Development of synthetic routes to novel heterocyclic colour couplers

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Declaration

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

This thesis describes the results of research carried out in The University of Edinburgh, Chemistry Department, under the supervision of Dr Hamish McNab since 1st October 1998, the date of my admission as a research student.

Signed :

Date : 8/11/02

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Lecture course attended

- Organic research seminars and Colloquia, The University of Edinburgh, Chemistry Department (3 years attendance)
- Current awareness in organic chemistry, The University of Edinburgh, Chemistry Department (5 lectures, 2 years attendance)
- Royal Society of Chemistry, Perkin Division, Scottish Regional Meeting (3 years attendance)
- Royal Society of Chemistry, Perkin Division, Heterocyclic group, Autumn meeting (1 year attendance)
- Royal Society of Chemistry Symposium, Imperial College, London (1 year attendance)
- Combinatorial chemistry (Glaxo SmithKline), The University of Edinburgh, Chemistry Department (5 lectures)
- Advanced organic synthesis, Dr Alison Hulme, The University of Edinburgh, Chemistry Department (10 lectures)
- Pesticides, Dr Hamish McNab, The University of Edinburgh, Chemistry Department (5 lectures)
- Chemical carcinogens, Dr R. Michael Paton, The University of Edinburgh, Chemistry Department (5 lectures)

Abstract

Studies into a potential new synthetic route to pyrazolotriazole colour couplers showed that flash vacuum pyrolysis (FVP) of 3-methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine produced 1-isothiocyanato-1-phenylethene. The mechanism probably involves a [1,5]shift within the bicyclic system to form a spiro-intermediate, which undergoes extrusion of molecular nitrogen and of a substituted nitrile to form a cyclic carbene, the rearrangement of which yields the product. This reaction pathway was found to be general and provided a clean, high yielding route to previously unknown alkyl-substituted alkenylisothiocyanates.

A novel synthetic route to various [1,3]thiazolo[3,2-*b*][1,2,4]triazole derivatives was discovered through FVP of 4-amino-3-allylthio-4*H*-1,2,4-triazoles. The mechanism is thought to proceed *via* initial [3,3]-sigmatropic shift of the allyl group followed by cleavage of the *N-N* bond to generate a thiaza-allyl radical, which then undergoes cyclisation, rearrangement and alkyl group extrusion to give the thiazolotriazole products. This methodology provides a three step synthetic route to thiazolotriazoles with the ability to vary substituents at all three positions on the ring system.

A clean and efficient two step route to benzyl type radicals from benzylamine type precursors was developed using FVP of their pinacolone imines. Using this imine derivative of benzylamine as a model system, radical cleavage of the C-N bond produced benzyl radicals (which coupled to give bibenzyl) and an iminyl radical (which cleaved to provide acetonitrile). This methodology was applied to the synthesis of a novel 5,5,5-fused heterocycle, 7*H*-3-thia-6*a*-aza-cyclopent[*a*]pentalene, and a 6,5,5-fused heterocycle, 9*H*-pyrrolo[1,2-*a*]indole. Further applications of this methodology to new heterocyclic systems were limited due to problematic synthesis of starting materials.

FVP of 2-azolylnitrobenzene derivatives provided a convenient new route to 6,5,5-fused heterocycles. Homolysis of the nitro group at high temperatures is thought to produce the corresponding phenyl radical. In the presence of a pendant 2-methyl group on the azole, translocation of this phenyl radical produces a benzyl type radical which then cyclises with subsequent loss of a hydrogen atom to give the tricycle. This methodology has provided an efficient two step route to three novel 6,5,5-heterocycles, 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole, 9*H*-imidazo[1,2-*a*]indole and 2-methyl-8*H*-3,3a,4-triaza-cyclopenta[*a*]indene, and one known tricycle. This two step synthetic route to 6,5,5-fused heterocycles has been shown to have scope for further exploitation in the synthesis of systems with potential photographic applications as magenta colour couplers.

Contents

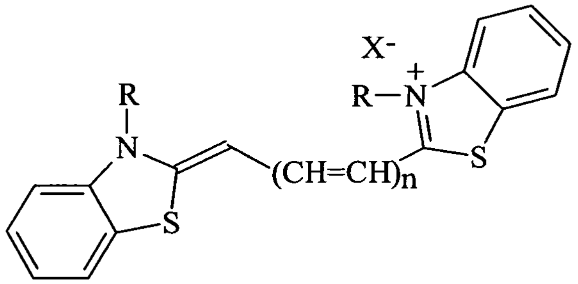
A. INTRODUCTION

Part of this thesis is devoted to the exploration of new routes to 5,5,5-fused heterocycles with potential applications in colour photography as magenta colour couplers. This introduction will describe the photographic process and then review the synthesis of 5,5,5-fused heterocyclic systems as reported in the literature, as well as outlining potential applications of some of the compounds described.

The photographic process

The majority of modern photographic processes are based on the use of silver halides,[1] with silver bromide (photographic film) and silver chloride (photographic paper) the most commonly used. The silver halides are dispersed as small crystals in layers of gelatin, with the resulting mixture known as the 'photographic emulsion'. This emulsion is usually hardened, to increase durability towards heat and abrasive damage, with crosslinkers such as oxiranes.[1]

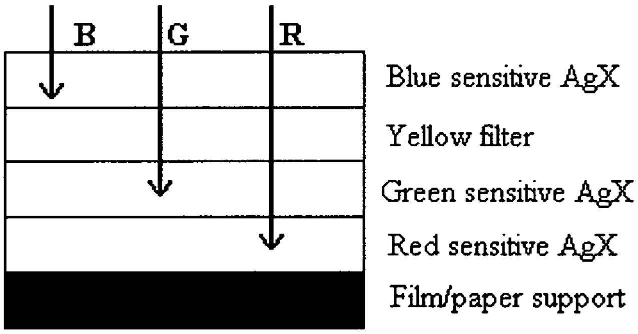
One problem associated with the use of silver halides is that they are either colourless or yellow, which means that they are only sensitive to UV and blue light. This problem was overcome with the development of sensitiser dyes, which extend the sensitivity range of the silver halides to cover the entire visible spectrum. The best known examples of these dyes are the cyanines, which are monoacid salts in which two nitrogen containing heterocycles are linked by an odd numbered conjugated carbon chain. Typical examples are shown below **1-3**. Through the use of such dyes, the silver halide can be made sensitive to green and red light.



1 n=0 yellow
2 n=1 magenta
3 n=2 cyan

Colour photographic media are usually prepared by coating three sensitised silver halide layers onto a suitable paper or film base. This is known as the integral tri-pack, a simplified representation of which is shown in Figure 1.

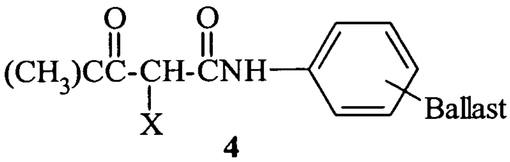
Figure 1: Simplified representation of the integral tri-pack



Modern colour photography utilises all the above features, as well as incorporating colour forming couplers into the sensitised silver halide layers of the integral tri-pack.[1,2,3] Three different colours are applied, yellow (blue absorbing), magenta (green absorbing) and cyan (red absorbing). Combinations of these colours, known as the primary subtractive colours,[3] will result in various colours. For example, a 1:1 mixture of cyan and yellow gives green (through the subtraction/absorption of red and blue light).

The yellow filter screens out blue light to avoid exposure of the lower layers, and is removed by bleaching upon developing.

Colour couplers are generally small aromatic compounds, which do not absorb visible light until developed. Typical yellow forming couplers are the benzoylacetanilides and pivaloylacetanilides **4** type couplers (X = H or halogen). The latter reportedly form dyes with greater light stability, but are slow in forming.[3]



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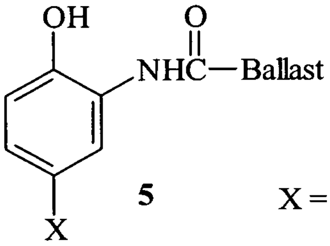
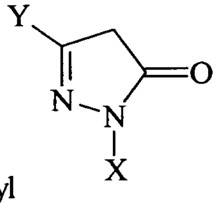
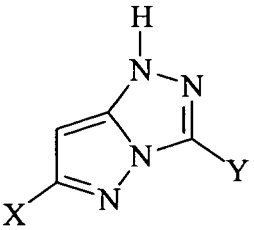
Practically all cyan dyes are formed from either substituted phenol- or naphthol- type couplers,[3.] *e.g.* **5**.



5 X = H, Cl, OAr, OR, SAr

Magenta dyes were traditionally derived from 2-pyrazolin-5-ones, **6** (X, Y = various substituents), but this dye class has a secondary blue absorption that limits their use. More recently, various azapentalene derivatives, which have a low blue absorption, have been developed e.g. pyrazolo[5,1-*c*][1,2,4]triazoles **7**.[4]





X = H, alkyl, aryl
Y = H or halogen

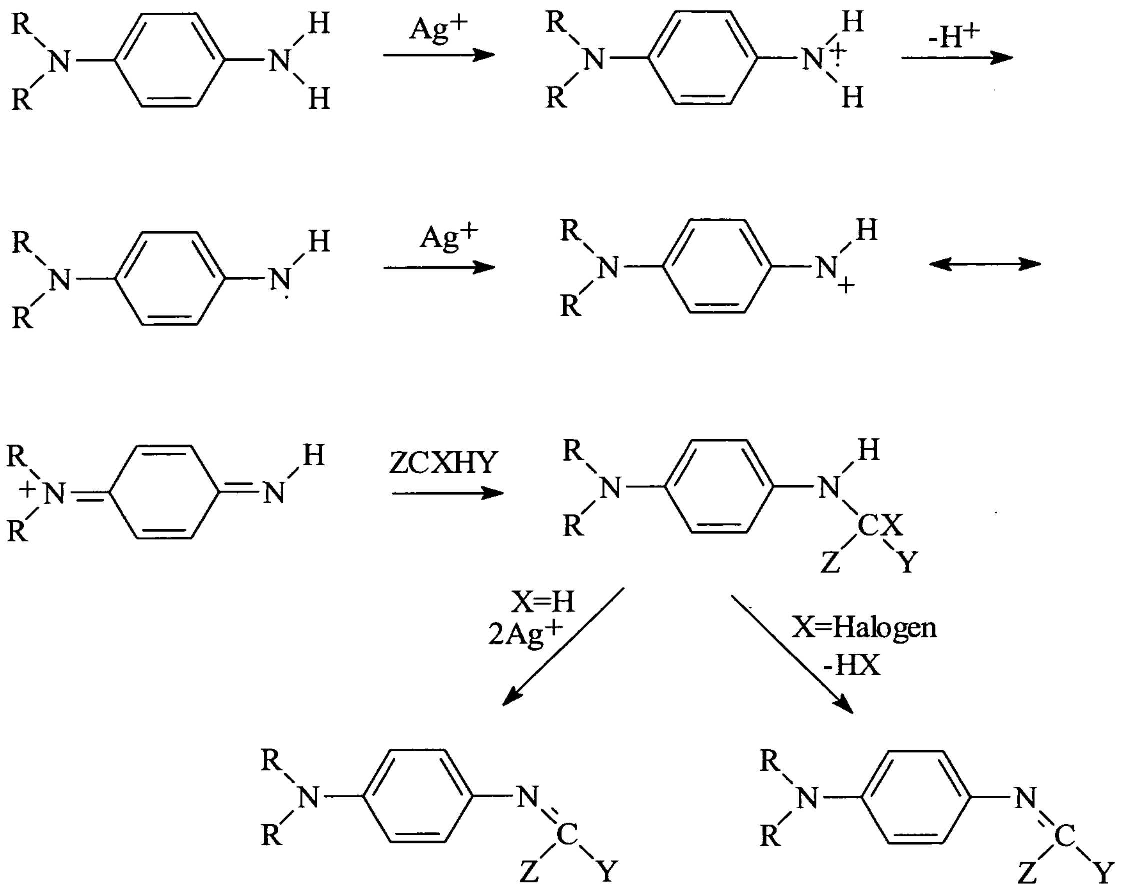
6

7

X = H, Cl, OR, SR
Y = H, alkyl, aryl

When this integral tri-pack methodology is employed, it is essential that the couplers cannot migrate from their layer, and this non-migratory behaviour can be achieved using one of two methods. The first method involves attaching a long carbon chain 'ballast group' which also incorporates an acid solubilising group *e.g.* SO_3H. This allows the coupler to be dissolved in alkali then dispersed in the appropriate emulsion, and is subsequently held in place by interactions with the gelatin. The second method replaces the acid solubilising group with an oil solubilising group. The coupler is then dissolved in a suitable solvent then dispersed in the appropriate emulsion 'oil in water fashion', with the final dye being formed, upon development, in the oil phase.

In the development process, exposed silver halide oxidises the colour developer, which in turn reacts with the colour couplers to produce the corresponding dye.[3] Typical colour developer classes are the *p*-phenylenediamines and *p*-aminophenols. A typical mechanism of the reaction between a *p*-phenylenediamine developer and a coupler, represented as ZCHXY, is shown in Scheme 1.



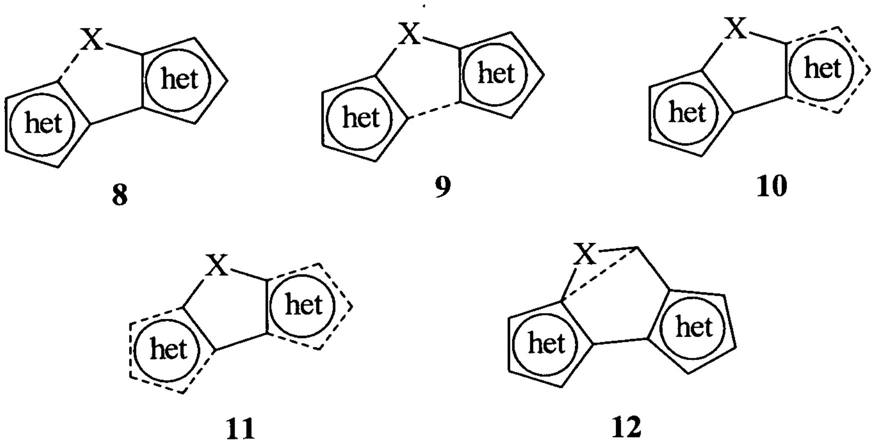
Scheme 1

Z and Y represent part of a chain or ring structure, and X represents either a hydrogen atom or leaving group (typically a halogen). When X=halogen, only two equivalents of silver halide are required, but when X=H four equivalents are required to form the dye.

Preamble

Reports of 5,5,5-fused heterocycles in the literature are relatively scarce. A large proportion of material published is focussed on the synthesis of thiophene containing systems, although there are a few exceptions to this with a reasonable number of more "exotic" systems having been reported. However, there is no real chemical similarity apparent between these systems, and for this reason the literature reviewed in this introduction has been grouped depending on the synthetic strategy employed in building the system rather than on the system produced. The general synthetic strategies employed are represented schematically in Figure 2. For example, **8** represents the synthesis of the 5,5,5-system through construction of the central ring *via* bond formation between one of the terminal rings and a substituent on the adjacent ring (dashed lines show bonds formed in final step).

Figure 2: Representations of ring syntheses



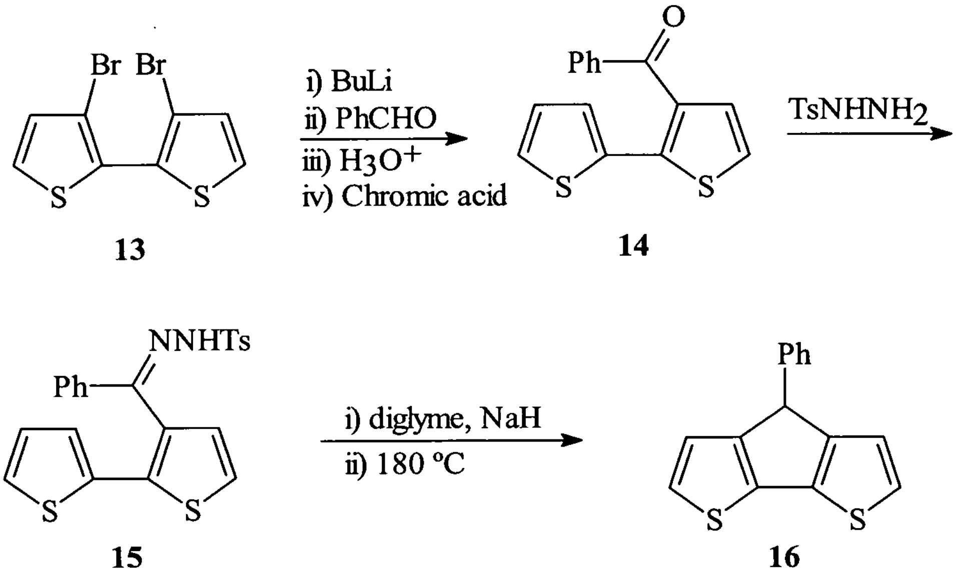
Structure **9** also represents construction of the central ring, but in this case the bond is formed directly between terminal rings. Structures **10** and **11** represent formation of one or both terminal rings respectively, whereas **12** represents a ring contraction step.

1. Synthesis of 5,5,5-fused heterocycles *via* central ring formation

(a) new heterocycle – substituent bond

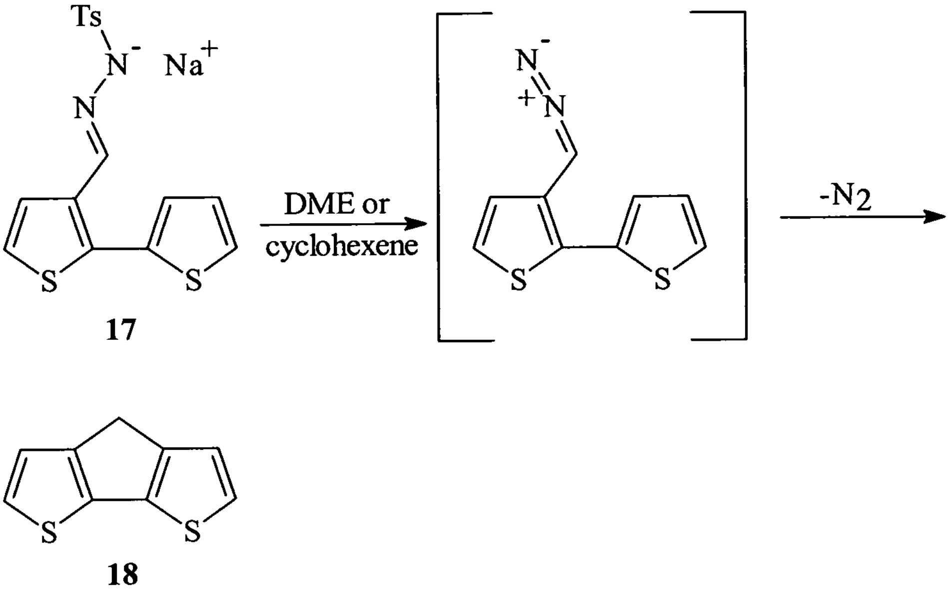
There is quite a lot of variation in the type of 5,5,5-fused heterocycles which have been prepared using this general methodology, although almost all contain at least one thiophene ring. The actual mode of cyclisation utilised also varies widely, taking in photochemical reactions, condensation reactions, as well as cyclisations of nitrenes and carbenes.

An example of one such carbene cyclisation in the synthesis of 4-phenyl-4*H*-cyclopenta[2,1-*b*][3,4-*b*']dithiophene **16** (Scheme 2) was reported by Skramstad and Storflor.[5]



Scheme 2

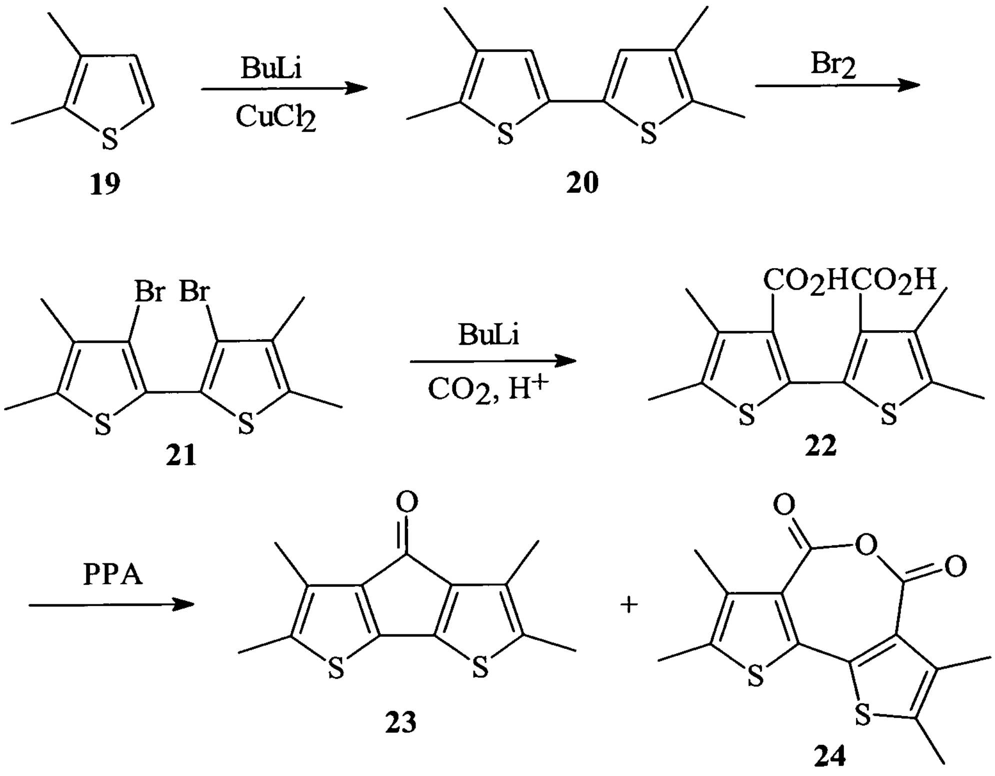
Conversion of the dibromo compound **13** to 3-benzoyl-2,2'-bithienyl **14** occurred in low yield (22%). Compound **14** was subsequently reacted with tosylhydrazine to give the tosylhydrazone **15** in 68% yield. Carrying out a Bamford-Stevens reaction on **15** (formation of the sodium salt of **15** followed by heating, which produces a carbene intermediate through loss of N_2) produced the 5,5,5-heterocycle **16** in 69% yield. There are two other reported syntheses of this system which use the same general synthetic strategy, both of which occur in lower yields than the example shown above in Scheme 2. The parent system **18** (Scheme 3) was synthesised by Munro and Sharp also using carbene chemistry.[6]



Scheme 3

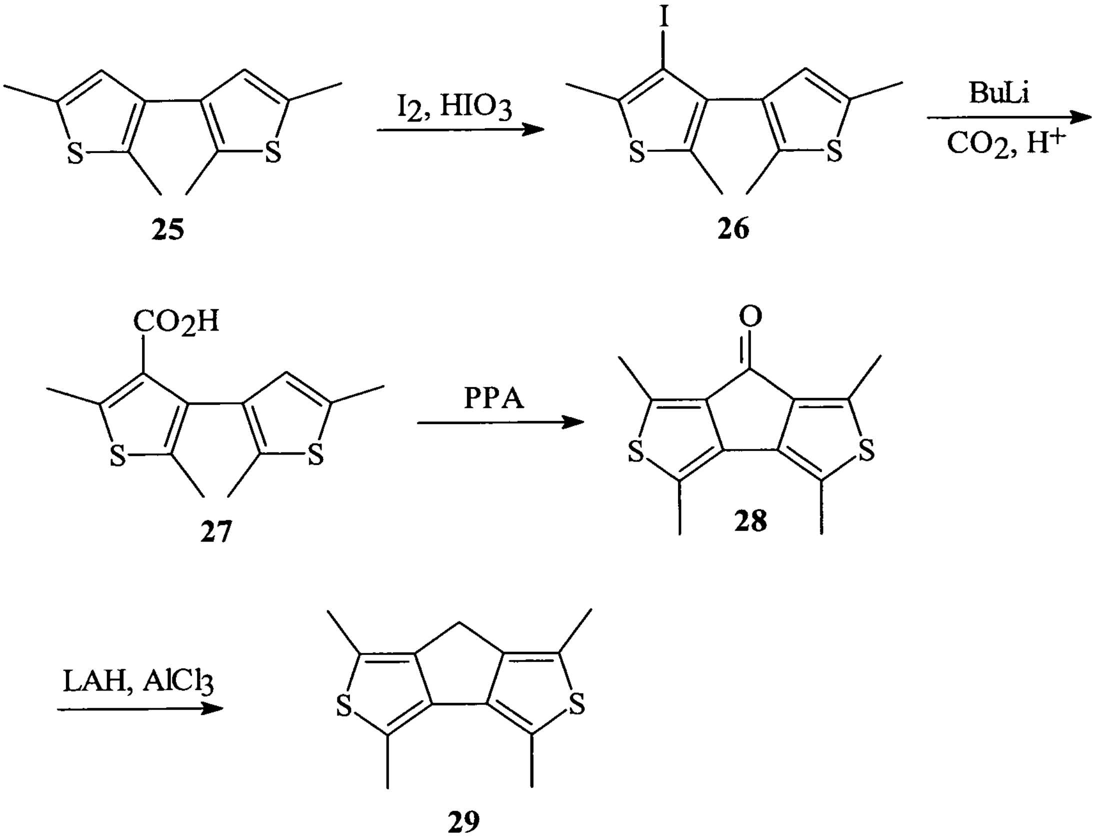
Generation of the sodium salt of the tosylhydrazone **17** was carried out as shown in Scheme 2. Thermolysis of **17** gave a 10% yield of the parent system, 4*H*-cyclopenta[1,2-*b*:3,4-*b*']dithiophene **18**. An alternative cyclisation method was used by Wiersema and Gronowitz [7] which utilised the ring closure of the dicarboxy-bithienyl **22** to synthesise the tetramethyl-derivative **23** as shown in Scheme 4. 2,2',3,3'-Tetramethyl-5,5'-bithienyl **20** was prepared in 68% yield from a butyl lithium/cupric chloride coupling of the monomer **19**. Bromination of **20** with Br_2 in chloroform gave the dibromo-compound **21** (88%) which was reacted with butyl lithium followed by subsequent reaction with carbon dioxide gave the diacid **22** in

69% yield. The cyclisation of **22** in PPA gave the desired tricycle **23** in very poor yield, with the reaction reported as being irreproducible.



Scheme 4

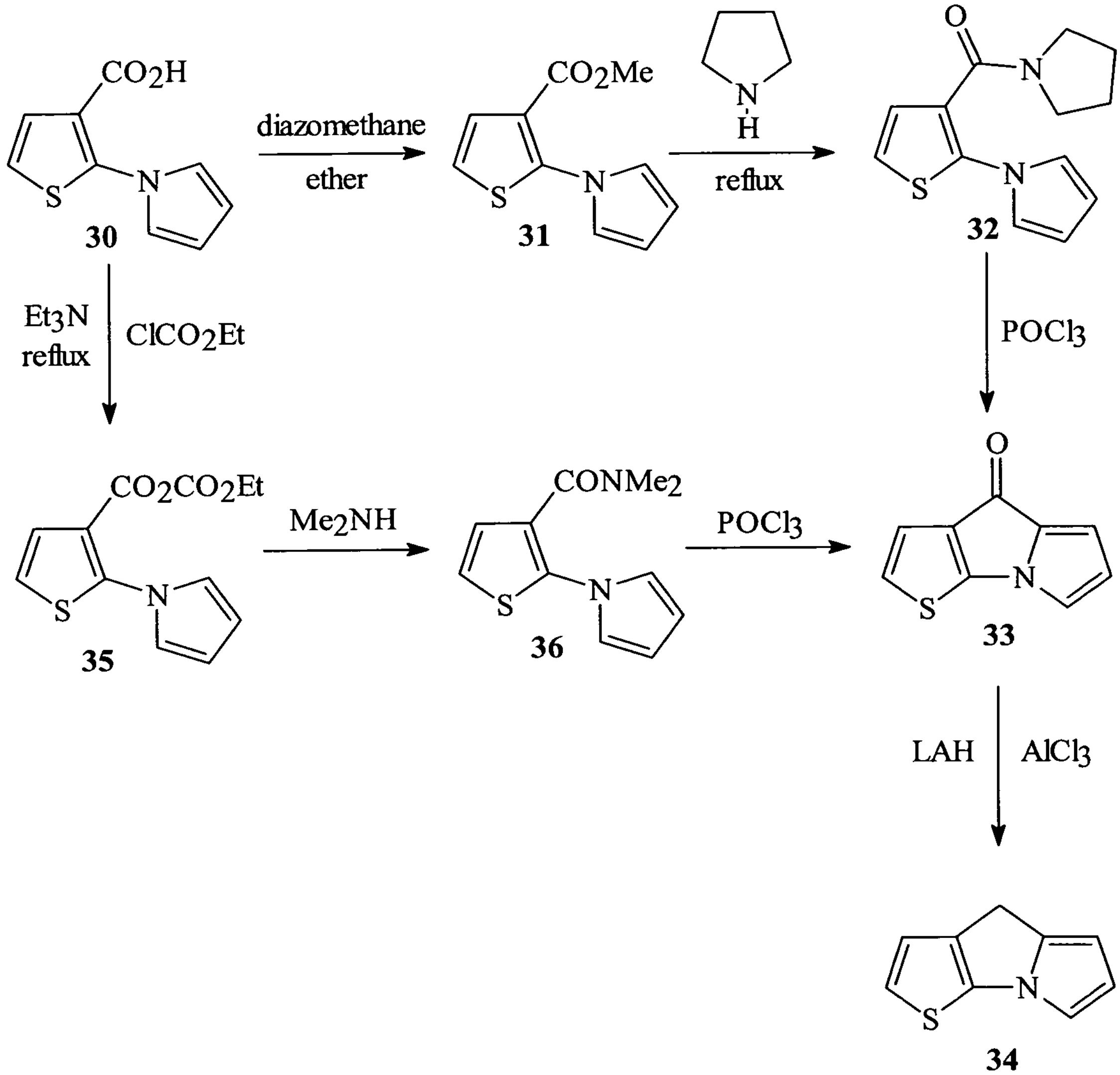
The main product obtained from the cyclisation of **22** in PPA was reported to be the anhydride **24**, which also seemed to cause difficulties in purifying the small amount of **23** which was obtained. It would therefore seem that this particular cyclisation methodology was not suitable for the synthesis of this type of compound, although the same authors have reported the successful synthesis of the isomeric tricycle **28** as shown in Scheme 5. The fact that the synthesis of **28** was successful using the same cyclisation conditions used for the attempted synthesis of **23** indicates that it is the diacid nature of **22** which is causing the problem during the cyclisation step. Monoiodination of the tetramethyl-compound **25** was carried out using iodine/hydroiodic acid to give **26** in good yield (81%). Treatment of **26** with butyl lithium followed by subsequent reaction with carbon dioxide gave the monoacid **27** in 81% yield. The cyclisation of **27** in PPA gave the cyclopentadithiophene-7-one **28** (77%), the reduction of which with lithium aluminium hydride (LAH) produced 1,3,4,6-tetramethyl-7*H*-cyclopenta[1,2-*c*][3,4-*c*']dithiophene **29** in excellent yield (97%).



Scheme 5

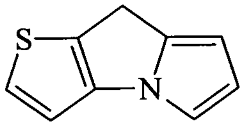
So far, all the examples covered have used linked thiophene moieties as the building blocks for the synthesis of the tricycles. There are several examples in the literature which utilise other heterocyclic building blocks to synthesise 5,5,5-fused heterocycles using the same general synthetic strategy. One such example was reported by Rault *et al.*[8] which used this synthetic strategy to prepare thieno[2,3-*b*]pyrrolizine **34** as shown in Scheme 6. Esterification of **30** with diazomethane gave **31**, which was condensed with pyrrolidine to give the pyrrolidinocarboxamide **32**.

Cyclisation of **32** in phosphoryl chloride gave the thienopyrrolizinone **33**, the reduction of which gave the parent thieno[2,3-*b*]pyrrolizine **34**. It is reported that improved yields of **34** were obtained from the cyclisation of the dimethyl thienamide **36** although no yields are quoted for comparison.[8] There is also no indication as to why the authors chose to synthesise **36** *via* the mixed anhydride **35** rather than utilise the acid chloride of **30**.



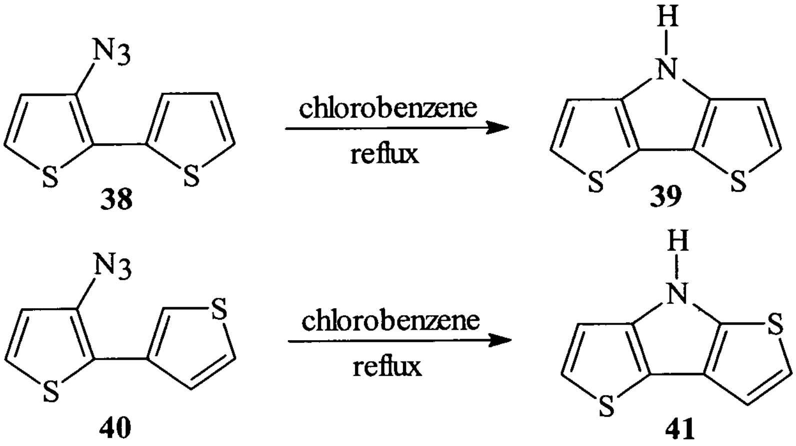
Scheme 6

The same paper also outlines the synthesis of the isomeric thieno[3,2-*b*]pyrrolizine **37** using the same methodology.[8]



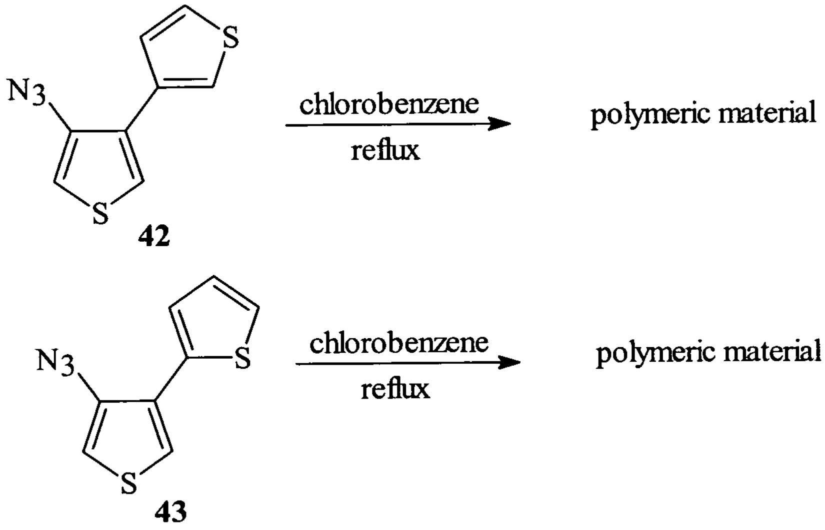
37

Several examples of the syntheses of 5,5,5-fused heterocycles using this same general synthetic strategy have been reported but, unlike all of the above, with the cyclisation step creating a new bond between one of the ring carbons and a heteroatom substituent. One such example reported by Zanirato *et al.* [9] utilised the thermolysis of azidobithienyls to effect ring closure *via* the nitrene. Two successful examples are shown in Scheme 7.



Scheme 7

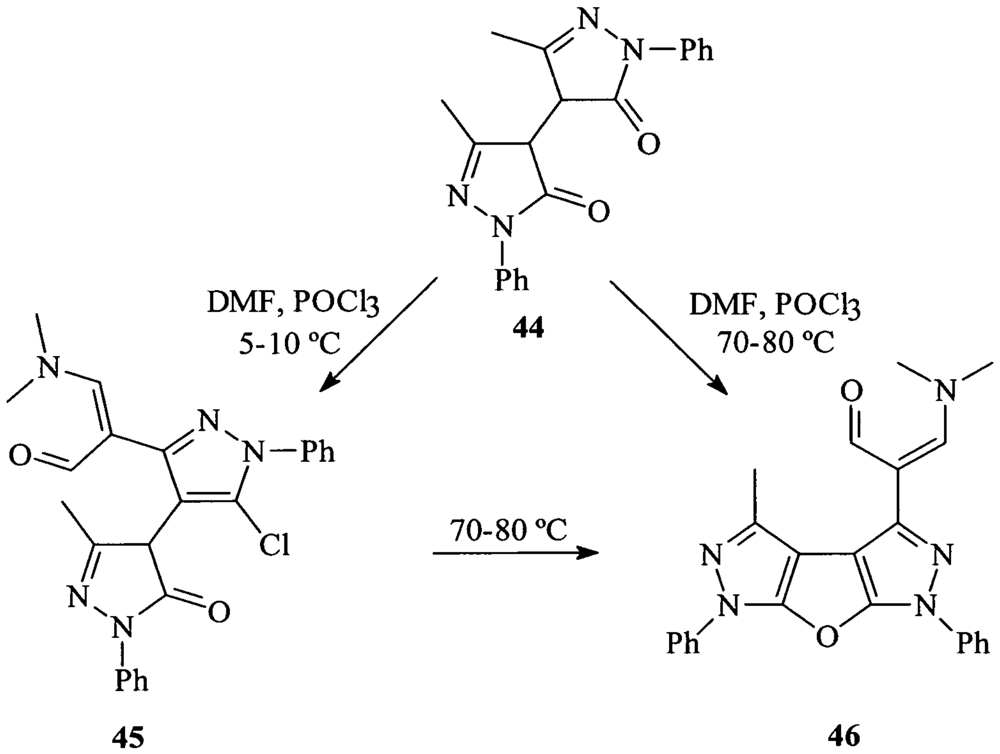
The starting materials **38** and **40** were obtained through the reaction of the appropriate lithio-bithienyl with toluene-*p*-sulfonyl azide. Thermolysis of the azides **38** and **40** in refluxing chlorobenzene gave 4*H*-dithieno[3,2-*b*][2'3'-*d*]pyrrole **39** (87%) and 4*H*-dithieno[2,3-*b*][2'3'-*d*]pyrrole **41** (88%) respectively. Attempts to effect the cyclisation of two other azides **42** and **43** shown in Scheme 8 proved unsuccessful. This showed that azides **42** and **43** have greater thermal stability than azides **38** and **40**, and propose the reason for this may be due to the relative position of the π-bonds involved in the cyclisation compared with the positioning in the products expected. Another possible reason for the differences in reactivity is that the central ring in the products that would be obtained from the cyclisation of **42** and **43** would be bis- and mono-quinonoid respectively, and therefore less stable than **39** and **41**.



Scheme 8

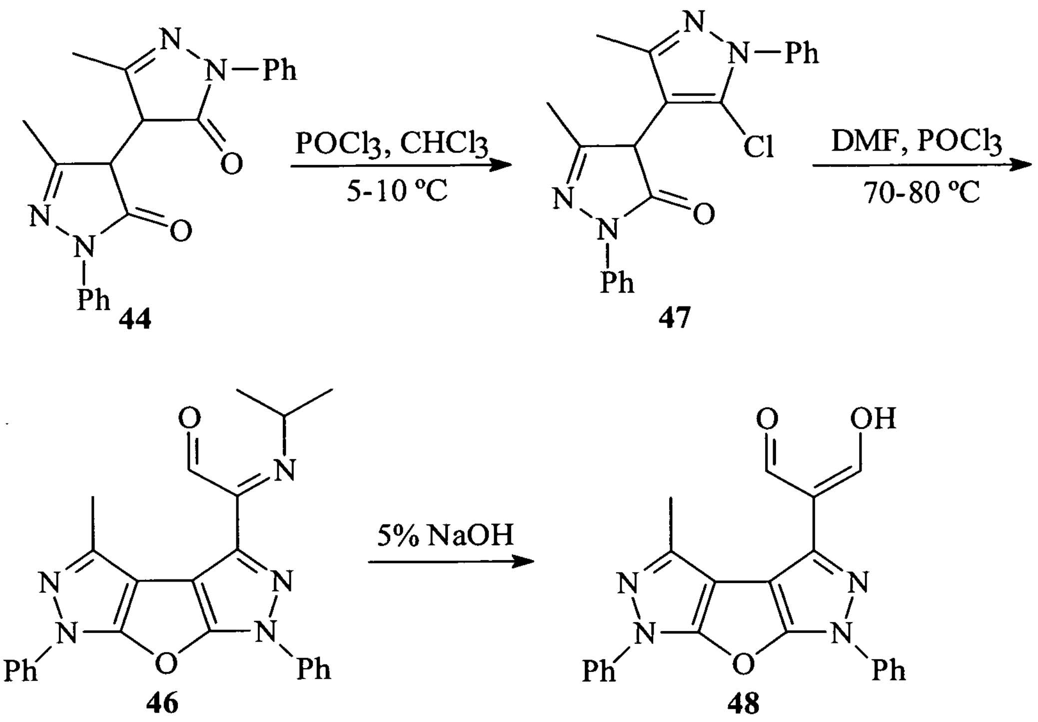
It is therefore clear that this nitrene cyclisation methodology is not widely applicable to this type of system. An alternative mode of cyclisation was discovered by Awad [10] whilst carrying out studies on the Vilsmeier-Haack reaction. Attempting this reaction on **44** (Scheme 9) at low temperatures gave the product **45** in which one of the methyl substituents has been formylated along with substitution of one carbonyl group with a chlorine atom. There is no mention of any material being isolated in which both methyl substituents have been formylated, although this is perhaps unlikely due to steric reasons. Heating of **45** gave the cyclised product, 3-(1-formyl-

2-dimethylaminoethenyl)-4-methyl-1,6-diphenyl-furo[2,3-c][5,4-c']dipyrazole **46**, *via* elimination of HCl, with no yield quoted.



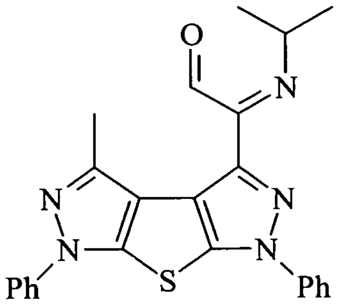
Scheme 9

An alternative route to this compound, described in the same paper, is shown in Scheme 10. In this case, the reaction proceeds through the chloro-derivative **47**, with the formylation and cyclisation steps taking place in one stage to give **46**. It is not clear why DMF and $POCl_3$ was used to effect the cyclisation of **47**, as the same author carried out an almost identical cyclisation using only heat, as shown in Scheme 9 (**45** to give **46**). The cyclised product **46** was readily hydrolysed with aqueous sodium hydroxide to give the malonaldehyde derivative **48**.



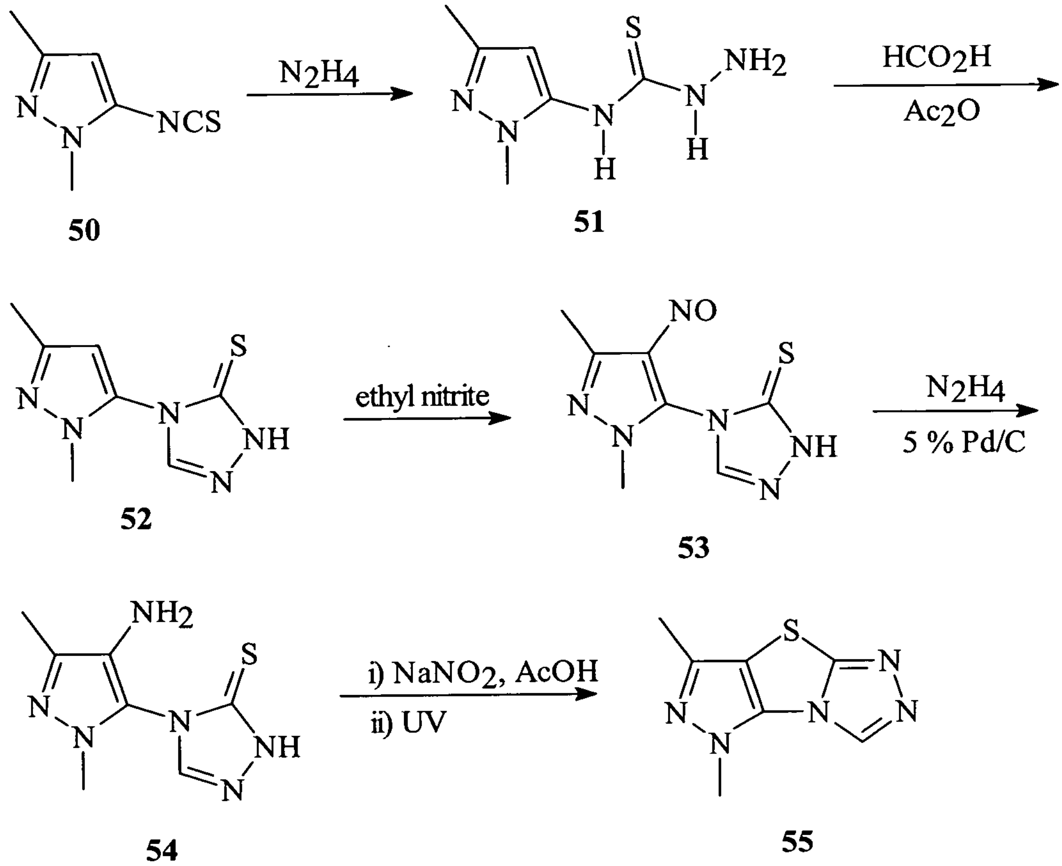
Scheme 10

Awad used the same methodology to synthesise the thieno-analogue of **46**, the thieno[2,3-c][5,4-c']dipyrazole tricycle **49.** [11]



49

Synthesis of another tricycle containing a pyrazole moiety, this time using photochemical methods to effect the cyclisation, was reported by Vicentini *et al.* [12] as shown in Scheme 11.



