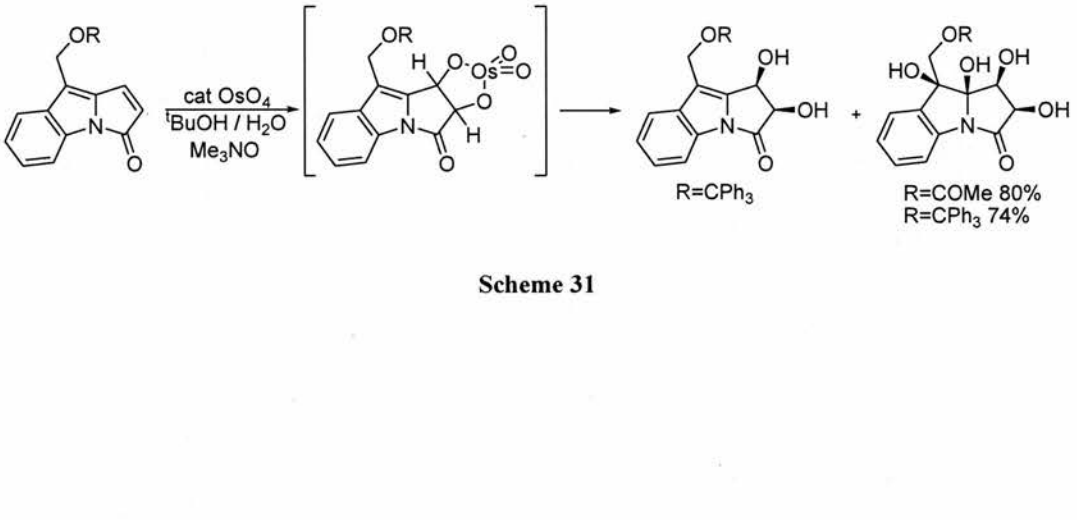


Scheme 30

In general the reactions of pyrrolizinones with organometallics are not clean and tend to be poor yielding, thus they are not of general use.

Reaction with osmium tetroxide.

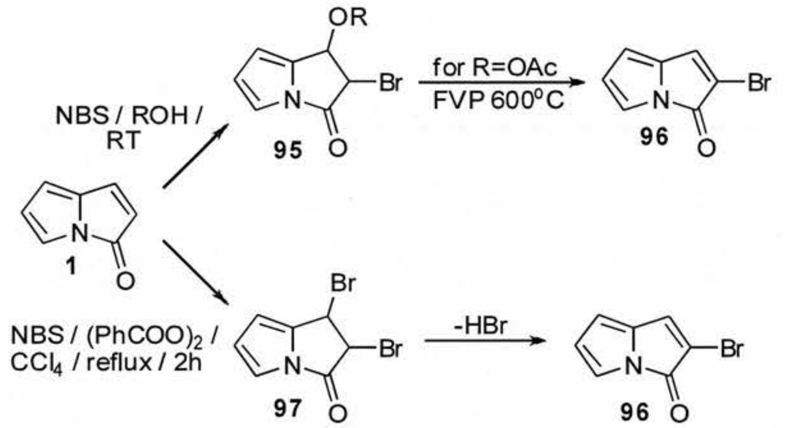
It has been shown that benzopyrrolizin-3-ones can be oxidised to 1,2-*cis* diols using triethylamine and osmium tetroxide.[27]



Scheme 31

Reaction with NBS.

Pyrrolizin-3-one reacts with NBS at RT in protic solvents giving the disubstituted product **95** which can then be pyrolysed in some instances to remove the R group to give **96**. The other conditions are refluxing in carbon tetrachloride, this forms the dibromide species **96** which then eliminates HBr to form the singly brominated species **95**. The direct formation of **96** would require initial radical abstraction of vinylic hydrogen atom this is believed to be disfavoured thus the initial formation of the dibromo species is the favoured route (**Scheme 32**).[25]

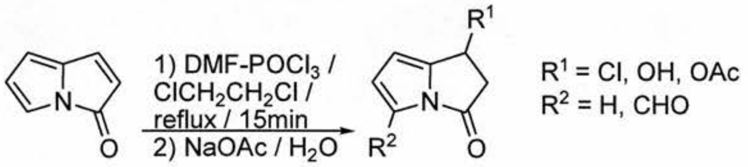


Scheme 32: Reaction of pyrrolizin-3-one with NBS.

This is another reaction demonstrating the reactions of the 1,2-bond this is unaffected by the presence of a fused benzene ring on the "west" ring of the pyrrole, but again the presence of a fused benzene ring on the "east" ring clearly blocks this reaction.

Electrophilic aromatic substitution.

This chemistry produces the potential to introduce substituents into the "West" ring of the pyrrolizinone. This is achieved by the use of the Vilsmeier Haack reaction though in poor yield and with competing addition at the 1,2-position,[20] giving a complex mixture of products.

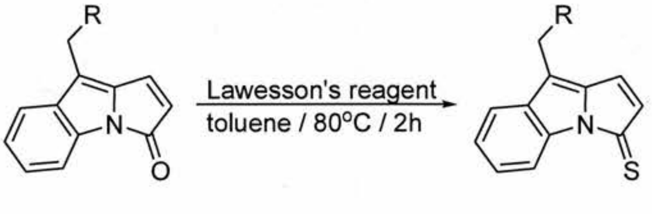


Scheme 33

In the presence of a fused benzene ring on the "east" ring of the pyrrolizinone it could be suggested that the competing reaction would be blocked, and a fused benzene ring on the "west" ring would block this reaction totally.

Thionation with Lawesson's reagent.

The thionation of the carbonyl O is easily achieved by the use of Lawesson's reagent (**Scheme 34**).



Scheme 34

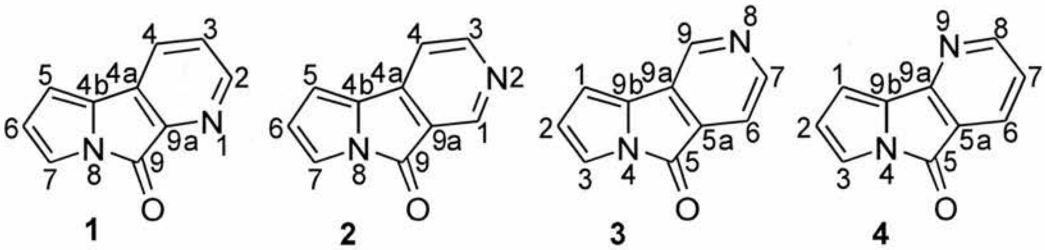
The thionation reaction is in principle independent of the presence of fused benzene rings in the "east" or "west" rings of the pyrrole as it is a reaction involving the carbonyl.

Results and Discussion.

In this chapter the aim is to demonstrate the use of the cascade reaction to generate the four pyrridopyrrolizinones **1, 2, 3,** and **4**. In addition to this the chemistry of these compounds was investigated by probing the chemistry of **3** and comparing it to that of pyrrolizin-3-one and other appropriate pyrrolizinones.

Nomenclature Of The Pyridopyrrolizinones.

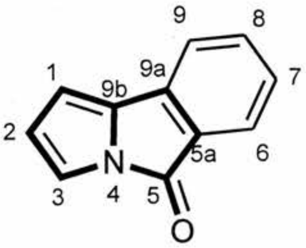
The systematic numbering scheme for the pyridopyrrolizinones varies from one isomer to the next (**Figure 5**), and has the effect of numbering the carbonyl carbon as either 5-one or 9-one; as this is one of the key features of pyrrolizinones it is favourable to use a numbering scheme that keeps the numbering constant around the ring.



1 **2** **3** **4**

Figure 5: Systematic numbering scheme for pyridopyrrolizinones.

Thus a simplified system is used for naming and numbering these compounds, based on the parent compound pyrrolo[2,1-*a*]isoindol-5-one (**Figure 6**). Although it is not made explicitly clear from the name, the pyrrolizinone substructure can be seen from the part in bold.



Pyrrolo[2,1-*a*]isoindol-5-one

Figure 6

Keeping this numbering system the position of the nitrogen on the pyridine ring is indicated by the aza prefix. These compounds will therefore be referred to as azapyrrolo[2,1-*a*]isoindol-5-ones (**Figure 7**).

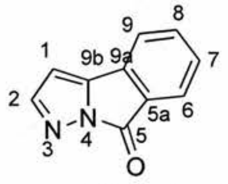
6-azapyrrolo[2,1-*a*]isoindol-5-one 7-azapyrrolo[2,1-*a*]isoindol-5-one

8-azapyrrolo[2,1-*a*]isoindol-5-one 9-azapyrrolo[2,1-*a*]isoindol-5-one

Figure 7:Nomenclature of the pyridopyrrolizinones.

The term "pyridopyrrolizinone" will also be used in the text to distinguish these derivatives from the other azapyrroloisoindolones **(figure 8)** which are not discussed in this chapter.

1-azapyrrolo[1,2-*a*]isoindol-5-one **2-azapyrrolo[1,2-*a*]isoindol-5-one**



3-azapyrrolo[1,2-*a*]isoindol-5-one

Figure 8

The synthesis of pyridopyrrolizinones.

There are four different isomers of pyridopyrrolizinones **(Figure 1) 1**, **2**, **3** and **4**, which differ only in the position of the nitrogen around the pyridine ring. These were chosen as targets because previous work on substituted pyrrolizinones[7] had suggested that either the presence of a basic nitrogen in the compound made them more acceptable to ring opening or that the ability of the "pyrrole" group to act as a leaving group caused rapid ring opening. This is demonstrated in the case of the azapyrrolizine **98** which is reported to ring open 76 times more rapidly than pyrrolizin-3-one itself.[28] It can be suggested that this ring opens more rapidly for both of these reasons **(Table 1).** The rate of ring opening can be explained by considering the second nitrogen as being basic and therefore increasing the concentration of methoxide thus increasing the rate of ring opening. Or the imidazole group could be considered as a better leaving group than pyrrole. The latter of these proposals is supported by the observation that the pyrrolizinone **99** ring opens 342 times more rapidly than pyrrolizin-3-one **10** indicating that the ewg stabilises the negative charge in the intermediate making it a better leaving group.

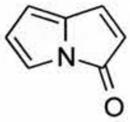
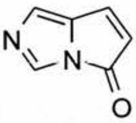
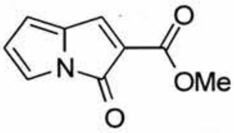
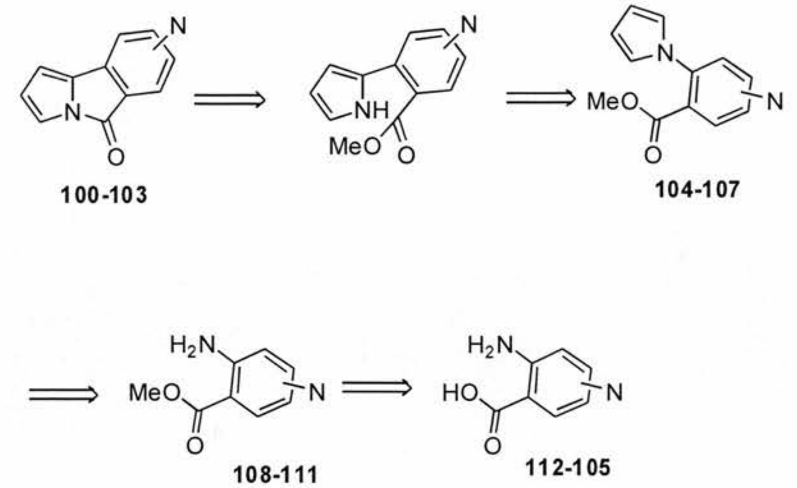
	Relative rate of ring opening in MeOH
	1
	76
	342

Table 1: Relative rate of ring opening of pyrrolizinones.

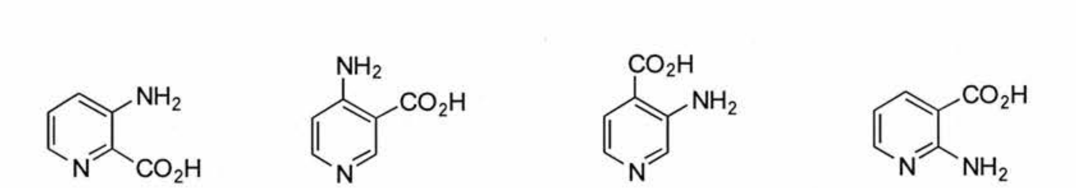
A retrosynthetic analysis of the pyridopyrrolizinones is used to rationalise the general synthesis developed (**Scheme 35**).



Scheme 35: Retro synthesis of pyridopyrrolizinones.

The first step in the retrosynthesis is the breakage of the N to the carbonyl carbon bond and the migration around the pyrrole as discussed **(page 14)**. This can be achieved by the pyrolysis of an appropriately substituted pyrrole **104-107**. The next step of the retro synthesis is the formation of the pyrrole which can be achieved by the reaction of the appropriately substituted aminopyridine carboxylic acid methyl ester **108-111** with 2,5-dimethoxytetrahydrofuran. The esters can be synthesised from aminopyridine carboxylic acids **112-115**.

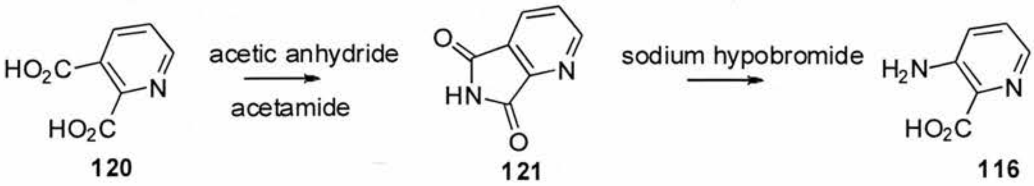
From this retrosynthetic analysis it is clear that there are four isomers of the required acid starting material (**Figure 9**). Two of these acids **117** and **119** were commercially available the other two were synthesised.



3-aminopicolinic acid **116** 4-aminonicotinoc acid **117** 3-aminoisonicotinic acid **118** 2-aminonicotinic acid **119**

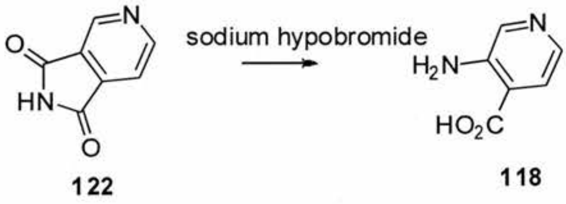
Figure 9

First 3-aminopicolinic acid **116**, was prepared by a literature reaction[29] from quinolinic acid **120**; quinolinanhydride was formed *in situ* by reaction with acetic anhydride and the acetic acid generated was distilling off. To this, acetamide was added to give quinolinimide **121**. The quinolinimide **121** was then decomposed using sodium hypobromite, the standard reactivity of pyridine directs the decomposition towards the desired isomer. The acid was isolated by addition of copper acetate to form a copper salt, which was easily isolated by filtration. The copper salt was then decomposed to copper sulfide using hydrogen sulfide, generated by the reaction of iron sulfide and hydrochloric acid in Kipp's apparatus. After filtration of the copper sulfide the product was obtained upon the removal of the solvent (**Scheme 36**).



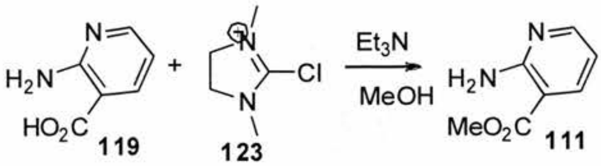
Scheme 36: Hofmann reaction of quinolinimide.

The second isomer, 3-aminoisonicotinic acid **118**, was prepared in a similar way but did not require the copper salt workup formation. The decomposition of the appropriate imide **122** with sodium hypobromide yielded the desired product which crystallises from solution upon workup (**Scheme 37**).



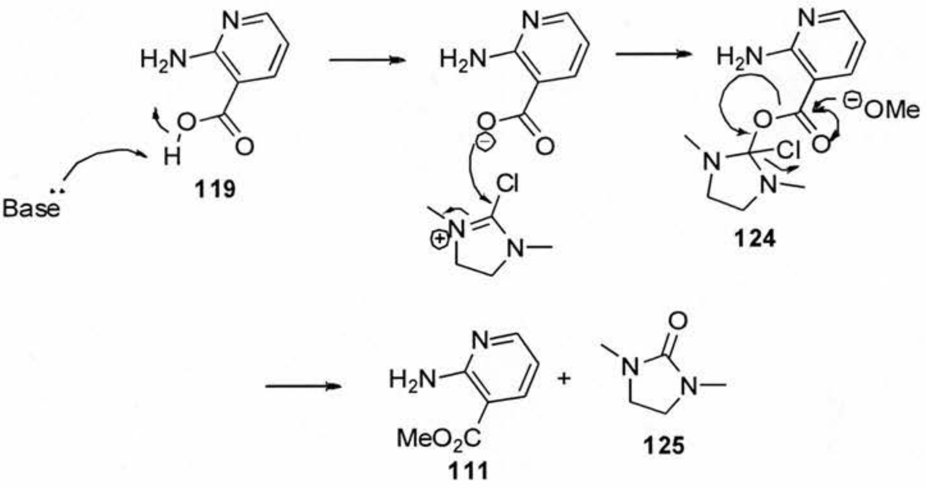
Scheme 37

The next step was the formation of the ester. This was achieved for two of the isomers by the literature reaction[22] of the acid with 2-chloro-1,3-dimethyl-2imidazolidinium chloride (DMC) **123** in methanol with triethylamine as the base. This produced the desired product when the reaction was carried out on 2-aminonicotinic acid **119** and this synthesis was then extended to 3-aminopicolinic acid **111 (Scheme 38)**. Surprisingly the other two isomers of the acid did not react to give the desired ester under these conditions.



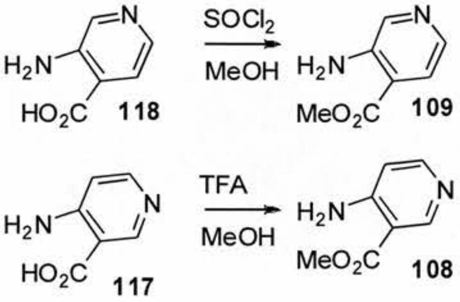
Scheme 38

It is believed that the DMC is used to form a better leaving group for the reaction enabling the reaction to proceed under much milder conditions **(scheme 39)**. The triethylamine deprotonates the acid which then attacks the DMC to give the intermediate **124**. Methoxide then attacks the carbonyl with **125** acting as a better leaving group than OH.



Scheme 39

The other two esters were synthesised by literature methods.[22] The reaction of 3-aminoisonicotinic acid **118** with thionyl chloride in methanol produced the desired ester **110**. This reaction was attempted on 4-aminonicotinic acid **117** but did not yield the desired ester **109**. The ester **109** in this case was prepared by a standard literature reaction of the acid as a TFA salt with methanol under acidic conditions; this is an equilibrium which is driven in the favour of the product by the use of methanol both the solvent and reagent; the reaction proceeds with a 76% yield. The TFA salt was used for solubility reasons, the starting acid is completely insoluble in methanol, thus the very soluble TFA salt was generated by dissolving the acid in water and acetonitrile and adding TFA until the solution was acidified (**Scheme 40**).



Scheme 40

Having generated the esters the following stage of the synthesis was the formation of *N*-substituted pyrroles **104-107** (**Figure 10**), this is achieved in all cases by reaction of the ester with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid. In this reaction precautions were taken to remove all air from the solvent by passing nitrogen through the acetic acid before use in the reaction. This was done to stop the pyrrole formed from decomposing. Also the solvent was removed as rapidly as possible to prevent degradation of the product.

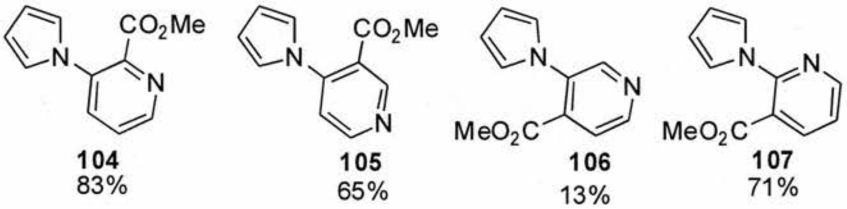
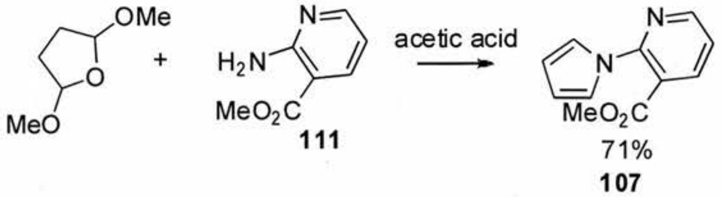


Figure 10

This is a standard reaction for the formation of *N*-substituted pyrroles[30] eg. (**Scheme 41**). This was achieved for all four isomers giving the desired pyrroles as the FVP precursors. The precursor **106** was only produced in 13% yield, upon the production of this isomer the pyrrole appeared to blacken very quickly and the yield was greatly decreased. Thus to achieve the synthesis of the pyrrolizinone in this case the precursor was prepared and quickly pyrolysed, this led to reduced yield on the pyrolysis step.



Scheme 41

These pyrrole precursors are easily identified by their characteristic ^{1}HMR spectra, these compounds all show two triplets at δ_H 7.02-6.84 and 6.24-6.36, that are characteristic of the pyrrole protons. Also observed are the clear signals from the pyridine ring at higher chemical shift but clearly the splitting pattern is dependent upon the position of the N in the pyridine ring. As one example this is well demonstrated in the case of **107 (figure 11)**.

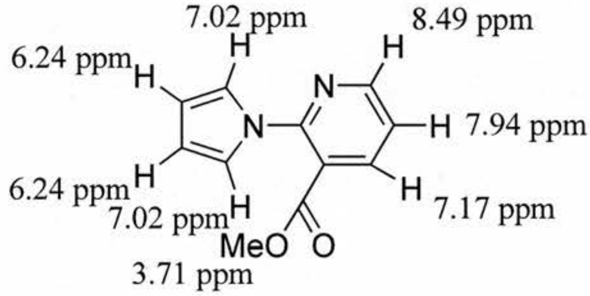
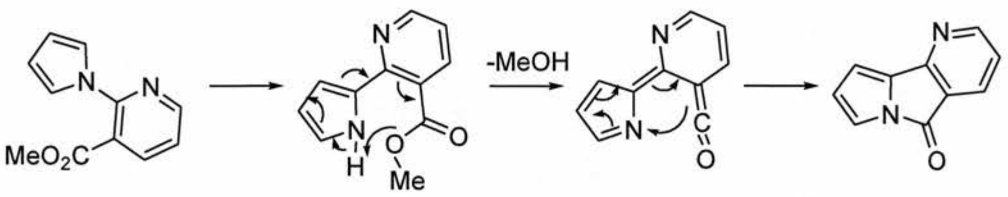


Figure 11: nmr properties of 107

As a final stage in the synthesis of the pyridopyrrolizinones the pyrrole precursor was pyrolysed at 950 °C to give the pyridopyrrolizinone. The FVP temperature was previously found to be the optimum temperature for the cyclisation to form benzopyrrolizinones.[12] The mechanism is believed to follow the cascade process (**Scheme 42**). Firstly there is a thermal migration of the pyridine group to the 2-position of the pyrrole ring, which is believed to be the rate determining step in this reaction. This is followed by the elimination of methanol to form a ketene intermediate which rapidly cyclises to form the pyridopyrrolizinone.



Scheme 42: The cascade process.

All four isomers were synthesised by this route, it was observed that the pyrolysis proceeded more cleanly when no inlet heating was used. In each case the pyrolysate formed as a yellow crystalline solid at the bend of the U-tube. Upon even gentle heating of the inlet oven the yield was reduced and the product appeared to have a slight brown colour instead of its usual yellow colour. It is assumed that the starting materials are not particularly thermally stable and that prolonged exposure to heat causes them to degrade resulting to less clean products and lower yields.

Structure of pyrridopyrrolizinones.

The structures of these compounds have been confirmed by NOESY, HSQC and X-ray crystal structure.

X-ray crystal structure.

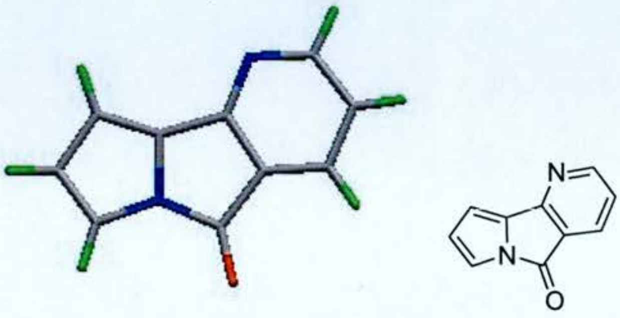


Figure 12: Crystal structure of 79.

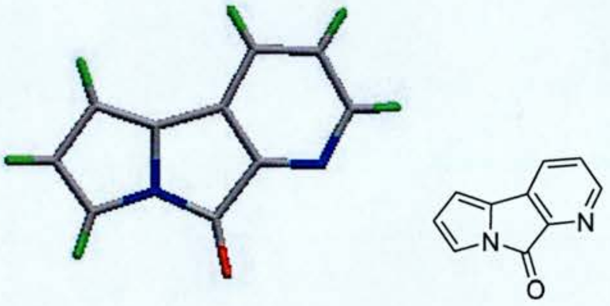


Figure 13: Crystal structure of 76.

It can be seen from the crystal structures that the position of the nitrogen atom in the rings is unequivocally confirmed, it can also be noted that the molecule is planar and that the position of the nitrogen in the pyridine ring does not have any significant effect on the bond lengths or angles in other parts of the molecule.

	9-isomer	6-isomer
C-N bond length /Å	1.411(2)	1.404(2)
C-O bond length /Å	1.211(2)	1.214(2)

Table 2: Key bond lengths from the crystal structures.

The most characteristic of any lactam interaction are the bonds of the amide linkage which is highlighted in bold in **Figure 15**. The typical values for bond lengths for amide linkages in γ-lactams are 1.344 and 1.226 for the C-N and C-O bond respectively. In the typical γ-lactams the lone pair of the nitrogen is involved in resonance only with the carbonyl functionality. As can be seen from the table above for both of the compounds above the C-N bonds are significantly longer and in both cases the C-O bonds are shorter indicating that there is less involvement of the nitrogen lone pair in resonance into the carbonyl function. This is in accordance with other similar systems studied.[7] It is also noticeable that the position of the nitrogen in the pyridine ring has no significant effect on the bond lengths involved. A comparison of these two crystal structures with that already known for the parent compound pyrrolizin-3-one and that of the benzopyrrolizin-3-one can be drawn. The bond lengths in figure 11 show that the fused benzene ring makes the C1-C2 bond much longer, this also applies to the pyridine examples. It can also be seen that the C3-N4 bond is lengthened and the N4-C5 bond is shortened this implies that the lone pair on the nitrogen is pushed into the pyrrole ring away from the carbonyl. This also applies to the pyridine examples indeed data the pyridine analogues are very consistent in the pyrrolizinone ring compared with the benzopyrrolizinone.

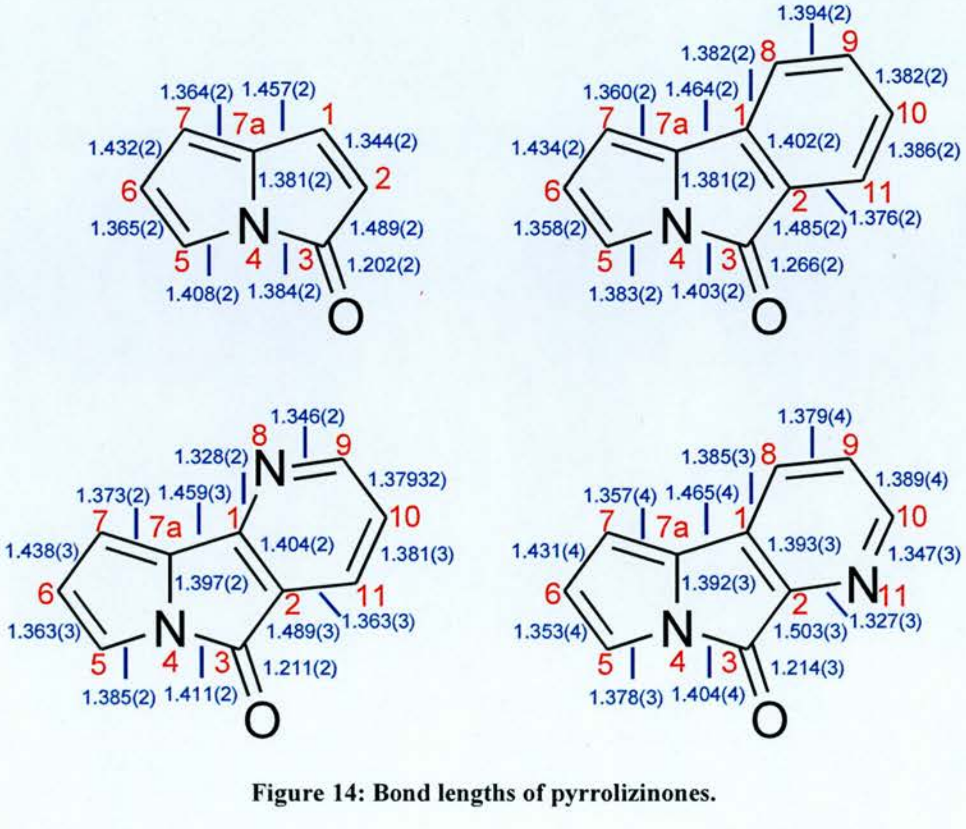


Figure 14: Bond lengths of pyrrolizinones.

There is also some evidence that one of the resonance structures around the pyridine ring is more favoured than the other, it can clearly be seen that in 9-aza analogue there is a trend towards alternating long and short bonds around the ring.

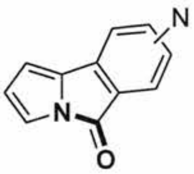


Figure 15: The amide linkage.

NMR Spectra of pyridopyrrolizinones

Other observations may be made with regard to the ^{1}H NMR chemical shifts of each of the protons in the system. It can be clearly seen that the position of the nitrogen in pyridine ring has little effect on the chemical shifts of the protons in "west" ring of the pyrrolizinone. It is thus clear that the chemistry of the "west" ring is independent of the fused pyridine ring on the "east" side of the molecule. However the chemical shifts on the pyridine ring are greatly affected by the position of the nitrogen. As expected the nitrogen has effect of deshielding adjacent protons producing noticeably higher chemical shifts (**Table 3**).

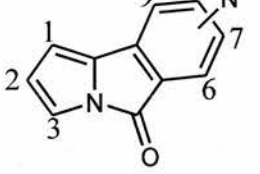


Figure 16: Azapyrrolo[2,1-*a*]isoindol-5-ones.

Proton/Carbon	6-aza	7-aza	8-aza	9-aza
1	6.33/108.90	6.29/111.53	6.33/109.12	6.48/110.21
2	6.20/116.26	6.44/118.41	6.24/118.41	6.21/121.71
3	7.09/116.56	7.11/114.56	7.08/117.86	6.98-7.06/118.51
6	-	8.80/155.84	8.58/149.04	7.81/133.32
7	8.44/147.38	-	8.67/141.00	6.98-7.06/118.51
8	7.61/125.69	8.65/146.71	-	8.44/154.11
9	7.30/126.32	7.23/118.52	7.53/118.93	-

Table 3: Chemical shifts of the protons and associated carbons in the azapyrrolizin-3-ones.

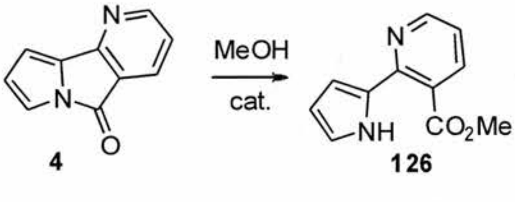
Also of note is the typical ^{13}C NMR chemical shift of the carbonyl carbon this is usually found at $\delta(^{13}C)$ 160; this is also the case with these aza-systems. From HSQC experiments each non quaternary carbon was assigned to its particular proton, this revealed some trends in the chemical shifts of these carbons. It can be noted that the carbons in the pyrrole ring appear at similar chemical shifts in each of the four compounds. C1 appears at the lowest shift with C2 and C3 appearing at higher chemical shifts. In the pyridine ring the effect of the nitrogen atom on the chemical shift is clearly demonstrated with the highest chemical shifts appearing at the carbons adjacent to the pyridine nitrogen as expected. This supports the conclusions drawn from the ^1H NMR spectra, that the “west” ring is not particularly affected by the position of the of the nitrogen atom in the pyridine ring.

Reactivity Of Pyridopyrrolizinones.

The reactivity of the pyridopyrrolizinones is best described by considering the three main sites of reaction of pyrrolizinones, the carbonyl centre, the pyrrole ring and the enone double bond in the "east" ring. In the case of pyridopyrrolizinones the double bond is blocked by the presence of the pyridine ring therefore only reaction at the carbonyl and in the pyrrole ring is possible. It was chosen to use **79** as a typical pyridopyrrolizinone to demonstrate the reactivity at these positions.

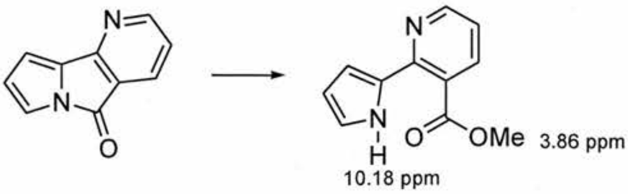
Reactions at the carbonyl centre.

The reaction with methanol is a well known reaction of pyrrolizinones.[7] and so the reaction of 9-azapyrrolo[2,1-*a*]isoindol-5-one **4** with methanol was studied. The pyrrolizinone **4** was dissolved in [$^2H_4$] methanol producing a bright yellow solution and the ^{1}H NMR spectra recorded periodically. It was observed that this compound appeared to be relatively stable with respect to ring opening in methanol. The ring opening took 14 days to reach completion to the ester **126** under these conditions, upon which the solution had decolourised. The same reaction was carried out in the presence of one drop of Hünig's base this time in MeOH, this catalysed the reaction and it reached completion instantaneously.



Scheme 43: Ring opening in methanol.

This was clearly indicated by the disappearance of the signals due to **4** and the clear observance of signals due to **126**. The most distinctive of these were the ester methyl signal at 3.86 ppm and the NH signal at 10.18 ppm **(scheme 44)**.



Scheme 44

It has been shown in previous work[12] that similar compounds also containing basic nitrogen atoms **98** and **127** (**Figure 16**) catalyse the ring opening. It was observed that when the N is in the "west" ring of the pyrrolizinone as in the imidazole systems the rate of ring opening was greatly increased. This can be rationalised by considering the pK_a of the basic nitrogen atoms (**Table 4**).

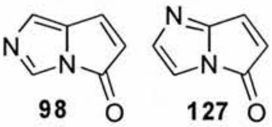


Figure 17

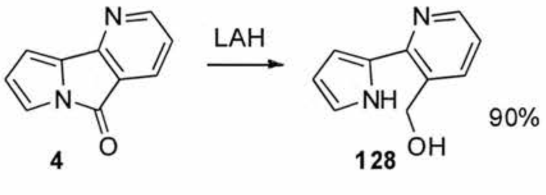
	$pK_a\,(BH^+)$
Imidazole	7.1
Pyridine	5.2

Table 4

The pK_a data show that the imidazole system is around one hundred times more basic than the pyridine system, which may explain why the rate of ring opening is much enhanced in the imidazole system. Alternatively, the imidazole is a better leaving group than the pyrrole system.

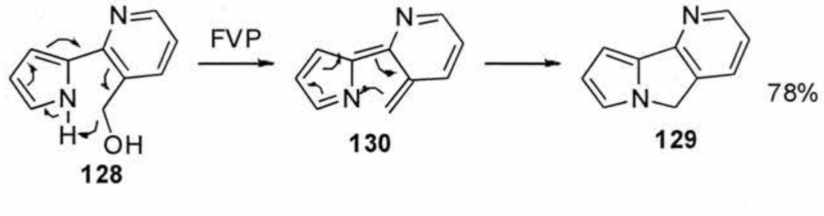
Reaction with LAH.

This is a reported reaction for pyrrolizinones,[19] (**Scheme 45**) but the product of this reaction is rather unusual for the LAH reduction of an amide. The usual reaction of LAH reduction of an amide results in the removal of the carbonyl oxygen leaving the amine. However in the reaction with pyrrolizinones the NH-pyrrole is a good leaving group which leads to the formation of a ring opened product. This is demonstrated by the reaction of **4** with LAH which leads to the alcohol **128**, in 90% yield (**Scheme 45**). Special care was required in this reaction as the usual workup for LAH reactions is an acidic workup; for this reaction this would not have been suitable due to the presence of a basic nitrogen. Instead the use of a basic workup was used, even in the presence of dilute base **128** was still isolated.



Scheme 45

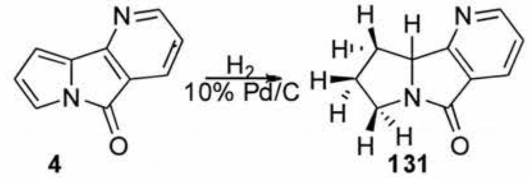
The alcohol **128** can be pyrolysed to generate the pyridopyrrolizine **129**; this proceeds *via* the loss of water to generate the intermediate **130** followed by cyclisation onto the nitrogen atom (**Scheme 46**). This reaction proceeds in 73% yield, the pyrrolizine **98** is the product that would be expected if the LAH reduction proceeded in the standard manner. Thus this is a general viable route to pyrrolizines from pyrrolizinones.



Scheme 46

Reaction on pyrrole ring.

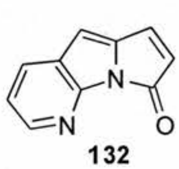
The hydrogenation of 9-azapyrrolo[2,1-*a*]isoindol-5-one **4** was carried out at 200 psi over 10% Pd/C yielding the hydrogenation product **131**. This demonstrates the reactivity of the pyrrole side of the pyrrolizinone. This is also an example of how the fused pyridine ring on the "east" ring of the molecule prevents hydrogenation of this double bond but does not effect the chemistry of the "west" ring of the pyrrolizinone (**Scheme 47**).The reasons for the facile hydrogenation of the pyrrole ring is discussed in greater depth later **(page 97).**



Scheme 47: Hydrogenation of pyridoptrrolizinones.

Attempted synthesis of 5-azapyrrolo[1,2-*a*]isoindole-3-one.

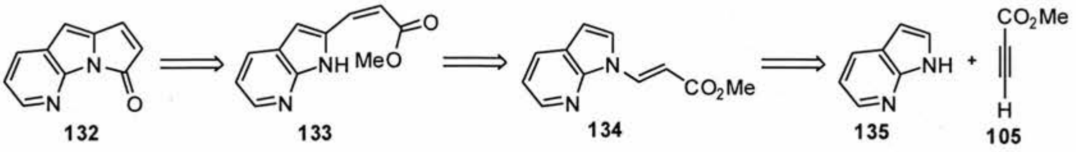
The synthesis of 5-azapyrrolo[1,2-*a*]isoindole-3-one **132** was attempted as it is an analogue of the pyridopyrrolizinones, in **132** the pyridine ring is attached to the "west" ring of the pyrrolizinone (**Figure 18**).



132

Figure 18

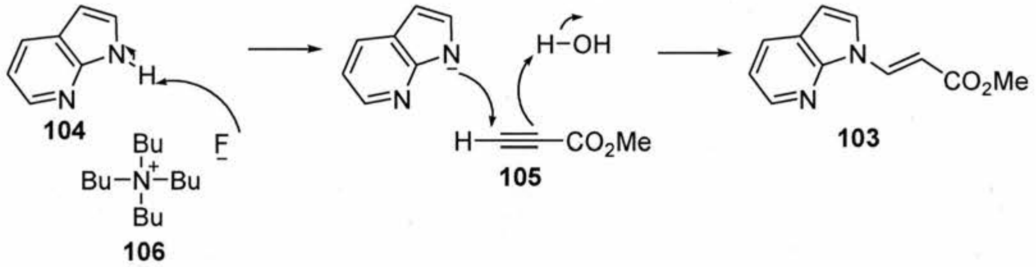
A retrosynthetic analysis of this compound (**Scheme 48**) was carried out, the ring closure step may be carried out by the FVP of the 2-propanoate **133**. It was believed that this could be obtained by the thermal rearrangement of the *N*-substituted ester **134**. From previous experience[31] it was reasonable to suggest that under FVP conditions the *N*-substituent would migrate to the 2-position as this is the mechanism for the synthesis of the pyridopyrrolizinones. The *N*-propenoate can be made by the previously reported route to *N*-substituted indole derivatives by reaction of 7-azaindole **135** with methyl propynoate in the presence of TBAF as a base.



Scheme 48: Retro synthesis of 5-azapyrrolo[1,2-*a*]isoindole-3-one.

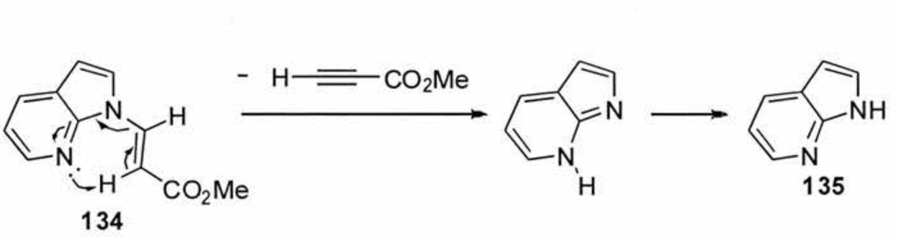
It is clear that there are again four possible isomers of this system again differing in the position of the nitrogen in the pyridine ring. The attempted synthesis of **132** was chosen because of the availability of the starting material 7-azaindole **135**; the other azaindoles are not commercially available.

The synthesis therefore started from 7-azaindole **104**, the reaction with propynoic acid methyl ester **105** in the presence of TBAF **106**, used to deprotonate the nitrogen thus activating it towards reaction with methyl propynoate **444**. This produces the *N*-propenoate **134** in a 2:3 ratio of *cis:trans* isomers (**Scheme 49**). There was no need to separate the isomers as in the FVP step rapid isomerisation would occur.



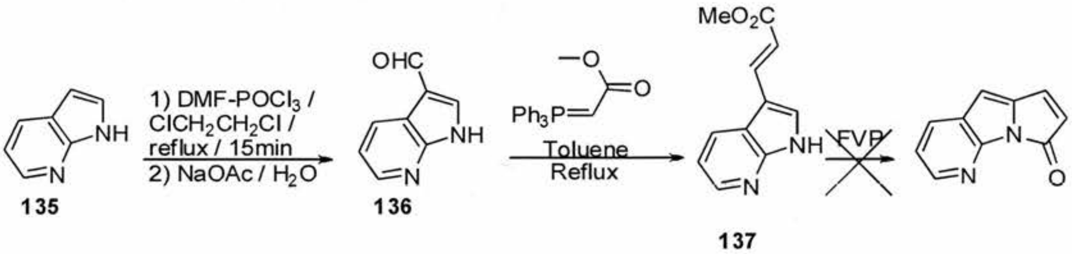
Scheme 49

The pyrolysis of this *N*-propenoate **134** did not produce the desired pyrrolizinone. Instead of migrating to the 2-position the propynoic acid methyl ester had been eliminated from the reaction giving 7-azaindole **135** as the sole product. It is suggested that the mechanism of this reaction involves the nitrogen of the "pyridine" ring, which abstracts a hydrogen facilitating the loss of the propynoic acid methyl ester (**Scheme 50**).



Scheme 50

In an attempt to overcome this problem the 3-propenoate **137** was synthesised; this also should undergo a migration under FVP conditions to give the 2-propenoate which could then cyclise to form the pyrrolizinone. A Vilsmeier reaction was carried out to formylate the 3-position of the 7-azaindole producing **136**, which gave the 3-propenoate **137** after Wittig reaction. The pyrolysis of this compound did not yield any recognisable product, in this case the precursor proved to be very involatile and decomposed in the inlet oven before it vaporised (**Scheme 51**).



Scheme 51

Conclusions.

It has been shown that the cascade mechanism can be extended to the synthesis of the four pyridopyrrolizone isomers **1**, **2**, **3**, and **4**. The structure of two of the isomers were confirmed by X-ray crystallography confirming the position of the nitrogen atoms in the cyclisation. The chemistry of the pyridopyrrolizinones has been compared to that of the parent molecule pyrrolizin-3-one in the hydrogenation reaction of the pyrrole ring and in reaction with methoxide and LAH at the carbonyl, it has also been shown that FVP of the ring opened alcohol **128** produces the pyrrolizine **129**.

Catalysis in FVP reactions.

The following chapters use catalysts in the FVP furnace tube, this is a relatively new concept that has been investigated within the group.[31] The transition metal oxides WO_3 and ZnO were chosen because of their high melting points and both showed catalytic properties in FVP.

The use of WO_3 as a catalyst has been reported in the literature and a significant amount is known about its structure and surface at elevated temperatures.[32] However, the literature studies on WO_3 are all approached from a physical chemistry point of view and few synthetic uses are reported. The literature studies of WO_3 surface reactions all use very carefully prepared surfaces by vapour deposition, in our work the WO_3 surface was not carefully prepared as for synthetic purposes this would not be viable as the complicated step would have detracted from the simplicity of our strategy.

A number of properties of the surface of WO_3 have been reported. Firstly it is reported that the surface contains Lewis acid sites. Secondly it is reported that the pyrolysis of hydrocarbons over the surface produces Brønsted acid sites, therefore during a pyrolysis the first small amount to pass over the surface is sacrificed to produce these Brønsted acid sites. It is also reported that these sites are stronger than 100% sulfuric acid. Thirdly a direct correlation is noted between the number of the Brønsted acid sites and the ability to decompose propan-2-ol. Fourthly it is also noted that the WO_3 surface also coordinates to alkenes. It can therefore be considered that the surface of WO_3 is a mixture of Lewis and Brønsted acid sites **(figure 19)**.

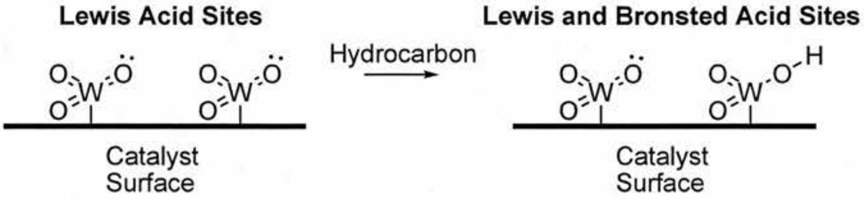


Figure 19: The formation of Bronsted acid sites on WO3

The crystallographic phases of WO_3 are also reported to change as it is heated, the first phase change occurs at ~450 °C and the second occurs at ~750 °C, this coincides with an observed colour change which occurs at ~450 °C where the WO_3 change from pale green to orange.

The use of WO_3 as a catalyst in FVP reactions had been previously investigated, for these reactions the WO_3 chosen for use was a commercially available WO_3 powder. This was packed into the furnace tube in two portions of 10 g and held in place by firmly placed silica wool producing two discs of WO_3 in the central area of the furnace tube. The catalyst is activated by roasting in air at 600 °C before cooling to the desired temperature for the reaction required **(figure 20)**.

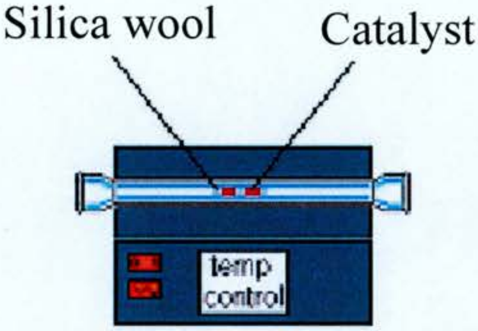
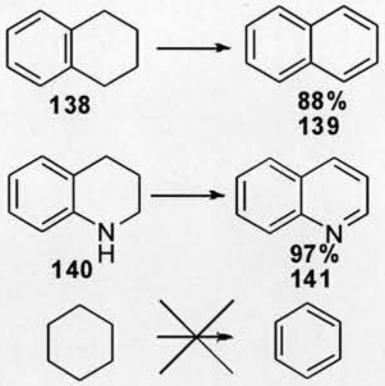


Figure 20: Catalyst in the furnace tube

During the previous work within the group it has been shown that WO_3 can be used as dehydrogenation catalyst in FVP reactions.[33] It was demonstrated that WO_3 would dehydrogenate and aromatise many compounds, it was shown that tetrahydronaphthalene **138** can be cleanly converted to naphthalene **139** (T_f = 500 °C) in an 88% yield. It can also be shown that tetrahydroquinoline **140** can be converted to quinoline **141** (T_f = 500 °C) in an almost quantative yield (97%). However the FVP of cyclohexane over WO_3 does not give benzene only unreacted starting material is recovered **(scheme 52)**.



Scheme 52: Dehydrogenation reactions with WO_3

It is belived that the Brønsted acid sites are responsible for the dehydrogenation reactions. It believed that as in the case of **138** and **140** the starting material must be on the thermodynamic path towards the stable fully aromatic system for the catalyst to produce dehydrogenation. This is supported by the fact that cyclohexane is not dehydrogenated to give benzene. This is also related to the previously known fact that alkenes coordinate to the surface of WO_3 suggesting that in the absence of an alkene the pyrolysate simply passes over the catalyst surface without interaction, therefore no reaction occurs. This suggests that dehydrogenation reactions begin adjacent to the original alkene followed by sequential dehydrogenation's around the ring **(figure 21)**.

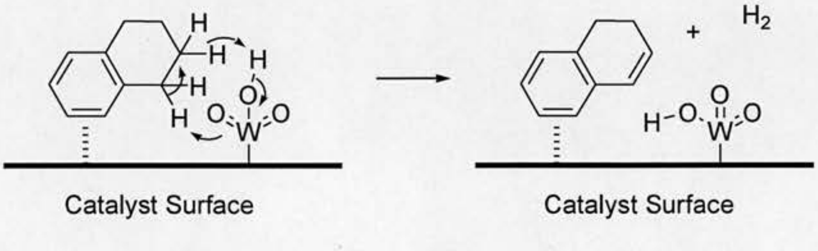
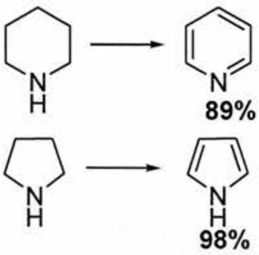


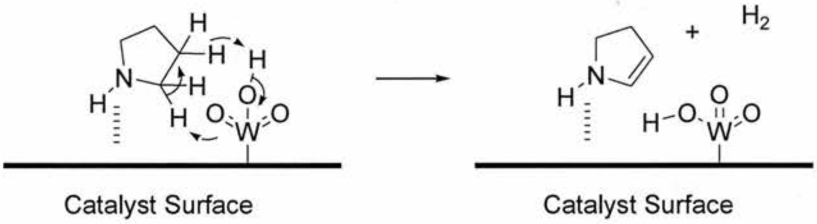
Figure 21: Proposed mechanism for dehydrogenation

During my research on dehydrogenation reactions I investigated whether the precursor required the presence of an alkene in the precursor, thus the precursor would not be on the downward thermodynamic path towards aromaticity. The first reactions investigated were the dehydrogenation of piperidine to give pyridine and the reaction of pyrrolidine to give pyrrole, both of these reactions occur in high yields **(scheme 53)**.



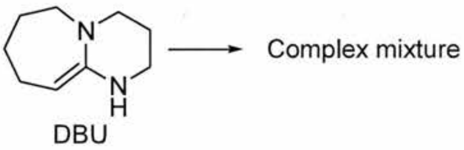
Scheme 53: Dehydrogenation of piperidine and pyrolidine

In these cases the reaction must by a similar mechanism as before, however this suggests that a previously unreported property of WO_3 must be acting to give these results. It is from these reactions that it is suggested that the WO_3 surface not only can coordinate to alkenes but also to an NH. This is supported by the previously reported observation that cyclohexane does not dehydrogenate to give benzene and that the reaction of tetrahydroquinoline to give quinoline occurs in a higher yield than the reaction of tetrahydronaphthalene to give naphthalene **(scheme 54)**.



Scheme 54: Dehydrogenation of pyrrolidine

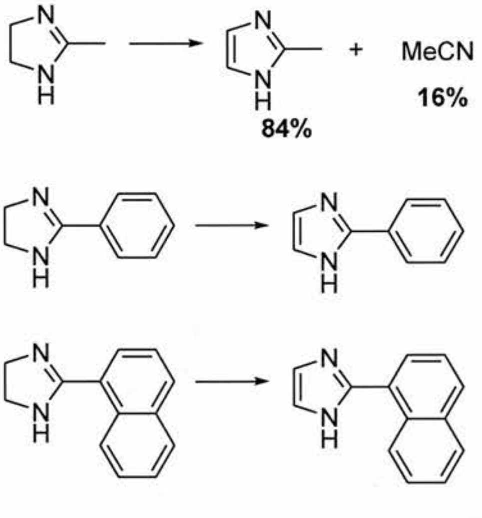
It was also investigated whether it was necessary for the product of the dehydrogenation to be aromatic, so the FVP of DBU over WO_3 was studied. The FVP was carried out at temperatures from 450 – 600 °C over WO_3. This proved to be unsuccessful in producing any clean products, with the NMR spectrum of the crude pyrolysate showed the presence of multiple compounds none of which could be identified **(scheme 55)**.



Scheme 55: Attempted dehydrogenation of DBU

From these results a set of preconditions for successful dehydrogenation by WO_3 in FVP has been set out. The precursor must have possible coordinating sites eg. either on alkene or an NH to coordinate and the desired product must be aromatic. Given these conditions the chemistry of dehydrogenation over WO_3 was extended to more synthetically useful reactions.

This was extended to the dehydrogenation of substituted imidazolines, to give substituted imidazoles. It was believed that these reactions would work well as the precursor possesses an NH as well as a double bond and the product is aromatic, thus meeting all of our new preconditions for successful reaction. It was shown that all of these reactions proceeded cleanly and in high yields, in the methyl, phenyl and naphth-1-yl cases **(scheme 56)**.



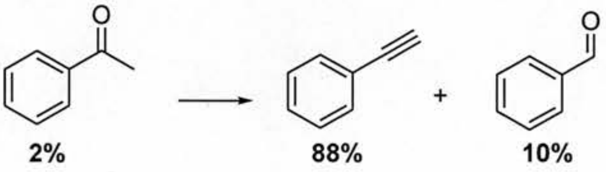
Scheme 56: Dehydration of 2-methylimidazoline

The use of WO_3 as a dehydration agent has also been demonstrated,[2] a number of substituted amides have been converted to their corresponding nitriles all in high yields.

R = Ph	**97%**	**400 °C**
R = o-$H_2NC_6H_4$	**87%**	**350 °C**
R = o-HOC_6H_4	**85%**	**400 °C**
R = *t*-Bu	**87%**	**350 °C**
R = $Me(CH_2)_4$	**88%**	**300 °C**

Scheme 57: Dehydration of amides

It can clearly be seen that these require very low furnace temperatures between 300 – 400 °C. The dehydration of acetophenone had also been demonstrated to give the corresponding acetylene but these reactions require a significantly higher furnace temperature (625 °C) **(scheme 58)**.



Scheme 58: Dehydration of ketones

The FVP of acetophenone was further studied by the present author and the reaction was scaled up and it was found that the amount of product decreased as the reaction was scaled up but at 500 mg scale only 53% phenylacetylene was present **(figure 22)**.

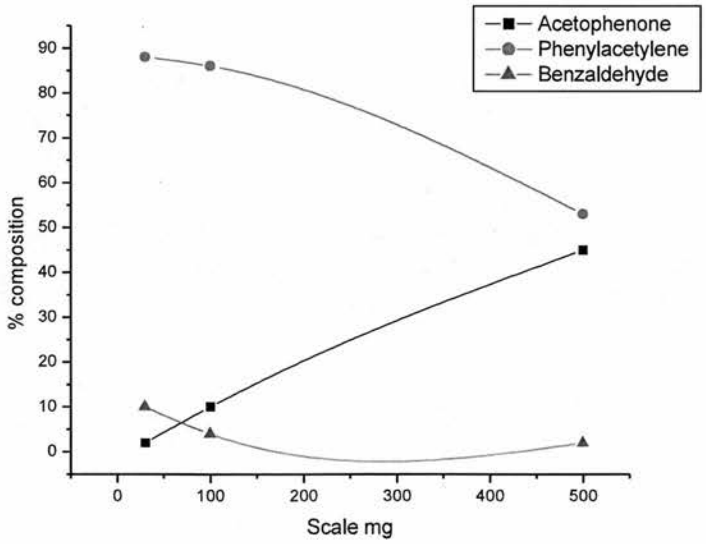
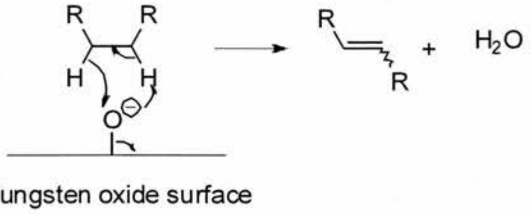


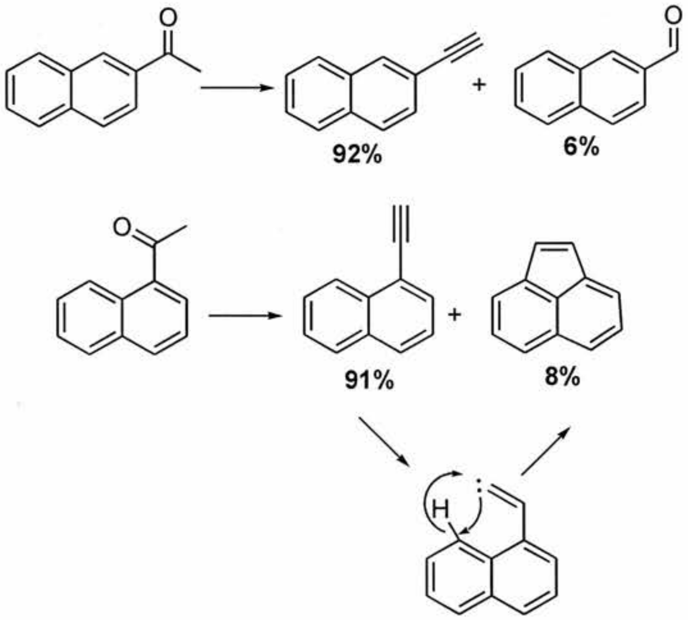
Figure 22: Scale up of acetophenone FVP

During the pyrolysis a small amount of water was observed suggesting that the catalytic sites are being destroyed and the WO_3 surface is acting as a reagent in this reaction and as a catalyst as is the case in the previously reported reactions. It is also noteworthy that the furnace temperature required is much higher (625 °C) as compared to 400 °C required for other dehydrations. It is suggested that at higher furnace temperatures enough energy is present to facilitate the dehydration by the formation of water on the surface of the WO_3 which is then easily expelled and in so doing destroying the catalytic site **(scheme 59)**. After the reaction the WO_3 is dark blue in colour and this is believed to be a non-stoichiometric oxide as reported in the literature.[32] The WO_3 can be regenerated by heating in air, after five minutes the WO_3 returns to being orange in colour, and is ready to be used again in another reaction. The same sample of WO_3 can therefore be used indefinitely.



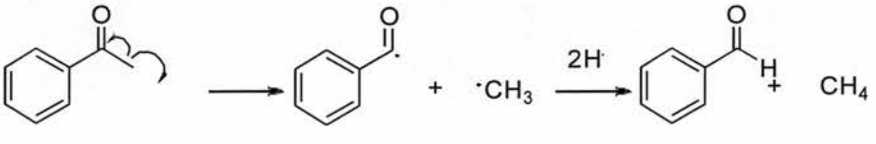
Scheme 59: Possible destruction of catalytic sites

In a follow up to this successful dehydration reaction the dehydration of 1-acetyl-naphthalene to give 1-ethynylnaphthalene was also investigated. In this case a small amount of acenaphthene was produced. This is due to the acetylene being in equlibrium with the carbene which subsequently inserts into the CH bond. The dehydration of 2-acetyl-naphthelene was also investigated with 2-ethynyl-naphthalene being produced in good yield **(scheme 60)**.



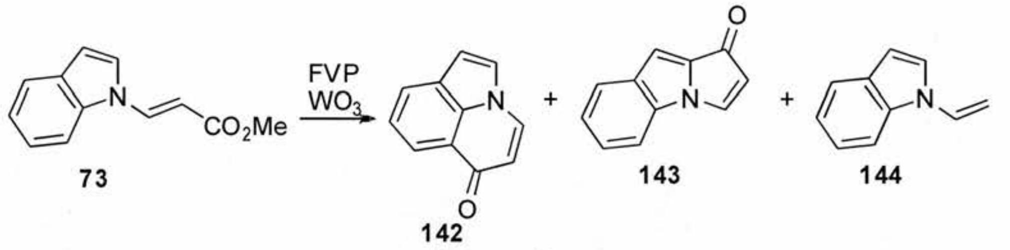
Scheme 60: Dehydration of naphthalenes

In the cases of 2-acetylnaphthalene and acetophenone a small amount of the corresponding aldehyde is also observed, this was unexpected and must be formed by a competing radical mechanism. It is suggested that the WO_3 catalyses the radical cleavage of the methyl group which can then subsequently abstract H$^{\cdot}$ from the side of the furnace tube **(scheme 61)**.



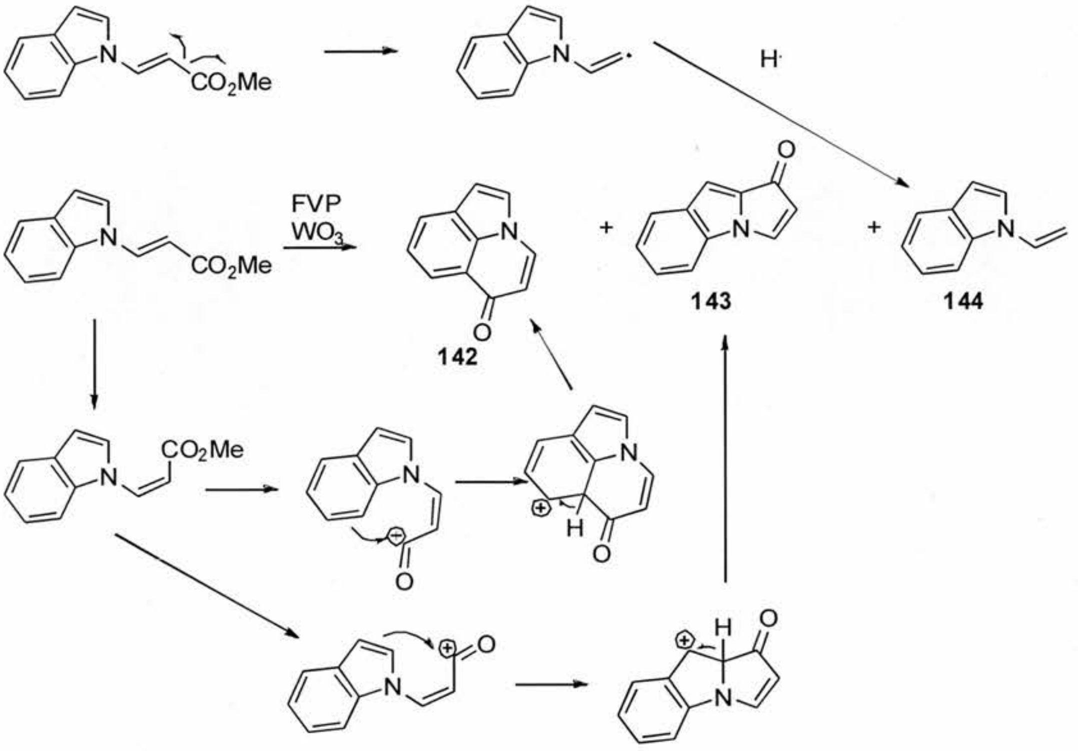
Scheme 61: Radical formation of aldehydes

Other work within the group has also shown WO_3 to be a cyclisation catalyst.[33] The aim of this work was to investigate the formation of **142**, it was first noted that the FVP of **73** over WO_3 produced the desired product **143** but also formed benzopyrrolizin-1-one and *N*-vinylindole **144 (scheme 62)**.



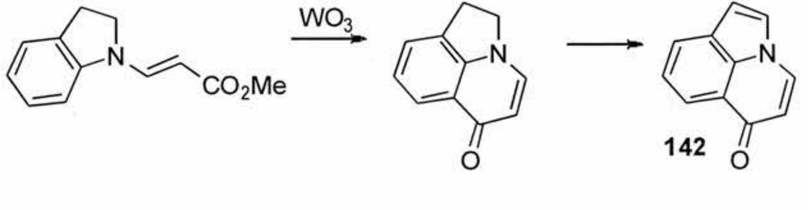
Scheme 62:

From this result it was assumed that WO_3 surface catalyses an intramolecular Friedel Crafts substitution. The mechanism is believed to follow *E-Z* isomerisation followed by an intramolecular substitution reaction. This must occur on the surface of the catalyst as ionic mechanisms are not observed in FVP reactions as the thermal energy required for ionisation is much higher than that obtainable from an FVP furnace. At low temperatures the vinyl product is the major product this is obtained by radical cleavage of the ester followed by abstraction of H$^{\cdot}$. As the furnace temperature was increased the amount of **142** and the benzopyrrolizin-1-one increased but at no temperature was a clean product obtained **(scheme 63)**. It can be suggested that product **142** is favoured over **143** for steric reasons due to the size of the ring being formed. This reaction is discussed in further detail later **(page 74)**.



Scheme 63: Mechanism of FVP of 73 over WO3

As this reaction did not produce one clean product another route was investigated which involved the use of the an indoline derivative. This produces the cyclisation much more cleanly as the indoline system is more electron rich than in the indole system. As **142** is the major product it is believed that the ring closure occurs first; this is then followed by dehydrogenation to give the final product **142 (scheme 64)**.



Scheme 64: FVP of 144

This cannot proceed by dehydrogenation followed by cyclisation as for this to happen the product distribution would be expected to be similar to the case of the FVP of the indole derivative **73**.

Other compounds are known to have catalytic effects in FVP reactions, the use of ZnO_2 has been shown to dehydrogenate alcohols to aldehydes and ketones.[34] It is believed that many other compounds may be of use as catalysts in FVP, the metal oxides are of particular interest as it has already been shown that two of these have been shown to be active in FVP. The metal oxides also have the advantage that most have high melting points, which is required for FVP.

Pyrrolizin-1-one introduction.

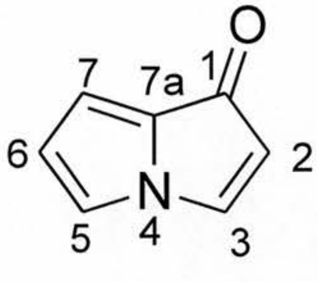


Figure 23: Pyrrolizin-1-one

Pyrrolizin-1-one is an interesting potentially antiaromatic compound, with only one reported synthesis in the literature.[35] The literature synthesis is a five-step method with an overall yield of 0.8%, and as such nothing is known about the chemistry of this compound. The reported synthesis of pyrrolizin-1-one starts from the diacid **145a**, which reacts with PCl_5 to generate the di-acid chloride **145** which undergoes an intramolecular electrophilic substitution reaction to give 1-oxo-1*H*-pyrrolizine-2-carbonyl chloride **146 (scheme 65)**.

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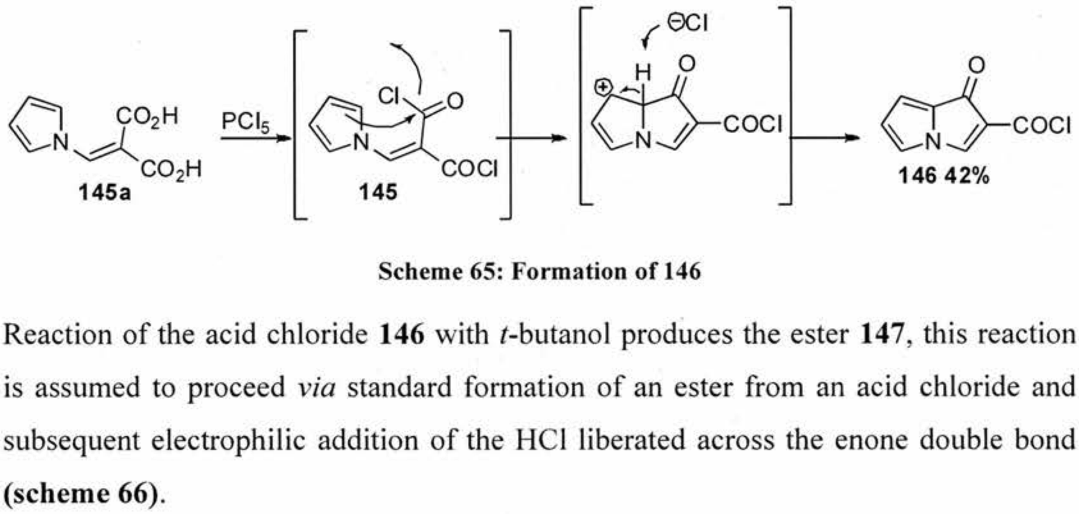
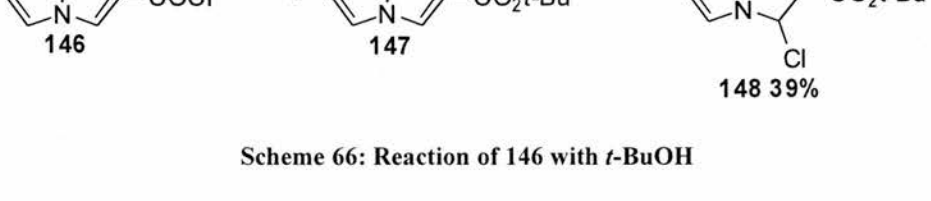


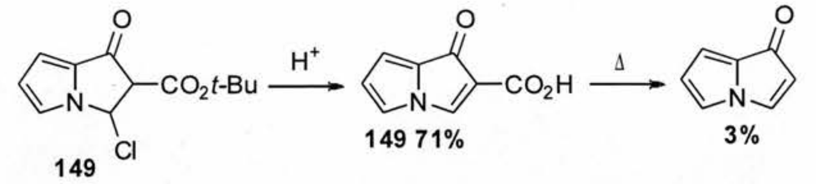
Scheme 65: Formation of 146

Reaction of the acid chloride **146** with *t*-butanol produces the ester **147**, this reaction is assumed to proceed *via* standard formation of an ester from an acid chloride and subsequent electrophilic addition of the HCl liberated across the enone double bond **(scheme 66)**.



Scheme 66: Reaction of 146 with *t*-BuOH

Acid catalysed hydrolysis of the ester followed by elimination of HCl gave the β-keto acid **149**, which can be decarboxylated to give pyrrolizin-1-one 6 **(scheme 67).**



Scheme 67: Ester hydrolysis and decarboxylation to give pyrrolizin-1-one

The spectroscopic properties and full assignment of its ^1H NMR spectrum are also reported **(figure 24)**. The long range coupling from H2-H6 is directly comparable to that observed in pyrrolizin-3-one.

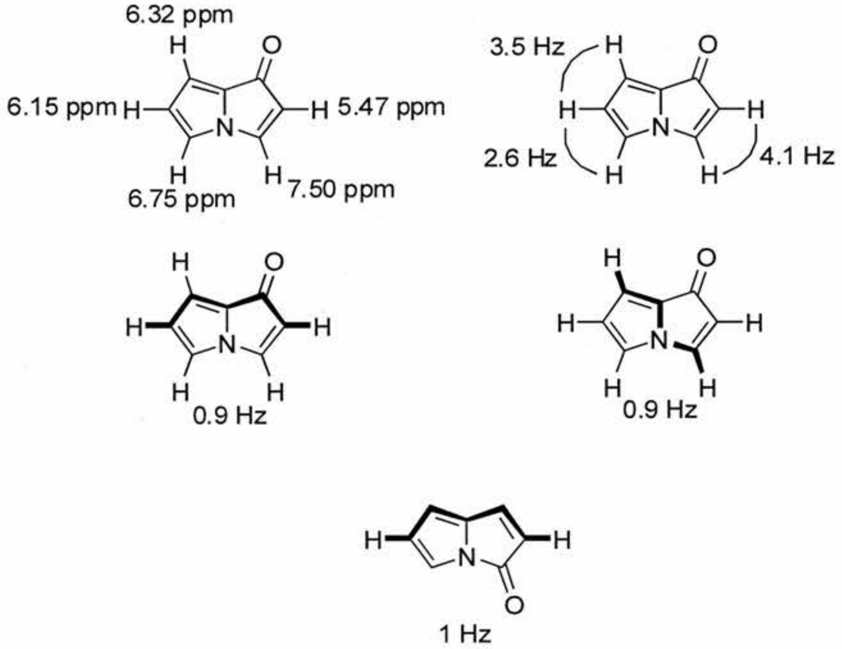
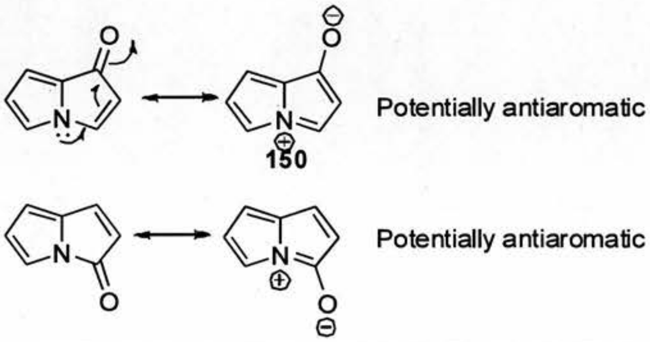


Figure 24: 1H NMR properties of pyrrolizin-1-one

The enone protons H2 at 5.47 ppm shows a characteristic coupling to H3 at 7.50 ppm of 4.1 Hz, the large difference in chemical shift between H2 and H3 is indicative of the push-pull delocalisation of the nitrogen lone pair through to the carbonyl oxygen **(scheme 68)** to give the resonance structure **150**. H2 also shows a further coupling to H6 at 6.15 ppm of 0.9 Hz and H3 shows coupling to H7 also of 0.9 Hz. The pyrrole proton H6 shows coupling to H6 of 3.5 Hz with H6 showing coupling to H5 at 6.75 ppm of 2.6 Hz, this is standard for a 1,2-disubstituted pyrrole. Like pyrrolizin-3-one the resonance form **150** can be suggested to be potentially antiaromatic. No chemistry of pyrrolizin-1-one has been reported, due to the poor yielding synthesis.



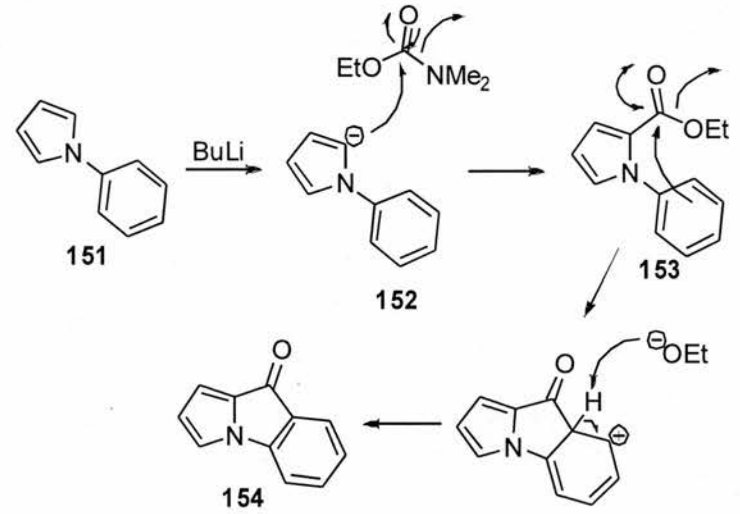
Scheme 68: Resonance structure of pyrrolizin-1-one

Synthesis of fused ring pyrrolizin-1-one analogues.

The synthesis of substituted pyrrolizin-1-ones has been reported as mostly fused ring analogues, with the ring closure of the ring containing the carbonyl group being the key step in the synthesis.

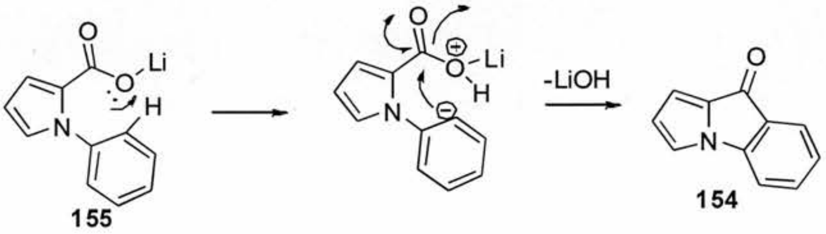
Intramolecular Friedel Crafts reactions:

The reaction of 1-phenyl-1*H*-pyrrole **151**, dimethylcarbamic acid ethyl ester and BuLi has been reported to produce pyrrole-[1,2*a*]-indol-9-one **154 (scheme 69)**.[36] The reaction is assumed to proceed by deprotonation of the pyrrole ring at the 2-position by the BuLi to give the intermediate **152** which can then attack the carbonyl with the dimethylamino acting as the leaving group to give **153**. This can then undergo an intramolecular Freidel Crafts reaction to give **154**.



Scheme 69: Formation of 154

The reaction of **151** with BuLi and CO_2 has also been reported to produce **154** and it is suggested that the BuLi deprotonates the pyrrole to give **152**, this then reacts with CO_2 followed by *O*-lithiation to give **155**. Subsequent deprotonation of the phenyl ring followed by attack of the carbonyl and loss of LiOH to give the benzopyrrolizin-1-one **154 (scheme 70)**.[37]



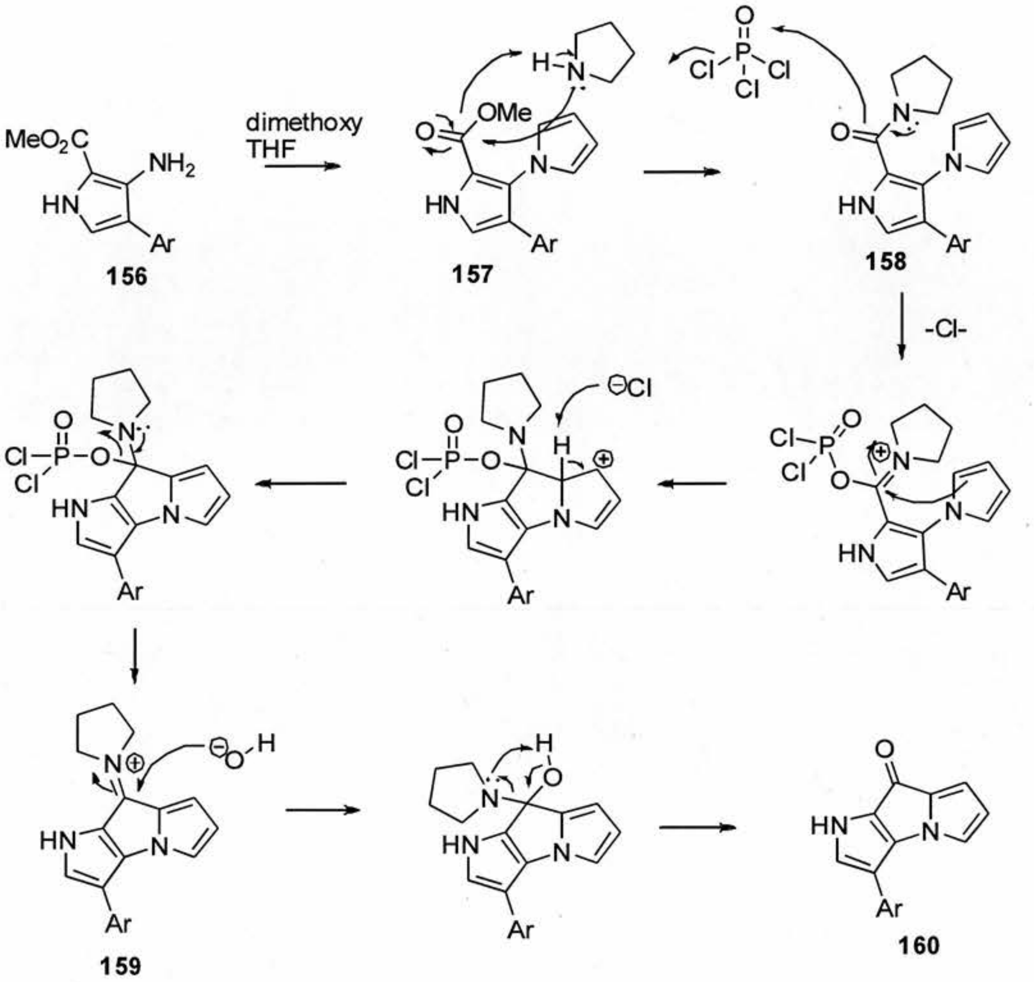
Scheme 70: Reaction of 151 with BuLi and CO_2

The formation of the pyrrole fused pyrrolizinone **160** has been reported by P. Dallemagne *et al*,[38] the reaction of the trisubstituted pyrrole **156** with dimethoxy THF produces the dipyrrole species **157**. This then undergoes nucleophilic substitution at the carbonyl with pyrrolidine to give **157**. The reaction of **157** with $POCl_3$ produces cyclisation by a Bischler-Napieralski reaction with the formation of the iminium salt **159**, base hydrolysis of the salt yields the pyrrolizinone **160**. The yield for the final step varies greatly depending on the Ar group from 5% for phenyl to 32% for 4-fluorophenyl.

Ar	Yield (%)
Phenyl	5
4-Fluoro-phenyl	32
4-Chloro-phenyl	16
4-Me-phenyl	23
4-MeO-phenyl	10

Table 5: Yields for imine cyclisation

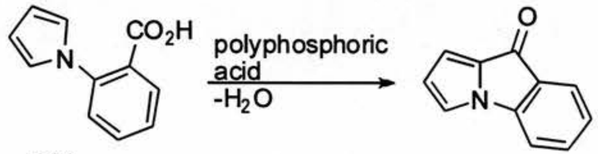
It is shown that there is no obvious correlation between the electron withdrawing nature of the substituents and the yield of the cyclised product, though the yield of cyclised product is increased when the pyrrole NH was protected. The yield of the 4-chlorophenyl derivative is increased from 16% to 72% with the Me protection of the pyrrole NH.



Scheme 71: Formation of pyrrolizinone *via* imminium salt

Intramolecular dehydration reaction:

The synthesis of pyrrole-[1,2*a*]-indol-9-one **162** has also been reported by intramolecular electrophillic substitution of **161** to close the carbonyl containing ring **(scheme 72).**[39] This uses the polyphosphoric acids affinity for water to facilitate the dehydration.



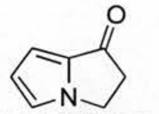
161

32%

Scheme 72: Dehydration of 161

The synthesis of dihydropyrrolizin-1-one analogues.

A number of natural products; butterfly pheremones **(figure 6)**, are related to pyrrolizin-1-ones; these are mainly derivatives of 2,3-dihydropyrrolizin-1-one.



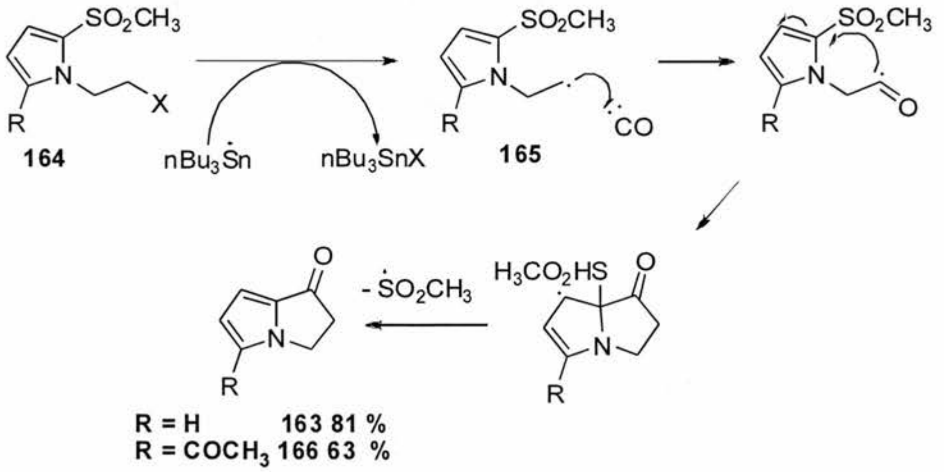
nordainidone

Figure 6: Butterfly pheremones related to pyrrolizin-1-one

There are a number of reported syntheses of 2,3-dihydropyrrolizin-1-one **163**, they are mostly either radical cyclisations or Hoesch reactions.

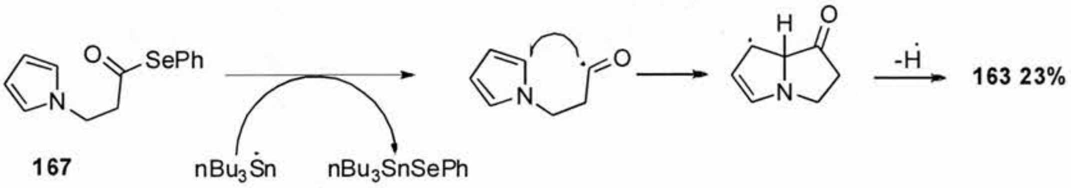
Radical synthesis of 2,3-dihydropyrrolizin-1-one:

The syntheses of **163** by radical mechanisms are based on intramolecular radical acylation reactions. In a synthesis proposed by Miranda *et. al.* the methylsulfonylpyrrole **164** is treated with nBu_3SnH and AIBN to generate the radical species **165**. The introduction of CO (80 atm) to the reaction mixture generates the acyl radical which cyclises followed by loss of the methylsulfonyl radical to give **163**; this method also was applied to the substituted analogue **166** albeit with reduced yield **(scheme 73)**.



Scheme 73: Radical cyclisation of 164 with CO

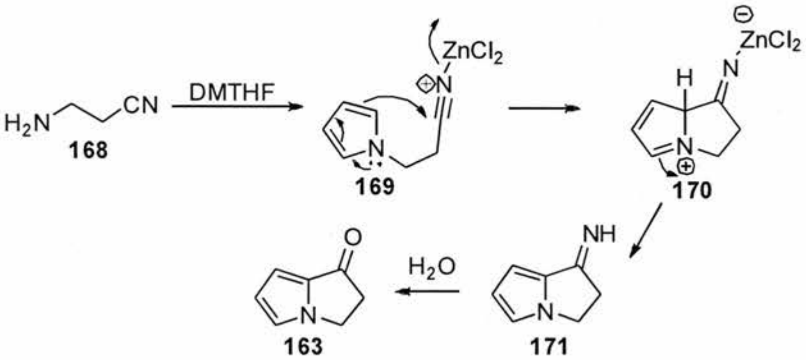
The radical cyclisation of the acyl radical was used in another synthesis by Allin *et al.* this synthesis uses a different radical precursor to eliminate the need for high pressure of CO.[40] The synthesis of **163** from the acyl selenide precursor **167** which generates the acyl radical followed by a subsequent cyclisation, followed by loss of a H radical to give **163 (scheme 74)**.



Scheme 74: Radical cyclisation from acyl selinide

The Hoesch reaction to 2,3-dihydropyrrolizin-1-one:

Another reaction to produce **163** is the Hoesch reaction of 1-β-cyanoethylpyrrole.[39] 1-β-Cyanoethylpyrrole was prepared by the reaction of the amine **168** with dimethoxy THF, the Hoesch reaction proceeds *via* the intramolecular cyclisation reaction of the activated species **169** to give the intermediate **170**. Loss of a proton and decomplexation gives the imine **171** that hydrolyses upon workup yielding **163 (scheme 75)**.

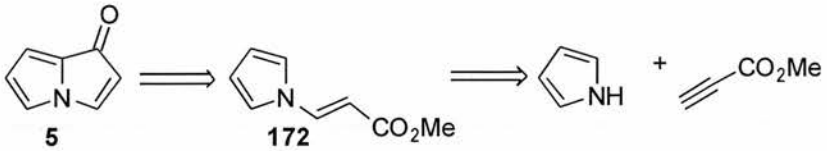


Scheme 75: Hoesch reaction.

Results and discussion: Pyrrolizin-1-one.

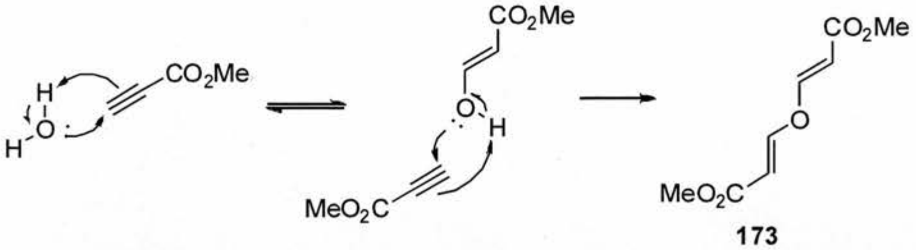
Synthesis of pyrrolizin-1-one

From the retrosynthetic approach **(scheme 76)**, the simple idea to synthesise pyrrolizin-1-one can be seen. It was proposed that using the new WO_3 catalysed intramolecular electrophilic substitution cyclisation reaction **(scheme 62)** the ester **172** could be used to produce pyrrolizin-1-one. The ester **172** is accessible from the reaction of commercially available methyl propiolate and pyrrole. This is a significantly simpler approach than the previously reported five step literature route.



Scheme 76: Retrosynthesis of pyrrolizin-1-one

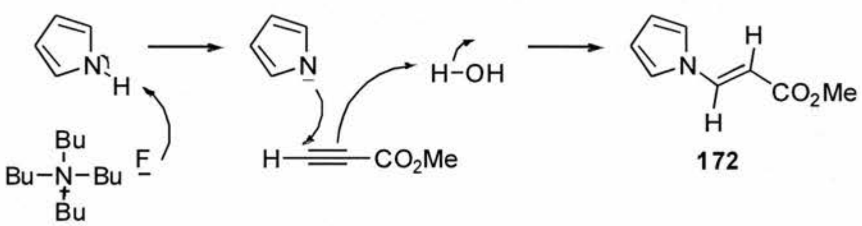
The synthesis of (*E*)-3-pyrrol-1-yl-acrylic acid methyl ester reproducibly had previously proved problematic, using the method of R. G. Tyas[2] for the reaction of indoles with methypropiolate, various conditions for the reaction of pyrrole with methyl propiolate were investigated. Firstly the same conditions were used, pyrrole was mixed with one equivalent of TBAF at room temperature for 30 min then methyl propiolate was added dropwise, the solvent was removed and then the dark oil was distilled to try to obtain the product. This produced a complex mixture in which little product was recognisable. Secondly all of the reagents were mixed together in equimolar quantities and heated under reflux for 1.5 h, the solvent was removed and the dark oil was extracted with hot hexane. The solvent was removed and the products separated by chromatography, the mixture was found to be a 1:1 mixture of (*E*)-3-pyrrol-1-yl-acrylic acid methyl ester **172** and 3-((*E*)-2-methoxycarbonyl-vinyloxy)-acrylic acid methyl ester **173**. From this result it was apparent that the methyl propiolate was undergoing a base catalysed condensation with itself and the water present in the TBAF solution **(scheme 77)**.



173

Scheme 77: Formation of 173

From the previous result it had became obvious that the addition of the methyl propiolate had to be carried out after all of the pyrrole had been deprotonated and the TBAF therefore consumed. As such the optimum conditions for this reaction involved pyrrole being dissolved in acetonitrile and heated under reflux with TBAF solution for 1 h to deprotonate the pyrrole, then the methyl propiolate was added dropwise and heating continued for a further 2 h. After cooling and removal of the solvent a black oil was obtained, extraction of this oil with hot hexane gave **172** in 88% yield as a white solid, sufficiently pure for CHN analysis **(scheme 78)**. Evidence of this mechanism is observed in that glassware used for this reaction becomes etched by the HF generated in situ. This reaction under these conditions has been shown to be reproducible, and these conditions have been used to react methyl propiolate with other heterocycles.

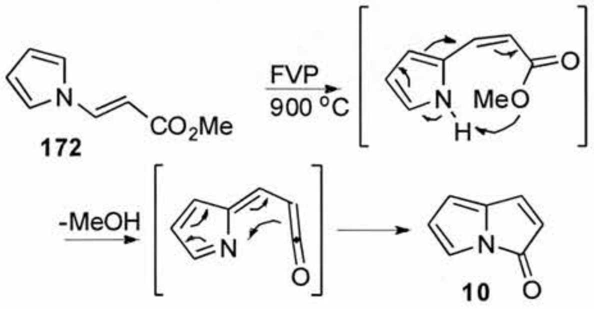


172

Scheme 78:Reaction of pyrrole with methyl propiolate

Only the *E* isomer of methyl-3-(pyrrol-1-yl)-acrylate was ever observed in this reaction characterised by the large coupling constant (14.1 Hz) observed between the protons of the double bond (δ_H 5.89 and 7.84).

FVP of methyl-3-(pyrrol-1-yl)-acrylate under various conditions was studied. At 500 °C, only starting material was recovered; at 900 °C, the sole product of this reaction was pyrrolizin-3-one **(scheme 79)**. This reaction proceeds *via* a migration to the 2-position then *E/Z* isomerisation to give the Z-isomer required for reaction, followed by loss of methanol to give the ketene then cyclisation to give pyrrolizin-3-one.

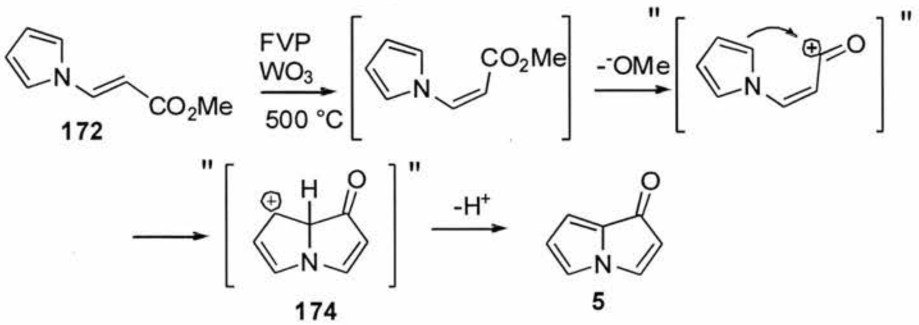


Scheme 79:Thermal product of FVP of 172

This demonstrates that although this is not the most efficient synthesis of pyrrolizin-3-one,[1] the pure thermal product obtained by the FVP of **172** is pyrrolizin-3-one.

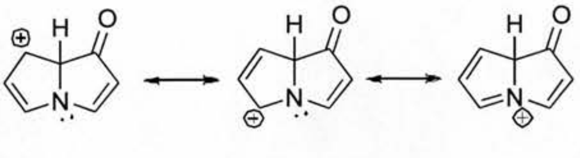
The FVP of **172** was carried out with a plug of silica wool in the furnace tube and a furnace temperature of 500 °C, again starting material was quantitatively recovered. This rules out the possibility of the silica wool playing a role in the reaction mechanism.

When **172** is subjected to FVP over a WO_3 catalyst pyrrolizin-1-one is formed, it is believed that the WO_3 surface facilitates an intramolecular electrophilic substitution reaction similar to a Freidel Crafts acylation **(scheme 80)**. At lower furnace temperatures a small amount of *N*-vinylpyrrole was observed but was not present at higher temperatures.



Scheme 80: Mechanism of formation of pyrrolizin-1-one

It is proposed that at active sites on the surface of the catalyst **173** undergoes *E/Z* isomerisation followed by loss of methanol to give the carbocation **174**, the carbocation is resonance stabilised by conjugation of the N lone pair **(scheme 81)**.



Scheme 81: Resonance stabilisation of the carbo cation intermediate.

This mechanism is only possible on the catalyst surface as ionic mechanisms do not occur under FVP conditions; in the gas phase the energy required to produce ionic species is extremely high as there is no solvation shell to stabilise the ion.

The composition of the pyrolysate at different furnace temperatures was investigated **(figure 24), (table 6).** The percentage compositions are calculated from NMR spectra of the crude pyrolysates, the enone doublet at 5.47 ppm was used to measure the relative amount of pyrrolizin-1-one. The three proton singlet from the starting ester at 3.79 ppm was used to calculate the amount of unreacted starting material, while the amount of the vinyl compound was calculated using the vinyl proton doublet at 5.65 ppm.

Furnace Temperature °C	% Composition starting material	% Composition pyrrolizin-1-one	% Composition N-vinyl pyrrole
200	100	0	0
250	79	21	0
300	54	39	7
350	0	82	18
400	0	100	0

Table 6: Temperature profile of pyrrolizin-1-one

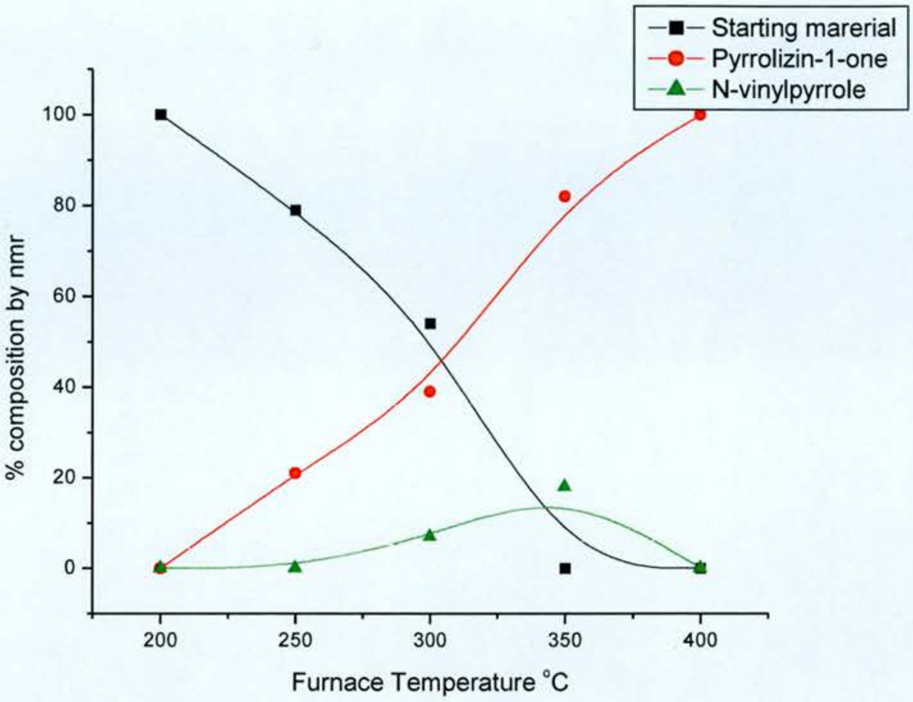
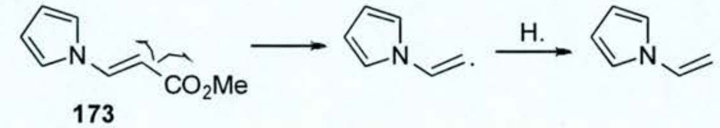


Figure 24: Temperature profile of pyrrolizin-1-one

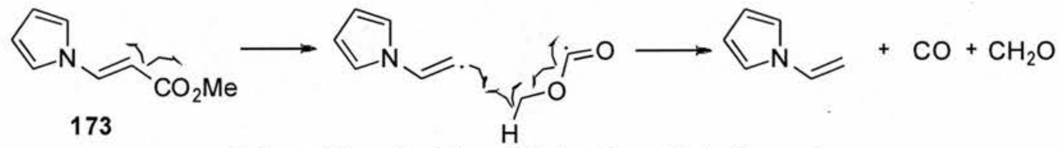
It can be clearly seen from this graph that pyrrolizin-1-one starts being formed at T_f = 250 °C, at 300 °C the appearance of *N*-vinylpyrrole was observed, increasing to a maximum of 18% at 350 °C. At 400 °C only pyrrolizin-1-one was formed with no N-vinylpyrrole observed. The general trend is as the temperature increases the amount of pyrrolizin-1-one increases, however the formation of *N*-vinylpyrrole must be considered. It is possible that the *N*-vinylpyrrole is formed by radical cleavage of the *E*-isomer of **172** at temperatures where *E-Z* isomerisation is no quantative **(scheme 82)**.



173

Scheme 82: Radical mechanism for formation of *N*-vinyl pyrrole

The most likely result of this radical mechanism would be the formation of CO and formaldehyde **(scheme 83)**, though no evidence of this has been observed. The absence of a significant pressure increase that would be expected by this mechanism could be explained due to the small scale of the reaction.



Scheme 83: radical loss of Co2 to form *N*-vinyl pyrrole

It is however evident that when sufficient energy is present for cyclisation this is the preferred reaction pathway. Further more it is also apparent from the NMR spectra of the pyrolysates at various temperatures that no *Z*-isomer of **173** is observed in the product mixtures. This suggests that *E/Z*-isomerisation plays a role in the rate determining step.

Following this study the scale up of this pyrolysis had to be investigated, the FVP was carried out on three different scales, 50, 100 and 200 mg. It was observed that the amount of pyrrolizin-1-one dropped dramatically as the reaction was scaled up **(figure 25)**. This is a typical example of how different sites on the surface of the WO_3 catalyse different reactions. It is believed that the site that catalyses the "electrophilic" substitution reaction is a minor site on the surface that becomes destroyed as the reaction proceeds. This is not likely to be the same site that facilitates dehydrogenation reactions as these are not generally subject to such scale up problems. The catalyst can be reactivated by roasting in air as is the normal procedure for reactivation, thus in this reaction the catalyst can be reused indefinitely.

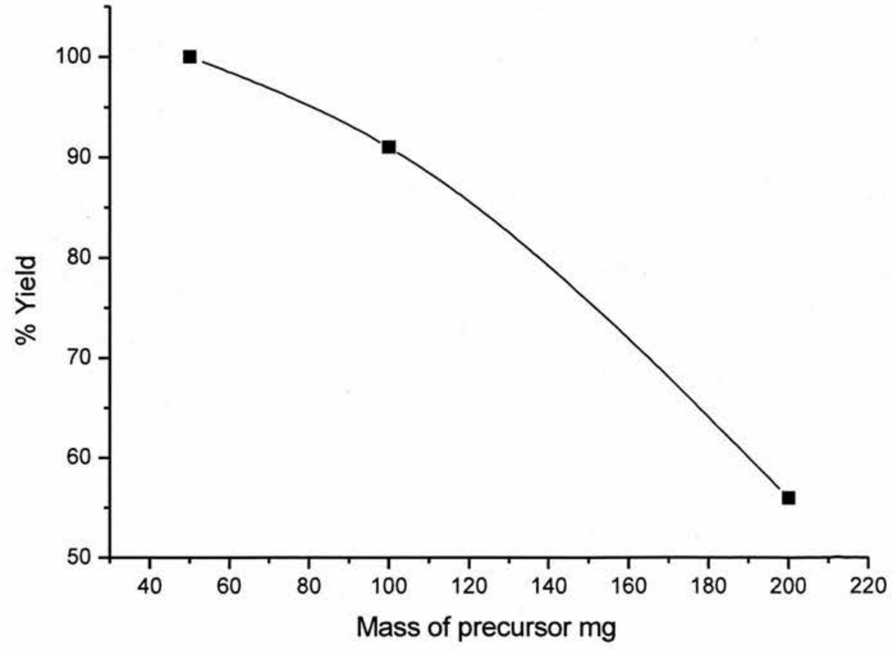
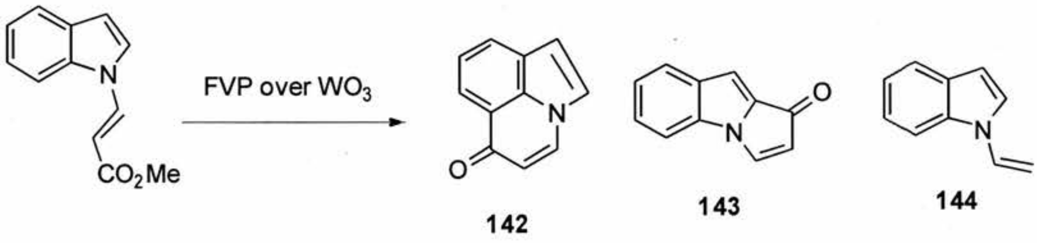
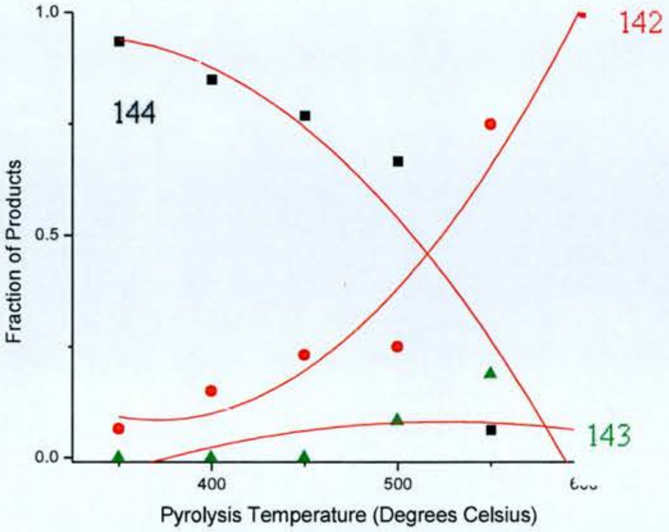


Figure 25: Scale up of pyrrolizin-1-one FVP

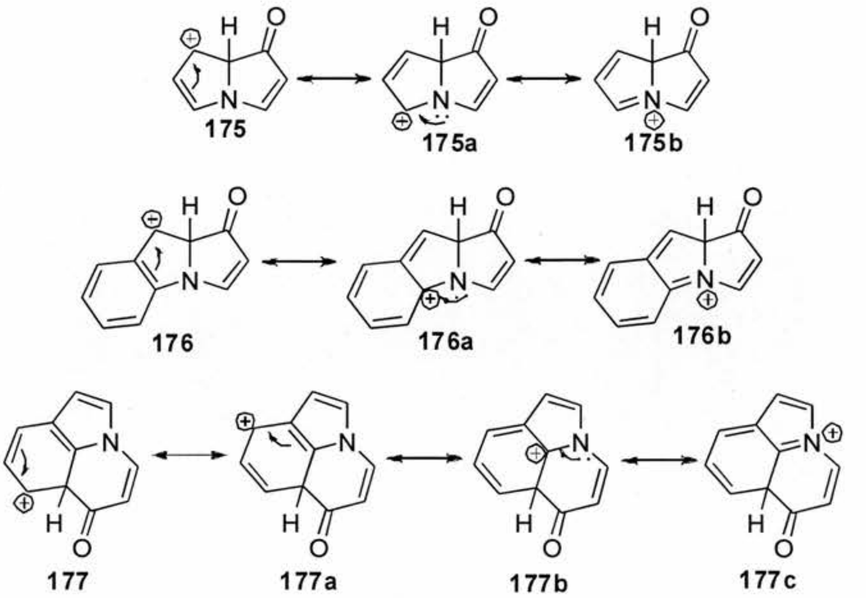
This can be directly compared to the FVP of the indole analogue which has already been briefly mentioned **(page 48)**, the temperature profile for this reaction shows some major differences.



Scheme 84

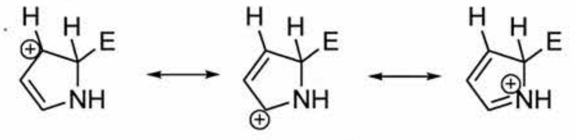


It can be seen that at 350 °C that the major product was **144**, this can be compared to the pyrrolizin-1-one example, where at this temperature there is 82% product and only 18% vinyl compound. In the pyrrolizin-1-one example at 400 °C only this product is observed however in the indole example case at this temperature the product composition is 85% vinyl **144** and 15% **142**. The vinyl compound **144** is persistent in the product mixture until 600 °C when the only product observed is **142**. Benzopyrrolizin-1-one is only observed in the product mixture between 450 and 600 °C reaching a maximum at 550 °C. The resonance structures of the carbocationic intermediates can be used to explain these observations **(scheme 85)**.

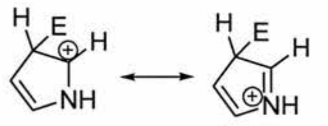


Scheme 85: Intermediates of cyclisation reactions.

The best way to compare these reactions is to consider the resonance stabilisation of the intermediates. In the reaction to give pyrrolizin-1-one the intermediate **175** has two other resonance forms **175a** and **175b** available with the positive charge being stabilised by donation of the nitrogen lone pair **(scheme 85)**. This is similar to the generally accepted reason for pyrrole being more reactive towards electrophiles at the 2-position than the 3-position **(scheme 86)**.



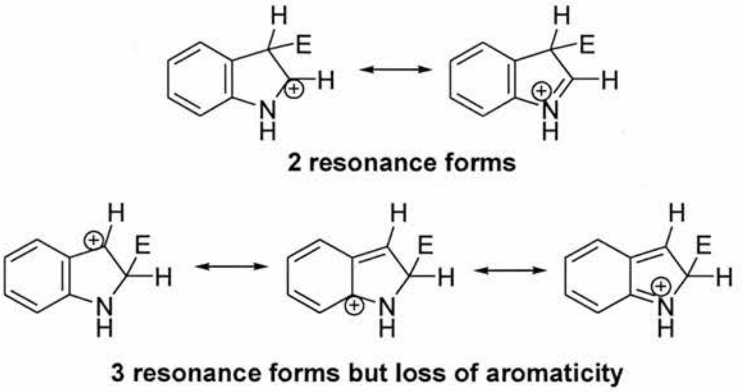
3-resonance forms



2-resonance forms

Scheme 86: Resonance forms in the reaction of pyrrole with electrophiles

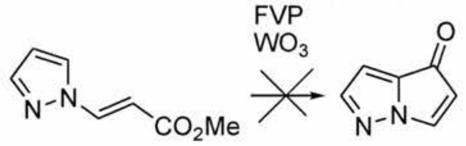
In the reaction to give the minor product benzopyrrolizin-1-one **143** the intermediates **176a** and **176b** may stabilise the intermediate through the donation of the nitrogen lone pair. This also applies to the formation of **143** where the intermediate **177** has three resonance forms to stabilise the intermediate, however in each of these intermediates the aromaticity of the benzene ring has been lost. This is the accepted reason why indole is more reactive at the 3-position than at the 2-position towards electrophilic substitution reactions **(scheme 87)**.



Scheme 87

From this suggestion it can be argued that the indole analogue requires higher furnace temperatures to produce cyclisation due to higher activation energy required because of lack of resonance stabilisation. Also the preferential formation of **142** over **143** can be explained by ring strain and the preferential formation of a six membered ring over a five membered ring. It can also be suggested that formation of the vinyl compound **144** is only preferred when there is not enough energy to give cyclisation. The formation of the vinyl compound is thought to be catalysed by a different site on the surface than the cyclisation and it is suggested that the formation of the vinyl compound has a lower activation energy it is catalysed by the WO_3 at a lower rate to that of the cyclisation. Once cyclisation has occurred the mechanism that leads to the vinyl compound is no longer open thus at higher temperatures no vinyl compound is observed.

To further support this mechanism the use of a less electron rich nucleophile was used in the reaction. It was decided that the use of a pyrazole precursor would have the desired properties as the presence of an extra electronegative nitrogen in the ring would reduce the electron donating ability to form the intermediate. The precursor was generated by the reaction of pyrazole with methyl propiolate using TBAF as previously discussed. The FVP of this precursor does not generate the cyclised product **(scheme 88)**.



Scheme 88

This further supports the electrophilic substitution mechanism indicating that cyclisation will only occur onto an electron rich ring.

This series of reactions lays down an initial set of guidelines for catalyst supported intramolecular electrophlilic substitution cyclisation reactions.

Firstly the ring that cyclisation occurs onto must be electron rich such as the cases where cyclisation goes onto a benzene ring or onto a pyrrole ring. The presence of an electronegative atom in the ring will hinder the cyclisation.

Secondly for facile reactions with low furnace temperatures the cationic intermediate must be resonance stabilised, if there is no resonance stabilisation much higher furnace temperatures are required.