Scheme 11

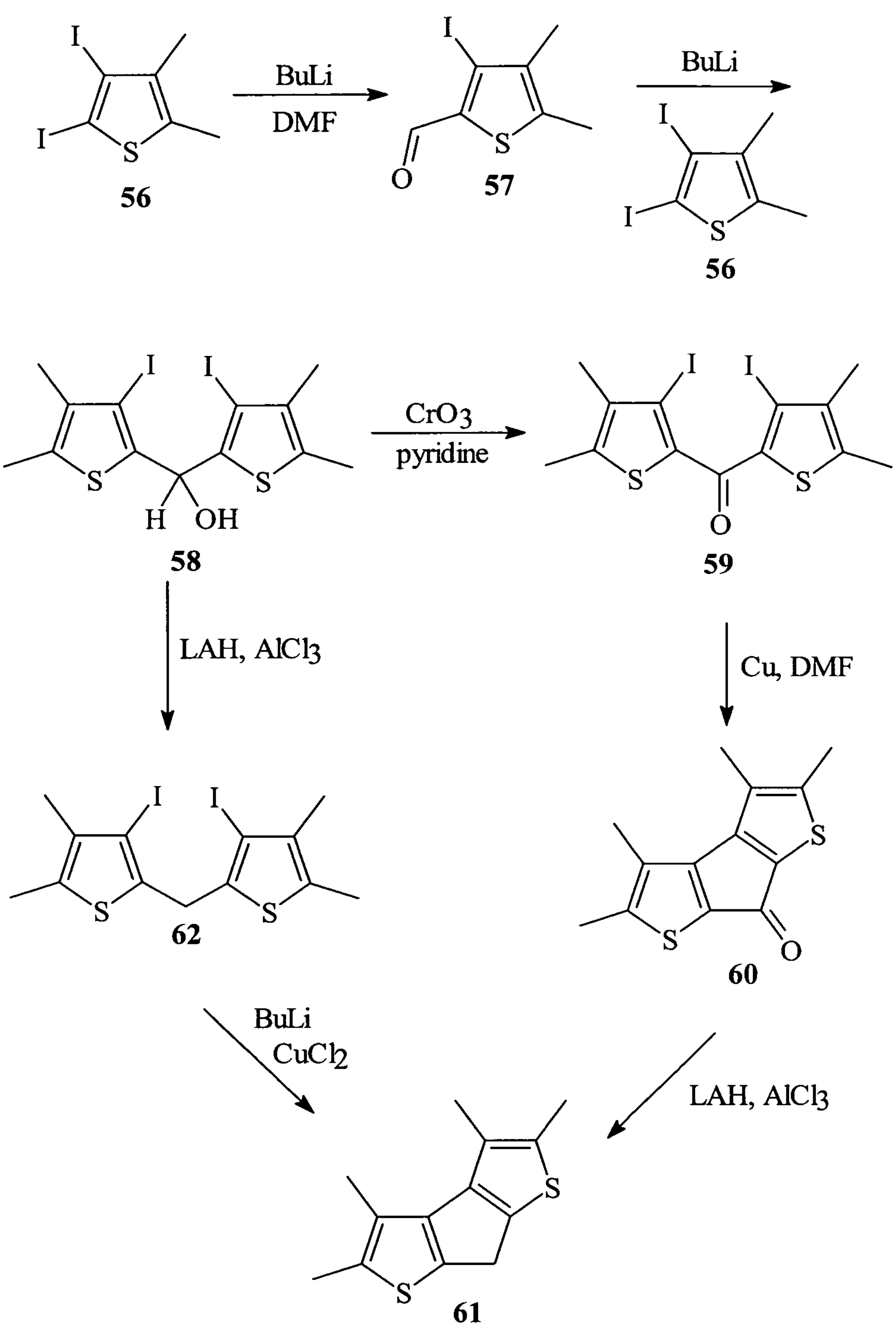
Condensation of the isothiocyanate **50** with hydrazine hydrate gave the thiosemicarbazide **51** in 72% yield. Cyclisation of **51** with formic acid/acetic anhydride gave a 51% yield of the key pyrazolyl-1,2,4-triazole-thione intermediate **52**. Nitrosation of **52** followed by reduction with hydrazine hydrate in the presence of palladized charcoal gave **54** in quantitative yield. Diazotisation of **54** under UV irradiation (λ ≥ 300 nm) produced 5,7-dimethylpyrazolo[3',4'][4,5]thiazolo[2,3-*c*]-1,2,4-triazole **55** in 68% yield.

As can be seen from the examples above, this general synthetic strategy is applicable to the synthesis of a reasonably varied selection of 5,5,5-fused heterocycles. The other method of forming the central ring, making a bond directly between the terminal rings, has not been employed in such a variety of syntheses. With very few exceptions this methodology has only been used in the synthesis of various cyclopentadithiophene and thiophenodithiophene systems, and it is these syntheses which are reviewed in the next section.

1. Synthesis of 5,5,5-fused heterocycles *via* central ring formation

(b) new heterocycle – heterocycle bond

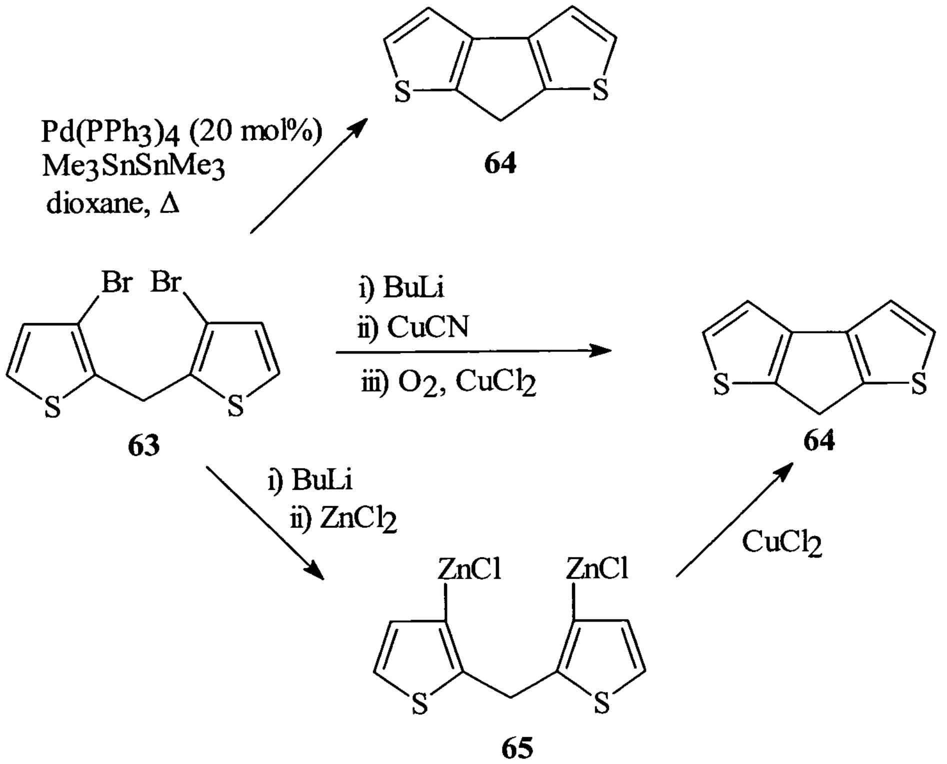
The 5,5,5-fused heterocycles synthesised by this method of ring formation, brought about by making a new carbon-carbon bond directly between the two terminal rings, are not as varied in structure as those discussed in the previous section, with most of the systems reported being cyclopentadithiophene and thiophenodithiophene based. The conditions used to bring about the cyclisation do not show the same variety either, with the majority of the cyclisations being effected *via* copper (II) chloride catalysed reactions or Ullmann-type coupling reactions.



Scheme 12

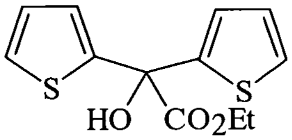
One such example was reported by Wiersema and Gronowitz [7] towards the synthesis of 2,3,4,5-tetramethyl-3,7-dihydro-2*H*-cyclopenta[1,2-*b*;4,3-*b'*]dithiophene **61** as shown in Scheme 12. Treatment of **56** with butyl lithium followed by reaction with

DMF gave the aldehyde **57** in 73% yield. Reaction of the aldehyde **57** with the halogen-lithium exchange product of **56** gave the dithienylcarbinol **58** (80%) which was oxidised to give an 87% yield of the ketone **59**. The Ullmann-type coupling of **59** gave the tricyclic ketone **60** in 75% yield. Reduction of **60** gave the cyclopentadithiophene **61** in 65% yield, so alternative cyclisation conditions were investigated in an attempt to maximise the yield. Reduction of **58** with LAH/$AlCl_3$ gave **62** in excellent yield (92%). However, the cyclisation of **62** with butyl lithium/copper (II) chloride gave the expected product **61** in only 10% yield. The synthesis of the parent system of this 5,5,5-heterocycle was also investigated by Iyoda *et al.* [13], using the three sets of cyclisation conditions shown in Scheme 13. These conditions were also used in the synthesis of various compounds outlined later in this introduction, so they will be discussed here then subsequently referred to in less detail. The first set of conditions employed involved treatment of the dibromo compound **63** with butyl lithium/copper (I) cyanide followed by an oxidative coupling reaction to give the parent 3,7-dihydro-2*H*-cyclopenta[1,2-*b*;4,3-*b*']dithiophene **64** in 40% yield. Two alternative sets of conditions were employed, with the palladium catalysed conditions giving a slightly higher yield (50%) of the desired compound **64**. Finally, using butyl lithium/zinc (II) chloride followed by copper (II) chloride to effect the cyclisation gave a 55% yield of **64**.



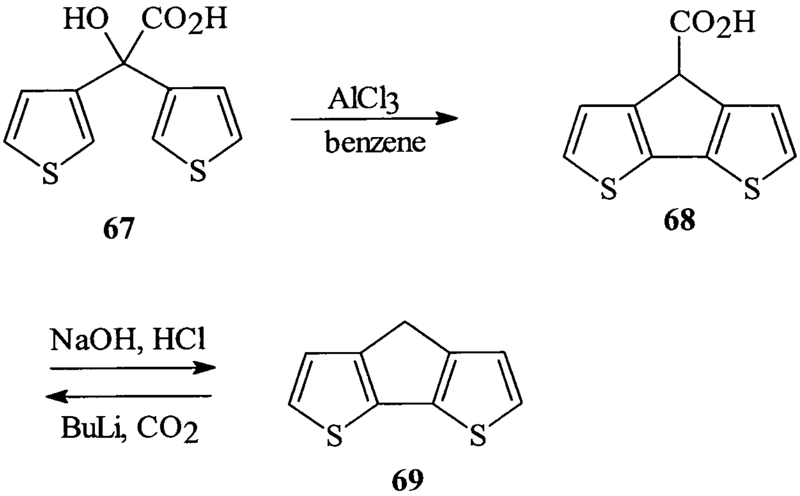
Scheme 13

Jeffries *et al.* [14] attempted to synthesise **64** using cyclisation conditions they had employed previously in the synthesis of indeno[1,2-*b*]thiophenes, by treating ethyl(2,2'-dithienyl)glycolate **66** with aluminium chloride in benzene. [15]



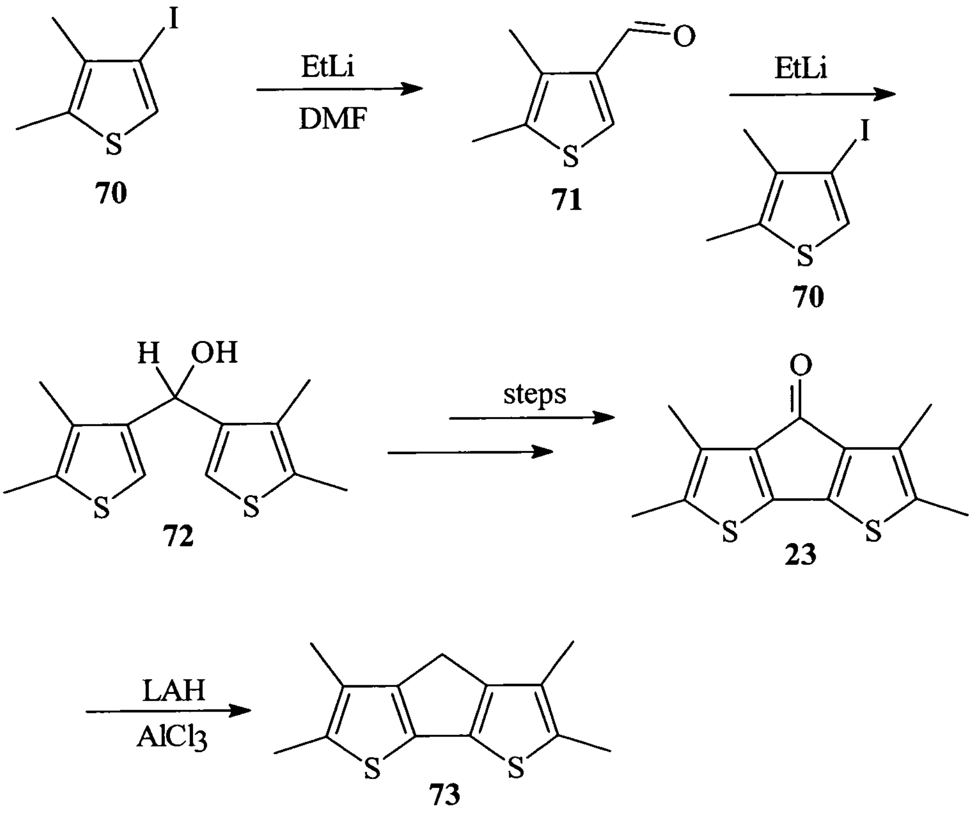
66

These conditions were unsuccessful in this case, but proved to be useful in the synthesis of the isomeric system 4*H*-cyclopenta[2,1-*b*][3,4-*b*']dithiophene **69** [14] as shown in Scheme 14. Treatment of 3,3'-dithienylglycolic acid **67** with aluminium chloride in benzene gave the cyclised product **68** in 75% yield, which was decarboxylated to give 4*H*-cyclopenta[2,1-*b*][3,4-*b*']dithiophene **69** (79%).



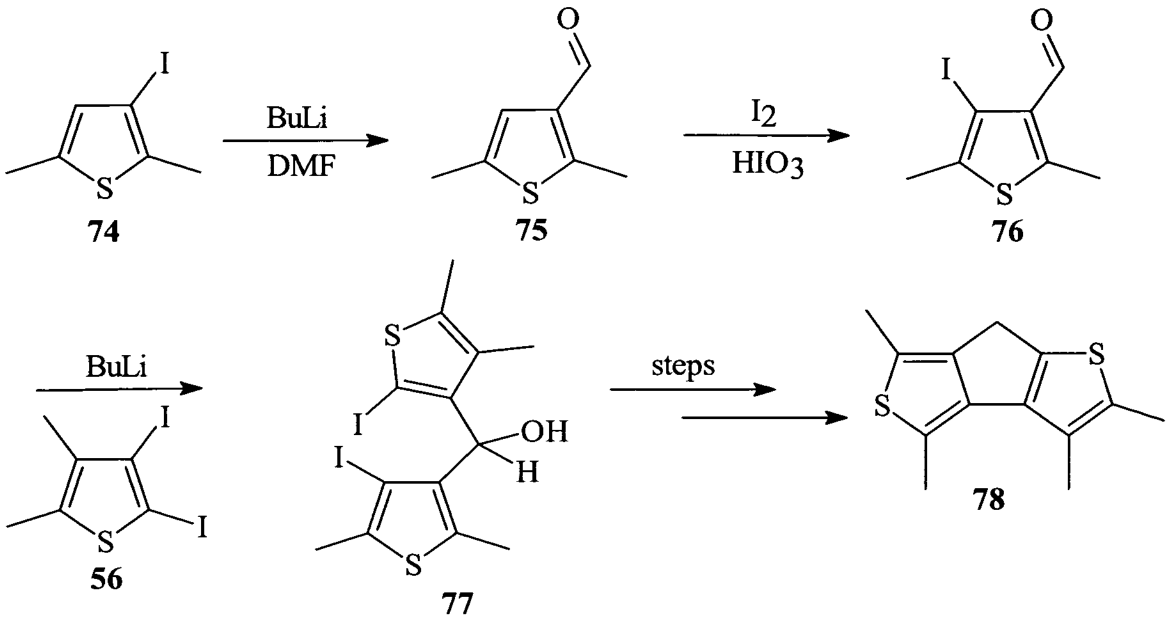
Scheme 14

The tetramethyl derivative of **69** (Scheme 14), compound **73**, was prepared by Wiersema and Gronowitz [7] as shown in Scheme 15. The aldehyde **71** was prepared from the treatment of **70** with ethyl lithium followed by reaction with DMF in 80% yield. Reaction of **71** with lithiated **70** gave the dithienylcarbinol **72** (91%). Oxidation of **72** followed by iodination then an Ullmann coupling reaction gave the ketone **23**, with all steps occurring in high yield. The reduction, however, proved problematic and **73** was produced in only 10% yield.



Scheme 15

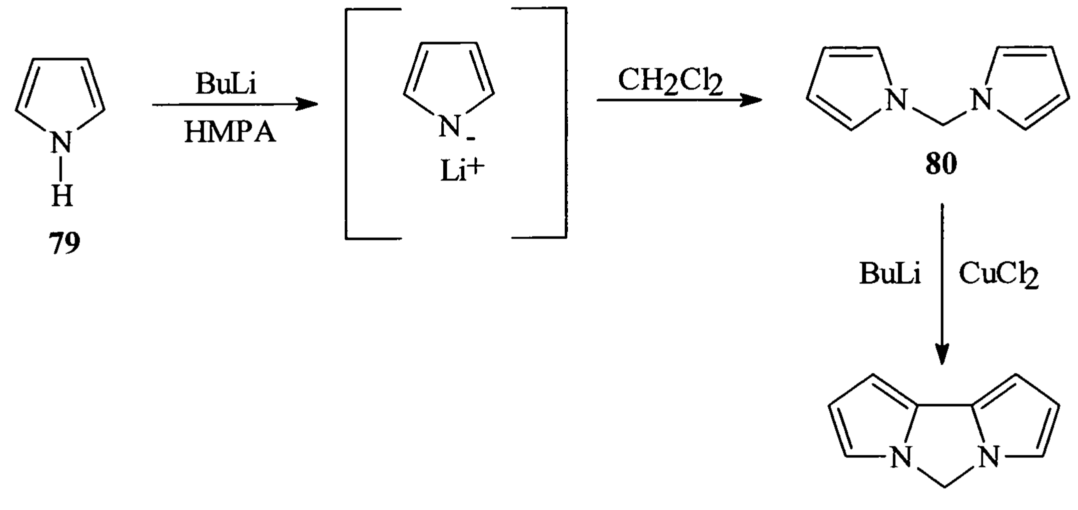
Attempts to solve this problem by reducing **72** then carrying out the coupling reaction proved unsuccessful. Wiersema and Gronowitz also used this methodology to produce the unsymmetrical cyclopentadithiophene **78** as shown in Scheme 16.[7] Difficulties were encountered in obtaining the mono-aldehyde **75** but this was overcome through making slight modifications to the reaction conditions, in terms of the number of equivalents of butyl lithium used.



Scheme 16

Oxidation of **77** followed by an Ullmann coupling and reduction gave 2,3,4,6-tetramethyl-7*H*-cyclopenta[1,2-*b*][3,4-*c*']dithiophene **78** in 86% yield.

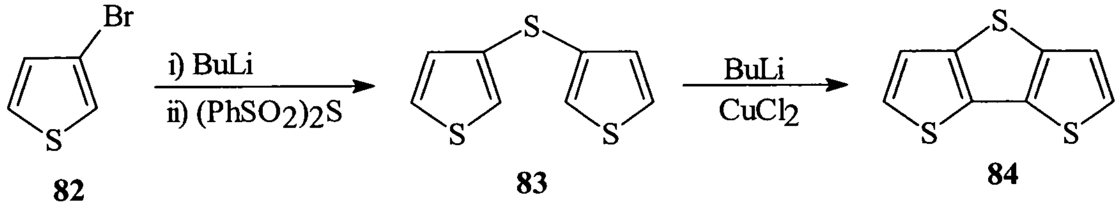
All the above examples have focussed on the synthesis of cyclopentadithiophenes. One example of the use of this ring formation strategy in the synthesis of a dipyrrolo-imidazole system **81** as shown in Scheme 17 was reported by Burger and Dreier.[16]


81

Scheme 17

Treatment of pyrrole **79** with butyl lithium in HMPA followed by reaction with dichloromethane gave *N,N'*-dipyrrolylmethane **80** in 85% yield. Treatment of **80** with butyl lithium followed by oxidative coupling with copper (II) dichloride gave dipyrrolo[1,2-*c*][2,1-*e*']-2*H*-imidazole **81** in low yield (24%).

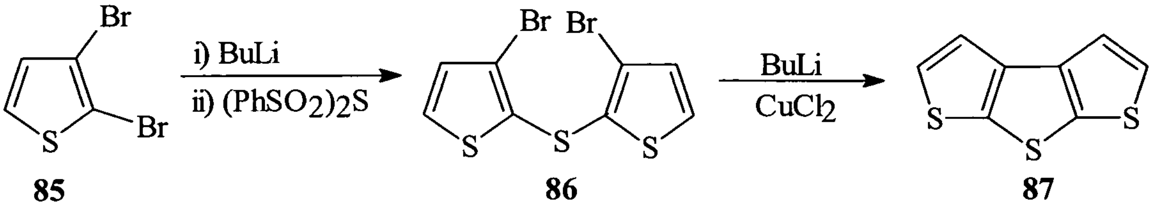
There are several reported examples of the synthesis of various 5,5,5-fused heterocycles using this general strategy where, unlike all of the above, the atom linking the bi-heteroaryl system is a heteroatom (either sulfur or silicon).


82 **83** **84**

Scheme 18

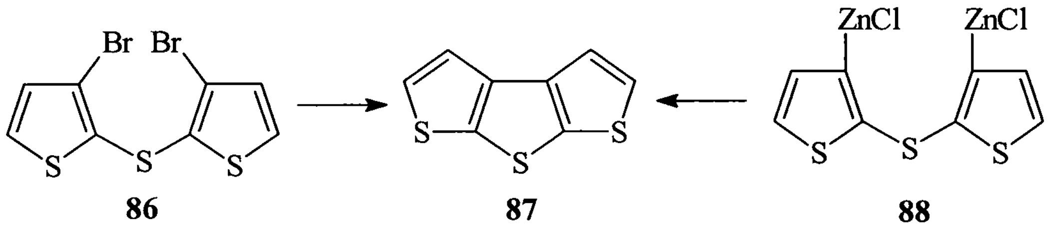
One such example was reported by de Jong and Janssen [17] who described the synthesis of dithieno[3,2-b][2,3-d]thiophene **84** as shown in Scheme 18. Treatment of **82** with butyl lithium followed by reaction with bis(phenylsulfonyl)sulfide gave

83 in 68% yield. Oxidative coupling of **83** gave the desired tricycle **84** (52%). The same authors used identical methodology to produce the isomeric dithieno[2,3-b][3,2-d']thiophene **87** in 21% overall yield as shown in Scheme 19.



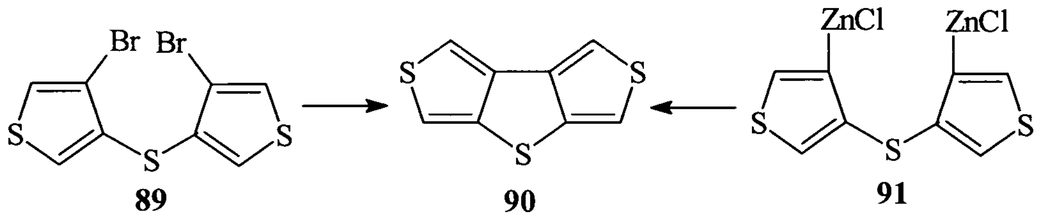
Scheme 19

Iyoda *et al.* [13] also reported the synthesis of **87** (Scheme 20) in varying yields (45-75%) from the dibromo compound **86** using three different cyclisation methods (refer to discussion preceding Scheme 13 for further details on cyclisation methodologies). Two of these methodologies are direct, one passes through the intermediate **88**.



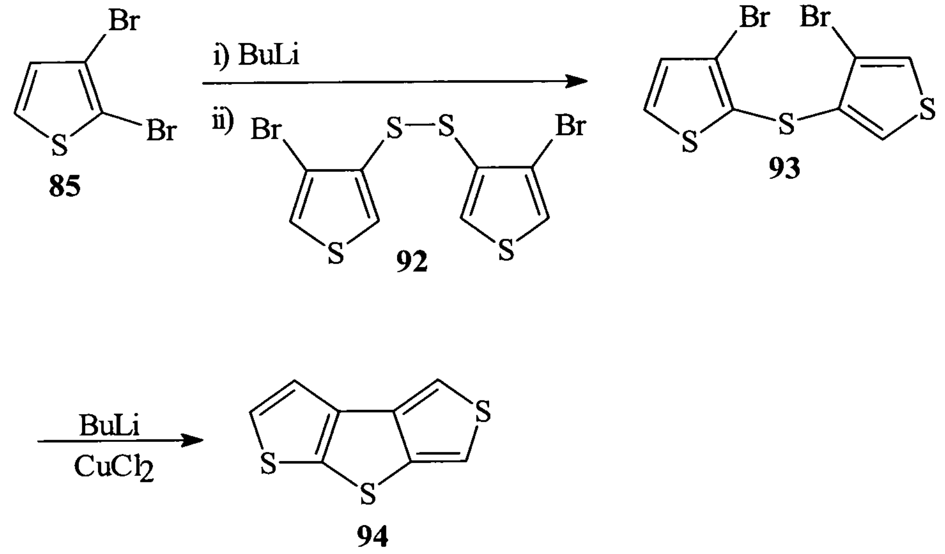
Scheme 20

The same authors [13] used the same three sets of conditions to synthesise dithieno[3,4-*b*][3,4-*d*']thiophene **90** from compound **89** (Scheme 21) in yields ranging from 50-78%.



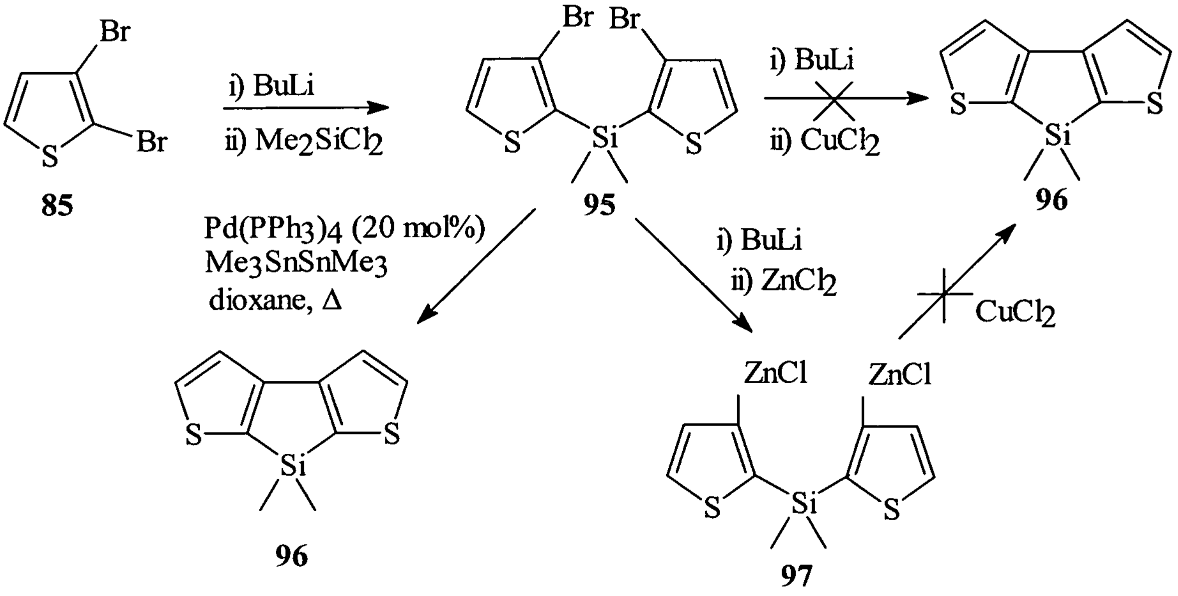
Scheme 21

The synthesis of **90** *via* a copper (II) chloride mediated coupling reaction was also reported by de Jong and Janssen [17] although the yields quoted were much lower (*ca.* 20%) than those reported above. The same authors also reported the synthesis of the unsymmetrical isomer, dithieno[2,3-*b*][3,4-*d*']thiophene **94** shown in Scheme 22. Oxidative coupling of the dibromo compound **93** gave the desired tricycle in 29% yield.[17]



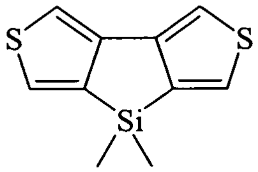
Scheme 22

There are two examples of 5,5,5-fused heterocycles in the literature where the atom linking the bi-heteroaryl system is silicon. Iyoda *et al.* [13] described the synthesis of **96** (Scheme 23) and **98**, using the same cyclisation methods as used in the synthesis of **64** and **87** (refer to discussion preceding Scheme 13 for further details on cyclisation methodologies).



Scheme 23

On this occasion, attempts to cyclise the dibromo compound **95**, and the organozinc compound **97** using copper (II) chloride surprisingly failed, and no other major products were obtained. However, the palladium catalysed cyclisation proceeded smoothly to give 7-dimethylsila-7*H*-cyclopenta[1,2-*b*][4,3-*b*']dithiophene **96** in 72% yield. The isomer of **96**, 7-dimethylsila-7*H*-cyclopenta[1,2-*c*][3,4-*c*']dithiophene **98** was synthesised using all three cyclisation methods in yields ranging between 30-64%.



98

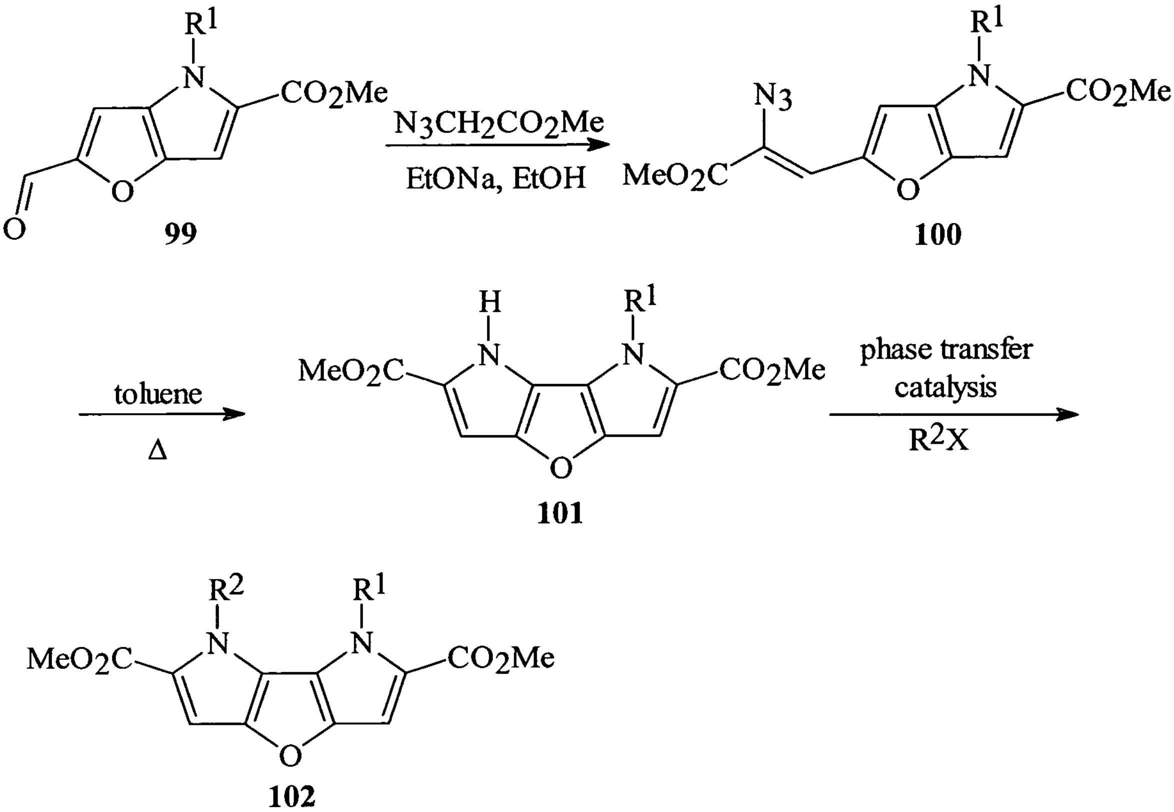
The above examples show that the three different cyclisation methodologies employed by Iyoda *et al.* [13] are useful synthetic tools to varying degrees when applied to the synthesis of fused 5,5,5-systems.

The majority of the syntheses described above using this general cyclisation strategy are targeted towards tricyclic fused thiophene systems, with very few other heterocycles targeted. The general synthetic methodology described in the next section, which involves formation of the terminal ring *via* a ring annulation step, allows for more variation in the type of 5,5,5-fused heterocycle produced.

2. Synthesis of 5,5,5-fused heterocycles *via* terminal ring formation

There are various reported examples of the synthesis of this class of heterocycle *via* the stepwise formation of the ring system from a monocyclic heterocycle building block. Examples in which the two terminal rings are formed simultaneously around a central heterocycle are covered in the next section, whereas this chapter details examples in which the two subsequent annulation steps are carried out independently.

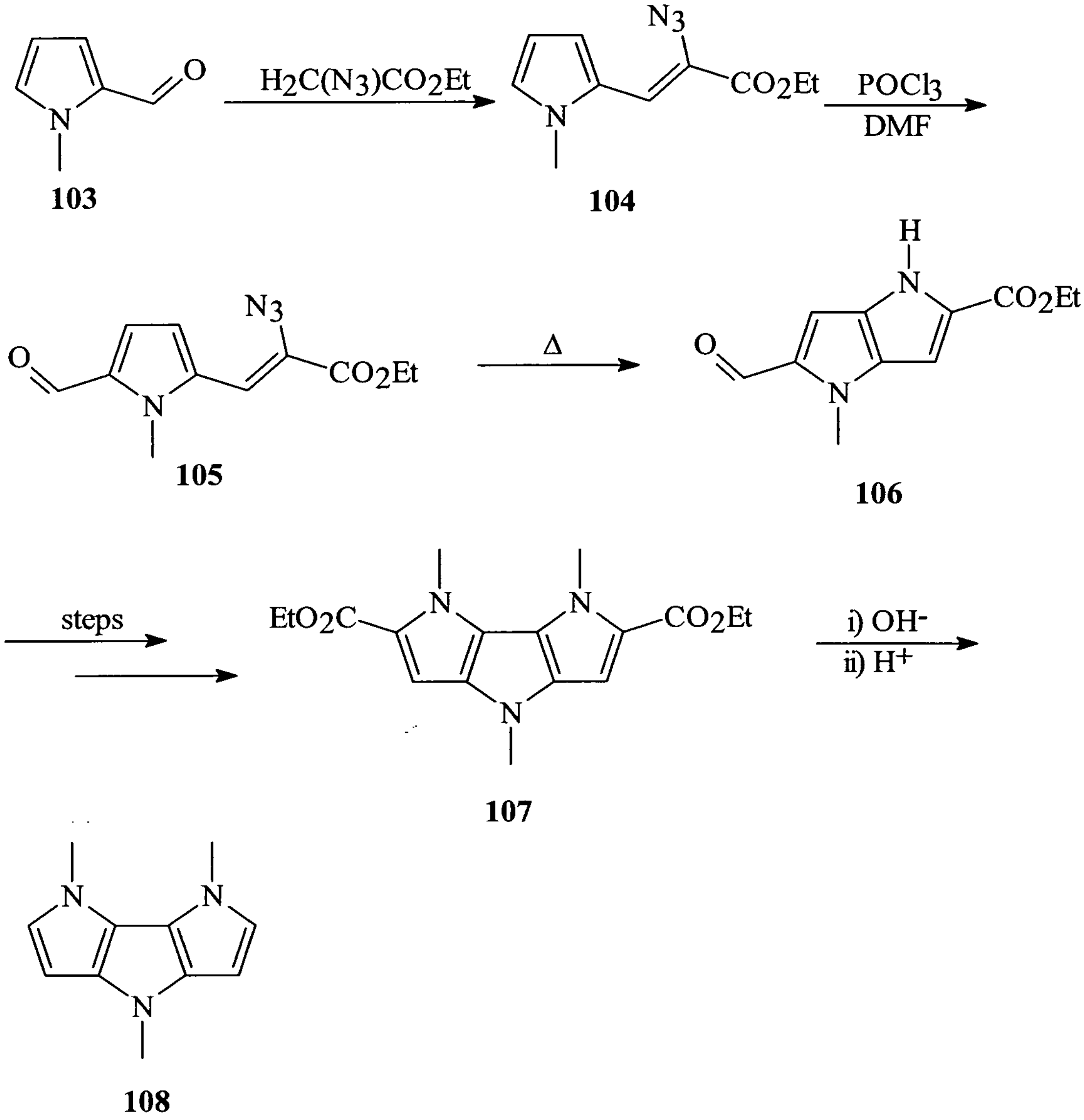
Krutosikova and co-workers [18] reported the synthesis of some substituted furo[3,2-*b*][4,5-*b*']dipyrroles **102** *via* the appropriate substituted vinylazide **100** as shown in Scheme 24. This method of using a substituted vinylazide to prepare fused pyrrole rings (*via* the nitrene intermediate) was first used by Rees and Moody [19] to prepare substituted indoles.



Scheme 24

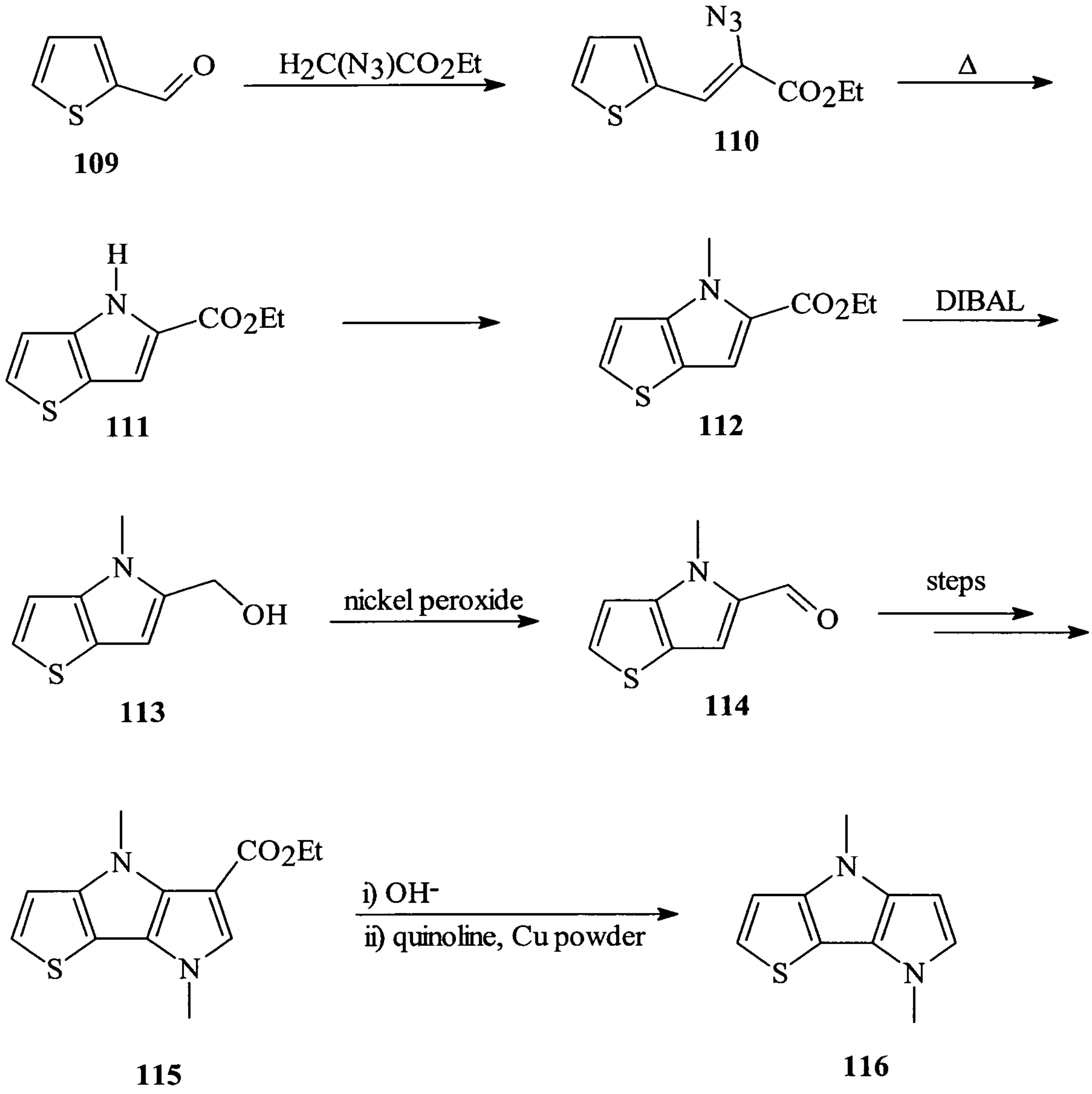
Reaction of the 2-formylfuro[3,2-*b*]pyrrole substrate **99** with methyl azidoacetate in the presence of sodium ethoxide was reported to give the vinylazide **100** in good yield. Thermolysis of **100** was carried out in boiling toluene to give the 1-substituted-7*H*-furo[3,2-*b*][4,5-*b*']dipyrrole-2,6-dicarboxylates **101** in 66% (R^1=Me) and 74% yield (R^1=benzyl). Phase transfer catalysis conditions (triethylbenzylammonium chloride/50% NaOH/toluene/R^2X) were employed to effect *N*-substitution in good yields (*ca.* 85% in all cases).

A similar synthetic strategy was employed by Aratani *et al.* [20] to synthesise 1,4,7-trimethyl-4,7-dihydro-1*H*-dipyrrolo[3,2-*b*;2',3'-*d*]pyrrole **108** and 4,7-dimethyl-4,7-dihydro-pyrrolo[3,2-*b*]thieno[2,3-*d*]pyrrole **116** as shown in Scheme 25 and Scheme 26 respectively. Reaction of *N*-methylpyrrole-2-carboxaldehyde **103** with ethyl azidoacetate gave **104** (Scheme 25) which was then formylated to give **105**. Thermolysis of **105** gave the bicyclic system **106** in 61% yield. *N*-Methylation of **106** followed by an identical pyrrolo-annulation followed by another *N*-methylation step gave the 5,5,5-system **107**. Alkaline hydrolysis of **107** followed by decarboxylation produced 1,4,7-trimethyl-4,7-dihydro-1*H*-dipyrrolo[3,2-*b*;2',3'-*d*]pyrrole **108** in 34% yield.



Scheme 25

The same paper also describes the synthesis of 4,7-dimethyl-4,7-dihydro-pyrrolo[3,2-*b*]thieno[2,3-*d*]pyrrole **116** *via* a similar synthetic route, as shown in Scheme 26.