Thirdly when insufficient energy is present to produce *E-Z* isomerisation a different site on the catalyst surface is more active which catalyses the formation of *N*-vinyl compounds

Chemistry of pyrrolizin-1-one

As there is a great amount known about the chemistry of pyrrolizin-3-one, the chemistry of pyrrolizin-1-one that was investigated was intended to develop a comparison between the two isomers. Therefore the chemistry investigated was the reactivity with nucleophiles, hydrogenation and cycloaddition reactions.

Reactions of pyrrolizin-1-one

Reactions with nucleophiles.

The chemistry of pyrrolizin-3-one with nucleophiles has been well reported. The site of reaction depends on whether the nucleophile is hard or soft this has already been discussed in more detail **(page 23).** Hard nucleophiles such as methoxide and hydride react exclusively at the carbonyl and soft nucleophiles such as sulfur nucleophiles undergo nucleophilic addition across the double bond, intermediate nucleophiles such as nitrogen nucleophiles can react at both depending on the particular nucleophile chosen **(figure 26)**.

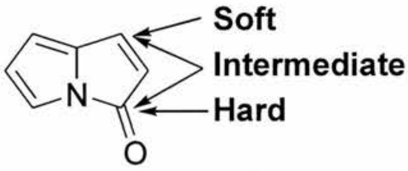
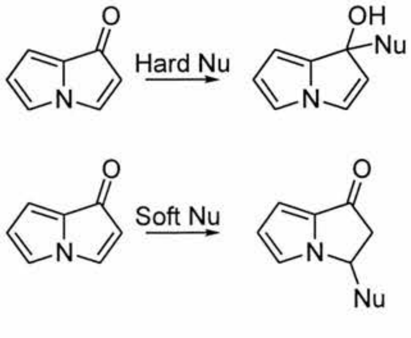


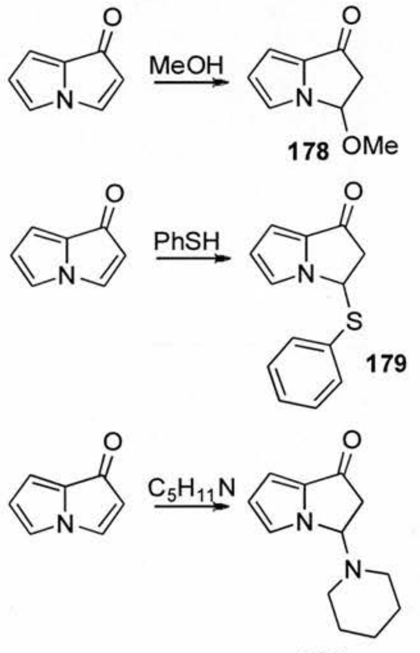
Figure 26: Reactivity of nucleophiles

It was proposed that pyrrolizin-1-one might show similar properties with hard nucleophiles undergoing nucleophilic addition reactions at the carbonyl and soft nucleophiles undergoing conjugate addition across the enone double bond **(scheme 89)**.



Scheme 89: Proposed reaction of pyrrolizin-1-one with nucleophiles.

With this in mind the reactivity of pyrrolizin-1-one with nucleophiles was studied, the nucleophiles chosen were methoxide as an example of a hard nucleophile, thiophenol as a soft nucleophile and pipperidine as an intermediate nucleophile. In each of these cases the reaction proceeded *via* addition across the enone bond **(scheme 90)**.



Scheme 90:Reaction of pyrrolizin-1-one with nucleophiles

When methanol and thiophenol were used as the nucleophiles a drop of Hunigs base was needed to catalyse the reactions. All of these addition products showed the typical coupling constants for the two CH_2 protons of ~18Hz eg. in the ^{1}H NMR spectrum of 3-methoxy-2,3-dihydropyrrolizin-1-one **(Figure 27)**,

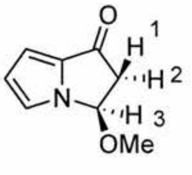
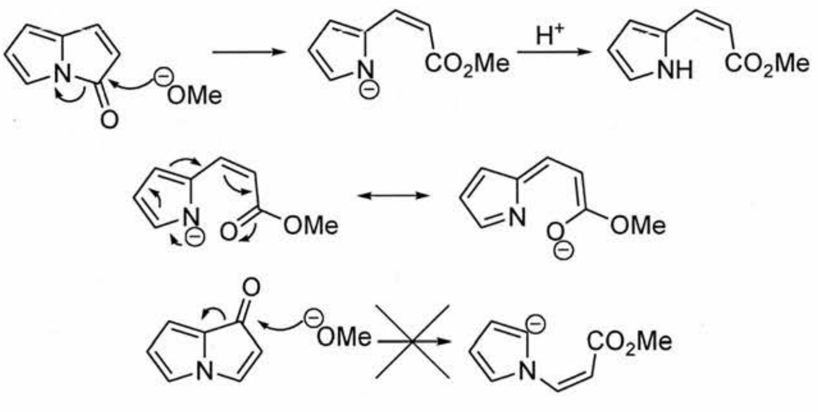


Figure 27:Structure of 178

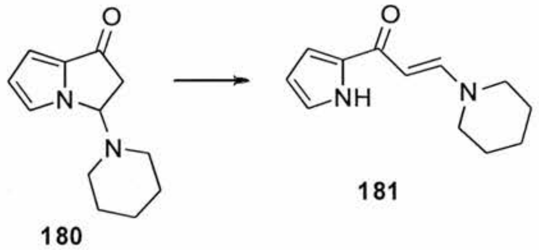
Proton H1 at 2.96 ppm shows a coupling to H3 at 5.83 ppm of 1.8 Hz, whilst proton H2 at 3.29 ppm shows a coupling to H3 of 6.3 Hz as predicted by the Karplus equation, and proton H1 shows a coupling to H2 of 18.4 Hz. This pattern applies to all of the addition products generated.

It is believed that the difference in reactivity towards nucleophiles between the two isomers is due to the ability of the pyrrole group in pyrrolizin-3-one to act as a leaving group in reactions at the carbonyl **(scheme 91)**, this mechanism is not possible in reactions with pyrrolizin-1-one. As can be seen the intermediate in the ring opening of pyrrolizin-3-one with methoxide can be stabilised by the delocalisation of the negative charge from the nitrogen through to the carbonyl as is previously discussed **(page 23)**. This is not possible in the case of pyrrolizin-1-one therefore increasing the activation energy required for this type of reaction.



Scheme 91

The reaction of pyrrolizin-1-one with piperidine was further studied, upon observation the initially formed addition product **180** under went ring opening to give **181** **(scheme 92)**. Due to steric reasons only the *E* isomer was observed this was confirmed by the coupling constant between the protons of the double bond of 12.7 Hz, typical of a *E* double bond.

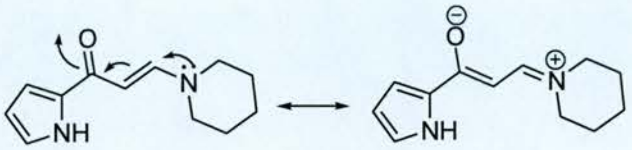


180

181

Scheme 92: Ring opening of 180

The ring opened product also shows some evidence of hindered rotation around the C-N-piperidine bond. Two of the CH_2 carbon signals in the ^{13}C NMR spectrum are extremely broad.



Scheme 93: Resonance structures of 181

The rate of ring opening of the piperidine adduct was observed by ^{1}H NMR spectroscopy, using the characteristic signals in the ^{1}H NMR spectrum, the 1H dd at 5.36 ppm from the addition product and the doublet at 5.71 ppm from the enone in the ring opened product **(figure 28)**. Though only four points were recorded the decay follows classic first order decay, as is expected for this type of reaction. This shows that the half life of the addition product is in the order of around 20 h at room temperature.

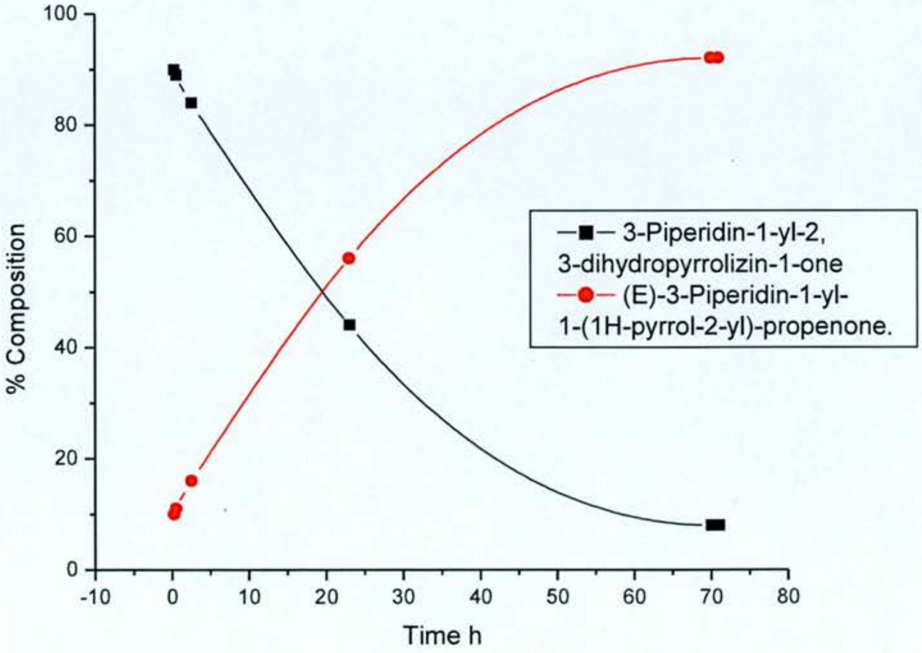
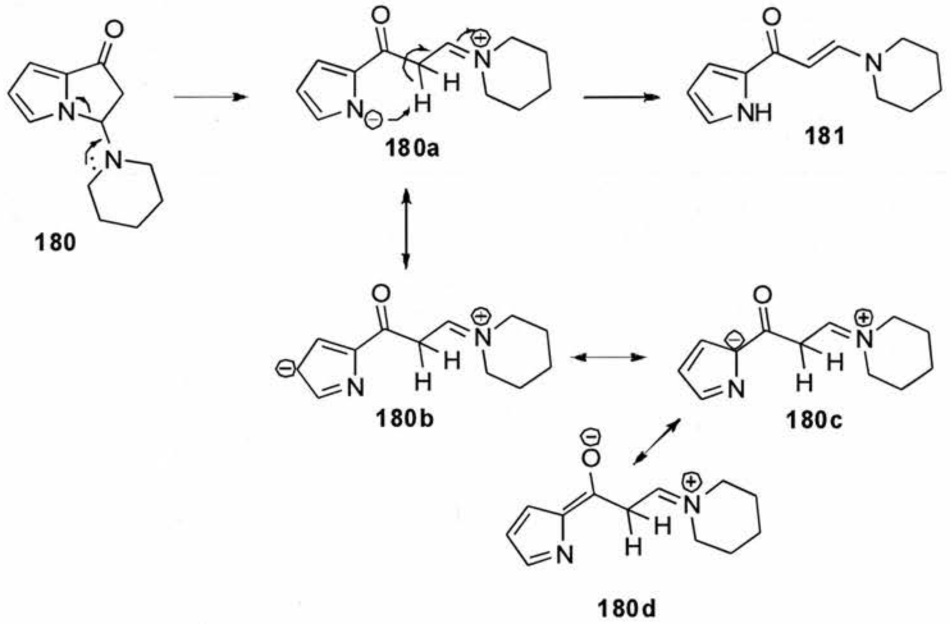


Figure 28: rate of ring opening in 181

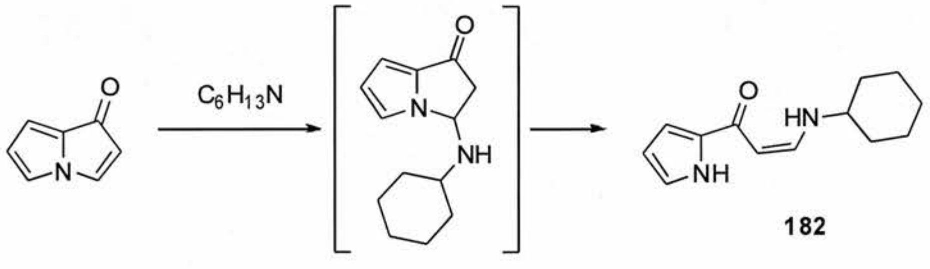
The mechanism of the ring opening is believed to go through the intermediate **180a** formed by the lone from the piperidine nitrogen pushing through to the pyrrole nitrogen with the pyrrole ring acting as a leaving group **(scheme 94);** this is similar to the ring opening of pyrrolizin-3-one **(scheme 22)**. The intermediate **180a** is readily resonance stabilised by delocalisation of the negative charge around the pyrrole ring and through to the carbonyl in the structures **180b, 180c** and **180d**. It is suggested that the pyrrole nitrogen the picks up the proton to give the final product **180**.



Scheme 94: Mechanism of ring opening of 180

Reaction with cyclohexylamine.

This ring opening with nitrogen nucleophiles was further studied by investigating the reaction with cyclohexylamine. In contrast to the reaction with piperidine the addition product was never observed, instead the ring opened product (Z)-3-cyclohexylamino-1-(1*H*-pyrrol-2-yl)-propenone **182** was the sole product of the reaction.



182a

Scheme 95:Reaction of pyrrolizin-1-one with cyclohexylamine

Furthermore only the *Z*-isomer was observed this was confirmed by the observation of the coupling constant of 7.0 Hz between the protons at 6.92 ppm and 5.83 ppm due to the protons in the double bond. It is believed that this is due to hydrogen bonding between the NH and the carbonyl holding the conformation in place **(figure 29)**.

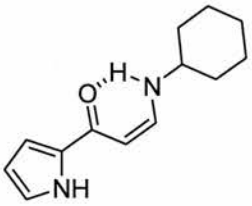
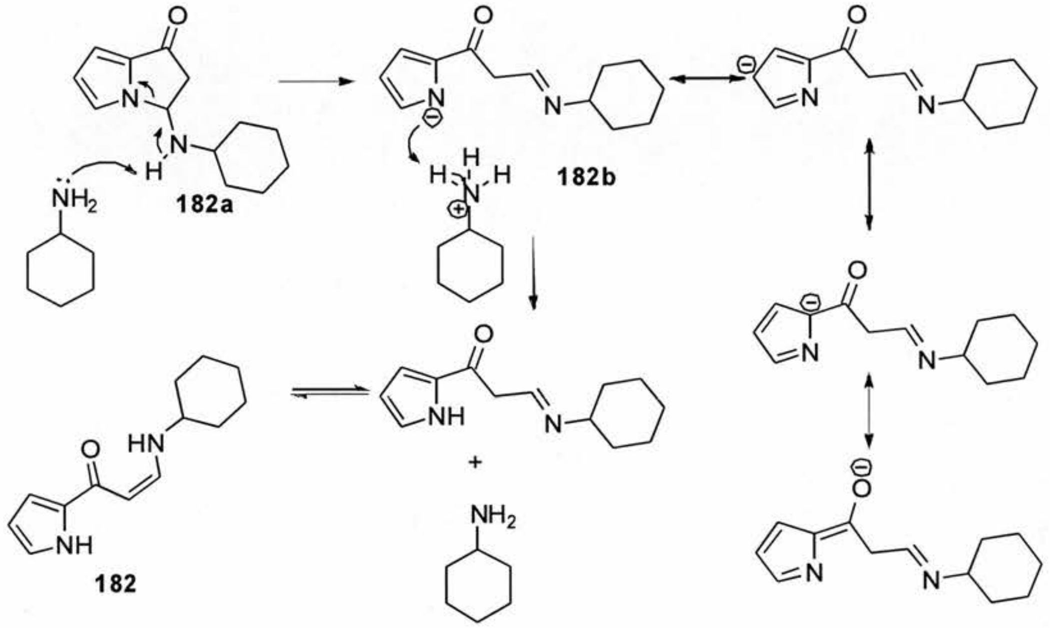


Figure 29:

It is assumed that the like the other reactions with nucleophiles the reaction proceeds *via* the addition intermediate **182a**. As there is no sign of the addition product it can be suggested the reaction must have a half life of only a few minutes, this would suggest that this reaction proceeds at least 600 times faster than the reaction with piperidine. This indicates that a different mechanism is followed, it is suggested that the rate of reaction is increased due to the presence of a proton on the nitrogen of the intermediate **182a**. It is proposed that the excess base deprotonates the nitrogen causing the ring opening to give the intermediate **182b** which is resonance stabilised by delocalisation of the negative charge through to the carbonyl. After protonation the final product is obtained.

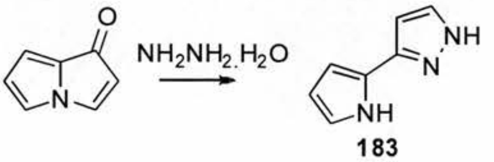


Scheme 96: Mechanism of reaction of pyrrolizin-1-one with cyclohexylamine

The proposed H-bonding in **182** is displayed **(figure 29)**, the stabilisation obtained by the formation of the H-bonded six-membered ring overrides the formation of the less sterically hindered *E*-isomer.

Reaction with hydrazine.

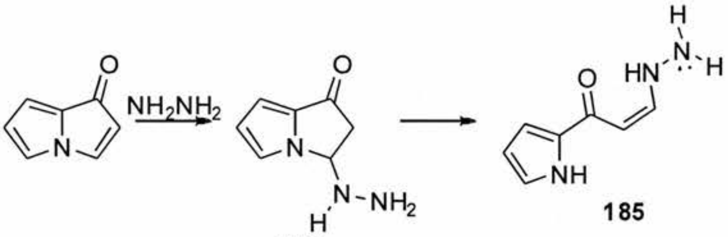
The reaction of pyrrolizin-1-one with hydrazine hydrate proceeds smoothly when the nucleophile is used as the solvent to give 3-(1*H*-pyrrol-2-yl)-1*H*-pyrazole **183 (Scheme 97)** (99%), however when carried out in a solvent such as DCM the reaction does not proceed cleanly.



183

Scheme 97: Reaction of pyrrolizin-1-one with hydrazine monohydrate

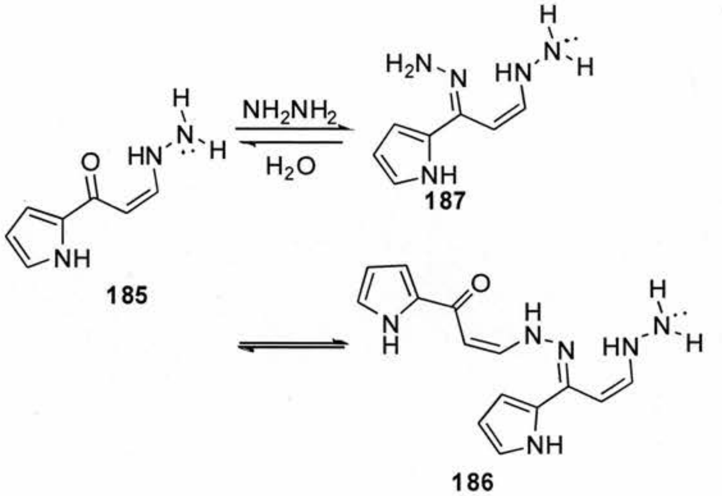
It is proposed that the reaction proceeds as in the reaction with cyclohexylamine to give the ring opened intermediate **185**. From this point there are many possible routes that the reaction can follow.



184

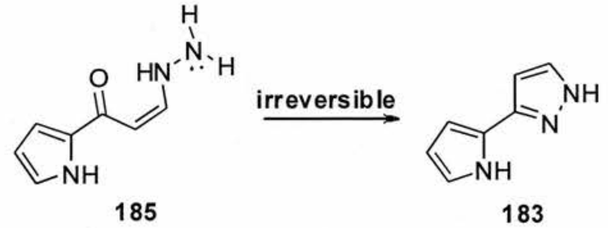
185

It can be suggested that **185** could react with another molecule of itself to give **186** along with the possibility of polymerisation or a molecule of hydrazine to give **187 (scheme 98)**, however these are in equlibrium and can be easily reversed.



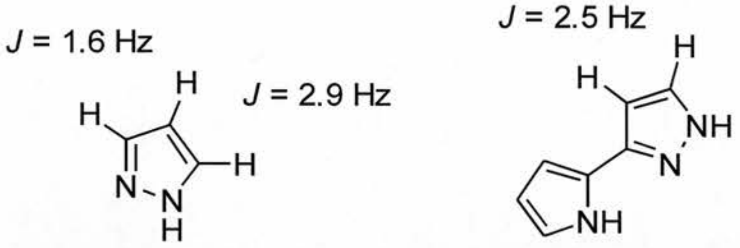
Scheme 98: Possible reactions of 185

However the other possible route available for the reaction is intramolecular cyclisation, this produces the pyrrolyl pyrazole **183**. Unlike the other possible products the formation of the pyrazole ring is irreversible due to its aromaticity and therefore non reactive towards nucleophiles under mild conditions. It is therefore this formation of the aromatic ring is the driving force for the reaction.



Scheme 99: Irreversible formation of 183

From the ^{1}H NMR spectrum it can be seen that the pyrazole ring adopts the tautomeric structure shown **(figure 30)**, the coupling constants are in agreement with what would be expected for a pyrazole ring in this tautomer. As shown **(Figure 30)** the coupling constant between the protons at the C3 and C4 positions in pyrazole is typically in the order of 1.6 Hz, and the coupling constant between the protons at the C4 and C5 positions in pyrazole is 2.9 Hz.



183

Figure 30: Coupling constants in pyrazoles

The coupling constant for the protons in the pyrazole ring in **183** is 2.5 Hz indicating the tautomer shown **(Figure 31)** is the correct form. Furthermore there is evidence in the ^{13}C spectrum that there is hindered rotation around the pyrrole-pyrazole bond.

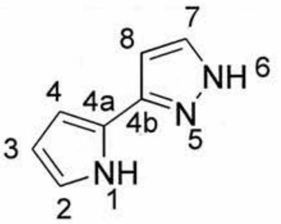


Figure 31:Numbering scheme for 183

From the ^{13}C spectrum it was observed that the quaternary at 144.65 ppm due to C4b was extremely broadened, as was the CH at 130.88 ppm from C8 and the quaternary at 125.24 ppm due to C4a was also broadened to a lesser extent. This all indicates a hindered rotation around the C4a-C4b bond. This is probably due to the lone pair on N5 from the pyrazole ring co-ordinating to the pyrrole NH **(Figure 32)**, there is also only one NH signal observed in the ^{1}H NMR spectrum due to the other being highly shifted as a result of the hydrogen bonding.

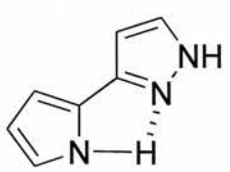
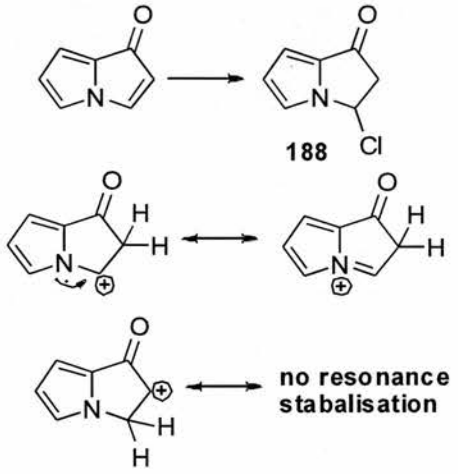


Figure 32:Structure of 183

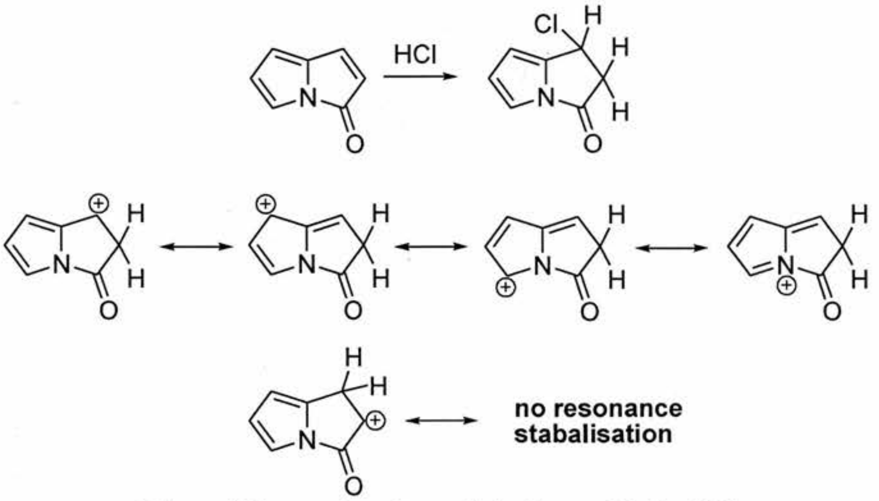
Reaction with HCl.

The reaction of pyrrolizin-1-one with dry HCl proceeds *via* an electrophilic addition mechanism to give 3-chloro-2,3-dihydropyrrolizin-1-one **188**, this reaction gives as expected only addition of the Cl at the 3-position due to the resonance stabilization of the intermediate, there is no possible stabilization for reaction at the 2-position.



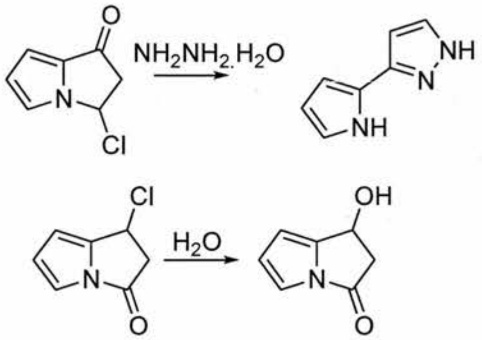
Scheme 100:Reaction of pyrrolizin-1-one with dry HCl

This is directly comparable to the reaction of pyrrolizin-3-one with dry HCl here the reaction goes exclusively at the 1-position for the same reason **(scheme 101)**.



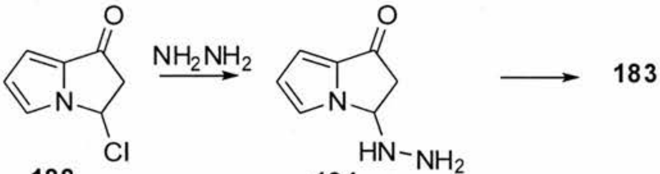
Scheme 101: reaction of pyrrolizin-3-one with dry HCl

In comparison with pyrrolizin-3-one, pyrrolizin-1-one shows similar reactivity towards electrophilic addition of HCl even though it has fewer resonance structures of the intermediate. In further comparison with pyrrolizin-3-one the 1-one analogue shows ready displacement of the Cl substituents with other nucleophiles, in this case hydrazine. When hydrazine hydrate was added to 3-chloro-2,3-dihydropyrrolizin-1-one **188** in DCM in a two phase reaction mixture the sole product of the reaction was 3-(1*H*-pyrrol-2-yl)-1*H*-pyrazole **183 (Scheme 102)**. The displacement of the Cl substituents can be compared to the reaction of the pyrrolizin-3-one analogue with water.



Scheme 102: Reaction of 3-chloro-2,3-dihydropyrrolizin-1-one with hydrazine

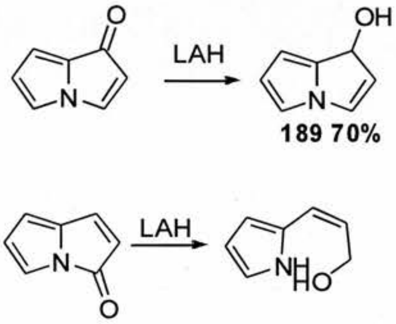
This supports the suggestion that the reaction of pyrrolizin-1-one with hydrazine **(scheme 103)** does proceed through the short lived intermediate **184** as this is clearly the same intermediate in this reaction **(scheme 97).**



Scheme 103: Reaction of 188 with hydrazine.

Reaction with LAH.

Reaction of pyrrolizin-1-one with LAH proceeds at the carbonyl, in the reaction H^- is considered a very hard nucleophile. This can be compared with the reaction of pyrrolizin-3-one with LAH in this case the reaction also proceeds at the carbonyl followed by ring opening to give the alcohol **(scheme 104)**.

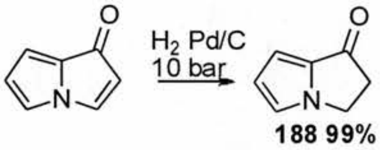


Scheme 104:Reaction of pyrrolizin-1-one with LAH

The pyrrolizin-1-one reaction does not ring open due to the inability of the pyrrole ring to act as a leaving group in the same way it can in the pyrrolizin-3-one example.

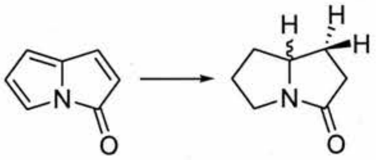
Hydrogenation of pyrrolizin-1-one.

Hydrogenation of pyrrolizin-1-one gives 2,3-dihydropyrrolizin-1-one **188** also known as concordance, a pheromone found in the Malay Tiger, a species of butterfly found in Malaysia.[41]



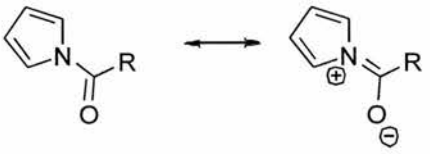
Scheme 105: Hydrogenation of pyrrolizin-1-one

In contrast with pyrrolizin-3-one[24] the hydrogenation of pyrrolizin-1-one only saturates the enone bond, the hydrogenation of pyrrolizin-3-one gives hexahydropyrrolizin-3-one **(scheme 106)**.



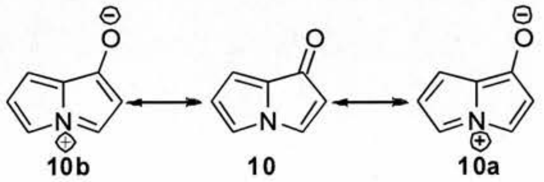
Scheme 106: Hydrogenation of pyrrolizin-3-one

It is reported that although pyrroles are difficult to hydrogenate as they are aromatic compounds, N-acyl pyrroles can be readily hydrogenated under mild conditions.[42] This is believed to be due to the electron withdrawing effect of the amide carbonyl **(scheme 107)**.



Scheme 107: Resonance form of *N*-acylpyrroles

The dipolar resonance form *N*-acylpyrrole plays an important role in its hydrogenation. In this resonance form the pyrrole ring no longer possesses a 6π electron configuration and is therefore not aromatic enabling the facile hydrogenation. This can be compared to the hydrogenation of pyrrolizin-1-one where the pyrrole ring does not get hydrogenated. Although resonance forms exist where the lone pair from the nitrogen has been donated through to the carbonyl **(scheme 108)**, it can be assumed that they are not important structures. It can therefore be shown that the carbonyl needs to be located adjacent to the pyrrole nitrogen for this effect to be observed.

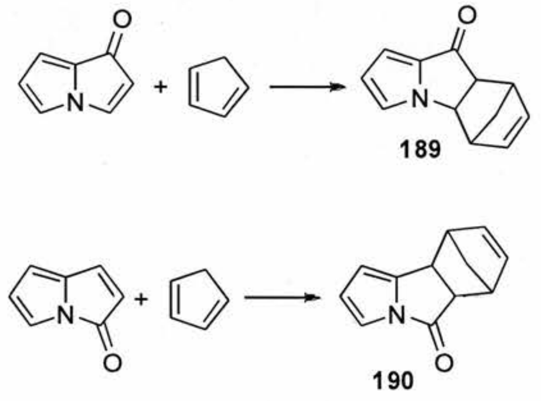


Scheme 108:Resonance forms of pyrrolizin-1-one

In this case pyrrolizin-1-one behaves like a standard pyrrole and once the enone bond has been hydrogenated no further hydrogenation occurs.

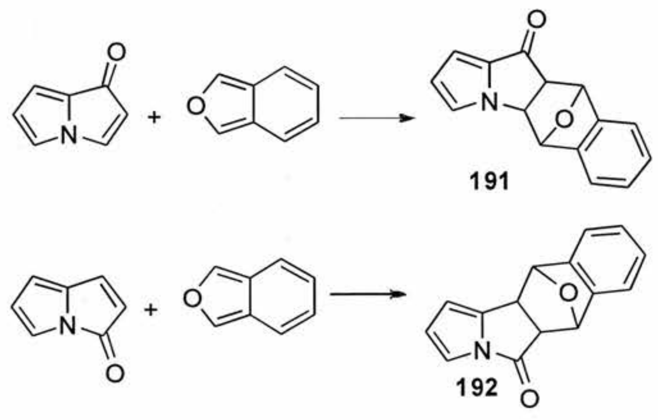
Cycloaddition reactions.

The reaction of pyrrolizin-1-one with cyclopentadiene was investigated with the reaction proceeding under reflux in toluene. These are much harsher conditions than those required for the analogous reaction with pyrrolizin-3-one. So pyrrolizin-1-one is a much poorer dienophile than pyrrolizin-3-one.



Scheme 109: Reaction of pyrrolizinones with cyclopentadiene

The reactivity towards dienes compared with pyrrolizin-3-one is also demonstrated in the reaction with isobenzofuran. The reaction of pyrrolizin-1-one with isobenzofuran proceeds with good yield at room temperature within one hour, this is around the same time required for the reaction of pyrrolizin-3-one. However the reaction of pyrrolizin-3-one with isobenzofuran is higher yielding indicating its increased reactivity as a dienophile.

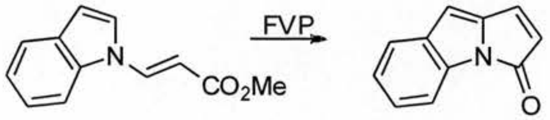


Scheme 110: Reaction of pyrrolizin-1-one with isobenzofuran.

As in the pyrrolizin-3-one case only the *endo* isomer is observed, this can be explained by the theory of secondary orbital overlap, although there is significant evidence that this theory may not be true.[43]

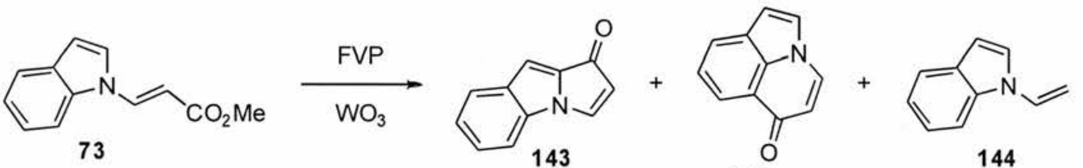
Synthesis if benzopyrrolizin-1-one.

The synthesis of benzopyrrolizin-1-one **143** by this method proves unsuccessful,[44] however the synthesis of 3-indol-1-yl-acrylic acid methyl ester had previously been reported,[27] and its pyrolysis to benzopyrrolizin-3-one **(scheme 111)**.



Scheme 111: Formation of benzopyrrolizin-3-one.

As previously discussed, the pyrolysis of **73** over WO_3 however does not produce benzopyrrolizin-1-one in synthetically useful yields. The major product of this reaction is pyrrole[3,2,1, *ij*]quinolin-6-one **142** with the maximum achievable yield of benzopyrrolizin-1-one being 20%.



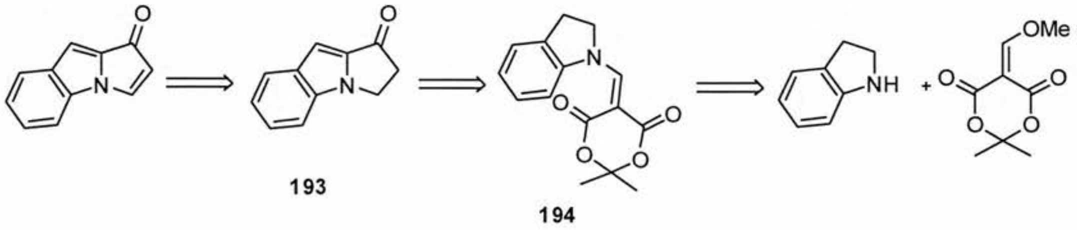
73 **143** **142** **144**

Scheme 112: FVP of 73

This reaction proceeds *via* the same mechanism as the formation of pyrrolizin-1-one, however the preferred product **142** is formed for two reasons. The formation of a six membered ring is more favourable than the formation of a five membered ring due to ring strain and resonance stabilisation of the intermediates, this is discussed in more detail earlier.

Retro synthesis of benzopyrrolizin-3-one.

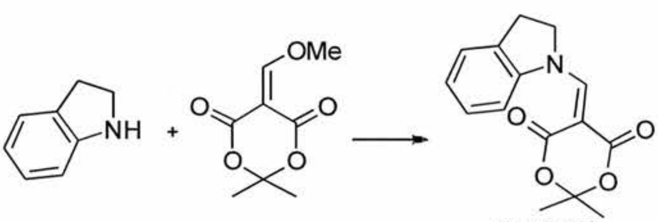
The synthesis of benzopyrrolizin-1-one however can be achieved by another route, a simple retrosynthetic approach to this compound demonstrates the simplicity of the process **(scheme 113)**.



Scheme 113: Retro synthesis of benzopyrrolizin-1-one

This approach was based on WO_3 behaving as a dehydrogenation catalyst, it was suggested that the dehydrogenation of **193** would give benzopyrrolizin-1-one. The synthesis of 2,3-dihydropyrrolo[1,2-*a*]indol-1-one **193** has been reported by several methods, however previous work within the group had developed a simple route to **193** by the FVP of 5-(2,3-dihydro-indol-1-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **194**,[4] this can be prepared by the reaction of indoline with methoxymethylene Meldrum's acid.

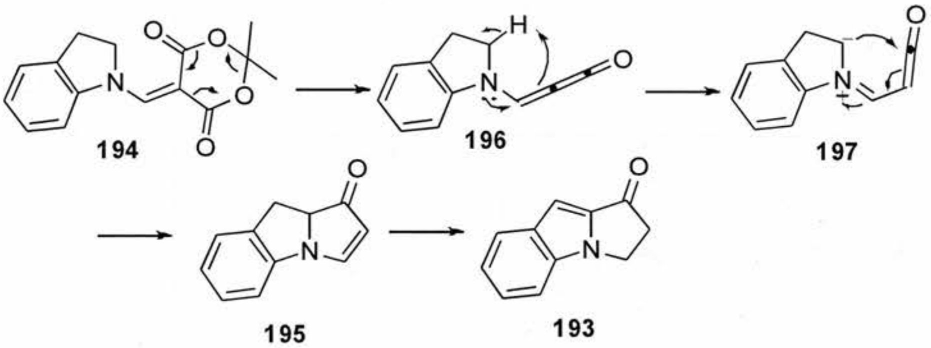
The reaction of methoxymethylene Meldrum's acid with indoline proceeds smoothly using acetonitrile as solvent with the product **194** precipitating from solution after 15 min **(scheme 114)**, the precipitate needs no further purification for use in the next stage of the reaction.



194 73%

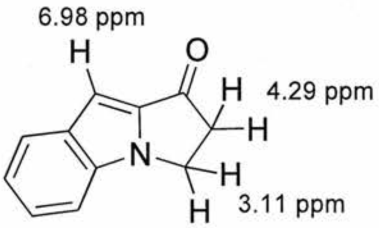
Scheme 114: Formation of 194

The FVP of **194** at 650 °C produces a yellow oil the NMR spectrum of which initially appears complicated, however if this oil is left to stand it becomes a white solid. The white solid is **193,** it is assumed that the original product of the FVP is **195** but this undergoes a series of H-shifts to give the final product **193**. The mechanism of this FVP is believed follow the standard FVP of Meldrum's acid derivatives of loss of CO_2 and acetone to form the methyleneketene **196**, a H-shift then occurs to give the dipole **197.** Then an intramolecular electrocyclisation reaction occurs to give **195**, this then undergoes tautomerisation to give **193 (scheme 115)**.[45]



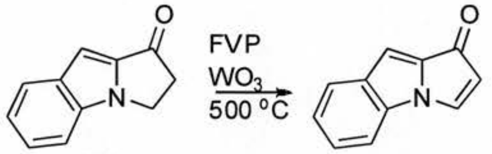
Scheme 115: Mechanism of formation of 193

The rate of tautomerisation could be increased by heating under reflux in toluene. The NMR spectrum of the crude pyrolysate shows many complex signals but none of the intermediates could be isolated. The NMR spectrum of the final product could clearly be identified in the mixture. In practice 2,3-dihydropyrrolo[1,2-*a*]indol-1-one **193** was recrystallised from acetone before the next stage of the reaction.



The formation of the more stable isomer **193** is clearly demonstrated by the NMR spectrum, the one proton singlet at 6.98 ppm and the two two proton triplets at 4.29 and 3.11 ppm.

2,3-Dihydropyrrolo[1,2-*a*]indol-1-one **193** was pyrolised over WO_3 at 500 °C to give benzopyrrolizin-1-one as the sole product in 91% yield as an orange solid **(scheme 116)**.



193 **143 91%**

Scheme 116: Formation of benzopyrrolizin-1-one

The formation of benzopyrrolizin-1-one does not show the same scale up problems as the synthesis of pyrrolizin-1-one, the synthesis of **143** has been carried out on 0.5 g scale with no sign of a drop in conversion. The ^1H NMR spectrum of **143** shows the characteristic doublets of an enone bond at 7.83 and 5.53 ppm with a coupling constant of 4.1 Hz, along with the singlet at 7.03 ppm; this can be directly compared with the enone doublets of pyrrolizin-1-one at 7.50 and 5.47 ppm also with a coupling constant of 4.1 Hz **(figure 32)**. The ^{13}C NMR spectrum of **143** shows the carbonyl at 185.64 ppm indicating standard ketone functionality. The chemistry of benzopyrrolizin-1-one towards nucleophiles is expected to be similar to that of pyrrolizin-1-one.

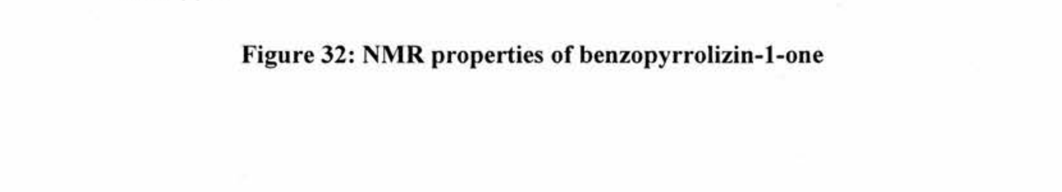


Figure 32: NMR properties of benzopyrrolizin-1-one

Conclusions.

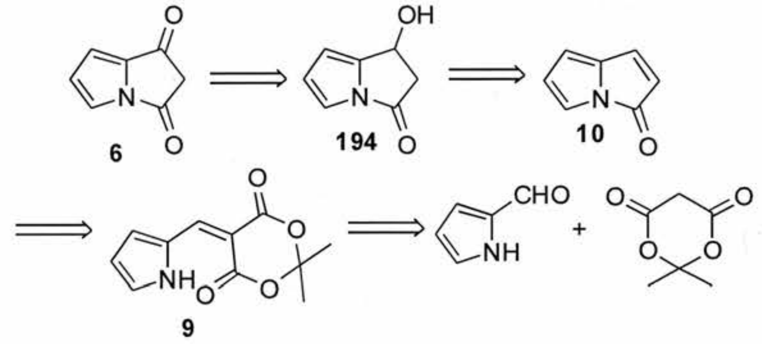
In this chapter the synthesis of pyrrolizin-1-one has been achieved by the use of WO_3 catalysis in FVP, it has been shown that the WO_3 bypasses the route to the pure thermal product pyrrolizin-3-one giving a route to pyrrolizin-1-one. This has developed a synthetic route to pyrrolizin-1-one that is a significant improvement on the previously reported method thus enabling the chemistry to be investigated. Pyrrolizin-1-one has been shown to be reactive towards nucleophiles in reaction with methanol, piperidine, thiophenol and cyclohexylamine. It was also shown that pyrrolizin-1-one can act as a pyrrole-pyrazole synthon in the synthesis of **183**. The hydrogenation has been shown to proceed with the enone bond becoming fully saturated while no reaction occurred in the pyrrole ring.

Results and discussion pyrrolizin-1,3-dione.

Synthesis of pyrrolizin-1,3-dione.

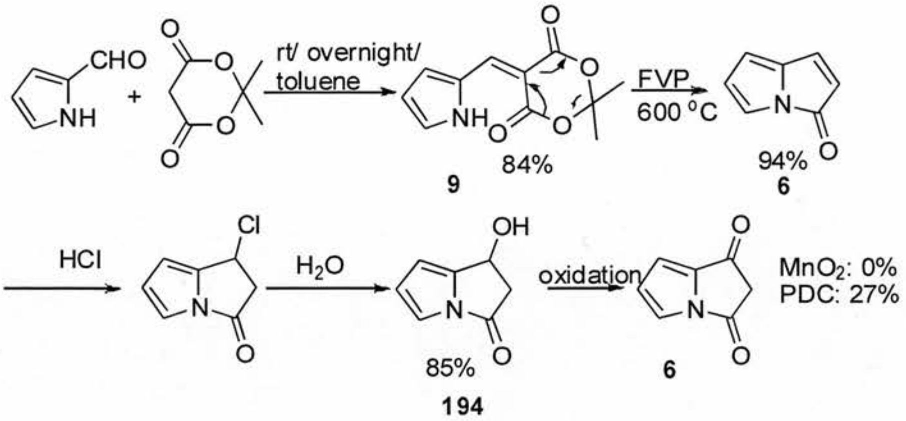
The synthesis of pyrrolizin-1,3-dione had been previously reported within the group, however the synthesis was low yielding and as such the chemistry had not been fully investigated.[46]

From a retro-synthetic point of view **(scheme 117)** it was suggested that the final step would be the oxidation of the alcohol **194,** the synthesis of this can be achieved from the reaction of pyrrolizin-3-one **10** with dry HCl followed by aqueous work up.[12] The formation of pyrrolizin-3-one is well documented with many routes to its formation. The best route to give pyrrolizin-3-one is from the Meldrum's acid derivative **9**, this is simply formed by the reaction of pyrrole-2-carboxaldehyde with Meldrum's acid.



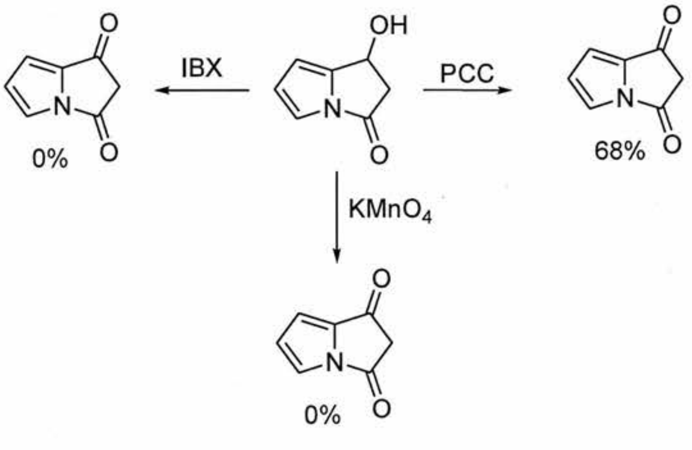
Scheme 117: Retro synthesis of pyrrolizin-1,3-dione

The reported synthesis started from pyrrole-2-carboxaldehyde, the reaction with Meldrum's acid produces the precursor **9**, the FVP of this produces pyrrolizin-3-one.[10] The electrophilic addition of HCl across the enone bond produces the chloro compound the chlorine is readily replaced by other nucleophiles in this case in the presence of water the hydroxy compound **194** is formed.[28] The oxidation conditions to produce pyrrolizin-1,3-dione had proved problematic, reaction with MnO_2 had been shown to produce no **6**, whereas reaction with PDC produced **6** in 28% yield. A derivative of **6** was obtained by Swern oxidation (see below).



Scheme 118: Previous synthesis of pyrrolizin-1,3-dione

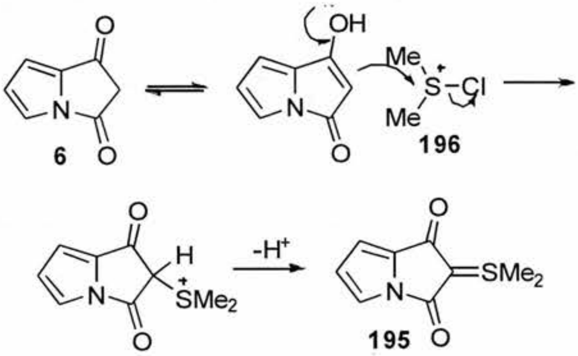
From this it was obvious that the problematic step in the synthesis was the final oxidation, so conditions were investigated by the present author. Conditions using IBX reagents was investigated but no product was observed, similarly reaction with $KMnO_4$ also produces no pyrrolizin-1,3-dione **6**. However returning to the chromate oxidising agents, the use of PCC as the oxidant gave **6** in 68% yield, this reaction required vigorous stirring and nitrogen bubbled through the mixture to keep the PCC mobile and to stop it from aggregating at the bottom of the flask. This proved to be an efficient and reproducible route to pyrrolizin-1,3-dione **6 (scheme 119)**.



Scheme 119:Conditions for dione formation

Swern oxidation of 194

Although the dione **6** was not obtained by Swern oxidation another product **195** was isolated in a low yield (12%). This compound showed the characteristic *S*-Me singlet at δ_H 3.01, and by the ylide carbon resonance at δ_C 64.87, the value for the carbon resonance in sulfonium ylides known to be variable, however this value is in the range expected for dicarbonyl stabilised examples.[47]



Scheme 120: Swern oxidation of pyrrolizine-1,3-dione

It is believed that this reaction proceeds by the initial formation of the desired dione **6**, which then reacts with an activated Swern species such as **196** to give the final product **195**. In the ^{1}H NMR spectrum, the methyl singlet is unchanged at –35 °C which suggests that **195** adopts either structure **195a** or **195b** as found for other sulfonium ylides, ruling out the other possible structures **195c** or **195d**.

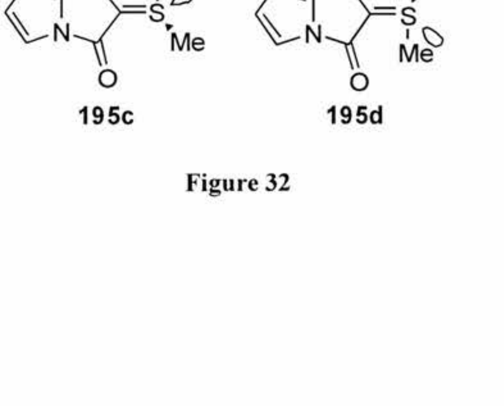
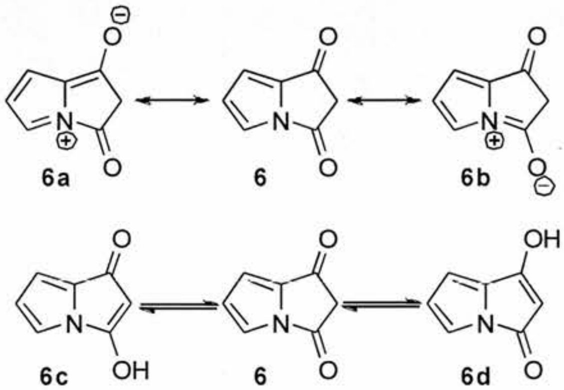


Figure 32

The different isomers only differ due to the positioning of the lone pair, in **195a** the two methyl isomers point towards the amide carbonyl, in **195b** the two methyls point towards the ketone carbonyl, in **195c** one methyl and the lone pair point towards the amide carbonyl and in **195d** one methyl and the lone pair point towards the ketone carbonyl.

Structure of pyrrolizin-1,3-dione.

Pyrrolizin-1,3-dione can be considered to be in a number of different resonance and tautomeric forms, firstly the resonance forms arising from the donation of the N lone pair through to the carbonyls thus **6a** and **6b** can be proposed as resonance structures. Secondly the two enol tautomers **6c** and **6d** can also be considered **(121)**.



Scheme 121: Tautomerisation of 6

The NMR properties of pyrrolizin-1,3-dione can be compared to that of pyrrolizin-1-one and that of pyrrolizin-3-one **(figure 33)**.

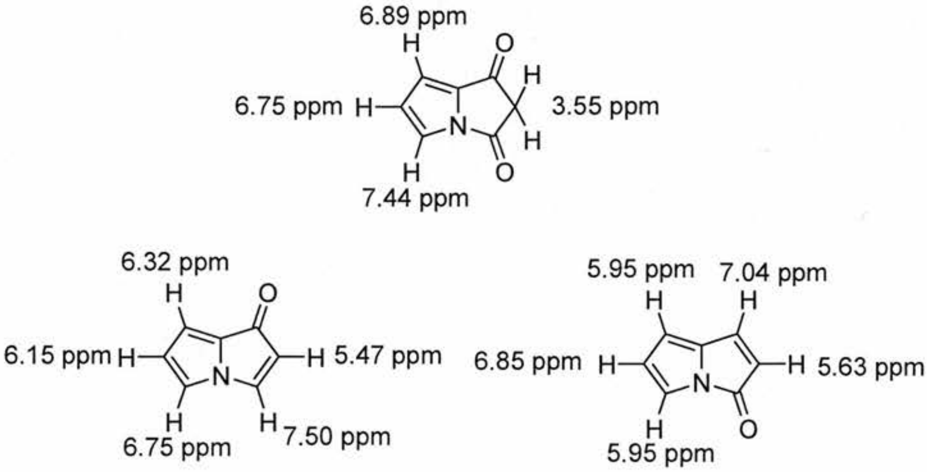


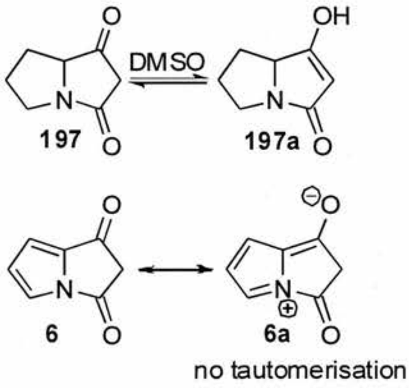
Figure 33: NMR properties of pyrrolizine-1,3-dione, pyrrolizin-3-one and pyrrolizin-1-one.

	H1	H2	H3	H5	H6	H7
Pyrrolizin-3-one	7.04	5.63		5.95	6.85	5.95
Pyrrolizin-1-one		5.47	7.50	6.75	6.15	6.32
Pyrrolizin-1,3-dione		3.55		7.44	6.75	6.89

Table 7: Chemical shifts in pyrrolizinones in $CDCl_3$.

It can be seen that the chemical shifts of the pyrrole protons of pyrrolizin-1,3-dione appear at significantly higher chemical shifts than those in pyrrolizin-1-one and those in pyrrolizin-3-one. This is indicative of the extra carbonyl group producing a second mechanism for electrons to be withdrawn from the pyrrole ring **(scheme 121)** suggesting that the resonance forms **6a** and **6b** are important forms. However as neither of the enol tautomers **6c** or **6d** are observed it can be assumed that these do not play a role in the higher chemical shifts that are observed.

This lack of enantomerisation can be contrasted to that of the tetrahydro-derivative **197** which is known to exist as 1:1 mixture of keto and enol tautomers in DMSO solution,[48] however it appears as the keto tautomer. It is proposed that the keto enol enantomerisation is not observed in pyrrolizine-1,3-dione due to the resonance form **6a**. this would suggest that this provides significant contribution to the overall structure of the molecule **(scheme 122)**.



Scheme 122: Tautomerisation of 197

The IR spectrum of pyrrolizine-1,3-dione can also be considered as a good demonstration of the ketone and the amide characteristic properties **(Figure 34)**.

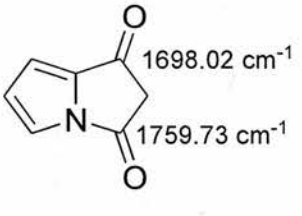
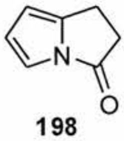
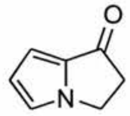


Figure34: IR properties of pyrrolizin-1,3-dione

It can clearly be seen that pyrrolizine-1,3-dione has two characteristic carbonyl signals, ketone carbonyl is seen at 1698 cm^{-1} as well as a carbonyl at 1759 cm^{-1} diagnostic of pyrrolizine type amide. This is high for that expected for a normal amide but these values can be compared those of dihydropyrrolizin-1-one **188** and dihydropyrrolizin-3-one **198 (Table 8)**. This is an unusual example of a lactam having higher frequency absorption than a ketone in a similar structural environment.