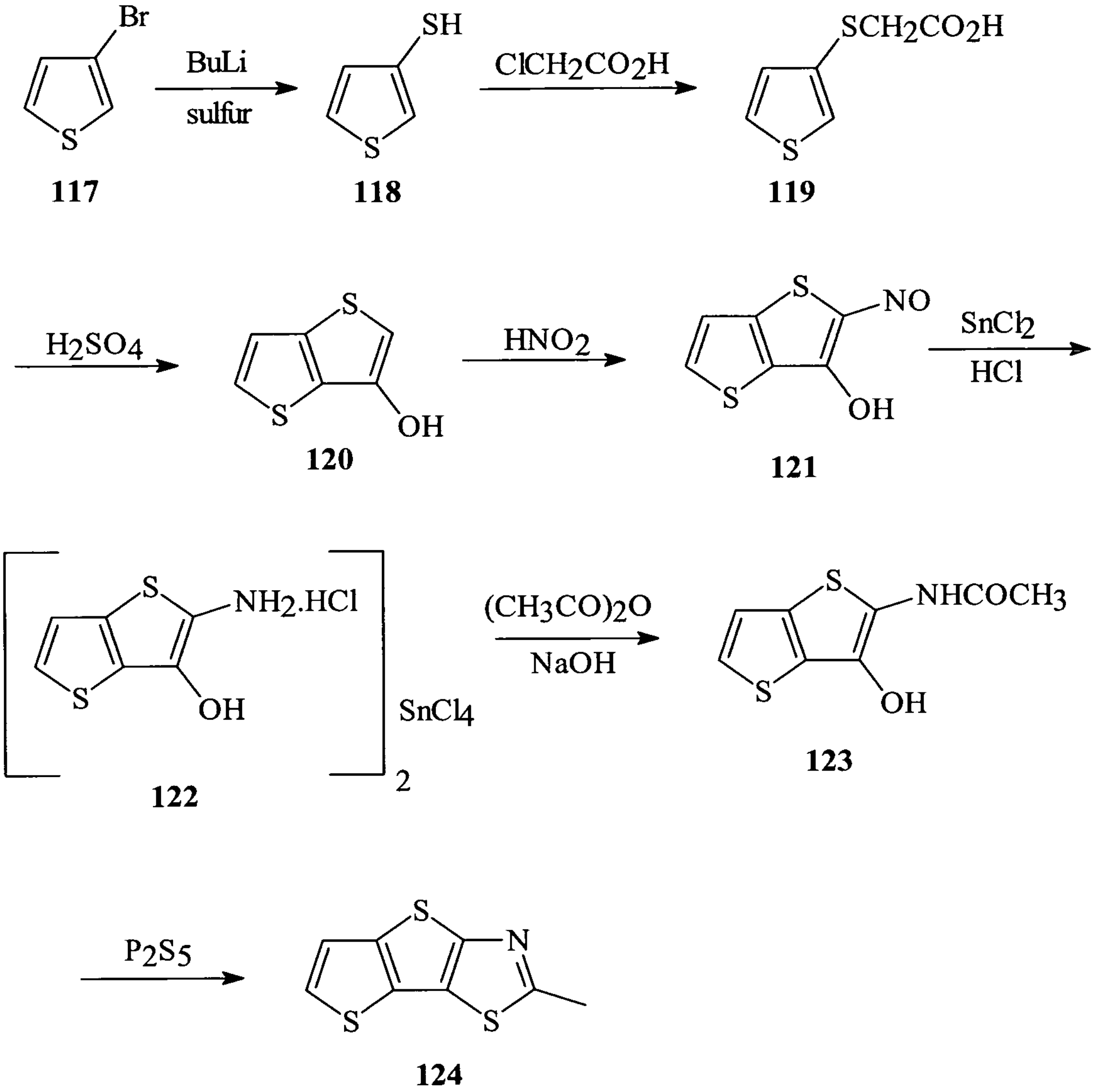


Scheme 26

Pyrrolo-annulation of **109** *via* the azide **110** gave the thienopyrrole **111**. Reduction of the *N*-methylated compound **112** with an excess of DIBAL gave the alcohol **113** which was oxidised to the aldehyde **114** in 71% overall yield using nickel peroxide.

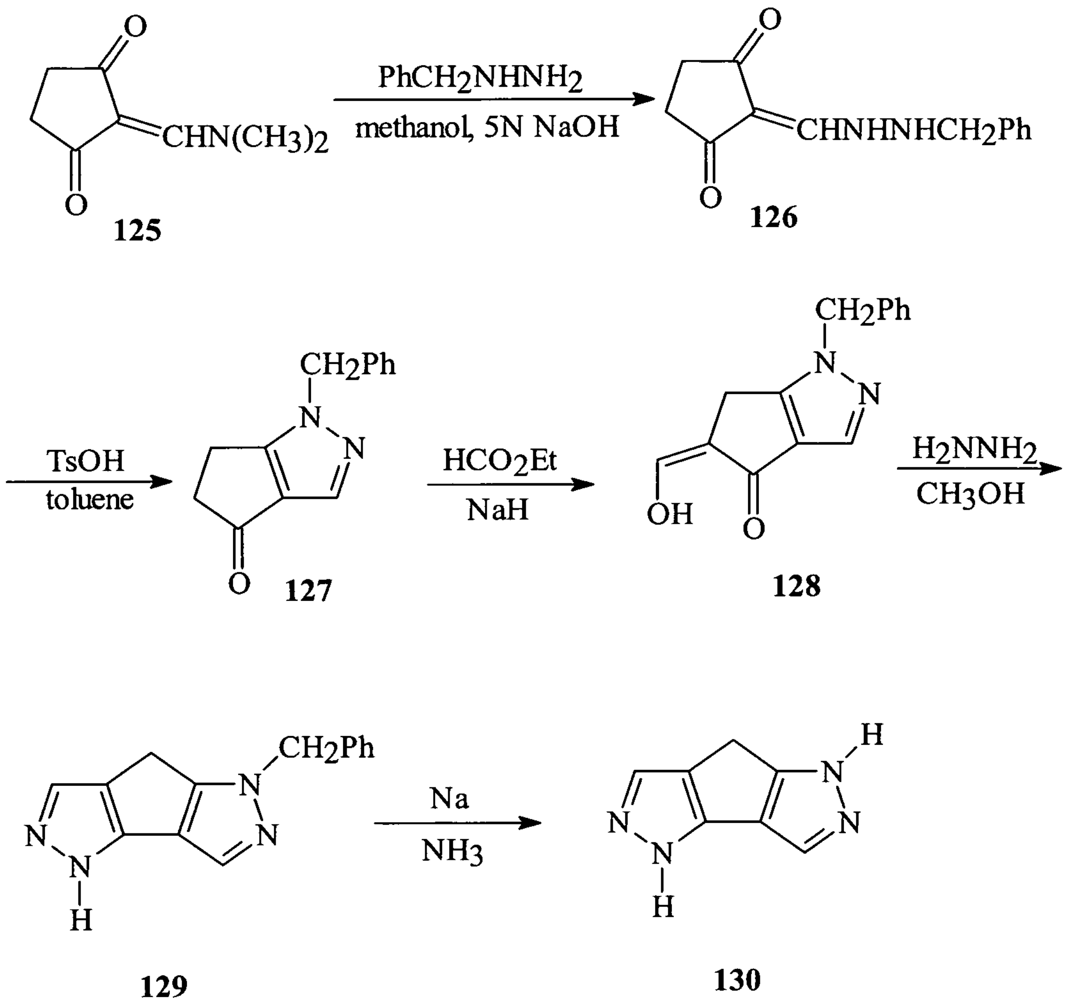
Pyrrolo-annulation of **114** as previously described, followed by *N*-methylation gave the 5,5,5-system **115** in 49% yield. Alkaline hydrolysis of **115** followed by decarboxylation by heating in quinoline with copper powder gave 4,7-dimethyl-4,7-dihydro-pyrrolo[3,2-*b*]thieno[2,3-*d*]pyrrole **116** (59%).

Synthesis of the unsymmetrical 2-methylthieno[3,2-*b*]thieno[2,3-*d*]thiazole system **124** was described by Abramenko and Zhiryakov [21], starting from 3-bromothiophene **117** as shown in Scheme 27. Treatment of **117** with butyl lithium followed by subsequent reaction with elemental sulfur gave thiophene-3-thiol **118** in 69% yield. Reaction of **118** with a slight excess of chloroacetic acid gave 3-thienylglycolic acid **119** in good yield (77%). Cyclisation of **119** was effected by treatment with *conc.*H_2SO_4 at 100 °C, to give 3-hydroxythieno[3,2-*b*]thiophene **120** in low yield (14%). 2-Nitroso-3-hydroxythieno[3,2-*b*]thiophene **121** was synthesised (84%) by nitrosation of **120** with sodium nitrite. The nitroso-compound **121** was converted to the double tin salt **122** of 2-amino-3-hydroxythieno[3,2-*b*]thiophene in 51% yield by reduction of **122** with stannic chloride in *conc.*HCl. This salt, **122**, was reacted with acetic anhydride in aqueous alkaline media to give a 63% yield of 2-acetamido-3-hydroxythieno[3,2-*b*]thiophene **123**. Reaction of **123** with phosphorus pentasulfide gave the cyclised product, 2-methylthieno[3,2-*b*]thieno[2,3-*d*]thiazole **124**, in 31% yield.



Scheme 27

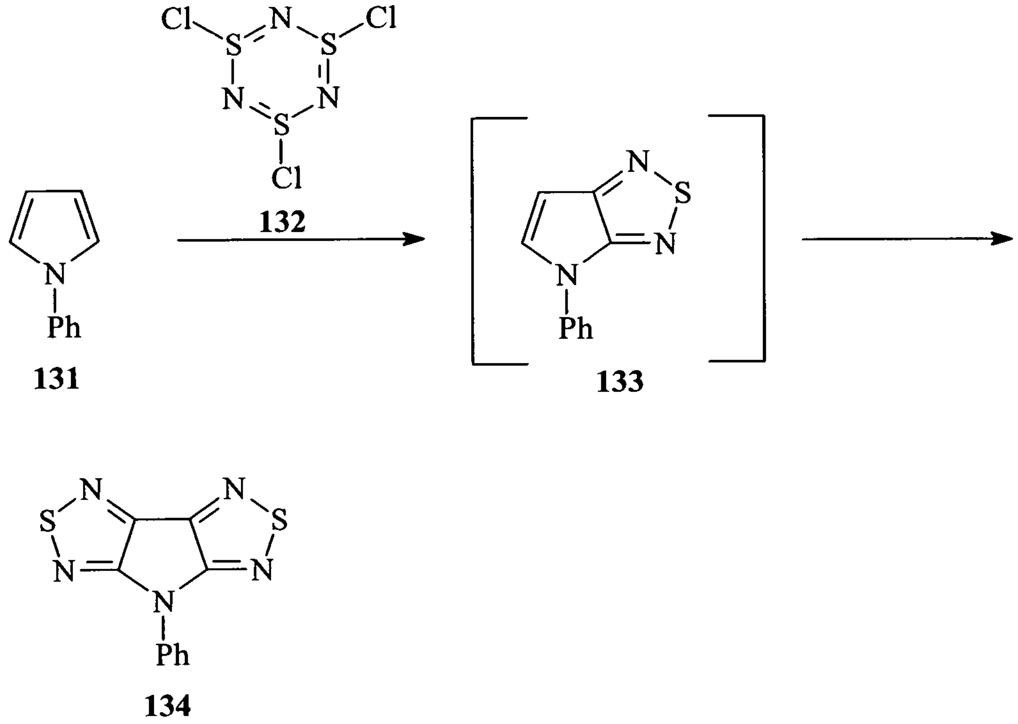
Synthesis of a cyclopenta[1,2-*c*][3,4-*c*']dipyrazole **130** *via* a stepwise ring formation process was reported by Peet and Le Tourneau [22] starting from the enamine dione **125** as shown in Scheme 28. Treatment of **125** with benzyl hydrazine through a Michael addition-elimination gave **126** (53%). Cyclisation of **126** to give cyclopyrazolone **127** in 44% yield was effected with *p*-toluenesulfonic acid in refluxing toluene. Cyclopyrazolone **127** was reacted with sodium hydride then formylated with ethyl formate to give the enol **128** in excellent yield (86%). Cyclisation of **128** with hydrazine in methanol gave the protected cyclopentadipyrazole **129** (86%), the de-protection of which with sodium in ammonia gave the parent system **130** in 50% yield.



Scheme 28

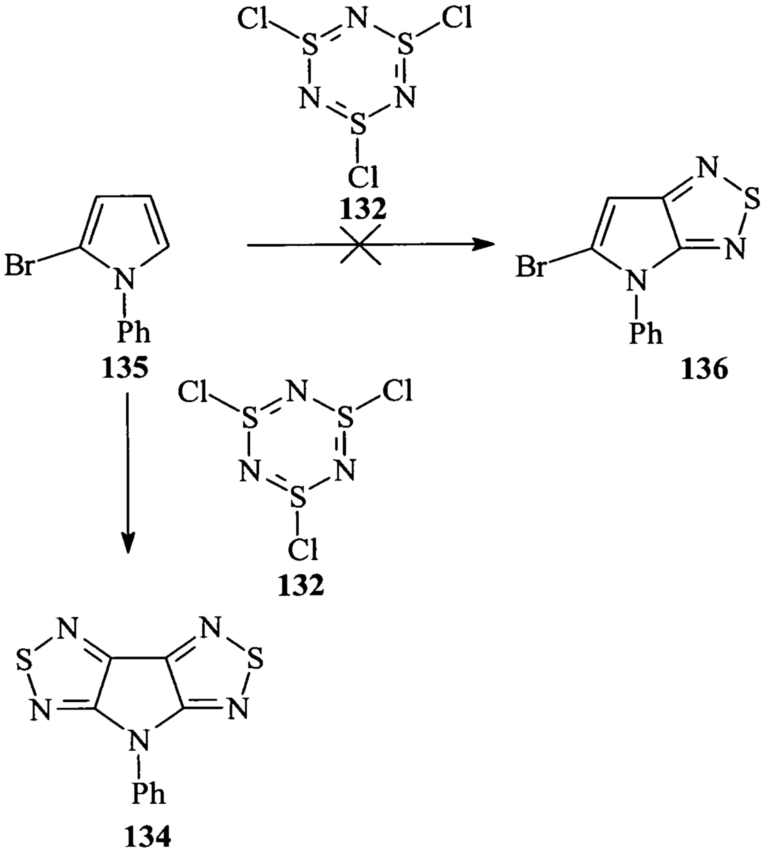
Another example of the use of this general ring-building strategy towards the preparation of a 5,5,5-fused heterocycle was reported by Duan and Rees,[23] which utilised the reaction of trithiazyl trichloride **132** with a pyrrole **131** to give a pyrrolobis(thiadiazole) **134** as shown in Scheme 29. It appears that the trithiazyl trichloride **132** reacts across the 2,3- and 4,5-positions of the pyrrole **131** to give the

7-phenylpyrrolo[2,3-*c*][4,5-*c*’]bis[1,2,5]thiadiazole product **134** in 43% yield. Attempts to synthesise the parent compound proved to be difficult, even when various *N*-protected pyrroles were used as starting material.[23]



Scheme 29

It should be noted that in this case the proposed bicyclic intermediate **133** was not isolated. The possible reason given for this is that the remaining carbon-carbon double bond in **133** may have more enamine character and would therefore be more reactive to **132** than the starting pyrrole **131**. An attempt to prevent formation of the second thiadiazole ring, and therefore to isolate the proposed bicyclic intermediate **136**, was carried out by using the 2-bromo-1-phenylpyrrole **135** starting material as shown in Scheme 30. It was hoped that the 2-bromo-substituent would block the formation of the second thiadiazole ring. However, this proved not to be the case, with the 2-bromo-substituent appearing to accelerate the reaction (with respect to the unsubstituted pyrrole example shown in Scheme 29), as well as increasing the yield of the reaction from 43% to 75%. This effect of reducing reaction time and increasing the yield of the reaction was also found to occur when other bromo-substituted pyrroles were used as starting materials. No attempts to produce a bicyclic compound through the utilisation of an inert substituent on the 2-position of the pyrrole ring were reported.

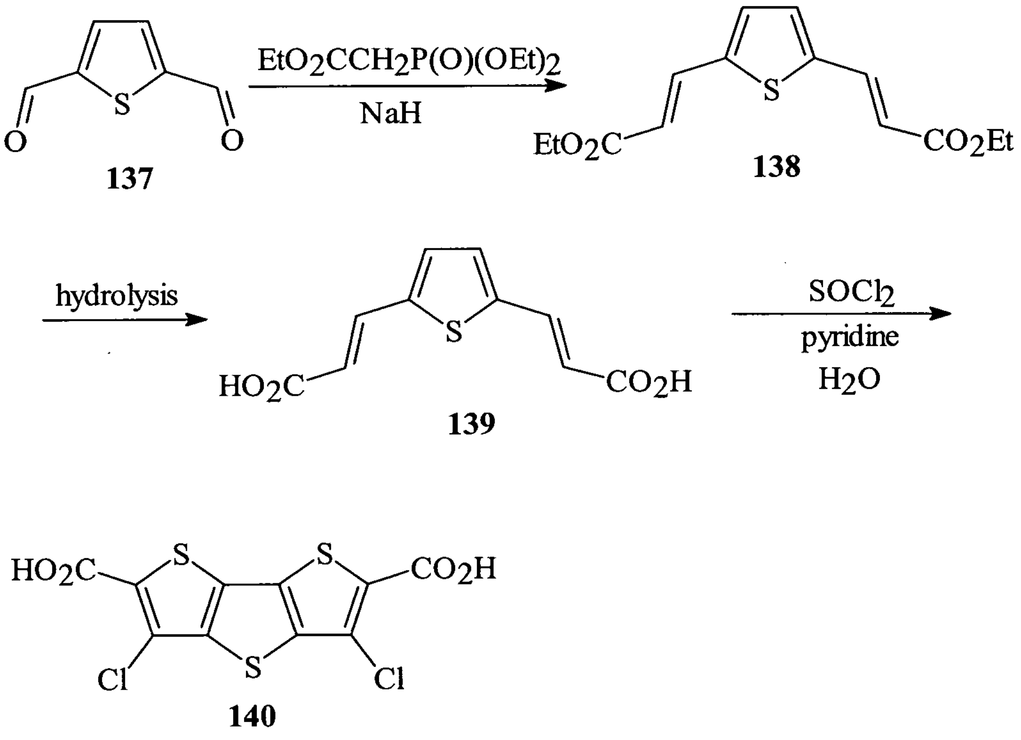


Scheme 30

As the bicyclic intermediate **136** is not isolated/detected, this synthesis may also be viewed as an example of formation of the two terminal rings in the one step. More "formal" examples of this type of synthesis of 5,5,5-fused heterocycles are reviewed in the next section.

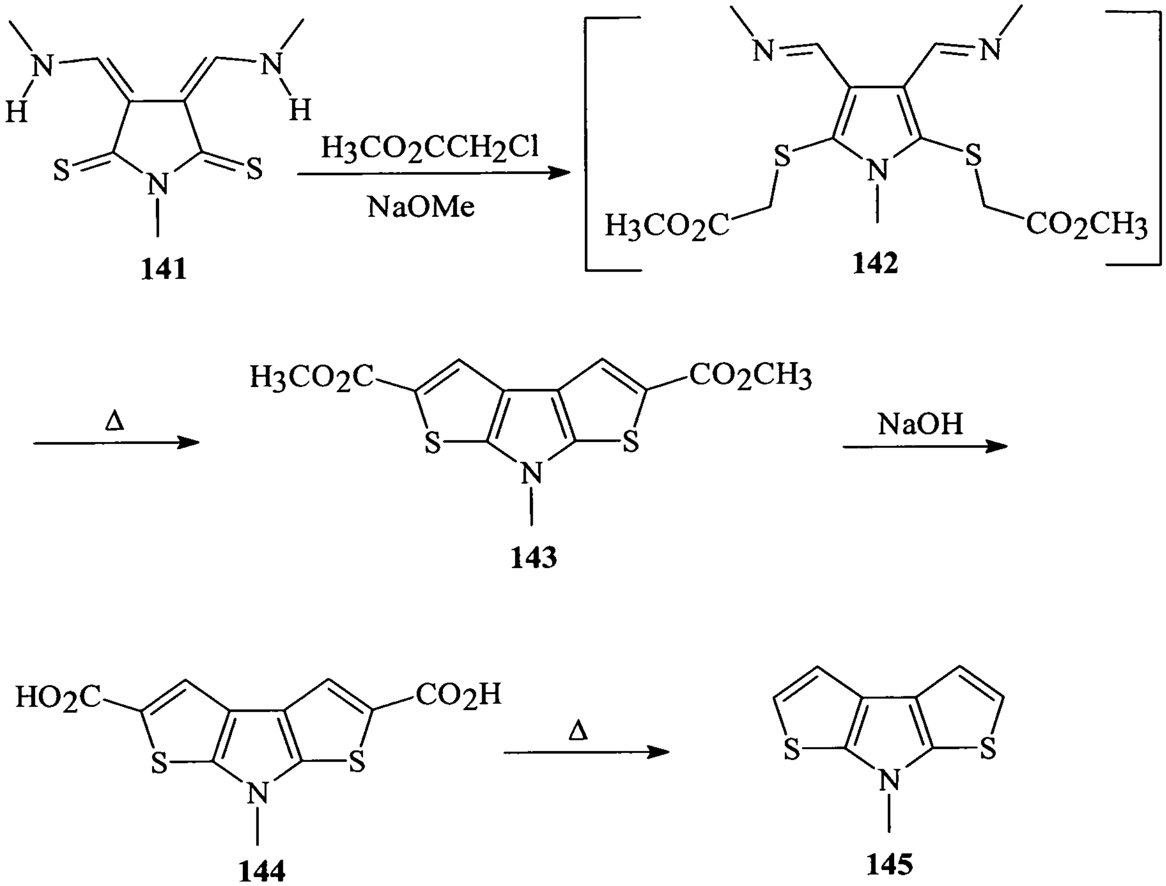
3. Synthesis of 5,5,5-fused heterocycles *via* simultaneous formation of both terminal rings

Most examples of 5,5,5-fused heterocycles synthesised using this general synthetic strategy are of the thienodipyrrole type, although there are a few reports in the literature of the synthesis of other types of system which will be looked at first. One such example reported by Capron *et al.* describes the synthesis of a thienodithiophene **140** as shown in Scheme 31.[24] Reaction of the dialdehyde **137** with the appropriate phosphonate gave the diester **138**, which was hydrolysed to give the di-acid **139** in 70% overall yield. Cyclisation of **139** with $SOCl_2$ in pyridine, followed by treatment with water gave the cyclised product **140**, with no yield quoted.



Scheme 31

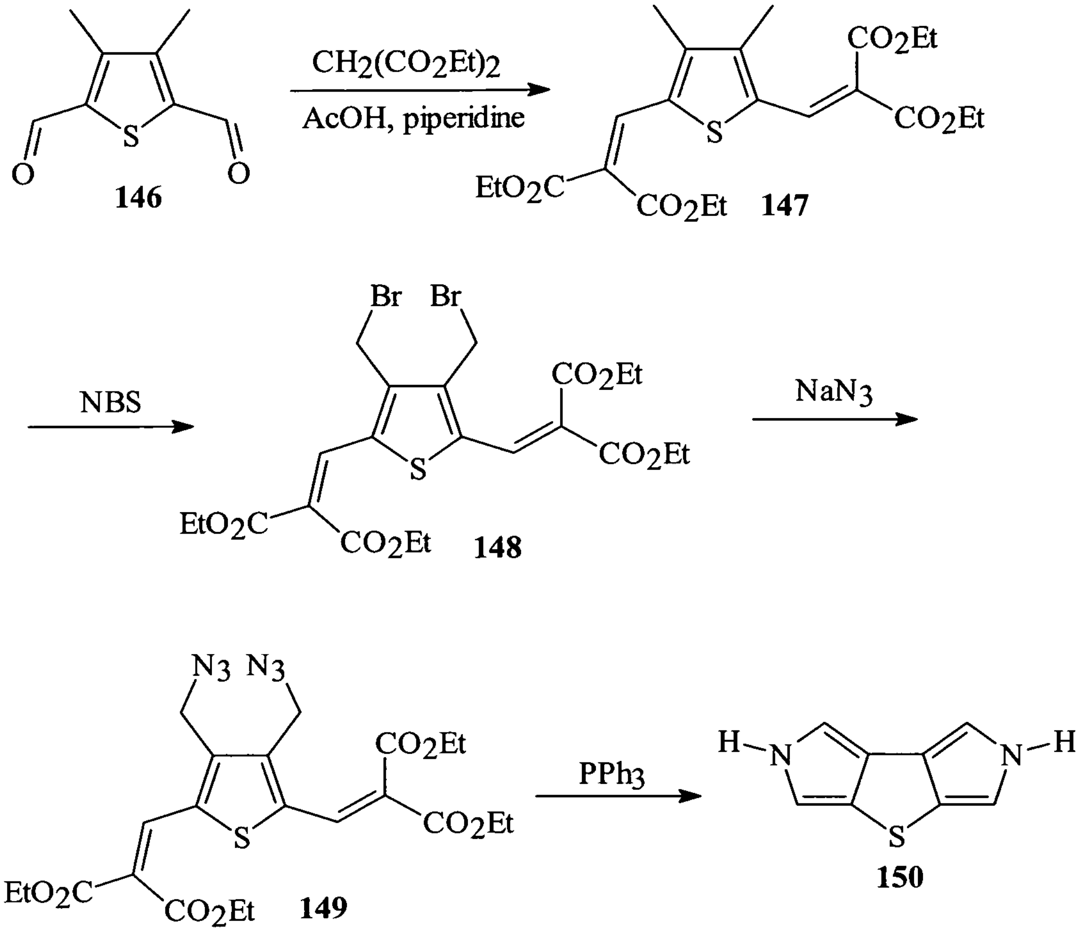
The other example of the synthesis of a non-thienodipyrrole type tricyclic system was reported by Panfilova *et al.* who described the synthesis of 1-methylbisthieno[2,3-*b*][2,3-*d*']pyrrole **145** as shown in Scheme 32.[25]



Scheme 32

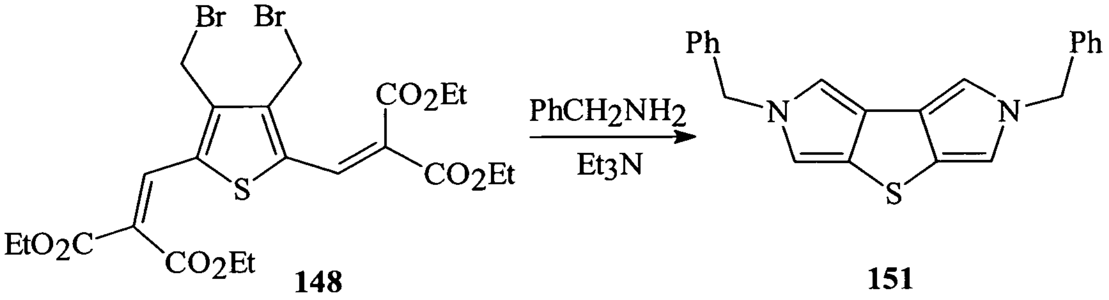
Alkylation of the pyrroledithione **141** (the synthesis of which is not described) with methyl chloroacetate gave **142** which, when boiled in methanol, gave the cyclised product **143**. Hydrolysis followed by decarboxylation gave the parent system, 1-methylbisthieno[2,3-*b*][2,3-*d*']pyrrole **145**, in 21% yield. As stated previously, the above two examples are rare, in that the majority of work reported using this general synthetic strategy is on the synthesis of various thienodipyrrole systems. Sha and

Tsou [26] reported the synthesis of thieno[2,3-c][4,5-c']dipyrrole **150** as shown in Scheme 33.



Scheme 33

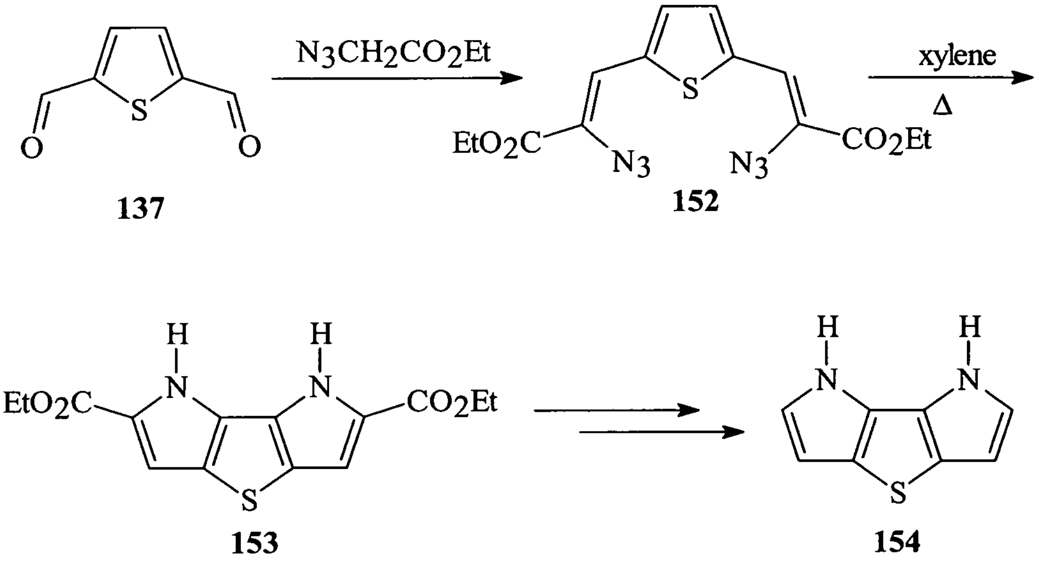
Reaction of the dialdehyde **146** with diethyl malonate gave **147** in 92% yield. The dibromo compound **148** was also prepared in 92% yield *via* the reaction of **147** with NBS. The dibromo compound was then reacted with sodium azide to give the diazide **149** (74%). Cyclisation of **149** with triphenylphosphine gave a 59% yield of thieno[2,3-c][4,5-c']dipyrrole **150**. The pathway of this novel intramolecular cyclisation reaction between a phosphineimine intermediate and the alkylidenemalonate is proposed to occur through hydration of a phosphineimine intermediate, followed by cyclisation. Loss of TPPO and diethylmalonate then occurs to give the final product **150**.[27] The same authors [26] used a different cyclisation strategy to prepare an *N,N'*-disubstituted derivative **151** as shown in Scheme 34.



148 **151**

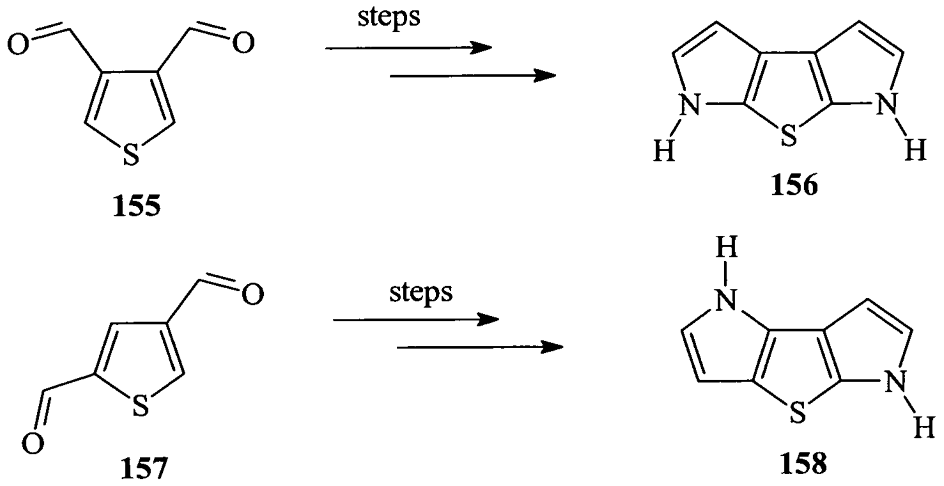
Scheme 34

Reaction of the dibromo compound **148** with benzylamine in the presence of triethylamine gave 3,6-dibenzylthieno[2,3-*c*][4,5-*c*']dipyrrole **151** in 43% yield. A large body of work was carried out by Farnier *et al.* [28] towards the synthesis of several thienodipyrrole systems. The synthesis of 4*H*,5*H*-thieno[3,2-*b*][4,5-*b*']dipyrrole **154** is shown in Scheme 35.



Scheme 35

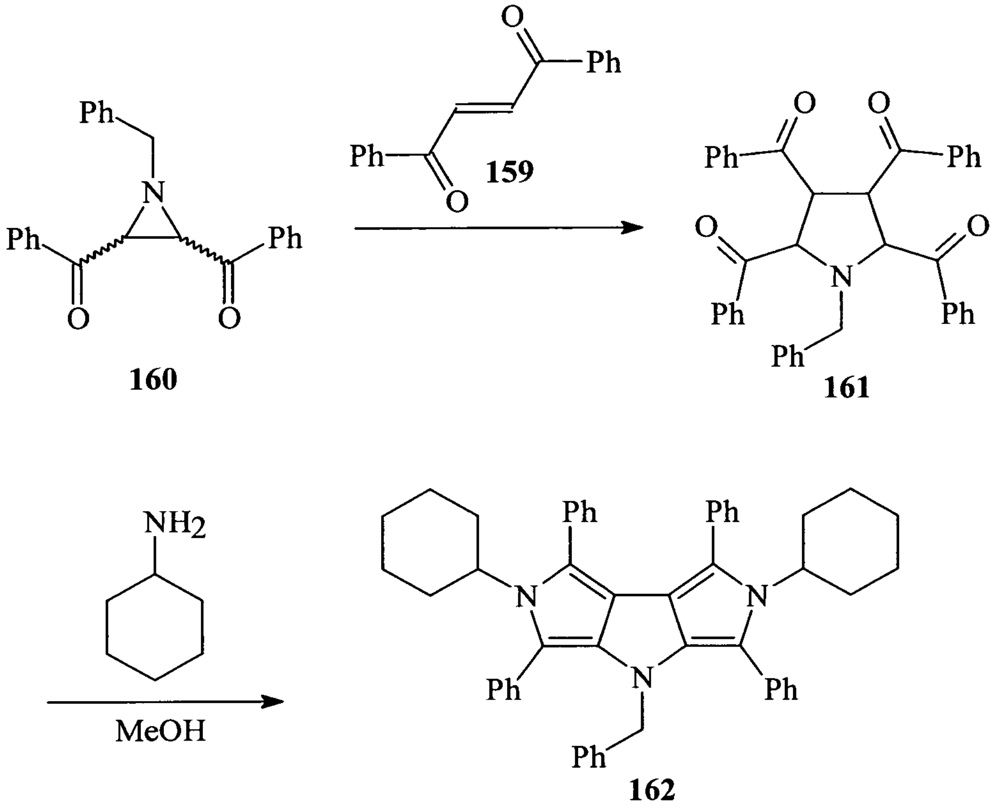
Reaction of the dialdehyde **137** with the appropriate azide gave the thermolysis precursor **152** in 41% yield. Cyclisation of **152** in boiling xylene gave the tricyclic product **153** in 76% yield. Hydrolysis of **153** (aqueous sodium hydroxide) followed by decarboxylation (copper powder, quinoline) gave the parent compound, 4*H*,5*H*-thieno[3,2-*b*][4,5-*b*']dipyrrole **154**, in 35% yield. The same authors also prepared the isomers **156** and **158**, using the same synthetic methodolgy, shown in Scheme 36.



Scheme 36

Both 2*H*,7*H*-thieno[2,3-*b*][5,4-*b*']dipyrrole **156** and 2*H*,5*H*-thieno[2,3-*b*][4,5-*b*']dipyrrole 158 were prepared in overall yields comparable to that obtained for the synthesis of 4*H*,5*H*-thieno[3,2-*b*][4,5-*b*']dipyrrole **154**.

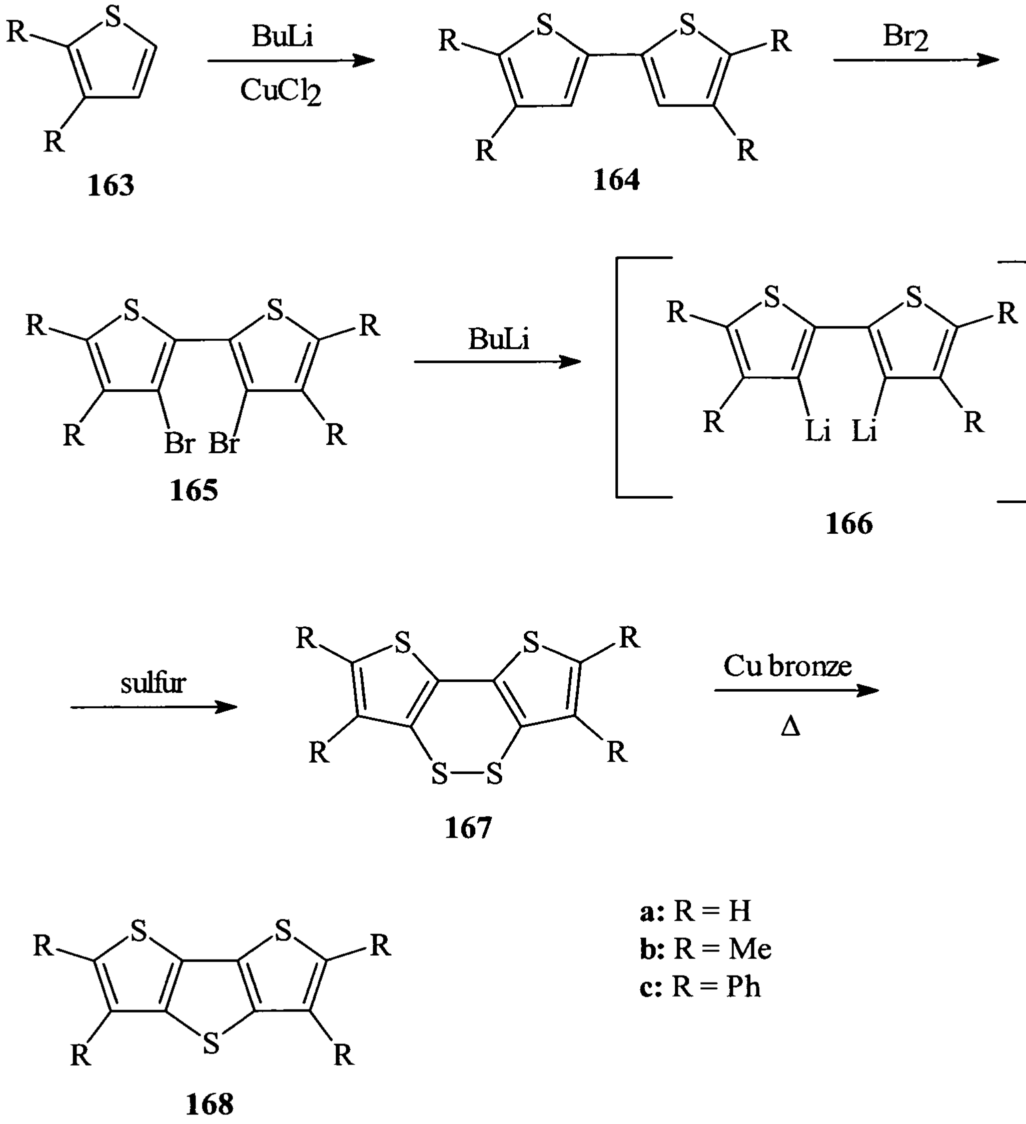
There is one example in the literature, reported by Lown and Akhtar,[29] of the use of this general synthetic strategy towards the synthesis of a pyrrolodipyrrole system as shown in Scheme 37. Synthesis of 2,3,4,5-tetrabenzoyl-1-benzylpyrrolidine **161** from the reaction between *trans*-1,2-dibenzoylethylene **159** and 2,3-dibenzoyl-1-benzylaziridine **160** occurred in 65% yield (undetermined stereochemistry). Reaction of **161** with cyclohexylamine gave tetraphenyldipyrrolo[3,4-b][3,4-d']pyrrole **162** (87%).



Scheme 37

4. Synthesis of 5,5,5-fused heterocycles *via* ring contraction

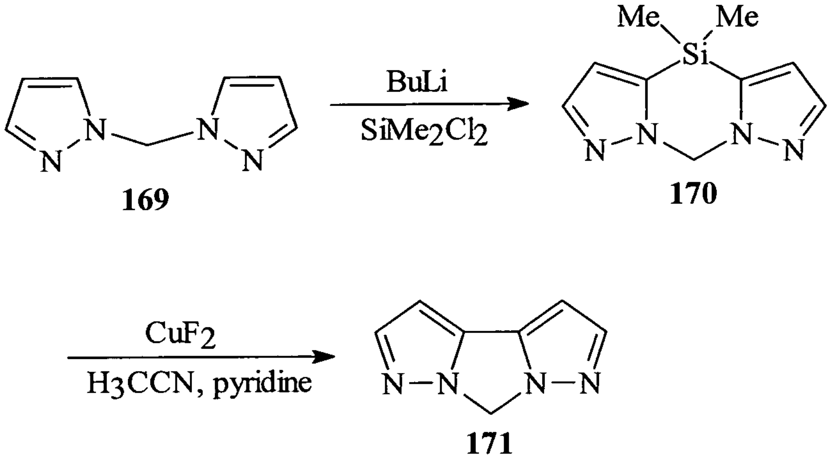
There are very few reports in the literature which refer to the synthesis of 5,5,5-systems *via* ring contraction. However, examples published include ring contractions *via* extrusion of sulfur, or by the use of a desilylating-oxidising system, which effectively brings about the extrusion of a dimethylsilyl moiety. An example of the former was reported by Schroth *et al.* [30] The common 3,3'-dibromo-2,2'-dithienyl intermediates **165a-c** (Scheme 38) were prepared *via* lithiation and subsequent coupling of the appropriate thiophene **163**, followed by bromination of the coupled product **164**. The disulfane bridge was introduced by an *in situ* bromo-lithium exchange followed by reaction with elemental sulfur to give the dithiins **167a,b,c**. Synthesis of the substituted dithiins **167b** (Me, 64%) and **167b** (Ph, 61%) occurred in higher yield than in the case of the unsubstituted example **167a** (H, 19%), which is due to the possibility of competing lithiation taking place at the unsubstituted thiophene carbon atoms. Attempts to bring about sulfur extrusion by photochemical methods and by treatment of the dithiins **167a,b,c** with triethyl phosphite, a thiophilic agent, were unsuccessful. However, sulfur extrusion effected by treatment of the dithiins **167a,b,c** with copper bronze at elevated temperatures (200-320 °C) did give the dithienothiophenes **168a,b,c** in yields between 47-69%.



Scheme 38

An example of the synthesis of a 5,5,5-system *via* extrusion of a dimethylsilyl group was reported by Diez-Barra *et al.* [31] in which a novel desilylating-oxidising system is utilised to bring about the ring contraction (Scheme 39). Treatment of bis(pyrazol-1-yl)methane **169** with butyl lithium at 0 °C followed by subsequent reaction with dimethylsilyl dichloride gave 9*H*-4,4'-dimethyldipyrazolo[5,1-*b*][1',5'-*e*]1,3,5-

siladiazine **170** in 63% yield. Reaction of **170** with CuF_2 in acetontrile/pyridine (2:1) produced 8*H*-dipyrazolo[1,5-*c*][5',1'-*e*]imidazole **171** in low yield (15%).

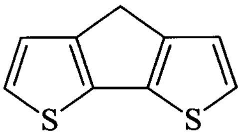


Scheme 39

Attempts to extend the scope of this reaction by using various substituted bis(pyrazol-1-yl)methanes proved unsuccessful, probably due to steric interactions between the substituents and the dimethylsilyl group. This novel desilylating-oxidising system combines the good desilylation ability of fluoride ions with the oxidation ability of copper (II). Pyridine is required in the system in order to solubilise the inorganic salt and to activate the copper (II) by coordination.[32]

Potential applications of 5,5,5-fused heterocycles

As can be seen from the literature reviewed in this introduction, a large proportion of the research carried out into the synthesis of 5,5,5-fused heterocycles has been focussed on fused thiophenic systems. Perhaps the main reason for this is that they are useful building blocks used in the preparation of thiophene oligomers. These oligomers function as organic semiconductors, with potential applications ranging from photodiodes,[33] light emitting devices (LED),[34] and thin film transistors.[35] Other examples of 5,5,5-systems with potential applications in these areas are cyclopentadithiophenes (such as compound **18**),[6] dipyrrolopyrrole **108**,[20] and thienopyrrolopyrrole **116**.[20]



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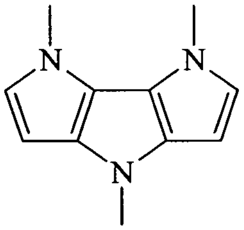

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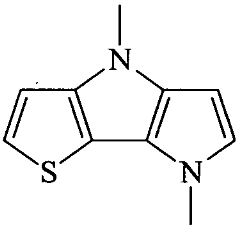
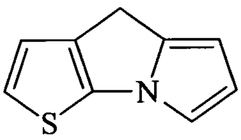


116

Several of the systems described in this introduction have been prepared due to their potential pharmacological activity. For example, the thienopyrrolozine **34** [8] was prepared due to its potential use as a building block in the synthesis of thieno-analogues of mitomycin **172**, which has attracted considerable interest due to its apparent antitumour activity.[36]



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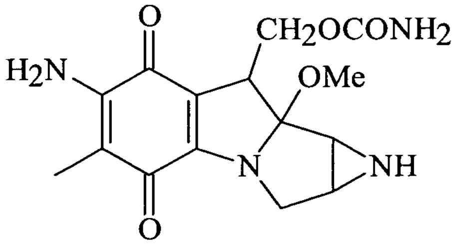
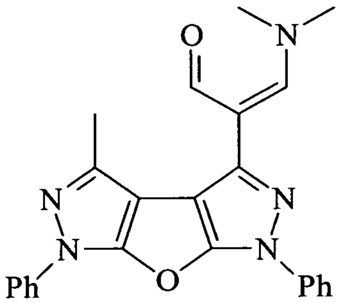


172

The furodipyrazole **46** and thienodipyrazole **49** [10, 11] were also synthesised with a view to studying their pharmacological activity. These particular systems were targeted by the author due to the claimed activity of pyrazole containing compounds being used as antibacterial agents.[37]



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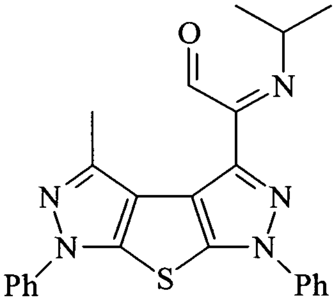

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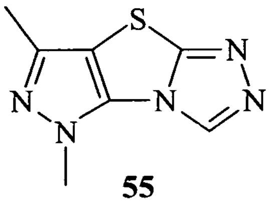
Another example of a 5,5,5-system which was targeted for potential use as a fungicide is the pyrazolothiazolotriazole **55**. [12]. This system is an analogue of tricyclazole **173**, which is a highly selective fungicide [38] patented by Eli Lilly.



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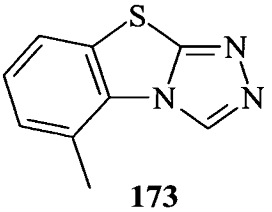


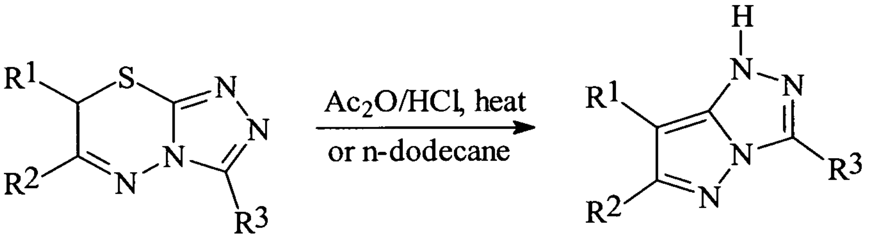
173

There are currently no reports in the literature detailing how successful any of these compounds were in achieving their proposed function. As for the other systems outlined in this introduction, no proposed application was stated. However, the synthesis of this type of system remains a challenging task, and this may be what attracts researchers to this area.

B. DISCUSSION

1. Gas phase chemistry of triazolothiadiazines

It has been reported in the literature [39,40] that, in the solution phase, triazolothiadiazines **174** undergo thermal ring contraction *via* sulfur extrusion to give the photographically important pyrazolo[5,1-*c*]1,2,4-triazoles **175**, as shown in Scheme 40. Under these conditions, a bimolecular process involving the triazolothiadiazine and the solvent takes place to effect the sulfur extrusion. [39] This type of bimolecular process can not take place in the gas phase due to the absence of solvent. It was therefore decided to study the gas phase chemistry of triazolothiadiazines, under Flash Vacuum Pyrolysis (FVP) conditions (see Experimental section for brief description of general FVP methodology), in order to determine whether or not a similar reaction pathway would be followed.

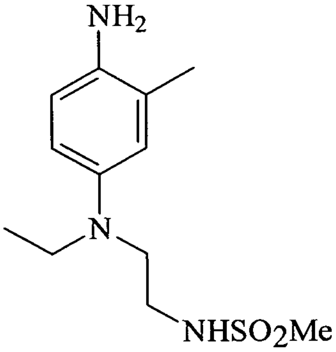


174 **175**

Scheme 40

The triazolothiadiazine starting materials were obtained from Kodak Ltd, and were synthesised as outlined in the patent by Clarke *et al.* [39] Pyrolysis of derivatives **174a-c** (Table 1, p.56) by a previous member of the McNab group had yielded multi-component pyrolysates with complex ^{1}H-NMR spectra. [41]

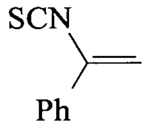
Carrying out thin layer chromatography (TLC) on the crude pyrolysates (silica plates) confirmed that the pyrolysates were multicomponent mixtures. Spraying of the silica plates with colour developer 3 (CD3) **176** followed by oxidation with aqueous potassium persulfate in an attempt to mimic development conditions produced no coloured spots. This indicated that no colour couplers were formed during pyrolysis of the triazolothiadiazine starting materials *i.e.* no pyrazolotriazole systems had been produced, therefore the same reaction had not occurred as takes places in the solution phase.



176

It was observed from the ^{1}H-NMR spectra of the pyrolysates obtained upon FVP of **174 a, b, c** that the spectra were dominated by alkene CH's at δ_H 5.5 and 5.3, which were the main component of the pyrolysate (*ca.* 30%). At this stage the alkene was not identified. It was therefore necessary to identify this alkene, and to postulate the mechanism of formation under the conditions employed. It was also necessary to determine if the reaction taking place could be used in a general fashion.

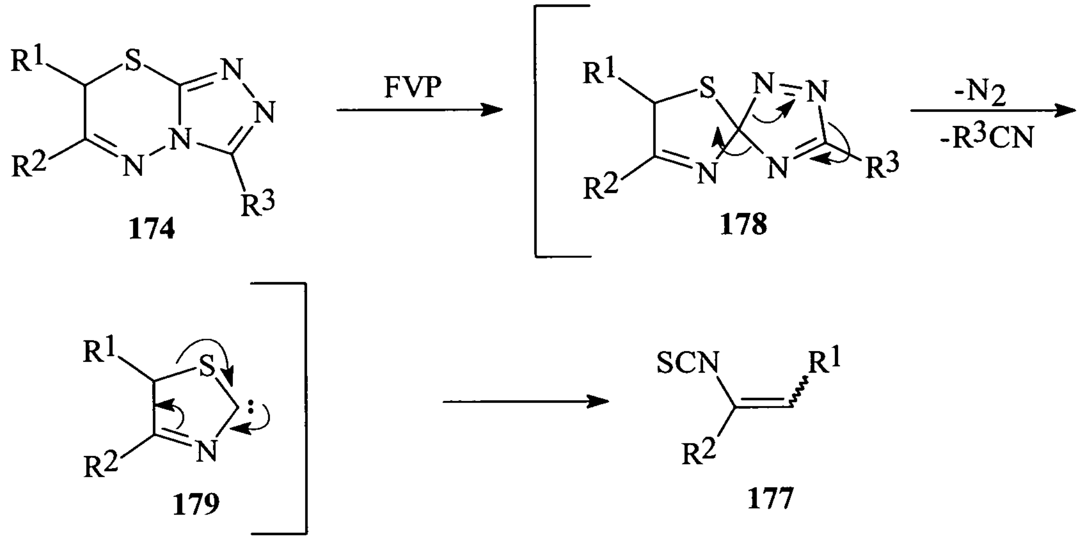
Table 1 shows the triazolothiadiazine derivatives studied. These particular derivatives were chosen to provide a wide range of differing substitution patterns, which would allow the generality of the reaction taking place to be assessed. Pyrolysis of **174d** at a furnace temperature of 750 °C gave a complex pyrolysate as expected, with the alkene CH's at δ_H 5.59 and 5.34 dominating the ^{1}H-NMR spectrum. The reaction mixture was separated by dry flash chromatography (silica), hexane as eluent, and the alkene component was obtained in *ca.* 25% yield. No other components were isolated from the chromatography. Further analytical data was to prove invaluable in determining the structure of the pyrolysis product. The mass spectrum of this major component showed the molecular ion peak at *m/z* 161 (M^+, 20%). The mass spectrum data also showed a dominant peak at *m/z* 105 (70). The IR-spectrum of the alkene showed a strong absorption at 2300 cm^{-1}. This absorbance is characteristic of an isothiocyanate moiety. Putting all this information together allowed the pyrolysis product to be identified as 1-isothiocyanato-1-phenylethene **177d**. A report in the literature states that **177d** is known to oxidize to PhC(O)NCS over the period of several days,[42] the fragmentation of which would give a PhCO moiety at *m/z* 105 which ties in well with the mass spectrum data . However, as stated previously, no PhC(O)NCS, or any other side product(s), were obtained from column chromatography of the crude pyrolsate. This instability also explains the difficulties experienced in identifying the compound by previous workers. [41]



177d

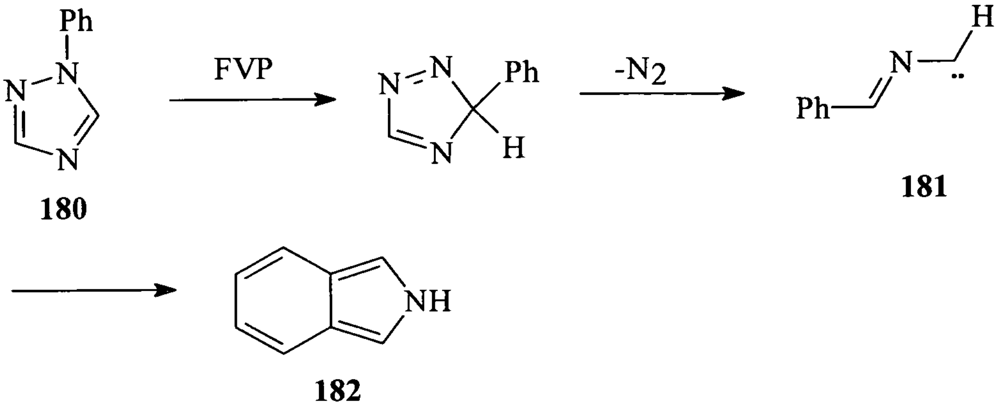
The identity of **177d** was confirmed by independent synthesis using the method of Cambie *et al.* [42] The reaction of a potassium thiocyanate/iodine mixture with styrene to give an iodothiocyanate intermediate which, through treatment with boron trifluoride etherate, is rearranged to an iodoisothiocyanate. This intermediate was then reacted with potassium t-butoxide to give the alkenyl isothiocyanate **177d** (all analytical data consistent with that of the product obtained by FVP).

The proposed general reaction mechanism for the formation of the alkenyl isothiocyanate from a triazolothiadiazine starting material under FVP conditions is shown in Scheme 41. The [1,5]shift which breaks the thiadiazine nitrogen – nitrogen bond produces the spiro-intermediate **178**. This sigmatropic shift sets up the potential for extrusion of molecular nitrogen and a nitrile compound, to produce the reactive carbene intermediate **179**. Collapse of the carbene intermediate **179** would produce the alkenylisothiocyanate **177**.



Scheme 41

The first two steps in this proposed mechanism are analogous to the gas phase behaviour of 1-phenyl-1,2,4-triazole **180** observed by Gilchrist *et al.*,[43] which is summarised in Scheme 42. In this case, a [1,5]shift of the phenyl group from nitrogen to carbon followed by extrusion of molecular nitrogen gives the carbene intermediate **181**. Cyclisation of **181** gave isoindole **182**. This report of extrusion of small, stable molecules to produce a carbene provides some precedent for the step from **178** to the carbene **179**.



Scheme 42

There are also several literature reports which describe the extrusion of molecular nitrogen from 1,2,3 – triazole rings to produce carbene intermediates. [44, 45] Although the gas phase behaviour of 1-phenyl-1,2,4-triazole **180** can be used as justification for the first two steps in the proposed mechanism of formation of **177**, there is no such literature precedence for the final step, the collapse of the carbene intermediate **179** to give the product. However, the fact that there is strong justification for the first two steps in the process suggests that this is a feasible mechanistic pathway.

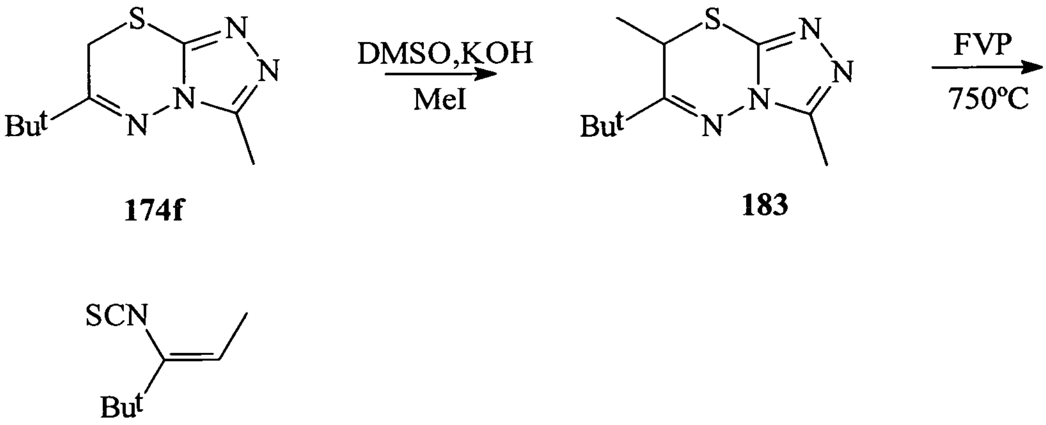
Once the alkene had been identified and the mechanism of formation rationalised, the gas phase behaviour of the other triazolothiadiazine derivatives shown in Table 1 was studied in order to determine the generality of the reaction.

Table 1: FVP of various triazolothiadiazine derivatives **174a-g**, **183**

174	R^1	R^2	R^3	yield of **177** (%)
a	H	Ph	H	30*
b	H	Ph	CF_3	30*
c	H	Ph	Ph	30*
d	H	Ph	Me	25-30
e	Me	Ph	Me	-
f	H	t-Bu	Me	60-75
g	H	t-Bu	t-Bu	70-75
183	Me	t-Bu	Me	**184** (60-75)

* as estimated from ^{1}H-NMR of crude pyrolysate

Pyrolysis of compounds **174a-d** in which R^2= Ph gave the expected isothiocyanates in far lower yields than in the R^2= t-Bu examples, **174f** and **g**. The pyrolysates in these two cases, in contrast to the other examples, were very clean, with only the product and acetonitrile present in the ^{1}H-NMR spectra. The reason for this difference in reaction efficiency is unknown, but the difference observed in yield of product recovered may simply be due to the fact that the stability of the phenyl-substituted isothiocyanates is poor compared to the t-butyl derivatives.[42] Pyrolysis of **174e** was attempted with a view to obtaining a tri-substituted alkene product, but the pyrolysate obtained from FVP of **174e** was particularly complex, and no identifiable product was obtained from chromatography of the mixture. It was therefore decided, due to the high yields obtained from pyrolysis of compounds **174f,g**, to attempt to synthesise a triazolothiadiazine derivative in which R^1= Me and R^2= ^{t}Bu, in the hope that pyrolysis of this compound would lead to a clean pyrolysate containing the desired tri-substituted alkene product. This was successful, via the route shown in Scheme 43.



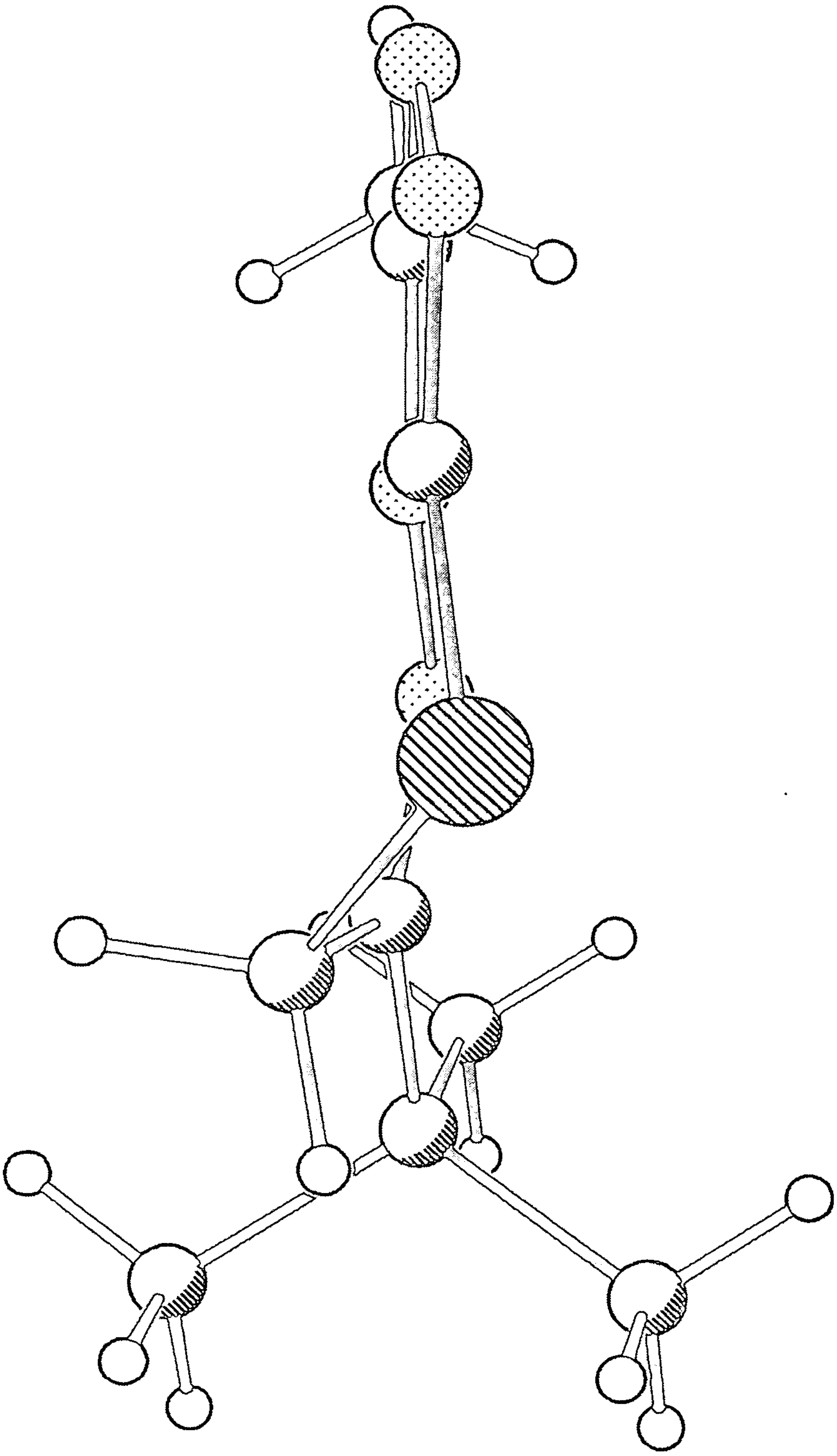
174f **183**

184

Scheme 43

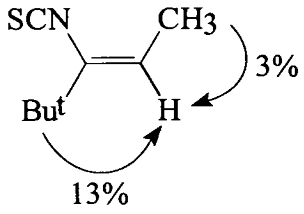
Methylation of **174f** using iodomethane in DMSO containing potassium hydroxide gave 3,7-dimethyl-6-t-butyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **183** in 91% yield. It is interesting to note that methylation of **174f** using these conditions, suggested by chemists at Kodak, gave only one product, **183**, a single isomer of the mono-methylated thiadiazine. This can probably be explained by the X-ray crystal structure of **174f** (Figure 3). This shows that the thiadiazine ring adopts a boat-like conformation, which has the consequence that the second potential site of alkylation is partially blocked by the steric bulk of the t-Bu group. Attempts to synthesise the di-alkylated compound using 5 eq. of MeI and a prolonged reaction time proved unsuccessful, and was not pursued further.

Figure 3: X-ray crystal structure of **174f**



Pyrolysis of **183** at a furnace temperature of 750 °C gave **184** in 60-75% yield as a clean product in a solution of acetonitrile, as rationalised from the mechanism shown in Scheme 41.

The pyrolysis of **183** produced a single isomer of the alkene **184**. Nuclear Overhauser Effect (NOE) NMR experiments (which determine whether or not protons are within *ca.* 3 Å in space) were carried out to determine which isomer had been obtained. Irradiation of the protons resonating at δ 1.11 (attributed to the t-butyl protons) enhanced the resonance at δ 5.38 (attributed to the alkene proton) by 13%, with no effect on the methyl protons (δ 1.73) observed. Similarly, irradiation of the protons at δ 1.73 (methyl) enhanced the resonance at δ 5.38 (alkene proton) by 3% with no effect on the resonance of the t-butyl protons. These data show that the isomer obtained was indeed that shown as **184**.

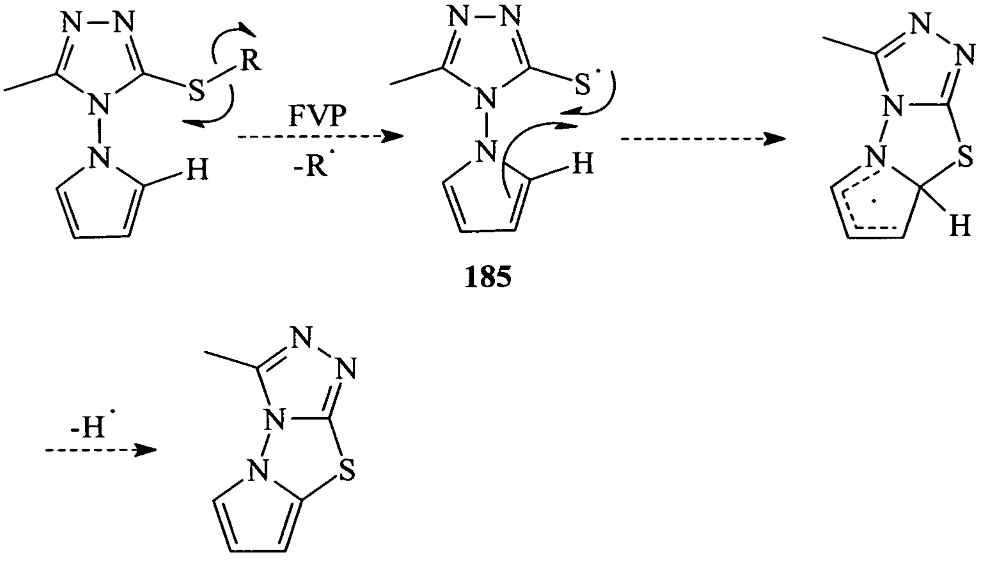


184

Although it was disappointing that this chemistry did not lead to the production of the desired pyrazolotriazole coupler systems, two positive aspects can be drawn from this body of work. The first of these is that this chemistry has provided a clean, high yielding route into previously unknown alkenyl isothiocyanate compounds. The second conclusion to be drawn from this work is that the gas phase thermolysis of these triazolothiadiazines to give the isothiocyanate products is very different from the solution phase chemistry, which gives a ring contraction *via* sulfur extrusion.

2. FVP of 4-amino-3-allylthio-1,2,4-triazoles

As stated in the introduction, a large proportion of the work described in this thesis involves studies towards the syntheses of fused 5,5,5- and 6,5,5-heterocycles for potential applications as colour couplers in photographic film. The majority of these syntheses involve generation of benzyl-type radicals under FVP conditions (as described in the next section) with an aim of producing fused tricycles with a bridging CH_2 group. However, the work in this section covers the attempted synthesis of 5,5,5-systems through the generation and cyclisation of thiyl radicals in an attempt to produce systems containing a bridging sulfur atom. These systems would not have a use as colour couplers as the sulfur atom blocks the coupling site. However, as the aim of this work was to try to establish if the general strategy was viable (*i.e.* generation of a bicyclic radical intermediate which could cyclise to produce a fused tricycle), this was not of concern. The general cyclisation strategy proposed for the synthesis of these sulfur-containing systems is shown in Scheme 44.

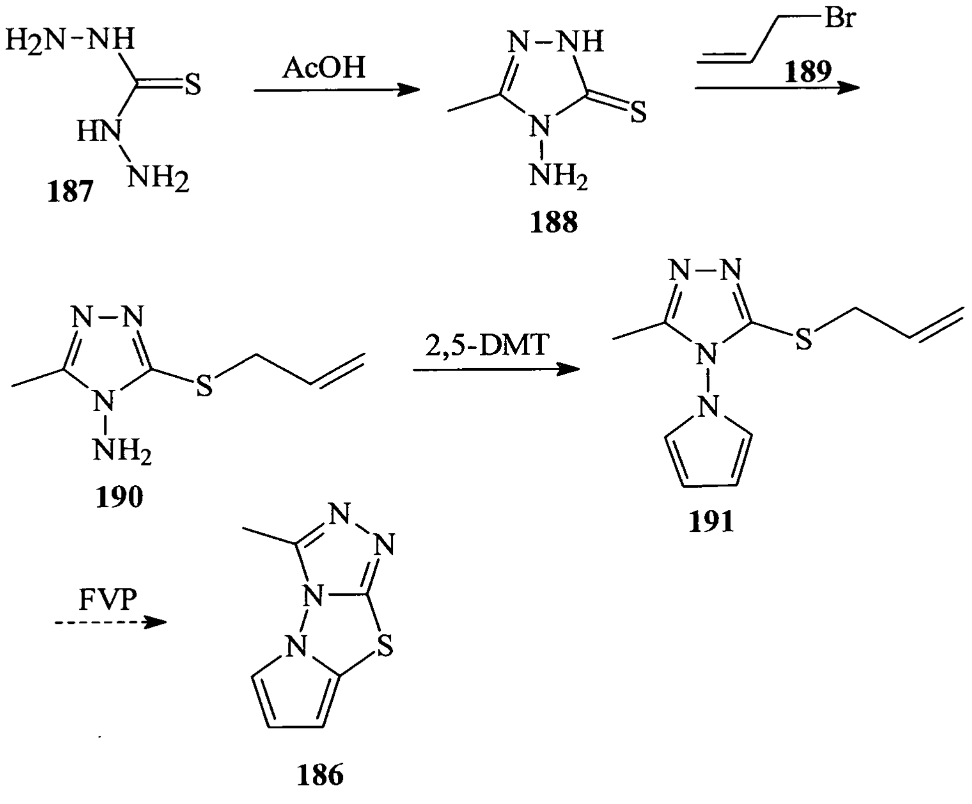


185

186

Scheme 44

The thiyl radical **185** could be generated through cleavage of the S-R bond in the precursor, which could then cyclise onto the pyrrole ring, with subsequent loss of a hydrogen atom producing the tricycle **186**. The R-group in this case had to be easy to introduce onto the sulfur, and be removed cleanly and efficiently to give the radical under FVP conditions. Previous work in the literature [46] has shown precedent for the allyl group being used as a radical leaving group, due to the stability of the allyl radical formed. It would also be easy to form the *S*-allyl compound from the reaction of the thione **188** with allyl bromide **189**. The proposed synthetic route to the target compound **186** is shown in Scheme 45.

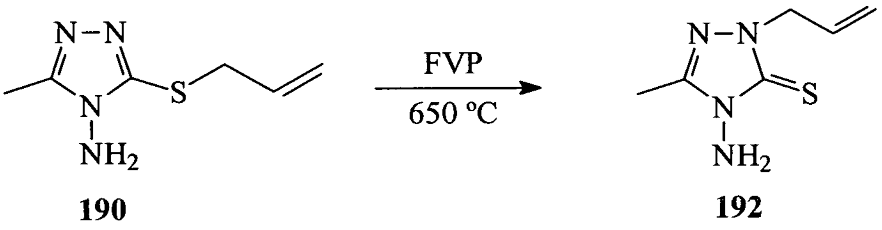


Scheme 45

The aminotriazole **188** was chosen as starting material for several reasons. The 1,2,4-triazole unit was viewed as being of interest for other areas of work (the benzyl-type radical chemistry described in the following section) so it was decided that it would be beneficial to study the chemical behaviour of the triazole unit under the FVP conditions used to induce radical generation. Also, the particular triazole **188** used offered a straightforward route to the bicyclic precursor **191** through manipulation of the amino functionality, as well as containing the thione functionality necessary for building the *S*-allyl moiety, required for the potential generation of the sulfur radicals.

The aminotriazole **188** was synthesised from the condensation of acetic acid with thiocarbohydrazide **187** in 97% yield.[47] Allylation of the thione **188** to give **190** (81%) was carried out using allyl bromide **189** in dimethylformamide (DMF) containing potassium carbonate. It was noted at this stage that only one set of resonances attributable to the allyl peaks was observed in the ^{1}H-NMR spectrum of the compound indicating that allylation had not occurred on both sulfur and nitrogen. Evidence that allylation had occurred exclusively on sulfur was provided from analysis of the ^{13}C-NMR spectrum of **190**. Allylation on nitrogen (either at the exocyclic amino group or at the ring N2 atom) would have produced a compound with a thione group. These are known to show signals in the range δ_C 166-167 ppm in triazole-3-thiones,[48] whereas the spectrum of **190** shows no peaks at $\delta_C > 155$ ppm, confirming that mono-allylation had occurred exclusively on sulfur.

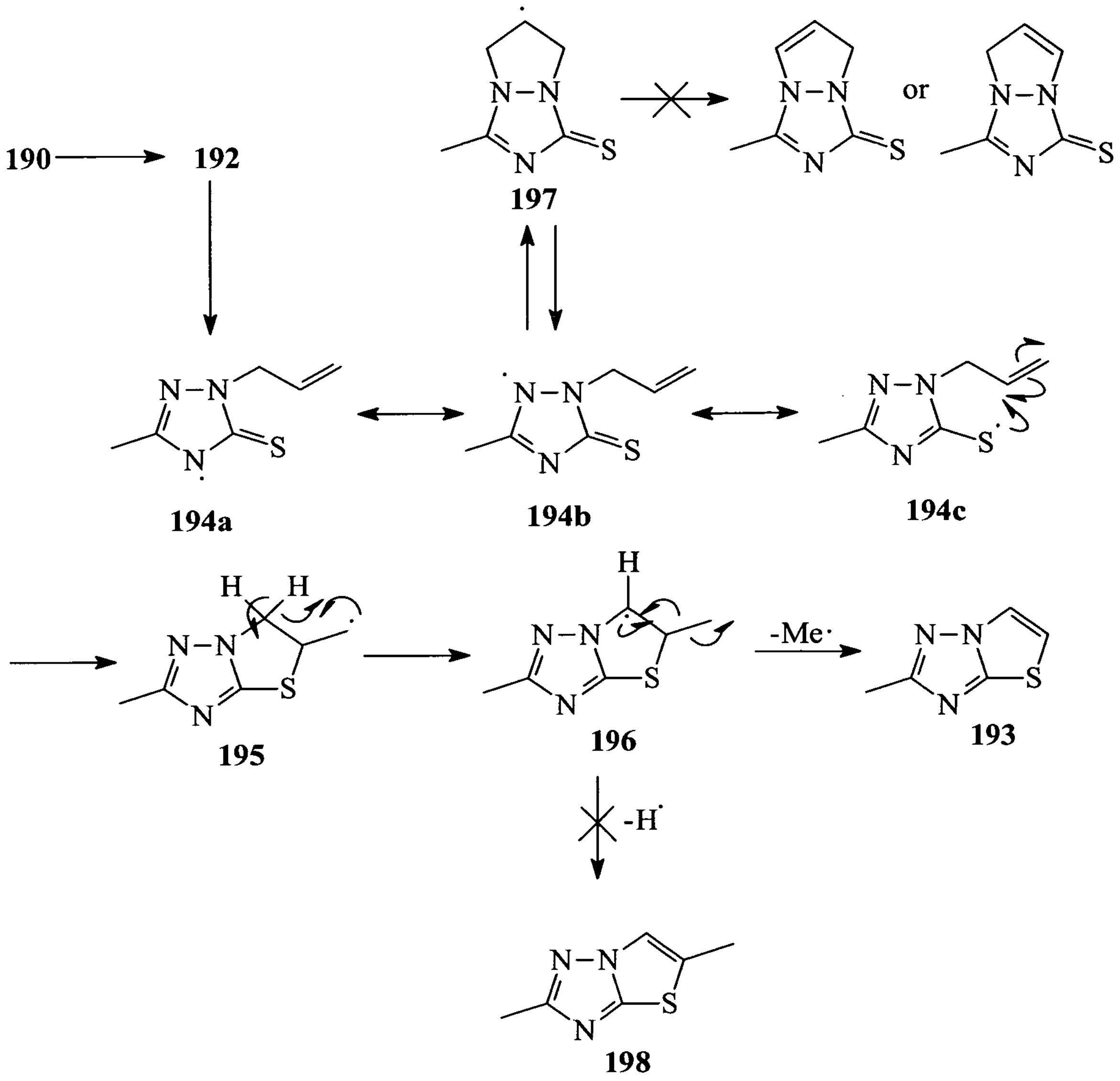
The *N,N'*-linked bicyclic FVP precursor **191** was formed in 87% yield through formation of a pyrrole ring derived from the amine functionality in **190** using 2,5-DMT (2,5-dimethoxytetrahydrofuran) in acetic acid.[49] Pyrolysis of **191** at a furnace temperature of 750 °C gave a pyrolysate which showed no evidence of the cyclised product **186** in the ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum of the pyrolysate was dominated by two large sets of peaks that were attributed to pyrrole (δ_H 6.70 and 6.22) which were partially masking one other component. The presence of pyrrole was confirmed by spiking a sample of the pyrolysate with an authentic pyrrole sample – this led to the relevant peaks increasing in intensity. This showed that cleavage of the *N-N* bicycle linkage in **191** took place at 750 °C rather than cleavage of the *S*-allyl bond, leading to the formation of pyrrole and one other component. In order to simplify identification of this other component, it was decided to pyrolyse the aminotriazole **190** at a range of furnace temperatures. Cleavage of the *N-N* bond in this case would produce ammonia, which would not be observed in the ^{1}H-NMR spectrum of the pyrolysate, thereby simplifying the identification of any other component(s). Pyrolysis of **190** at a furnace temperature of 650 °C gave a mixture of two products in a 9:1 ratio as determined from the ^{1}H-NMR spectrum. The major component was isolated by chromatography on silica, and it was observed from the ^{1}H/^{13}C-NMR and mass spectrum to be isomeric with the starting material **190**. This analytical data allowed the compound to be identified as the *N*-allyl compound **192** (Scheme 46). For example, the thione function in **192** is evident from the signal at δ_C 165.99 in the ^{13}C-NMR spectrum (as discussed previously).



Scheme 46

There has been a previous report of this type of [3,3]sigmatropic shift occurring in the triazole series, and it is possible that in this example the shift is taking place to some extent during the sublimation stage of the pyrolysis. [48] The minor component was not isolated from the product mixture during chromatography. With this sigmatropic shift taking place at reasonably low furnace temperatures, it was evident that this type of shift was favoured over radical cleavage of the *S*-allyl bond with the consequence being that none of the desired tricycle could be produced. At higher furnace temperatures of 750-850 °C, FVP of **190** gave a single major product (identical with the minor product obtained in the 650 °C pyrolysis described above), which was purified by distillation. The ^{1}H-NMR spectrum of this material showed three signals in a 1:1:3 ratio [δ_H 7.69 (J 4.5 Hz), 6.91 (J 4.5 Hz) and 2.50], whilst the mass spectrum showed a molecular ion at *m/z* 139 corresponding to a loss of 31 Daltons (= CH_5N). This data allowed the material to be identified as the known 2-methyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **193** (Scheme 47). [50] All analytical data (see Experimental section) corresponded well with those reported.[50]

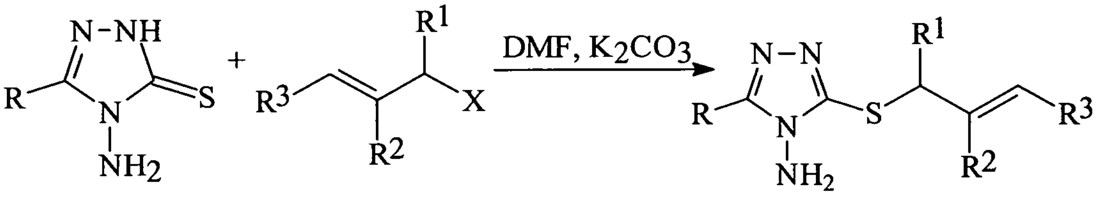
A possible mechanism for this unexpected transformation is shown in Scheme 47. After the initial [3,3]sigmatropic shift takes place to give **192**, cleavage of the *N-N* bond could occur to give the resonance stabilised radical **194**. This species then adds exclusively from its sulfur centre **194c** in 5-*exo-trig* fashion to the double bond of the allyl group. The primary radical generated, **195**, can achieve greater stability by hydrogen shift from the site adjacent to the bridgehead nitrogen atom to give the secondary radical **196**. Aromatisation is then achieved through cleavage of the C-C bond (with ejection of a methyl radical) to give the product **193**.



Scheme 47

Two instances of high selectivity in the chemistry of these radicals are apparent in this sequence. Firstly, no products were obtained from an alternative cyclisation route which would formally involve the nitrogen-centred canonical form **194b** (to give the secondary radical intermediate **197**). This suggests that either the formation of **197** is reversible or that thiyl radicals are more reactive than aminyl radicals in such competitive cyclisation situations. Alternatively, the 5-*exo*-*trig* mode of cyclisation [51] (to give **195**) may be inherently favoured over the 5-*endo-trig* mode to give **197**. Secondly, no trace of the dimethylthiazolo[3,2-*b*][1,2,4]triazole **198**, which might have been formed by loss of a hydrogen atom from **196**, was observed in the crude pyrolysate. This is consistent with the fact that C-C cleavage is normally observed in preference to C-H cleavage under competitive conditions in the gas phase.[46]

The synthetic potential of this two step sequence from 4-amino-1,2,4-triazole-3-thiones to [1,3]thiazolo[3,2-*b*][1,2,4]triazoles was then investigated using the 5-unsubstituted compound **204**, the 5-methyltriazoles **205** and **206**, and the 5-phenyltriazoles **208** – **210** as substrates (see Scheme 48 for details).



199 R = H
188 R = Me
200 R = Ph

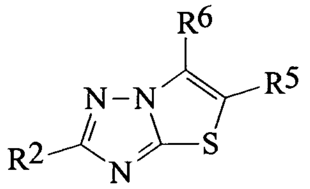
189 $R^1 = R^2 = R^3 = H$, X = Br
201 $R^1 = R^3 = H$, R^2 = Me, X = Cl
202 $R^1 = R^2 = H$, R^3 = Me, X = Cl
203 R^1 = Me, $R^2 = R^3 = H$, X = Cl

204 $R = R^1 = R^2 = R^3 = H$
190 R = Me, $R^1 = R^2 = R^3 = H$
205 $R = R^2$ = Me, $R^1 = R^3 = H$
206 $R = R^3$ = Me, $R^1 = R^2 = H$
207 $R = R^1$ = Me, $R^2 = R^3 = H$
208 R = Ph, $R^1 = R^2 = R^3 = H$
209 R = Ph, $R^1 = R^3 = H$, R^2 = Me
210 R = Ph, $R^1 = R^2 = H$, R^3 = Me

Scheme 48

The triazole precursors **188**, **199** and **200** (Scheme 48) were readily obtained by literature methods as described in the Experimental section.[52, 53] Allylation of the triazoles **188** and **200** using allyl bromide **189** or 2-methylprop-2-enyl chloride **201** in DMF containing anhydrous potassium carbonate gave products which were obtained as single isomers in 54 – 81% yields. The product obtained from the reaction of the 5-unsubstituted compound **199** and allyl bromide decomposed on work up under these conditions, but the allylated product **204** was obtained in satisfactory yield (79%) when the reaction was carried out using acetonitrile as solvent. The corresponding reaction of **188** with either but-2-enyl chloride **202** or 3-chlorobut-1-ene **203** gave a mixture of *S*-allylated isomers in 86:14 and 93:7 ratio respectively. The ^{13}C-NMR DEPT spectrum of the mixtures confirmed that both isomers had a CH_2 group adjacent to the sulfur atom (δ_C *ca.* 35 ppm) and therefore they are likely to be the *E* and *Z* isomers of **206**. Recrystallisation from toluene gave a single compound, which is likely to be the *E* isomer. No trace of the regioisomer **207** was apparent in the crude spectra. Similarly, the butenyl compound **210** was obtained from the reaction of the 5-phenyl substituted precursor **200** with but-2-enyl chloride **202**. As described previously, all allylated compounds were assigned as the *S*-allyl compounds by the absence of a signal corresponding to the thione function in the ^{13}C-NMR spectra of the compounds.

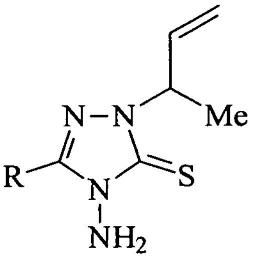
In all cases the pyrolysis step was carried out at a furnace temperature in the range 750 – 850 °C, and the products purified by Kugelrohr distillation with chromatography not generally required. The range of products is shown in Scheme 49.



193 R^2 = Me, R^5 = R^6 = H
211 R^2 = R^5 = Me, R^6 = H
213 R^2 = R^6 = Me, R^5 = H
214 R^2 = R^5 = R^6 = H
215 R^2 = Ph, R^5 = R^6 = H
216 R^2 = Ph, R^5 = Me, R^6 = H
217 R^2 = Ph, R^5 = H, R^6 = Me

Scheme 49

Pyrolysis of the 2-methyl-prop-2-enyl derivative **205** gave the expected 2,5-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **211** in 48% yield. In the case of the butenyl precursor **206**, the initial sigmatropic shift produces **212** and hence leads to 2,6-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **213** (54%).



212

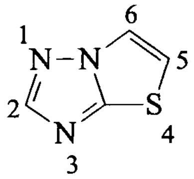
Pyrolysis of the 5-unsubstituted derivative **204** gave the expected unsubstituted [1,3]thiazolo[3,2-*b*][1,2,4]triazole **214** in moderate yield (45%).

Pyrolysis of the phenyl-substituted triazoles **208** – **210** proceeded as expected and the [1,3]thiazolo[3,2-*b*][1,2,4]triazoles **215** – **217** were obtained in 23, 48 and 54% yields respectively. The mass spectrum of compound **215** shows the expected molecular ion at *m/z* 201 amu, with the methyl substituted compounds **216** and **217** showing a molecular ion at *m/z* 215 amu. The ^{1}H-NMR spectra of compounds **215** – **217** showed the expected methyl and methine resonances for the appropriate substitution patterns (see Experimental section). Small amounts of benzonitrile were detected in the ^{1}H-NMR spectra of the crude pyrolysates obtained from FVP of **208** – **210**, presumably due to breakdown of the heterocycle at the high temperatures required for the initial *N-N* bond cleavage, and chromatography was required to purify **217**. Pyrolysis of **209** and **210** at 750 °C rather than 850 °C did not significantly reduce the level of benzonitrile, and no further optimisation was carried out. In general, the 2,6-dimethyl products **213** and **217** were obtained in a less pure state than the other derivatives. The 2,5-disubstitution pattern in the [1,3]thiazolo[3,2-*b*][1,2,4]triazole ring system is apparently quite rare, [54] and both **211** and **216** are new compounds.

Although many spectroscopic studies of the [1,3]thiazolo[3,2-*b*][1,2,4]triazole system have been carried out, no systematic study of their ^{13}C-NMR spectra has been reported. [54] The parent compound **214** apparently only shows three signals in the proton-decoupled spectrum, at δ_C 156.34, 119.86 and 113.85. However, a ^{1}H coupled spectrum revealed the bridgehead quaternary signal (C-3a) also at δ_C 156.34 and the following coupling constants: C-2, $^1J_{CH}$ 208.7; C-5, $^1J_{CH}$ 195.2, $^2J_{CH}$ 10.2; C-6, $^1J_{CH}$ 198.2, $^2J_{CH}$ 7.2 Hz. Assignment of the ^{13}C spectra for the ring carbons of **193** and **214** is summarised in Table 2.

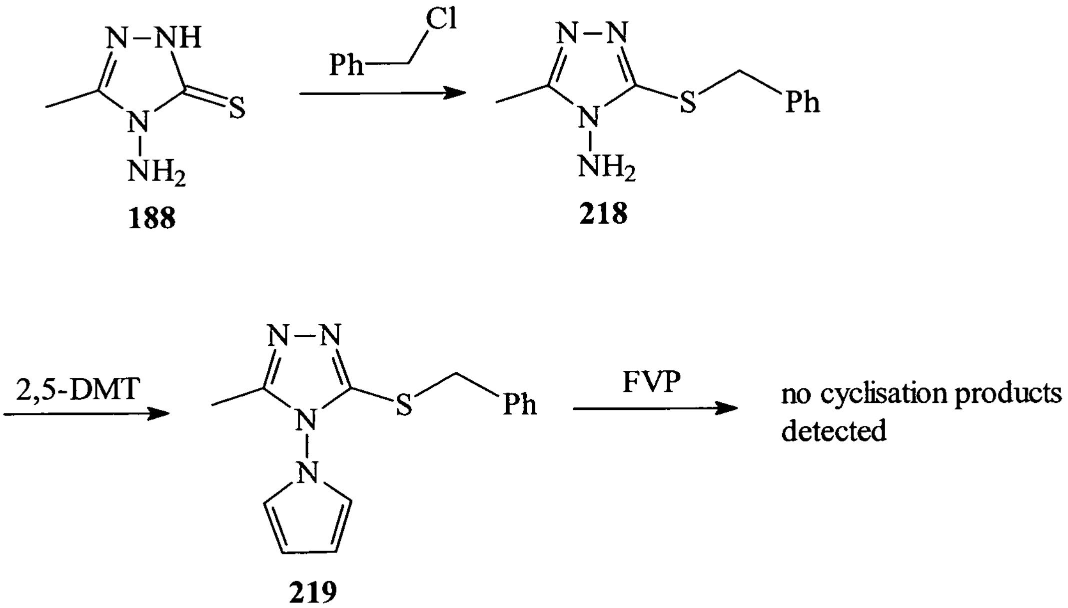
Table 2: Assignment of ^{13}C-NMR ring carbon resonances (δ_c) in **193** and **214**

Compound	**C-2**	**C-3a**	**C-5**	**C-6**
214	156.34	156.34	113.85	119.86
193	166.52	156.84	112.14	119.66



Because methyl substitution at an adjacent position is likely to cause a high frequency shift of that signal (*cf.* data for thiazoles [55, 56]) comparison of the spectra of **193**, **213** and **214** allowed the assignment of the C-5 (δ_C 112-114) and C-6 (δ_C 119-120) resonances in **193** and **214**.

In a final attempt to achieve synthesis of a fused 5,5,5-heterocyclic system from the above chemistry, the benzyl group was used in place of the allyl group as a potential radical leaving group under FVP conditions (Scheme 50).



Scheme 50

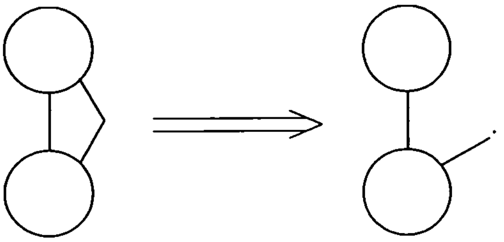
The reaction between the thione **188** and benzyl chloride produced **218** in poor yield (20%), with the linked bicycle **219** (75%) produced from the reaction of 2,5-DMT with **218**. FVP of **219** at furnace temperatures in the range of 650 – 850 °C produced no cyclised product, with only small amounts of bibenzyl observed in the ^{1}H-NMR spectrum of the crude pyrolysates. This showed that this particular strategy was not suitable for the synthesis of fused 5,5,5-heterocycles.