198


188

	1-one carbonyl	3-one carbonyl
Pyrrolizine-1,3-dione	1698	1759
Dihydropyrrolizin-1-one	1705	
Dihydropyrrolizin-3-one		1734

Table 8: IR properties pyrrolizinones

The UV spectrum of pyrrolizine-1,3-dione **(figure 35)** can also be compared to that of pyrrolizin-3-one, it can clearly be seen that **6** has no absorbance in the visible region of the spectrum. This can be contrasted to that of **10** which has a absorbs in the visible region, the second absorbance is believed to originate from the enone bond causing its deep red colour. This explains pyrrolizine-1,3-dione is observed as a white solid unlike pyrrolizin-3-one which has a second absorbance in the visible region.

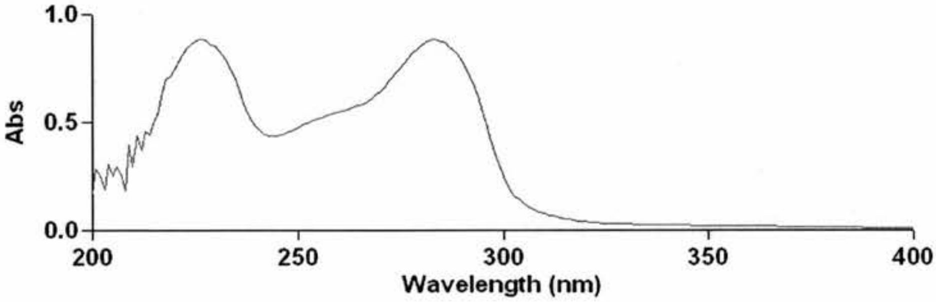


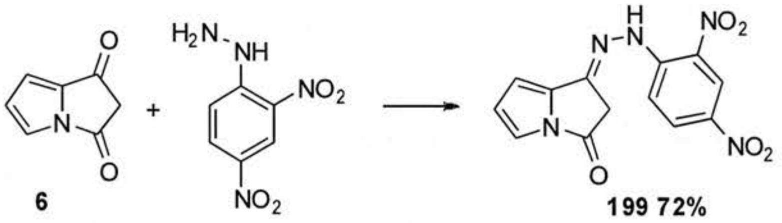
Figure 35: UV spectrum of pyrrolizine-1,3-dione

Chemistry of pyrrolizine-1,3-dione.

For the purpose of the investigation of the chemistry of pyrrolizine-1,3-dione it was decided each of the functional groups would be looked at individually.

Ketone chemistry.

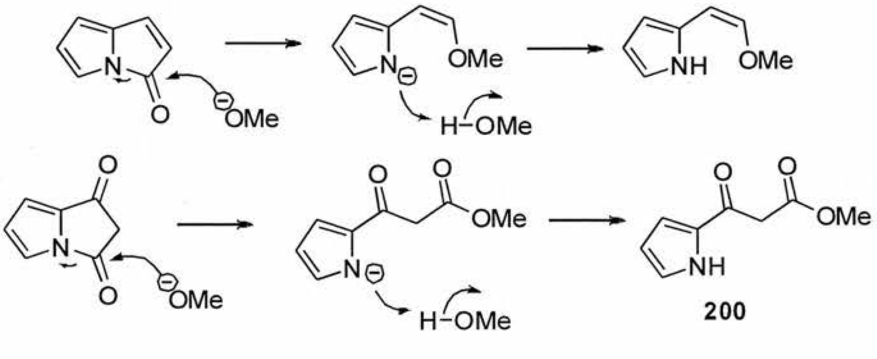
The ketonic character of pyrrolizin-1,3-dione **6** was demonstrated by the classic reaction with Brady's reagent. The formation of the 2,4-dinitropheylhydrazone derivative **199** demonstratres the ketone functionality of of **6** and also acts an example of its acid stability.



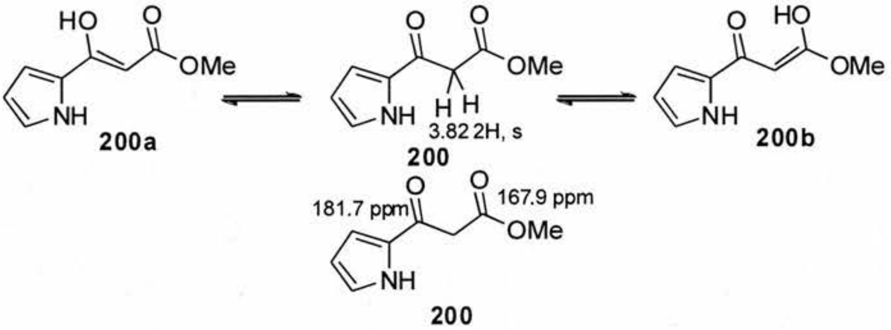
Scheme 123: reaction of pyrrolizin-1,3-dione with Brady's reagent

Amide chemistry.

The reaction of pyrrolizine-1,3-dione with methanol follows the typical reaction of a pyrrolizin-3-one, in that ring opening occurs instantly upon the addition of one drop of Hunig's base. This reaction proceeds by methoxide attacking the carbonyl, with the pyrrole ring acting as a leaving group which gives the final product **200** after protonation.



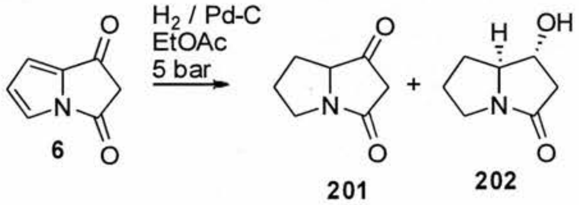
Scheme 124: Ring opening of pyrrolizin-1,3-dione



The ring opened product **200** is clearly recognisable in its ^{1}H NMR spectrum, the presence of an NH at 9.73 ppm is clear evidence for the ring opening. The product is observed only in the keto tautomer **200**, neither of the enol tautomers **200a** or **200b** were observed. This was clearly demonstrated by the presence of a 2H singlet at 3.82 ppm and in the ^{13}C NMR spectrum the two carbonyls are observed at 181.7 and 167.9 ppm these are clearly indicative of ketone and ester carbonyls respectively.

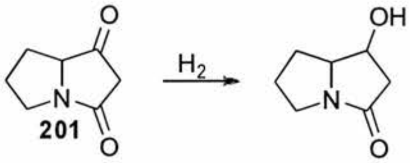
Pyrrole chemistry.

The standard pyrrole chemistry of pyrrolizin-1,3-dione is demonstrated by the hydrogenation reaction **(scheme 125)**. In this reaction a mixture pyrrolizidine-1,3-dione **201** and 1-hydroxypyrrolizinidin-3-one **202** is observed.



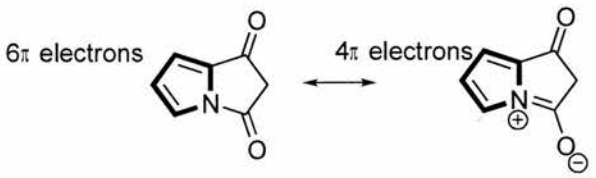
Scheme 125: Hydrogenation of 1-hydroxypyrrolizin-3-one and pyrrolizine-1,3-dione

It is proposed that the dione **6** is first hydrogenated to the pyrrolizidine **201** this can then undergo further hydrogenation to give **202 (scheme 126)**.



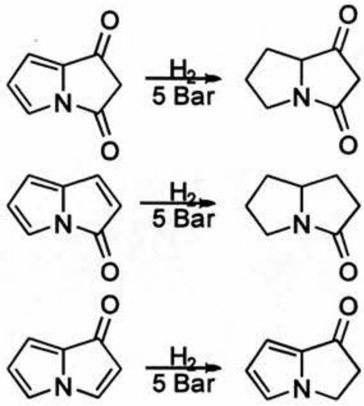
Scheme 126: Further hydrogenation 201

This also demonstrates how *N*-acyl pyrroles can be readily hydrogenated as a result of the nitrogen lone pair being delocalised through to the carbonyl reducing the aromaticity of the pyrrole ring **(scheme 127)** as discussed earlier in the case of pyrrolizin-1-one and pyrrolizin-3-one.



Scheme 127: Delocalisation of lone pair in pyrrolizine-1,3-dione

This result is directly comparable with the hydrogenation of pyrrolizin-3-one and pyrrolizin-1-one **(scheme 128)**.



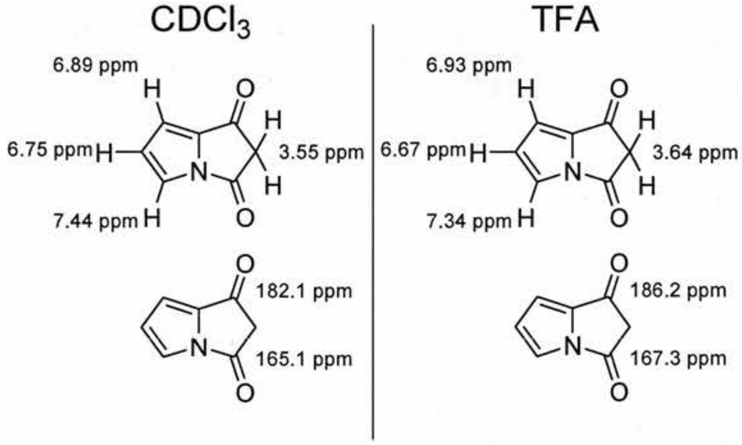
Scheme 128: hydrogenation of pyrrolizines

It can be seen how pyrrolizine-1,3-dione behaves like pyrrolizin-3-one as an *N*-acyl pyrrole enabling the "aromatic" pyrrole ring to be hydrogenated. This also further demonstrates the reasons why the pyrrole ring in pyrrolizin-1-one does not hydrogenate under comparable conditions.

Active methylene chemistry.

Reaction with TFA.

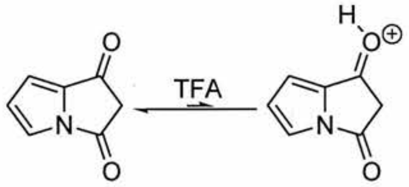
It can clearly be seen that there is very little difference in chemical shifts in pyrrolizine-1,3-dione in TFA and in $CDCl_3$ **(figure 36)**.



Proton	$CDCl_3$	TFA	Carbon	$CDCl_3$	TFA
2-position	3.55	3.64	1-position	182.1	186.2
5-position	7.44	7.34	3-position	165.1	167.3
6-position	6.75	6.67			
7-position	6.89	6.93			

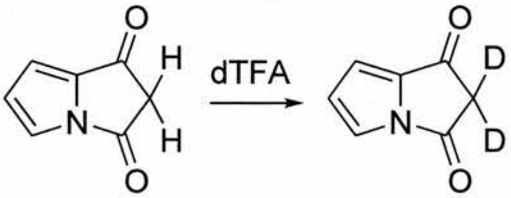
Figure36: Comparison of chemical shifts of pyrrolizine-1,3-dione in $CDCl_3$ and TFA

This indicates that there is very little protonation occurs upon exposure to acid **(scheme 129)**, the differences observed are those expected due to solvent effects and not protonation.



Scheme 129: Protonation of pyrrolizine-1,3-dione

The reactivity with dTFA was also investigated, pyrrolizine-1,3-dione was dissolved in dTFA in an NMR tube and the ^{1}H NMR spectrum was recorded at regular intervals. Deuterium exchanged into the CH_2 position diminishing the signal intensity. **(Scheme 130).**



Scheme 130: Reaction of pyrrolizin-1,3-dione with dTFA

The reaction was observed by ^{1}H NMR spectroscopy comparing, the ratio of the CH_2 signal at 3.66 ppm to that one of the pyrrole ring at 6.89 ppm. The relative size of the CH_2 peak decreased over time as can be seen by the graph **(figure 37)**. The half life of the reaction was 3 h.

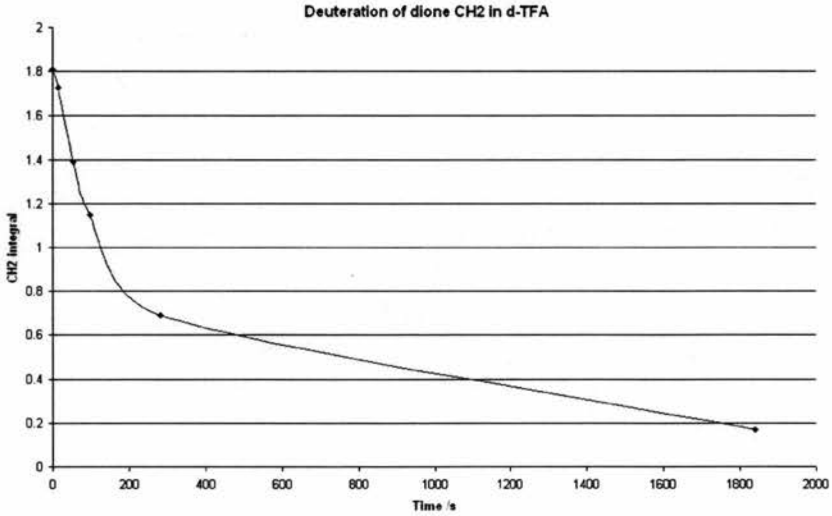
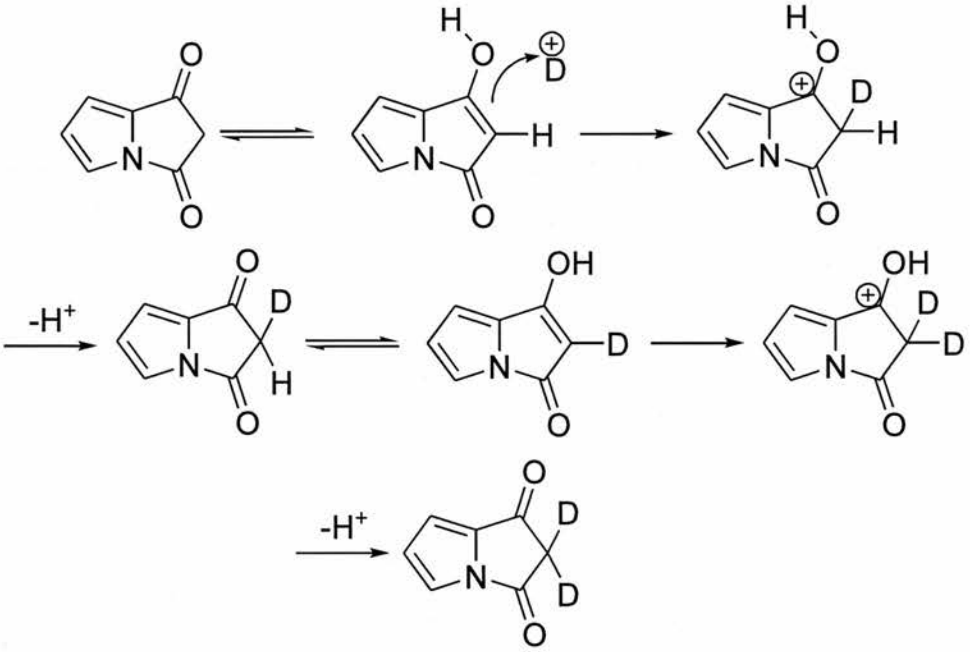


Figure 37: Deuteriation of 6 in DTFA

The observation that deuterium exchange occurs rapidly at the CH_2 position. indicates that this position would be reactive towards electrophiles and that very mild conditions would be required.

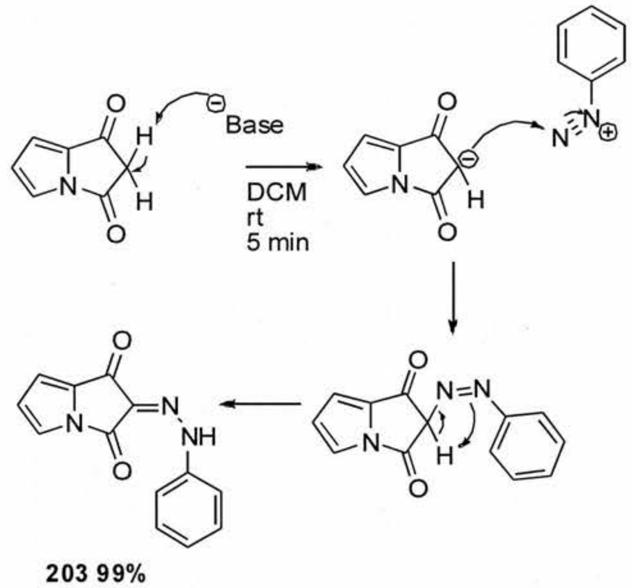
In this reaction the reactive species is likely to be the enol tautomer, but as this is not observed it is suggested that the keto enol tautomerisation lies heavily on the side of the keto compound. However if tautomerisation is rapid and the enol species is very reactive the rapid deuteriation of the CH_2 position can be explained **(scheme 131)**.



Scheme 131: Reaction with d-TFA

Reaction with benzenediazonium fluoroborate.

The reaction of pyrrolizine-1,3-dione with benzenediazonium fluoroborate was carried out **(scheme 132)**. As it had already been observed that the pyrrolizine-1,3-dione ring opens in neucleophilic solvents such as MeOH **(scheme 132)** it was decided that the reaction would be carried out in non nucleophilic solvents. DCM was chosen as the solvent for this reaction, to solubilise the fluoroborate salt a few drops of Hunigs base was required, this also serves to catalyse the reaction. The reaction proceeded to completion within five minutes upon which the solvent and Hunigs base was removed by evaporation. This acts as an example of reaction of electrophiles with **6**.



203 99%

Scheme 132: reaction of pyrrolizine-1,2-dione with diazonium salts

The X-ray crystal structure of **203** was obtained and the bond lengths can be compared with those of pyrrolizin-3-one.

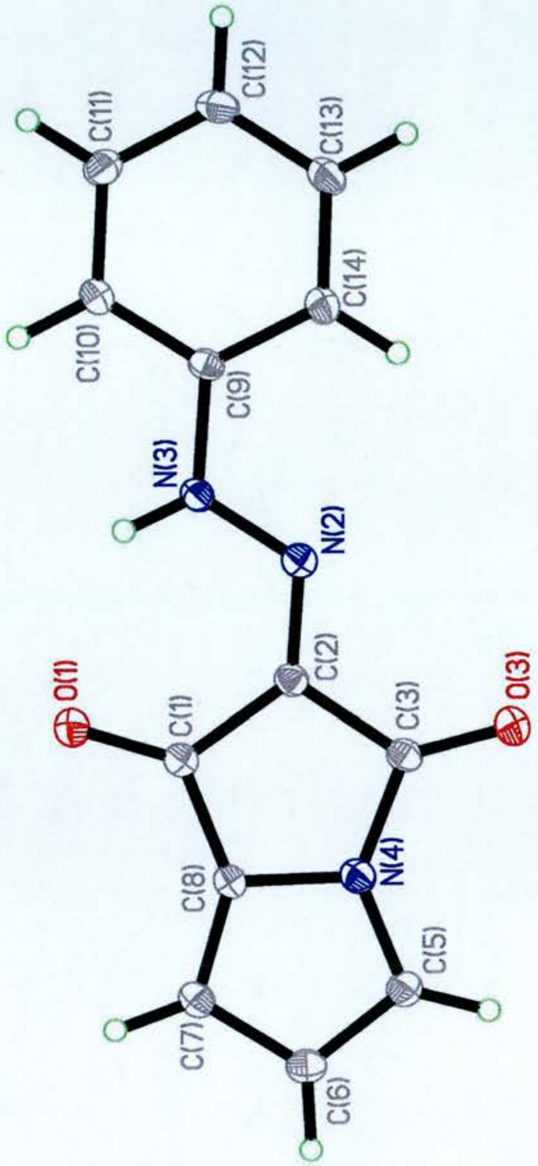


Figure 37: Ortep diagram of 203

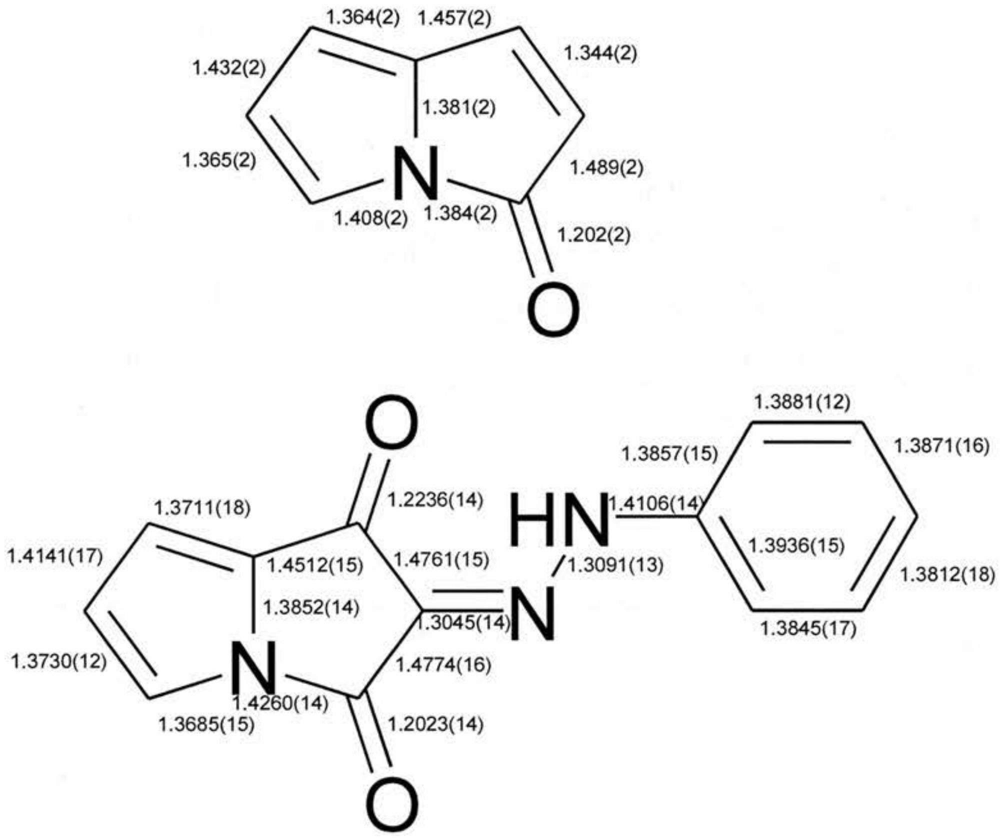
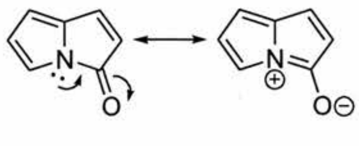


Figure 37: Bond lengths in 203 and 10

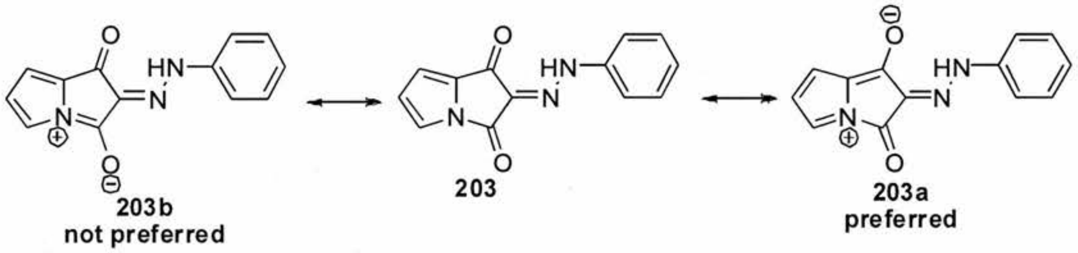
	Pyrrolizin-3-one	Pyrrolizine-1,3-dione
N4-C3	1.384	1.426
C3-O3	1.202	1.202
C1-O1		1.224
N4-C5	1.408	1.369
C5-C6	1.365	1.373
C6-C7	1.432	1.414
C7-C8	1.364	1.371

On comparison with the crystal structure of pyrrolizine-1,3-dione with pyrrolizin-3-one several key observations can be made. It can clearly be seen that there are significant differences in the amide carbonyl linkages. As has been previously discussed, in pyrrolizin-3-one it is observed that the N4-C3 bond has been shortened and the C3-O3 bond has been lengthened showing evidence of donation of the nitrogen lone pair through to the carbonyl **(scheme 133)**.



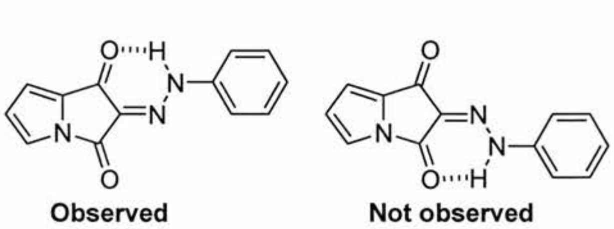
Scheme 133: donation of lone pair in pyrrolizin-3-one

In the pyrrolizine-1,3-dione derivative **203** it can clearly be seen that the N4-C3 bond is significantly longer than in pyrrolizin-3-one, also observed is the shortening of the N4-C5 bond and to a certain extent the lengthening of the formal double bonds and the shortening of the formal single bonds in the pyrrole ring. It is also noticed that the ketone carbonyl bond is significantly longer than the amide carbonyl.[49] This indicates that the bridgehead nitrogen lone pair preferentially delocalises through the pyrrole ring to the ketone carbonyl **(scheme 134)**. This plays an important role later in the in the reaction of the Meldrumsation of pyrrolizine-1,3-dione **(scheme 134)**.



Scheme 134: Preferred resonance structure of 203

Furthermore H-bonding between the NH and the pyrrolizine-1,3-dione ketone carbonyl is observed, not to the amide group, further indicating the increased electron density at the ketone carbonyl over the amide carbonyl **(figure 38)**.



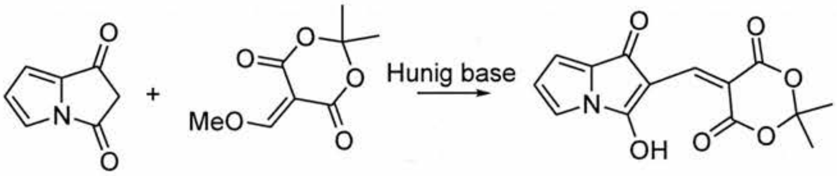
Observed

Not observed

Figure 38: H-bondong observed in 203

Reaction with methoxymethylene Meldrum's acid.

Following the reaction with the diazonium salt the reaction with more electrophiles was investigated. Reaction of pyrrolizine-1,3-dione **4** with methoxymethylene Meldrum's acid **14** in dichloromethane containing a drop of Hünig's base provides the 'Meldrumsated' product **15** (81 %) (**scheme 135**). Again the drop of base is believed to catalyse the reaction, in this case the solvent was removed after the reaction had proceeded to completion to give the product as a red waxy solid. To purify this the product was dissolved in ether and washed with 2M HCl to remove any basic residues, giving the product as a red crystalline solid recrystallised from ethanol.



Scheme 135: reaction of pyrrolizin-1,3-dione with MMMA

The various tautomeric structures of **204** can be considered, and the most probable tautomer can be assigned by inspection of the ^{13}C NMR spectrum. Upon initial inspection the two non-conjugated tautomers **204b** and **204c** can be eliminated as only 4 CH resonances are present. Further inspection shows two quaternary signals at δ_C 162.42, this is the region expected for the dioxanedione moiety eliminating the two tautomers **204e** and **204d**. Comparison of the two remaining tautomers shows that the tautomer **204f** is most likely, as the 1-hydroxy tautomer **204a** would be expected to show a pyrrolizin-3-one type resonance at about δ_C 165 ppm, however the two remaining C-O quaternaries appear at δ_C 177.81 and 176.91 ppm indicating that the tautomer is **204f** and not the pyrrolizin-3-one type **204a**.

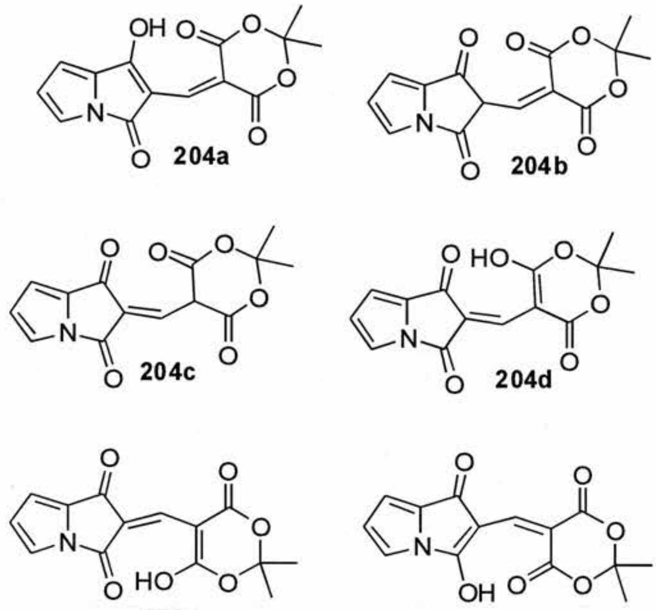
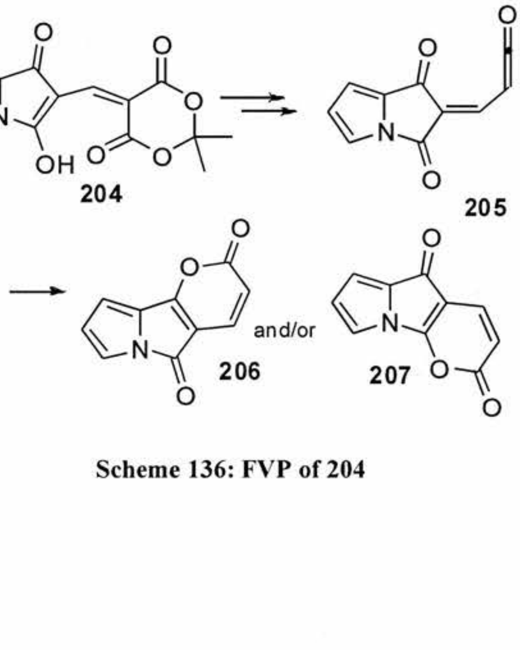

204a 204b 204c 204d 204e 204f

Figure 39: Tautomers of 204

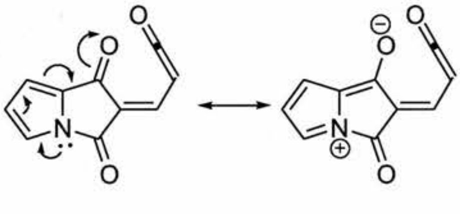
Like the FVP reactions of other Meldrum's acid derivatives, the FVP of the pyrrolizine-1,3-dione derivative **204** was expected to generate the ketene **205**. This intermediate could then electrocyclise onto one (or both) of the carbonyl groups to give one (or both) of the pyronopyrrolizinones **206** and **207 (scheme 136)**. Before the reaction was carried out there was no indication which of these would be the preferred product.



Scheme 136: FVP of 204

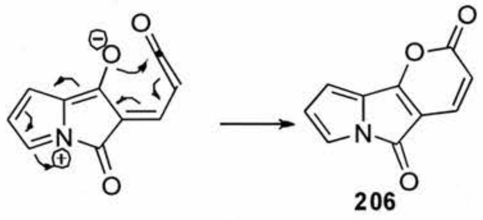
The FVP of **204** at 700 °C provided a single isomeric pyronopyrrolizinone, the comparison of the possible structures is similar to that used for the assignment of the tautomer in the "Meldrumsated" compound **204**. In this case a typical pyrrolizin-3-one type carbonyl observed at δ_C 166.81 ppm, with no ketone type signal at *ca.* δ_C 180 ppm indicated that **206** is the product of the FVP. The ketene **205** therefore preferentially cyclises onto the ketone carbonyl rather than the lactam carbonyl, with high selectivity >94%. The relative energies of the two possible products was investigated using DFT calculations, and it was found that the formed isomer **206** was 37 kJmol^{-1} more stable than the other possible isomer **207**. It can therefore be argued that this is a case of the thermodynamically more stable isomer being the preferred product.[50]

However the reason may be more subtle than this, consideration of the carbonyl that the cyclisation occurs onto helps to make sense of this observation. As it is observed in the bond lengths in **203** for the two carbonyl groups it was observed that the keto bond length was significantly longer than the amide carbonyl bond. It can be assumed that the ketene intermediate in this reaction would show similar properties properties indicating that lone pair from the bridgehead nitrogen is delocalised more onto the keto carbonyl than the amide carbonyl **(scheme 137)**.



Scheme 137: Proposed preferred resonance form of 205

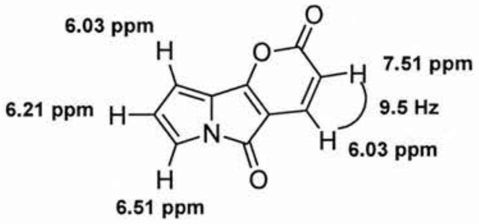
It is proposed that the reaction proceeds from the more electron rich carbonyl cyclising onto the ketene to give the pyrone **206**.

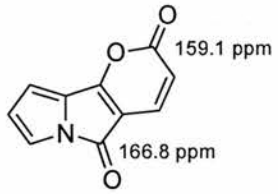


Scheme 138: Mechanism of formation of the pyrone 206

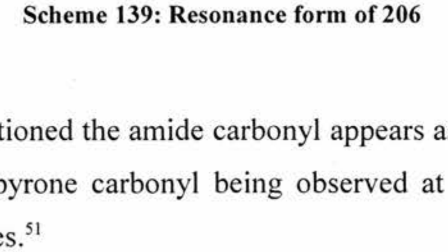
Structure of the pyrone 206.

As an example of a new type of ring system the typical NMR properties are discussed briefly.





It can clearly be seen that the enone bonds show the typical large separation and coupling constant (9.5 Hz) of protons in a push pull system, suggesting that the nitrogen lone pair may be delocalised through conjugation to the pyrone carbonyl as seen in resonance structure **206a (shseme 139)**.

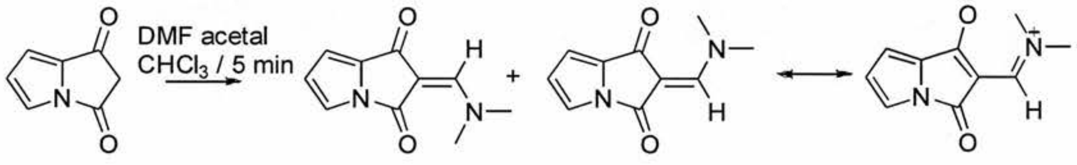


Scheme 139: Resonance form of 206

As has been already mentioned the amide carbonyl appears as 166.8 ppm typical for a pyrrolizinone, with the pyrone carbonyl being observed at 159.1 ppm, this can be compared to other pyrones.[51]

Reaction with DMF acetal.

The reaction of the dione with DMF acetal was observed in chloroform giving the product **208** in 97% yield. The product shows hindered rotation around the C-N and the C-C bonds, the ^{1}H NMR spectrum at room temperature shows the presence of two rotomers **(scheme 140)**. The two isomers were inseparable as such it was not possible to assign the signals to one isomer or the other.



208
1:1 >99%

Scheme 140: Reaction of the dione with DMF acetal

There are three hindered rotations observed **(figure 39)** two of the hindered rotations **A** and **B** are due to the rotations around the C-N bond in each of the two isomers. The third hindered rotation **C** arises from the rotation around the C-C double bond.

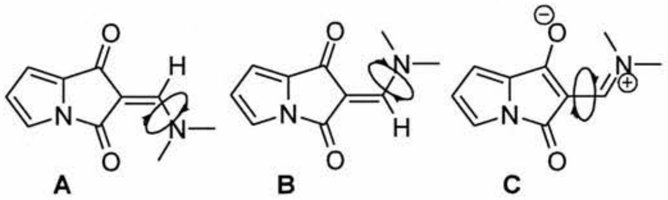


Figure39: Hindered rotations in 208

In order to investigate these rotations the ^{1}H NMR of **208** was recorded at different temperatures to give the coalescence temperature from which the energy required for rotation around the bonds involved can be calculated.

$$\Delta G^{\ddagger}=19.13T_c(9.97+\log_{10}T_c/v)$$

This can clearly be seen from the NMR spectra where these coalesences appear **(figure 40)**.

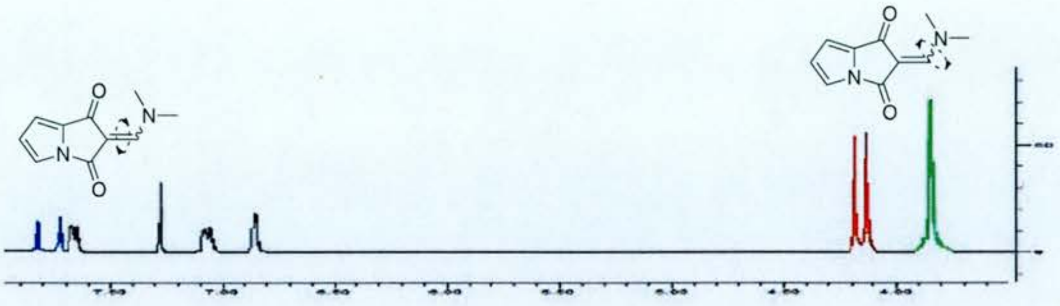
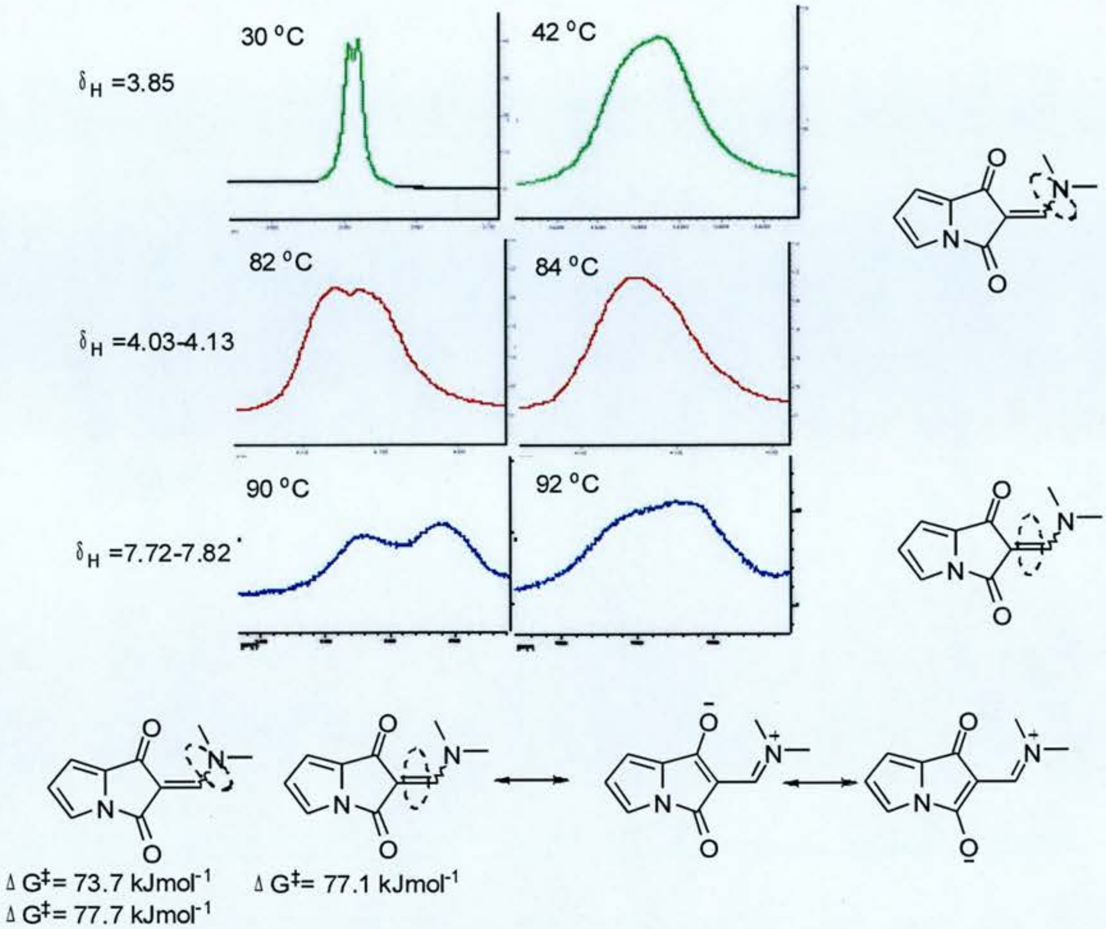


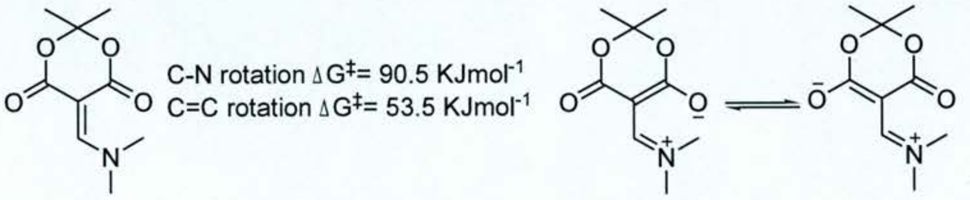
Figure 40: Room temperature NMR of 208

The pairs of singlets at 3.85 ppm and 4.03 and 4.13 ppm are due to the hindered rotations around the C-N bond **A** and **B**. The signals at 7.82 and 7.72 ppm is due to the rotation around the C-C bond **C**. The coalescence temperature for each signal was recorded and the energy of rotation was calculated. **(scheme 141)** shows how the coalescence was measured by increasing the temperature at which the NMR spectrum was recorded. It can be seen that the coalescence temperature was found to be accurate within 2 °C. The energies for rotation around the C-N bond for each isomer and the energy for rotation around the C-C double bond are similar within experimental error. This energy was within the range of energies that rotation occurs at room temperature, thus the isomers are inseparable at room temperature.



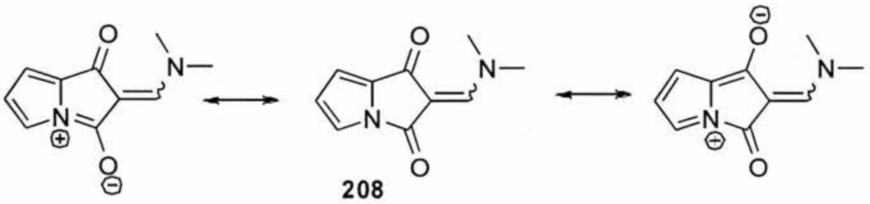
Scheme 141: Coalescence of 208

This result can be directly compared to dimethylaminomethylene Meldrum's acid **209** **(scheme 142)**, as can clearly be seen the energy for rotation around the C-N bond in **209** is higher than that for **208** also the energy for rotation around the C-C bond in **209** is significantly lower than that for **208**.



Scheme 142: Energies for rotation in 209

This shows that the dipolar resonance structures in the Meldrum's compound are significantly more important than the equivalent dipolar resonance structures of **209**. It is suggested that pyrrolizin-1,3-dione is less electron withdrawing than Meldrum's acid. The reason for this can be explained by considering that there are two competing processes in the dione compound **208** that both form dipolar resonance forms. The first is the resonance forms that lead to the hindered rotations that have been discussed the second is the delocalisation of the bridgehead nitrogen lone pair onto the carbonyl groups **(scheme 143)**. This is demonstrated by the crystal structure of **203**, this leads to the carbonyls being more electron rich and therefore less electron withdrawing increasing the energy required for rotation around the C-C double bond and the C-N bond.



Scheme 143: Other resonance structures of 208

Conclusions.

It has been shown in this chapter that the synthesis of pyrrolizin-1,3-dione has been greatly improved with the yield of the final step being increased from 27 to 68%. This has enabled the chemistry of pyrrolizine-1,3-dione to be investigated; it was shown that **6** shows similar amide chemistry to pyrrolizin-3-one through its ring opening with nucleophiles. The ketone chemistry has been demonstrated in the reaction with the diazonium fluoroborate salt and the formation of the Brady's derivative **199**. The pyrrole chemistry was demonstrated in the hydrogenation reaction and can be compared to that of pyrrolizin-3-one showing how *N*-acyl pyrroles can be readily hydrogenated. Finally the active methylene chemistry was demonstrated in the reaction with MMMA and DMF acetal, this was furthered by the FVP of the MMMA derivative to give a fused pyrone.

Azaindolizines and cyclazines.

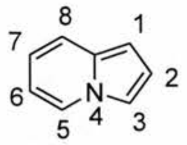


Figure 42: Indolizine

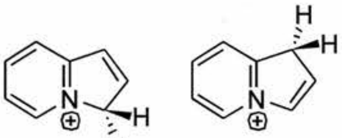
Indolizine is a fused 6-5-ring system, the delocalisation of the lone pair on the bridgehead nitrogen through the rings gives it an aromatic 10π electron configuration. The numbering scheme above (**figure 42**) will be used throughout this chapter for consistency, as the introduction of heteroatoms changes the systematic numbering around the ring and the naming of the ring systems involved. The use of the prefix aza is used to indicate the presence of a second nitrogen at the indicated position **(figure 43)**.

5-azaindolizine **210** **6-azaindolizine** **211**

7-azaindolizine **212** **8-azaindolizine** **7**

Figure 43: Nomenclature of azaindolizines

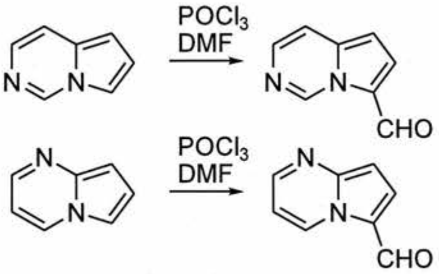
Indolizine has been shown to protonate either at the 3-position or at the 1-position with protonation at the 3-position predominating.[52] Protonation at these sites gives rise to the cations **213** and **214 (figure 44)**, these give rise to the pyridinium sextet in the six membered ring.



213 **214**

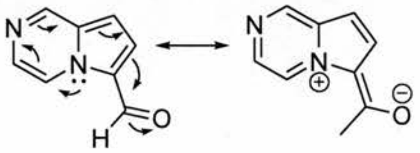
Figure 44: Pyridinium cations of indolizine

The site of the protonation of the azaindolizines can be considered as a balance between the availability of pyridine type nitrogen or the formation of a pyridinium sextet. In the case of 6,7 and 8-azaindolizines **211, 212** and **7** protonation occurs at the non bridgehead nitrogen however in the case of 5-azaindolizine **210** protonation occurs at the 3-position giving rise to the sextet in the six membered ring.[47]
The reactivity of azaindolizines towards electrophiles has been reported. 6-Azaindolizine **211**[53] and 8-azaindolizine **7**[54] have been shown to undergo Vilsmeier formylation at the 3-position **(scheme 144)**.



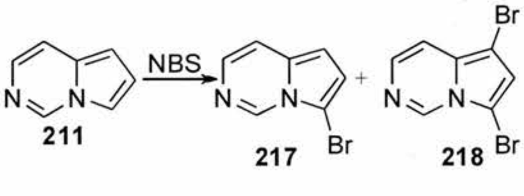
Scheme 144: Vilsmeier formlyation of 6- and 8-azaindolizines

Vilsmeier formylation of 7-azaindolizine **212** is unclear, it is reported that **212** does not undergo formylation,[55] but it is subsequently reported that formylation occurs at the 1-position the assignment is based on NMR evidence and early theoretical calculations.[56] The reported formylation at the 1-position requires much more forcing conditions than for any of the other azaindolizines, however there is some NMR evidence that formylation may have occurred at the 3-position which would have been expected in comparison with the other azaindolizines. The coupling constant quoted for the protons in the pyrrole ring J = 4.3 Hz is slightly high for a pyrrole type coupling constant. This could be due to donation of the lone pair from the bridgehead nitrogen through to the carbonyl group, this in effect gives a resonance structure with an unsymmetrically substituted pyrroline **(scheme 145)**. The increased coupling constant is beginning to become more reflective of that of a pyrroline.[57] This mechanism is not available for formylation at 1-position suggesting that spectrum may have been miss assigned. The effects of an electron withdrawing group attached to the 3-position is discussed in detail later **(page 160).**



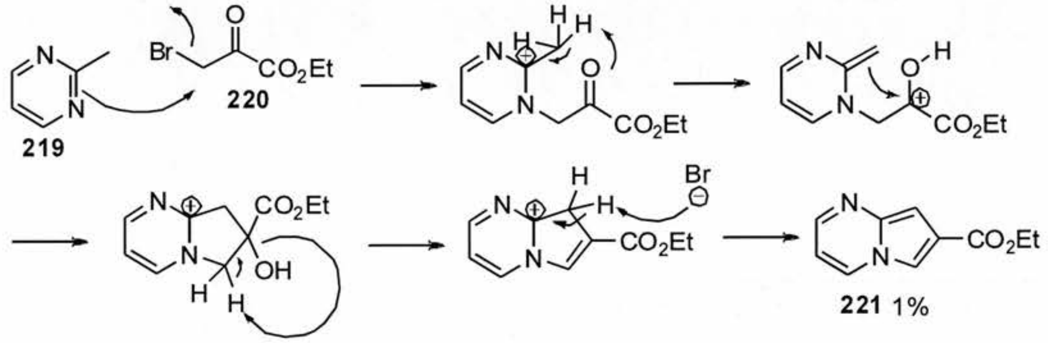
Scheme 145: Resonance forms of 3-formyl-7aza-indolizine

The bromination of 6- and 7-azaindolizines **211** and **212** has also been reported,[50,53] it is shown that there is a propensity for dibromination. In the presence of one equivalent of NBS 6-azaindolizine **211** gives a mixture of 3-bromo-6-azaindolizine **217** and 1,3-dibromo-6-azaindolizine **218 (scheme 146)**. This agrees with the suggestion that azaindolizines react with electrophiles preferentially at the 3-position. However it has also been reported that 7-azaindolizine **212** undergoes bromination to give 1-bromo-7-azaindolizine and 1,3-dibromo-7-azaindolizine, this may also be miss assignment of spectra. It is possible that assignment of the position of substitution for 7-azaindolizine **212** may have been based on calculations of Mulliken atomic charges, this is not a reliable method for prediction of site of reaction.[55]



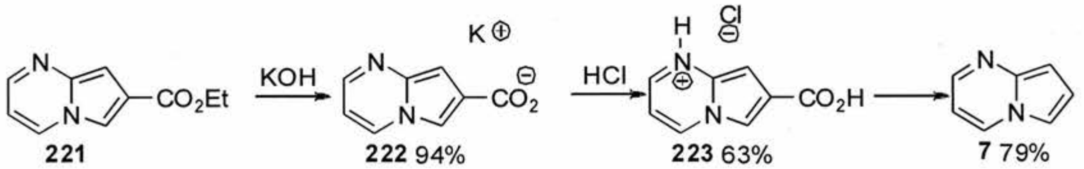
Scheme 146: Bromination of 6-azaindolizine

Of the azaindolizines that which has been least investigated is 8-azaindolizine. This is partially due to the fact that there is only one reported synthesis.[47] This synthesis starts from 2-methylpyrimidine **219** which itself is not a commercially available material. This reaction proceeds via a Chichibabin reaction between 2-methylpyrimidine and an α-halo ketone **(scheme 147)**, in this case ethyl bromopyruvate **220**.



Scheme 147: Chichibabin reaction of 2-methylpyrimidine with ethyl bromopyruvate

This reaction gives 2-carbethoxy-8-azaindolizine **221**, however it should be noted that it only proceeds in a 1% yield after reaction at room temperature for 1-3 days. This is followed by base hydrolysis to give the KOH salt of the carboxylic acid **222** 94%, neutralisation to give the HCl salt **223** 63% and then decarboxlyation to give 8-azaindolizine **7** 79% **(scheme 148)**.

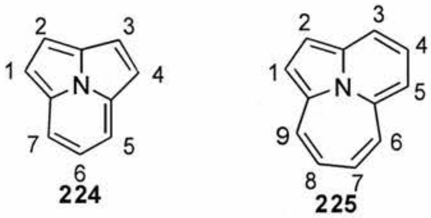


Scheme 148: Formation of 8-azaindolizine

The limiting step in this synthesis is obviously the first step only proceeding in a 1% yield giving an overall yield of 0.5% from 2-methypyrimidine **219** which itself is not commercially available. Even though low yielding this strategy has been used to form many substituted analogues of 8-azaindolizine.[49]

Part of the rationale behind the synthesis of azaindolizines was in the field of the formation of azacyclazines. Cyclazines are another class of compound that require their own numbering scheme.

As was proposed by Boekelheide,[58] "the word cyclazine is reserved for the general case of a conjugated, unsaturated cyclic molecule held planar by three covalent bonds to an internal nitrogen". As many different possible cyclazines exist with differing ring sizes and different points of attachment to the nitrogen, differentiation is made between them by adding numbers in brackets, which indicate the number of atoms on the ring between points of attachment and the numbering follows IUPAC rules.

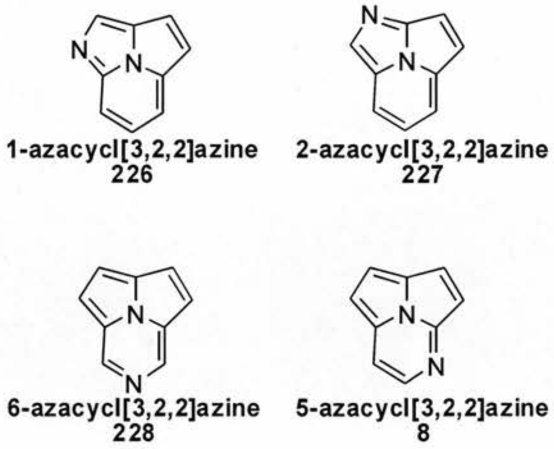


224
cycl[3,2,2]azine

225
cycl4,3,2]azine

Figure 45: Nomenclature of cyclazines

Following this convention **224** would be named cycl[3,2,2]azine and **225** cycl[4,3,2]azine rather than their systematic names pyrrole[2,1,5-*cd*]indolizine and 9b-azabenzo[*cd*]azulene. Upon substitution of one of the peripheral carbons with a nitrogen atom the prefix aza is used to indicate the position of the nitrogen. The numbering scheme is not changed on introduction of a heteroatom to emphasise the connection between closely related compounds **(figure 46)**.