In conclusion, this work provided a short, clean synthetic route to [1,3]thiazolo[3,2-*b*][1,2,4]triazoles *via* a novel pyrolysis sequence. The synthetic route discovered allows substitution at all three ring positions and therefore complements traditional condensation routes from triazoles to [1,3]thiazolo[3,2-*b*][1,2,4]triazoles [54]. Despite the many positive outcomes of this piece of work, the main objective of developing a synthetic route to fused 5,5,5-heterocycles was not achieved. The next section describes further work which was carried out in an attempt to develop general routes to fused tricyclic nitrogen-containing systems.

3. Synthesis of tricyclic fused heterocycles

As stated previously, there are currently no synthetic methods that are applicable to a wide variety of fused tricyclic heterocycles. The aim of the work carried out in this chapter was to develop general methodology that would be applicable to the synthesis of a variety of potential colour coupler systems *via* a gas phase radical cyclisation strategy. It was hoped that this could be achieved through the generation of benzyl-type radicals from a linked bicyclic precursor (Figure 4).

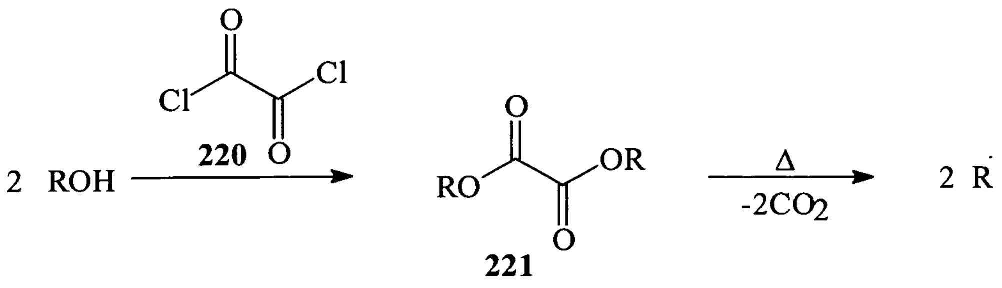
Figure 4: Proposed method of central ring formation



Three different types of potential radical generator precursors were studied, and these are discussed in the following three sub-sections.

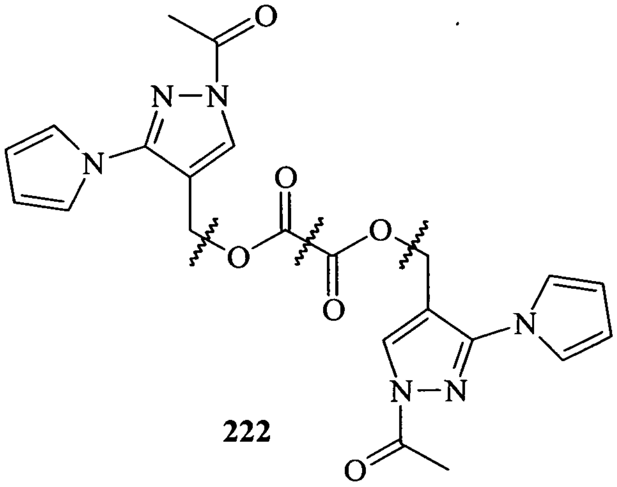
a) Studies towards the synthesis of oxalate radical precursors

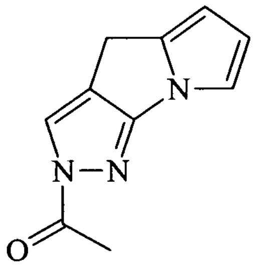
There is literature precedence for the use of oxalates as generators of carbon-centred radicals.[57] These precursors are typically formed from the reaction of an alcohol and oxalyl chloride **220**, as shown in Scheme 51. Thermolysis of the oxalate product **221** gives, through the loss of two molecules of carbon dioxide, two molecules of the desired radical intermediate.



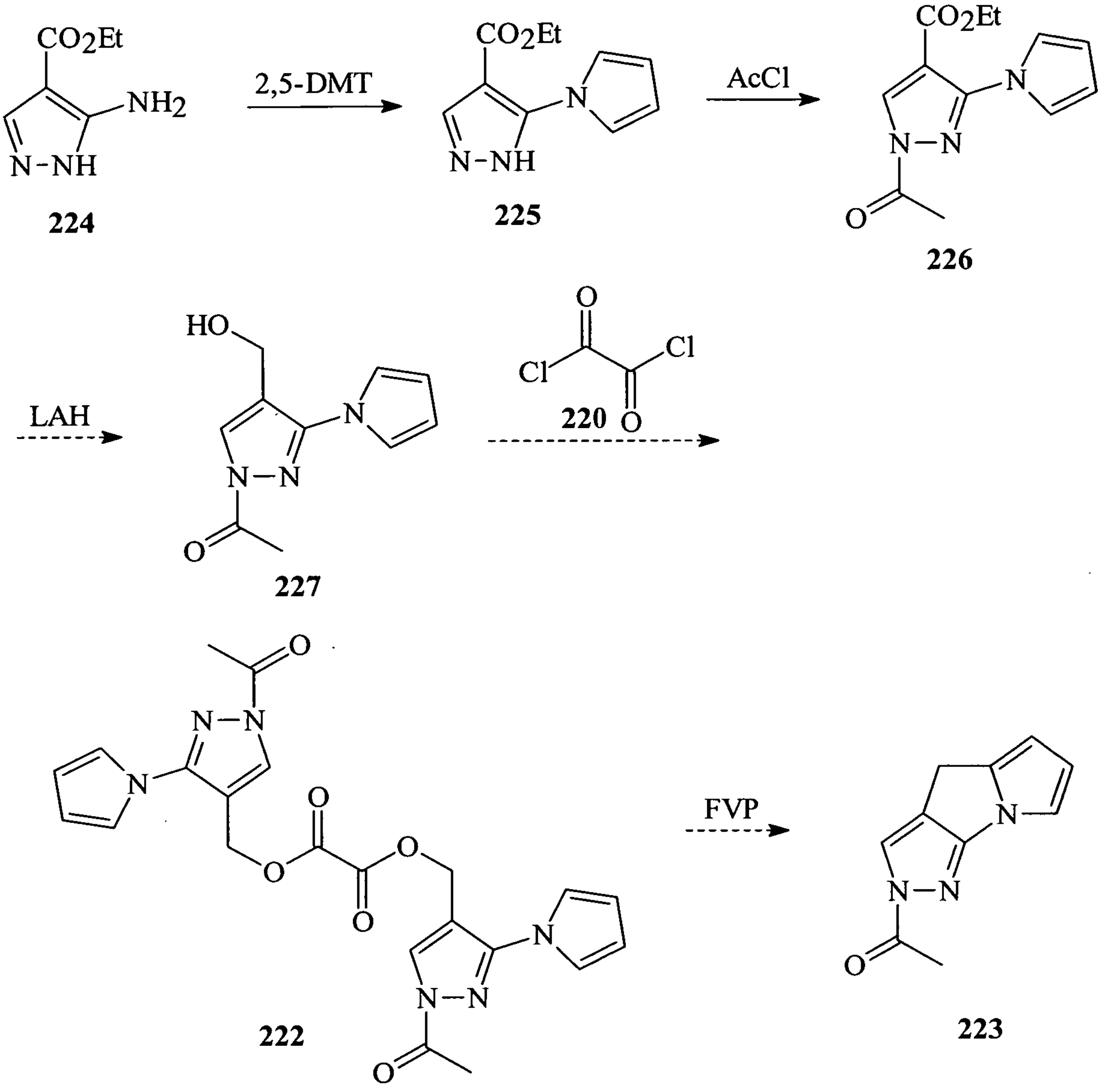
Scheme 51

It was hoped that this general methodology could be used to give the target pyrazolo[4,3-*b*]pyrrolizine system **223** from the oxalate precursor **222**.


222

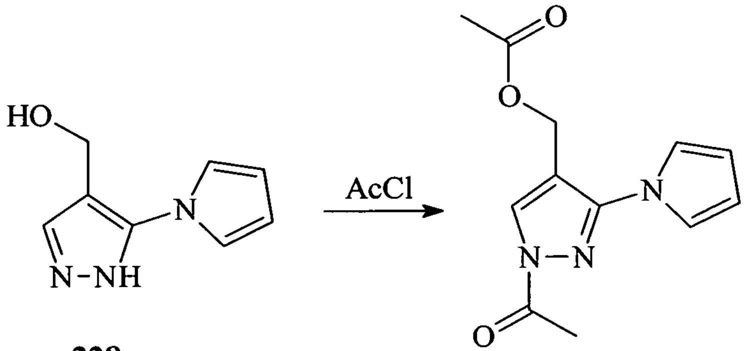

223

Thermal radical cleavage of the bonds shown could generate the benzyl-type radicals as desired, which could then cyclise onto the pyrrole ring to give the target 5,5,5-system **223**. This route was particularly attractive as it offered the potential to synthesise the target system **223** in a small number of steps from the commercially available pyrazole **224**. The proposed synthetic route is shown in Scheme 52. Thus, formation of the 3-pyrrolylpyrazole **225** from the reaction of **224** with 2,5-DMT occurred in 70% yield. This step set up the linked bicycle as required. It was then necessary to reduce the ester functionality to the primary alcohol so that the oxalate could be formed. However, in order to eliminate the possibility of side reactions during oxalate formation, it was first necessary to protect the pyrazole nitrogen by acylation.



Scheme 52

Reaction of **225** with acetyl chloride gave the *N*-acetyl compound **226** in 61% yield. Only one isomer was obtained, but no further studies were carried out to determine which. The isomer shown as **226** was chosen to represent the obtained acylated product by analogy with the methylated compound discussed later in this section (p. 76). Reduction of the ester functionality in **226** with LAH did not yield the desired compound, **227**, but gave instead the unprotected hydroxymethylene pyrazole **228** (Scheme 53). The LAH was therefore shown to be reducing the ester group as well as removing the acetyl protecting group from the pyrazole nitrogen. Attempts to acylate selectively on the pyrazole nitrogen atom (Scheme 53) using one equivalent of acetyl chloride were unsuccessful, with only the di-acylated compound **229** plus starting material recovered. It was therefore clear that a different pyrazole protection strategy was required, one which would be stable in the presence of LAH.

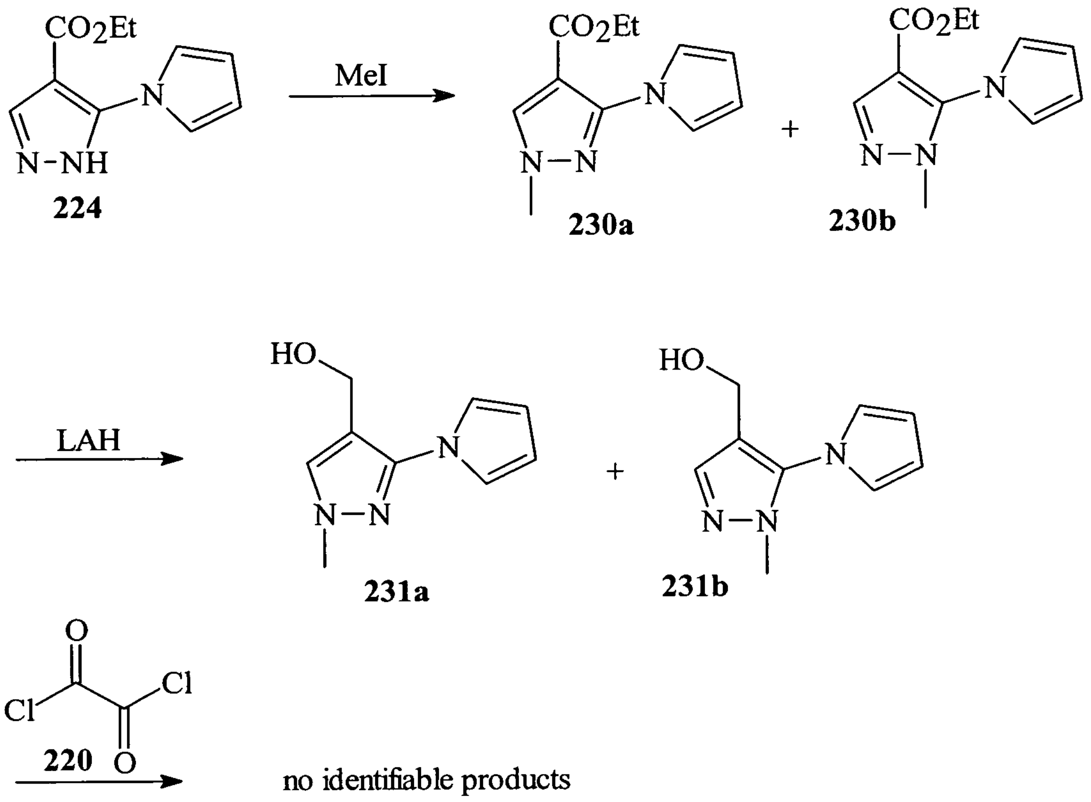


228

229

Scheme 53

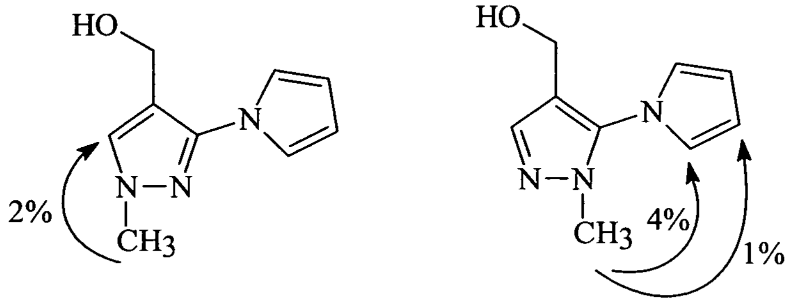
It was decided that methylation of the pyrazole nitrogen would be a suitable strategy, as the methyl group would not be affected by the conditions employed in LAH reduction of the ester group. The *N*-methylated compound would also be simple to synthesise, albeit with the unfortunate consequence of producing two isomers, as shown in Scheme 54.



Scheme 54

It was anticipated that this problem could be overcome by separating the isomers after synthesis of the oxalates, which would be expected to be crystalline solids. Methylation of **224** with methyl iodide in DMSO containing potassium hydroxide produced, as expected, the isomers **230a** and **230b**, in a combined yield of 82%. Reduction of the **230a/230b** mixture produced the hydroxymethylenepyrazole isomers **231a** and **231b** (53% combined yield). At this stage, the isomers were distinguished by NOE experiments (Figure 5).

Figure 5: NOE summary for compounds **231a** and **231b**



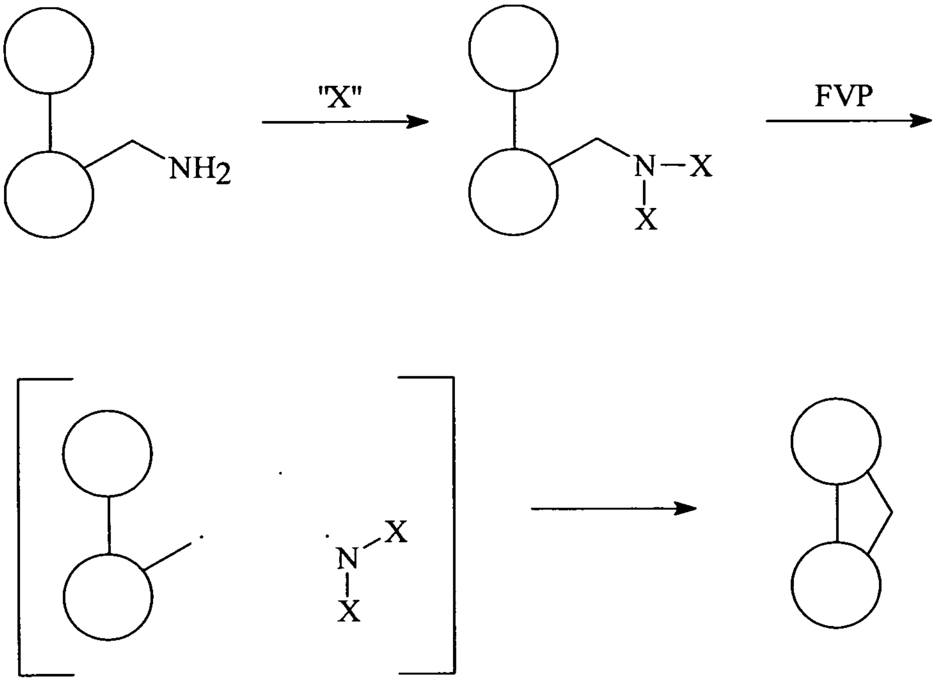
231a **231b**

Irradiation of the resonance at δ 3.73 (attributed to the methyl resonance of the major component) enhanced the resonance at δ 7.20 (attributed to the pyrazole ring proton) by 2%. This shows that the major isomer is that shown as **231a**. This conclusion was confirmed by irradiation of the resonance attributed to the methyl protons of the minor component at δ 3.56. This irradiation enhanced only the pyrrole ring proton resonances, which shows that the minor component is indeed that shown as **231b**. The ratio of **231a**:**231b** was estimated to be 4:1 from the ^{1}H-NMR spectrum of the isomeric mixture. Unfortunately, attempts to form the corresponding oxalates from **231a** and **231b** using the standard method of Trahanovsky *et al.*[57] proved unsuccessful. The ^{1}H-NMR spectrum of the product mixture showed that the reaction had not proceeded in the manner anticipated, with the mixture containing many components, none of which could be identified. This suggested that the oxalates had not been produced, and this was confirmed by the mass spectrum of the product mixture, which showed no peak corresponding to that of the expected products. This complex product mixture may have been obtained due to interactions between the nitrogen lone pairs and oxalyl chloride, which would provide three possible reaction centres in addition to the hydroxyl group. If this was the case, there would be numerous possible products from this reaction, despite protecting the pyrazole nitrogen with the methyl group. This suggests that the strategy of radical formation from oxalate precursors is not suitable for target 5,5,5-systems with nitrogen containing heterocycles.

It therefore became necessary to investigate alternative potential radical precursors, the synthesis of which would be compatible with the starting materials chosen. It was decided that, since the majority of the target systems were nitrogen-containing heterocycles, a nitrogen centred radical precursor would be desirable. The design and synthesis of such a precursor is discussed in the following section.

b) Development and applications of nitrogen based radical precursors

As stated previously, the ideal benzyl-type radical generator for use in the synthesis of nitrogen containing heterocycles would be nitrogen based *i.e.* the radical generator could be built around a primary amine, then radical cleavage of the carbon-nitrogen bond would generate the benzyl type radical along with the nitrogen centred radical leaving group. A schematic representation of this is shown in Scheme 55.

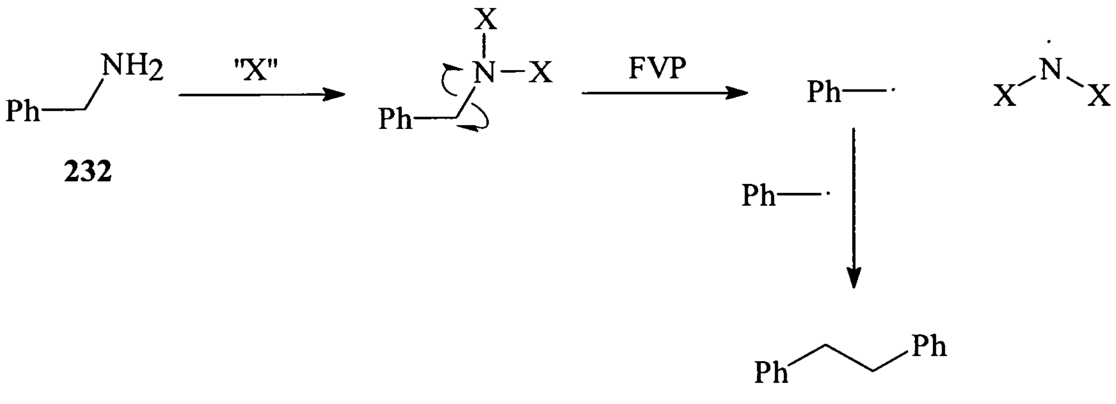


Scheme 55

As there were no reports of this type of radical generator in the literature, it was necessary to develop a system that would carry out this function. So that the developed system could be considered successful, it would have to pass the following three criteria:

1. The radical leaving group should be simple to synthesise from an accessible primary amine starting material.
2. The radical cleavage of the carbon–nitrogen bond under FVP conditions should occur efficiently and cleanly.
3. The nitrogen centred radical leaving group should not interfere with the anticipated cyclisation of the benzyl-type radical, and should be easily removed from the pyrolysate after the cyclisation reaction has occurred.

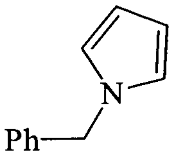
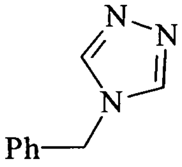
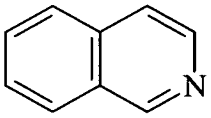
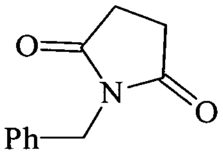
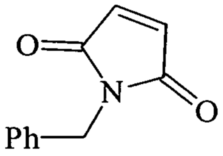
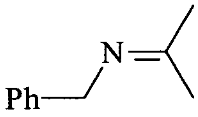
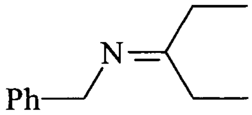
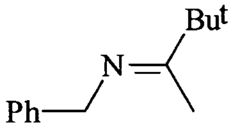
The development of this system was carried out using benzylamine **232** as a model amine starting material (Scheme 56), for several reasons. As well as being easily accessible, cleavage of the carbon-nitrogen bond in the gas phase would produce benzyl radicals similar to those required for synthesis of tricyclic fused heterocycles (Scheme 55). Also, the efficiency of this radical cleavage could be easily assessed through monitoring bibenzyl **233** production in the ^{1}H-NMR spectrum of the crude pyrolysate.



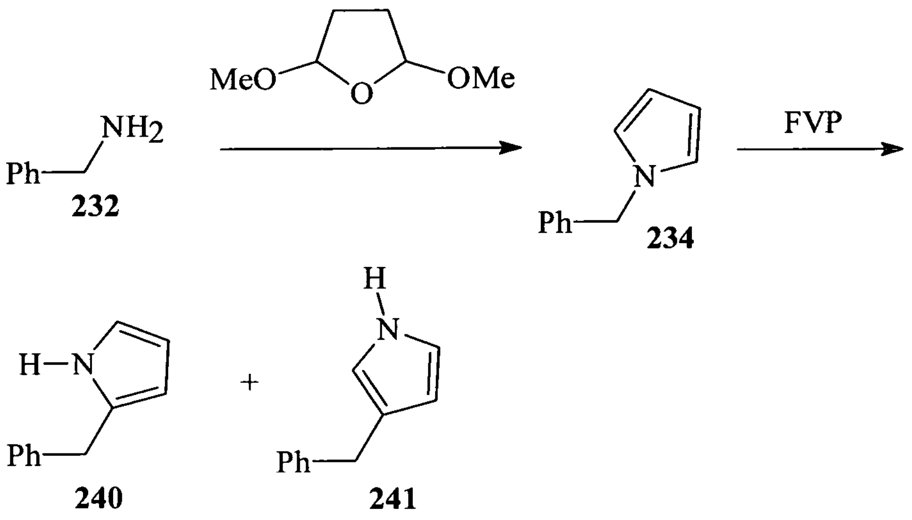
Scheme 56

The design of these potential radical precursors was initially focussed on studying precursors containing potential *N*-centred radical leaving groups that were predicted (either intuitively or from literature precedence) to be reasonably stable, and therefore have a greater likelihood of forming. The systems studied are shown in Table 3.

Table 3: Potential radical precursors studied

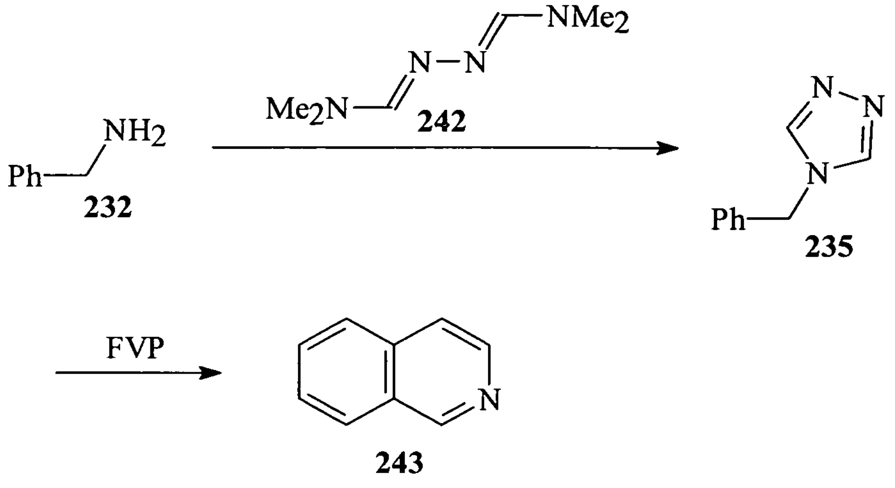
Reaction of benzylamine with:	**Precursor formed**	**Product(s) of FVP of precursor**
2,5-DMT	 **234**	**240** and **241**
DMF azine **242**	 **235**	 **243**
succinic anhydride	 **236**	starting material
commercially available	 **237**	starting material
acetone	 **238**	ethylbenzene **251** and bibenzyl **233** (5:1 ratio)
diethyl ketone	 **239**	unidentified mixture
pinacolone **253**	 **252**	bibenzyl **233**

As can be seen from the data shown in Table 3, FVP of compounds **234** – **239** did not produce the desired result *i.e.* production of clean bibenzyl. However, some of these pyrolyses did give results that were interesting for other reasons. Pyrolysis of 1-benzylpyrrole **234**,[58] prepared from the reaction of benzylamine **232** with 2,5-DMT, at a furnace temperature of 850 °C produced a crude pyrolysate which contained 2-benzylpyrrole **240**, 3-benzylpyrrole **241** and starting material **234** in a 2:1:1 ratio as deduced from the ^{1}H-NMR spectrum resonances attributable to the methylene moieties.[59] The mechanism by which this occurs (Scheme 57) could proceed *via* a [1,5]shift of the benzyl group from nitrogen to carbon. The fact that no bibenzyl was detected in the ^{1}H-NMR spectrum of the crude pyrolysate suggests that this sigmatropic shift occurs more rapidly than the anticipated radical cleavage of the benzyl carbon – nitrogen bond. The presence of starting material is most likely due to the reaction not going to completion. However, it is possible that as all three products are in dynamic equilibrium, a further [1,5]shift of the benzyl group from carbon to nitrogen in **240** or **241** could take place to produce the starting material, although previous work in the McNab group suggests that this type of shift, from C → N, does not occur in the gas phase.[60]



Scheme 57

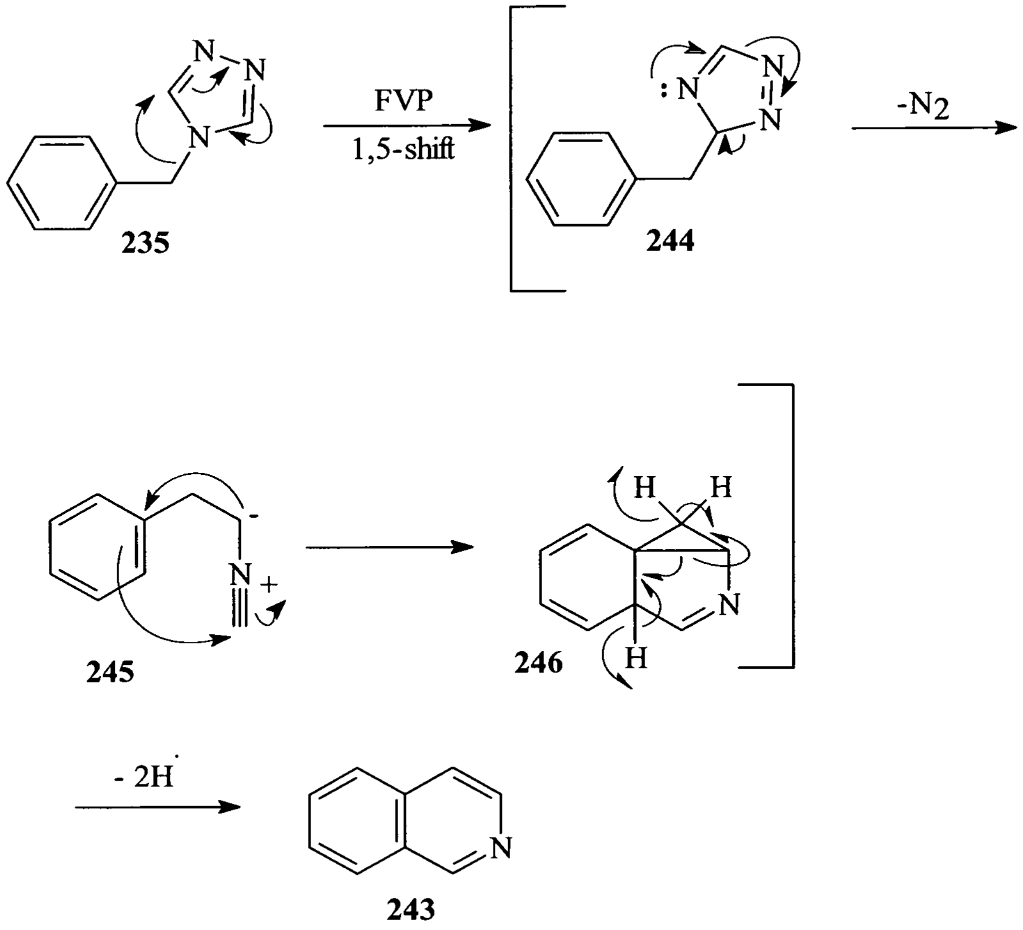
This result was disappointing, as it was anticipated that the pyrrole radical formed would be stable enough to facilitate the radical cleavage of the carbon – nitrogen bond. Since the [1,5]shift of the benzyl group to the 2- and 3-positions of the pyrrole ring appeared to be favoured over radical cleavage of the C – N bond, an attempt to reduce the occurrence of the [1,5]shift was necessary. It was hoped that replacing the pyrrole ring with a 1,2,4-triazole moiety to give **235** would perhaps make the radical cleavage a more competitive pathway, given that any benzyl shift would be restricted to the triazole ring carbon in the 2-position. The potential radical precursor **235** was prepared in 70% yield from the reaction of benzylamine **232** with DMF azine **242** in toluene using toluene-*p*-sulfonic acid as catalyst,[61] as shown in Scheme 58.



Scheme 58

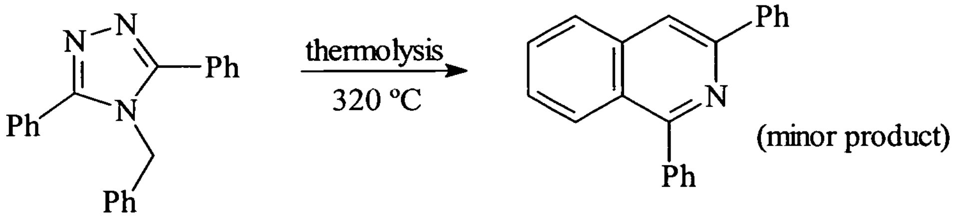
Pyrolysis of **235** at a furnace temperature of 850 °C produced a multi-component pyrolysate. The ^{1}H-NMR spectrum, although complex, showed the presence of one main product. Flash chromatography of the crude pyrolysate produced a clean sample of this major component, which was identified as isoquinoline **243** (23%) by comparison the ^{1}H-NMR spectrum with literature data.[62]

The mechanism by which this reaction occurs is proposed in Scheme 59 and, as in the pyrolysis of **234**, it appears that a rapid [1,5]shift occurs preferentially over the desired radical cleavage step. This benzyl shift produces **244** and sets up the possibility of N_2 extrusion from the triazole ring, which would produce a 1,3-dipolar reactive intermediate **245**. As discussed in an earlier section, there are several literature precedents for the extrusion of molecular nitrogen from heterocycles under FVP conditions.[43, 44, 45] Cyclisation of this dipolar intermediate completes the skeleton of the structure to give **246**, although the aromaticity of the system would be lost at this stage. Loss of molecular hydrogen would reinstate the aromaticity of the system, thereby producing isoquinoline **243**.



Scheme 59

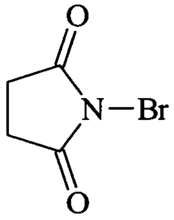
There is literature precedence for this type of transformation.[63] It was reported that thermolysis of **247** at 320 °C in an evacuated ampoule produced the substituted isoquinoline (Scheme 60), in very poor yield (2%).



247

Scheme 60

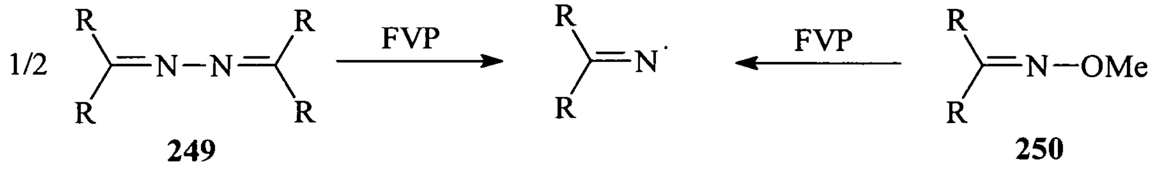
With the previous two examples producing unexpected results, it was decided to utilise a substrate in which the position adjacent to the bond to be broken is blocked, therefore eliminating the possibility of any sigmatropic shift taking place. Two such substrates were studied, 1-benzylpyrrolidine-2,5-dione **236** and 1-benzylmaleamide **237**. These substrates were studied because of the wide use of the analogous *N*-bromosuccinimide (NBS) **248** in solution phase radical reactions.[64] It was therefore hoped that the succinimidyl co-radical which would be generated would be stable enough to facilitate cleavage of the C – N bond in **236**.



248

Unfortunately, both **236**, prepared using the method of Reddy *et al.*,[65] and **237**, which is commercially available, proved to be stable at pyrolysis temperatures up to 850 °C. This was verified from the ^{1}H-NMR spectra of the pyrolysates, which showed that only clean starting material was present in both cases. It was therefore becoming apparent that the use of a simple ring system as the nitrogen centred radical leaving group was not suitable under the conditions employed, and that a different approach to the design of the FVP radical precursor was required.

There have been several literature studies into the gas phase generation and behaviour of iminyl radicals. [46] These iminyl radicals are typically generated through the FVP of a hydrazone **249** or oxime derivative **250** as shown in Scheme 61, [46] and it was decided to investigate if they could also be generated from the pyrolysis of various model alkyl substituted imines which would provide a carbon based radical as co-product. These aliphatic imines would be simple to prepare from the condensation of benzylamine **232** and various ketones.

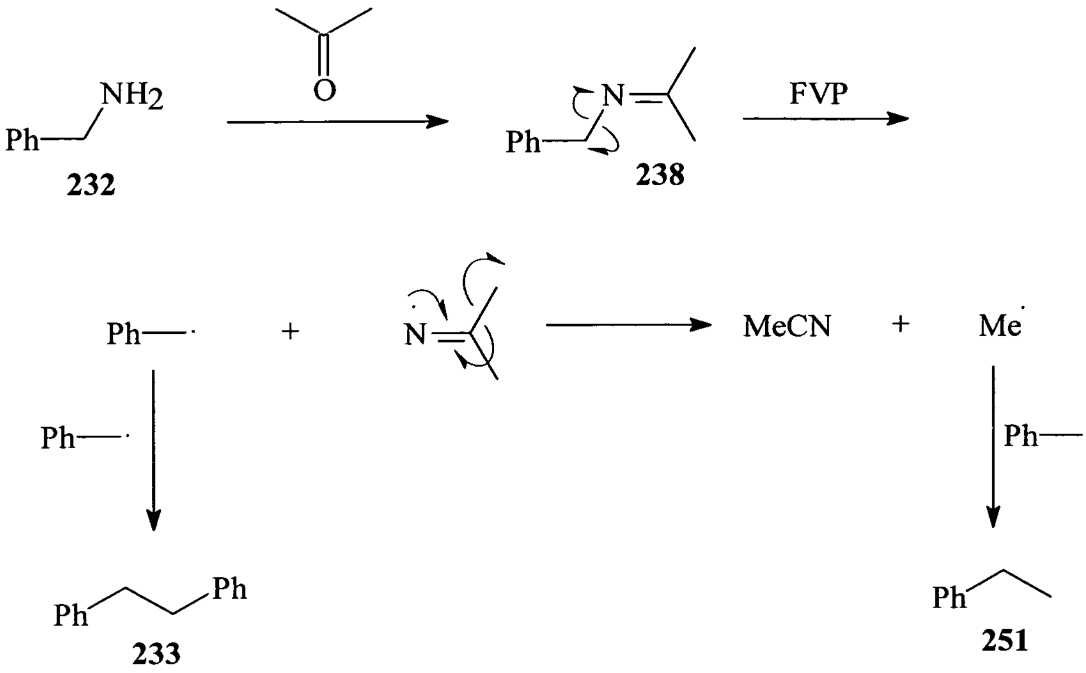


249
250

Scheme 61

It was hoped that rearrangement of the iminyl radical to form a stable nitrile would be the driving force for the radical cleavage of the carbon – nitrogen bond, which would also produce the desired benzylic radical. As before, the efficiency of this process could be assessed through monitoring bibenzyl **233** production in the ^{1}H-NMR spectrum of the crude pyrolysate.

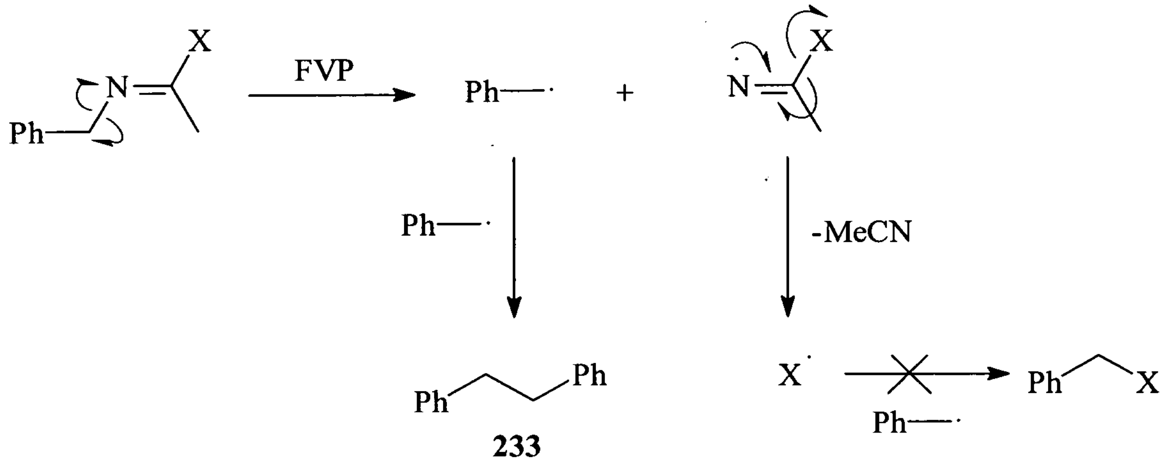
The first imine studied was benzyl-isopropylidene-amine **238**, the product of the condensation of benzylamine **232** with acetone (Scheme 62). This imine was found to be susceptible to hydrolysis, so the condensation reaction was carried out in toluene containing 4 Å molecular sieves under a nitrogen atmosphere. This methodology was utilised in the synthesis of all the imines prepared. Pyrolysis of **238** at a furnace temperature of 850 °C gave a crude pyrolysate that gave a complex ^{1}H-NMR spectrum. However, two components were identified from the spectrum, ethylbenzene **251** and bibenzyl **233** in a 5:1 ratio.



Scheme 62

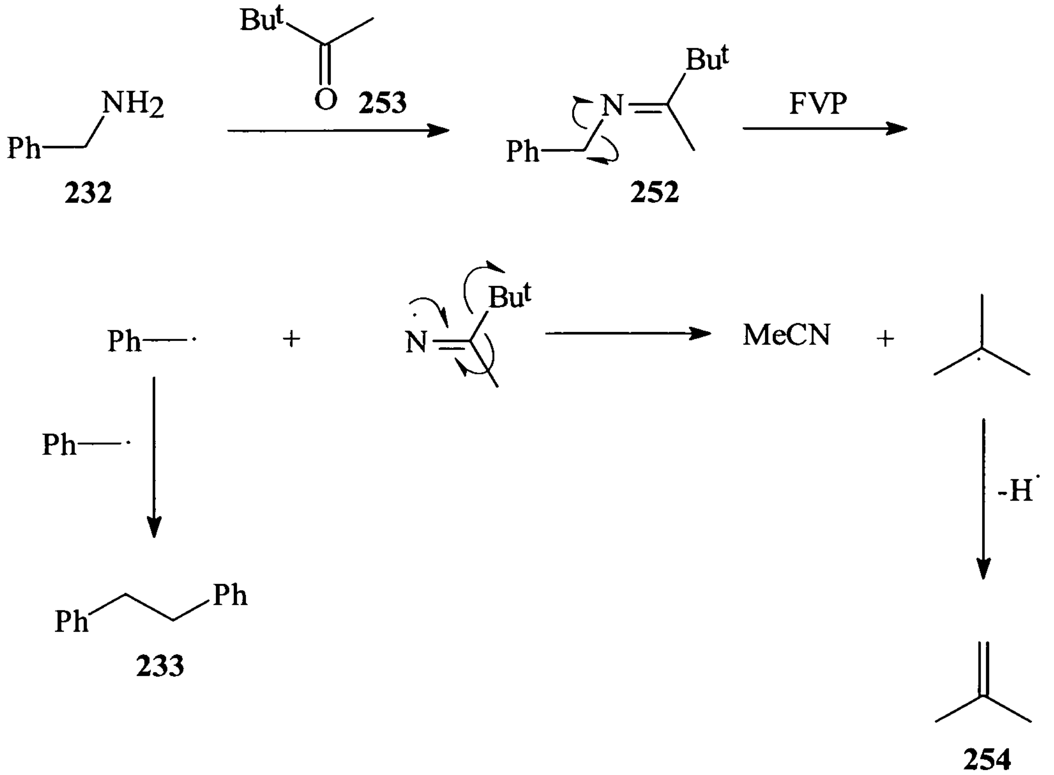
This result was encouraging, as it shows that the carbon - nitrogen bond was undergoing radical cleavage as desired. However, once this bond was broken to produce the benzyl radical and the iminyl radical, a side reaction was taking place, which was impacting on the efficiency of the benzyl radical coupling. The benzyl radical was effectively being "capped" with a methyl radical (formed as shown in Scheme 62) to produce ethylbenzene **251**, in a radical coupling process that appears to be favoured over the formation of bibenzyl **233**. Work carried out at the time of writing confirmed that this cross coupling reaction is indeed favoured over bibenzyl production.[66] This side reaction could also cause problems during the synthesis of the target heterocycles, so it was therefore necessary to fine tune this imine chemistry further in order to eliminate the possibility of such side reactions taking place.

As an initial experiment, the gas phase behaviour of benzyl-(1-ethyl-propylidene)-amine **239** was studied in order to determine if the same type of side reactions encountered with compound **238** occurred. The pyrolysis of **239** was, as expected, problematic, with the ^{1}H-NMR spectrum of the crude pyrolysate appearing very complex. No components could be identified from the spectrum in this case. It was therefore apparent that, although this imine based chemistry had potential applications in this area, the substitution pattern of the imine would have to be carefully selected in order to provide an efficient generator of benzyl radicals. Pyrolysis of **238** showed that the desired radical cleavage takes place, but also highlighted the fact that the fate of the iminyl radical plays an important part in the efficiency of bibenzyl formation. The ideal imine precursor would therefore behave under FVP conditions as shown in Scheme 63.



Scheme 63

The radical cross coupling reaction could be avoided if the radical produced from the breakdown of the iminyl radical was able to rearrange or selectively react to give a stable, non-reactive species. This would then enable the benzyl radicals to couple and produce the desired product, bibenzyl **233**. Following this logic, it was anticipated that the imine **252** (see Table 3), formed in high yield (70%) from the condensation reaction of benzylamine **232** with pinacolone **253**, would produce a benzyl radical, acetonitrile and a *t*-butyl radical under FVP conditions. It was hoped that the *t*-butyl radical formed would lose a hydrogen atom to produce isobutene **254**, as shown in Scheme 64, which would not react with any of the other substrates present. The formation of this side product also has the advantage that isobutene **254** is a gas at room temperature, and so would be removed when the cooled product trap was brought up to ambient temperature.

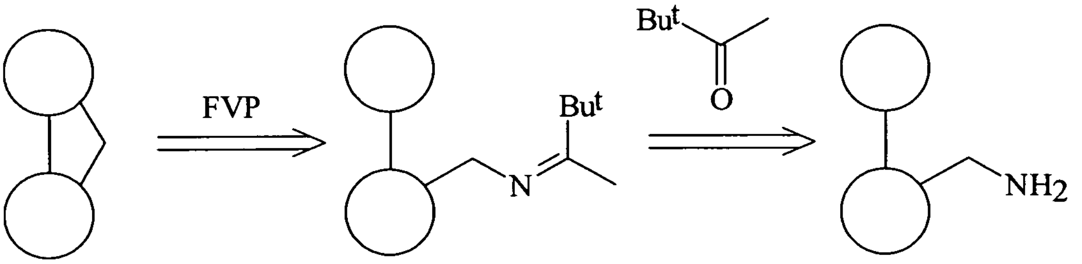


Scheme 64

This theory was shown to be valid from the pyrolysate obtained from the FVP of **252** at a furnace temperature of 750 °C. The ^{1}H-NMR spectrum of this crude pyrolysate was very clean, containing only two components, acetonitrile and bibenzyl **233**. These two components were present in an approximately 1:1 ratio as predicted by the mechanism shown in Scheme 64. Removal of the acetonitrile *in vacuo* allowed the yield of bibenzyl to be measured as 74%. This yield compares favourably with bibenzyl yields obtained from FVP of various substituted benzyl oxalates (40-80%).[57] As no starting material was present in the ^{1}H-NMR spectrum, the remainder of the material may have been consumed in side reactions involving capture of a hydrogen atom to produce toluene which would be removed along with the acetonitrile. As the formation of bibenzyl occurred in high yield this was not studied further.