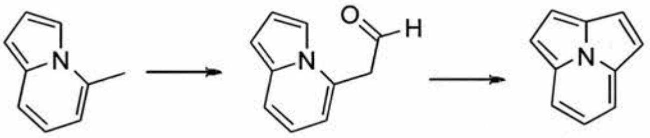
1-azacycl[3,2,2]azine 226 **2-azacycl[3,2,2]azine 227**

6-azacycl[3,2,2]azine 228 **5-azacycl[3,2,2]azine 8**

Figure 46: Nomenclature of azacyclazines

The cyclazine system relevant to this project is the cycl[3,2,2]azine system and in particular the azacycl[3,2,2]azines. Cycl[3,2,2]azines are stable aromatic compounds of which a lot is known. However of the azacycl[3,2,2]azines only three of the possible four unsubstituted ring systems, 1-, 2- and 6-azacycl[3,2,2]azine **226**, **227** and **228** respectively, are reported in the literature,[59,60,59] furthermore only a few highly substituted 5-azacycl[3,2,2]azine **8** has been reported.[58]

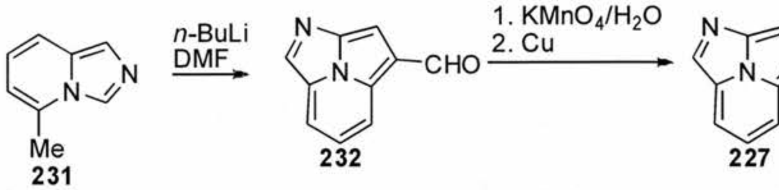
The most popular routes to cycl[3,2,2]azines are from indolizines. A few different strategies employed and one of these is intramolecular condensation reactions. Functionalisation of 5-methylindolizine **229** with *n*-butyllithium followed by treatment with *N,N*-dimethylamides gives the aldehyde **230** which is subsequently cyclodehydrated in glacial acetic acid to give cycl[3,2,2]azine **8**.[56]



229 **230** **8**

Scheme 149: Synthesis of cycl[3,2,2]azine

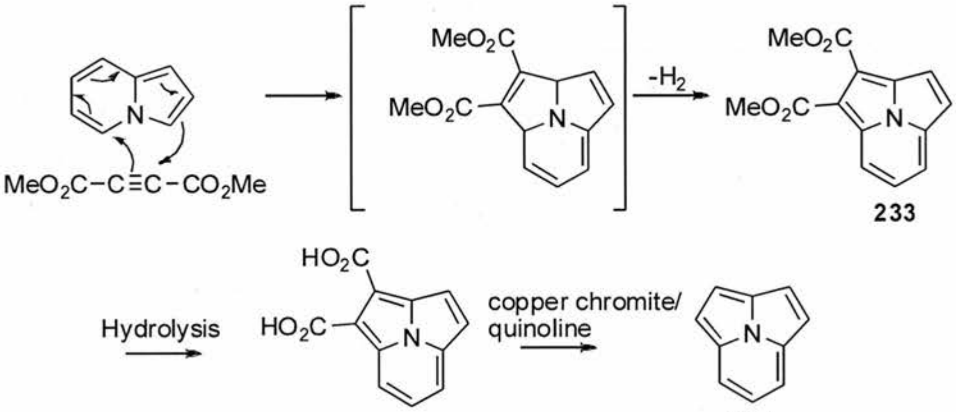
2-Azacycl[3,2,2]azine **227** has also been prepared by intramolecular cyclisation, 2-aza-5-methylazaindolizine **231** is reacted with *n*-BuLi and DMF to produce 4-formyl-2-azacycl[3,2,2]azine **232**. This is then subsequently converted to the cyclazine **227**.[61]



231 **232** **227**

Scheme 150: Synthesis of 2-azacycl[3,2,2]azine

The second route to cyclazines from indolizines is by cycloaddition reactions. Indolizines have been shown to react with dialkyl acetylenedicarboxylate in the presence of a dehydrogenation catalyst to give 1,2-dicarboxycycl[3,2,2]azine **233**.[62]



233 **234** **224**

Scheme 151: Cycloaddition synthesis of cycl[3,2,2]azine

The 1,2-dicarboxycycl[3,2,2]azine **233** is subsequently hydrolysed to the diacid **234** and then decarboxylated to the cycl[3,2,2]azine **224**.

The chemistry of cycl[3,2,2]azine is that of a stable aromatic compound, undergoing electrophilic substitution reactions, as such it is assumed that the lone pair on the central nitrogen is not significantly involved in the π bonding of the ring. The stabalisation gained by possessing a 10π electron ring current rules out the involvement of the lone pair on the nitrogen in the bonding system.

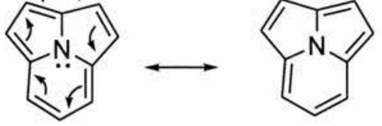


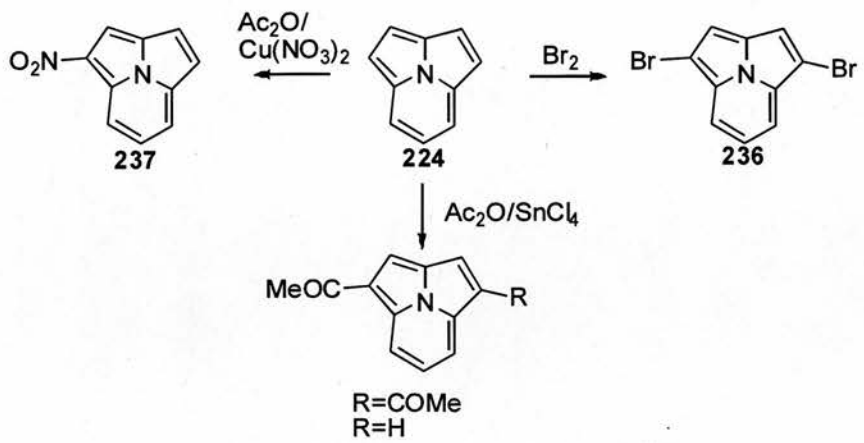
Figure 47: Resonance forms of cycl[3,2,2]azine

It has been shown that cycl[3,2,2]azine shows similar chemistry to that of cylclopentaindine **235 (figure 47)**,[6364] the non nitrogen bridged analogue, this is further evidence that the lone pair on the central nitrogen is not delocalised throughout the ring system. Lots of the chemistry is known about **224** but the following reactions are some of those which are relevant to work later in this chapter.

235

Figure 48: Cyclopentaindiene

On treatment of cycl[3,2,2]azine **224** with deuteriosulfuric acid deuteriation occurs at both the 1-position and the 4-position. In the case of 2-azacycl[3,2,2]azine **227** it has been shown to protonate the external nitrogen. Diacetylation of cycl[3,2,2]azine has been shown to occur at the 1- and 4-positions even though unchanged starting material is recovered, indicating that the rate of substitution by the second acetyl group is not significantly decreased by the presence of the first.[56] In the analogous bromination reaction no mono brominated could be isolated, the product obtained was the 1,4-dibromocycl[3,2,2]azine **236**. Nitration has been shown to occur at the 1-position to give 1-nitrocycl[3,2,2]azine **237**.

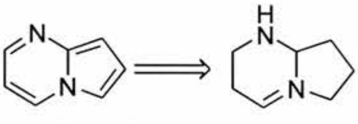


Scheme 152: Some relevant reactions of 224

The implication is that electrophilic substitution reactions occur at the 1-position, if a strongly electron withdrawing electrophile is used mono-substitution occurs, otherwise a second substitution occurs at the 4-position.

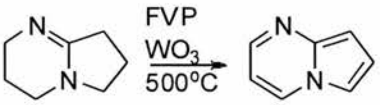
Synthesis of 8-azaindolizine.

It was proposed that another use of the dehydrogenation reactions of WO_3 catalysed FVP could be used in the formation of 8-azaindolizine **(scheme 153).** As is shown this is a very simple solution to the synthesis of a compound that was previously difficult to obtain. The idea was that DBN should dehydrogenate in one step to give 8-azaindolizine **7,** following the rules for dehydrogenation discussed earlier DBN meets all of the criteria, it possesses an NH and the proposed product is aromatic with 10π electrons.


7

Scheme 153: Retrosynthesis of 8-azaindolizine

This proposal was investigated and the inexpensive commercially available organic base DBN was pyrolysed over the WO_3 catalyst. This reaction proceeds cleanly to give 8-azaindolizine 7 (92%), however this reaction is not scalable, the reaction is limited to 60 mg.



7

Scheme 154: Dehydrogenation of DBN

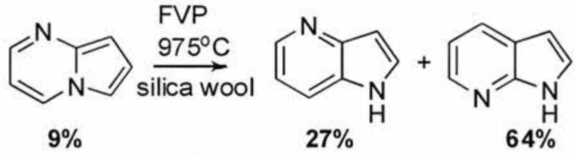
In this reaction the WO_3 surface no longer acts as a catalyst but as a reagent, the WO_3 surface after the reaction has changed from being orange to being a dark blue in colour. This is indicative of the WO_3 being reduced to a nonstoiciometric oxide by the DBN, water is also observed in the pyrolysate suggesting that the dehydrogenation proceeds by the formation of water from the WO_3 surface **(figure 21)**, the roasting process however completely regenerates the catalyst. Is is proposed that it is the reaction between the acidic catalyst surface and the basic DBN that temporarily destroys the catalytic sites.

The mechanism of this dehydrogenation is believed to that described **(scheme 54)** where the dehydrogenation occurs on the surface of the WO_3 with the Brønsted acid sites playing an important role in the reaction. This reaction produces 8-azaindolizine in a high yield, enabling its chemistry to be further investigated. Although this strategy is scale limited, the one step synthesis of 8-azaindolizine from commercially available starting material in one step is a great improvement upon the literature route (0.5% 4 steps) **(scheme 147 and 148)**.

Chemistry of 8-azaindolizine.

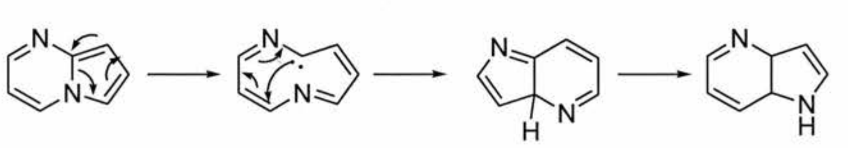
Rearrangement of 8-azaindolizine.

When 8-azaindolizine **7** was subjected to standard FVP at elevated temperature (950 °C with a silica wool plug at the end of the furnace tube) a rearrangement occurred producing 4- and 7-azaindole with a small amount of unreacted starting material. The silica wool plug has the effect of raising the furnace temperature by ~100 °C as has been previously demonstrated within the group. It is believed that the silica wool plug increases the amount of time that the compound spends in the hot zone of the furnace.



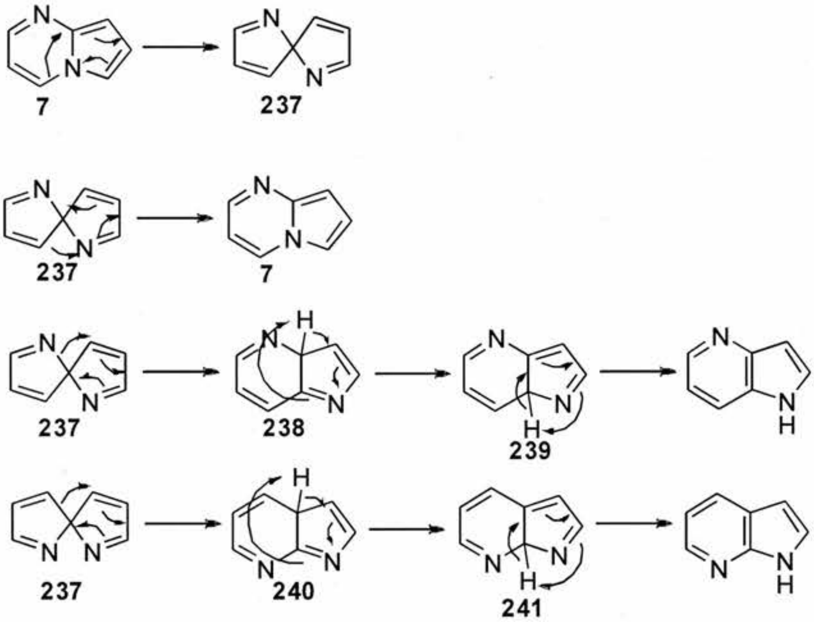
Scheme 155: Rearrangement of 8-azaindolizine

The formation of 4-azaindole could be explained by the consideration of a carbene mechanism **(scheme 156)**. It can be suggested that a carbene could be formed by the breaking of the C8a-N4 bond, this can then only go one of two ways the first would be the reverse reaction to return the starting material. Alternatively CH insertion followed by two hydrogen shifts gives 4-azaindole, but this mechanism does not however explain the formation of 7-azaindole. The major product cannot be explained by this mechanism therefore the reaction must follow a different route.



Scheme 156: Carbene mechanism

It is proposed that the reaction proceeds *via* a symmetrical spiro intermediate **237** where the N4-C5 bond has broken and a C5-C8a bond has formed. The symmetric intermediate **237** can then proceed in one of three directions, the formation of a new C-N bond to give the starting material **7**. The formation of the C-N bond to give **238** followed by two hydrogen shifts gives 4-azaindole *via* the intermediates **238** and **239**. The formation of a new C-C bond to give the intermediate **240** is followed by two H-shifts *via* **241** and **242** to give 7-azaindole.



Scheme 157: Mechanism of formation of 4- and 7-azaindole.

To investigate this mechanism a calculation was carried out (*ab-initio* [MP2/6-31G(d,p)]) to help show the energies involved in the various steps.

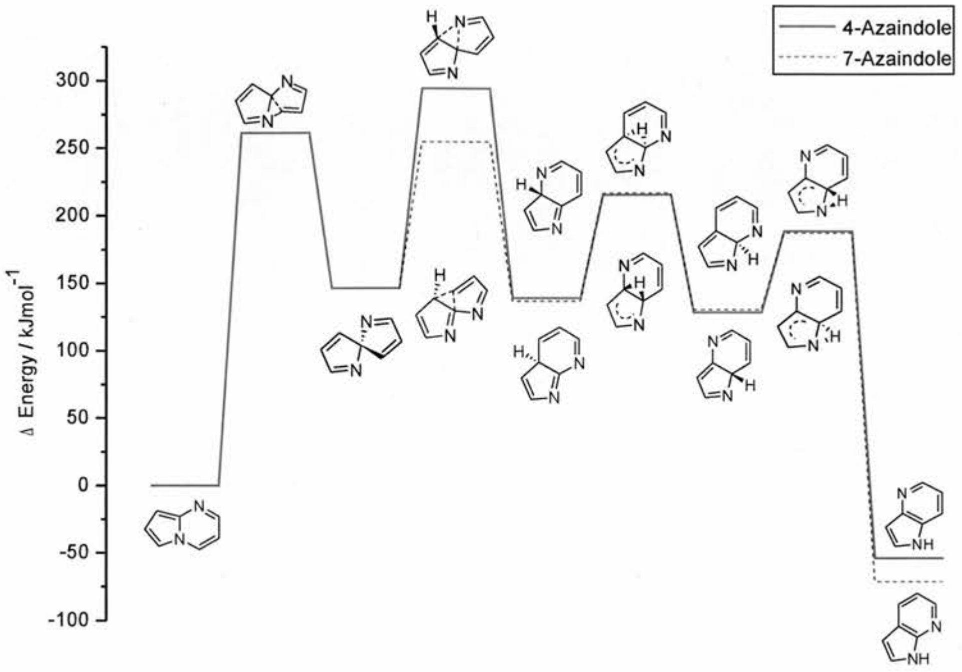
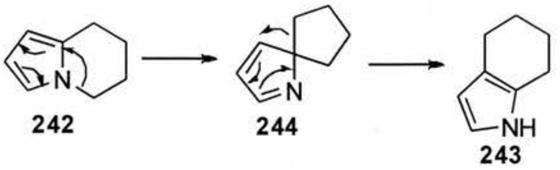


Figure 49: Spiro intermediate mechanism for rearrangement

The calculation shows that after the formation of the spiro intermediate the formation of a new C-N bond shown by the red line leading to 4-azaindole is 47 kJmol^{-1} higher in energy than the formation of a new C-C bond leading to 7-azaindole shown by the blue line. There is no significant differences in the energies required during the H-shift stages of the mechanism, it is also shown that 7-azaindole is more thermodynamically stable than 4-azaindole. Thus the calculation shows that 7-azaindole is both thermodynamically and kinetically the favoured product, this is reflected in the product ratios.

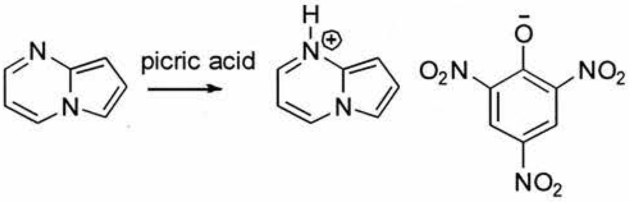
This is supported by similar reactions in the literature,[65] the rearrangement of **242** has been shown to produce **243** under flow pyrolysis conditions. It is believed that this proceeds *via* similar mechanism, **(scheme 158)** the C-N bond breaks and a new C-C bond is formed to give the intermediate **244**. In this example only one product is possible along with the reverse reaction to give starting material.



Scheme 158: rearrangement of 242

The formation of the picrate of 8-azaindolizine.

The picrate of 8-azaindolizine was readily formed upon addition of ethanolic picric acid (87%) **(scheme 159)**. The picrate was fully characterised using a variety of NMR methods, the exact assignment of protons was problematic but was resolved by the use of fully coupled carbon NMR spectra **(figure 51)** and COSY spectra.



Scheme 159: Picrate formation

The use of fully coupled carbon spectra enabled the assignment of C3, C5 and C7 due to the fact that CH signals adjacent to N atoms have significantly larger C-H coupling constants than normal **(figure 50)**. It can clearly be seen that the carbons C3, C5 and C8 all show large C-H coupling constants; 193.1, 185.2 and 185.1 Hz, respectively. The carbons not adjacent to N; C1, C2 and C6 all show smaller C-H coupling constants 176.1, 171.6 and 172.3 Hz respectively. The use of HSQC spectra enabled this information to be transferred to the proton dimension and COSY spectra enabled the full assignment of all of the spectra. This showed the protons on the pyrrole side of the molecule H1 at 6.54 ppm shows a coupling to H2 ppm at 7.02 ppm of 4.0 Hz and H2 shows a coupling to H3 at 7.57 ppm of 3.0 Hz. This is typical of a pyrrole type system; in the pyrimidene ring H5 at 8.82 ppm shows a coupling to H6 at 6.77 ppm of 7.0 Hz and H6 shows a coupling to H7 at 8.21 ppm of 4.1 Hz. One further long range coupling constant was observed between C1 and C5 although this was too small to measure, further confirming the NMR spectra of this compound.

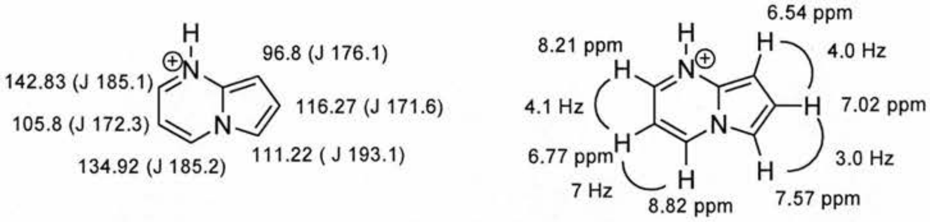


Figure 50: NMR properties of x7

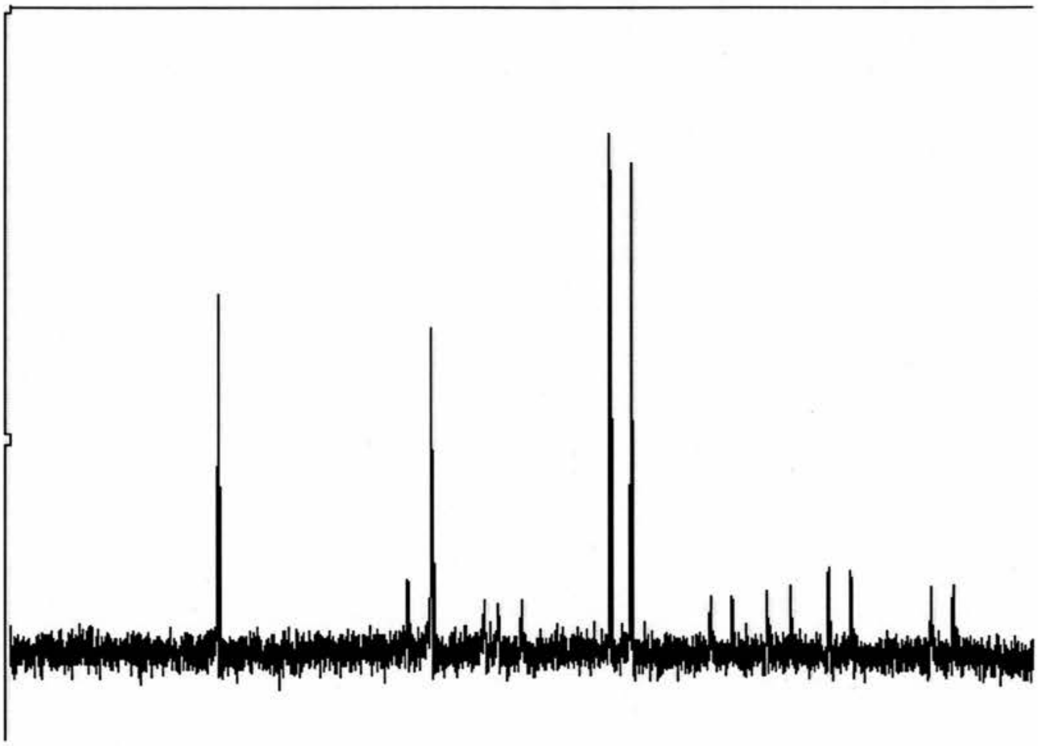


Figure 51: Fully coupled carbon spectrum of 8-azaindolizium picrate. Chemical shifts and coupling constants given below.

	δ_C / ppm	J C-H / Hz	δ_H / ppm
1	96.8	176.1	6.54
2	116.27	171.6	7.02
3	111.22	193.1	7.57
5	134.92	185.2	8.82
6	105.80	172.3	6.77
7	142.83	185.1	8.21

Reaction with electrophiles.

Reaction with TFA.

On exposure to TFA the 8-azaindolizine readily forms the protonated salt **(figure 52)**.

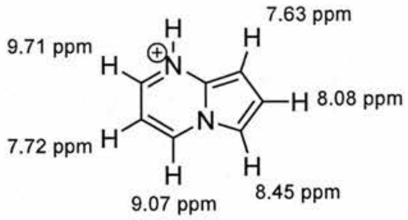


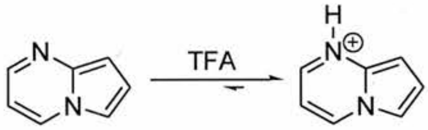
Figure 52: Chemical shifts of 8-azaindolazine in TFA

This can be compared to the chemical shifts observed in the unprotonated species, it can clearly be seen **(table 9)** that the protons are at much higher chemical shifts indicating that 8-azaindolizine is easily protonated **(scheme 160)**.

Proton	$CDCl_3$	TFA
1	6.48	7.63
2	6.96	8.08
3	7.18	8.45
5	8.15	9.07
6	6.62	7.72
7	8.06	9.71

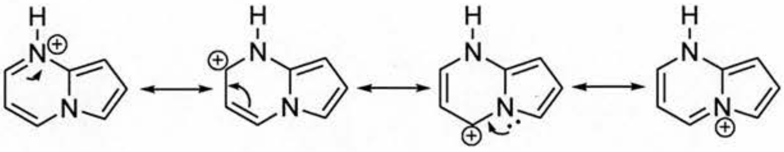
Table 9: Chemical shifts of 7 in $CDCl_3$ and TFA

This confirms that protonation occurs at the nitrogen as is previously reported in the literature.



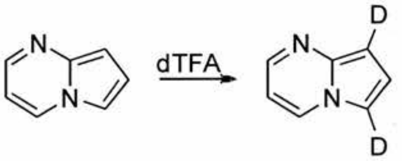
Scheme 160: Protonation of 8-azaindolizine

It is proposed that the protonated species is resonance stabilised by donation of the bridgehead nitrogen lone pair to delocalise the positive charge through the pyrimidine ring **(scheme 161)**.



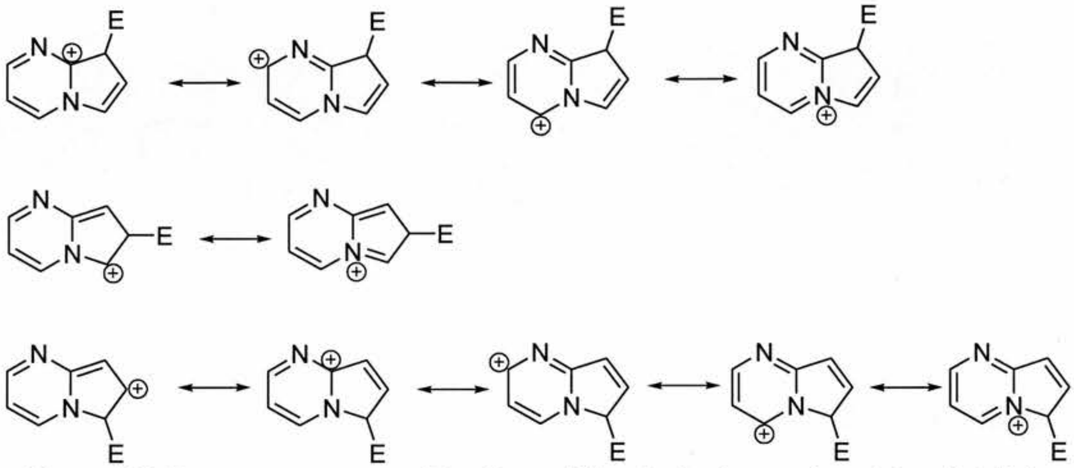
Scheme 161: Resonance stabalisation of protonated8-azaindolazine.

The deuterium exchange of 8-azaindolizine was observed in dTFA, exchange of the proton at C3 was instantaneous with the proton at C1 exchanging within the course of 1 h. No further exchange occurred over the course of five weeks indicating that the 3-position is the most reactive towards electrophilic substitution followed by the 1-position and that no exchange occurs at the 2-position.



Scheme 162: Deuteriation of 8-azaindolizine

This agrees with the reactivity with electrophiles that is predicted by considering the resonance structures obtained from the intermediate cations **(scheme 163)**.

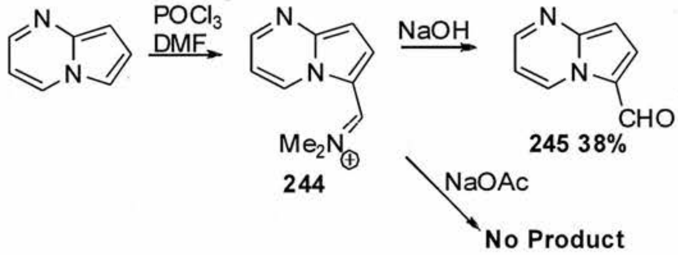


Scheme 163: Resonance structures of the electrophilic substitution reaction of 8-azaindolizine

As is demonstrated by the resonance structures the most reactive site for reaction with electrophiles is the 3-position with five resonance structures to stabilise the intermediate. This is followed by reaction at the 1-position with four resonances to stabilise the intermediate, reaction at the 2-position is less likely. Reaction in the pyrimidine ring with electrophiles is ruled out as the presence of the second electronegative nitrogen disfavours reaction with electrophiles.

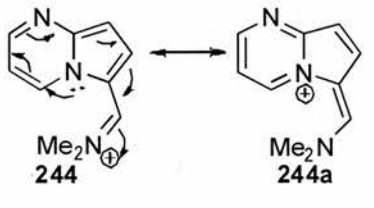
Vilsmeier formylation of 8-azaindolizine.

The reaction of 8-azaindolizine **7** with electrophiles was investigated, the previously reported reaction Vilsmeier formylation[49] was repeated with identical results. Formylation proceeded smoothly at room temperature in 15 min to give 3-formyl-8-azaindolizine **245** (38%). The workup required for this reaction is indicative of the chemistry of 8-azaindolizine, upon workup with sodium acetate solution no organic material was extracted into ether. The reaction required workup with 2M NaOH to hydrolyse the intermediate salt **244** to give the final product **245 (scheme 164).**



Scheme 164: Formylation of 8-azaindolizine

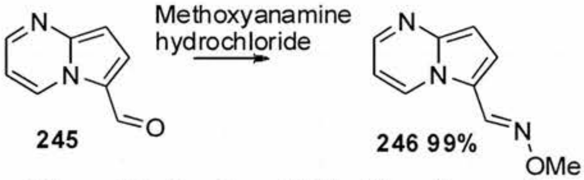
It is suggested that the stabalisation of the positive charge by donation of the lone pair from the bridgehead nitrogen through the ring system, and the aromaticity obtained in the pyrimidine ring through this mechanism, stabilises the intermediate **244**. This would make the resonance form **244a** an important resonance structure of this salt, as such a stronger base is required to give the required hydrolysis to produce the final product **245**.



Scheme 165: Resonance stabalisation of 244

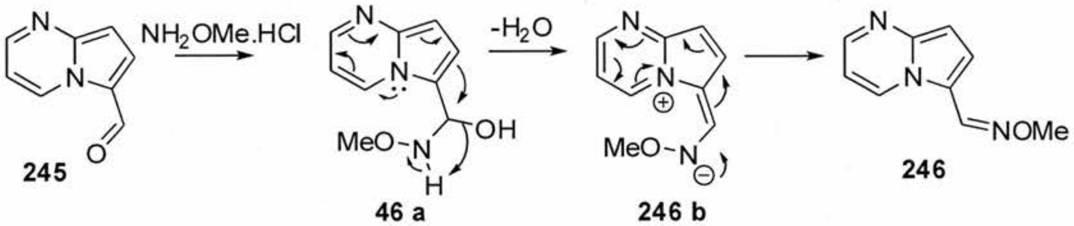
These are extremely mild conditions for formylation reactions, the formlyation of pyrrolizin-3-one proceeds only under refluxing for 15 min and can be worked-up using a sodium acetate solution, the standard literature conditions for formylation involve reaction under reflux for 1h. These results indicate the highly reactive nature of 8-azaindolizine towards electrophiles **(scheme 163)**.

The reaction of the aldehyde **245** with methoxyamine hydrochloride proceeds cleanly and quantitatively with 5 min at room temperature **(scheme 166)**, this is extremely fast for this type of reaction, the normal conditions for this reaction involve heating under reflux for 1 h.



Scheme 166: Reaction of 245 with methoxyamine hydrochloride

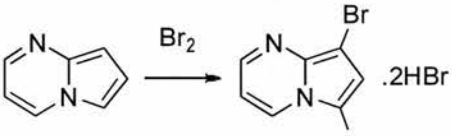
It is proposed that the dipolar resonance structure **245a** of **245** makes the carbonyl carbon more electron rich thus increasing the rate of reaction **(scheme 167)**.



Scheme 167:mechanism of formation of 246

Bromination of 8-azaindolizine.

Bromination of 8-azaindolizine with a bromine solution instantly produces a dibromocompound that precipitates from solution, most likely as the bis hydrobromide salt. The dibromide salt is suggested due to the CHN analysis, although protonation of the bridgehead nitrogen is unlikely due to its delocalisation.



247

Scheme 168: Bromination of 8-azaindolizine

The ^{1}H NMR spectrum of **247** confirms the structure showing a singlet at 7.33 ppm, proton carbon coupling confirms the position of the bromine substituents. The CH at 144.88 ppm shows a H-C coupling constant of 186.0 Hz, the CH at 131.31 ppm has a C-H coupling constant of 188.7 Hz. These are the coupling constants expected for a CH adjacent to a N, thus they are the two CHs in the pyrimidine ring. The CH at 118.97 ppm has a C-H coupling constant of 182.4 Hz this expected of a CH situated between two bromo substituted carbons. The CH at 108.69 ppm has a C-H coupling constant of 172.5 Hz, this is the value expected for a normal CH.

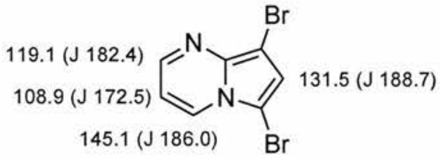
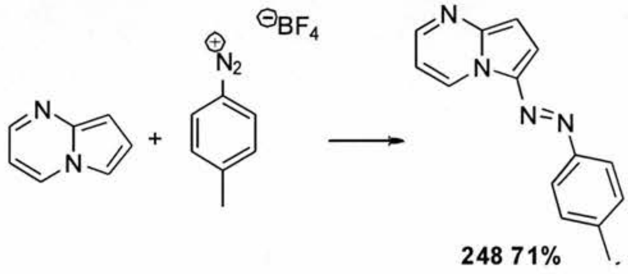


Figure 52: Full coupled carbon NMR data on 247

No other dibromosubstituted pattern could account for these coupling constants. It is also noted that the first substitution does not significantly effect the rate of the second substitution with both occurring instantaneously, this substitution pattern agrees with the predictions for the reactivity with electrophiles from the resonance stabalisation structures **(scheme 163)**.

Reaction of 8-azaindolizine with diazonium salt.

The reaction of 8-azaindolizine with *p*-tolyldiazonium fluoroborate in the presence of a drop of Hunigs base produces 3-(p-tolylazo)-8-azoindolizine **248** as a red solid, the ^{1}H NMR spectrum shows temperature dependent coalescence, indicating hindered rotation.



Scheme 169: Formation of 248

The rotation was monitored by variable temperature NMR spectroscopy **(figure 53)** the doublet at 9.62 ppm (50 °C) changes dramatically as the temperature decreases. At –40 °C it can clearly be seen that it has become two peaks, at 13 °C it is observed that the coalescence temperature is reached.

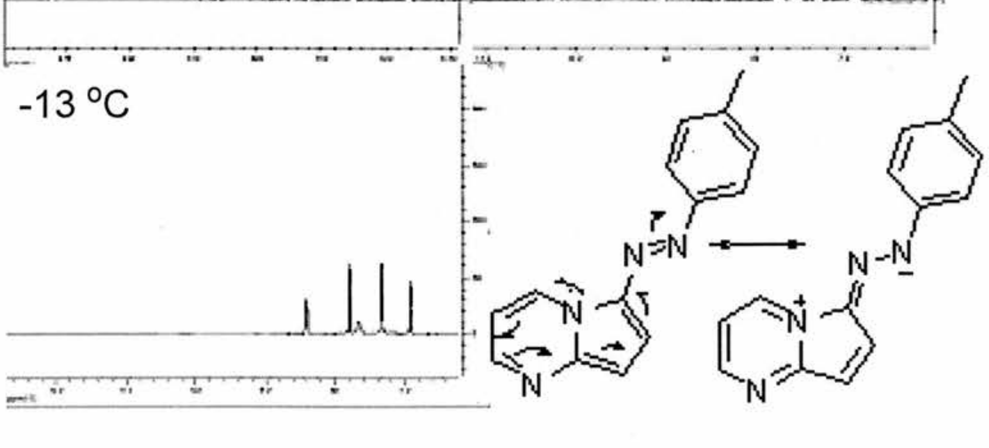
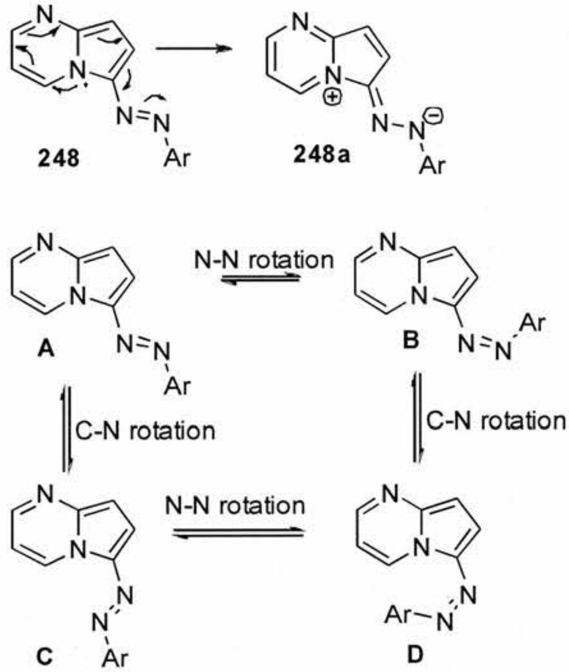


Figure 53: Variable temperature NMR of 248

Assignment of the proton NMR spectrum was required to understand the observations in the variable temperature NMR spectra. The proton most effected by the by the varying temperature is the one at 9.62 ppm, this is attributed to H2, the high chemical shift is believed to be due to being adjacent to the azo linkage as well as the deshielding effect of the proximity through space of the aromatic ring.

The diazo compound **248** has a dipolar resonance form **248a** that helps explains coalescence **(scheme 170)**. The nature or the process causing the coalescence is not completely clear, four possible rotations must be considered.



Scheme 170: Hindered rotations in 248

As the largest effect was observed at H2 it is proposed that the hindered rotation observed would most likely be due to a rotation that would cause greatest effect at this position. It can therefore be assumed that the rotation is probably not the C-N rotation from **A** to **C** and not the N-N rotation from **C** to **D** as neither would have much effect at H2. It is therefore most likely that the hindered rotation being observed is either the C-N rotation from **D** to **B** or the N-N rotation from **A** to **B**, as azo compounds are unlikely to be found in the *Z*-isomer the most likely rotation is that from **A** to **B**.

From this the energy required for rotation around can be calculated:

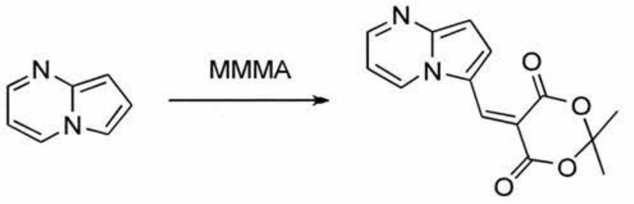
$$\Delta G^{\ddagger}=19.13T_c(9.97+\log_{10}T_c/v)$$

$$\text{C-N rotation } \Delta G^{\ddagger}= 51.2 \text{ kJmol}^{-1}$$

In theory all four rotations should also be observed, but as can be seen **(figure 170)**, the signal that show coalescence from these rotations are more complex and overlapping therefore the energy for these rotation were not able to be calculated.

Reaction of 8-azaindolizine with MMMA.

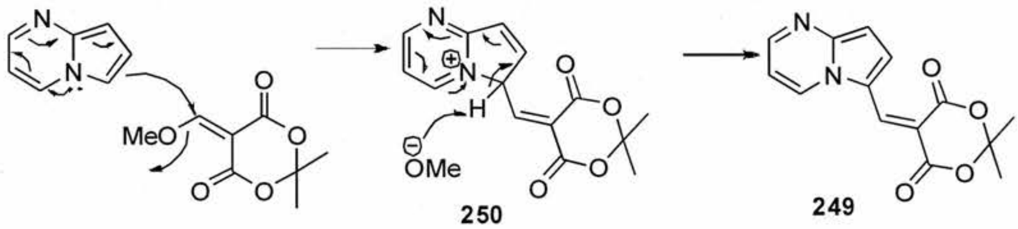
The reaction of 8-azaindolizine with MMMA proceeds quickly in comparison with other Meldrum's reactions at carbon atoms. The reaction goes to completion within 10 min to give 8-azaindolizin-3-yl-methylene-2,2-dimethoxy-[1,3]dioxane-3,6-dione **249 (scheme 171)**. This is another example of the reactivity of **7** towards electrophiles, as reactions with MMMA require highly electron rich substrates.



249

Scheme 171: Reaction of 8-azaindolizine with MMMA

It is believed that the ability of 8-azaindolizine to donate the bridgehead nitrogen lone pair through the conjugation of the pyrimidine ring and the pyrrole ring to the 3-position makes 8-azaindolizine very electron rich along with the formation of the 6 π electron aromatic pyrimidinium ring in the intermediate **250** facilitating this reaction **(scheme 172)**.



250 **249**

Scheme 172: Reaction of 7 with MMMA

The ^1H NMR spectrum of **249** showed some peculiar properties, in particular the resonances due to protons at C1 and C2 were of interest.

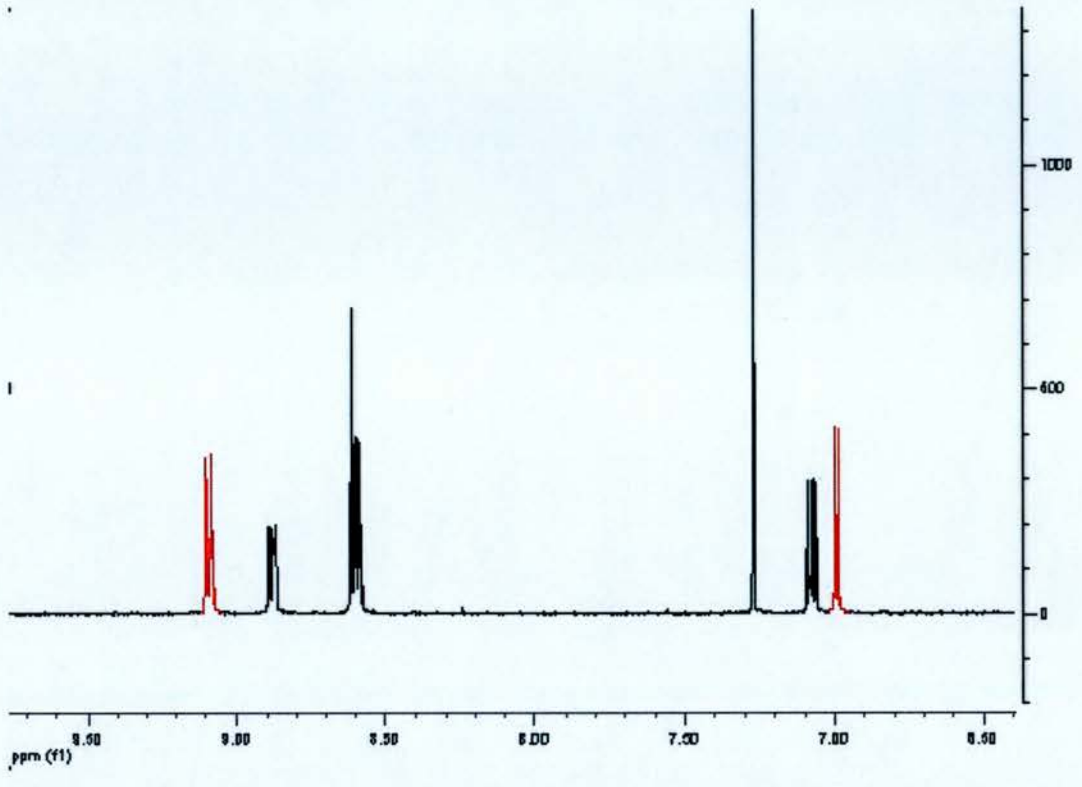


Figure 54: Proton NMR spectrum of 294

The protons from C1 and C2 are the doublets are widely separated at 6.9 and 9.1, this is indicative of a "push pull" mechanism through the bonding of the pyrrole ring. Also of interest is the coupling constant of 5.2 Hz which is very large for a pyrrole **(figure 55)**.

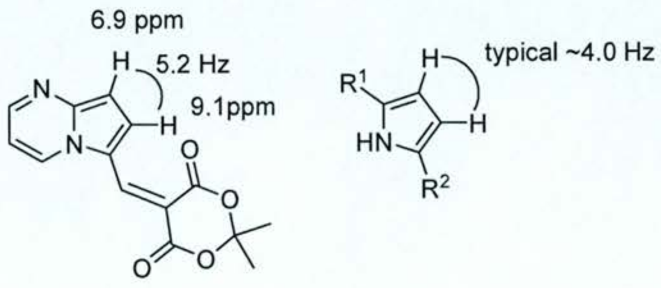
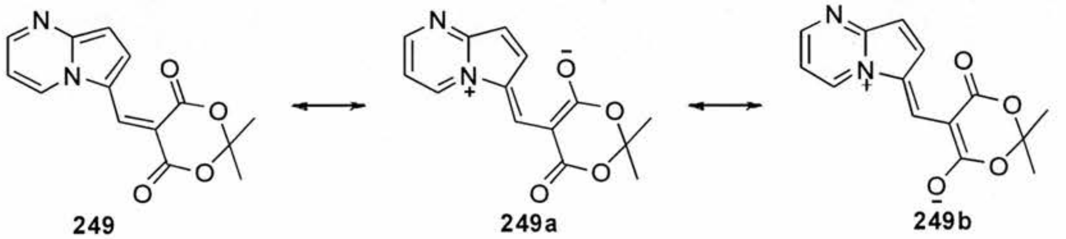


Figure 55: 249

This can be explained by considering the donation of the lone pair from the bridgehead nitrogen around the ring system and onto the oxygen atons of the Meldrums acid group **(scheme 173)**. Also, the proximity of the Meldrum's carbonyl groups to the proton at C2 would also have a deshielding effect further increasing the chemical shift.



Scheme 173: Resonance structures of 249

The dipolar resonance structures **249a** and **249b** shown in scheme can explain both of these NMR phenomena, the donation of the bridgehead nitrogen through the rings sets up a "push pull" system through the bonding in the pyrrole ring. This is the reason for the large difference in chemical shift in the two protons. While in the resonance forms **249a** and **249b** a 3-pyrroline type ring is set up, the coupling constants for 3-pyrrolines is much larger than that for pyrroles typically in the region 6 Hz.[pyrroline] This indicates that resonance forms **249a** and **249b** must make important contributions to the structure of the molecule.

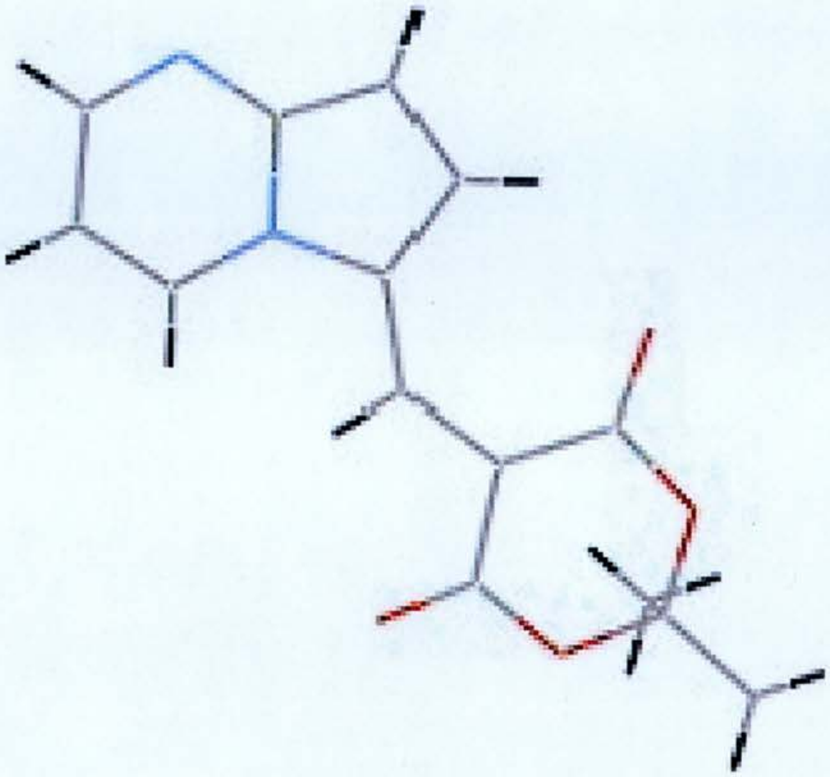


Figure 55: Crystal structure of 249

The structure and position of reaction has been confirmed by X-ray crystal structure.

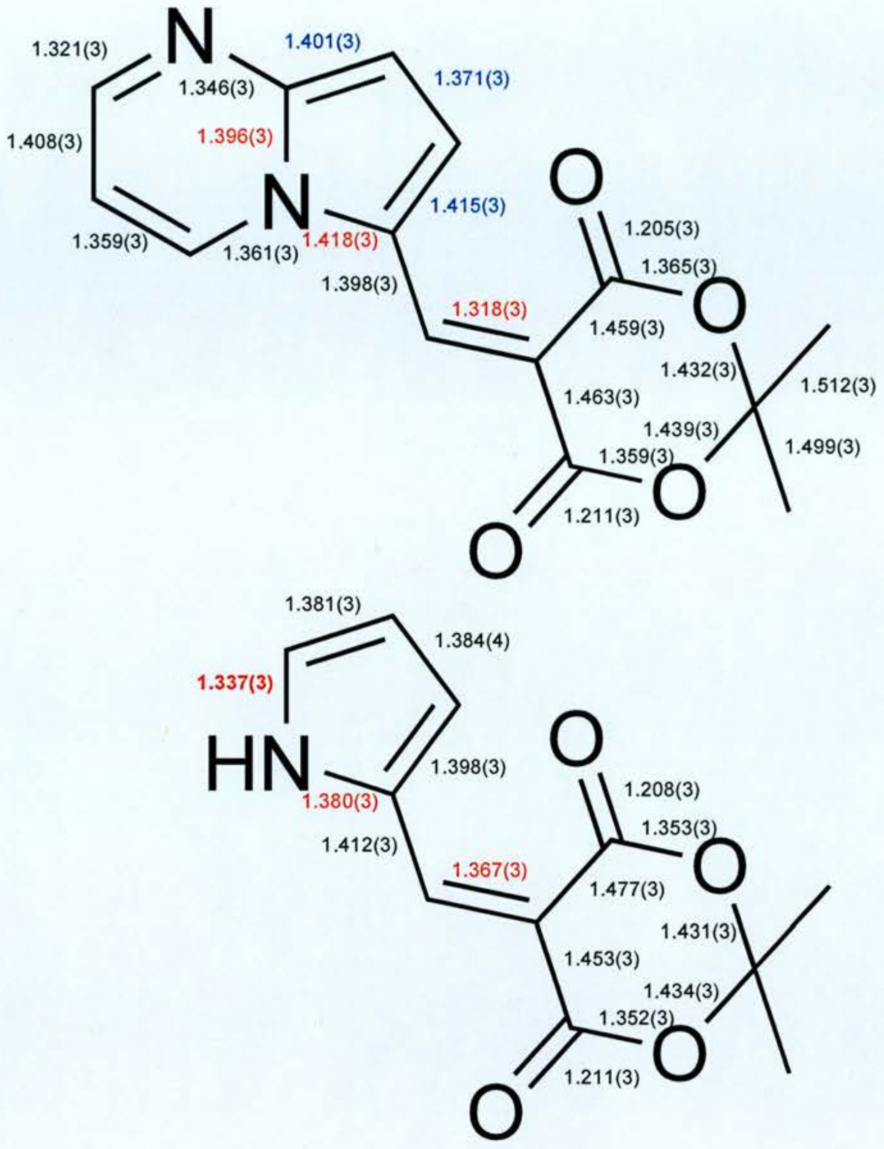
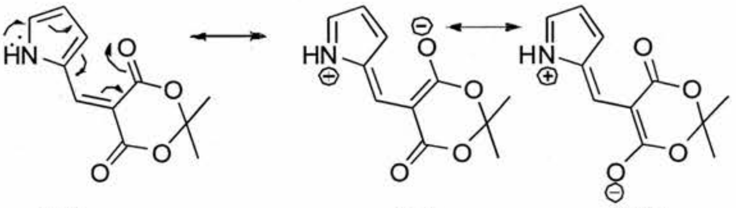


Figure 56: Bond lengths of 249 and 250

Pyrrole	Bond length	8-azaindolizine	Bond length
N1-C5	1.337(3)	N4-C9	1.396(3)
C4-C5	1.381(3)	C1-C9	1.401(3)
C3-C4	1.384(4)	C1-C2	1.371(3)
C2-C3	1.398(3)	C2-C3	1.415(3)
N1-C2	1.380(3)	C3-N4	1.418(3)
C2-C6	1.412(3)	C3-C10	1.398(3)
C7-C7	1.367(3)	C10-C11	1.318(3)

Table 10

Direct comparison between the Meldrum's derivative **249** and the Meldrums derivative of pyrrole **250** can be made. Firstly by considering the pyrrole analogue, the effect of the Meldrum's group can clearly be seen. Delocalisation of the nitrogen lone pair through to the carbonyl groups is clearly demonstrated **(Figure 55)**. It can clearly be seen that the N1-C5 bond is shorter than the other bonds in the ring, also the C4-C5, C3-C4 and C2-C3 bond show no significant difference in bond lengths. It is suggested that this shows the shortening of the formal single bonds and the lengthening of the formal double bonds as is expected if the dipolar resonance forms **250a** and **250b** have an important contribution to the structure.



250 **250a** **250b**

Scheme 174: Resonance structures in 250

Using this information the crystal structure of the 8-azaindolizine derivative **249** can be considered, it can be noted that the N4-C9 bond is not significantly short as is observed in the pyrrole analogue. However, the effects in the C1-C9, C1-C2 and C2-C3 bonds are much more significant, it can clearly be seen that there is lengthening of the formal double bonds and shortening of the formal single bond to the extent where the single bond is measured to be shorter than the double bonds. This is considered as evidence that there is a strong push of electrons through the pyrrole ring. The fact that the N4-C9 bond is longer than the equivalent in the pyrrole analogue may be attributed to the fused ring, there is not any clear evidence of donation through the pyrimidine ring.

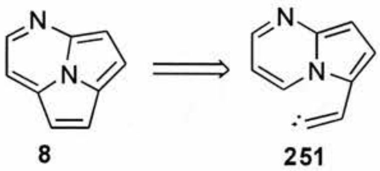
The C6-C7 bond in the pyrrole analogue can also be compared to the C10-C11 bond in the 8-azaindolizine derivative, it can be seen that the bond is significantly longer in the pyrrole case. This conflicts some of the previous observations, the suggestion is that this shows the donation of the lone pair through to the carbonyls in the pyrrole derivative as this bond would be expected to be lengthened. However, this also suggests that there less donation in the 8-azaindolizine derivative as the bond is observed to be clearly shorter.

Conclusions.

The synthesis of 8-azaindolizine **7** by the FVP/WO_3 method not only demonstrates the use of WO_3 as a dehydrogenation agent in this reaction but also has shown a great improvement on the literature synthesis of this compound. This has enabled the chemistry of 8-azaindolizine to be further investigated, and it has been shown that the chemistry is that of electrophilic substitution reactions as was predicted for the compound as an aromatic molecule. However, the reactivity toward electrophiles was surprising, with only extremely mild conditions required as demonstrated by the reaction of 8-azaindolizine towards MMMA. This reactivity has been explained using the facile donation of the bridgehead nitrogen lone pair through the conjugation making the 3-position very electron rich and producing resonance stabalisation of the intermediate of electrophilic substitution reactions.

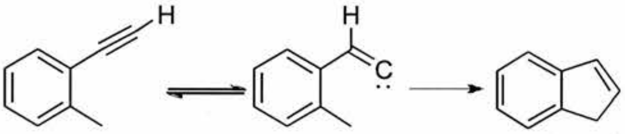
Cyclazine synthesis.

It was proposed that the chemistry of 8-azaindolizine **7** could be further extended to the synthesis of cyclazines *via* the carbene **251 (scheme 175)**.



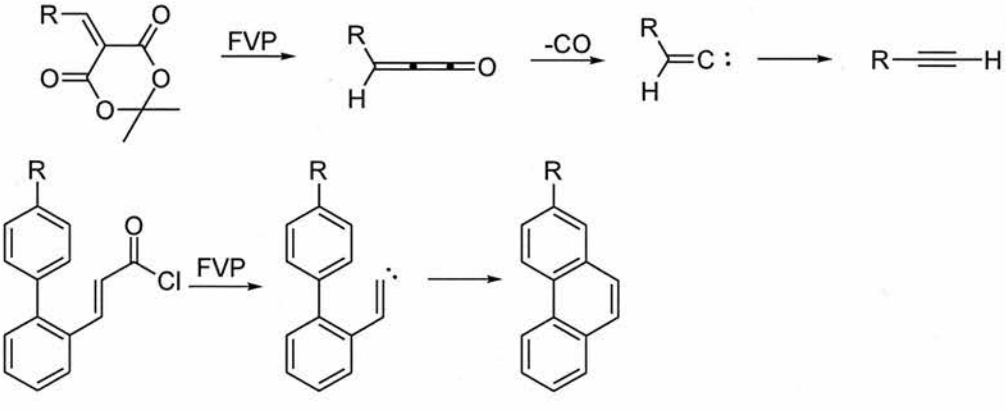
Scheme 175: Retro synthesis of 8

There are many examples in the literature of how methylene carbenes can be generated from acetylenes by FVP,[66] the carbenes generated have also been shown to undergo CH insertion to give cyclised products provided they are given enough energy **(Scheme 176)**.



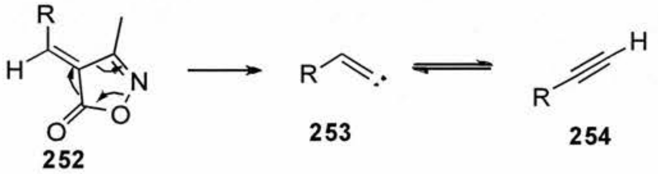
Scheme 176: Formation of carbenes

A number of different precursors have been reported to produce carbenes including the use of acid chlorides and Meldrum's acid derivatives **(Scheme 177)**.