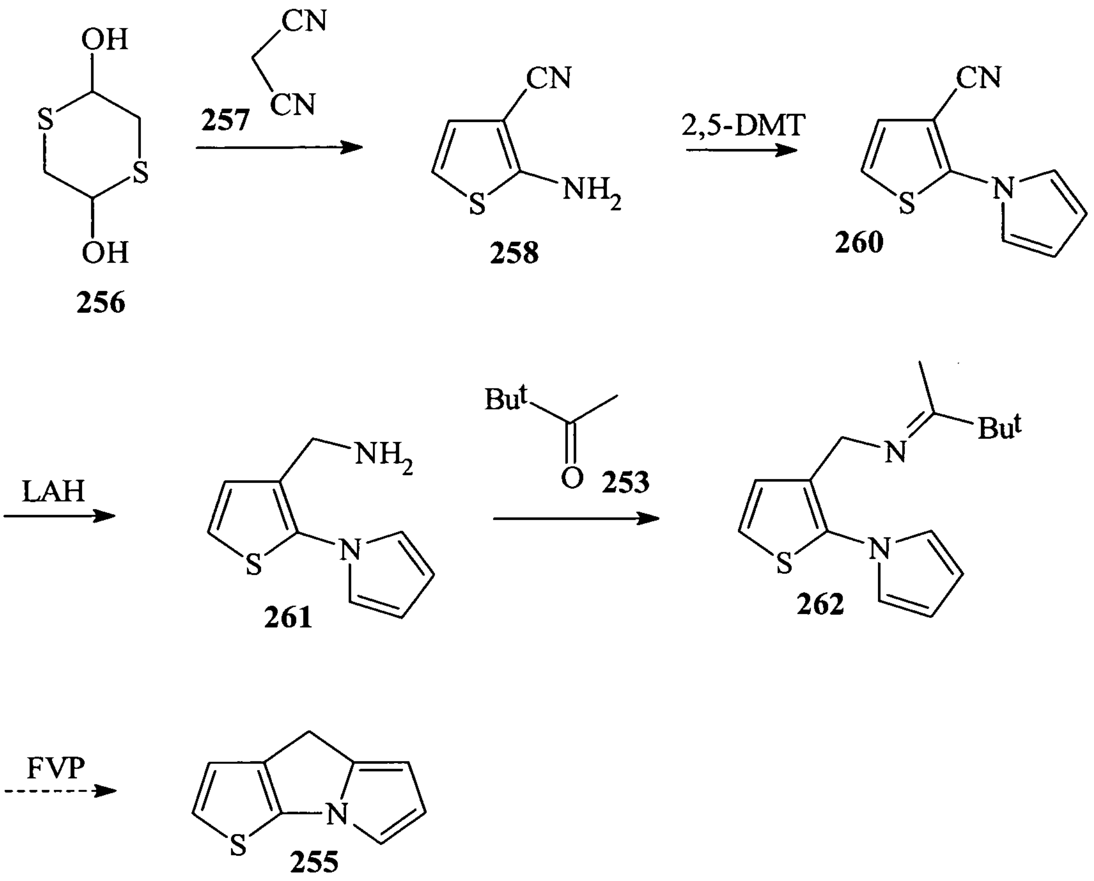
This successful development of a clean, efficient generator of benzyl radicals now meant that the general synthetic strategy shown in Figure 6 became a viable route to fused tricyclic heterocycles.

Figure 6: Proposed cyclisation methodology for synthesis of fused tricycles.



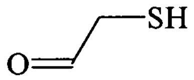
This methodology was then applied to the attempted syntheses of several 5,5,5- and 6,5,5-systems, which are discussed below.

The first 5,5,5-system targeted was the thiophene containing system, 4*H*-thieno[2,3-*b*]pyrrolizine **255**, shown in Scheme 65. The synthesis of **255** would be a severe test of the methodology due to the strain that would be expected in 5,5,5-fused systems. However, it was thought that by incorporating a thiophene ring in the tricyclic system (longer bonds than in pyrrole) there would be less strain than there would be in an all nitrogen system.[67]



Scheme 65

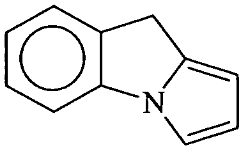
2-Aminothiophene-3-carbonitrile **258** was prepared in 81% yield from the reaction of 2,5-dihydroxy-1,4-dithiane **256** and malononitrile **257** using the method of Matsumoto [68] The dithiane **256** is effectively a "masked" version of the thiol **259** shown below.



259

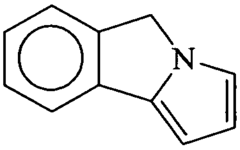
This reaction was carried out starting with an aqueous solution of malononitrile **257** at pH 3, to which the dithiane **256** was added. The pH of the solution is gradually raised to pH 12 through the addition of aqueous sodium hydroxide, during which the formation of the thiophene **258** takes place. The pyrrole ring was then built around the amine using 2,5-DMT to give 2-(pyrrol-1-yl)-thiophene-3-carbonitrile **260** in excellent yield (99%). Reduction of the nitrile functionality in **260** to a primary amine with LAH in 96% yield gave compound **261**. This bicyclic system was now set up to build the imine radical precursor around the primary amine, as first shown in Figure 6. The imine **262** was synthesised from the condensation of pinacolone **253** with the bicyclic amine **261** (66%). The imine **262** was found to hydrolyse rapidly, but fortunately the crude material obtained did not require further purification and could be stored under anhydrous conditions until it was required.

Pyrolysis of the imine radical precursor **262** at a furnace temperature of 700 °C gave a pyrolysate with a complex ^{1}H-NMR spectrum. This showed that no starting material was present in the pyrolysate, although there was a small amount of the bicyclic amine **261** present. This was most likely formed from hydrolysis of the imine **262** in the inlet tube, with the hydrolysed product distilling through the furnace tube into the product trap unchanged. Crucially, there was no peak present at *ca.* δ 3.8 which would be typical of the resonance attributed to the protons from the CH_2 bridge as inferred from the chemical shift of δ 3.75 in the pyrroloindole system **263**.[69]



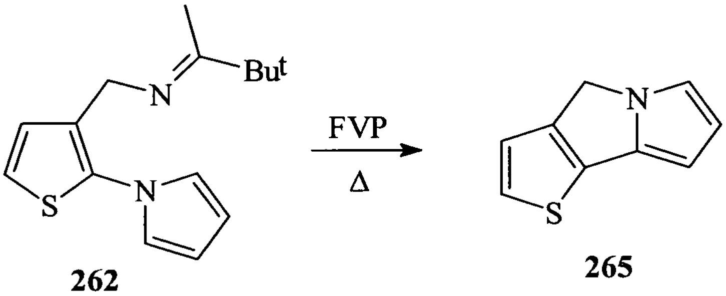
263

The major component in the ^{1}H-NMR spectrum of the crude pyrolysate showed a singlet at δ 4.82, but nothing else could be identified due to the complexity of the spectrum. The crude pyrolysate was flash chromatographed (silica, hexane as eluent) in an attempt to enable identification of this main component. The separation was successful, and a pure sample of this main component was obtained. The ^{1}H-NMR spectrum of this compound showed five resonances for single protons between δ 7.18 – 6.10 which could be assigned to the two thiophene protons and three pyrrole protons, as well as the singlet at δ 4.82 integrating to two protons. The mass spectrum of this compound showed a molecular ion at *m/z* 161 amu, which is the molecular mass of the expected tricycle **255**. It therefore seemed that this main component was isomeric with the expected product. At this stage, it was noted that the chemical shift of the CH_2 in a compound prepared by a previous member of the McNab group,[60] **264** shown below, is quoted as being δ 4.92 which corresponds well with the CH_2 chemical shift of δ 4.82 observed for the compound obtained from the pyrolysis of **262**.



264

This led to the hypothesis that the compound obtained from FVP of **262** was the tricycle, 7*H*-3-thia-6*a*-aza-cyclopent[*a*]pentalene **265**, as shown in Scheme 66.



Scheme 66

Further NMR work [NOE, Heteronuclear Multiple Quantum Correlation (HMQC) and Heteronuclear Multiple Bond Correlation (HMBC)] was carried out in an attempt to prove this hypothesis. Assignment of the molecular skeleton was possible by studying the chemical shifts and coupling patterns of the resonances in the ^{1}H-NMR spectrum. For example, the doublet observed at δ 6.71 could be one of two pyrrole protons expected to give this coupling pattern. However, the fact that it has the highest chemical shift of the two pyrrole doublets observed shows that this resonance is attributable to the CH adjacent to the pyrrole nitrogen. The HMQC (one bond proton-carbon correlation) enabled the proton resonances to be correlated to resonances in the ^{13}C-NMR spectrum (values shown in parentheses) as shown in Figure 7. The HMBC spectrum (long range proton-carbon correlation) was obtained with the aim of fully assigning the molecule. Unfortunately, the quaternaries were not defined, and remain unassigned.

Figure 7: Assignment of ^{1}H/^{13}C-NMR resonances of **265**. Fig. A shows ^{1}H-NMR chemical shifts with ^{13}C-NMR shifts in parentheses. Fig. B shows NOE correlations.

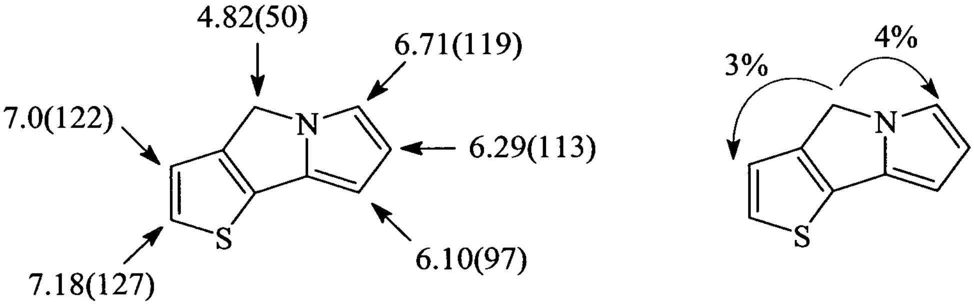
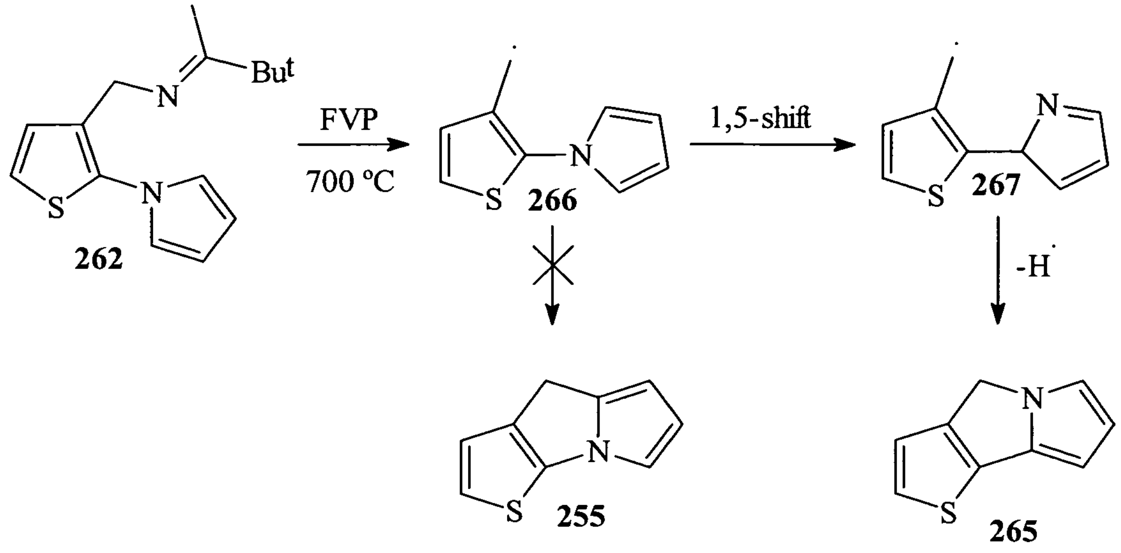


Fig. A

Fig. B

The NOE work showed a relationship between the resonance at δ 4.82 to both δ 7.0 and 6.71, providing confirmation that the isomer obtained was indeed 7*H*-3-thia-6*a*-aza-cyclopent[*a*]pentalene **265** (Scheme 66).

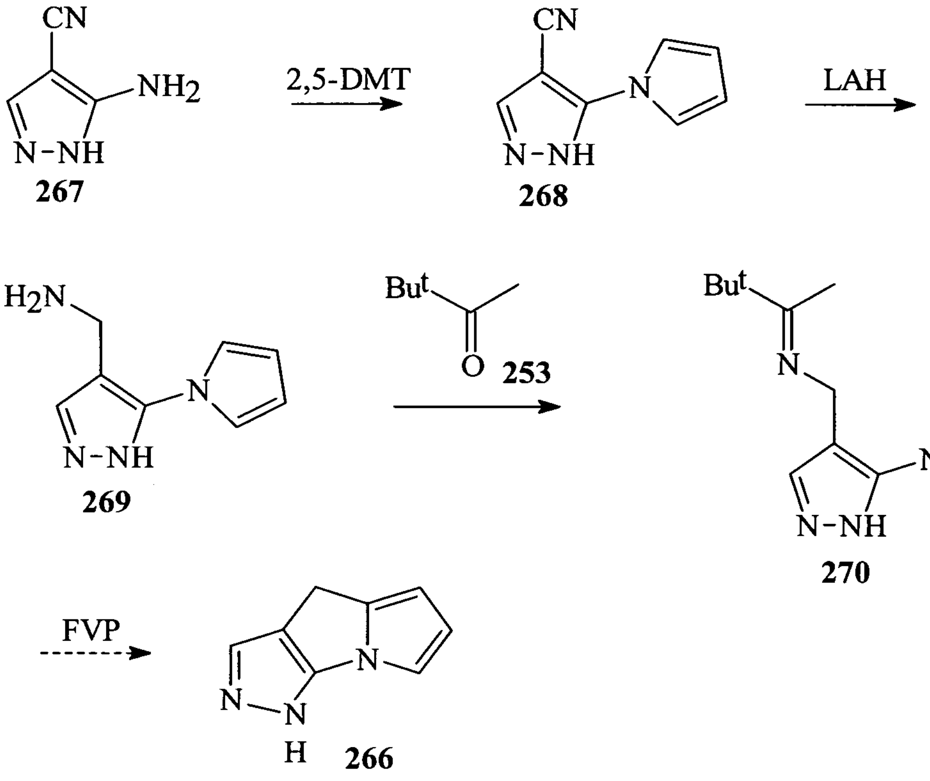
Now that the tricycle had been identified, it was necessary to postulate a mechanism of formation. The most likely mechanistic pathway is shown in Scheme 67.



Scheme 67

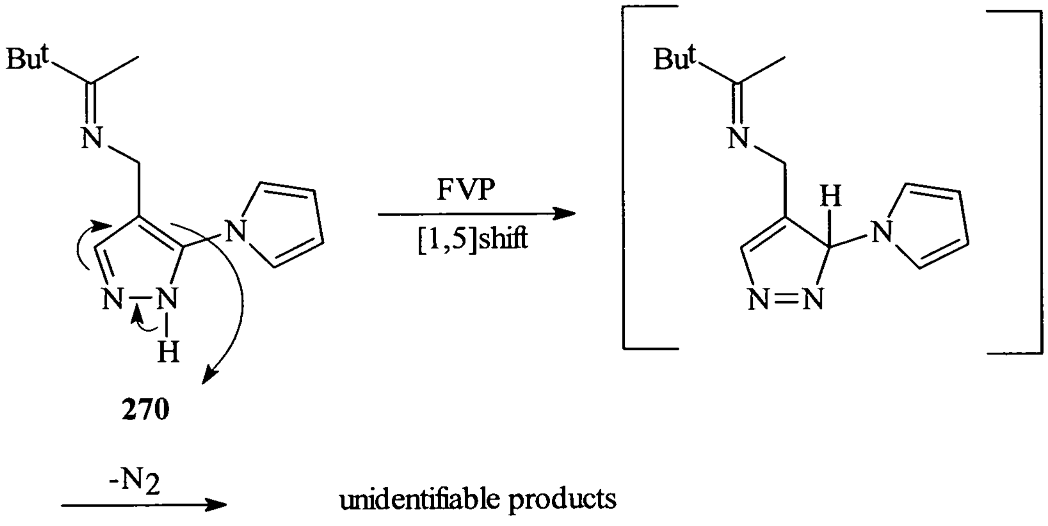
Pyrolysis of the imine precursor **262** at a furnace temperature of 700 °C would generate the benzyl type radical **266** as expected. However, instead of cyclisation occurring as anticipated, a [1,5]shift takes place preferentially to give the pyrrol-2-ylthiophene intermediate **267**. One possible explanation for why this sigmatropic shift occurs more rapidly than the cyclisation is that the adjacent radical could accelerate the shift. The acceleration of [3,3]sigmatropic shifts by adjacent anions is well known [70] although there is no known precedence for this type of radical accelerated [1,5]sigmatropic shift. There has been some work reported by Enholm *et al.*, which studied possible radical accelerated [3,3]sigmatropic shifts,[71] but this work has recently been disproved.[72] Once this shift has taken place, the benzyl type radical could then cyclise onto the nitrogen atom. Loss of a hydrogen atom would restore the aromaticity of the pyrrole ring to give the tricyclic product **265**, albeit in low yield (12%). Although it was disappointing that the reaction did not proceed as anticipated to produce the desired tricycle this example provided two positive results. Firstly, this piece of work showed that the imine precursor that had been developed did have potential as a radical generator under FVP conditions when applied to the synthesis of fused heterocycles. Secondly, the tricycle **265** produced is an example of a novel fused 5,5,5-system of which, as can be seen from the introductory chapter, there are relatively few examples.

Following the partial success of the above example, the methodology was applied to the attempted synthesis of another fused 5,5,5-system **266** as shown in Scheme 68.



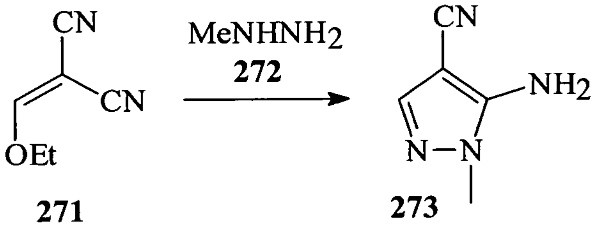
Scheme 68

The aminopyrazole starting material **267** (commercially available) was reacted with 2,5-DMT under the standard conditions employed previously,[49] to give the pyrrol-1-ylpyrazole **268** in a yield of 78%. Reduction of the nitrile functionality in **268** using LAH gave the primary amine **269** (49%). Attempts to purify **269**, an oil, were problematic. Distillation of **269** gave a material that was not the expected pure product, as shown from the complex ^{1}H-NMR spectrum. This material could not be identified. This showed that **269** was thermally unstable which raised potential concerns as to how the imine pyrolysis precursor would behave under FVP conditions. The crude amine **269** was judged to be sufficiently pure without distillation to be carried onto the next stage. Formation of the imine pyrolysis precursor **270** from the condensation reaction of **269** and pinacolone **253** occurred cleanly in good yield (69%). This material had to be handled carefully (minimal contact with open atmosphere) due to rapid hydrolysis of the imine double bond, which produced the amine starting material **269**. Pyrolysis of **270** at a furnace temperature of 750 °C produced a pyrolysate with a very complex ^{1}H-NMR spectrum. No components could be identified from the spectrum, and it appeared that the imine precursor **270** had been completely degraded under the FVP conditions employed. From the available literature covering FVP of pyrazoles, [73,74] it became clear that extrusion of molecular nitrogen from the pyrazole ring was the probable reason for this observed degradation of starting material.[74] The probable mechanism of this extrusion is shown in Scheme 69.



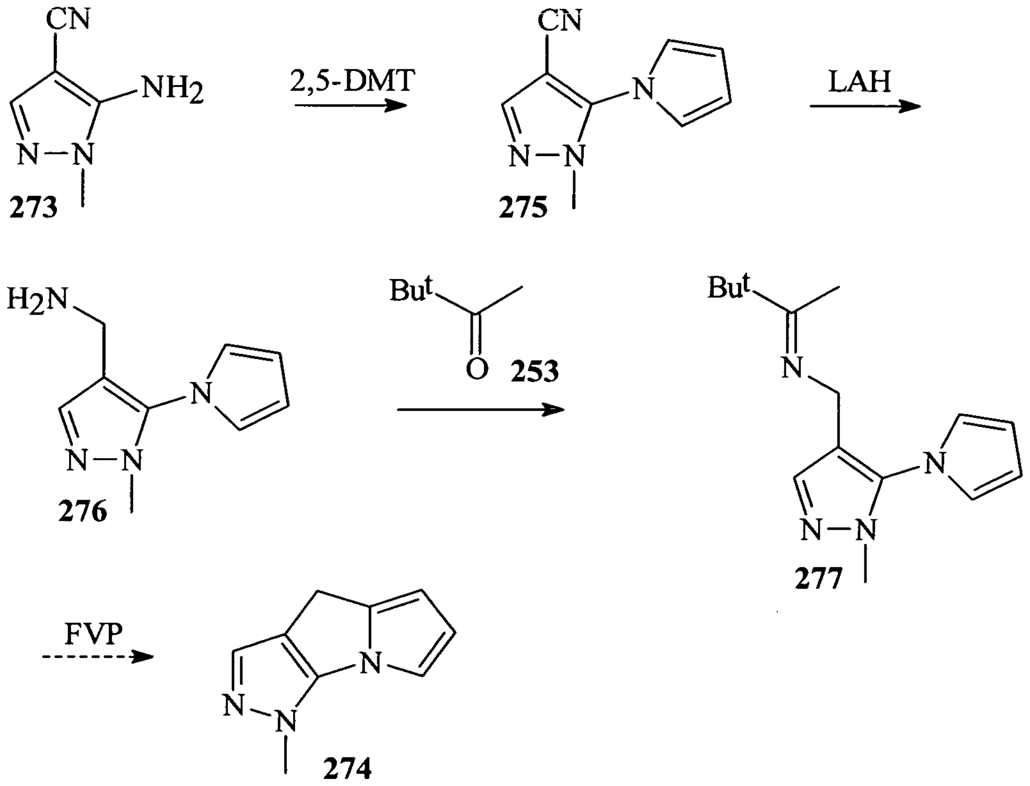
Scheme 69

A [1,5]shift of hydrogen from nitrogen to carbon sets the system up for extrusion of molecular nitrogen, causing opening of the pyrazole ring, which led to no identifiable products. In an attempt to reduce the extent of nitrogen extrusion, it was decided to replace the hydrogen on the pyrazole ring nitrogen with a substituent that would not migrate as readily. The methyl group was chosen as the desired pyrazole **273** could be prepared in a straightforward manner from the substituted hydrazine **272** as shown in Scheme 70.



Scheme 70

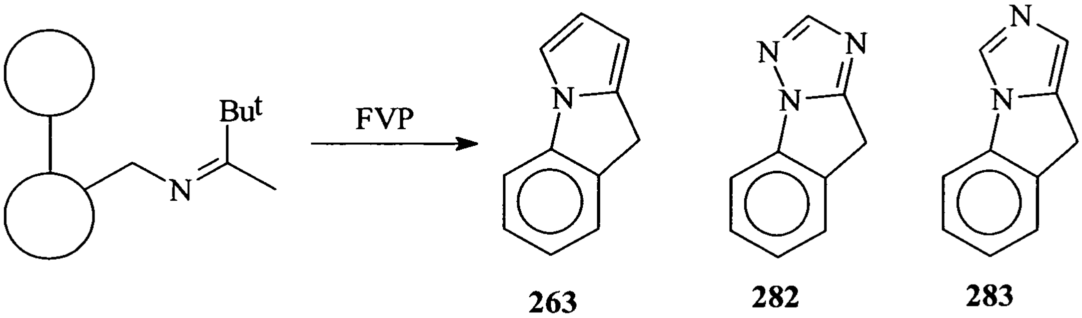
Compound **273** was prepared in 76% yield from ethoxymethylenemalonitrile **271** and methyl hydrazine **272**.[75] The proposed synthetic route to the fused tricycle **274** (Scheme 71) is identical to that shown in Scheme 68, only differing in the pyrazole starting material. Synthesis of the pyrrol-1-ylpyrazole **275** from the amine **273** occurred in excellent yield (88%). Reduction of the nitrile functionality using LAH gave the primary amine **276** in 64% yield. Condensation of **276** with pinacolone **253** produced the imine pyrolysis precursor **277** in lower yield than typically obtained for these condensation reactions (54%). No work was carried out to optimise this step. Unfortunately, pyrolysis of **277** at a furnace temperature of 750 °C gave a multicomponent pyrolysate, much like that obtained upon FVP of **270**. The ^{1}H-NMR spectrum of the pyrolysate obtained upon FVP of **277** was also complex, and again, no components were identified.



Scheme 71

The fact that there was no resonance present in the ^{1}H-NMR spectrum that could unambiguously be assigned to the CH_2 bridge in **274** showed that no cyclisation had taken place. It again appeared that, even though steps were taken to try to minimise nitrogen extrusion, the starting material had been destroyed under the reaction conditions through a process favoured over the anticipated cyclisation pathway. This conclusion was reinforced by mass spectral data for the pyrolysate, which showed no peaks that could be attributed to any starting materials or identifiable products. The reasons for these failures to cyclise are not known, but it may be that the ring strain in the targeted 5,5,5-tricyclic system is too great for it to be synthesised using this FVP methodology.

At the time of this result, Kodak also expressed an interest in various 6,5,5-fused heterocycles for use as potential magenta colour couplers. This provided an opportunity for the suitability of the cyclisation methodology to be tested in the synthesis of 6,5,5-systems, in which it was expected that the ring system would not be as strained as in the 5,5,5-heterocycles (bridgehead angles more favourable in 6,5,5-system). It was hoped that this imine radical generator methodology would therefore be applicable to the synthesis of 6,5,5-systems. The 6,5,5-systems targeted are shown in Scheme 72.

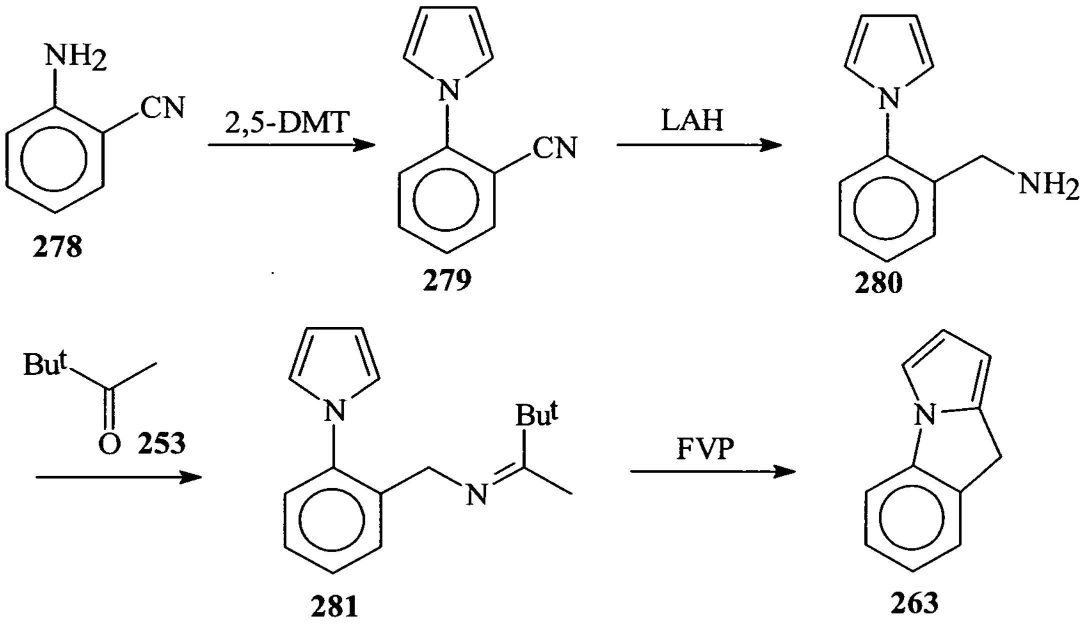


Scheme 72

If it were possible to produce any of the systems in Scheme 72 using the radical cyclisation methodology described above, this would provide more evidence for the theory that the 5,5,5-systems targeted (**266** and **274**) are too strained to be prepared using this methodology.

The proposed synthetic route to the pyrrole containing system **263** is shown in Scheme 73. Formation of 2-(pyrrol-1-yl)-benzonitrile **279** from 2-amino-benzonitrile **278** occurs in 58% yield, which sets up the required linked bicyclic intermediate. Reduction of the nitrile moiety in **279** using LAH gave the primary amine **280** (80%). Condensation of **280** with pinacolone **253** produced the pyrolysis precursor **281** cleanly in a yield of 60%. Pyrolysis of **281** at a furnace temperature of

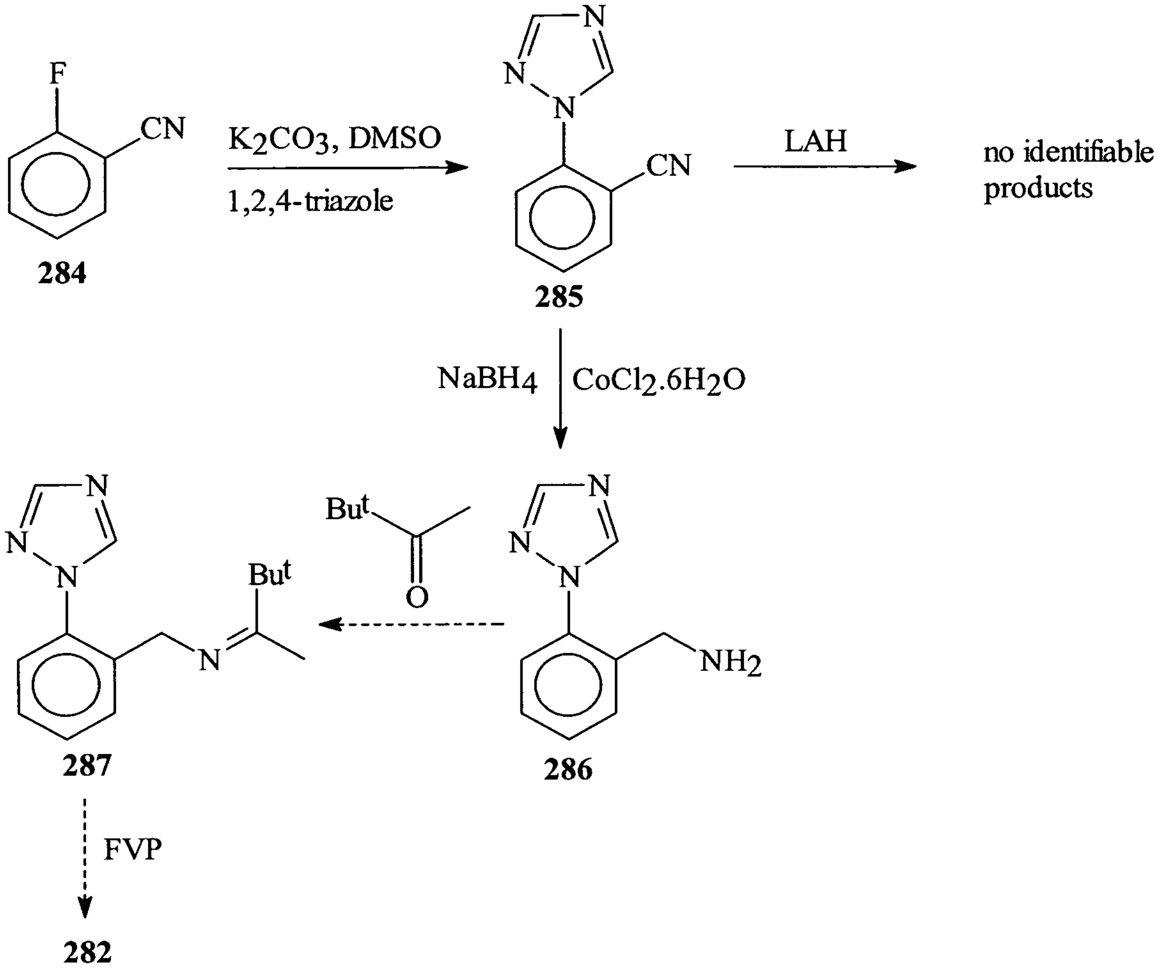
750 °C produced a pyrolysate with a clean ^{1}H-NMR spectrum, showing the presence of only two components. These components were identified through comparison of the ^{1}H-NMR spectrum with literature data [69] as the expected tricycle, 9*H*-pyrrolo[1,2-*a*]indole **263** (72%), and acetonitrile generated by the collapse of the iminyl radical produced from the radical cleavage of the carbon – nitrogen bond.



Scheme 73

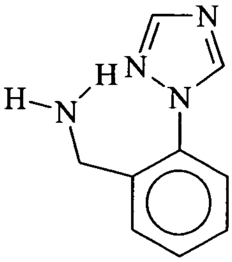
The clean, high yielding synthesis of **263** showed that the radical cyclisation methodology developed could be applied to the synthesis of fused tricyclic heterocycles. It is interesting to note that the synthesis of **263** occurred cleanly, with no degradation of starting material or product, and that no alternative cyclised products were obtained from an initial [1,5]shift taking place analogous to that shown in Scheme 67. These points suggest that both the degradation of starting material observed in the pyrazole case and the [1,5]shift observed in the thiophene example are substrate or system specific. However, it was important to establish the generality of the methodology through the attempted application to the synthesis of compounds **282** and **283** (Scheme 72).

The proposed synthetic scheme for compound **282** is shown below (Scheme 74). The formation of the linked bicyclic compound **285** from the reaction between 2-fluorobenzonitrile **284** and 1,2,4-triazole occurred in 71% yield.[76] The reduction of the nitrile functionality in **285** with LAH proved unsuccessful. No identifiable compounds were recovered from the reaction mixture, and it appears that the LAH conditions were effecting degradation of the 1,2,4-triazole ring. Alternative milder conditions were sought in the literature, which led to the discovery of reduction conditions developed by Ganem *et al* .[77] These conditions utilised a 10 mol% amount of cobaltous chloride hexahydrate as catalyst in THF/H_2O, with sodium borohydride as the hydride source.



Scheme 74

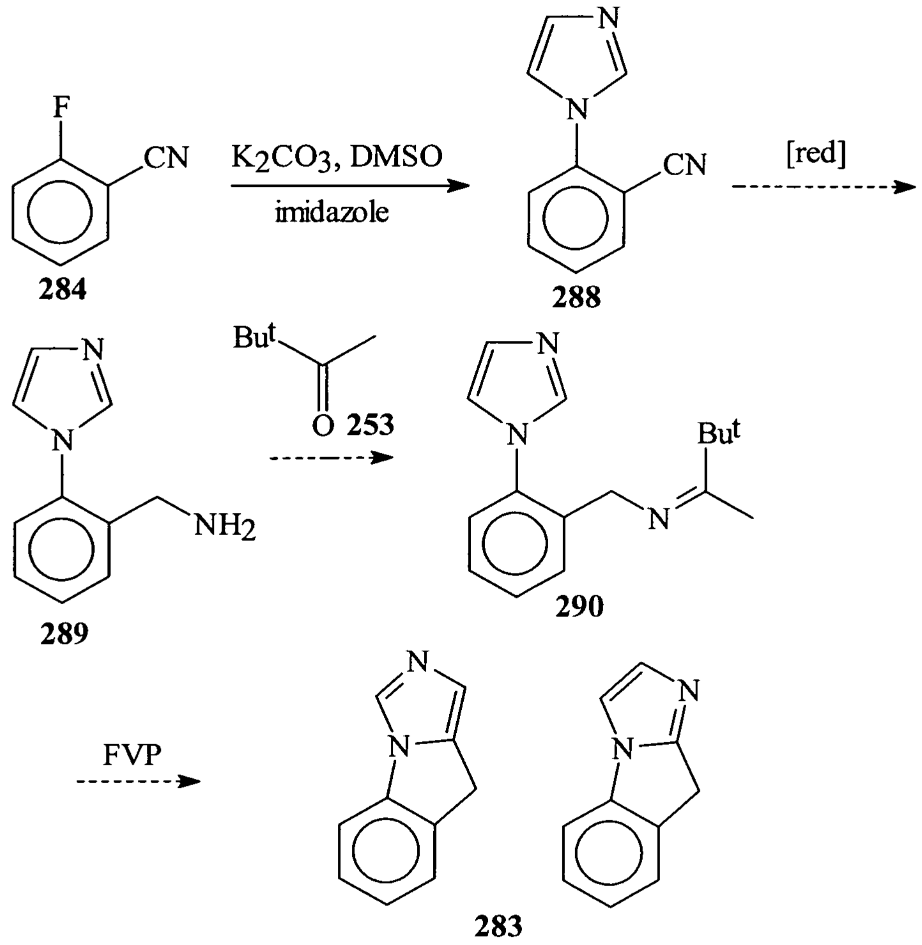
The use of these conditions gave a 15% yield (after chromatography) of a material that had spectral properties consistent with those expected for compound **286**. The key resonance in the ^{1}H-NMR spectrum for the methylene moiety was present at δ 3.51 which compares reasonably well with that observed for the analogous compound **280** (δ 3.76). However, the mass spectrum obtained for the material showed a base peak at *m/z* 173, which is one amu less than the peak attributed to the expected product [*m/z* 174 (31%)]. This facile loss of a hydrogen atom was unexpected by comparison with **280**. All other spectral data, including an accurate mass, were consistent with that expected for the primary amine **286**. Attempts to crystallise the material proved unsuccessful, as did attempts to form a picrate salt. This doubt over the identity of the material was enhanced further upon attempting to synthesise the imine pyrolysis precursor **287**. The condensation reaction, which had proceeded efficiently in other examples, was unsuccessful in this case. Attempts to drive this reaction forward using extended reaction times and/or elevated temperatures were also unsuccessful. This provided further information that suggested that the material obtained in the previous step was not in fact the desired amine **286**. However, if the compound obtained was in fact the amine **286**, a possible reason for the lack of reactivity of the amino group could lie with the possibility of intramolecular hydrogen bonding, as shown below.



286

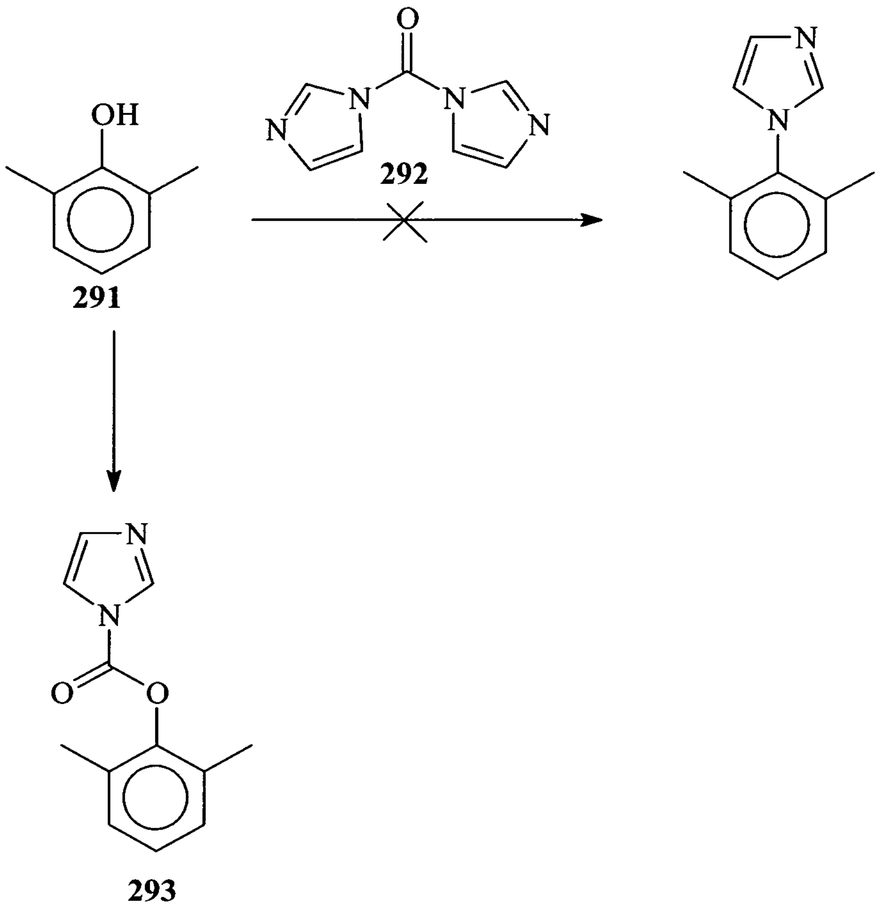
This issue remains unresolved. However, it is clear that the imine **287** could not be formed using the synthetic pathway shown in Scheme 74 due to problems either associated with the reduction of **285** or with the lack of reactivity of the reduction product **286**. It was therefore decided to attempt the synthesis of the imidazole containing tricycle **283** as shown in Scheme 75 which lacks the potential for H-bonding.

It was hoped that this synthesis would provide an insight into the problems encountered with the reduction step, as well as producing a novel tricyclic system. The reaction between 2-fluorobenzonitrile **284** and imidazole produced the bicyclic compound **288** (55%). The yield obtained for the synthesis of **288** was variable, as the crystallisation from ethanol appeared to be unreliable, even when the process was repeated in an identical manner.



Scheme 75

Alternative conditions were sought in order to optimise the yield and a recent report in the literature quoted a set of conditions which claimed remarkably to form this type of linked bicycle from a substituted phenol **291** and carbonyl diimidazole (CDI) **292** as shown in Scheme 76.[78] However, these conditions were shown to produce only compound **293** (as shown by ^{13}C-NMR and mass spectral data), and this finding was confirmed by a later publication.[79] The decision was therefore taken to persevere with the original conditions and to try to complete the tricycle synthesis.



Scheme 76

The attempted reduction of **288** using LAH proved unsuccessful (Scheme 75). As with the previous triazole-containing example, it appears that the conditions used were too harsh for the imidazole ring, with no identifiable material obtained from the reaction. Attempts to effect the reduction using the alternative conditions (cobaltous chloride hexahydrate with sodium borohydride) also proved unsuccessful. Again, no identifiable material was obtained from the reaction mixture.

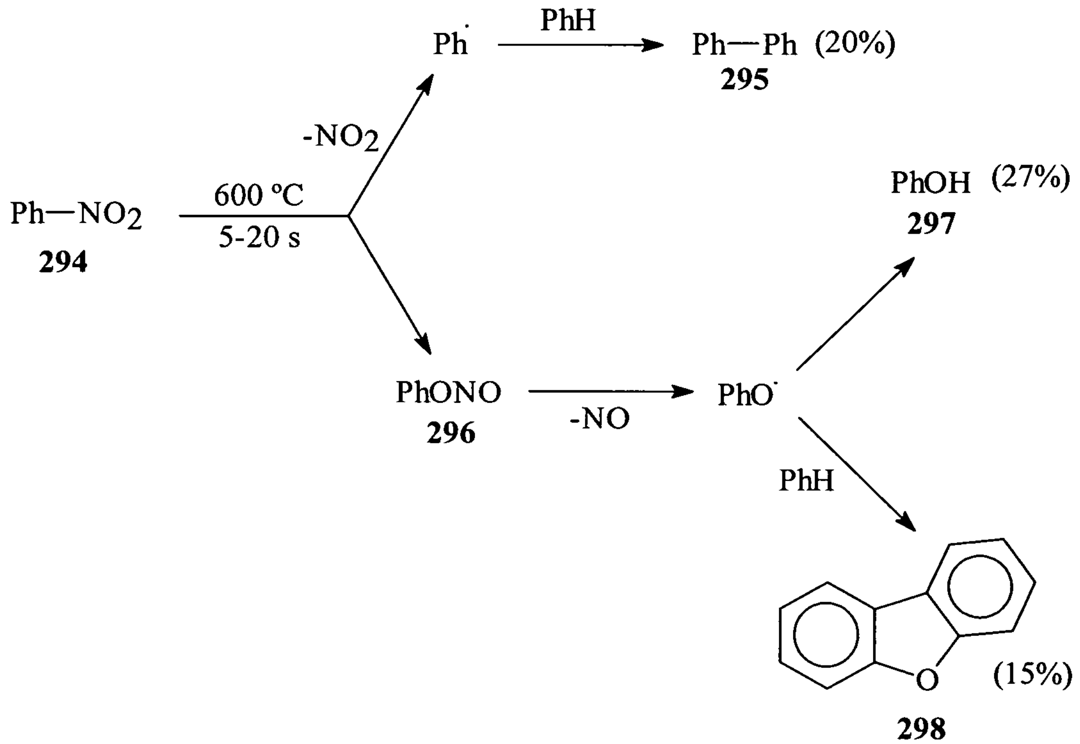
These problems encountered with reduction steps meant that there was no opportunity to test further the general applicability of the imine based radical generator. This was disappointing as the successful development of this novel radical generator and the application to one 5,5,5-system **265** (Scheme 66) and one

6,5,5-system **263** (Scheme 73) showed promise. However, the problems encountered in the attempted synthesis of the bicyclic amines **286** and **289** serve to demonstrate that the methodology is perhaps not widely applicable to the synthesis of these types of systems. The discovery of a cyclisation methodology with the potential for wide ranging use in the synthesis of fused heterocycles is discussed in the next section.

c) Use of the nitro group as a radical precursor

The difficulties observed in synthesis of suitable starting materials which would enable further exploitation of the iminyl radical chemistry (as described in the previous section) led to the search for an alternative radical route into fused tricyclic systems, which is described in this section.