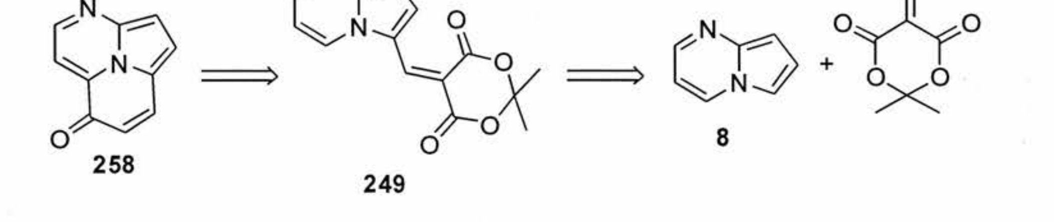
Scheme 177: Generation of carbenes

The other popular precursor for the generation of carbenes is isoxazolones, it is known that under FVP the isoxazolone **252** looses CO_2 and acetonitrile to give the carbene **253**. At low furnace temperatures the carbene **253** is in equlibrium with the acetylene **254** at high temperatures the carbene the can undergo cyclisation reactions, at low temperatures the acetylene is recovered **(Scheme 178)**. [67]



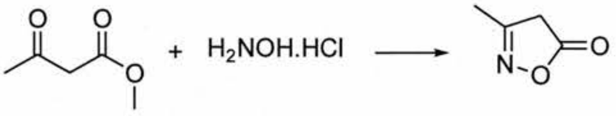
Scheme 178: Carbene formation from isoxazolones

It was proposed that the cyclazine **8** could be generated from the carbene **251**, it was suggested that this carbene could easily be generated from the isoxazolone **255** by loss of acetonitrile and CO_2, under conditions FVP this would be in equlibrium with the acetylene **256**. The reaction of isoxazolones with aldehydes has also been previously been reported so the required isoxazolone is **255** could be generated from the reaction of **257** and the aldehyde **245**. The generation of the aldehyde **245** has been previously shown **(scheme 179)**. It was also suggested that the cyclazinone **258** may be generated by the FVP of the Meldrum's acid derivative of 8-azaindolizine **249**, the synthesis of this precursor has been previously been discussed.



Scheme 179: Retrosynthesis of cyclazines.

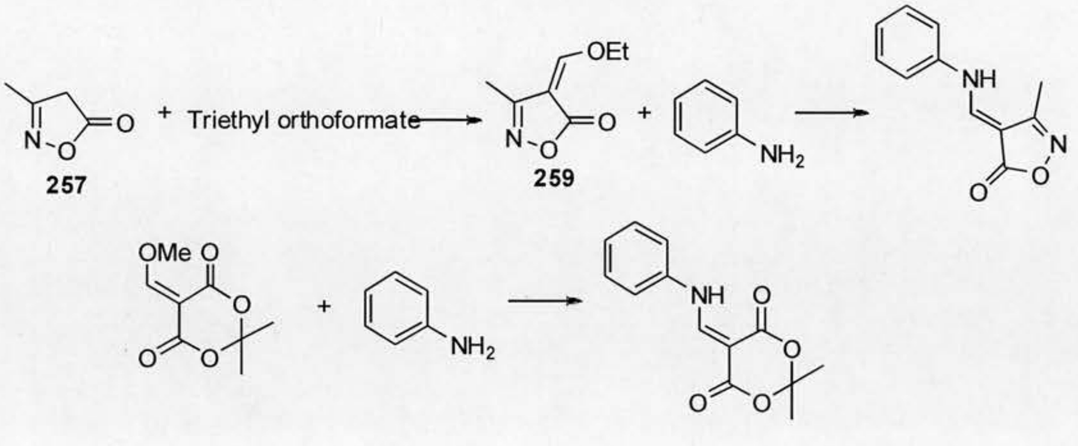
The synthesis of isoxazolones is reported in the literature, the methyl isoxazolone used here is prepared by the reaction of hydroxylamine hydrochloride with methyl acetoacetate, the product is purified by distillation **(Scheme 180).**[63]



Scheme 180: Formation of isoxazolones

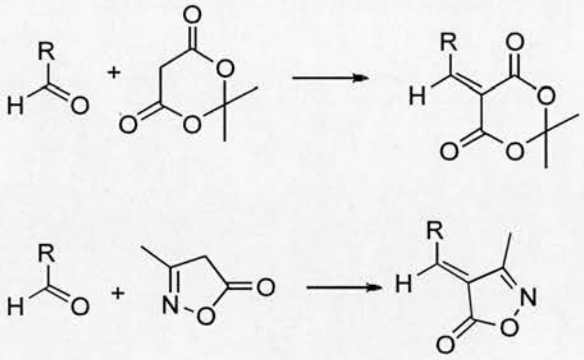
The reaction of the aldehyde **245** with the isoxazolone **257** was attempted in the hope to generate the required precursor. This proved problematic with the product being obtained as a red oily residue, in which the desired product was observed in the ^{1}H NMR spectrum of the crude product. Attempts to purify the product by distillation and recrystallisation proved unsuccessful, with decomposition occurring upon distillation, and poor solubility in all solvents preventing recrystallisation. Purification of the product by chromatography was also impossible as the product showed no solubility in any solvents other than DMSO.

Due to these problematic results another strategy for the formation of the desired precursor was required. It was noticed that the reported literature reactions of isoxazolones showed similarities to those known for Meldrums acid. It is reported that isoxazolones react with primary amines in the presence of triethyl orthoformate, it is believed that the isoxazolone reacts *in situ* with trimethyl orthoformate to form the intermediate **259** which then reacts with the amine. This can be compared with the reaction of MMMA with primary amines and is well demonstrated by their reactions with aniline **(Scheme 181)**.



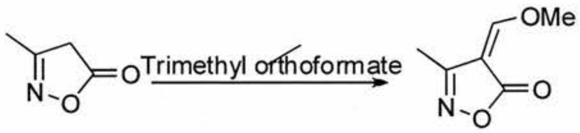
Scheme 181: Reactions of isoxazolones and MMMA

Also the reaction of the isoxazolone with aldehydes has been demonstrated in the literature, the conditions required are the same as those used for the reaction of MMMA with aldehydes **(Scheme 182)**. These reactions are catalysed by the use of one drop of acetic acid and one drop of piperidine.



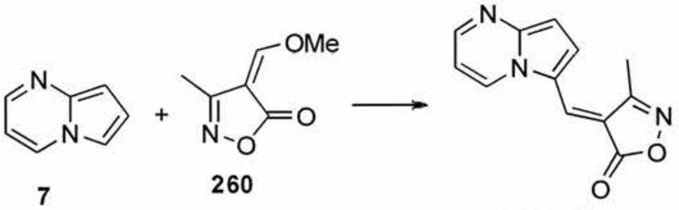
Scheme 182: Reactions with aldehydes

As these reactions demonstrate how isoxazolones show similar chemistry to Meldrum's acid, it was therefore believed that it would be possible to prepare methoxymethylene isoxazolone. Methoxymethylene isoxazolones are not well known in the open literature with only one report to their synthesis.[68] The methyl isoxazolone **257** was dissolved in trimethyl orthoformate and heated under reflux for five minutes, after removal of the solvent **260** was obtained as a white solid.



Scheme 183: formation of 260

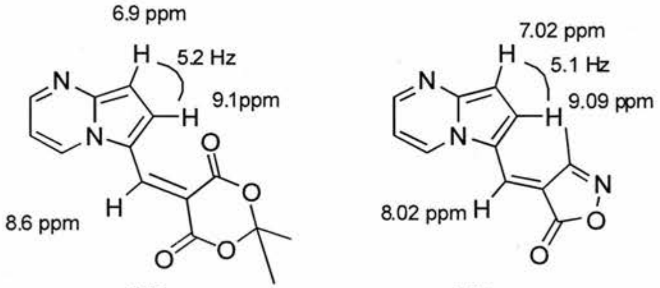
The reaction of the methoxymethylene isoxazolone **260** with 8-azaindolizine **7** was carried out using acetonitrile as solvent. Within five minutes the product **261** had precipitated from the solution. This was recrystallised from acetonitrile, and was found to be only sparingly soluble in DMSO.



7 **260** **261 68%**

Scheme 184: Formation of 261

The ^{1}H NMR spectrum showed the characteristic singlet at 8.02 ppm along with the characteristic doublets from the pyrrole ring at 9.09 and 7.02 ppm with a coupling constant of 5.2 Hz. This can be compared with the NMR of the meldrum's derivative **249 (figure 57)**.

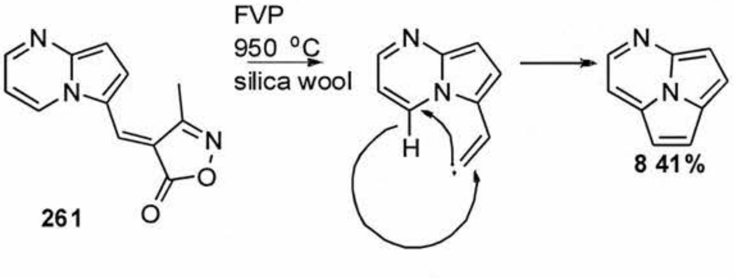


249 **261**

Figure 57: NMR properties of 249 and 261

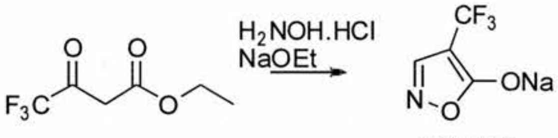
The direct comparison of the NMR properties of **249** and **261** shows very similar effects on the pyrrole type protons. It can clearly be seen that the H2 proton is significantly deshielded, and the coupling constant between H1 and H2 in each case is significantly enlarged. Also of note is the proton at 8.02 ppm, it can be seen that in the isoxazolone derivative **261** this is not as deshielded as the equivalent proton in the Meldrum's derivative. This is due to the Meldrum's group being more electron withdrawing than the isoxazolone group.

As has already been discussed the FVP of isoxazolone derivatives provides a route to carbenes that under FVP conditions are in equlibrium with acetylenes **(scheme 178)**. The FVP of the isoxazolone **261** at high temperatures produced 5-azacycla[3,2,2]azine **8** this proceeds *via* the formation of the carbene **251** by the above mechanism **(scheme 185)**. The carbene then inserts into the CH bond to form the cyclazine, this reaction requires very high furnace temperature 950 °C with a plug of silica wool **(scheme 185)**. The high temperature required for the cyclisation reflects the strain in the ring that is produced. However the yield of this reaction in relatively poor, the loss of yield is due to the precursor being involatile, thus requiring a high inlet temperature of 210 °C resulting in severe decomposition of the precursor.



Scheme 185:FVP of 261

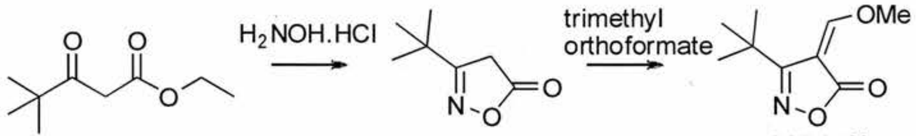
The problem with the volatility of the precursor was linked to the lattice energy of the of the crystal structure. This was also reflected in the low solubility of **249**, so it was decided that the use of a different isoxazolone derivative might be able to increase the volatility of the precursor. The synthesis of 3-trifluoro-4*H*-isoxazolone was attempted, a literature route to 3-trifluoromethyl-5-hydroxyisoxazole sodium salt **262** was followed **(scheme 186).** However attempts to free the isoxazolone from the salt were unsuccessful, as was an attempt to react the salt with trimethyl orthoformate.



262 80%

Scheme 186: formation of 262

As this did not yield a different precursor, 3-*t*-butyl-4*H*-isoxazol-5-one **263** was also synthesised by the reaction of ethyl pivaloylacetate **264** with hydroxylamine hydrochloride, in 75% methanol/water at room temperature overnight to give **263** as a white solid recrystallised from ethyl acetate hexane (1:1) **(scheme 187)**. Reaction of **263** with trimethyl orthoformate gave **265** after 5 min at reflux.



264 **263 68%** **265 84%**

Scheme 187: Formation of 263

The *t*-butyl isoxazolone **265** is another example of methoxymethylene isoxazolones and shows characteristic NMR properties of these compounds **(figure 58)**.

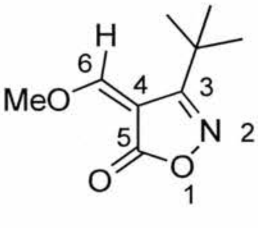
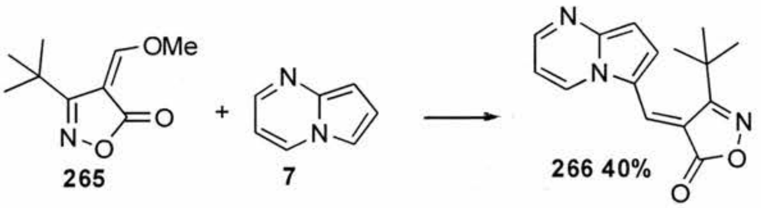


Figure 58

The peaks of interest in the proton spectrum was the singlet at 7.46 ppm due to the proton at C6. In the carbon spectrum the carbonyl is observed at 173.5 ppm, with the quaternary adjacent to the nitrogen appearing at 167.2 ppm and the CH at 164.6 ppm. The reaction of **265** with 8-azaindolizine produced the isoxazolone derivative **266** after 15 min **(scheme 188)**.



Scheme 188: Formation of 266

Unlike **261** the *t*-butyl isoxazolone **266** was soluble in chloroform, indicating that it has a lower lattice energy than the methyl derivative **261** that should be reflected in its sublimation temperature. The ^{1}H NMR spectrum of **266** shows the typical singlet due to H9 at 7.88 ppm and the pyrrole doublets at 9.13 and 6.89 ppm with a coupling of 4.8 Hz **(figure 59)**. This shows again the delocalisation of the lone pair from the bridgehead nitrogen through to the carbonyl but the slightly lower coupling constant indicated that the delocalisation is perhaps slightly less probably due to the steric bulk of the *t*-butyl. Thus the dipolar resonance structure **266a** is perhaps not as important as in Meldrum's derivative **249** or the methylisoxazolone derivative **261**.

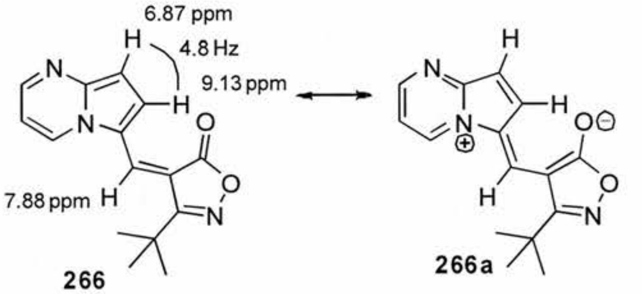
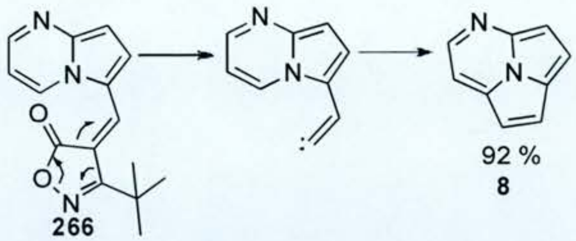


Figure 59: NMR properties of 266

The FVP of **266** at 975 °C with silica wool produces 5-azacycla[3,2,2]azine **8** by the same mechanism as before this time with the loss of trimethylacetonitrile and CO_2 **(scheme 189)**.



266

8

Scheme 189: FVP of 266

The inlet temperature required for this reaction is 135 °C, this is significantly lower than the 210 °C required for the methyl analogue. The bulk of the *t*-butyl group now controls the crystal packing, as there is only very week attractive forces between *t*-butyl groups the lattice energy is lower, this is clearly demonstrated **(figure 60)** where the large bulk of the *t*-butyl can be seen to dominate the shape of the molecule. In the methyl isoxazolone case it can be seen that there is much less bulk and therefore there is increased π-stacking in the crystals making them more stable with a higher lattice energy.

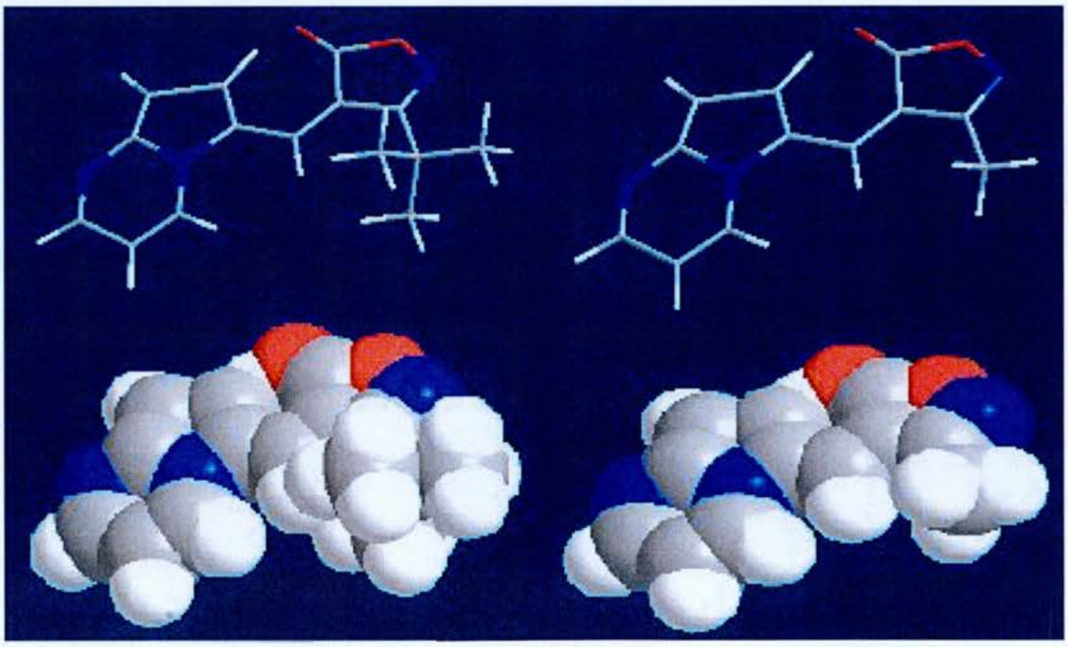


Figure 60: Comparison of *t*-butyl and Me-isoxazolones (Chemdraw 3D representation).

Structure and chemistry of 5-azacycla[3,2,2]azine.

This cyclazine **(figure 61)** is of particular interest as a new compound and despite of a lot of research on this class of compound in the literature it is the only example of the four parent azacyclazines isomers not to have previously prepared.

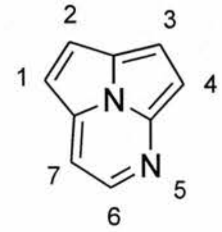


Figure 61: Numbering scheme for 8

The ^{1}H NMR spectrum of **8** shows 6 doublets, unfortunately in every solvent used two of the signals overlap **(figure 62)**.

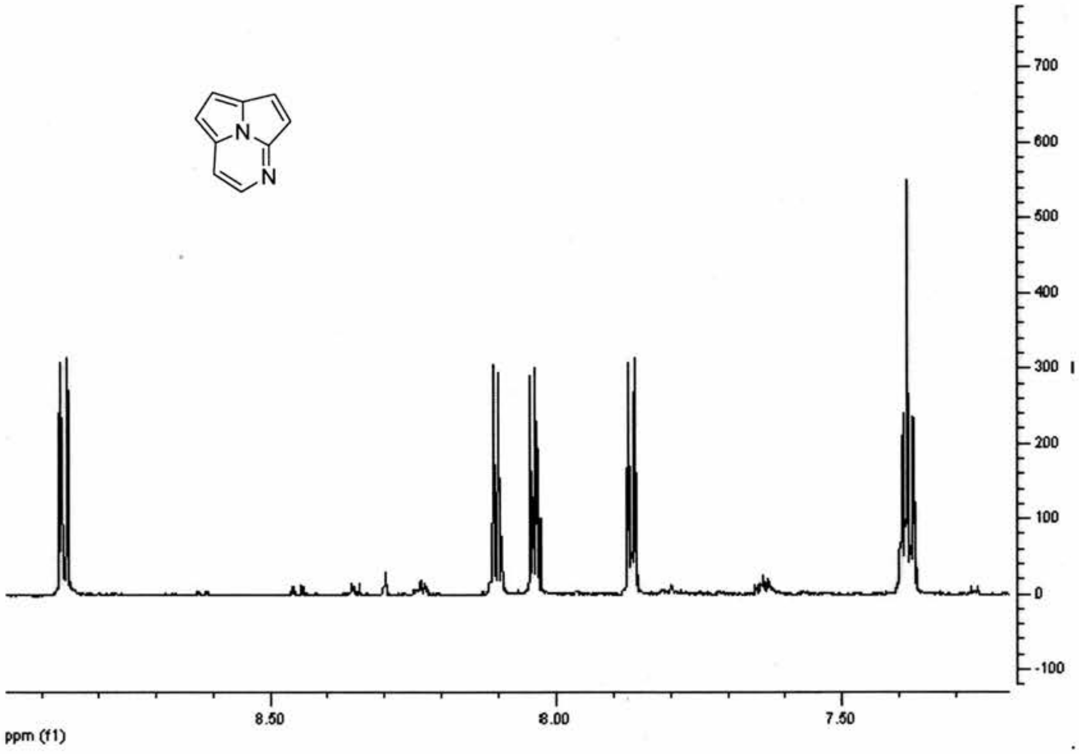


Figure 62:NMR spectrum of crude 5-azacycl[3,2,2]azine

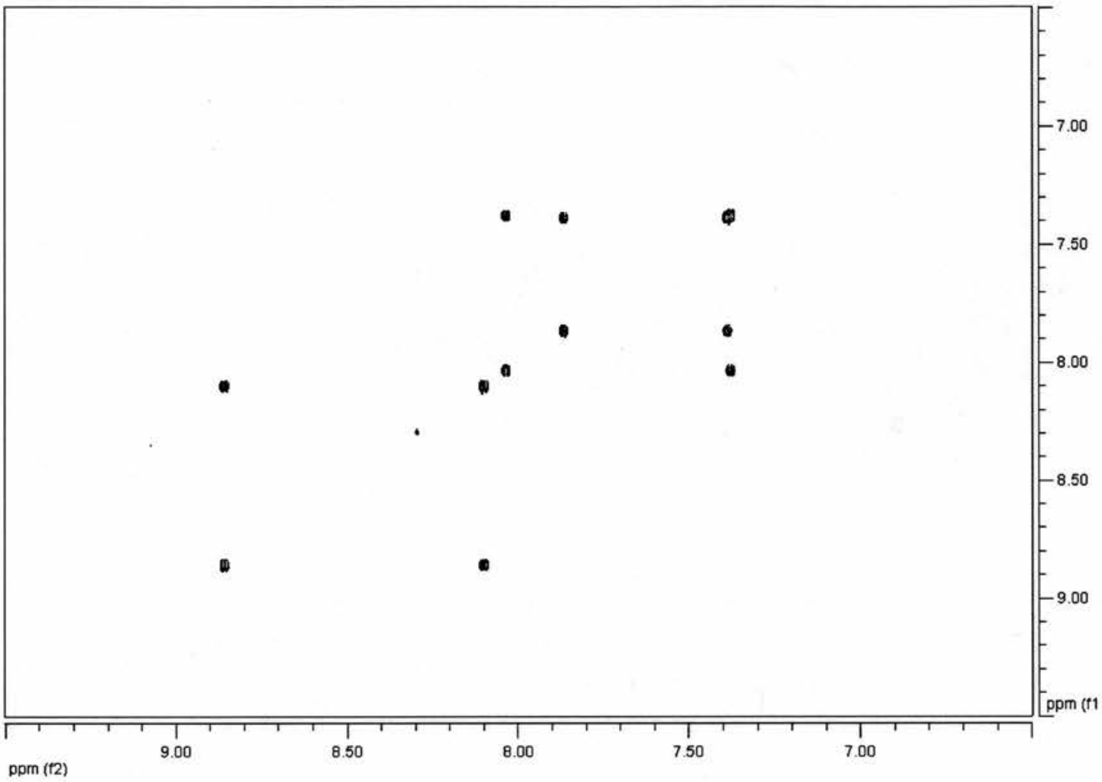


Figure 63: COSY NMR spectrum of 5-azacycl[3,2,2]azine

It can clearly be seen in the NMR spectrum of the crude pyrolysate **(figure 62)** that even though very high furnace temperature was required the product was obtained cleanly with very little decomposition. This is surprising when the strain in the product is considered, it might be expected that the cyclazine might ring open but this does not occur. The ^{1}H NMR spectrum of **8** shows a doublet at 8.84 ppm with a coupling of 5.5 Hz to the doublet at 8.08 ppm. The doublet at 8.01 ppm with a coupling constant of 4.5 Hz is coupling to one of the protons in the 2H overlapping signal at 7.36 ppm, this is also shown in the COSY spectrum where the proton at 8.01 ppm clearly couples to one of the protons at 7.36 ppm. The doublet at 7.85 ppm shows a coupling of 4.1 Hz to one of the protons in the overlapping signal at 7.36 ppm this also is clearly seen in the COSY spectrum **(figure 63)**. In the NOESY spectrum no across ring correlation was observed, as is quite common for planar aromatic heterocycles. However other observations can help to assign the NMR spectrum.

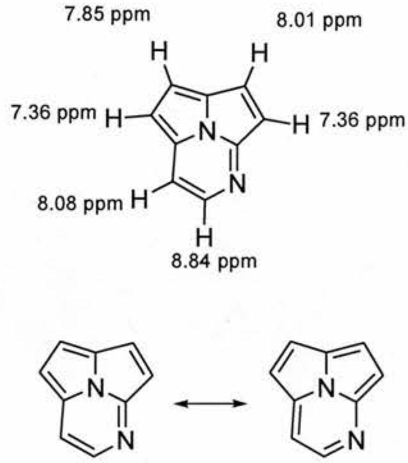
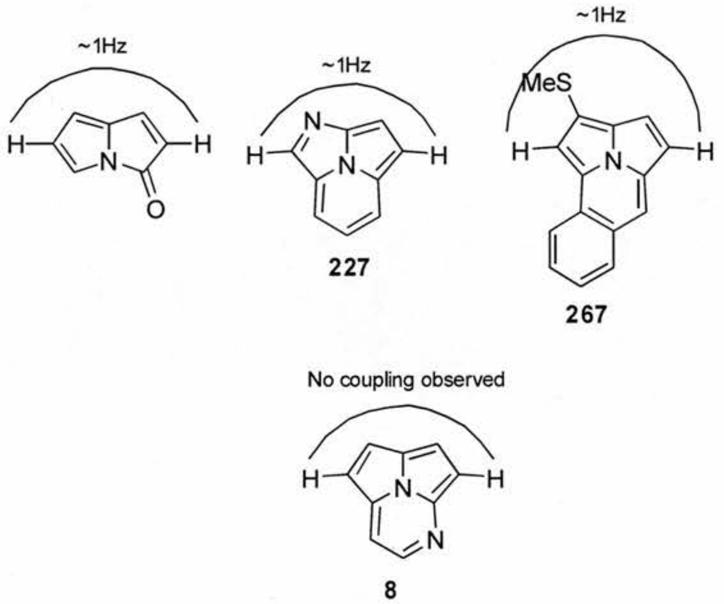


Figure 64: ^{1}H NMR assignment and electron ring current of 5-azacycl[3,2,2]azine

The assignment of the H1 and H4 protons is supported by comparison with the NMR of pyrrolizin-3-one, and other 2-azacycl[3,2,2]azines **227** and **267**. In pyrrolizin-3-one a typical long range coupling constant is observed between H2 and H6 **(figure 65)**, this is also observed in 2-azacycl[3,2,2]azine **227** and **267**. However this is not observed in the NMR spectrum of 5-azacycl[3,2,2]azine **8**. It is believed that the reason for this not being observed is because H1 and H4 are coincident. This is also supported by the assignment of substituted cyclazines where it is observed that when a substituent is present at the 2-position the proton at the 1-position has a typical chemical shift of 6.8-7.2 ppm.

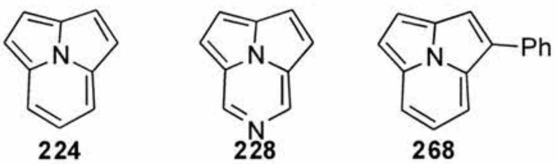


227 267 8

Figure 65

The high chemical shift of all of the protons can be explained by the 10 π electron ring current **(figure 65)**, not only does this produce the higher chemical shifts but also explains the similarity in coupling constants between the pyrrole type protons of 4.1 and 4.5 Hz. These coupling constants are intermediate between that expected for a pyrrole and that for a pyrroline.

The ^{1}H NMR spectrum of 5-azacycl[3,2,2]azine **8** can be compared with those of other cyclazines **(figure 66)**; the parent cycl[3,2,2]azine **224**, 6-azacycl[3,2,2]azine **228** and 4-phenylcycl[3,2,2]azine **268** **(table 11)**.



224 228 268

Figure 66: Other cyclazines

Compound	H1	H2	H3	H4	H5	H6	H7	Coupling constant Hz
8	**7.36**	**7.85**	**8.01**	**7.36**		**8.84**	**8.08**	$J_{1,2}$=4.1;$J_{3,4}$=4.5;$J_{6,7}$=5.5
224	**7.20**	**7.51**	**7.51**	**7.20**	**7.86**	**7.59**	**7.86**	
228	**7.44**	**7.64**	**7.64**	**7.44**	**9.21**		**9.21**	$J_{1,2}$=$J_{3,4}$=4.5
268	**7.40**	**7.64**	**7.98**		**8.42**	**7.89**	**8.16**	$J_{1,2}$=4.3;$J_{5,6}$=$J_{6,7}$=7.8

Table 11: chemical shifts of cyclazines

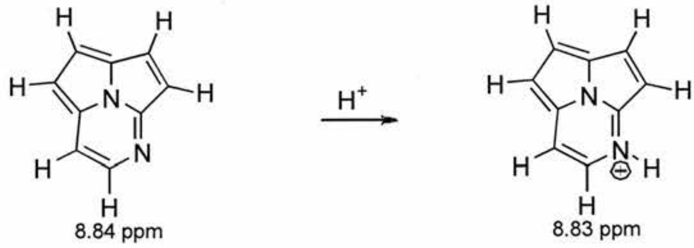
The ^{1}H NMR spectrum of 5-azacyclazin[3,2,2]azine shows similar chemical shifts to those of other cyclazines, in particular it can be seen that the coupling constants in the five membered rings are typically in the range 4.0-4.5 Hz with chemical shifts around 7.2-7.8 ppm. The highest frequency protons are H5 and H7 in the parent system **224**, this is reflected in **8** where H7 is deshielded though with H6 being the highest shifted due to being adjacent to the nitrogen atom.

Chemistry of 5-azacycl[3,2,2]azine.

The chemistry of 5-azacycl[3,2,2]azine **8** was expected to similar to be that of other cyclazines, typical of a stable aromatic system. The cyclazine **8** was predicted to undergo electrophilic substitution reactions, however attempts to achieve these reaction was in general unsuccessful.

Reaction with TFA.

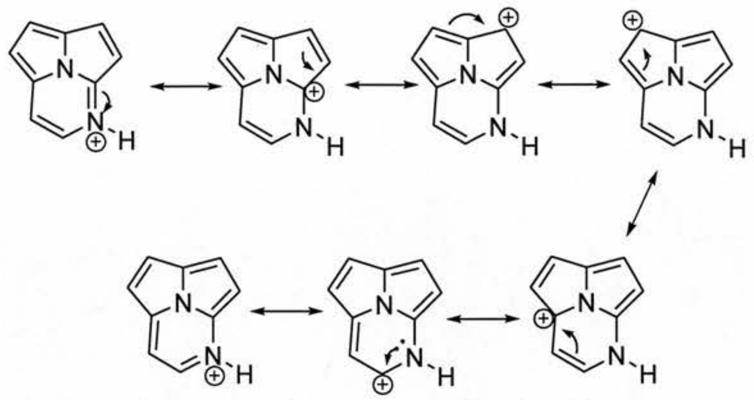
The ^{1}H NMR spectrum of the protonated species **8a** in TFA was recorded, it was noted that although there was a trend of protons appearing at higher chemical shifts **(scheme 190)**. However it is worth noticing that the proton H6 actually appears at a similar chemical shift. It is proposed that this is due to the extra resonance structures that **8a** can use to stabilise the positive charge whereas pyridine only has four. Thus the deshielding effect is felt further away from the nitrogen in the reaction with the cyclazine.



8a

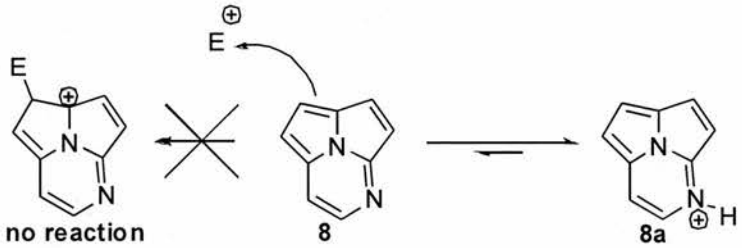
Scheme 190: Effect of protonation on the NMR spectrum of 5-azacycl[3,2,2]azine

The reactivity of 5-azacycl[3,2,2]azine with DTFA was investigated by NMR, no incorporation of deuterium was observed even after a prolonged period (2 months). It is believed that the stabilisation of the protonated species **8a** is responsible for this lack of reactivity **(scheme 191)**.



Scheme 191: Resonance stabilisation of 8a

As the positive charge can be distributed around the ring giving seven resonance forms the equilibrium lies heavily on the protonated side reducing the possibility for electrophilic substitution to occur **(scheme 192).**



Scheme 192: Reaction with dTFA

This also shows how 5-azacycl[3,2,2]azine cannot be considered as a substituted 8-azaindolizine, a substituted 6-azaindolizine or a pyrrolizine, the three possible fused ring substructures **(figure 67)**, as each of these structures shows incorporation of deuterium under similar conditions.

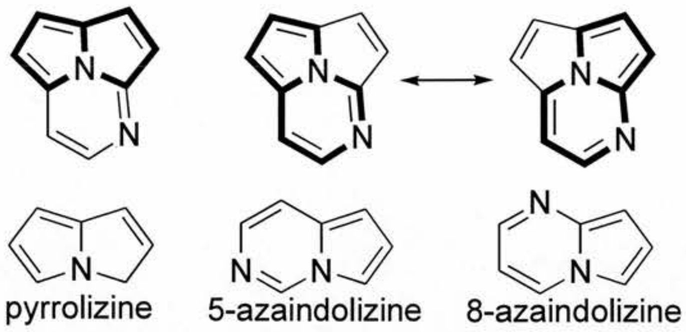
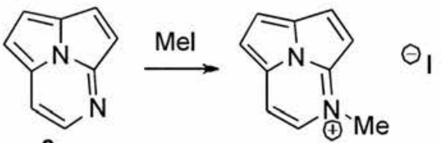


Figure 67: Fused ring substructures of 5-azacycl[3,2,2]azine

Reaction with Methyl iodide.

The reaction of 5-azacycl[3,2,2]azine with methyl iodide was also investigated, by dissolving **8** in neat MeI and heating in a sealed tube, after 15 min the product **269** had formed as a brown oil. This demonstrated the quaternisation of the pyrimidine nitrogen **(scheme 193)**.



8 **269 89%**

Scheme 193: Reaction of 8 with MeI

The ^{1}H NMR spectrum of **269** was very distinctive as the quaternary methyl salt **(figure 68)** it can clearly be seen that all of the protons have been significantly shifted to higher frequency. It can be seen that H1 and H4 have been shifted from 8.01 ppm to 8.27 ppm, H2 and H3 have been shifted from 7.36 ppm to 8.27 ppm, the largest shift observed was that for H6 going from 8.84 to 9.65 ppm. The chemical shift of the *N*-methyl 5.06 ppm is indicative for the methyl of a quaternary methyl salt.

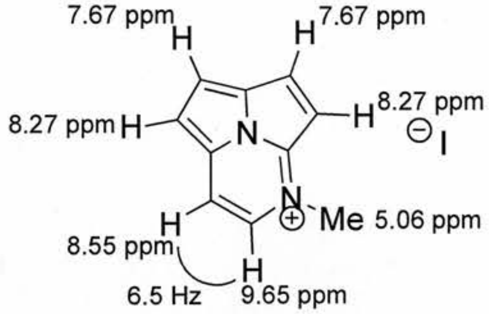
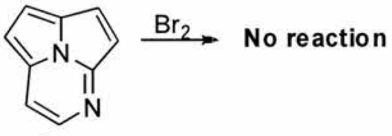


Figure 68: NMR of 269

Other reactions proved unsuccessful, the attempted bromination of **8** with Br_2 was unsuccessful with unreacted starting material being recovered albeit in a reduced yield **(scheme 194)**. No other reactions with electrophiles were attempted.

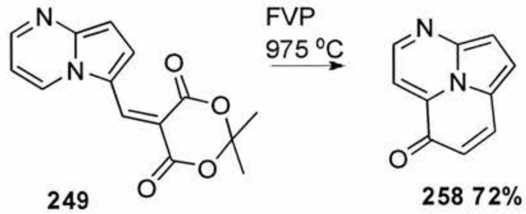


8

Scheme 194: Treatment of 8 with Br_2

8-Azacycl[3,3,2]azin-5-one

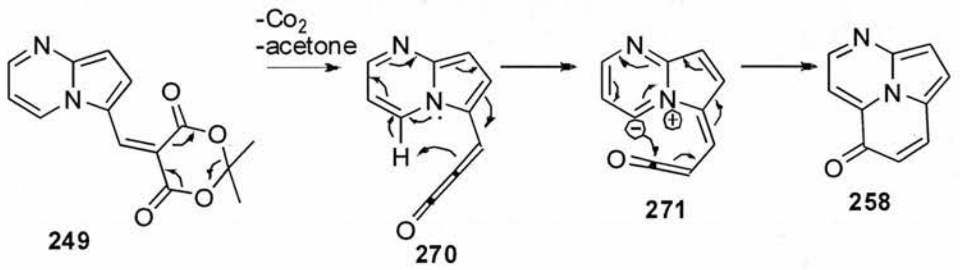
The FVP of the Meldrum's derivative of 8-azaindolizine **249** at 950 °C produces 8-azacycl[3,3,2]azin-5-one **258 (scheme 195)**, it is believed that this reaction proceeds *via* an intramolecular eletrocyclocyclisation reaction similar to that in the synthesis of benzopyrrolizin-1-one.



249 **258** 72%

Scheme 195: Formation of 258

The mechanism of this reaction **(scheme 196)** proceeds by the normal loss of CO_2 and acetone to give the methyleneketene **270**. Donation of the lone pair on the bridgehead nitrogen through the conjugated double bond system to the methyleneketene allows the methyleneketene to abstract H5 from the 8-azaindolizine ring system to form the dipole **271**. The reaction then proceed *via* an intramolecular electrocyclisation to give **258**.



Scheme 196: Mechanism of formation of 258

The mechanism is supported by the high temperature required for the reaction to proceed as it is believed that a large amount of energy would be required to generate the intermediate **271**. Many dipolar species related to **272** have been reported in pyridine chemistry **(figure 69).**[69]

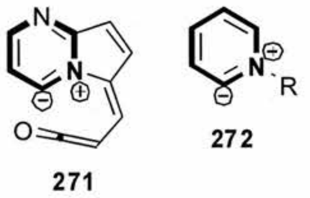


Figure 69:

The NMR spectrum was assigned **(figure 70).** H1 at 7.86 ppm couples with proton H2 at 7.40 ppm (*J* 4.9 Hz), the enone protons at 8.13 ppm and 7.17 ppm show a coupling of 9.7 Hz this is typical of an enone bond with a push pull mechanism. The pyrimidine protons at 8.35 ppm and 9.01 ppm due to H6 and H7 respectively show a coupling of 4.9 Hz.

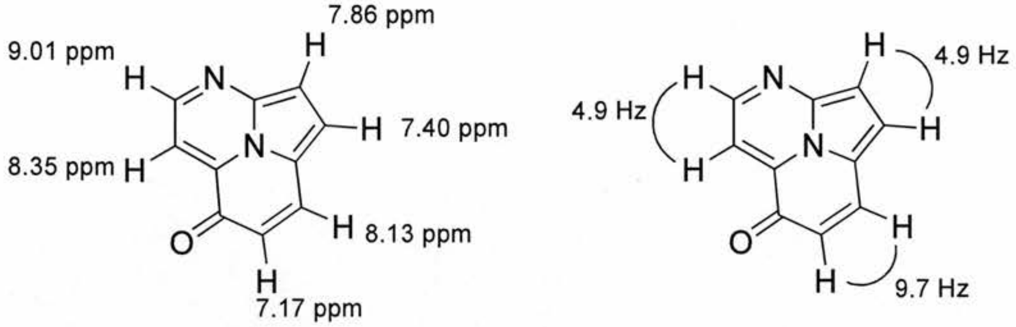
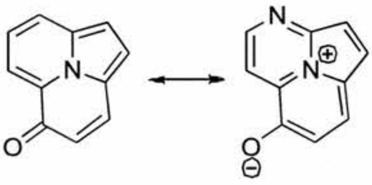


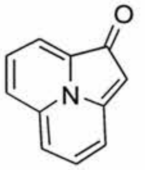
Figure 70: NMR properties of 258

The enone bond can be compared to that of that of other enones where it is generally accepted that there is a push pull mechanism through the double bond **(scheme 197)**.

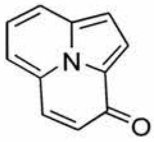


Scheme 197:

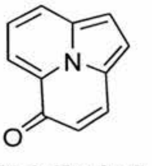
By comparrison with other cyclazinones **(figure 71)** and **(table 12)**, it can clearly be seen that the NMR spectrum of 8-azacyclazin-5-one has good correlation.[70]



cycl[3,3,2]azin-1-one
273



cycl[3,3,2]azin-3-one
274



cycl[3,3,2]azin-5-one
275

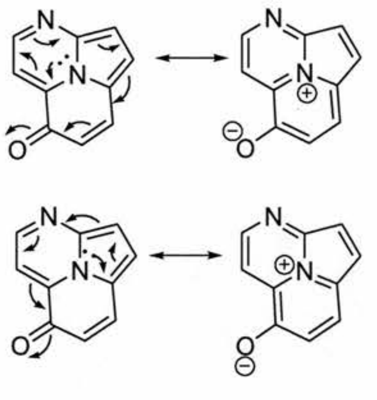
Figure 71: Cyclazin-ones

Compound	**H1**	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**Coupling constant Hz**
258	7.86	7.40	8.13	7.17		8.35	9.01		$J_{1,2}$=$J_{6,7}$=4.9;$J_{3,4}$= 9.7
273		5.90	7.43	7.88	7.52	8.13	8.11	8.33	$J_{3,4}$=$J_{4,5}$=8.1
274	7.25	8.05		7.47	7.94	7.80	7.67	8.12	$J_{1,2}$=4.9;$J_{4,5}$=9.7; $J_{6,7}$=7.4; $J_{8,9}$=8.3
275	7.29	7.57	8.10	7.16		8.64	7.81	8.24	$J_{1,2}$=4.8;$J_{3,4}$=9.6; $J_{6,7}$=8.0;$J_{7,8}$=8.2

Table 12: NMR properties of other cyclazin[3,3,2]azines

The protons are found at similar chemical shifts throughout the cycl[3,3,2]azinone series, the exception being H7 of 8-azacycl[3,3,2]azin-5-one being at significantly higher chemical shift, due to the desheilding effect of the extra nitrogen in the ring. The coupling constant in the enone bond of **258** (9.7 Hz) is similar to that seen in cycl[3,3,2]azin-3-one and –5-one **274** and **275** 9.7 Hz and 9.6 Hz respectively. These are also indicative of enone bonds in other 6-membered systems where there is delocalisation of a lone pair through to the carbonyl group.

It is reasonable to suggest that the cyclazinones **273**, **274** and **275** should be considered as substituted indolizines. With that the lone pair on the central nitrogen now involved in the bonding. It has already been observed that delocalisation of the lone pair from the bridgehead nitrogen in 8-azaindolizine to electron withdrawing substituents in the 3-position can occur **(scheme 198)**. As well as this mechanism for a second mechanism exists that by donation of the lone pair in the other direction around the indolizine ring delocalises the lone pair out to electron withdrawing groups at the 5-position. As the carbonyl group of 8-azacycl[3,3,2]azin-5-one **258** can be considered to be an electron withdrawing at both the 3- and 5- position of 8-azaindolizine, the lone pair could be delocalised in two directions.



Scheme 198: delocalisation od bridgehead lone pair in 258

Evidence for this can be seen by comparison of ^{1}H NMR spectra of 8-azaindolizine **7**, 8-azacycl[3,3,2]azin-5-one **258** and the Meldrum's derivative **249** another example of 8-azaindolizine with an electron withdrawing group at the 3-position.

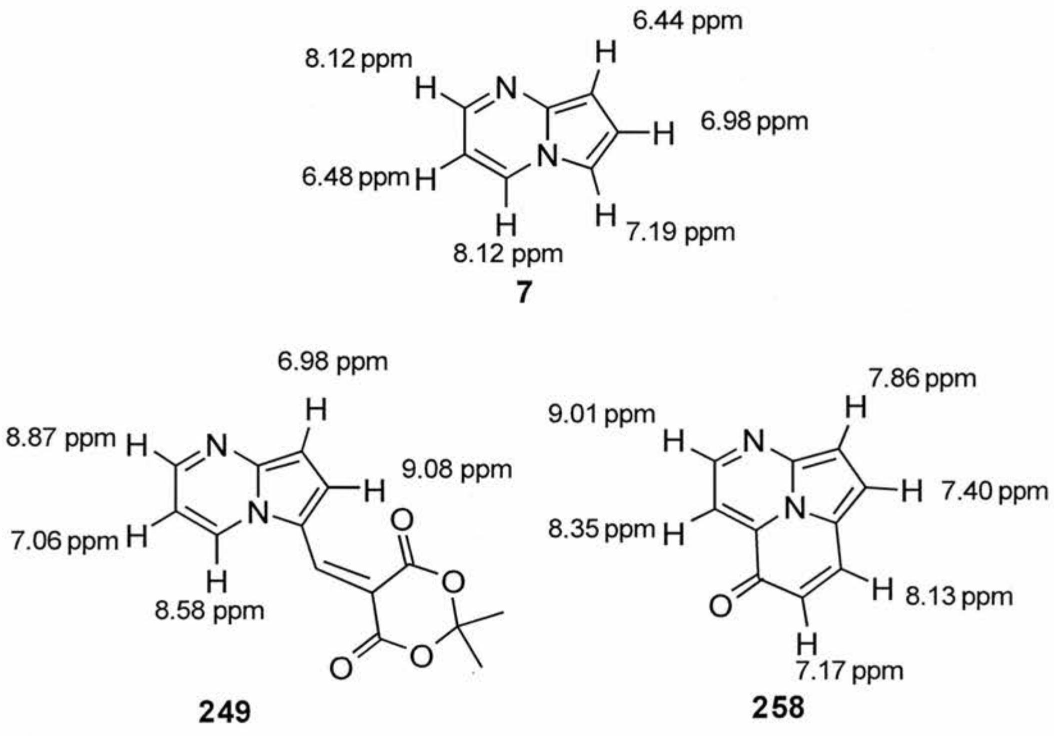
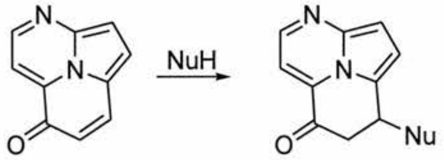


Figure 73: NMR properties of 258

As demonstrated by the NMR spectrum of **249** the presence of an electron withdrawing group at the 3-position of 8-azaindolizine **7** increases the chemical shift of all of the protons in the ring. This is reflected in the NMR spectrum of 8-azacycl[3,3,2]azin-5-one **258** in which also the chemical shift of the all of the ring protons are also increased, this indicates that **258** is behaving as a substituted 8-azaindolizine. Although the chemistry of **258** has not been investigated it could be suggested that it would resemble that of a substituted indolizine, though reaction with electrophiles at the 1-position is unlikely as the enone acts as an electron withdrawing group. The most likely site for reaction is the eneone double bond, which should be open to attack by nucleophilic addition **(scheme 199)**.



Scheme 199: proposed reaction with nucleophiles

Conclusions:

The chemistry of 8-azaindolizine has been furthered in the synthesis of the cyclazine **8** and the cyclazinone **258**. The electrophilic substitution chemistry of 8-azaindolizine has been used to generate the FVP precursors, the pyrolysis of these precursors produces the cyclazine **8** and **258**. This has been shown to be a much more efficient route to this type of ring system producing the cyclised products in three steps from commercially available starting materials. The synthesis of **8** is also a very good demonstration of the use of FVP to generate carbenes and their subsequent cyclisation by CH insertion.

Abbreviations

General Experimental

aq.	aqueous
bp	boiling point
°C	degrees Celsius
cm^3	cubic centimetres
conc.	concentrated
g	grams
h	hours
lit.	literature
min	minutes
mmol	millimoles
mol	moles
mp	melting point
sat.	saturated

Chemicals

DCM	dichloromethane
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
LAH	lithium aluminium hydride
MMMA	methoxymethylene Meldrums acid
$MgSO_4$	anhydrous magnesium sulfate
NBS	*N*-bromosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pd/C	palladium on carbon
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Spectroscopy

br	broad
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
δ_H, δ_C	chemical Shift
EI	electron impact ionisation
ESI	electrospray Ionisation
J	coupling constant
m	multiplet
MHz	megaHertz
m/z	molecular ion mass
NMR	nuclear magnetic resonance
quat	quaternary carbon
s	singlet
t	triplet

Flash vacuum pyrolysis

FVP	flash vacuum pyrolysis
P	pressure
t	time of pyrolysis
T_f	furnace temperature
T_i	inlet temperature

Miscellaneous

B3LYP	Becke 3-parameter, Lee Yang Parr

Instrumental and General Techniques

Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectroscopy was recorded on a Varian Gemini 200 spectrometer operated by Mr. J. Montgomery, Bruker AC250 spectrometer operated by Mr J. Millar and Bruker WH360 spectrometer operated by Mr J Montgomery. ^{1}H NMR spectra quoted were recorded on Bruker AC250 spectrometer unless otherwise stated.

^{13}C NMR spectroscopy was performed on a Bruker WH360 (90 MHz) operated by Mr J. Montgomery and Bruker AC250 (63 MHz) operated by Mr J. Millar. ^{13}C NMR spectra were recorded on Bruker AC250 spectrometer unless otherwise stated.

Spectra were recorded in [^{2}H] chloroform, unless otherwise stated. Chemical shifts (δ_H and δ_C) are quoted in ppm relative to tetramethylsilane and all coupling constants are given in Hertz (Hz).

Melting Points

All melting points were determined using Gallenkamp Capillary Tube Melting Point apparatus and are uncorrected.

Boiling Points

All boiling points were determined using Kugelrohr apparatus with a standard Hg thermometer.

Chromatography

Thin-layer chromatography was carried out on pre-coated aluminium sheets (0.2 mm, silica gel, Merck, grade 60) impregnated with an ultra-violet indicator. Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 Mesh, 60 A) or alumina gel (basic Brockman 1, standard grade, ~150 Mesh, 58 A). Crude material was pre-adsorbed onto silica or alumina gel and then loaded onto the column. Solvent systems are specified for each reaction system.

Mass Spectroscopy

Low resolution EI and high resolution EI/ESI were performed on a Thermomat 900XP spectrometer operated by Mr. A. T. Taylor. All spectra were recorded under EI conditions, unless otherwise stated.

Elemental Analysis

Elemental analyses were performed by Ms. Sylvia Williamson at the University of St. Andrews Elemental Analysis Service.

Solvents

All solvents used in the experimental section were of laboratory grade and were used as supplied. Dried solvents were sodium dried.

Flash vacuum pyrolysis

The apparatus used for flash vacuum pyrolysis is illustrated (**Figure 10**). It is based on the design by W. D. Crow of the Australian National University.

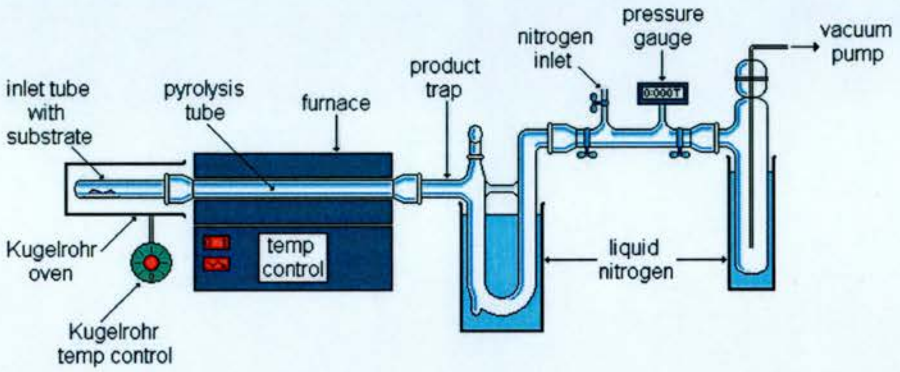


Figure 73

The system is evacuated by use of an Edwards Model ED100 high capacity oil pump to maintain the pressure in the region of 0.030 Torr. A glass Büchi oven is used to heat the inlet tube in which the substrate is placed until it volatilises. The gaseous substrate passes through a silica tube (30 × 2.5 cm) heated by a Carbolite electronically controlled laboratory tube furnace (model number MTF 12/38/250). The estimated contact time in the hot zone is of the order of ten milliseconds and the gaseous phase of the substrate under vacuum ensures that intramolecular reactions are strongly favoured. The products are captured at the exit of the furnace in a U-shaped trap cooled in liquid nitrogen. Upon completion of the reaction the pump is isolated and the trap allowed to warm to room temperature under a dry nitrogen atmosphere.

"Small scale" pyrolyses are those involving 20-50 mg of substrate. The entire pyrolysate is dissolved into a suitable solvent (usually $CDCl_3$) for examination by NMR spectroscopy of the crude reaction products. "Large scale" pyrolyses are those involving 0.1 g or more of substrate.

In some cases a pyrolysate may be thermally unstable under the standard FVP conditions described above. In the event of such a pyrolysate being formed, the U-shaped trap can be exchanged for a dry ice/acetone 'cold-finger' trap, as illustrated **(fiugre 74)**, allowing unstable products to collect on the 'cold-finger' surface and be kept cold for the duration of a pyrolysis. Products can then be removed from the trap, under a dry nitrogen atmosphere, into a suitable solvent for immediate NMR spectroscopic analysis.

Controllable parameters are quoted as follows: inlet temperature (T_i), furnace temperature (T_f), pressure range (P_{range}) and total pyrolysis time (t).

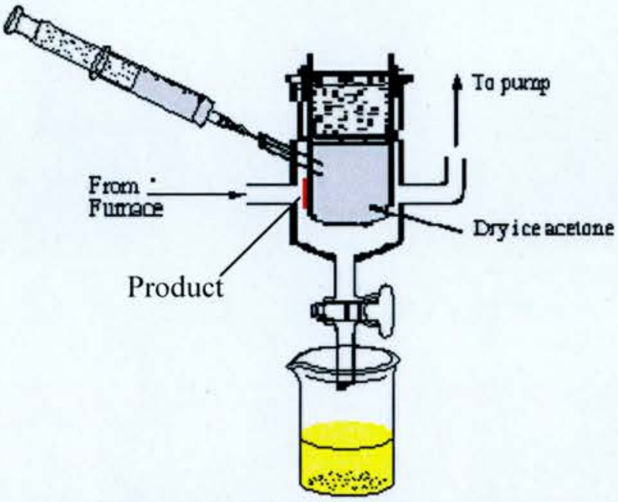
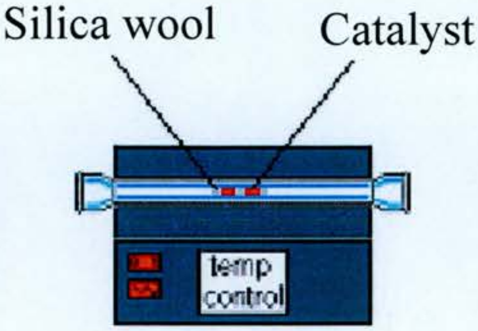


Figure 74: Cold finger apparatus.

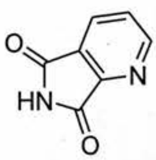
FVP over catalysts



To carry out an FVP experiment over a powered 'catalyst', a loose plug of silica wool is first inserted near the centre of the furnace tube. The appropriate amount of catalyst (typically 10 g) is poured into the tube, followed by a second silica wool plug and a second batch of catalyst. Finally, a third silica wool plug is inserted after the second batch of catalyst. When tungsten trioxide (WO_3) is used, this provides a catalyst zone of about 1-2 cm. The furnace tube is then heated in air at 600 °C in air before use. When the vacuum is applied before the FVP experiment itself, it is important to reduce the pressure slowly, to avoid the catalyst being drawn into the trap. Similarly, at the end of the pyrolysis, nitrogen gas should be introduced into the system as slowly as possible.

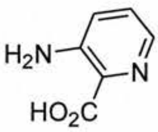
When catalysts are used, the rate of sublimation of precursor should be as slow as possible – *e.g.* 100 mg h^{-1} – though this can be increased in certain cases. In contrast to the 'empty-tube' FVP experiment, in some cases, FVP over catalysts can be scale dependent due to deactivation of the active sites of the catalyst. When WO_3 is used, the catalyst can invariably be re-activated by heating in air at 600 °C for 30 min. Tungsten trioxide undergoes phase transitions at high temperatures. At room temperature it is a green colour, but at 600 °C it appears orange. It invariably darkens during the FVP process but in some cases (associated with the deactivation) it becomes blue-black, probably due to the formation of a non-stoichiometric oxide.

Quinolinimide 121.[66]



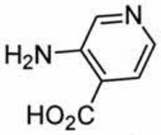
Quinolinic acid (16.8 g, 101 mmol) and acetic anhydride (22 cm^3, 230 mmol) were mixed and heated to 120 °C while the acetic acid (19 cm^3) generated was distilled off. The mixture was cooled to 100 °C and acetamide (13.4 g, 227 mmol) was added over 5 min. The mixture was heated under reflux for 2.5 h, then cooled to room temperature and filtered. The residue was washed with water and purified by boiling with ethanol (50 cm^3) and hot filtration to give the title compound (9.1 g, 59%) as a light brown solid: mp 229-231 °C [lit.,[71] 230-231 °C], δ_H ([$^2H_6$]DMSO) 11.79 (1H, s), 9.01 (1H, dd, *J* 7.5, 0.9), 8.31 (1H, dd, *J* 7.2, 5.1) and 7.82 (1H, dd, *J* 5.1, 0.9).

3-Aminonicotinic acid 111.[80]



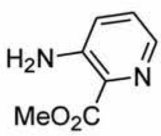
Quinolinimide (8.0 g, 54 mmol) was dissolved in an ice-cold solution of sodium hydroxide (10% 160 cm^3). To this was added an aqueous ice-cold sodium hypobromite solution [prepared by adding bromine (3.0 cm^3, 58 mmol) to an ice cold aqueous sodium hydroxide solution (15%, 56 cm^3) over 15 min]. The solution was stirred at room temperature for 1 h and then at 85 °C for 1 h. The solution was cooled to room temperature and acidified to pH 5 using sulfuric acid. The solution was stirred at 4 °C for 3 d. The mixture was filtered and the mother liquor was treated with copper (II) acetate-monohydrate (3.2 g, 16 mmol) in hot water (64 cm^3) containing glacial acetic acid (1.6 cm^3). This mixture was cooled and filtered through celite, the metallic blue precipitate was washed with water. The precipitate (including celite) was resuspended in water (64 cm^3) and saturated with hydrogen sulfide generated from the reaction of HCl with iron sulfide. The resulting mixture was filtered to remove the black copper sulfide leaving an orange solution. The solvent was removed to leave the title compound (3.61 g, 44%) as orange crystals: mp 210-212 °C (lit.[80] 210 °C), δ_H ([$^2H_6$] DMSO) 7.84 (1H, d, *J* 4.0), 7.33 (1H, dd, *J* 8.3, 4.0) and 7.26 (1H, d, *J* 8.3).

3-Aminoisonicotinic acid 109.[80]



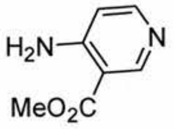
3,4-Pyridinedicarboxamide (4.95 g, 30 mmol) was added to an ice-cold solution of sodium hypobromite [prepared by adding bromine (1.75 cm^3, 34 mmol) to an ice cold aqueous sodium hydroxide solution (10%, 100 cm^3) over 15 min] and the solution was heated to 85 °C for 30 min. The solution was cooled and acidified to pH 3 with sulfuric acid. The mixture was then filtered leaving the title compound (3.9 g, 83%) as a yellow solid. mp 278-281 °C [lit.,[80] 280 °C]; δ_H ($[^2H_6]$ DMSO) 8.49 (1H, s), 8.00 (2H, m) and 7.00 (2H, s), δ_C 167.79 (quat), 147.09 (quat), 136.48 (quat), 130.88 (CH), 125.93 (CH) and 118.30 (CH).

Methyl 2-aminonicotinate 119.[80]



To a mixture of 2-aminonicotinic acid (540 mg, 3.91 mmol) and DMC (963 mg, 5.70 mmol) in MeOH (10.0 cm^3) was added triethylamine (1.154 g, 11.4 mmol). The mixture was stirred under nitrogen for 1 h. The solvent was removed and the residue was purified by dry flash chromatography. This yielded methyl 2-aminonicotinate (0.273 g, 53%) as a white solid; mp 76-79 °C [lit.,[80] 76-79 °C]; δ_H 8.22 (1H, dd, *J* 4.9, 1.9), 8.13 (1H, dd, *J* 7.8, 1.9), 6.63 (1H, dd, *J* 7.8, 4.9), 6.52 (1H, bs, NH_2) and 3.89 (3H, s).

Methyl 3-aminopicolinate 116.[67]

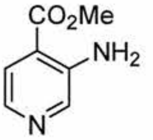


This was prepared using the same method as for methyl 2-aminonicotinate from 3-aminopicolinic acid (500 mg, 3.6 mmol) giving methyl 3-aminopicolinate (418 mg, 82%): mp 143-146 °C [lit.[72], 139-146 °C]; δ_H 8.03 (1H, dd, *J* 4.1, 1.4), 7.19 (1H, dd, *J* 8.4, 4.1), 7.04 (1H, dd, *J* 8.4, 1.4), 5.81 (2H, bs) and 3.95 (3H, s); δ_C 147.42 (quat), 138.90 (CH), 128.44 (CH), 128. 42 (quat), 128.00 (quat), 125.23 (CH) and 31.88 (Me).

Methyl 4-aminonicotinate 117.

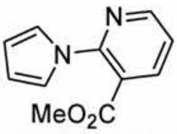
4-Aminonicotinic acid (0.500 g, 3.6mmol) was dissolved in the minimum amount of acetonitrile/water (1:1), the solution was then acidified to pH 5 using TFA. The solvent was removed to leave 4-aminonicotinic acid as its TFA salt, which was dissolved in methanol (40 cm^3) and concentrated sulfuric acid (4 cm^3) was added. The mixture was heated under reflux for 18 h, then cooled to room temperature and basified using aqueous sodium hydroxide solution (2 M). The solution was then extracted three times with chloroform. The combined organic extracts were then washed once with water and dried over $MgSO_4$, the solvent was removed and the residue was recrystallised from ethyl acetate to give the title compound as white crystals (387 mg, 76%), mp 167-169 °C [lit.[80], 170 °C]: δ_H 8.88 (1H, s), 8.17 (1H, d, *J* 5.9), 6.51 (1H, dd, *J* 5.9, 0.5), 6.28 (2H, s) and 3.89 (3H, s); δ_C 168.35 (quat), 155.30 (quat), 153.47 (CH), 152.51 (CH), 111.08 (CH), 108.01 (quat) and 52.10 (Me).

Methyl 3-aminoisonicotinate 118.



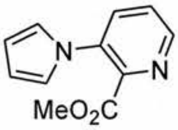
3-Aminoisonicotinic acid (250 mg, 1.6 mmol) was mixed with thionyl chloride (0.2 cm^3) in methanol (10 cm^3) and the solution heated under reflux for 1 h, the solvent was removed and the residue was recrystallised from ethyl acetate to give the title compound as white crystals mp 85-87 °C [lit.,[81] 86-87 °C]: δ_H 8.35 (1H, s), 7.24 (1H, d, *J* 6.1), 6.98 (1H, d, *J* 6.1), 6.72 (2H, s) and 3.45 (3H, s).

Methyl 2-pyrrol-1-yl-nicotinate 107.



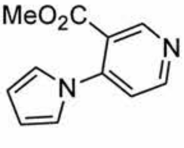
Methyl 2-aminonicotinate (250 mg, 1.6 mmol) was mixed with 2,5-dimethoxytetrahydrofuran (211 mg, 1.6 mmol) in glacial acetic acid (5 cm^3). The mixture was heated under reflux for 20 min and the solvent was removed to yield methyl 2-(pyrrol-1-yl)-nicotinate as a yellow oil after Kugelrohr distillation bp 72 °C (0.1 Torr) (0.19 g, 65%). (Found: M$^+$ 202.0743 $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H 8.49 (1H, dd, *J* 4.6, 1.9), 7.94 (1H, dd, *J* 8.3, 1.9), 7.17 (1H, m), 7.02 (2H, app t, *J* 2.0), 6.24 (2H, app t, *J* 2.0) and 3.71 (3H, s); δ_C 167.62 (quat), 153.64 (CH), 151.40 (quat), 140.20 (CH), 121.10 (2CH), 120.56 (quat), 111.29 (3CH) and 53.07 (Me); *m/z*: 202 (M$^+$ 78%), 171 (59), 144 (78), 117 (67), 86 (100) and 51 (87).

Methyl 3-(pyrrol-1-yl)-picolinate 105.



This was prepared by the same method as above from methyl 3-aminopicolinate (0.500 g, 3.2 mmol) to give the title compound as a yellow oil (0.38 g, 65%) bp 64 °C (0.1 Torr); (Found M$^+$ 202.0743 $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H 8.62 (1H, dd, *J* 1.5, 4.7), 7.75 (1H, dd, *J* 1.5, 8.1), 7.52 (1H, dd, *J* 8.1, 4.7), 6.84 (2H, app t, *J* 2.2), 6.36 (2H, app t, *J* 2.2) and 3.83 (3H, s); δ_C 166.12 (quat), 148.01 (CH), 145.82 (quat), 136.88 (quat), 134.56 (CH), 126.46 (CH), 122.07 (2CH), 111.21 (2CH) and 53.33 (Me); *m/z* 202 (M$^+$ 100%), 171 (15), 159 (14) and 144 (75).

Methyl 2-(pyrrol-1-yl)-nicotinate 106.



This was prepared by the same method as above from methyl 4-aminonicotinate (500 mg, 3.2 mmol) to give the title compound as a yellow oil (0.38 g, 65%) bp 72 °C (0.1 mm Torr); (Found M$^+$ 202.0742 $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H 8.96 (1H, s,), 7.74 (1H, d, *J* 5.2), 7.31 (1H, d, *J* 5.2), 6.89 (2H, app t, *J* 2.2), 6.38 (2H, app t, *J* 2.2) and 3.83 (3H, s); *m/z* 202 (M$^+$ 100%), 170 (45), 144 (76), 99 (41) and 56 (35).

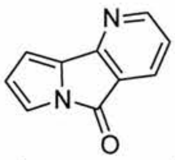
Methyl-3-(pyrrol-1-yl)-isonicotinate 104.

This was prepared by the same method as above from methyl methyl 3-aminoisonicotinate (500 mg, 3.2 mmol) to give a black oil from which the product could not be cleanly isolated. The product was quickly transferred to an inlet tube and pyrolysed immediately in the synthesis of **3**.

Pyrolysis reactions of methyl-2-(pyrrol-1-yl)-nicotinates.

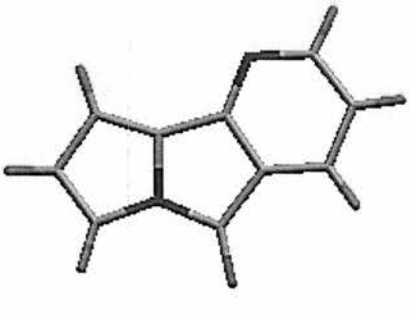
The pyrolysis reactions were all carried out using the equipment described (**Figure 73**), in this case the furnace temperature was kept at a constant 950 °C The inlet oven was not used so the inlet temperature was ambient warmed only by the radiant heat from the furnace. It was observed that heating of the inlet caused an increased amount of the production of an unidentified by-product, which lowered yields.

9-Azapyrrolo[2,1-*a*]isoindol-5-one 4.



Methyl 2-(pyrrol-1-yl)-nicotinate (50 mg, 0.2 mmol) was heated under FVP conditions as described above (P 2.8 × 10^{-3} Torr, 20 min), affording a yellow pyrolysate, which gave after after column chromatography 9-azapyrrolo[2,1-*a*]isoindol-5-one (32.8 mg, 78%) as a yellow crystalline solid [sublimes 45 °C (0.1 Torr)];(Found M^+ 170.0499, $C_{10}H_6N_2O$ requires *M* 170.0480) δ_H 8.44 (1H, dd, *J* 5.2, 1.5), 7.81 (1H, dd, *J* 7.7, 1.5), 6.98-7.06 (2H, m), 6.48 (1H, dd, *J* 3.2, 1.0) and 6.21 (1H, t, *J* 3.2); δ_C 161.31 (CO), 157.11 (quat), 154.49 (CH), 135.37 (quat), 133.32 (CH), 127.11 (quat), 121.71 (CH), 118.51 (2CH) and 110.21 (CH), *m/z* 170 (M^+ 72%), 142 (100), 116 (48), and 73 (88).

Crystal data and structure refinement for 9-azapyrrolo[2,1-*a*]isoindol-5-one HM0503.[73]



Contact	Laura Budd, L.E.Budd@sms.ed.ac.uk

A. CRYSTAL DATA

Empirical formula	$C_{10} H_6 N_2 O$
	$C_{10} H_6 N_2 O$
Formula weight	170.17
Wavelength	0.71073 A
Temperature	150 K
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 11.1236(6) A alpha = 90 deg.
	b = 5.8539(3) A beta = 101.364(4) deg.
	c = 12.1687(7) A gamma = 90 deg.
Volume	776.85(7) A^3
Number of reflections for cell	1239 (4 < theta < 24 deg.)
Z	4
Density (calculated)	1.455 Mg/m^3
Absorption coefficient	0.098 mm^-1
F(000)	352

B. DATA COLLECTION

Crystal description	yellow plate
Crystal size	0.40 x 0.16 x 0.08 mm
Instrument	Bruker SMART
Theta range for data collection	1.867 to 30.010 deg.
Index ranges	-14<=h<=15, -5<=k<=8, -16<=l<=17
Reflections collected	8891
Independent reflections	2148 [R(int) = 0.024]
Scan type	\f & \w scans
Absorption correction	Semi-empirical from equivalents
	(Tmin= 0.84, Tmax=0.99)

C. SOLUTION AND REFINEMENT.

Solution	direct (SIR92 (Altomare et al., 1994))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	noref
Data	2146
Parameters	118
Goodness-of-fit on F^2	0.8129
Conventional R [F>4sigma(F)]	R1 = 0.0503 [1075 data]
Rw	0.1142
Final maximum delta/sigma	0.000229
Weighting scheme	Sheldrick Weights
Largest diff. peak and hole	0.30 and -0.21 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic

displacement parameters (A^2 x 10^3) for hm0503. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	3856(2)	1192(3)	9083(2)	30
N(2)	3002(1)	2230(3)	9642(1)	29
C(12)	3188(2)	-811(3)	8504(1)	27
C(4)	1818(2)	4178(3)	10560(2)	34
C(6)	1862(2)	1141(3)	9421(1)	27
C(7)	1984(1)	-793(3)	8694(1)	27
N(8)	1129(1)	-2313(3)	8278(1)	32
C(9)	1519(2)	-3943(3)	7651(2)	34
C(10)	2686(2)	-4098(3)	7430(2)	33
C(11)	3555(2)	-2483(3)	7865(2)	33
C(3)	2970(2)	4097(3)	10335(2)	33
C(5)	1109(2)	2326(3)	9987(2)	32
O(1)	4887(1)	1866(2)	9089(1)	39

Table 3. Bond lengths [A] and angles [deg] for hm0503.

C(1)-N(2)	1.411(2)
C(1)-C(12)	1.489(3)
C(1)-O(1)	1.211(2)
N(2)-C(6)	1.397(2)
N(2)-C(3)	1.385(2)
C(12)-C(7)	1.404(2)
C(12)-C(11)	1.362(3)
C(4)-C(3)	1.363(3)
C(4)-C(5)	1.438(3)
C(4)-H(15)	0.997
C(6)-C(7)	1.459(3)
C(6)-C(5)	1.373(2)
C(7)-N(8)	1.328(2)
N(8)-C(9)	1.346(2)
C(9)-C(10)	1.379(3)
C(9)-H(19)	0.999
C(10)-C(11)	1.381(3)
C(10)-H(18)	0.998
C(11)-H(17)	0.997
C(3)-H(14)	0.997
C(5)-H(16)	0.995
N(2)-C(1)-C(12)	104.24(14)
N(2)-C(1)-O(1)	125.71(18)

C(12)-C(1)-O(1)	130.04(18)
C(1)-N(2)-C(6)	112.51(15)
C(1)-N(2)-C(3)	137.20(15)
C(6)-N(2)-C(3)	110.26(14)
C(1)-C(12)-C(7)	108.66(16)
C(1)-C(12)-C(11)	131.12(17)
C(7)-C(12)-C(11)	120.22(18)
C(3)-C(4)-C(5)	108.97(17)
C(3)-C(4)-H(15)	125.6
C(5)-C(4)-H(15)	125.5
N(2)-C(6)-C(7)	106.36(14)
N(2)-C(6)-C(5)	107.06(16)
C(7)-C(6)-C(5)	146.57(17)
C(6)-C(7)-C(12)	108.14(16)
C(6)-C(7)-N(8)	127.34(16)
C(12)-C(7)-N(8)	124.53(18)
C(7)-N(8)-C(9)	113.88(16)
N(8)-C(9)-C(10)	125.33(18)
N(8)-C(9)-H(19)	117.3
C(10)-C(9)-H(19)	117.4
C(9)-C(10)-C(11)	119.66(18)
C(9)-C(10)-H(18)	120.2
C(11)-C(10)-H(18)	120.1
C(10)-C(11)-C(12)	116.38(17)
C(10)-C(11)-H(17)	121.8
C(12)-C(11)-H(17)	121.9
N(2)-C(3)-C(4)	106.68(16)
N(2)-C(3)-H(14)	126.6
C(4)-C(3)-H(14)	126.7
C(4)-C(5)-C(6)	107.03(15)
C(4)-C(5)-H(16)	126.5
C(6)-C(5)-H(16)	126.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for hm0503.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

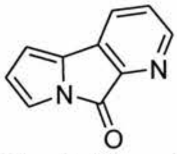
	U11	U22	U33	U23	U13	U12
C(1)	30(1)	30(1)	29(1)	9(1)	3(1)	-3(1)

N(2)	28(1)	28(1)	30(1)	3(1)	5(1)	-3(1)
C(12)	27(1)	28(1)	26(1)	6(1)	5(1)	-1(1)
C(4)	45(1)	25(1)	32(1)	-1(1)	7(1)	6(1)
C(6)	25(1)	26(1)	27(1)	7(1)	2(1)	-4(1)
C(7)	25(1)	27(1)	27(1)	8(1)	1(1)	-4(1)
N(8)	34(1)	29(1)	32(1)	3(1)	3(1)	-3(1)
C(9)	40(1)	28(1)	31(1)	4(1)	-2(1)	-3(1)
C(10)	40(1)	29(1)	29(1)	0(1)	6(1)	7(1)
C(11)	30(1)	37(1)	31(1)	7(1)	6(1)	2(1)
C(3)	39(1)	25(1)	31(1)	3(1)	-1(1)	-7(1)
C(5)	26(1)	33(1)	37(1)	11(1)	5(1)	1(1)
O(1)	28(1)	43(1)	44(1)	5(1)	5(1)	-11(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for hm0503.

	x	y	z	U(eq)
H(14)	3658	5171	10615	38
H(15)	1516	5334	11043	41
H(16)	236	1970	9998	39
H(17)	4406	-2540	7719	39
H(18)	2900	-5368	6956	39
H(19)	914	-5139	7320	40

6-Azapyrrolo[2,1-*a*]isoindol-5-one 1.



This was prepared by the pyrolysis of methyl 3-(pyrrol-1-yl)-picolinate as above (P 2.6 × 10^{-3} Torr, t 20 min), (50 mg) to give 6-azapyrrolo[2,1-*a*]isoindol-5-one (37.4 mg, 89%), [sublimes 55 °C (0.1 Torr)]:(Found M^+ 170.0499, $C_{10}H_6N_2O$ requires *M* 170.0480) δ_H 8.44 (1H, dd, *J* 1.4, 4.9), 7.61 (1H, dd, *J* 7.7, 1.4), 7.30 (1H, dd, *J* 7.7, 4.9), 7.09 (1H, dd, *J* 3.2, 0.8), 6.33 (1H, dd, *J* 3.2, 0.8), and 6.20 (1H, t, *J* 3.2); δ_C 159.86 (quat), 149.85 (quat), 147.38 (CH), 131.40 (quat), 131.26 (quat), 126.32 (CH), 125.69 (CH), 116.56 (CH), 116.26 (CH) and 108.90 (CH); *m/z* 170 (M^+ 89%), 142 (100), 115 (51), 86 (29) and 73 (88), *m/z* 170 (M^+ **95%**), 143 (100), 115 (51), and 73 (84).

Crystal data and structure refinement for 6-azapyrrolo[2,1-*a*]isoindol-5-one hm6001.[74]

Contact	Simon Parsons, S.Parsons@ed.ac.uk

A. CRYSTAL DATA

Empirical formula	$C_{10} H_6 N_2 O$
	$C_{10} H_6 N_2 O$
Formula weight	170.17
Wavelength	0.71073 A
Temperature	150 K
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 3.8530(5) A alpha = 90 deg.
	b = 18.735(2) A beta = 96.264(8) deg.
	c = 10.9027(13) A gamma = 90 deg.
Volume	782.33(17) A^3
Number of reflections for cell	1720 (2 < theta < 27 deg.)
Z	4
Density (calculated)	1.445 Mg/m^3
Absorption coefficient	0.097 mm^-1
F(000)	352

B. DATA COLLECTION

Crystal description	yellow needle
Crystal size	1.00 x 0.09 x 0.09 mm
Instrument	Bruker SMART
Theta range for data collection	2.171 to 25.025 deg.
Index ranges	-4<=h<=4, -22<=k<=22, -12<=l<=12
Reflections collected	7504
Independent reflections	1386 [R(int) = 0.064]
Scan type	\w
Absorption correction	Semi-empirical from equivalents
	(Tmin= 0.67, Tmax=0.99)

C. SOLUTION AND REFINEMENT.

Solution	direct (SIR92 (Altomare et al., 1994))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	noref
Data	1125

Parameters	119
Goodness-of-fit on F^2	0.8079
Conventional R [F>4sigma(F)]	R1 = 0.0478 [771 data]
Rw	0.0977
Final maximum delta/sigma	0.000100
Weighting scheme	w = 1/sigma(F**2) with robust-resistant modifier after Prince.
Largest diff. peak and hole	0.14 and -0.13 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for hm6001. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	-200(8)	3695(1)	3892(3)	26
O(1)	1578(6)	3883(1)	4824(2)	35
N(2)	-2184(7)	4144(1)	3056(2)	24
C(3)	-2960(9)	4861(1)	2949(3)	31
C(4)	-5011(9)	4947(1)	1870(3)	32
C(5)	-5559(9)	4266(2)	1286(2)	30
C(6)	-3796(8)	3779(1)	2037(2)	23
C(7)	-2886(8)	3024(1)	2213(2)	22
C(8)	-3756(8)	2411(1)	1539(2)	26
C(9)	-2408(8)	1782(1)	2045(2)	28
C(10)	-308(9)	1782(1)	3165(2)	30
N(11)	581(7)	2371(1)	3836(2)	27
C(12)	-765(8)	2967(1)	3328(2)	23

Table 3. Bond lengths [A] and angles [deg] for hm6001.

C(1)-O(1)	1.214(3)
C(1)-N(2)	1.404(4)
C(1)-C(12)	1.502(3)
N(2)-C(3)	1.378(3)
N(2)-C(6)	1.392(3)
C(3)-C(4)	1.353(4)
C(3)-H(3)	0.950
C(4)-C(5)	1.431(4)
C(4)-H(4)	0.950
C(5)-C(6)	1.357(4)
C(5)-H(5)	0.950
C(6)-C(7)	1.465(4)
C(7)-C(8)	1.385(3)
C(7)-C(12)	1.393(4)
C(8)-C(9)	1.380(4)
C(8)-H(8)	0.950
C(9)-C(10)	1.389(4)
C(9)-H(9)	0.949
C(10)-N(11)	1.347(3)
C(10)-H(10)	0.949
N(11)-C(12)	1.327(3)

O(1)-C(1)-N(2)	126.0(2)
O(1)-C(1)-C(12)	130.4(3)
N(2)-C(1)-C(12)	103.5(2)
C(1)-N(2)-C(3)	137.4(2)
C(1)-N(2)-C(6)	112.8(2)
C(3)-N(2)-C(6)	109.8(2)
N(2)-C(3)-C(4)	106.8(2)
N(2)-C(3)-H(3)	126.6
C(4)-C(3)-H(3)	126.5
C(3)-C(4)-C(5)	109.0(2)
C(3)-C(4)-H(4)	125.4
C(5)-C(4)-H(4)	125.6
C(4)-C(5)-C(6)	106.9(3)
C(4)-C(5)-H(5)	126.5
C(6)-C(5)-H(5)	126.6
N(2)-C(6)-C(5)	107.6(2)
N(2)-C(6)-C(7)	106.9(2)
C(5)-C(6)-C(7)	145.5(3)
C(6)-C(7)-C(8)	133.7(3)
C(6)-C(7)-C(12)	107.3(2)
C(8)-C(7)-C(12)	119.0(3)
C(7)-C(8)-C(9)	115.9(3)
C(7)-C(8)-H(8)	122.0
C(9)-C(8)-H(8)	122.0

C(8)-C(9)-C(10)	120.6(2)
C(8)-C(9)-H(9)	119.7
C(10)-C(9)-H(9)	119.7
C(9)-C(10)-N(11)	124.5(2)
C(9)-C(10)-H(10)	117.7
N(11)-C(10)-H(10)	117.8
C(10)-N(11)-C(12)	113.5(2)
C(1)-C(12)-C(7)	109.4(2)
C(1)-C(12)-N(11)	124.2(2)
C(7)-C(12)-N(11)	126.4(2)

Symmetry transformations used to generate equivalent atoms:

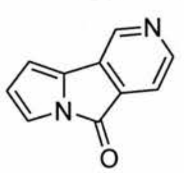
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for hm6001.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	24(2)	32(2)	23(2)	-2(1)	10(2)	-6(2)
O(1)	41(2)	35(1)	26(1)	-6(1)	-4(1)	-7(1)
N(2)	30(2)	22(1)	22(1)	-2(1)	4(1)	-1(1)
C(3)	34(2)	24(2)	35(2)	-3(1)	9(2)	-2(2)
C(4)	31(2)	27(2)	37(2)	4(1)	8(2)	4(2)
C(5)	30(2)	33(2)	26(2)	3(1)	0(2)	1(2)
C(6)	20(2)	30(1)	19(1)	-4(1)	6(1)	-3(2)
C(7)	19(2)	28(1)	20(1)	-1(1)	6(1)	-2(1)
C(8)	27(2)	31(2)	19(1)	-1(1)	3(1)	-2(2)
C(9)	29(2)	27(2)	27(2)	-5(1)	5(2)	-4(2)
C(10)	34(2)	24(1)	33(2)	5(1)	6(2)	1(2)
N(11)	26(2)	29(1)	26(1)	1(1)	3(1)	0(1)
C(12)	21(2)	29(2)	18(1)	0(1)	4(1)	-2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for hm6001.

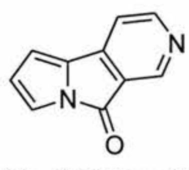
	x	y	z	U(eq)
H(3)	-2201	5226	3522	37
H(4)	-5936	5388	1552	38
H(5)	-6900	4173	518	36
H(8)	-5192	2424	773	31
H(9)	-2923	1345	1625	33
H(10)	562	1337	3478	37

8-Azapyrrolo[2,1-*a*]isoindol-5-one 3.



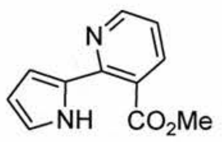
This was prepared by the pyrolysis of crude methyl-3-(pyrrol-1-yl)-isonicotinate as described above (P 2.8 × 10^{-3} Torr, t 25 min), (50 mg) to give the title compound as a yellow solid (5.46 mg, 13%), [sublimes 52 °C (0.1 Torr)].(Found M^+ 170.0499, $C_{10}H_6N_2O$ requires *M* 170.0480) δ_H 8.67 (1H, d, *J* 1.1), 8.58 (1H, d, *J* 4.8), 7.53 (1H, dd, *J* 4.8, 1.1), 7.08 (1H, dd, *J* 3.1, 0.8), 6.33 (1H, dd, *J* 3.1, 0.8), and 6.24 (1H, t, *J* 3.1); δ_C 161.1 (quat), 149.0 (CH), 141.0 (CH), 133.2 (quat), 131.5 (quat), 129.3 (quat), 118.9 (CH), 118.4 (CH), 117.8 (CH) and 109.1 (CH); *m/z* 170 (M^+ 94%), 142 (100), 115 (55), 86 (31) and 73 (86).

7-Azapyrrolo[2,1-*a*]isoindol-5-one 2.



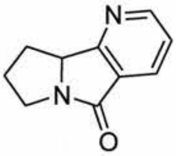
This was prepared by the pyrolysis of methyl 4-(pyrrol-1-yl)-nicotinate (P 2.7 × 10^{-3} Torr, t 25 min), (50 mg) to give the title compound as a yellow solid (36.1 mg, 86%), [sublimes 48 °C (0.1 Torr)].(Found M^+ 170.0499, $C_{10}H_6N_2O$ requires *M* 170.0480) δ_H 8.80 (1H, s), 8.65 (1H, d, *J* 5.1), 7.23 (1H, d, *J*, 5.1), 7.11 (1H, dd, *J* 3.3, 0.8), 6.44 (1H, dd, *J* 3.3, 0.8) and 6.29 (1H, t, *J* 3.3); δ_C 155.84 (CH), 146.71 (CH), 118.52 (CH), 118.41 (CH), 114.56 (CH) and 111.53 (CH) (only CH signals quoted), *m/z* 170 (M^+ 89%), 142 (100), 115 (51), 86 (29) and 73 (88).

Methyl 2-(1*H*-pyrrol-2-yl)-nicotinate 126.



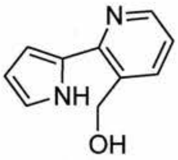
A solution of 9-azapyrrolo[2,1-*a*]isoindol-5-one (30 mg, 0.2 mmol) and diisopropylethylamine (2 drops, cat) were added together in methanol (5 cm^3). The solution was stirred at room temperature for 5 min during which time the solution decolourised. Removal of the solvent gave methyl 2-(1H-pyrrol-2yl)-nicotinate (25 mg, 70.%) bp 78 °C (0.1 Torr). (Found: M^+ 202.0742 $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H 10.18 (1H,s), 8.46 (1H, dd, *J* 4.8, 1.8), 7.77 (1H, dd, *J* 7.8, 1.8), 7.00 (1H, *J* 7.8, 4.8), 6.84 (1H, m), 6.63 (1H, m), 6.20 (1H, m) and 3.86 (3H, s); δ_C 168.26 (CO), 149.71 (CH), 147.15 (quat), 136.53 (CH), 128.41 (quat), 122.38 (quat), 119.49 (CH), 118.39 (CH), 110.53 (CH), 109.41 (CH) and 51.73 (Me); *m/z* 202 (M^+, 71%), 170 (76), 143 (92), 114 (83) and 85 (100).

7,8,9,9a-Tetrahydropyrido[2,3-*a*]pyrrolizin-5-one 131.



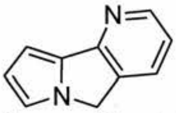
A solution of 9-azapyrrolo[2,1-*a*]isoindol-5-one (30 mg 0.2 mmol) in toluene (15 cm^3) was hydrogenated at 200 psi in the presence of 5% Pd/C (5 mg) catalyst for 2 h. The mixture was filtered through celite to remove the catalyst and the filtrate was concentrated to yield 7,8,9,9a-tetrahydropyrido[2,3-*a*]pyrrolizin-5-one as a brown oil (20 mg, 65%) bp 73°C (0.1 Torr);(Found M^+ 174.0795, $C_{10}H_{10}N_2O$ requires M 174.0793) δ_H 8.64 (1H, dd, *J* 4.9, 1.6), 8.01 (1H, dd, *J* 7.7, *J* 1.6), 7.33 (1H, ddd, *J* 7.7, 0.4, 0.3), 4.67 (1H, m), 3.72 (1H, dt, *J* 11.7, 8.2,), 3.40 (1H, m), 2.25-2.45 (3H, m) and 1.62 (1H, m); δ_C 152.52 (CH), 132.32 (CH), 123.50 (CH), 77.26 (CH), 42.32 (CH_2), 29.05 (CH_2) and 28.46 (CH_2) (CH signals only quoted).

2-(1*H*-Pyrrol-2-yl)-pyridin-3-ylmethanol 128.



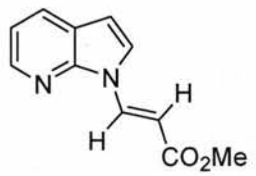
To a suspension of $LiAlH_4$ (25 mg, 0.6 mmol) in dry ether (30 cm^3) a solution of 9-azapyrrolo[2,1-*a*]isoindol-5-one (52.5 mg, 0.3 mmol) in dry ether (30 cm^3) was added dropwise over a period of 30 min. The resulting solution was heated under reflux for 30 min. Wet ether (15 cm^3) was added followed by aqueous NaOH (3.5 cm^3, 4 M) the organic layer was separated and washed with water and dried over $MgSO_4$. The solvent was removed to yield 2-(1*H*-pyrrol-2-yl)-pyridin-3-ylmethanol (48 mg, 90%), bp 68°C (0.1 Torr); Found M^+ 174.0794 $C_{10}H_{10}N_2O$ requires *M* 174.0793) δ_H 10.04 (1H, s, NH), 8.36 (1H, dd, *J* 4.8, *J* 1.5), 7.74 (1H, dd, *J* 7.7, 1.5), 7.02 (1H, dd, *J* 7.7, 4.8), 6.88 (1H, ddd, *J* 3.9, 2.6, 1.4), 6.61 (1H, dd, *J* 2.6, 1.4), 6.27 (1H, dd, *J* 3.9, 2.6), 4.83 (2H, s, CH_2) and 2.23 (OH, s); δ_C 146.68 (CH), 135.16 (CH), 131.95 (quat), 129.81 (quat), 129.01 (quat), 119.40 (CH), 118.99 (CH), 109.58 (CH), 109.42 (CH) and 61.85 (CH_2); *m/z* 174 (M^+, 100%), 118 (74), 94 (49), 78 (62), 63 (40) and 39 (88).

5*H*-Pyrido[2,3-*a*]pyrrolizine 129.



2-(1*H*-Pyrrol-2-yl)-pyridin-3-ylmethanol (32 mg, 0.2 mmol)) was pyrolysed under FVP conditions (T_f 750 °C, T_I 65°C, P 2.8×10^{-2} Torr, *t* 15 min). A yellow pyrolysate was produced in the bend of the U-tube and 5*H*-pyrido[2,3-*a*]pyrrolizine was isolated as a brown oil (21 mg, 73%), bp 72 °C (0.1 Torr), (Found M^+ 156.0687 $C_{10}H_8N_2$ requires M^+ 156.0688); δ_H 8.44 (1H, dt, *J* 5.1, 0.8), 7.60 (1H, ddt, *J* 6.1, 1.6, 0.8), 7.03 (1H, m), 7.02 (1H, dd, *J* 7.7, 5.1), 6.62 (1H, dt, *J* 3.7, 0.8), 6.43 (1H, dd, *J* 3.7, 2.5), and 4.95 (2H, s); δ_C 149.23 (CH), 134.74 (2 quat), 130.58 (CH), 119.35 (CH), 118.53 (CH), 114.29 (CH), 101.18 (CH), 80.68 (quat) and 49.00 (CH_2); *m/z* 156 (M^+ 55%), 128 (39), 75 (58), 51 (78) and 39 (100).

Methyl (3-Pyrrolo[2,3-*b*]pyridin-1-yl)-acrylate 134.



A solution of 7-azaindole (1.00 g, 8.5 mmol), methyl propyoate (0.89 g, 8.5 mmol) and a solution of TBAF (1M) (8.94 cm^3) in THF (50 cm^3) was stirred at room temperature for 30 min, water (10 cm^3) was added to the brown solution and the product extracted into ethyl acetate (3 × 50 cm^3). The solvent was removed under vacuum and the residue was recrystalised from ethanol affording methyl-3-(pyrrolo[2,3-*b*]pyridin-1-yl)acrylate (*Z:E* 2:3) as white needles (1.42 g, 75%), mp 102-103 ˚C; (Found M^+ 202.0745. $C_{11}H_{10}N_2O_2$ requires *M* 202.0742); δ_H (*Z*-isomer) 8.70 (1H, d, *J* 4.0), 8.23 (1H, dd, *J* 1.6, *J* 4.8), 7.78 (1H, t, *J* 1.7), 7.78 (1H, t, *J* 1.7), 7.78 (1H, t, *J* 1.7), 7.03-7.12 (1H, m), 5.73 (1H, d, *J* 10.8) and 3.67 (3H, s); δ_H (E-isomer) 8.52 (1H, d, *J* 14.4), 8.28 (1H, dd, *J* 4.8, 1.6), 7.81 (1H, t, *J* 1.6), 7.33 (1H, d, *J* 3.9), 7.03-7.12 (1H, m), 6.54 (1H, d, *J* 3.9), 6.19 (1H, d, *J* 14.5), and 3.71 (3H, s),; δ_C (*Z*-isomer) 167.97 (CO_2), 148.14 (quat), 143.29 (CH), 136.55 (CH), 132.27 (CH), 129.92 (CH), 121.77 (quat), 118.75 (CH), 104.73 (CH), 100.54 (CH) and 51.81 (Me); δ_C (*E*-isomer) 166.43 (CO_2), 147.82 (quat), 144.44 (CH), 129.92 (2CH), 124.61 (CH), 122.56 (quat), 118.75 (CH), 106.28 (CH), 102.62 (CH) and 51.92 (Me), *m/z* 202 (M^+, 100%), 162 (75), 143 (92), 114 (83) and 77 (51).

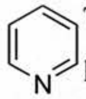
Attempted synthesis of methyl-3-(pyrrolo[2,3-*b*]pyridin-1-yl)-acrylate.

Methyl 3-(pyrrolo[2,3-*b*]pyridin-1-yl)-acrylate (50 mg) was pyrolysed under FVP conditions (T_f 700 °C, T_i 125 °C, *P* 2.7×10^{-2} Torr, *t* 15 min) giving a brown precipitate purified by column chromatography to give 7-azaindole (43 mg, 50%), mp 106-109 ˚C [lit.,[78] 106 - 107]. δ_H 12.00 (1H, bs), 8.35 (1H, d, *J* 4.8), 7.96 (1H, d, *J* 7.9), 7.39 (1H, m), 7.10 (1H, m) and 6.51 (1H, d, *J* 3.5). No trace of the desired product was observed.

Catalysis in FVP experimental.

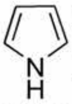
The products were identified by comparison of their NMR spectra with literature values.[75]

Pyridine.



The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 400 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of piperidine (50 mg), (T_f 400 °C/ WO_3, T_i 68 °C, P $3X10^{-2}$ Torr, t 15 min) gave pyridine as a colourless oil.

Pyrrole.



The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 400 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of pyrrolidine (50 mg), (T_f 400 °C/ WO_3, T_i 20 °C, P $3X10^{-2}$ Torr, t 15 min) gave pyrrole as a colourless oil.

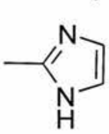
FVP of cyclohexane.

The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 400 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of cyclohexane (50 mg), (T_f 400 °C/ WO_3, T_i 20 °C, P 3×10^{-2} Torr, t 15 min), unreacted cyclohexane was recovered.

FVP of DBU.

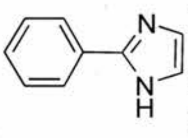
The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 400 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of DBU (50 mg), (T_f 400 °C/ WO_3, T_i 20 °C, P 3 × 10^{-2} Torr, t 15 min) produced a complex mixture in which no products were identified.

2-Methylimidazole.



The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 500 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of 2-methylimidazoline (50 mg), (T_f 500 °C/ WO_3, T_i 148 °C, P 3 × 10^{-2} Torr, t 15 min) gave 2-methylimidazole (84 %), δ_H 7.01 (2H) and 2.25 (3H); and MeCN (16 %).

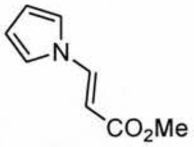
2-Phenylimidazole.



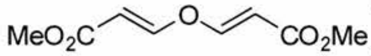
The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 500 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of 2-phenlyimidazoline (50 mg), (T_f 500 °C/ WO_3, T_i 127 °C, P 3 × 10^{-2} Torr, t 15 min) gave 2-phenlyimidazole, δ_H 7.70 (2H, m), 7.41 (2H, m) and 3.77 (3H, s).

Pyrrolizin-1-one experimental.

Methyl (E)-3-(pyrrol-1-yl)-acrylate 172.

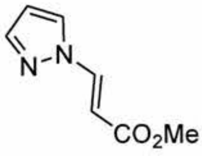


To a solution of pyrrole (1.00 g, 14 mmol) in acetonitrile (10 cm^3) a solution of TBAF in THF (1M, 6 cm^3) was added, the resulting solution was heated under reflux for 1 h before the dropwise addition of a solution of methyl propiolate (1.17 g, 14 mmol) in acetonitrile (10 cm^3). The mixture was heated under reflux for a further 3 h. After cooling the solvent was removed to give a dark oil. The dark oil was heated with hexane, and the hexane layer decanted while hot, upon cooling of the hexane layer the product formed as white crystals (1.86 g 88%), mp 58-61 °C, (Found C, 63.80; H, 5.90; N, 9.25. $C_8H_9NO_2$ requires C, 63.60; H, 6.00; N, 9.26%); δ_H 7.84 (1H, d, *J* 14.1), 6.94 (2H, t, *J* 2.2), 6.33 (2H, t, *J* 2.2), 5.89 (1H, d, *J* 14.1) and 3.79 (3H, s); δ_C 167.60 (quat), 140.92 (2CH), 120.45 (CH), 112.86 (2CH), 102.05 (CH) and 51.67 (CH_3); *m/z* 151 (M^+ 100%), 120 (92), 92 (99), 65 (98) and 53 (71).



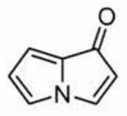
If this reaction is carried out but the methyl propiolate is added at the same time as the TBAF solution methyl (Z)-3-((E)-2-methoxycarbonyl-vinyloxy)-acrylate is isolated (~50%), mp 154-155 °C [lit.,[76]]; δ_H 7.58 (2H, d, *J* 12.2), 5.66 (2H, d, *J* 12.2) and 3.74 (6H, s); δ_C 166.43 (2quat), 157.34 (2CH), 103.96 (2CH) and 51.63 (2CH_3); *m/z* 186 (M^+ 30%), 155 (62), 116 (73), 85 (98) and 59 (100).

(E)-3-Pyrazol-1-yl-acrylic acid methyl ester



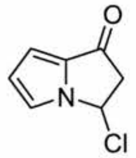
To a solution of pyrazole (0.79 g, 15 mmol) in acetonitrile a solution of TBAF in THF was added (1M, 15 cm^3), the resulting solution was heated under reflux for 1 h before the dropwise addition of a solution methyl propiolate (1.00 g, 15 mmol) in acetonitrile (10 cm^3). The mixture was heated under reflux for a further 3 h. After cooling the solvent was removed to give a dark oil. The dark oil was heated with hexane, and the hexane layer decanted while hot, upon cooling of the hexane layer the product formed as white crystals (1.91 g, 81%), mp 146 °C [lit.,[77] 147 °C]; δ_H 7.98 (1H, d, *J* 14.0), 7.71 (1H, d, *J* 1.5), 7.64 (1H, d, *J* 2.6), 6.43 (1H, dd, *J* 2.6, 1.5), 6.35 (1H, d, *J* 14.0) and 3.78 (3H, s); δ_C 166.96 (quat), 143.40 (CH), 139.66 (CH), 130.08 (CH), 109.01 (CH), 105.33 (CH) and 51.69 (CH_3).

Pyrrolizin-1-one 5.



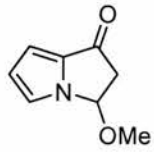
The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 450 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of methyl (*E*)-3-(pyrrol-1-yl)-acrylate (50 mg), (T_f 450 °C/ WO_3, T_i 68 °C, P 3×10^{-2} Torr, t 15 min) gave pyrrolizin-1-one as a yellow solid, mp 51-53 °C [lit.,[78] 52-53 °C]; δ_H 7.50 (1H, d, J 4.1), 6.75 (1H, d, 2.6), 6.62 (1H, t, J 3.5), 6.15 (1H, m) and 5.47 (1H, d, J 4.1). FVP of methyl (*E*)-3-(pyrrol-1-yl)-acrylate (50 mg), (T_f 350 °C/ WO_3, T_i 68 °C, P 3×10^{-2} Torr, t 15 min) gave a mixture of pyrrolizin-1-one (81%) and *N*-vinylpyrrole (19%).

3-Chloro-2,3-dihydropyrrolizin-1-one



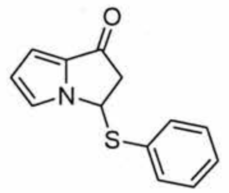
Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in DCM and dry HCl gas was passed through the solution for 30 min. The solution was then neutralised by the addition of anhydrous potassium carbonate, which was then filtered and the solvent evaporated to give 3-chloro-2,3-dihydropyrrolizin-1-one (77 mg, 98%) as a colourless oil; (Found M^+ 157.01029, C_7H_6ClNO requires M 157.01029) bp 78 °C (0.5 Torr); δ_H 7.20 (1H, dd, J 2.5, 1.0), 6.77 (1H, dd, J 3.9, 1.0), 6.63 (1H, dd, J 3.9, 2.5), 6.40 (1H, dd, J 6.4, 2.1), 3.69 (1H, dd, J 18.8, 6.4), and 3.29 (1H, dd, J 18.8 and 2.1); δ_C 184.90 (quat), 132.33 (quat), 122.52 (CH), 118.99 (CH), 109.18 (CH), 64.35 (CH) and 51.09 (CH_2); *m/z* 157 (M^+ 52%), 155 (M^+ 100), 120 (90), 92 (95) and 65 (98%).

3-Methoxy-2,3-dihydropyrrolizin-1-one 178.



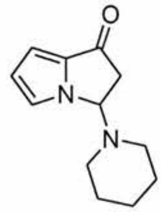
Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in MeOH (1 cm^3) followed by the addition of one drop of Hunig's base. The solution was stirred at room temperature for 15 min before the solvent was evaporated to give 3-methoxy-2,3-dihydropyrrolizin-1-one as a brown oil (68 mg 99%), bp 71 °C (2 Torr); (Found M$^+$ 151.06308, $C_8H_9NO_2$ requires *M* 151.06278) δ_H 7.18 (1H, dd, *J* 2.4, 1.0), 6.74 (1H, dd, *J* 3.8, 1.0), 6.57 (1H, dd, *J* 3.8, 2.4), 5.83 (1H, dd, *J* 6.3, 1.8), 3.38 (3H, s), 3.29 (1H, dd, *J* 18.4, 6.3) and 2.96 (1H, dd, *J* 18.4, 1.8); δ_C 187.19 (quat), 132.90 (quat), 122.35 (CH), 117.62 (CH), 107.95 (CH), 84.32 (CH), 53.73 (CH_3) and 45.93 (CH_2); *m/z* 151 (M$^+$ 25%), 108 (10), 93 (99) and 65 (100).

3-(Phenylsulfanyl)-2,3-dihydropyrrolizin-1-one 179.



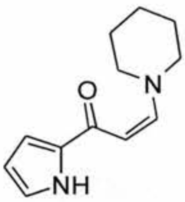
Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in thiophenol (1 cm^3) one drop of Hunigs base was added and the mixture was stirred for 15 min at room temperature. The excess thiophene was removed to give 3-(phenylsulfanyl)-2,3-dihydropyrrolizin-1-one (98 mg, 86%), mp 122 °C; (Found M$^+$ 229.05541, $C_{13}H_{11}NOS$ requires *M* 229.05559); δ_H 7.5 (1H, d, *J* 8.4), 7.10-7.40 (5H, m), 6.63 (1H, dd, *J* 4.0, 1.1), 6.55 (1H, dd, *J* 4.0, 2.4), 5.72 (1H, dd, *J* 7.6, 3.2), 3.44 (1H, dd, *J* 18.6, 7.6) and 2.95 (1H, dd, 18.6, 3.2); δ_C 186.43 (quat), 134.88 (2CH), 132.97 (quat), 129.36 (2CH), 127.48 (CH), 127.12 (quat), 122.17 (CH), 117.68 (CH), 107.82 (CH), 59.33 (CH) and 46.57 (CH_2); *m/z* 229 (M$^+$ 5%), 186 (2), 120 (100), 92 (31) and 65 (95).

3-(Piperidin-1-yl)-2,3-dihydropyrrolizin-1-one 180.



Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in piperidine (1 cm^3) and stirred at room temperature for 15 min. Excess piperidine was evaporated to give 3-(piperidin-1-yl)-2,3-dihydropyrrolizin-1-one (102 mg, >99%); δ_H 7.09 (1H, dd, *J* 2.2, 1.0), 6.67 (1H, dd, *J* 3.9, 1.0), 6.48 (1H, dd, *J* 3.9, 2.2), 5.36 (1H, dd, *J* 7.4, 2.2), 3.17 (1H, dd, *J* 18.5, 7.4), 2.87 (1H, dd, *J* 18.5, 2.2), 2.66 (4H, m) and 1.54 (6H, m); δ_C 188.52 (quat), 133.19 (quat), 123.34 (CH), 116.39 (CH), 106.88 (CH), 75.15 (CH), 47.92 ($2CH_2$), 43.39 (CH_2), 25.76 ($2CH_2$) and 24.28 (CH_2). Other characterisation was carried out on the ring opened product (E)-3-(piperidin-1-yl)-1-(1*H*-pyrrol-2-yl)-propenone **181** due to stability.

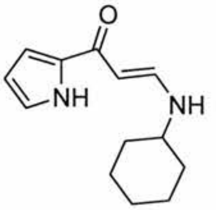
(E)-3-(Piperidin-1-yl)-1-(1*H*-pyrrol-2-yl)-propenone 181.



Method A: solution of 3-piperidin-1-yl-2,3-dihydropyrrolizin-1-one in $CDCl_3$ was left at room temperature for 8 hours, the isomerisation was monitored by NMR spectroscopy. Once the reaction was complete the solvent was removed and the product recrystallised from ethyl acetate/hexane 1/1 to give (E)-3-(piperidin-1-yl)-1-(1*H*-pyrrol-2-yl)-propenone as a white solid (102 mg, >99%), data below.

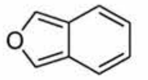
Method B: A solution of pyrrolizin-1-one (60 mg, 0.5 mmol) in piperidine (1 cm^3) was warmed to 50 °C for 5 min, the excess piperidine was removed to give (E)-3-(piperidin-1-yl)-1-(1*H*-pyrrol-2-yl)-propenone (>99%); mp 74 °C; (Found M^+ 204.12556, $C_{12}H_{16}N_2O$ requires *M* 204.12571); δ_H 9.61 (1H, bs), 7.74 (1H, d, *J* 12.7), 6.97 (1H, m), 6.78 (1H, m), 6.28 (1H, m), 5.71 (1H, d, 12.7), 3.38 (4H, m) and 1.70 (6H, m); δ_C 179.24 (quat), 151.24 (CH), 133.78 (quat), 121.66 (CH), 111.36 (CH), 109.84 (CH), 90.61 (CH), 25.61 (CH_2, broad) and 24.09 ($2CH_2$); $2CH_2$ missing due to restricted rotation; δ_H (acetone d_6) 10.76 (1H, bs), 7.60 (1H, d, *J* 12.7), 6.99 (1H, m), 6.82 (1H, m), 6.17 (1H, m), 5.84 (1H, d, *J* 12.7), 3.40 (4H, m) and 1.69 (6H, m); δ_C (acetone d_6) 180.15 (quat), 152.23 (CH), 123.33 (CH), 112.95 (CH), 110.57 (CH), 92.56 (CH), 40.20 ($2CH_2$), 27.19 ($2CH_2$) and 25.57 (CH_2) one quaternary signal over lapping; *m/z* 204 (M^+ 10%), 138 (64) and 84 (100).

(Z)-3-Cyclohexylamino-1-(1*H*-pyrrol-2-yl)-propenone 182.



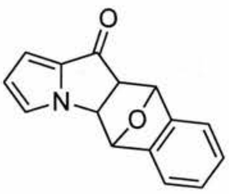
Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in cyclohexylamine (1 cm^3) and stirred at room temperature for 15 min. the excess cyclohexylamine was evaporated to give (*Z*)-3-(cyclohexylamino)-1-(1*H*-pyrrol-2-yl)-propenone (104 mg, 95%), bp 79 °C (2 Torr); (Found M^+ 218.14140, $C_{13}H_{18}N_2O$ requires *M* 218.14136); δ_H 10.11 (1H, bs), 9.85 (1H, bs), 6.92 (2H, m), 6.70 (1H, d *J* 3.2), 6.21 (1H, m), 5.48 (1H, d, *J* 7.0), 3.09 (1H, m), 1.49-2.05 (6H, m) and 1.48-1.01 (4H, m); δ_C 180.90 (quat), 150.85 (CH), 133.13 (quat), 121.72 (CH), 111.02 (CH), 109.76 (CH), 89.52 (CH), 57.06 (CH), 34.04 ($2CH_2$), 25.18 (CH_2) and ($2CH_2$); *m/z* 218 (M^+ 100%), 191 (19), 135 (16) and 94 (15).

Isobenzofuran



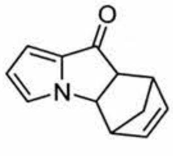
FVP of 1,4-epoxy-1,2,3,4-tetrahydonaphthalene (50 mg), (T_f 650 °C, T_i 52 °C, P 3×10^{-2} Torr, t 15 min) onto the cold finger gives isobenzofuran as a white solid, which is not isolated but instead is directly used in further reactions.

5,10-Epoxy-4a,5,10,10a-tetrahydro-5*H*-benzo[*f*]pyrrolo[2,1-*a*]indol-11-one 192.



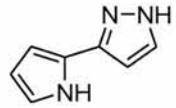
A solution of pyrrolizin-1-one (50 mg) in acetone was added to a cold (-78 °C) solution of freshly prepared isobenzofuran in acetone (1 cm^3). The resulting solution was allowed to warm to room temperature and left to decolourise for 1 h. The solvent was evaporated to give 5,10-epoxy-4a,5,10,10a-tetrahydro-5*H*-benzo[*f*]pyrrolo[2,1-*a*]indol-11-one as a white solid, mp 137 °C, (Found M$^+$ 237.0687, $C_{15}H_{11}NO_2$ requires *M* 237.0790) δ_H 7.27 (1H, m), 7.25 (1H, m), 7.11 (1H, td, *J* 7.4, 1.2), 6.96 (1H, td, *J* 8.6, 1.0), 6.91 (1H, m), 6.22 (1H, dd, *J* 4.0, 2.3), 6.13 (1H, dd, *J* 1.0, 6.1), 5.66 (1H, d, *J* 6.0), 5.60 (1H, d *J* 4.9), 5.25 (1H, dd, *J* 7.2, 4.9) and 4.04 (1H, dd, 6.0, 7.2); δ_C 186.58 (quat), 141.28 (quat), 138.87 (quat), 134.15 (quat), 127.86 (CH), 127.30 (CH), 121.52 (CH), 120.44 (CH), 120.40 (CH), 116.86 (CH), 107.84 (CH), 80.58 (CH), 80.23 (CH), 58.84 (CH) and 58.31 (CH).