There are various reports in the literature which provide precedent for the generation of aryl radicals from nitroaryl precursors under flow pyroysis and FVP conditions. One example of the use of a nitro radical generator under flow pyrolysis conditions, reported by Fields and Meyerson, [80, 81] is shown in Scheme 77.



Scheme 77

Flow pyrolysis of a benzene solution of nitrobenzene **294** at atmospheric pressure with a contact time between 5 – 20 seconds can follow two different reaction pathways. Homolysis of the C – N bond generates a phenyl radical, which reacts with the benzene carrier gas to produce biphenyl **295** in 20% yield. Alternatively, rearrangement to **296** followed by N – O homolysis can generate the phenoxyl radical which can go on to produce either **297** (27%) or **298** (15%). The exact mechanism of formation of dibenzofuran **298** is unknown.

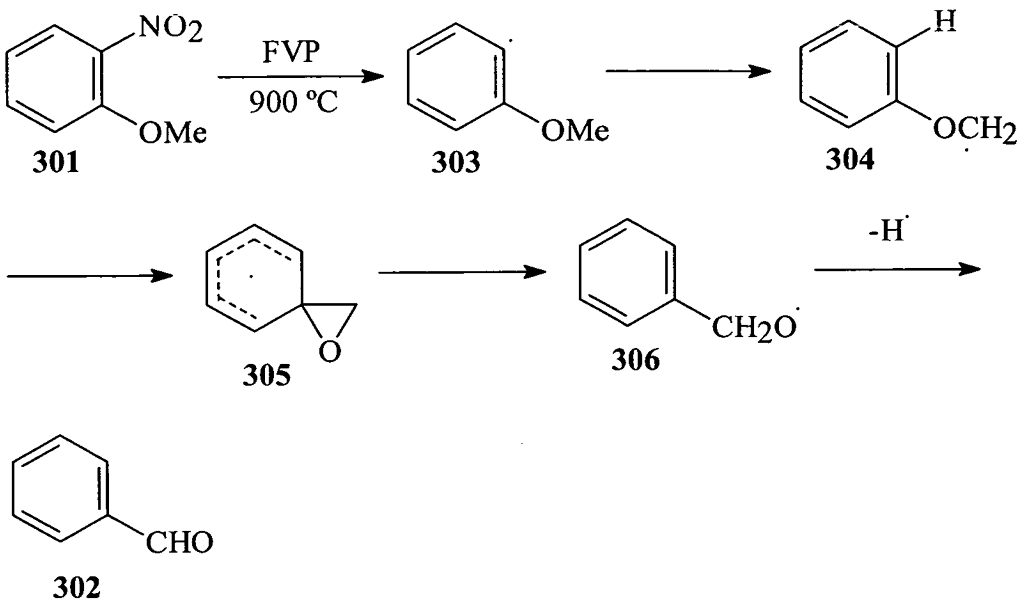
Although this report suggests that flow pyrolysis of aromatic nitro compounds can provide complex product mixtures, study of literature reports on FVP of aromatic nitro compounds suggests that the mechanistic pathways followed, and therefore the products obtained, are governed by substituent effects. For example, Wiersum [82] reported that FVP of compounds **299a–c** (Scheme 78) produced the phenols **300a–c** through a mechanism similar to that proposed by Fields and Meyerson. [80, 81]

$$\underset{\textbf{299}}{\text{Aryl-NO}_2} \xrightarrow{\text{FVP}} \text{Aryl-ONO} \xrightarrow{\text{-NO}^{\cdot}} \text{Aryl-O}^{\cdot} \xrightarrow{\text{RH}} \underset{\textbf{300}}{\text{Aryl-OH}}$$

a: Aryl = 1-pyrenyl
b: Aryl = 3-fluoranthyl
c: Aryl = 6-chrysenyl

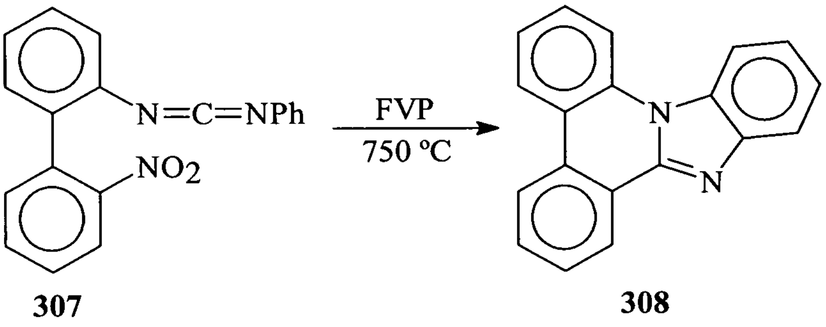
Scheme 78

In contrast, work carried out by de Mayo [83] showed that FVP of 2-methoxynitrobenzene **301** produced benzaldehyde **302** *via* the postulated mechanism involving the phenyl radical **303** as shown in Scheme 79. FVP of **301** produces the phenyl radical **303** through homolysis of the C – N bond. Rearrangement of the radical produces **304** which can cyclise to form the spiro radical intermediate **305**. Ring opening of **305** produces the radical **306** which forms benzaldehyde **302** through loss of a hydrogen atom.



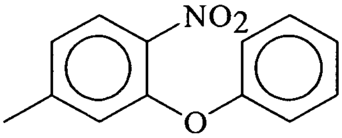
Scheme 79

Similarly, reports by Rees *et al.* [84,85] showed that FVP of **307** produced the pentacycle **308** (Scheme 80).

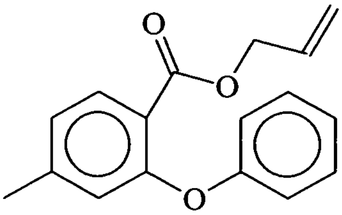


Scheme 80

Although the authors postulated a mechanism involving a dipolar intermediate, the work by de Mayo suggests that a radical mechanism is more likely. Such a mechanism has been proposed for the reaction shown in Scheme 80.[86] Further studies carried out in the McNab group confirmed that the mechanistic pathway of aryl nitro compounds under FVP conditions does involve a phenyl radical intermediate. [86] Studies of the reactivity of the nitro compound **309** under FVP conditions showed that the obtained product profile was identical to that produced from FVP of the allyl ester **310**, the reaction of which is known to proceed through a phenyl radical intermediate.[87]



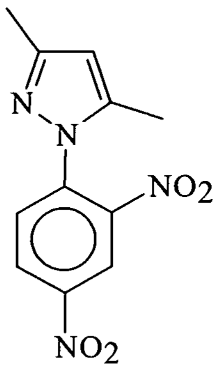
309



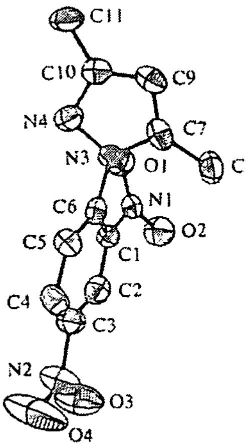
310

It is important to note that neither this work, or the work by de Mayo or by Rees and co-workers reported the production of any rearrangement products. This difference in reactivity observed by Wiersum [82] (rearrangement of nitro group leading to production of phenols) compared to that observed by de Mayo [83] and Rees [84, 85.] (generation of phenyl radicals) can be rationalised by examination of the structure of the pyrolysis precursors. The key difference in the structure of the pyrolysis precursors is that the compounds used by de Mayo, **301**, and Rees, **307**, have substituents *ortho* to the nitro group whereas the compounds used by Wiersum, **299a-c**, do not have *ortho* substituents. These *ortho* substituents could cause deformation of the nitro group out of the plane of the aryl ring, therefore disrupting the conjugation of the nitro group and the aryl ring. This would weaken the C – N bond and make it more likely that this bond would be broken under FVP conditions in preference to any nitro group rearrangement taking place. Confirmation that the nitro group is twisted out of the aryl group plane through the presence of an *ortho* substituent was provided by a literature publication of the X-ray crystal structure of the dinitro compound **311**,[88] as shown in Figure 8.

Figure 8: X-ray crystal structure of **311**

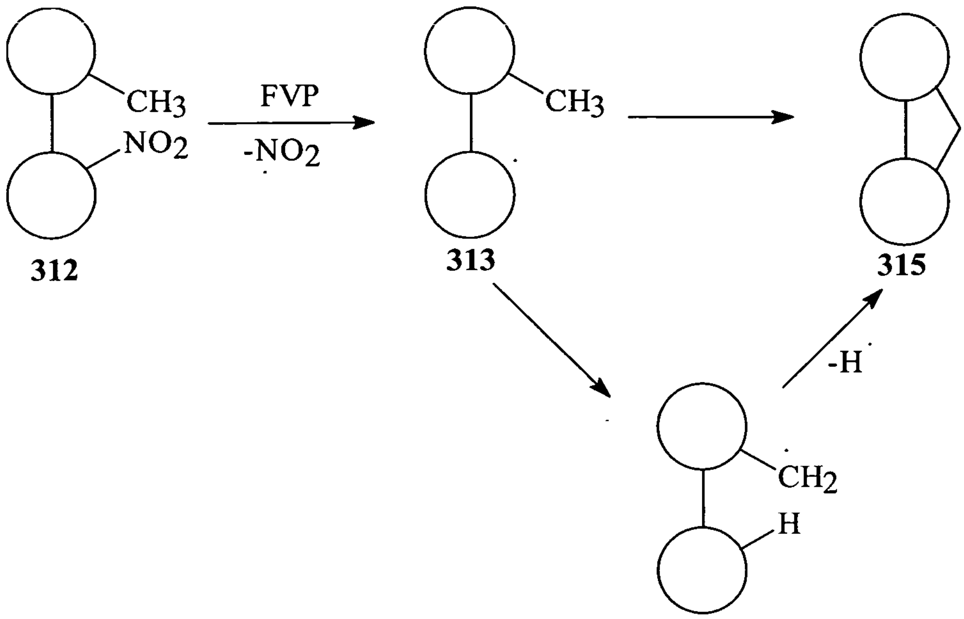


311



Further X-ray crystallography studies carried out confirmed that this twisting of the *ortho* nitro group is a general phenomenon.[86]

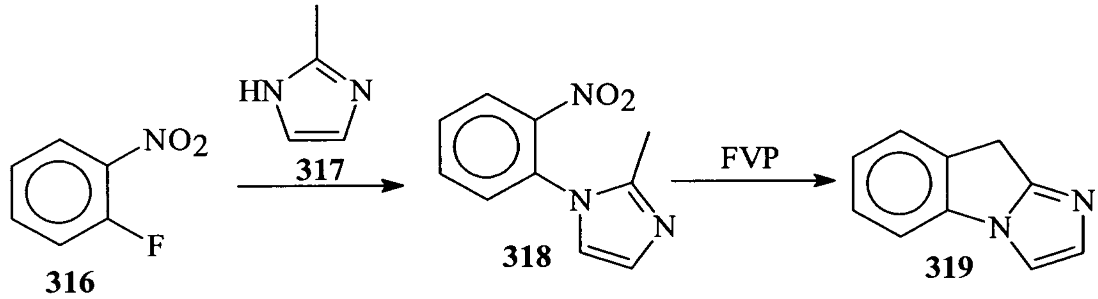
It was hoped that this method of generating aryl radicals from nitro precursors could be adapted in such a way that they would be useful in the synthesis of fused 6,5,5-heterocycles under FVP conditions. As in the previous section, the general strategy that was studied involved the synthesis of a bicyclic intermediate, but this time utilising a pendant methyl group on the ring without the nitro group to enable the cyclisation to occur as illustrated in Scheme 81. Previous work in the McNab group had shown that this use of a pendant methyl group in conjunction with a phenyl radical generated from FVP of a nitro precursor could be utilised in the formation of 5 – membered rings.[86]



Scheme 81

When applied to the synthesis of novel tricyclic heterocycles, it was thought that FVP of the bicycle **312** would result in homolysis of the C – N bond producing the aryl radical **313**. This intermediate could then cyclise, either directly onto the pendant methyl group, or *via* a radical translocation pathway that would form the benzylic type radical **314,** to give the tricyclic system **315**. It has been reported that the dissociation energies (D values) of the appropriate C – H bond gives an indication of the stability of a particular radical, in that the lower the D value, the more stable the radical formed.[89] The data provided suggests that the benzyl type radicals are more stable than phenyl radicals, so it is thought that the reaction would proceed *via* the radical translocation mechanism. This proposed synthetic route would have several advantages over the methodology developed in the previous section. The bicyclic precursors would be easier to prepare, as the *o*-nitro group facilitates the aromatic nucleophilic substitution by the azole in the same way as the cyano group did in the previous section. However, the *o*-nitro group is a better electron-withdrawing group than the cyano group and so these reactions could be expected to proceed more efficiently. Also, suitable methyl-substituted heterocycles are widely available (see later), so the methodology should be applicable to a wide range of systems. However, the major advantage that this methodology would offer over that discussed in the previous section is that a reduction step is not required, which was the major problem encountered in the synthesis of the imine radical precursors.

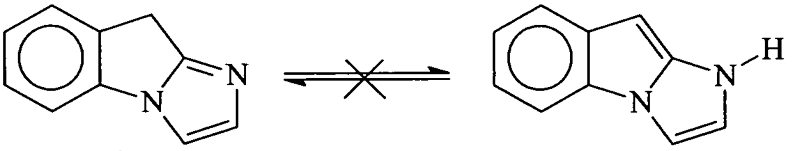
Once the synthetic route had been proposed in theory, it was necessary to attempt the synthesis of a model system in order to determine if the methodology was actually applicable to fused 6,5,5-heterocycles. Scheme 82 shows the model system targeted.



Scheme 82

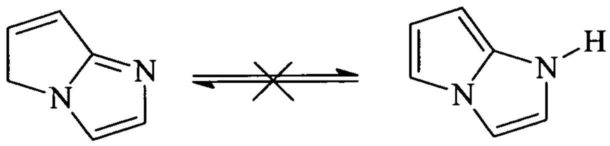
The reaction between 2-fluoronitrobenzene **316** and 2-methylimidazole **317** in DMF containing potassium carbonate (125 °C for 24 h) gave 2-methyl-1-(2-nitrophenyl)-1*H*-imidazole **318** in 52% yield. Small scale FVP of **318** at a furnace temperature of 850 °C gave a clean pyrolysate which contained only one major component as shown by the ^{1}H-NMR spectrum. The spectrum showed the expected set of resonances attributable to aromatic CHs, as well as one new resonance not observed in the ^{1}H-NMR spectrum of the starting material **318**. This resonance (δ_H 3.90) integrated to two protons, proving that the methylene bridge had been formed. This ^{1}H-NMR spectroscopic data along with the ^{13}C-NMR (δ_C 29.23, attributable to a methylene moiety as shown by the Distortionless Enhancement by Polarisation Transfer (DEPT) spectrum) and the mass spectrum data [*m/z* 156, attributable to starting material **318** – HNO_2 (47 amu)] enabled the major component to be identified as the previously unknown 6,5,5-heterocycle, 9*H*-imidazo[1,2-*a*]indole **319**, obtained in a yield of 40 – 45% after distillation.

It is interesting to note that the ^{1}H-NMR spectrum of the crude pyrolysate showed only the 9*H*-tautomer **319**, with no trace of the possible 1*H*-tautomer **319a** evident.



319 **319a**

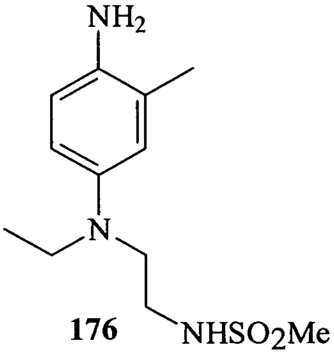
This absence of tautomerism is comparable with the behaviour observed for the analogous bicyclic system **320** (Scheme 83),[90] which exists only as the 5*H*-tautomer **320**.



320 **320a**

Scheme 83

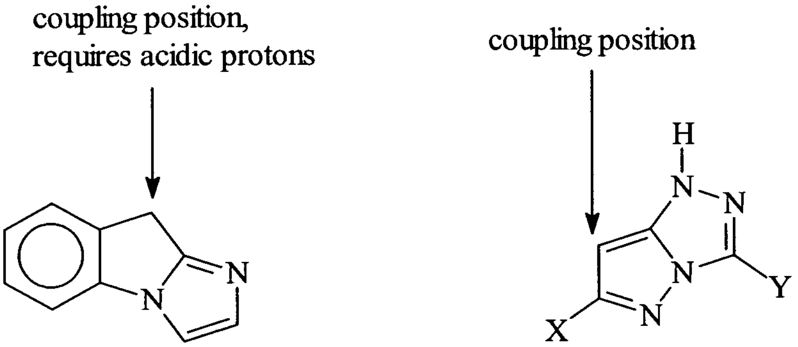
In an attempt to form a magenta dye with **319**, the crude pyrolysate was subjected to TLC. Spraying of the silica plates with colour developer 3 (CD3) **176** followed by oxidation with aqueous potassium persulfate in an attempt to mimic development conditions produced no coloured spots.



176

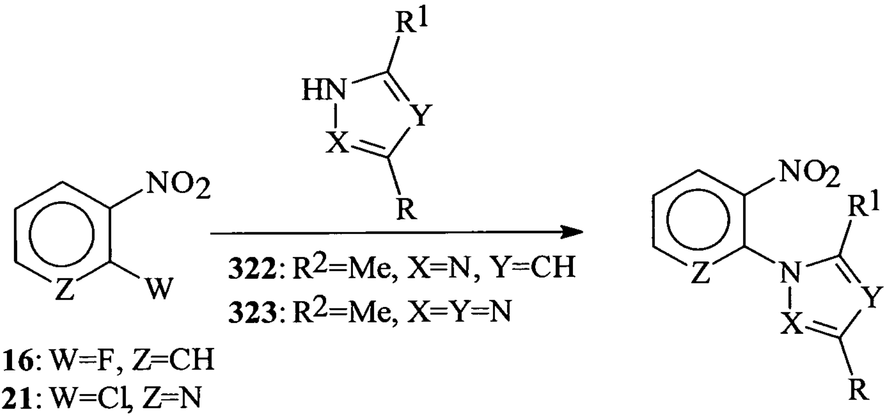
Although this was disappointing it was not entirely unexpected as to undergo the coupling reaction (see Introduction, Scheme 1), the protons at the coupling position must be suitably acidic (see Figure 9).[3] Comparing **319** with the known [4] pyrazolotriazole coupler **7** (Figure 9), it became evident that **319** does not contain enough electron withdrawing groups to make the protons at the coupling position acidic enough to couple.

Figure 9: Comparison of **319** and **7**



319 **7**

Therefore, in an attempt to produce further systems which would potentially produce dyes and to determine the generality of the methodology, precursors **324** – **326** (Scheme 84) were prepared and pyrolysed.



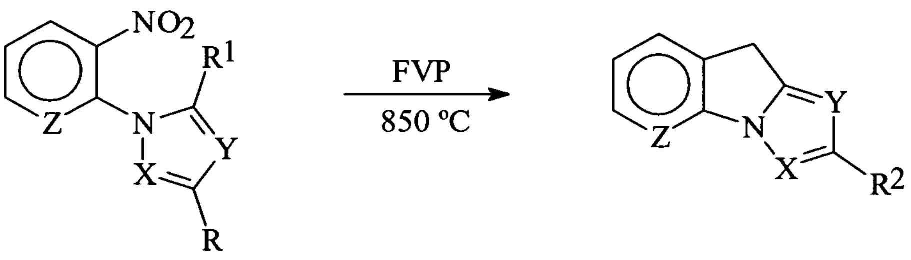
316: W=F, Z=CH
321: W=Cl, Z=N

324: R=R^1=Me, X=N, Y=Z=CH
325: R=R^1=Me, X=Y=N, Z=CH
326: R=R^1=Me, X=N, Y=CH, Z=N

Scheme 84

The reaction between 2-fluoronitrobenzene **316** and heterocycles **322** (commercially available) and **323** (provided by Kodak) in DMF containing potassium carbonate produced the bicyclic precursors **324** and **325** in 74% and 66% respectively. The pyridine containing precursor **326** was produced in 32% yield from the reaction of 2-chloro-3-nitropyridine **321** and 3,5-dimethylpyrazole **322**. The synthesis of **326** was not as clean as the other derivatives, and chromatography of the reaction mixture was required to obtain a pure sample of the desired material.

The precursor compounds **324** – **326** were all pyrolysed on a small scale at a furnace temperature of 850 °C to give the 6,5,5-systems **327** – **329** as shown in Scheme 85.



324: R=R^1= Me, X= N, Y=Z= CH
325: R=R^1= Me, X=Y= N, Z= CH
326: R=R^1= Me, X= N, Y= CH, Z= N

327: R^2 = Me, X= N, Y=Z= CH
328: R^2 = Me, X=Y= N, Z= CH
329: R^2 = Me, X= N, Y= CH, Z= N

Scheme 85

FVP of **324**, **325** and **326** produced **327** (43%), **328** (59%) and **329** (42%) respectively. In all cases, the desired product was the only major component detected by ^{1}H-NMR spectroscopy with all compounds purified by a simple Kugelrohr distillation. As with compound **319**, the ^{1}H-NMR spectra of compounds **327** – **329** showed only the presence of the 9*H*-tautomers (as seen from the CH_2 peaks at *ca.* δ 3.8 in the ^{1}H-NMR spectra). Attempts to scale up these pyrolyses proved problematic, with lower yields obtained due to the fact that the products condensed at the furnace tube exit rather than in the cooled U-tube trap. This part of the tube is still very hot, and it is thought that these elevated temperatures along with the presence of the reactive co-products derived from the nitro-group are responsible for product decomposition.

$$N_2O_3\,(g) \rightleftharpoons NO\,(g) + NO_2\,(g)$$

Scheme 86

During the pyrolyses, a blue solid was observed in the product trap at the level of the liquid nitrogen. This blue solid is thought to be dinitrogen trioxide (see Scheme 86), which was observed to change state to give a brown gas when warmed to room temperature. The brown gas is thought to be NO_2, which is known to be derived from dinitrogen trioxide.[91] Although no attempts were made to characterise these gases, it is thought that at high temperatures these "NO_X" co-products would be very reactive, and contribute to the decomposition of the desired tricyclic products. In an attempt to minimise this problem, a novel set of trapping conditions was devised. Instead of using a U-tube cooled with liquid nitrogen to condense the pyrolysate, a cold finger trap cooled with dry ice/acetone was employed. The cold finger joint with the furnace tube was pushed as far into the furnace as possible, and both this joint and the inlet tube joint insulated with tin foil. This gave two advantages over the standard set up. Firstly, the desired product was condensed directly onto a surface cooled to -80 °C as opposed to the warmer surface of the furnace tube exit. Secondly, the reactive co-products did not condense at -80 °C, but were trapped in a liquid nitrogen cooled U-tube connected to the cold finger in series. These two factors minimise the possibility of product decomposition. Once the pyrolysis was complete, nitrogen gas was released through the system, which was dismantled before the U-tube could warm to room temperature. This allowed the co-products to be removed from the system before they were in the gaseous state, so that they had no further contact with the product. The cold finger was then dismantled whilst still cold, and the product washed off immediately with acetone and stored at -18 °C until required.

Despite initial problems encountered in trapping the products cleanly, this methodology has provided a two step synthetic route to 3 novel heterocycles, **319**, **328** and **329** as well as one known compound, **327**.[92] Compound **329** is also the first reported example of this heterocyclic system.

Since compound **329** is a novel heterocyclic system, it was decided to carry out a systematic study of its $^1H/^{13}C$-NMR spectra [HMQC, HMBC and Nuclear Overhauser Effect Spectroscopy (NOESY)] in order to provide a complete assignment of the system. A study of the $^1H/^{13}C$-NMR spectra (HMQC and HMBC) of **327** was also carried out for comparison. The HMQC spectrum for **329** made it possible to correlate proton resonances with ^{13}C-NMR resonances. Figure 10 shows the HMBC spectrum for **329**, with Figure 11 showing the key HMBC relationships which enabled the full assignment of **329**.

Figure 10: HMBC spectrum obtained for compound **329**

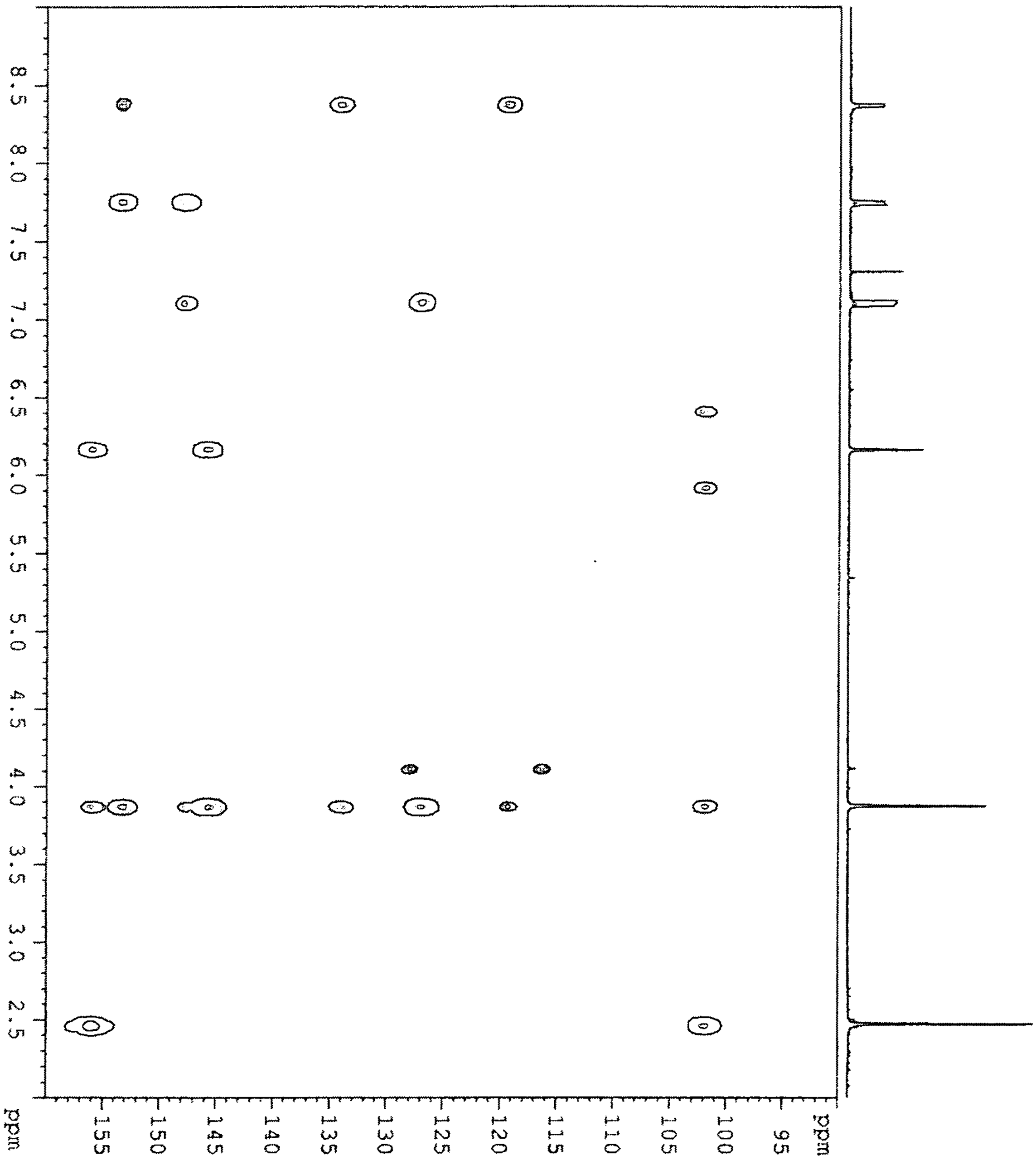
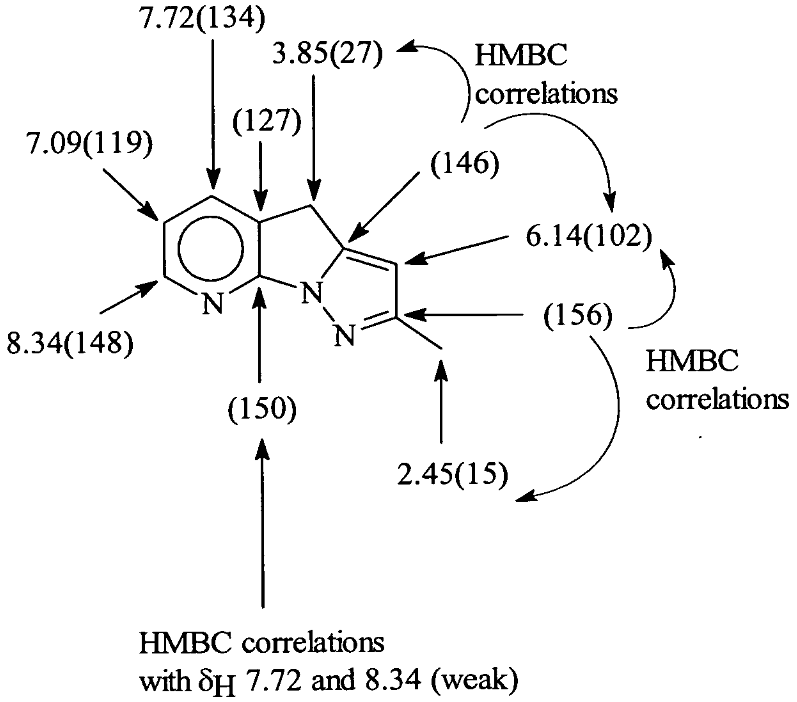
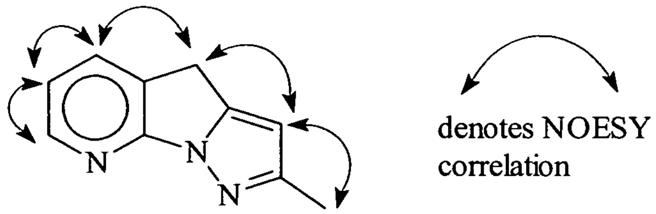


Figure 11: Key HMBC relationships plus assignment of ^{1}H-NMR chemical shifts and ^{13}C-NMR chemical shifts (in parentheses) for **329**



An initial assignment of the pyridine protons (δ_C values in parentheses) based on reported coupling patterns (*ca.* $J_{H2\text{-}H4}$ 5 Hz, $J_{H2\text{-}H3}$ 8 Hz) [93] provided a basis on which to assign the remainder of the molecule. The quaternary at δ_C 150 showed 3-bond correlations with protons at δ_H 8.34 (weak) and 7.72. The quaternary at δ_C 146 showed 2-bond correlations with protons at δ_H 6.14 and 3.85. Similarly, relationships for the other quaternary carbons enabled full assignment of **329** (Figure 11). This assignment was confirmed by the NOESY spectrum, a summary of which is shown in Figure 12.

Figure 12: NOESY summary for **329**



The key piece of information in from the NOESY work was that the CH_2 resonance showed relationships with both the pyrazole proton and the pyridine proton at δ7.72. This confirms the assignment of the pyridine protons by inspection. Following the NOESY relationships around the molecule, as shown in Figure 12, confirmed the assignment deduced from the HMBC spectrum. For comparison, HMQC and HMBC spectra were obtained for **327** (see Figure 13 for HMBC spectrum). The main problem in fully assigning **327** was in distinguishing between the two doublet and two triplet resonances attributed to the benzene ring. The two doublets were identified by determining which of the carbons had an HMBC correlation with the CH_2 protons, which enabled the assignment as shown in Figure 14.

Figure 13: HMBC spectrum obtained for compound **327**

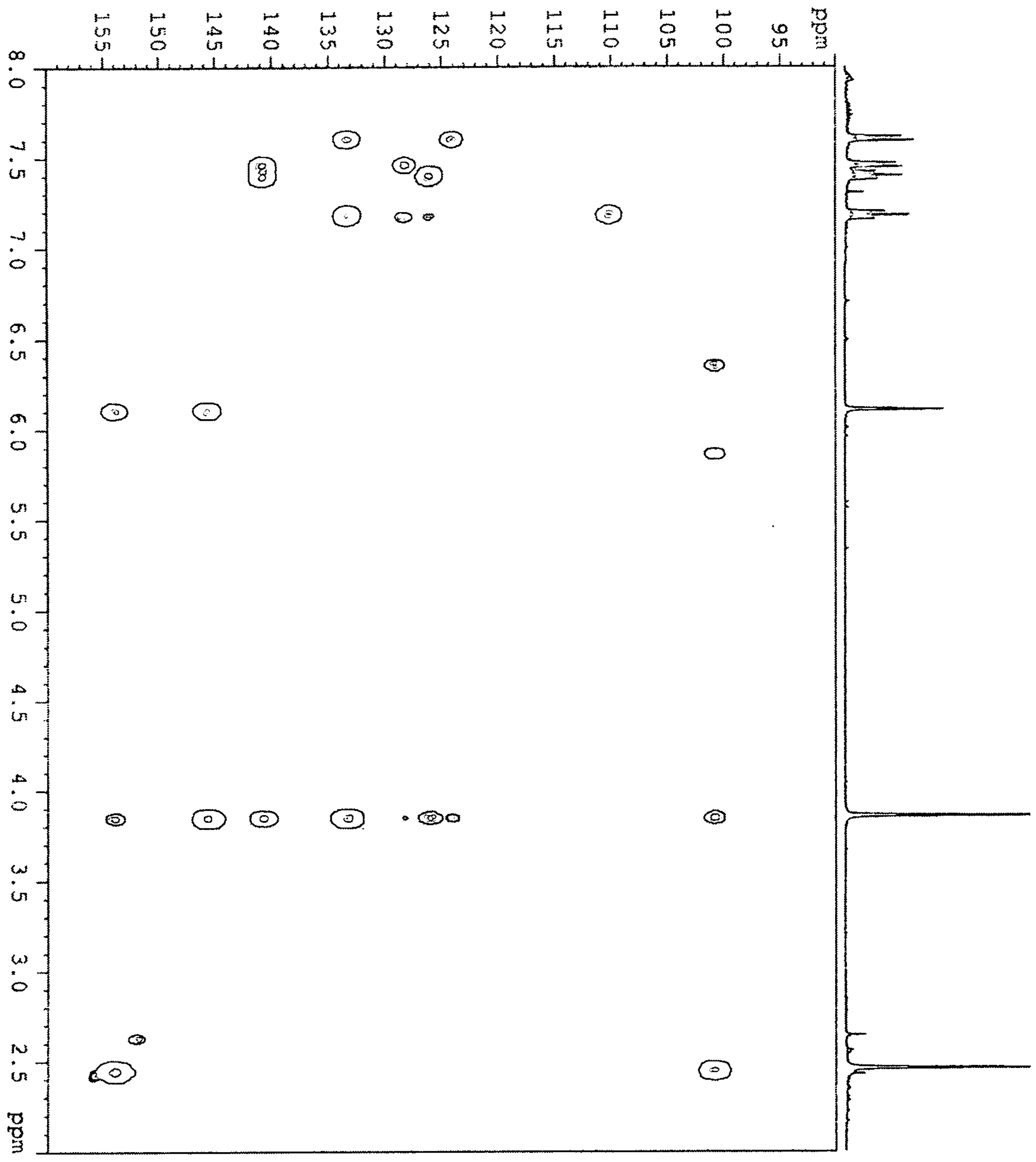
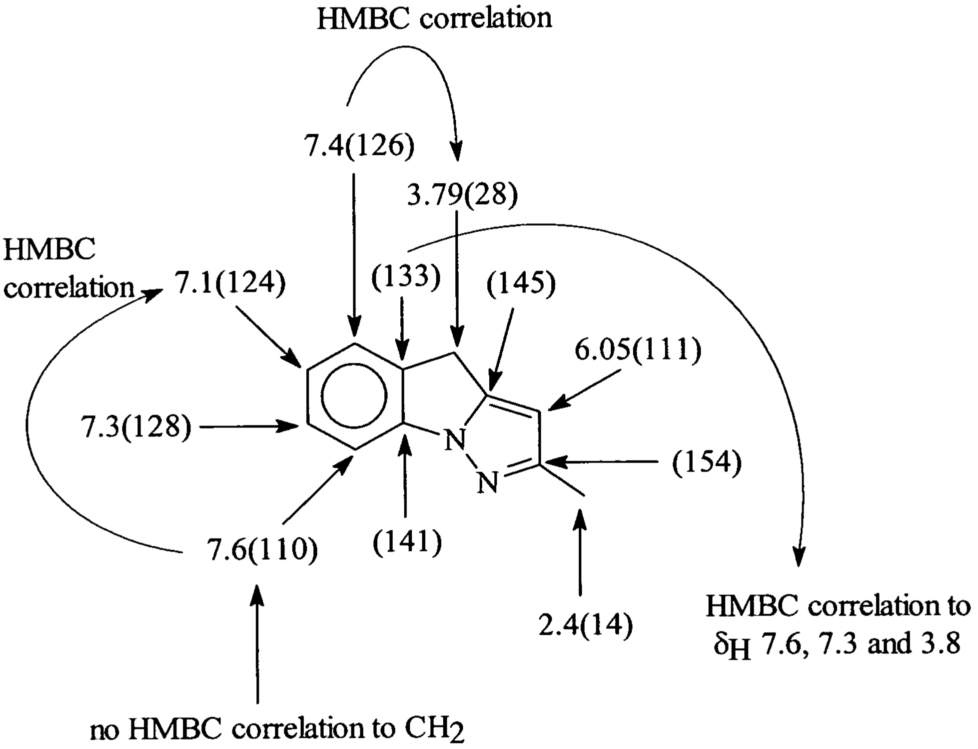


Figure 14: Key HMBC relationships plus assignment of ^{1}H-NMR chemical shifts and ^{13}C-NMR chemical shifts (in parentheses) for **327**



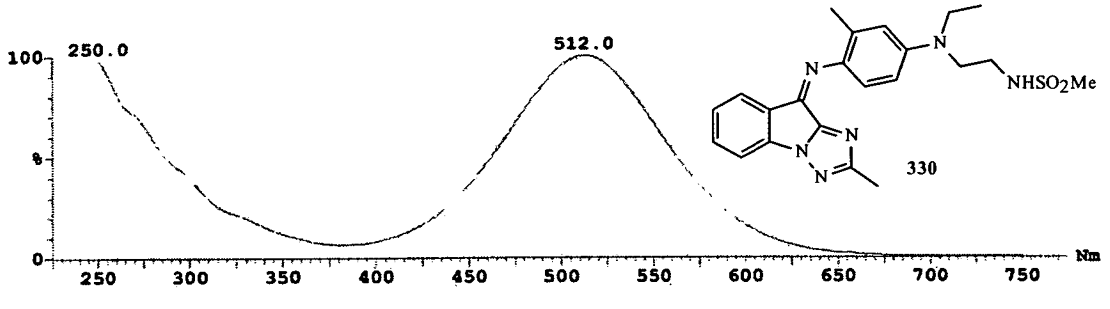
The other key HMBC relationships shown in Figure 14 enabled full assignment of the spectra of compound **327**, also shown in Figure 14 (δ_C values in parentheses). The full assignment for both compounds enables comparisons to be made. As expected, the CH and quaternary carbon adjacent to the nitrogen atom in **329** have higher chemical shifts (δ_C and δ_H) than in the benzene analogue **327**. Also, the hydrogen atom *para* to the nitrogen atom in **329** has a higher chemical shift (δ_H 7.72) compared to the corresponding hydrogen chemical shift in **327** (δ_H 7.4). The effect is not so pronounced at more remote parts in the molecule. The only other point in the system that seems to be affected by is the quaternary at the methyl substituent on the pyrazole ring. In the pyridine system **329** this quaternary is at δ_C 156 whereas it is observed at δ_C 154 in the benzene system **327**. This suggests that the pyridine nitrogen is having an effect through the other nitrogen atoms in the system, as no other 4-bond effects are observed

Samples of **327** – **329** were sent to Kodak in order to determine if they would form magenta dyes. This process was unsuccessful for compounds **327** and **329**. However, the triazole containing system **328** did form a magenta dye when treated under development mimicking conditions. The fact that **328** formed a magenta dye whereas **327** and **329** did not suggests two things:

1. At least three electron withdrawing groups (*i.e.* nitrogen atoms) are required for this type of fused tricycle to couple.
2. Triazole containing systems are more likely to couple than pyrazole containing systems.

The UV absorbance spectrum (provided by Kodak Ltd) for the CD3 dye of **328**, compound **330**, is shown in Figure 14.

Figure 14: UV spectrum for **330**



The ideal absorbance for a magenta dye is between 500 – 600 nm (λ_{max} 550 nm) .[3] As can be seen from Figure 14, **330** absorbs between *ca.* 450 – 600 nm, with λ_{max} 512 nm. This unwanted absorption into the blue region would give the dye a more reddish appearance. Therefore, a bathochromic shift ("red shift") would be required for a compound like **330** to produce a better quality of magenta dye. This shift could be achieved through the incorporation of further electron withdrawing groups into the system, which would have the effect of increasing the wavelength absorbed by the developed coupler system.

Systems based on the tricycle **328** have been claimed for use as couplers in the patent literature,[94] but no claim appears to have been made on this type of system with further electron withdrawing groups in the 6-membered ring. This provides scope for exploitation of this methodology in the synthesis of heterocycles with potential applications as magenta colour couplers. Indeed, work extending the application of this methodology to the synthesis of such 6,5,5-heterocycles has been subsequently carried out in the McNab group with very positive results, allowing further correlation of dye hue with structure.

In conclusion, the application of this methodology to the synthesis of fused tricyclic heterocycles has provided a ground breaking two step route to a variety of fused 6,5,5-heterocycles, one of which forms a magenta dye. The general methodology offers considerable scope for use in the synthesis of other tricyclic systems.

C. EXPERIMENTAL

Abbreviations

NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
ppm	parts per million
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet (^{1}H-NMR spectra)
quat	quaternary (^{13}C-NMR spectra)
m	multiplet
J	coupling constant
FAB	fast atom bombardment
m/z	mass to charge ratio
M^+	molecular ion mass
FVP	flash vacuum pyrolysis
T_{in}	inlet temperature (°C)
T_f	furnace temperature (°C)
P	pressure (Torr)
t_{FVP}	time of pyrolysis
mol	moles
mp	melting point (°C)
bp	boiling point (°C)
h	hours

min	minutes
2,5 – DMT	2,5 – dimethoxytetrahydrofuran
CDI	carbonyl diimidazole
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
LAH	lithium aluminium hydride
THF	tetrahydrofuran

Instrumentation and general techniques

Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were recorded on Bruker WH360 (360 MHz), Bruker AC250 (250 MHz), Bruker AC200 (200 MHz), and Varian Gemini 200 (200 MHz) spectrometers. ^{13}C NMR spectra were obtained on Bruker AC250 (63 MHz) and AC200 (50 MHz) instruments.

The Bruker WH360 was operated by Dr D.Reed, the Bruker AC250 by Mr J. R. A. Millar, the Bruker AC200 by Mr W. G. Kerr and the Varian Gemini 200 by Mr D. Cartwright.

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

Mass Spectrometry

Low resolution electron impact mass spectra were recorded by Mr H. G. McKenzie on a Finnigan 4600 instrument. High resolution and FAB mass spectra were obtained on a Kratos MS50 TC instrument operated by Mr A. T. Taylor.

All spectra were obtained by electron impact instruments unless otherwise stated.

Elemental Analysis

Microanalyses were carried out on a Perkin Elmer 240 CHN Elemental Analyzer by Mrs L. Eades and Mr S. Franklin.

Structure Determination

X-ray crystal structure data were obtained by Dr R. O. Gould and Dr S. Parsons on a Stoe STADI-4 four circle diffractometer with graphite monochromator.

Chromatography

Thin-layer chromatography was carried out on precoated 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 Å). The crude materials were generally preabsorbed onto silica gel and then loaded onto the column.

Solvents

THF and ether were distilled from sodium, using benzophenone as indicator. All other solvents used were dried over molecular sieves or used without further purification.

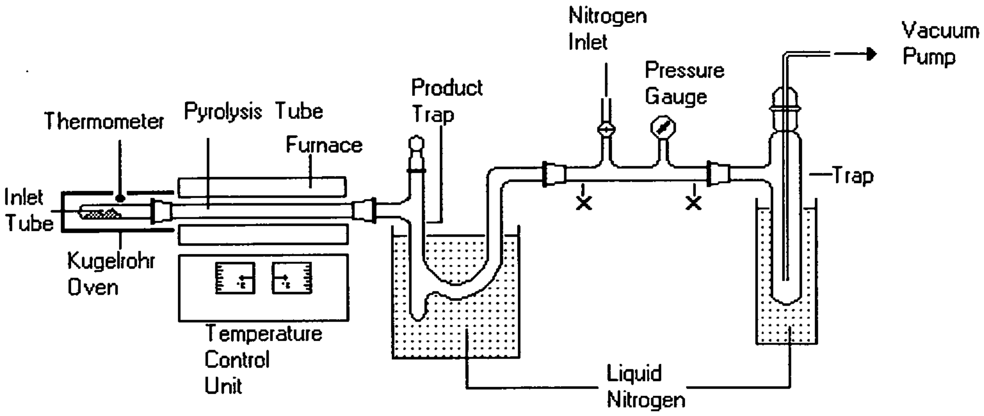
Flash vacuum pyrolysis (FVP)

Flash vacuum pyrolysis involves gaseous molecules being subjected to high temperatures for very short periods of time, usually 10^{-2}-10^{-3} seconds.