5,8-methano-4a,5,8,8a-tetrahydro-5*H*-pyrrolo[2,1-*a*]indol-9-one 189.



A solution of pyrrolizin-1-one (60 mg, 0.5 mmol) in toluene (3 cm^3) was added to cyclopentadiene (33 mg), the solution was heated under reflux for 2 h. The solvent was removed to give 5,8-methano-4a,5,8,8a-tetrahydro-5*H*-pyrrolo[2,1-*a*]indol-9-one (48 mg, 52%), mp 122 °C; (Found M$^+$ 185.08338, $C_{12}H_{11}NO$ requires *M* 185.08352); δ_H 6.95 (1H, d, *J* 1.3), 6.51 (1H, dd, *J* 4.0, 1.0), 6.39 (1H, dd, *J* 4.0, 2.7), 6.14 (1H, dd, *J* 5.5, 3.0), 5.53 (1H, dd, *J* 5.8, 3.4), 4.96 (1H, dd, *J* 4.1, 6.5), 3.47 (1H, dd, *J* 4.4, 6.3), 3.32 (2H, m), 1.82 (1H, dt, 9.1, 1.8) and 1.66 (1H, m); δ_C 191.05 (quat), 136.35 (CH), 135.22 (quat), 131.38 (CH), 121.53 (CH), 116.59 (CH), 106.79 (CH), 59.43 (CH), 56.90 (CH), 50.46 (CH_2), 46.03 (CH) and 43.97 (CH); *m/z* 185 (M$^+$ 10%), 119 (100), 93 (49) and 65 (13).

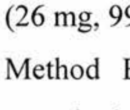
3-(1*H*-Pyrrol-2-yl)-1*H*-pyrazole 183.



Method A: To a solution of 3-chloro-2,3-dihydropyrrolizin-1-one (32 mg, 0.2 mmol) in DCM (0.5 cm^3) hydrazine monohydrate (10 mg, 0.2 mmol) was added with vigorous stirring. After 15 min water was added and the product extracted into DCM. The organic layer was washed with water, dried over $MgSO_4$ and the solvent removed to give 3-(1*H*-pyrrol-2-yl)-1*H*-pyrazole (26 mg, 99%), data below.

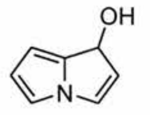
Method B: Pyrrolizin-1-one (60 mg, 0.5 mmol) was dissolved in hydrazine monohydrate (1 cm^3), a red colour immediately developed, after 25 min the red colour had disappeared and the solution had became pale yellow in colour. Water was added (5 cm^3) and the product was extracted into DCM, the organic layer was washed with water, dried over $MgSO_4$ and the solvent removed to give 3-(1*H*-pyrrol-2-yl)-1*H*-pyrazole (66 mg, 99%), bp 68 °C; (Found M$^+$ 133.06332, $C_7H_7N_3$ requires *M* 133.06345); δ_H 9.12 (1H, bs), 7.54 (1H, d, *J* 2.5), 6.81 (1H, m), 6.49 (1H, m), 6.45 (1H, d, *J* 2.5) and 6.27 (1H, m); δ_C 144.65 (quat), 130.88 (CH), 125.24 (quat), 118.28 (CH), 109.28 (CH), 106.36 (CH) and 101.50 (CH); *m/z* 133 (M$^+$ 100%) and 104 (31).

2,3-Dihydropyrrolizin-1-one 163.



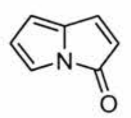
A solution of pyrrolizin-1-one (60 mg, 0.1 mmol), in ethyl acetate (15 cm^3) was hydrogenated over Pd/C (5%) at 10 bar for 1 h; the resulting mixture was filtered through celite to remove the catalyst. Evaporation of the solvent gave 2,3-dihydropyrrolizin-1-one (61 mg, >99%), bp 84 °C [lit.,[40] 82-85 °C]; δ_H 7.04 (1H, dd, *J* 2.3, 1.1), 6.73 (1H, dd, *J* 4.1, 1.1), 6.52 (1H, dd, *J* 4.1, 2.3), 4.31 (2H, t, *J* 6.3) and 3.09 (2H, t, *J* 6.3).

1*H*-Pyrrolizin-1-ol 189.



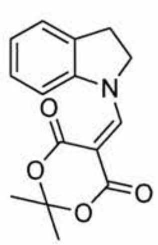
To a stirred suspension of LAH (18 mg, 0.5 mmol) in dry ether (1 cm^3), a solution of pyrrolizin-1-one (60 mg, 0.5 mmol) in dry ether (1 cm^3) was added dropwise. The mixture was allowed to stir at room temperature for 30 min, after which it had decolourised. Wet ether was added (5 cm^3) followed by careful addition of water (5 cm^3). The solution was extracted three times with ether and the organic layer dried over $MgSO_4$, the solvent was evaporated to give 1*H*-pyrrolizin-1-ol as a yellow oil that darkened very rapidly (42 mg, 70%), (rapidly decomposes); (Found 121.05214, C_7H_7NO requires *M* 121.05222); δ_H 6.87 (1H, d, *J* 4.0), 6.68 (1H, m), 6.27 (1H, m), 6.21 (1H, m), 5.78 (1H, m), 5.27 (1H, m) and 1.72 (1H, bs); δ_C 137.52 (quat), 129.48 (CH), 120.76 (CH), 113.30 (CH), 112.02 (CH), 105.31 (CH) and 69.57 (CH); *m/z* 121 (M$^+$ 12%), 94 (100), 78 (10) and 64 (99).

Pyrrolizin-3-one 6.



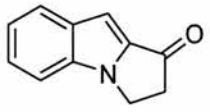
FVP of methyl (E)-3-(pyrrol-1-yl)-acrylate (50 mg, 0.3 mmol), (T_f 900 °C, T_i 65 °C, *P* 3 × 10^{-2} Torr, *t* 20 min) gave pyrrolizin-3-one as a red oil (39 mg, 79%), bp 60 °C (2 Torr) [lit.,[79] bp 35-40 °C (0.05 Torr); δ_H 7.04 (1H, d, *J* 6.0), 6.85 (1H, t, *J* 2.0), 5.95 (2H, d, *J* 2.0) and 5.63 (1H, d, *J* 6.0).

5-(2,3-Dihydro-indol-1-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 146.



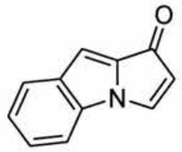
To a solution of MMMA (1.86 g, 10 mmol) in acetonitrile (5 cm^3) indoline (1.17 g, 10 mmol) was added and left to stand at room temperature for 1 h. A yellow precipitate was formed which was filtered off and washed with hexane to give 5-(2,3-dihydro-indol-1-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.99 g, 73%) sufficiently pure for use in the next step, mp 171-173 °C (from ethanol), [lit.,[80] 169-171 °C]; δ_H 8.56 (1H, s), 7.15-7.30 (4H, m), 4.30 (2H, td, *J* 8.0, 1.2), 3.24 (2H, d, *J* 8.0) and 1.71 (6H, s).

2,3-Dihydropyrrolo[1,2-*a*]indol-1-one 145.



FVP of 5-(2,3-dihydro-indol-1-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (50 mg, 0.2 mmol), (T_f 650 °C, T_i 155 °C, P 3×10^{-2} Torr, t 25 min) gave a yellow oil that solidifies to a white solid upon standing overnight this process can be accelerated by refluxing in toluene for 30 min followed by removal of the solvent. The white solid was recrystallised from acetone to give 2,3-dihydropyrrolo[1,2-*a*]indol-1-one as white crystals (27 mg, 91%), mp 145-148 °C [lit.,[81] 145-148 °C]; δ_H 7.74 (1H, d, J 8.1), 7.25 (3H, m), 6.98 (1H, s), 4.29 (2H, t, J 6.3) and 3.11 (2H, t, J 6.3).

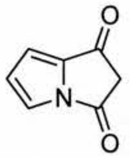
Pyrrolo[1,2-*a*]indol-1-one 143.



The furnace tube was packed with powdered WO_3 (2×10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 500 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of 2,3-dihydropyrrolo[1,2-*a*]indol-1-one (55 mg, 0.3mmol), (T_f 500 °C/ WO_3, T_i 76 °C, P 3×10^{-2} Torr, t 20 min) gave pyrrolo[1,2-*a*]indol-1-one as a orange solid (39 mg, 91%); mp 153 °C; (Found M^+ 169.0226, $C_{11}H_7NO$ requires M 169.0222); δ_H 7.83 (1H, dd, J 4.1, 0.7), 7.58 (1H, d, J 7.9), 7.36 (1H, t, J 8.2), 7.21 (1H, dd, J 8.2, 0.7), 7.09 (1H, td, J 7.9, 0.8), 7.03 (1H, s) and 5.53 (1H, d, J 4.1); δ_C 185.64 (quat), 143.30 (CH), 133.89 (quat), 132.34 (quat), 128.33 (CH), 125.3 (CH), 122.71 (CH), 122.05 (CH), 112.87 (CH), 110.71 (CH) and 109.23 (CH); *m/z* 169 (M^+ 100%), 143 (59), 115 (71), 88 (38) and 70 (30).

Pyrrolizine-1,3-dione experimental.

Pyrrolizine-1,3-dione 6.

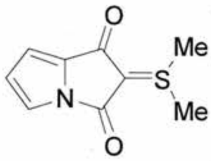


A solution of 1,2-dihydro-1-hydroxypyrrolizin-3-one (0.10 g, 0.7 mmol) in dichloromethane (5 cm^3) was added dropwise to a vigorously stirred suspension of pyridinium chlorochromate (0.63 g, 2.9 mmol) in dichloromethane (5 cm^3). The flask was wrapped in aluminium foil to ensure the absence of light, and nitrogen was constantly bubbled through the suspension to keep it mobile. The mixture was allowed to stir at room temperature for 1 h and was then filtered through a 1 cm silica plug. The filtrate was concentrated, the resulting solid was washed with hexane, and dried *in vacuo* to give pure pyrrolizine-1,3-dione 0.069 g (68%) as a yellow crystalline solid, m.p. 150-151 °C (from ethyl acetate), (Found: M$^+$, 135.0321, $C_7H_5NO_2$ requires M$^+$, 135.0320) (Found: C 61.5; H 3.9; N 9.9%. $C_7H_4NO_2$ requires C 62.2; H 3.7; N 10.4%); δ_H 7.44 (1H, dd, 1 H, *J* 2.9, 0.9), 6.89 (1H, dd, *J* 3.5, 0.9), 6.75 (1H, dd, *J* 3.5, 2.9) and 3.55 (2H, s); δ_C 182.07 (quat), 165.11 (quat), 136.14 (quat), 121.03, 118.55, 112.09 and 44.62 (CH_2); δ_H ([^{2}H]TFA) 7.39 (1H, dd, ^3J 3.0, ^4J 0.8), 6.93 (1H, dd, ^3J 3.7, ^4J 0.8), 6.67 (1H, dd, ^3J 3.7 and 3.0) and 3.64 (s, 2 H); δ_C ([^{2}H]TFA) 186.24 (quat), 167.25 (quat), 134.77 (quat), 122.36, 120.97, 116.03 and 43.64 (CH_2); *m/z* 135 (M$^+$, 100%), 94 (52), 93 (84) and 65 (42); ύ$_{max}$ 3110.62, 2959.23, 2360.44, 1759.73, 1698.02, 1551.45, 1431.89, 1360.53, 1289.18, 1250.61, 1130.08, 1022.09, 937.23, 915. 06, 892.88, 857.20, 775.24 and 600.71 cm^{-1}.

Attempted oxidation of 1,2-dihydro-l-hydroxypyrrolizin-3-one .

(i) 1,2-dihydro-1-hydroxypyrrolizin-3-one (58 mg, 5 mmol) was dissolved in DCM (0.32 cm^3), to this a solution of Deess Martin Periodinane (117 mg, 5 mmol) in DCM (1.2 cm^3) was added and stirred for 20 min.[5] After workup, the ^1H NMR spectrum showed evidence of complete decomposition.

(ii) Manganese dioxide (0.25 g, 9 mmol) was added to a stirred solution of 1,2-dihydro-1-hydroxypyrrolizin-3-one (100 mg, 9 mmol) in chloroform (20 cm^3) at room temperature.[6] After 24 h, the presence of pyrrolizine-1,3-dione was shown by signals at δ_H 7.40 (1H, dd), 6.85 (1H, dd), 6.71 (1H, t) and 3.47 (2H, s), but conversion was only *ca.* 10%.

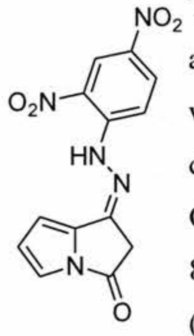


(iii) A solution of dimethylsulfoxide (0.74 g, 9.6 mmol) in dichloromethane (2 cm^3) was added dropwise over 5 min to a solution of oxalyl chloride (0.56 g, 4.4 mmol) in dichloromethane (5 cm^3) at -60 °C.[7] After stirring for 10 min, a solution of 1,2-dihydro-1-hydroxypyrrolizin-3-one (0.27 g, 2 mmol) in dichloromethane (2 cm^3) was added dropwise and the solution was stirred for 30 min. Triethylamine (1.00 g, 10 mmol) was added over 5 min and then the temperature was allowed to rise to 20 °C. Water (6 cm^3) was added, the organic layer was separated and the aqueous phase was extracted with dichloromethane (4 cm^3). The combined organic layers were washed with dilute HCl (4 cm^3), water (4 cm^3), dilute sodium bicarbonate (4 cm^3), water (20 cm^3), dried (Na_2SO_4) and the solvent removed. Dry-flash chromatography on silica, eluting with ethyl acetate/ethanol (3:1) gave 2-(dimethyl-λ^4-sulfanylidene)-pyrrolizine-1,3-dione **195** (12 mg, 3%); (Found: ESI M^+, 196.0432, $C_9H_{10}NO_2S$ requires M^+, 196.0433) δ_H 7.08 (1H, dd, *J* 2.8, 0.9), 6.46 (1H, dd, *J* 3.3, 0.9), 6.23 (1H, dd, *J* 3.2, 2.8) and 3.01 (6H, s); δ_C 181.5 (quat), 167.9 (quat), 131.1 (quat), 125.8 (CH), 117.7 (CH), 111.1 (CH), 64.39 (quat), 30.82 (CH_3); *m/z* 195 (M^+, 69%), 180 (19), 94 (100), 87 (27), 78 (17) and 59 (17).

FVP of 2 over zinc oxide.

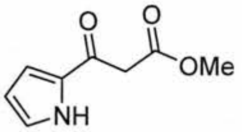
The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 200 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. 1,2-Dihydro-1-hydroxypyrrolizin-3-one (56.4 mg) was subjected to FVP with a plug of zinc oxide (10 g) inserted between two silica wool stoppers, at the centre of the furnace. (T_f 200 °C, t 40 min, P 0.028 Torr); the pyrolysate consisted entirely of pyrrolizine-3-one bp 60 °C (2 Torr) [lit.,[82] bp 35-40 °C (0.05 Torr); δ_H 7.04 (1H, d, *J* 6.0), 6.85 (1H, t, *J* 2.0), 5.95 (2H, d, *J* 2.0) and 5.63 (1H, d, *J* 6.0).

1-(2,4-Dinitrophenylhydrazono)-1,2-dihydropyrrolizin-3-one 199.



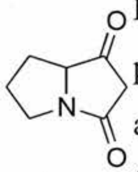
To a solution of pyrrolizine-1,3-dione (20 mg, 0.15 mmol) in ethyl acetate (1 cm^3), Brady's reagent (2 drops) was added, the precipitate was filtered off to give 1-(2,4-dinitrophenylhydrazono)-1,2-dihydropyrrolizin-3-one 89%; mp 189 °C; (Found: M^+, 315.0605, $C_{13}H_9N_5O_5$ requires M^+, 315.0604) δ_H 11.41 (1H, s), 9.19 (1H, d, *J* 9.2), 8.40 (1H, dd, *J* 2.5, 9.5), 8.08 (1 H, d, *J* 9.5), 7.45 (1H, d, J 3.0), 7.23 (1H, d, *J* 3.7) 6.83 (1H, m) and 3.54 (2H, s); δ_C 166.0 (quat), 144.7 (quat), 139.1 (quat), 130.2 (CH), 123.4 (CH), 121.1 (CH), 116.5 (CH), 116.4 (CH), 111.7 (CH) and 40.7 (CH_2) 3 quat not apparant, *m/z* 315 (M^+ 86%), 193 (45), 84.0 (100) and (71).

Methyl 3-oxo-3-(1*H*-pyrrol-2-yl)-propionate 200.



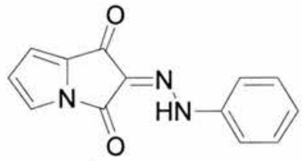
Pyrrolizine-1,3-dione (0.02 g, 0.15 mmol) was dissolved in methanol (1 cm^3) and *N,N*-diisopropylethylamine (1 drop) was added. The solution became deep red in colour, then the solvent was removed to yield methyl 3-oxo-3-(1*H*-pyrrol-2-yl)-propionate (0.025 g, 99%) bp 65 °C (0.3 Torr) as a red oil; (Found: M^+, 167.0577, $C_8H_9NO_3$ requires M^+, 167.0577) δ_H 9.73 (1H, br. s), 7.10 (1H, m), 6.96 (1H, m), 6.31 (1H, dt, ^3J 3.9 and 2.3), 3.82 (2H, s) and 3.75 (3H, s); δ_C 181.74 (quat), 167.98 (quat), 131.13 (quat), 125.97, 118.11, 111.23, 52.50 (CH_3) and 45.13 (CH_2); *m/z* 167 (M^+ 19%), 94 (100), 66 (38) and 44 (35).

Pyrrolizidine-1,3-dione 201.



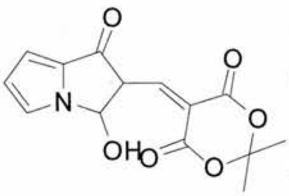
Palladium on charcoal (5%, 10 mg) was added to a solution of pyrrolizine-l,3-dione (20 mg, 0.15 mmol) in ethyl acetate (20 cm^3) and the mixture was hydrogenated at 3 atm for 3 h. The catalyst was filtered off on celite and the solvent removed to give a mixture of pyrrolizidine-1,3-dione (88%) and 1-hydroxypyrrolizidin-3-one (12%). Pyrrolizidine-1,3-dione δ_H 4.00-4.18 (1H, m), 3.76-3.9 (1H, m), 3.26 (1H, d, J 21.2), 3.05-3.20 (1H, m), 2.89 (1H, dd, J 21.2, 1.5), 1.80-2.15 (3H, m) and 1.50-1.69 (1H,m).[83] δ_C 205.84 (quat), 170.34 (quat), 69.99 (CH), 45.49 (CH_2), 43.21 (CH_2), 26.47 (CH_2) and 25.80 (CH_2). 1-Hydroxypyrrolizidin-3-one: 173.19 (quat), 67.87 (CH), 66.84 (CH), 45.49 (CH_2), 41.40 (CH_2), 27.10 (CH_2) and 22.92 (CH_2) consistent with literature data.[12] Products were identified by comparison of the NMR spectrum of the mixture with those of authentic samples.[12,83]

2-(Phenylhydrazono)-pyrrolizine-1,3-dione 203.



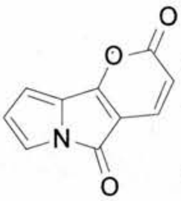
Benzenediazonium tetrafluoroborate (0.028 g, 0.15 mmol) was added to a solution of pyrrolizine-1,3-dione (0.02 g, 0.15 mmol) in dichloromethane (0.5 cm^3). *N,N*-Diisopropylethylamine was added dropwise to this stirred suspension until all solid had dissolved. After 15 min stirring a precipitate had formed, so the solvent was evaporated and the organic material was dissolved in ether leaving behind all inorganic material. Removal of the solvent yielded 2-(phenylhydrazono)-pyrrolizine-1,3-dione as a intense orange solid (0.043 g, 99%), m.p. 113 °C :(Found: M$^+$, 239.06893, $C_{13}H_9N_2O_2$ requires M$^+$, 239.06797) δ_H 13.22 (1H, s, 1 H), 7.43-7.51 (3H, m), 7.38 (2H, t, *J* 7.3), 7.21 (1H, t, *J* 7.3), 6.91 (1H, d, *J* 3.4) and 6.60 (1H, t, *J* 3.3); δ_C 176.00 (quat), 158.34 (quat), 140.83 (quat), 132.53 (quat), 129.39 (2CH), 127.15 (quat), 126.00, 119.73, 118.78, 115.95 (2CH) and 113.40; *m/z* 239 (M$^+$, 100%), 162 (10), 147 (63), 103 (20), 94 (98), 77 (100) and 51 (46).

5-(3-Hydroxy-1-oxo-1*H*-pyrrolizin-2-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 204.



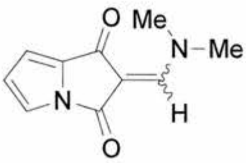
5-Methoxymethylene-2,2-dimethyl-[1,3]dioxane-4,6-dione **14** (0.032 g, 0.15 mmol) was added to a solution of pyrrolizine-1,3-dione (0.02 g, 0.15 mmol) in dichloromethane (1 cm^3). The solution was stirred for 15 min then hexane (5 cm^3) was added until a red oil settled; the yellow solvent layer was discarded. The red oil was then treated with dilute hydrochloric acid (2 M, 2 cm^3) and the organics extracted into dichloromethane. Removal of the solvent yielded 5-(3-hydroxy-1-oxo-1*H*-pyrrolizin-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **15** (0.042 g, 81%) as a red solid, m.p. 156 °C (Found: M$^+$, 289.05892, $C_{14}H_{11}NO_6$ requires M$^+$, 289.05809); δ_H 8.42 (1H, s), 7.47 (1H, d, *J* 2.5), 6.98 (1H, d, *J* 3.4), 6.58 (d, 1H, *J* 3.2 Hz), 1.78 (3H, s) and 1.76 (1H, br.s); δ_C 177.81 (quat), 176.91 (quat), 162.42 (2 quat), 144.62, 130.97 (quat), 122.78, 119.47, 117.72, 104.98 (2 quat), 96.18 (quat) and 26.75 (2Me), *m/z* 289 (M$^+$ 5%), 231 (57), 159 (100), 94 (38) and 57 (61).

4-Oxa-8a-azacyclopenta[*a*]indene-5,8-dione 206.



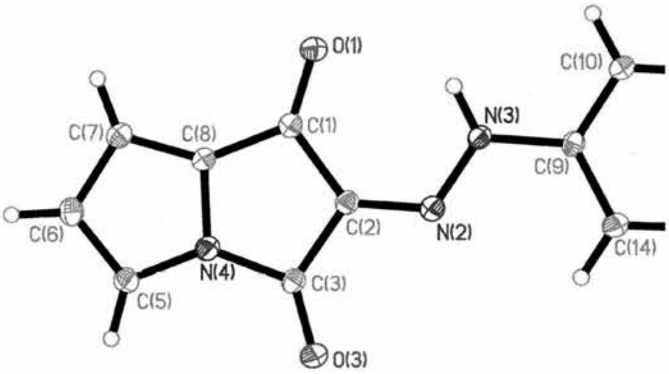
5-(3-Hydroxy-1-oxo-1*H*-pyrrolizin-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.02 g, 0.03 mmol) was subjected to FVP (T_f 700 °C, T_i 110 °C, *P* 0.034 Torr, *t* 15 min) to yield 4-oxa-8a-aza-cyclopenta[*a*]indene-5,8-dione as a dark orange solid (0.014 g, 96%) m.p. 125-127 °C (Found: M$^+$, 187.02639, $C_{10}H_5NO_3$ requires M$^+$, 187.02707); δ_H 7.51 (1H, d, *J* 9.5), 7.15 (1H, dd, *J* 3.9, 0.8), 6.51 (1H, dd, *J* 3.9 , 0.8), 6.21 (1H, t, *J* 3.9) and 6.03 (1H, d, *J* 9.5); δ_C 166.81 (quat), 159.12 (quat), 158.8 (quat), 137.98, 127.65 (quat), 121.47, 116.75, 114.26, 108.90 and 106.77 (quat) *m/z* 187 (M$^+$ 71%), 159 (100), 103 (32) and 94 (39).

2-(1-Dimethylaminomethylene)-pyrrolizine-1,3-dione 208.



Pyrrolizine-1,3-dione **4** (0.02 g, .015 mmol) was dissolved in chloroform (1 cm^3), to this solution *N,N*-dimethylformamide dimethyl acetal was added (3 drops). The solution instantly became black and the solvent was removed leaving a black solid. The residue was dissolved in dichloromethane and decolourising charcoal (0.5 g) was added, after filtration through celite the solvent was removed giving 2-(1-dimethylaminomethylene)-pyrrolizine-1,3-dione **19** (0.027 g, 95%) m.p 103 °C as an off white solid. This was 1:1 mixture of the E/Z isomers;(Found: M$^+$, 190.07412, $C_{10}H_{10}N_2O_2$ requires M$^+$, 190.07368); δ_H 7.82 (1H, s), 7.72 (1H, s), 7.65-7.67 (2H, m), 7.05-7.08 (2H, m), 6.86 (2H, m), 4.13 (3H, m), 4.03 (3H, s) and 3.85 (6H); δ_C 184.1 (quat), 183.7 (quat), 167.2 (2 quat), 135.6 (quat), 134.5 (quat), 122.9 (CH), 121.3 (CH), 120.0 (CH), 119.4 (CH),118.5 (CH), 116.3 (CH), 115.3 (CH), 27.6 (2 Me), 26.5 (Me) and 25.7 (Me); *m/z* 190 (M$^+$ 68%), 94 (100), 85(42) and 65 (38).

Crystal data and structure refinement for 2-(1-Dimethylaminomethylene)-pyrrolizine-1,3-dione HM7001_cif.[84]



A. CRYSTAL DATA

Empirical formula	$C_{13} H_9 N_3 O_2$
Formula weight	239.23
Wavelength	0.71073 A
Temperature	150 K
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 6.1911(3) A alpha = 90 deg. b = 7.8957(4) A beta = 91.924(3) deg. c = 21.7772(10) A gamma = 90 deg.
Volume	1063.94(9) A^3
Number of reflections for cell	4523 (3 < theta < 30 deg.)
Z	4
Density (calculated)	1.493 Mg/m^3
Absorption coefficient	0.105 mm^-1
F(000)	496

B. DATA COLLECTION

Crystal description	yellow block
Crystal size	1.27 x 0.63 x 0.35 mm
Instrument	Bruker SMART
Theta range for data collection	1.871 to 30.551 deg.
Index ranges	-7<=h<=8, -11<=k<=11, -28<=l<=30
Reflections collected	12310

Independent reflections	3085 [R(int) = 0.032]
Scan type	\w
Absorption correction	Semi-empirical from equivalents (Tmin= 0.82, Tmax=0.96)

C. SOLUTION AND REFINEMENT.

Solution	direct (SIR92 (Altomare et al., 1994))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	noref
Data	3085
Restraints	0
Parameters	163
Goodness-of-fit on F^2	0.9740
Conventional R [F>4sigma(F)]	R1 = 0.0464 [2337 data]
Rw	0.1205
Final maximum delta/sigma	0.000720
Weighting scheme	Sheldrick Weights
Largest diff. peak and hole	0.37 and -0.38 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for hm7001. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	1618(2)	1972(1)	5099(1)	23
O(1)	3431(1)	1387(1)	5189(1)	30
C(2)	256(2)	1794(1)	4534(1)	23
C(3)	-1859(2)	2615(1)	4617(1)	24
O(3)	-3400(1)	2771(1)	4271(1)	32
N(4)	-1687(2)	3262(1)	5228(1)	25
C(5)	-2952(2)	4151(2)	5618(1)	27
C(6)	-1745(2)	4403(2)	6151(1)	29
C(7)	309(2)	3653(2)	6087(1)	27
C(8)	308(2)	2946(1)	5512(1)	22
N(2)	684(2)	1080(1)	4011(1)	23
N(3)	2591(2)	406(1)	3941(1)	24
C(9)	3051(2)	-358(1)	3374(1)	22
C(10)	5126(2)	-958(2)	3294(1)	26
C(11)	5615(2)	-1721(2)	2741(1)	30
C(12)	4051(2)	-1875(2)	2274(1)	31
C(13)	1988(2)	-1279(2)	2364(1)	29
C(14)	1460(2)	-507(1)	2909(1)	26

Table 3. Bond lengths [A] and angles [deg] for hm7001.

C(1)-O(1)	1.2236(14)
C(1)-C(2)	1.4761(15)
C(1)-C(8)	1.4512(15)
C(2)-C(3)	1.4774(16)
C(2)-N(2)	1.3045(14)
C(3)-O(3)	1.2023(14)
C(3)-N(4)	1.4260(14)
N(4)-C(5)	1.3685(15)
N(4)-C(8)	1.3852(14)
C(5)-C(6)	1.3730(16)
C(5)-H(5)	0.950
C(6)-C(7)	1.4141(17)
C(6)-H(6)	0.950
C(7)-C(8)	1.3711(16)
C(7)-H(7)	0.950
N(2)-N(3)	1.3091(13)
N(3)-C(9)	1.4106(14)
N(3)-H(3)	0.880
C(9)-C(10)	1.3857(16)
C(9)-C(14)	1.3936(15)
C(10)-C(11)	1.3883(16)
C(10)-H(10)	0.950
C(11)-C(12)	1.3871(16)
C(11)-H(11)	0.950
C(12)-C(13)	1.3812(18)
C(12)-H(12)	0.950
C(13)-C(14)	1.3845(17)
C(13)-H(13)	0.950
C(14)-H(14)	0.950

O(1)-C(1)-C(2)	126.40(10)
O(1)-C(1)-C(8)	129.00(10)
C(2)-C(1)-C(8)	104.58(9)
C(1)-C(2)-C(3)	109.83(9)
C(1)-C(2)-N(2)	129.90(10)
C(3)-C(2)-N(2)	120.26(10)
C(2)-C(3)-O(3)	130.96(11)
C(2)-C(3)-N(4)	103.50(9)
O(3)-C(3)-N(4)	125.53(11)
C(3)-N(4)-C(5)	137.44(10)
C(3)-N(4)-C(8)	112.91(9)
C(5)-N(4)-C(8)	109.63(9)
N(4)-C(5)-C(6)	106.97(10)
N(4)-C(5)-H(5)	126.5
C(6)-C(5)-H(5)	126.5
C(5)-C(6)-C(7)	108.80(10)
C(5)-C(6)-H(6)	125.6

C(7)-C(6)-H(6)	125.6
C(6)-C(7)-C(8)	106.71(11)
C(6)-C(7)-H(7)	126.6
C(8)-C(7)-H(7)	126.6
C(1)-C(8)-N(4)	109.12(9)
C(1)-C(8)-C(7)	142.98(11)
N(4)-C(8)-C(7)	107.89(10)
C(2)-N(2)-N(3)	119.28(10)
N(2)-N(3)-C(9)	119.12(9)
N(2)-N(3)-H(3)	120.4
C(9)-N(3)-H(3)	120.4
N(3)-C(9)-C(10)	118.16(10)
N(3)-C(9)-C(14)	120.82(10)
C(10)-C(9)-C(14)	121.02(10)
C(9)-C(10)-C(11)	119.20(11)
C(9)-C(10)-H(10)	120.4
C(11)-C(10)-H(10)	120.4
C(10)-C(11)-C(12)	120.46(11)
C(10)-C(11)-H(11)	119.8
C(12)-C(11)-H(11)	119.8
C(11)-C(12)-C(13)	119.51(11)
C(11)-C(12)-H(12)	120.2
C(13)-C(12)-H(12)	120.2
C(12)-C(13)-C(14)	121.17(11)
C(12)-C(13)-H(13)	119.4
C(14)-C(13)-H(13)	119.4
C(9)-C(14)-C(13)	118.63(11)
C(9)-C(14)-H(14)	120.7
C(13)-C(14)-H(14)	120.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for hm7001.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

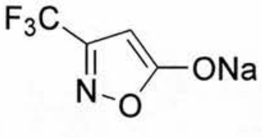
	U11	U22	U33	U23	U13	U12
C(1)	23(1)	22(1)	22(1)	1(1)	1(1)	-4(1)
O(1)	24(1)	40(1)	28(1)	-1(1)	-1(1)	1(1)
C(2)	24(1)	24(1)	21(1)	1(1)	1(1)	-2(1)
C(3)	27(1)	24(1)	21(1)	2(1)	0(1)	-1(1)
O(3)	28(1)	42(1)	26(1)	1(1)	-4(1)	4(1)
N(4)	27(1)	26(1)	23(1)	0(1)	-1(1)	1(1)
C(5)	27(1)	26(1)	28(1)	-1(1)	2(1)	3(1)
C(6)	33(1)	27(1)	27(1)	-4(1)	4(1)	1(1)
C(7)	30(1)	26(1)	24(1)	-2(1)	-2(1)	-1(1)
C(8)	23(1)	21(1)	22(1)	1(1)	-1(1)	-1(1)
N(2)	24(1)	23(1)	23(1)	1(1)	1(1)	-2(1)
N(3)	22(1)	29(1)	20(1)	-2(1)	-1(1)	-2(1)
C(9)	27(1)	21(1)	18(1)	1(1)	1(1)	-2(1)
C(10)	27(1)	29(1)	22(1)	1(1)	-2(1)	1(1)
C(11)	31(1)	31(1)	29(1)	-1(1)	3(1)	7(1)
C(12)	43(1)	27(1)	22(1)	-3(1)	1(1)	4(1)
C(13)	37(1)	28(1)	23(1)	-1(1)	-7(1)	1(1)
C(14)	26(1)	26(1)	25(1)	1(1)	-3(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for hm7001.

	x	y	z	U(eq)
H(5)	-4392	4523	5536	32
H(6)	-2214	4984	6504	35
H(7)	1466	3642	6385	32
H(14)	42	-87	2966	31
H(13)	911	-1401	2045	35
H(12)	4395	-2386	1894	37
H(11)	7032	-2141	2683	36
H(10)	6201	-849	3613	31
H(3)	3573	429	4242	36

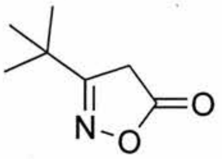
Azaindolizine and Cyclazine Experimental.

3-Trifluoromethyl-5 hydroxyisoxazole sodium salt 262.



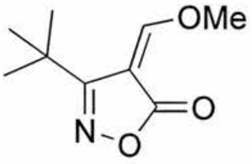
To a solution of hydroxylamine hydrochloride (2.33 g, 32.6 mmol) in ethanol (55 cm^3) cooled in an ice bath, sodium ethoxide (from 0.75g Na in ethanol 15 cm^3) was added, followed by the addition of ethyl trifluoro acetoacetate (5.0 g, 32.6 mmol). The resulting solution was heated under reflux for 4 h before cooling and the addition of further sodium ethoxide (0.75g Na in 15 cm^3 ethanol). This was allowed to stand at 4 °C overnight. A few drops of phenolphthalein was added and sodium ethoxide was added until the reaction mixture had became pale red, the precipitate was filtered off and washed with ethanol to give 3-trifluoromethyl-5 hydroxyisoxazole sodium salt (5.0 g, 80%), mp 207 °C [lit.,[85] 210 °C]; δ_H 4.22 (1H, s); δ_C 178.24 (quat), 154.98 (quat, q, *J* 33.7), 121.32 (quat, q, *J* 270.3) and 66.56 (CH).

3-*tert*-Butyl-4*H*-isoxazol-5-one 263.



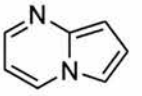
A solution of ethyl pivaloylacetate (4.0 g, 22 mmol) and hydroxylamine hydrochloride (3.1 g, 44 mmol) in methanol/water 3/1, was stirred overnight at room temperature. The methanol was removed and the aqueous layer extracted three times with ethyl acetate (50 cm^3), dried over $MgSO_4$, the solvent was removed to give 3-*t*-Butyl-4*H*-isoxazol-5-one (2.1 g, 68%): mp 108-109 °C [lit.,[86] 107-108°C]. δ_H 3.42 (2H, s) and 1.25 (9H, s), δ_C 175.5 (quat), 173.5 (quat), 34.6 (quat), 33.2 (CH_2) and 27.4 ($3CH_3$).

3-*t*-Butyl-4-[1-methoxymeth-(Z)-ylene]-4*H*-isoxazol-5-one 265.



A solution of 3-*t*-butyl-4*H*-isoxazol-5-one (1.61g, 11.2 mmol) in trimethylorthoformate (8 cm^3) was heated under reflux for 15 min. The solvent was removed and the white solid washed with hexane to give 3-*tert*-butyl-4-[1-methoxymeth-(Z)-ylene]-4*H*-isoxazol-5-one (1.72 g, 84%) mp 122-123 °C. (Found M$^+$ 183.08833 . $C_9H_{13}NO_3$ reqiures M 183.08899); δ_H 7.46 (1H, s), 4.24 (3H, s) and 1.27 (9H, s); δ_C 173.5 (quat), 167.2 (quat), 164.6 (CH), 99.9 (quat), 65.1 (CH_3), (34.1 quat) and 26.8 ($3CH_3$); *m/z* 183 (M$^+$,43%), 168 (100), 142 (60) and 69 (30).

Pyrrolo-[1,2-*a*]-pyrimidine 7.

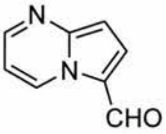


The furnace tube was packed with powdered WO_3 (2 × 10 g), held in place by loose plugs of silica wool and the catalyst was conditioned by heating in air at 600 °C for 30 min. The furnace temperature was reset to 450 °C, the FVP apparatus was assembled and the pyrolysis carried out in the usual way. To avoid disruption of the catalyst packing, care must be taken when the vacuum is applied and released, but otherwise no special precautions were taken. FVP of DBN over WO_3 (50 mg), (T_f 450 °C, T_i 65 °C, P 3 × 10^{-2} Torr, t 20 min), gave pyrrolo-[1,2-*a*]-pyrimidine, lit.,[49] as a yellow oil, (45 mg, 94%) bp 61 °C (2 mm Hg); δ_H 8.15 (1H, ddd, J 7.0, 1.6, 1.0), 8.06 (1H, dd, J 3.8, 1.6), 7.18 (1H, dd, J 3.0, 1.6), 6.96 (1H, dd, J 4.0, 3.0), 6.62 (1H, dd, J 4.0, 1.0) and 6.48 (1H, dd, J 7.0, 3.8); δ_C 142.92 (CH), 140.24 (quat), 131.66 (CH), 116.07 (CH), 109.60 (CH), 106.18 (CH) and 98.61 (CH); δ_H (TFA) 9.71 (1H, d, J 6.9), 9.07 (1H, d, J 5.3), 8.45 (1H, d, J 3.1), 8.08 (1H, dd, J 3.1, 4.2), 7.72 (1H, dd, J 5.3, 6.9) and 7.63 (1H, d, J 4.2).

FVP of pyrrolo-[1,2-*a*]-pyrimidine

FVP of pyrrolo-[1,2-*a*]-pyrimidine (50 mg), (T_f 950 °C/ silica wool, T_i 25 °C, P 3 × 10^{-2} Torr, t 20 min) dry flash chromatography (hexane : ethyl acetate 2:1), gave a mixture of unreacted starting material (8%), 4-azaindole (25%), mp 122-123 °C [lit.,[87] 124-125]; δ_H 8.49 (1H d, J 5.2), 7.71 (1H, d, J 7.5), 7.48 (1H, m), 7.13 (1H, d, J 5.2) and 6,76 (1H, m), and 7-azaindole; mp 105-106 °C [lit.,[88] 105-106 °C], δ_H 12.00 (1H, bs), 8.35 (1H, d, J 4.8), 7.96 (1H, d, J 7.9), 7.39 (1H, m), 7.10 (1H, m) and 6.51 (1H, d, J 3.5). consistent with specta reported earlier.

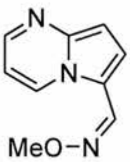
Pyrrolo-[1,2-*a*]-pyrimidine-6-carbaldehyde 245.



To a stirred solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg) in DMF (1 cm ^{3}) was added $POCl_3$ in DMF (1 cm^3).

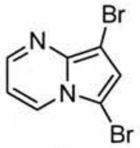
Work up A: After 20 min the solution was poured into aqueous NaOH (2M) and extracted with DCM. Evaporation of the DCM yielded no organic material. Work up B: After 20 min the solution was poured into aqueous NaOH (2M) and extracted with DCM. Evaporation of the DCM followed by recrystallisation from petroleum ether gave pyrrolo-[1,2-*a*]-pyrimidine-6-carbaldehyde as yellow crystals (25 mg 40%), mp 121-122 °C, [lit.,[49] 121-122 °C]; δ_H 9.82 (1H, d, *J* 7.0), 9.72 (1H, s), 8.47 (1H, d, *J* 4.0), 7.62 (1H, d, *J* 5.0), 6.94 (1H, dd, *J* 4.0, 7.0) and 6.75 (1H, d, *J* 5.0).

Pyrrolo-[1,2-*a*]-pyrimidine-6-carbaldehyde *O*-methyl oxime 246.



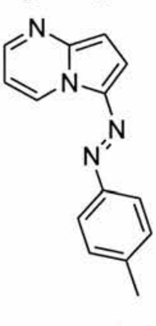
To a stirred solution of pyrrolo-[1,2-*a*]-pyrimidine-6-carbaldehyde (25 mg, 0.17 mmol) was added *O*-methylhydroxylamine hydrochloride (14 mg, 0.17 mmol). After 5 min water (5 cm^3) was added and the product was extracted into DCM and dried over $MgSO_4$. Evaporation of the solvent gave a mixture of isomers of pyrrolo-[1,2-*a*]-pyrimidine-6-carbaldehyde *O*-methyl oxime (29 mg, >99%), mp 134-138 °C; (Found M^+ 175.07391, $C_9H_9N_3O$ requires *M* 175.07401); major isomer δ_H 9.40 (1H, dm, *J* 7.1), 8.28 (1H, s), 8.26 (1H, d, *J* 4.0), 7.15 (1H, d, *J* 4.3), 6.79 (1H, dd, *J* 7.1, 4.0), 6.72 (1H, d, *J* 4.3) and 4.00 (3H, s); δ_C 144.58 (CH), 143.24 (quat), 141.86 (CH), 131.25 (CH), 122.06 (CH), 113.75 (quat), 107.74 (CH), 100.82 (CH) and 62.03 (CH_3); minor isomer: δ_H 8.40 (1H, d, *J* 7.2), 7.88 (1H, d, *J* 4.5), 7.59 (1H, s), 6.70 (1H, d, *J* 4.1) and 4.09 (3H, s) 2H overlapping; δ_C 144.98 (CH), 129.41 (CH), 124.09 (CH), 107.45 (CH) and 101.43 (CH) 1CH, 2quat and 1CH_3 overlapping; *m/z* 175 (M^+,100%), 160 (39), 143 (96), 117 (95), 90 (90) and 63 (81).

6,8-Dibromopyrrolo-[1,2-*a*]-pyrimidine 247.



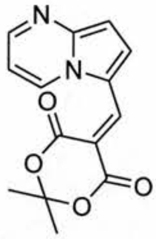
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg) in DCM, Br_2 solution in DCM (1M, 0.8 cm^3) was added dropwise, a precipitate immediately formed and was filtered off and washed with DCM before drying under vacuum to give 6,8-dibromopyrrolo-[1,2-*a*]-pyrimidine as its di HBr salt, mp >240 °C, (Found C, 19.25; H, 0.85; N, 6.3. $C_7H_4Br_2N_2$.2HBr requires C, 19.2; H, 1.35; N, 6.4%), (Found M^+ 273.87376, $C_7H_4Br_2N_2$ requires *M* 273.87357); δ_H 8.45 (1H, dd, *J* 1.6, 7.2), 8.21 (1H, dd, *J* 3.9, 1.6), 7.33 (1H, s) and 6.93 (1H, dd, *J* 7.2, 3.9); δ_C 144.88 (CH, dddd, *J* 186.0, 6.3, 3.1, 0.4), 137.11 (quat, m), 131.31 (CH, dm, *J* 188.7), 118.97 (CH, d, *J* 182.4), 108.69 (CH, ddd, *J* 172.5, 9.7, 2.6), 91.20 (quat, t, *J* 3.2) and 84.97 (quat, m); *m/z* 275 (M^+ 100%), 277 (48), 273 (50), 195 (16), 116 (31) and 80 (12).

6-*p*-Tolylazopyrrolo[1,2,*a*]pyrimidine 248.



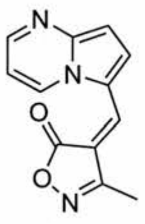
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg) in DCM tolyldiazonium fluoroborate was added along with two drops of Hunigs base. After 5 min a dark red colour had developed, the solvent was remove and dry flash chromatography (hexane: ethyl acetate, 4:1) gave 6-*p*-tolylazopyrrolo[1,2,*a*]pyrimidine as a red solid (71 mg 71%), mp 152-154 °C, (Found M^+ 237.114065, $C_{14}H_{13}N_4$ requires *M* 237.114020) δ_H (360 MHz, 50 °C) 9.62 (1H, d, *J* 7.2), 8.33 (1H, d, 4.0), 7.74 (2H, d *J* 8.3), 7.61 (1H, *J* 4.7), 7.27 (2H, d, *J* 8.3), 6.85 (1H, d, *J* 4.7), 6.82 (1H, dd, 7.2, 4.0) and 2.31 (CH_3); δ_C (360 MHz, 50 °C) 151.78 (quat), 146.62 (CH), 143.16 (quat), 139.45 (quat), 134.50 (quat), 131.58 (2CH), 129.63, 22.31 (3H, sCH), 129.36 (CH), 121.66 (2CH), 109.04 (2CH), 103.59 (CH) and 21.24 (CH_3), *m/z* (ESI) 237 (M^+ 100%), 116 (65) and 70 (52).

2,2-Dimethyl-5-pyrrolo[1,2-*a*]pyrimidin-6-ylmethylene-[1,3]dioxane-4,6-dione 249.



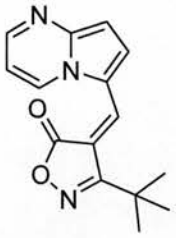
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg, 0.4 mmol) in acetonitrile (0.5 cm^3) was added MMMA (79 mg, 0.4 mmol) and the mixture was stirred at room temperature (15 min). The solvent was removed and the residue recrystallised from ethanol to give 2,2-dimethyl-5-pyrrolo[1,2-*a*]pyrimidin-6-ylmethylene-[1,3]dioxane-4,6-dione as a red solid (from ethanol) (60 mg, 52%), mp 181-182 °C (decomp); (Found M$^+$ 272.0796, $C_{14}H_{12}N_2O_4$ requires *M* 272.0797) δ_H 9.08 (1H, d, *J* 5.2), 8.87 (1H, d, *J* 7.0), 8.6 (1H, s), 8.58 (1H, d, *J* 4.1), 7.06 (1H, dd, *J* 7.0, 4.1), 6.98 (1H, d, *J* 5.2) and 1.79 (6H, s); δ_C 161.34 (quat), 165.29 (quat), 151.06 (CH), 150.91 (quat), 135.05 (CH), 132.99 (CH), 131.97 (CH), 119.95 (quat), 110.35 (CH), 108.33 (CH), 103.83 (quat), 100.31 (quat) and 27.34 (2CH$_3$); *m/z* 272 (M$^+$, 55%), 214 (43), 170 (100) and 142 (99).

3-Methyl-4-[1-pyrrolo[1,2-*a*]pyrimidin-6-ylmethylene]-4*H*-isoxazol-5-one 261.



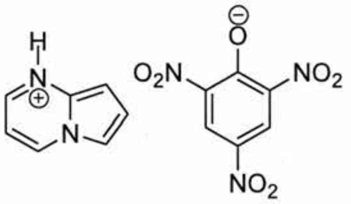
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg 0.3 mmol) in acetonitrile (0.5 cm^3) 4-[1-methoxy-methylene]-3-methyl-4*H*-isoxazol-5-one (0.3 mmol) was added; after 5 min the product had precipitated from solution. The precipitate was filtered off and recrystallised from acetonitrile to give 3-methyl-4-[1-pyrrolo[1,2-*a*]pyrimidin-6-ylmethylene]-4*H*-isoxazol-5-one (46 mg, 68%) as a red solid, mp > 300 °C; (Found M$^+$ 227.0694, $C_{11}H_9N_3O_2$ requires *M* 227.0694) δ_H 9.66 (1H, d, *J* 6.9), 9.09 (1H, d, *J* 5.1), 8.67 (1H, d, *J* 4.2), 8.08 (1H, s), 7.34 (1H, dd, *J* 6.9, 4.2), 7.02 (1H, d, *J*, 5.1) and 2.32 (3H, s); δ_C 162.18 (quat), 151.59 (CH), 147.34 (quat), 134.42 (CH), 130.03 (CH), 129.71 (CH), 120.21 (quat), 110.32 (CH), 106.72 (CH), 105.25 (CH), 104.28 (quat) and 12.79 (CH$_3$); *m/z* 227 (M$^+$, 75%), 186 (100), 116 (48) and 41 (34).

3-*t*-Butyl-4-[1-pyrrolo[1,2-*a*]pyrimidin-6-yl-methylene]-4*H*-isoxazol-5-one 266.



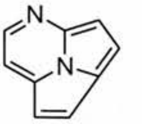
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (400 mg 2.4 mmol) in acetonitrile (2 cm^3) 3-*tert*-butyl-4-[1-methoxymethylene]-4*H*-isoxazol-5-one (320 mg, 2.4 mmol) was added. After 15 min the solvent was removed and the product purified by chromatography (hexane/ethylacetate 1/1) to give 3-*tert*-butyl-4-[1-pyrrolo[1,2-*a*]pyrimidin-6-yl-methylene]-4*H*-isoxazol-5-one as a red solid (256 mg, 40%), mp >270 ˚C,(Found M$^+$ 257.1169, $C_{14}H_{15}N_3O_2$ requires *M* 257.1164) δ_H 9.13 (1H, d, *J* 4.8), 8.45 (1H, d, *J* 4.0), 8.48 (1H, d, *J* 7.0), 7.88 (1H, s), 7.06 (1H, dd, *J* 7.0, 4.0), 6.98 (1H, d, *J* 4.8) and 1.50 (9H, s); δ_C 168.87 (quat), 149.71 (CH), 148.20 (quat), 131.24 (CH), 131.07 (CH), 128.85 (CH), 119.50 (quat), 109.98 (CH), 107.52 (CH), 106.69 (quat), 34.44 (quat) and 29.07 (3CH$_3$); *m/z* 257 (M$^+$ 87%), 178 (100), 115 (42) and 81 (32).

Pyrrolo[1,2-*a*]pyrimidin-1-ium picrate



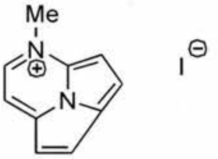
To a solution of pyrrolo-[1,2-*a*]-pyrimidine (50 mg), an ethanolic solution of picric acid was added until no more precipitate was formed (4 drops). The precipitate was filtered and recrystallised from ethanol to give pyrrolo[1,2-*a*]pyrimidin-1-ium picrate (142 mg, 97%), mp 163 ºC (decomp); (Found C, 45.38; H, 2.82; N, 19.62. $C_{13}H_9N_5O_7$ requires C, 44.98; H, 2.61; N, 20.16%) δ_H 8.82 (1H, dt, *J* 7.0, 1.5), 8.59 (2H, s), 8.21 (1H, dd, *J* 4.1, 1.5), 7.57 (1H, dd, *J* 3.0, 1.5), 7.02 (1H, dd, *J* 4.1, 3.0), 6.77 (1H, dd, *J* 7.0, 4.1) and 6.54 (1H, dt, *J* 4.0, 1.5); δ_C 160.60 (quat, t, *J* 6.1), 142.83 (CH, ddd, *J* 185.1, 6.4, 3.2), 141.76 (quat, m), 137.09 (quat, m), 134.92 (CH, dm, *J* 185.2), 125.13 (2CH, dd, *J* 168.1, 5.7), 124.3 (quat, t, *J* 4.8), 116.27 (CH, ddd, *J* 171.6, 7., 3.6), 111.22 (CH, dt, *J* 193.1, 7.9), 105.8 (CH, dd, *J* 172.3, 8.7, 3.3) and 96.8 (CH, ddd, *J* 176.1, 5.7, 4.1) 1 quat overlapping; *m/z* +ESI 119 (M$^+$, 100%) and -ESI 228 (M$^-$, 100).

Pyrimido[2,1,6-*cd*]pyrrolizine 8.



FVP of 3-*t*-butyl-4-[1-pyrrolo[1,2-*a*]pyrimidinmeth-(Z)-ylene]-4*H*-isoxazol-5-one (50 mg), (T_f 950 °C, T_i 135 °C, P 3 × 10^{-2} Torr, t 20 min), gave pyrimido[2,1,6-*cd*]pyrrolizine (39 mg, 92%) as a yellow oil, fluorescent green in solution, bp 68 °C (2 Torr); (Found M^+ 142.05221, $C_9H_6N_2$ requires M 142.05255); δ_H (acetone d_6) 8.84 (1H, d, J 5.5), 8.08 (1H, d, J 5.5), 8.01 (1H, d, J 4.5), 7.85 (1H, d, J 4.1) and 7.36 (2H, m); δ_C (acetone d_6) 144.45 (quat), 142.20 (CH), 134.19 (quat), 125.96 (quat), 125.70 (CH), 123.75 (CH), 112.83 (CH), 111.96 (CH) and 110.24 (CH); δ_H (TFA) 8.63 (1H, d, J 6.5), 8.20 (1H, d, J 6.5), 8.16 (2H, m), 7.51 (1H, d, J 4.4) and 7.37 (1H, d, J 4.7); *m/z* 142 (M^+, 100%) and 115 (34).

N-methylpyrimido[2,1,6-*cd*]pyrrolizin-3-ium iodide 269.

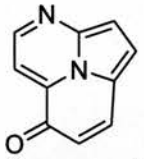


A solution of pyrimido[2,1,6-*cd*]pyrrolizine (15 mg) in methyl iodide (1 cm^3) was heated in a sealed glass tube at 80 °C for 15 min. The resulting precipitate was found to be *N*-methylpyrimido[2,1,6-*cd*]pyrrolizin-3-ium iodide (8 mg, 35%), mp 130 °C (decomp); (Found +ESI M^+ 157.07592, $C_{10}H_9N_2$ requires: 157.07602); δ_H 9.65 (1H, d J 6.5), 8.55 (1H, d, J 6.5), 8.27 (2H, m), 7.67 (2H, m) and 5.06 (3H, s); δ_C 138.26 (CH), 136.62 (quat), 134.19 (CH), 131.95 (CH), 129.20 (quat), 117.14 (CH), 111.26 (CH), 107.85 (CH) and 55.63 (CH_3) one quat overlapping; *m/z* +ESI 157 (M^+, 100%).

Reaction of *N*-methylpyrimido[2,1,6-*cd*]pyrrolizin-3-ium iodide with methoxide.

To a solution of N-methylpyrimido[2,1,6-*cd*]pyrrolizin-3-ium iodide in $MeOH_{d4}$ sodium (2 mg) was added and the reaction observed by NMR spectroscopy. After 2 min the solution had became black and no signals were observed in the NMR spectrum.

3,8b-Diaza-acenaphthylen-6-one 258.



FVP of 2,2-dimethyl-5-pyrrolo[1,2-*a*]pyrimidin-6-ylmethylene-[1,3]dioxane-4,6-dione (50 mg), (T_f 950 °C, T_i 135 °C, *P* 3 × 10^{-2} Torr, *t* 20 min), gave 3,8b-diazaacenaphthylen-6-one (72%) as a red solid that is fluorescent in solution, mp 98 °C, (Found M^+ 170.04703; $C_{10}H_6N_2O$ requires *M* 170.04746) δ_H 9.01 (1H, d, *J* 4.9), 8.35 (1H, d, 4.9), 8.13 (1H, d, *J* 9.7), 7.86 (1H, d, *J* 4.9), 7.40 (1H, d, *J* 4.9) and 7.17 (1H, d, *J* 9.7); δ_C 145.27 (CH), 130.44 (CH), 125.72 (CH), 125.01 (CH), 109.90 (CH) and 109.73 (CH), only CH signals quoted; *m/z* 170 (M^+, 6%), 142 (6), 114 (7), 63 (34) and 52 (100).

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