In principle, the substrate is distilled or sublimed through an electrically heated tube which is connected to a cold trap and vacuum line.

Figure 15 illustrates the apparatus used in such experiments and is based on the design of W.D. Crow of the Australian National University.

Figure 15: FVP apparatus



A glass Büchi oven was used to volatilise the substrate at temperatures lower than 300 °C which is then drawn through a silica tube (30 × 2.5 cm) heated by a Carbolite electronically controlled laboratory tube furnace. The products are collected at the exit of the furnace tube in a trap surrounded by liquid nitrogen. A “U-tube” trap is used for small scale pyrolyses (up to 2 g of substrate), which can be replaced by a larger “cold finger trap” for larger scale pyrolyses to avoid blockages. The system was evacuated and the vacuum maintained by an Edwards Model ED100 high capacity oil pump. The entire pyrolysate was either scraped from the trap for analysis or washed through with a suitable solvent. For small scale pyrolyses (50-

100 mg) the solvent of choice was frequently [^{2}H] chloroform enabling immediate examination by ^{1}H and ^{13}C-NMR spectroscopy.

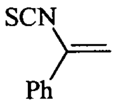
Standard pyrolysis parameters quoted throughout this section are furnace temperature, inlet temperature, pressure, sublimation time and mass of substrate.

1. Gas phase chemistry of triazolothiadiazines

Pyrolysis of 6-substituted -7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

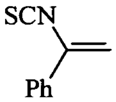
All the triazolothiadiazine starting materials, **174a-g, 178**, were obtained from Kodak Ltd. The triazolothiadiazines **174a-g, 178** were distilled at a pressure of 0.02 Torr into an empty silica furnace tube maintained at a temperature of 750 °C. The products were collected in a U-tube cooled by liquid nitrogen, and were washed from the trap with acetone at the end of the pyrolysis (unless stated otherwise). The acetone was then removed *in vacuo* and the remaining material stored at –18 °C.

Pyrolysis of 3-Methyl-6-phenyl -7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 174d



The starting material (0.50 g, 2.2 mmol) was pyrolysed, T_{in} = 210 °C, t_{FVP} = 1 h. The pyrolysate was collected in DCM, and the mixture separated by dry flash chromatography (silica, hexane as eluent) to give 1-isothiocyanato-1-phenylethene **177d** as a pale brown oil (0.10 g, 29%); δ_H 7.41 (5H, m), 5.59 (1H, d, *J* 1.5 Hz) and 5.34 (1H, d, *J* 1.5 Hz); δ_C 135.88 (quat), 133.96 (quat), 132.00 (quat), 129.40 (CH), 128.65 (CH), 125.10 (CH) and 110.35 (CH_2); *m/z* 161 (M^+, 20%), 105 (100), 77 (72) and 51 (22) (all spectra comparable with those of an authentic sample – see below).[42]

Preparation of authentic 1-isothiocyanato-1-phenylethene 177d



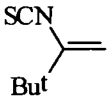
A cold solution of potassium thiocyanate (1.85 g, 0.019 mol) in chloroform (50 cm^3) was added to iodine (3.8 g, 15 mmol) and the mixture was stirred at 0 °C for 2 h. After this period a solution of styrene (0.8 g, 0.88 cm^3, 8 mmol) in chloroform (5 cm^3) was added and the mixture was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo* to give a dark oily solid, which was treated with saturated aqueous sodium thiosulfate (50 cm^3), then extracted with chloroform : pentane (1:10) (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), then concentrated *in vacuo* to give a light brown oil. A solution of the oil (1.8 g, 6.2 mmol) in chloroform (100 cm^3) was treated with boron trifluoride etherate (5.3 g, 0.04 mol) and stirred at 0 °C for 40 h. The reaction mixture was concentrated *in vacuo*, washed with water (40 cm^3), then extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give a red oil.

A mixture of this red oil (1.8 g, 6.5 mmol) and potassium *t*-butoxide (0.89 g, 8 mmol) in anhydrous ether (60 cm^3) was stirred at room temperature for 2 h. The mixture was quenched with water (50 cm^3), and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the product as a pale orange oil, (0.27 g, 26%); δ_H 7.35 (5H, m), 5.58 (1H, d, *J* 1.0 Hz) and 5.34 (1H, d, *J* 1.0 Hz); δ_C 137.64 (quat), 131.45 (quat), 130.35 (quat), 129.36 (CH), 128.60 (CH), 125.07 (CH) and 110.33 (CH_2).[42]

Pyrolysis of 3,7-dimethyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 174e

The starting material (0.50 g, 2.1 mmol) was pyrolysed, at an inlet temperature of 180 °C over a period of 1 h. The pyrolysate was collected in DCM, and was shown to contain several components, none of which could be identified after separation of the mixture using dry flash chromatography.

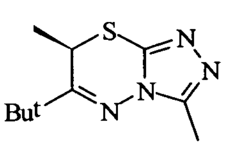
Pyrolysis of 6-*t*-butyl -3-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 174f



The starting material (0.50 g, 2.4 mmol) was pyrolysed, T_{in} = 120 °C, t_{FVP} = 1 h. The pyrolysate was collected in DCM then distilled at atmospheric pressure to give *1-isothiocyanato-1-t-butylethene* **177f** as a pale brown oil, (0.21 g, 62%), bp 95-105 °C. [Found, MH^+ (FAB) 142.0693. $C_7H_{12}NS$ requires *MH* 142.0691]; δ_H 4.93 (1H, s), 4.89 (1H, s) and 1.13 (9H, s); δ_C 146.10 (quat), 116.23 (quat), 107.36 (CH_2), 37.47 (quat) and 27.64 (CH_3); *m/z* 141 (M^+, 100%), 126 (32), 112 (12), 67 (28) and 55 (35).

Pyrolysis of 3,6-di-*t*-butyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **174g** produced material with identical spectral properties to **177f** in 70-75% yield.

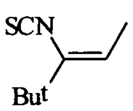
6-*t*-Butyl-3,7-dimethyl- [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 178



DMSO (10 cm^3) was added to potassium hydroxide (crushed pellets) (1.1 g, 0.02 mol) and the mixture was stirred for 5 min. 6-*t*-Butyl-3-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **174f** (1.0 g, 5 mmol) was then added and the mixture was stirred for 45 min at room temperature. Iodomethane (1.43 g, 5 mmol) was added dropwise with stirring, and the resulting mixture stirred for 45 min. Water (40 cm^3) was added, and the mixture was extracted with DCM (3 × 40 cm^3). The combined organic extracts were washed with water (3 × 30 cm^3), dried ($MgSO_4$), and the solvent removed *in vacuo* to give *6-t-butyl-3,7-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine* **183** as an orange solid, (1.02 g, 91%), mp 180-181 °C (from toluene). (Found, M^+ 224.1099. $C_{10}H_{16}N_4S$ requires *M* 224.1096); δ_H 3.81 (1H, q, *J* 7 Hz), 2.51 (3H, s), 1.32 (3H, d, *J* 7 Hz) and 1.30 (9H, s); δ_C 168.35 (quat), 150.69 (quat), 139.54 (quat), 40.85 (quat), 30.54

(CH), 27.48 (3 × CH_3), 19.27 (CH_3) and 10.12 (CH_3); *m/z* 224 (M^+, 92%). 143 (18), 78 (35) and 57 (100).

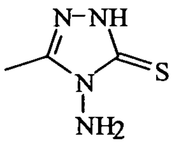
Pyrolysis of 6-*t*-butyl-3,7-dimethyl- [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 183



The starting material (0.10 g, 0.45 mmol) was pyrolysed, T_{in} = 180 °C, t_{FVP} = 1 h. The pyrolysate was collected in DCM, then the solvent was removed *in vacuo* to give *1-isothiocyanato-1-t-butylprop-1-ene* **184** as a pale brown oil, (0.052 g, 75%), bp 110-115 °C. (Found, M^+ 155.0768, $C_8H_{13}NS$ requires *M* 155.0769); δ_H 5.38 (1H, d, *J* 6.8 Hz), 1.73 (3H, d, *J* 6.8 Hz) and 1.11 (9H, s); δ_C 143.06 (quat), 118.20 (CH), 37.07 (quat), 29.56 (quat), 28.28 (CH_3) and 27.98 (3 × CH_3); *m/z* 155 (M^+, 24%), 140 (33), 98 (29), 78 (85), 63 (100) and 45 (77).

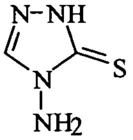
2. FVP of 4-amino-3-allylthio-1,2,4-triazoles

4-Amino-2,4-dihydro-5-methyl-3*H*-1,2,4-triazole-3-thione 188



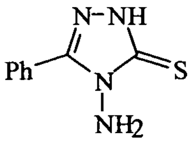
Thiocarbohydrazide **187** (5.3 g, 0.05 mol) was stirred with acetic acid (15 cm^3) and heated under reflux for 10 min. The reaction mixture was cooled, and the resulting precipitate collected by filtration, giving the product as white crystals, (6.31 g, 97%), mp 203-204 °C (lit.[47] mp 205-206 °C); δ_H ([^{2}H]$_6$DMSO), 13.40 (1H, s), 5.50 (2H, s) and 2.22 (3H, s).[47]

4-Amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 199



Thiocarbohydrazide **187** (5.3 g, 0.05 mol) was stirred with formic acid (10 cm^3) and heated under reflux for 10 min. The reaction mixture was cooled, and the resulting precipitate collected by filtration, giving the product as white crystals (3.22 g, 55%), mp 166-167 °C (lit.[52] mp 166-167 °C); δ_H ([^{2}H]$_6$DMSO), 13.51 (1H, s), 8.41 (1H, s) and 5.62 (2H, s).[52]

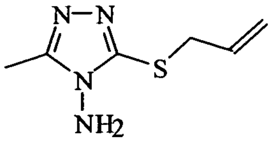
4-Amino-2,4-dihydro-5-phenyl-3*H*-1,2,4-triazole-3-thione 200



Benzoic acid hydrazide (1.0 g, 7.4 mmol) and potassium hydroxide (0.62 g, 0.011 mol) were stirred in ethanol (10 cm^3) until the solution became clear. Carbon disulfide (0.84 g, 0.011 mol) was added and the mixture stirred at room temperature for 3 h. The resulting precipitate was collected by filtration and washed with ether, then mixed with hydrazine hydrate (0.38 g, 0.012 mol) and water (2 cm^3). The mixture was heated under reflux until the solution became green.

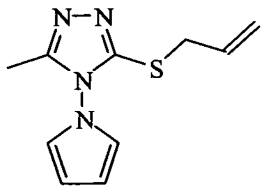
The solution was added to ice (20 cm^3) then made acidic with 1 M HCl $_{(aq)}$. The precipitate was collected by filtration then recrystallised from ethanol to give the product **200** as white needles, (0.49 g, 35%), mp 204-206 °C (lit.,[53] 204-206 °C); δ_H ($[^2H]_6$ DMSO) 7.60 (5H, m) and 5.83 (2H, s); *m/z* 192 (M^+, 100%) and 104 (45).

4-Amino-3-allylthio-5-methyl-4*H*-1,2,4-triazole 190



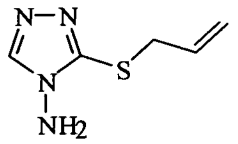
4-Amino-2,4-dihydro-5-methyl-3*H*-1,2,4-triazole-3-thione **188** (1.1 g, 8 mmol) was added to DMF (50 cm^3) containing potassium carbonate (1.0 g, 8 mmol). Allyl bromide **189** (0.96 g, 8 mmol) was added dropwise with stirring, then the mixture was stirred for 48 h. The insoluble potassium salts were removed by filtration, then the filtrate was concentrated *in vacuo*. DCM (20 cm^3) was added to the resulting mixture, then filtered to remove insoluble inorganics. The solvent was removed *in vacuo* to give *4-amino-3-allylthio-5-methyl-4H-1,2,4-triazole* **190** as a pale pink solid, (1.1 g, 81%), mp 77-80 °C (from toluene). (Found, MH^+ (FAB) 171.0710. $C_6H_{11}N_4S$ requires *MH* 171.0704); δ_H 5.91 (1H, m), 5.15 (1H, m), 4.83 (2H, s), 3.68 (2H, m) and 2.37 (3H, s); δ_C 153.48 (quat), 150.31 (quat), 132.62 (CH), 118.80 (CH_2), 36.04 (CH_2), and 10.23 (CH_3); *m/z* (FAB) 171 (MH^+, 100%). 131 (21), 91 (7) and 45 (8).

5-Methyl-4-(pyrrol-1-yl)-3-allylthio-4*H*-1,2,4-triazole 191



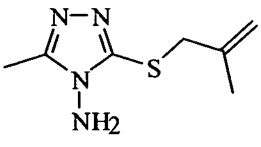
The aminotriazole **190** (2.55 g, 0.015 mol), 2,5-DMT (1.5 g, 0.015 mol) and acetic acid (50 cm^3) were heated under reflux for 30 min. The solvent was removed *in vacuo* to give a dark brown liquid, which solidified overnight to give *5-methyl-4-(pyrrol-1-yl)-3-allylthio-4H-1,2,4-triazole* **191** as a brown solid, (2.91 g, 87%), mp 61-62 °C (from hexane). (Found, C, 54.3; H, 5.4; N, 25.25. $C_{10}H_{12}N_4S$ requires C, 54.55; H, 5.45; N, 25.25%); δ_H 6.70 (2H, t, *J* 4.5 Hz), 6.33 (2H, t, *J* 4.5 Hz), 5.91 (1H, m), 5.14 (2H, m), 3.76 (2H, m) and 2.24 (3H, s); δ_C 152.38 (quat), 151.02 (quat), 132.04 (CH), 120.72 (2 × CH), 119.16 (CH_2), 109.77 (2 × CH), 34.99 (CH_2) and 9.31 (CH_3); *m/z* 220 (M^+, 56%), 205 (95), 173 (97), 154 (76), 124 (100), 106 (76) and 80 (58).

4-Amino-3-allylthio-4*H*-1,2,4-triazole 204



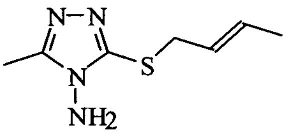
4-Amino-2,4-dihydro-*3H*-1,2,4-triazole-3-thione **199** (0.25 g, 2.1 mmol) was added to acetonitrile (10 cm^3) containing potassium carbonate (0.40 g, 2.5 mmol). Allyl bromide **189** (0.23 g, 2.1 mmol) was added dropwise with stirring, then the mixture stirred for 21 h. The insoluble potassium salts were removed by filtration, then the filtrate concentrated *in vacuo* at room temperature. Ethanol (10 cm^3) was added to the resulting mixture, then the solution was filtered to remove insoluble inorganics. The filtrate was concentrated *in vacuo* to give *4-amino-3-allylthio-4H-1,2,4-triazole* **204**, (0.26 g, 79%), mp 83-85 °C (from ethanol). (Found, C, 37.9; H, 4.65; N, 34.8. $C_5H_8N_4S.0.2H_2O$ required C, 37.6; H, 5.3; N, 35.1%. Found, M^+156.0469. $C_5H_8N_4S$ requires *M* 156.0470); δ_H ([^{2}H]$_6$ DMSO) 8.46 (1H, s), 6.08 (2H, s), 5.95 (1H, m) 5.24 (1H, m), 5.07 (1H, m) and 3.77 (2H, m); δ_C 150.40 (quat), 146.39 (CH), 133.72 (CH), 118.44 (CH_2) and 34.15 (CH_2); *m/z* 156 (M^+, 37%), 141 (25), 129 (20), 56 (80) and 41 (100).

4-Amino-5-methyl-3-(2-methylprop-2-enylthio)- 4*H*-1,2,4-triazole 205



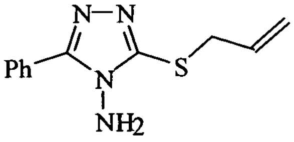
4-Amino-2,4-dihydro-5-methyl-*3H*-1,2,4-triazole-3-thione **188** (0.52 g, 4 mmol) was added to DMF (20 cm^3) containing potassium carbonate (0.5 g, 4 mmol). 2-Methylprop-2-enyl chloride **201** (0.36 g, 4 mmol) was added dropwise with stirring then the mixture was stirred at room temperature for 21 h. The insoluble potassium salts were removed by filtration, then the filtrate concentrated *in vacuo* to give a pink solid. The solid was dissolved in DCM (20 cm^3), then the mixture filtered to remove insoluble inorganic material. The solvent was removed *in vacuo* to give *4-amino-5-methyl-3-(2-methylprop-2-enylthio)-4H-1,2,4-triazole* **205** as a white solid, (0.6 g, 81%), mp 102-103 °C (from toluene). (Found, M$^+$ 184.0781. $C_7H_{12}N_4S$ requires *M* 184.0782); δ_H 4.64 (2H, s), 3.71 (2H, s), 2.39 (3H, s), and 1.86 (3H, s); δ_C 153.42 (quat), 150.62 (quat), 140.36 (quat), 115.03 (CH_2), 40.77 (CH_2), 20.99 (CH_3) and 10.24 (CH_3); *m/z* 184 (M$^+$, 55%), 169 (68), 130 (31), 102 (66) and 70 (100).

4-Amino-3-(but-2-enylthio)-5-methyl-4*H*-1,2,4-triazole 206



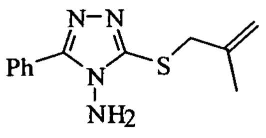
4-Amino-2,4-dihydro-5-methyl-*3H*-1,2,4-triazole-3-thione **188** (0.52 g, 4 mmol) was added to DMF (20 cm^3) containing potassium carbonate (0.5 g, 4 mmol). But-2-enyl chloride **202** (0.36 g, 0.39 cm^3, 4 mmol) was added dropwise with stirring then the mixture was stirred at room temperature for 21 h. The insoluble potassium salts were removed by filtration, then the filtrate was concentrated *in vacuo* to give a pink solid. The solid was dissolved in DCM (20 cm^3), then the mixture was filtered to remove insoluble inorganic material. The solvent was removed *in vacuo* to give *4-amino-3-(but-2-enylthio)-5-methyl-4H-1,2,4-triazole* **206** as a white solid, (0.26 g, 50%), mp 105-107 °C (from toluene). (Found, C, 43.6; H, 6.3; N, 28.75. $C_{10}H_{12}N_4S.{}^1/_2H_2O$ requires C, 43.5; H, 6.2; N, 29.0%. Found, M$^+$ 184.0790. $C_7H_{12}N_4S$ requires *M* 184.0783); δ_H 5.55 (1H, m), 5.50 (1H, m), 4.82 (2H, s), 3.60 (2H, s), 2.33 (3H, s), and 1.58 (3H, d, *J* 1 Hz); δ_C 153.28 (quat), 150.57 (quat), 130.50 (CH), 125.13 (CH); 35.65 (CH_2), 17.56 (CH_3) and 10.15 (CH_3); *m/z* 184 (M$^+$, 19%), 169 (74), 143 (49), 130 (71) and 55 (100).

4-Amino-3-allylthio-5-phenyl-4*H*-1,2,4-triazole 208



4-Amino-2,4-dihydro-5-phenyl-3*H*-1,2,4-triazole-3-thione **200** (0.96 g, 5 mmol) was added to DMF (30 cm^3) containing potassium carbonate (0.62 g, 5 mmol). Allyl bromide **189** (0.62 g, 5 mmol) was added dropwise with stirring, then the mixture was stirred for 48 h. The insoluble potassium salts were removed by filtration, then the filtrate was concentrated *in vacuo*. The resulting mixture was dissolved in DCM (20 cm^3), then filtered to remove insoluble inorganics. The filtrate was concentrated *in vacuo* to give *4-amino-3-allylthio-5-phenyl-4H-1,2,4-triazole* **208** as a white solid, (0.74 g, 64%), mp 132-134 °C (from toluene). (Found, C, 55.75; H, 5.2; N, 23.3%. $C_{11}H_{12}N_4S.{}^1/_4H_2O$ requires C, 55.8; H, 5.3; N, 23.7%); δ_H 8.00 (2H, m), 7.44 (3H, m), 5.99 (1H, m), 5.19 (2H, m), 4.82 (2H, s) and 3.81 (2H, m); δ_C 154.04 (quat), 152.06 (quat), 132.61 (2 × CH) 129.93 (2 × CH), 128.44 (CH), 127.99 (CH), 126.32 (quat), 119.12 (CH_2) and 36.10 (CH_2); *m/z* 232 (M^+, 39%), 217 (36), 129 (47), 103 (80) and 41 (100).

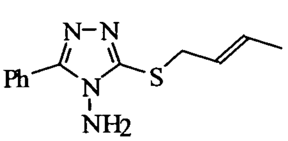
4-Amino-3-(2-methylprop-2-enylthio)-5-phenyl-4*H*-1,2,4-triazole 209



4-Amino-2,4-dihydro-5-phenyl-3*H*-1,2,4-triazole-3-thione **200** (0.96 g, 5 mmol) was added to DMF (30 cm^3) containing potassium carbonate (0.62 g, 5 mmol). 2-Methylprop-2-enyl chloride **201** (0.45 g, 5 mmol) was added dropwise with stirring, then the mixture was stirred for 48 h. The insoluble potassium salts were removed by filtration, then the filtrate was concentrated *in vacuo*. The resulting mixture was dissolved in DCM (20 cm^3), then filtered to remove insoluble inorganics. The filtrate was concentrated *in vacuo* to give *4-amino-3-(2-methylprop-2-enylthio)-5-phenyl-4H-1,2,4-triazole*

209 as a white solid, (0.66 g, 54%), mp 130-132 °C (from toluene). (Found, C, 58.3; H, 5.85; N, 22.5%. $C_{12}H_{14}N_4S$ requires C, 58.5; H, 5.7; N, 22.8%); δ_H 8.00 (2H, m), 7.40 (3H, m), 4.92 (2H, m), 4.84 (2H, m), 3.78 (2H, s) and 1.87 (3H, s); δ_C 153.97 (quat), 152.44 (quat), 140.23 (quat), 129.94 (2 × CH), 128.41 (2 × CH), 128.00 (CH), 126.23 (quat), 115.23 (CH_2), 40.62 (CH_2) and 21.03 (CH_3); *m/z* 246 (M^+, 88%), 201 (52), 143 (30), 103 (56) and 70 (100).

4-Amino-3-(but-2-enylthio)-5-phenyl-4*H*-1,2,4-triazole 210

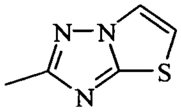


4-Amino-2,4-dihydro-5-phenyl-3*H*-1,2,4-triazole-3-thione **200** (0.96 g, 5 mmol) was added to DMF (30 cm^3) containing potassium carbonate (0.62 g, 5 mmol). But-2-enyl chloride **202** (0.45 g, 5 mmol) was added dropwise with stirring, then the mixture was stirred for 48 h. The insoluble potassium salts were removed by filtration, then the filtrate concentrated *in vacuo.* The resulting mixture was dissolved in DCM (20 cm^3), then filtered to remove insoluble inorganics. The filtrate was concentrated *in vacuo* to give *4-amino-3-(but-2-enylthio)-5-phenyl-4H-1,2,4-triazole* **210** as a white solid, (0.26 g, 50%), mp 145-147 °C (from toluene). (Found (FAB), MH^+ 247.1016. $C_{12}H_{14}N_4S$ requires MH^+ 247.1017); δ_H 7.99 (2H, m), 7.44 (3H, m), 5.66 (1H, m), 5.63 (1H, m), 4.78 (2H, s), 3.76 (2H, m) and 1.65 (3H, d, *J* 4.8 Hz); δ_C 153.94 (quat), 152.29 (quat), 130.89 (2 × CH), 129.91 (2 × CH), 128.43 (CH), 127.98 (CH), 126.36 (quat), 125.08 (CH), 35.78 (CH_2) and 17.67 (CH_3); *m/z* (FAB) 247 (MH^+, 100%), 193 (81), 121 (76) and 39 (57).

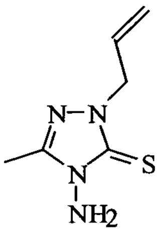
Pyrolysis of 5-substituted 4-amino-3-allylthio-1,2,4-triazoles

The aminotriazoles were distilled at a pressure of *ca.* 1 × 10^{-2} Torr into an empty silica furnace tube maintained at the stated temperature by an electrically heated furnace. The products were trapped in a U-tube cooled with liquid nitrogen, and were washed from the trap with solvent at the end of the pyrolysis.

Pyrolysis of 4-amino-3-allylthio-5-methyl-1,2,4-triazole 188

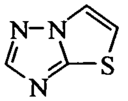


The starting material (0.30 g, 1.8 mmol) was pyrolysed, $T_f = 850$ °C, $T_{in} = 120$ °C, $t_{FVP} = 1.5$ h. The pyrolysate was collected in DCM, and distilled to give 2-methyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **193** as a golden liquid, (0.14 g, 54%), bp 120 °C (2.5 Torr); δ_H 7.69 (1H, d, *J* 4.5 Hz), 6.91 (1H, d, *J* 4.5 Hz) and 2.50 (3H, s); δ_C 166.52 (quat), 156.84 (quat), 119.66 (CH), 112.14 (CH) and 14.79 (CH_3); *m/z* 139 (M^+, 100%), 98 (73) and 58 (57). (All spectral data consistent with literature). [50]



Pyrolysis of the starting material **188** using the same conditions as above, but with $T_f = 650$ °C, gave a mixture of products, which was separated by dry flash chromatography (silica), hexane:ethyl acetate (6:1), to give *2-allyl-4-amino-5-methyl-1,2,4-triazole-3-thione* **192** as a pale yellow liquid, (0.10 g, 33%). (Found, M^+ 170.0622. $C_6H_{10}N_4S$ requires *M* 170.0626); δ_H 5.85 (1H, m), 5.28 (2H, m), 4.72 (2H, d, *J* 6 Hz), 4.65 (2H, s) and 2.37 (3H, s); δ_C 165.99 (quat), 148.66 (quat), 130.53 (CH), 119.23 (CH_2), 51.55 (CH_2) and 10.37 (CH_3); *m/z* 170 (M^+, 80%), 155 (64), 102 (45), 74 (42) and 56 (100).

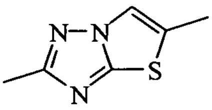
Pyrolysis of 4-amino-3-allylthio-4*H*-1,2,4-triazole 204



The starting material (0.14 g, 1.0 mmol) was pyrolysed, $T_f = 850$ °C, $T_{in} = 120$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in DCM, and distilled to give [1,3]thiazolo[3,2-*b*][1,2,4]triazole **214** as a pale yellow solid, (0.055

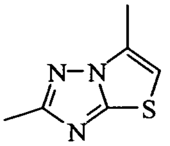
g, 55%), bp 50-55 °C (4 Torr) mp 96-98 °C (lit.,[50] 98-100 °C); δ_H 8.15 (1H, d, *J* 1.4 Hz), 7.81 (1H, d, *J* 4.4 Hz) and 6.91 (1H, dd, *J* 1.4 and 4.4 Hz); δ_C 156.34 (CH and quat), 119.86 (CH) and 113.85 (CH); *m/z* 125 (M$^+$, 100%), 98 (49), 71 (53) and 45 (65). (All spectral data consistent with literature).[50]

Pyrolysis of 4-amino-3-(2-methylprop-2-enylthio)-5-methyl-1,2,4-triazole 205



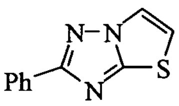
The starting material (0.20 g, 1.1 mmol) was pyrolysed, $T_f = 850$ °C, $T_{in} = 130$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in DCM, and distilled to give *2,5-dimethyl[1,3]thiazolo[3,2-b][1,2,4]triazole* **211** as a pale yellow liquid, (0.08 g, 48%), bp 85 °C (2 Torr). (Found, M$^+$ 153.0363. $C_6H_7N_3S$ requires *M* 153.0361); δ_H 7.41 (1H, s), 2.48 (3H, s) and 2.45 (3H, s); δ_C 165.13 (quat), 156.00 (quat), 126.40 (quat), 116.34 (CH), 14.68 (CH_3) and 13.94 (CH_3); *m/z* 153 (M$^+$, 100%), 112 (58) and 59 (95).

Pyrolysis of 4-amino-3-(but-2-enylthio)-5-methyl-1,2,4-triazole 206



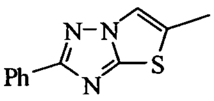
The starting material (0.20 g, 1.1 mmol) was pyrolysed, $T_f = 850$ °C, $T_{in} = 135$ °C, $t_{FVP} = 0.5$ h. The pyrolysate was collected in DCM, and distilled to give 2,6-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **213** as a pale yellow liquid, (0.09 g, 54%), bp 90 °C (2 Torr). (Found, M$^+$ 153.0355. $C_6H_7N_3S$ requires *M* 153.0361); δ_H 6.50 (1H, s), 2.50 (3H, s) and 2.49 (3H, s); δ_C 166.10 (quat), 129.26 (quat), 121.64 (quat), 106.11 (CH), 14.77 (CH_3) and 12.32 (CH_3); *m/z* 153 (M$^+$, 100%), 112 (48), 67 (98) and 42 (69). (All spectral data consistent with literature).[95]

Pyrolysis of 4-amino-3-allylthio-5-phenyl-1,2,4-triazole 208



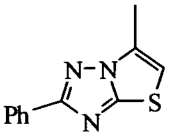
The starting material (0.10 g, 0.4 mmol) was pyrolysed, $T_f = 850$ °C, $T_{in} = 135$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in DCM, and distilled to give 2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **215** as a pale yellow liquid, (0.02 g, 23%), bp 75 °C (0.7 Torr). (Found, M^+ 201.0360. $C_{10}H_7N_3S$ requires *M* 201.0361); δ_H 8.15 (2H, m), 7.81 (1H, d, *J* 4.5 Hz), 7.44 (3H, m) and 6.99 (1H, d, *J* 4.5 Hz); δ_C 167.35 (quat), 157.40 (quat), 130.92 (quat), 129.66 (2 × CH), 128.60 (2 × CH), 126.53 (CH), 119.92 (CH) and 112.95 (CH); *m/z* 201 (M^+, 100%), 116 (26), 103 (41) and 76 (33). (All spectral data consistent with literature).[50]

Pyrolysis of 4-amino-3-(2-methylprop-2-enylthio)-5-phenyl-1,2,4-triazole 209



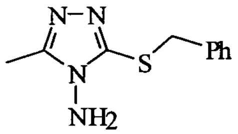
The starting material (0.20 g, 0.8 mmol) was pyrolysed, $T_f = 750$ °C, $T_{in} = 130$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in DCM, and distilled to give *5-methyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole* **216** as a pale yellow liquid, (0.08 g, 48%), bp 85 °C (2 Torr). (Found, M^+ 215.0512. $C_{11}H_9N_3S$ requires *M* 215.0517); δ_H 8.37 (2H, m), 7.77 (1H, s), 7.75 (3H, m) and 2.74 (3H, s); δ_C (2 quaternaries not apparent) 129.43 (CH), 128.56 (2 × CH), 127.30 (quat), 126.39 (2 × CH), 117.93 (quat), 116.56 (CH) and 14.10 (CH_3); *m/z* 215 (M^+, 31%), 169 (46), 128 (43), 104 (58), 77 (47) and 55 (100).

Pyrolysis of 4-amino-3-(but-2-enylthio)-5-phenyl-1,2,4-triazole 210



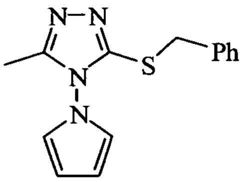
The starting material (0.20 g, 0.8 mmol) was pyrolysed, $T_f = 750$ °C, $T_{in} = 130$ °C, $t_{FVP} = 0.5$ h. The pyrolysate was collected in DCM, and distilled to give 6-methyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **217** as a pale yellow liquid, (0.09 g, 54%), bp 90 °C (2 Torr). (Found, M^+ 215.0513. $C_{11}H_9N_3S$ requires *M* 215.0517); δ_H 8.16 (2H, m), 7.46 (3H, m), 6.57 (1H, s) and 2.59 (3H, s); δ_C 166.81 (quat), 156.69 (quat), 130.98 (quat), 129.56 (CH), 128.56 (2 × CH), 126.56 (2 × CH), 119.92 (quat), 106.98 (CH) and 29.58 (CH_3); *m/z* 215 (M^+, 100%), 144 (25), 103 (50) and 72 (52). (All spectral data consistent with literature).[50]

4-Amino-3-benzylthio-5-methyl-4*H*-1,2,4-triazole 218



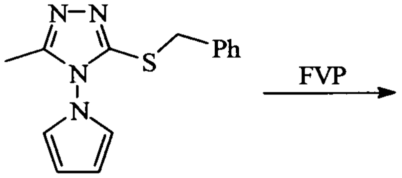
4-Amino-2,4-dihydro-5-methyl-3*H*-1,2,4-triazole-3-thione **188** (1.95 g, 0.015 mmol) was added to DMF (50 cm^3) containing potassium carbonate (1.88 g, 0.015 mmol). Benzyl chloride (1.89 g, 0.015 mmol) was added dropwise with stirring then the mixture was stirred at room temperature for 21 h. The insoluble potassium salts were removed by filtration, then the filtrate was concentrated *in vacuo* to give a pink solid. The solid was dissolved in DCM (20 cm^3), then the mixture was filtered to remove insoluble inorganic material. The solvent was removed *in vacuo* to give *4-amino-3-benzylthio-5-methyl-4H-1,2,4-triazole* **218** as an orange/brown solid, (0.65 g, 20%), mp 149-150 °C (from toluene). (Found, M^+ 220.0785. $C_{10}H_{12}N_4S$ requires *M* 220.0783); δ_H 7.25 (5H, m), 4.20 (2H, s), 3.93 (2H, s) and 2.33 (3H, s); δ_C 153.58 (quat), 149.48 (quat), 137.27 (quat), 128.71 (2 ×CH), 128.67 (2 × CH), 127.89 (CH), 38.97 (CH_2) and 10.32 (CH_3); *m/z* 220 (M^+, 21%), 106 (45), 91 (100), 65 (36) and 39 (26).

3-Benzylthio-5-methyl-4-(pyrrol-1-yl)-4*H*-1,2,4-triazole 219



4-Amino-3-benzylthio-5-methyl-4*H*-1,2,4-triazole **218** (0.16 g, 0.7 mmol), 2,5-DMT (0.09 g, 0.7 mmol) and acetic acid (30 cm^3) were heated under reflux for 30 min. The mixture was concentrated *in vacuo* to give a brown oil, which was washed with water, then extracted with DCM (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), and the solvent removed *in vacuo* to give a brown oil. The oil was distilled to give pure *3-benzylthio-5-methyl-4-(pyrrol-1-yl)-4H-1,2,4-triazole* **219** as a pale yellow oil, (0.14 g, 75%), bp 160 °C (0.5 Torr). (Found, M^+ 270.0933. $C_{14}H_{14}N_4S$ requires *M* 270.0939); δ_H 7.25 (5H, m), 6.47 (2H, t, *J* 4.5 Hz), 6.57 (2H, t, *J* 4.5 Hz), 4.33 (2H, s) and 2.20 (3H, s); δ_C 152.31 (quat), 151.09 (quat), 135.86 (quat), 128.88 (2 × CH), 128.43 (2 × CH), 127.63 (CH), 120.56 (2 × CH), 109.57 (2 × CH), 36.92 (CH_2) and 9.13 (CH_3); *m/z* 270 (M^+, 11%), 224 (21), 156 (33), 124 (22), 91 (100) and 65 (44).

Pyrolysis of 3-benzylthio-5-methyl-4-(pyrrol-1-yl)-4*H*-1,2,4-triazole 219

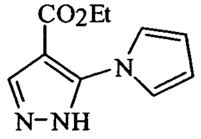


Pyrolysis of **219** at a furnace temperature of 750 °C, inlet temperature 150 °C, gave a pyrolysate in which only small amounts of bibenzyl **233** were observed in the ^{1}H-NMR spectrum (data consistent with literature data).[97]

3. Synthesis of tricyclic fused heterocycles

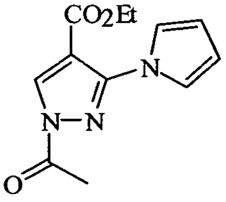
a) Studies towards the synthesis of oxalate radical precursors

3-(Pyrrol-1-yl)-4-carbethoxypyrazole 225



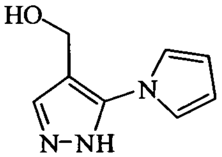
The amino pyrazole **224** (4.2 g, 0.027 mol), 2,5-DMT (4.32 g, 0.027 mol) and acetic acid (100 cm^3) were heated under reflux for 0.5 h. The mixture was reduced *in vacuo* to give a thick dark brown oil, which was washed with water (100 cm^3) then extracted with DCM (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), then the solvent was removed *in vacuo* to give a dark brown oil. The oil was triturated with hexane and filtered to give the product as a light brown solid. A suitable solvent for recrystallisation could not be found, so the brown solid was distilled to give the pure product as a white solid, (3.87 g, 70%), mp 165-166 °C, bp 170 °C (3 Torr). (Found, M$^+$ 205.8561. $C_{10}H_{11}N_3O_2$ requires M 205.0851); δ_H 7.90 (1H, s), 7.26 (2H, d, J 4.5 Hz), 6.14 (2H, d, J 4.5Hz), 4.14 (2H, q, J 7 Hz), and 1.19 (3H, t, J 7 Hz); δ_C 161.93 (quat), 147.99 (quat), 134.53 (CH), 121.24 (2 × CH), 108.87 (2 × CH), 104.00 (quat), 59.80 (CH_2) and 14.11 (CH_3); *m/z* 205 (M$^+$, 100 %), 161 (52), 133 (73) and 109 (19).

***N*-Acetyl-3-(pyrrol-1-yl)-4-carbethoxypyrazole 226**



A mixture of the *N*-pyrrolylpyrazole **225** (0.41 g, 2 mmol), triethylamine (0.18 g, 2 mmol) and DCM (20 cm^3) was stirred at room temperature. A solution of acetyl chloride (0.16 g, 2 mmol) in DCM (10 cm^3) was added dropwise with stirring, and the resultant mixture stirred at room temperature for 2 h. The mixture was poured into water and the lower organic layer collected. The aqueous layer was extracted with DCM (3 × 30 cm^3), and the combined organic extracts dried ($MgSO_4$), then concentrated *in vacuo* to give a pale brown oil which partially solidified on standing. The oily solid was distilled to give a pale yellow solid, (0.30 g, 61%), mp 91-92 °C (from toluene), bp 112 °C (1 Torr). (Found, M$^+$ 247.0958. $C_{12}H_{13}N_3O_3$ requires *M* 247.0957); δ_H 8.72 (1H, s), 7.51 (2H, d, *J* 4.5 Hz), 6.31 (2H, d, *J* 4.5 Hz), 4.31 (2H, q, *J* 7 Hz), 2.70 (3H, s) and 1.34 (3H, t, *J* 7 Hz); δ_C 168.63 (quat), 161.07 (quat), 149.74 (quat), 134.08 (CH), 121.36 (2 × CH), 110.37 (2 × CH), 109.51 (quat), 61.04 (CH_2), 21.29 (CH_3) and 14.02 (CH_3); *m/z* 247 (M$^+$, 61%), 205 (30), 155 (100), 133 (64) and 109 (79).

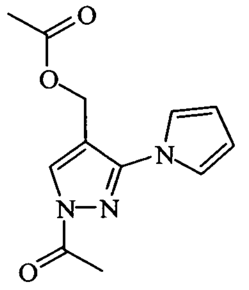
3-(Pyrrol-1-yl)-4-hydroxymethylenepyrazole 228



A solution of the *N*-acylated pyrazole **226** (0.3 g, 1.2 mmol) in dry THF (15 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of lithium aluminium hydride (0.18 g, 4.8 mmol) in dry THF (15 cm^3). The mixture was then heated under reflux under nitrogen for 2 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (20 cm^3) followed by water (20 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected. The aqueous layer was extracted with ether (3 × 20 cm^3), and the combined organic layers dried ($MgSO_4$), then concentrated *in vacuo* to give the product as a pale yellow oil, which solidified on standing, (0.18 g, 93%), mp 129-132 °C (from DCM), (Found, M$^+$ 163.0740. $C_8H_9N_3O$ requires *M* 163.0746); δ_H ([^{2}H]$_6$DMSO) 7.74 (1H, s), 7.26 (2H, d, *J* 4 Hz), 6.20 (2H, d, *J* 4 Hz), 5.07 (1H, t, *J* 4.9 Hz) and 4.37 (2H, d, *J* 4.9 Hz); δ_C ([^{2}H]$_6$DMSO) 146.93 (quat), 130.45 (CH), 120.14 (2 × CH), 110.64

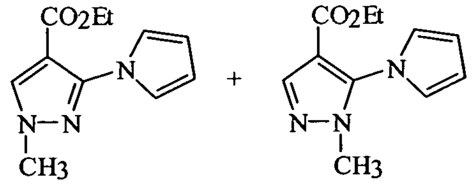
(quat), 109.24 (2 × CH), and 52.97 (CH_2); *m/z* 163 (M^+, 75%), 120 (44), 97 (69), 57 (79) and 41 (100).

Acetic acid 1-acetyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-ylmethyl ester 229



A mixture of the hydroxymethylene pyrazole **228** (0.1 g, 0.6 mmol), triethylamine (0.053 g, 0.6 mmol) and DCM (20 cm^3) was stirred at room temperature. A solution of acetyl chloride (0.047 g, 0.6 mmol) in DCM (10 cm^3) was added dropwise with stirring, and the resultant mixture stirred at room temperature for 2 h. The mixture was poured onto water (20 cm^3), the organic layer separated, and the aqueous layer extracted with DCM (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), then concentrated *in vacuo* to give a pale yellow oil, which was distilled to give the product **229** as a colourless oil, (0.11 g, 90%), bp 80 °C (4 × 10^{-3} Torr). (Found, M^+ 247.0948. $C_{12}H_{13}N_3O_3$ requires *M* 247.0957); δ_H 8.31 (1H, s), 7.22 (2H, d, *J* 4.5 Hz), 6.35 (2H, d, *J* 4.5 Hz), 5.08 (2H, s), 2.66 (3H, s) and 2.10 (3H, s); δ_C 170.32 (quat), 168.68 (quat), 150.23 (quat), 130.83 (CH), 119.86 (2 × CH), 111.65 (quat), 110.95 (2 × CH), 55.62 (CH_2), 21.18 (CH_3) and 20.76 (CH_3); *m/z* 247 (M^+, 36%), 97 (69), 57 (79) and 41 (100).

1-Methyl-3-(pyrrol-1-yl)-4-carbethoxypyrazole 230a and 2-methyl-3-(pyrrol-1-yl)-4-carbethoxypyrazole 230b

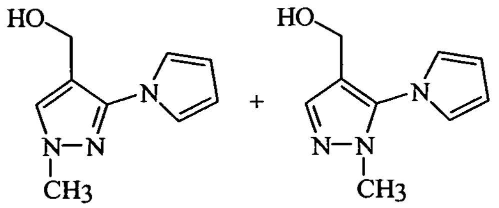


DMSO (5 cm^3) was added to potassium hydroxide (crushed pellets) (0.22 g, 4 mmol) and the mixture stirred for 5 min. The *N*-pyrrolylpyrazole **224** (0.2 g, 1 mmol) was then added and the mixture stirred for 45 min at room temperature. Methyl iodide (0.28 g, 2 mmol) was added dropwise with stirring, and the resulting mixture stirred for 45 min. Water (20 cm^3) was added, and the mixture extracted with DCM (3 × 20 cm^3). The combined organic extracts were washed with water (3 × 20 cm^3), dried ($MgSO_4$), then reduced *in vacuo* to give a pale brown oil, which was distilled to give the product as a pale yellow oil (inseparable *N*-methylated isomers, 5:1 **230a**:**230b** from ^{1}H-NMR), (0.18 g, 82%), bp 120-125 °C (1 Torr). (Found, M$^+$ 219.1010. $C_{11}H_{13}N_3O_2$ requires *M* 219.1008); *m/z* 219 (M$^+$, 96%), 197 (64), 174 (72), 147 (100), 123 (89) and 52 (65).

230a: δ_H 7.90 (1H, s), 7.38 (2H, d, *J* 4.5 Hz), 6.29 (2H, d, *J* 4.5 Hz), 4.28 (2H, q, *J* 7 Hz), 3.71 (3H, s) and 1.33 (3H, t, *J* 7Hz); δ_C 161.65 (quat), 148.46 (quat), 135.79 (CH), 121.39 (2 × CH), 109.34 (2 × CH), 104.83 (quat), 60.19 (CH_2), 39.36 (CH_3) and 14.11 (CH_3).

230b: δ_H 7.98 (1H, s), 6.80 (2H, d, *J* 4.5 Hz), 6.40 (2H, d, *J* 4.5 Hz), 4.26 (2H, q, *J* 7 Hz), 3.52 (3H, s) and 1.34 (3H, t, *J* 7 Hz); δ_C 161.65 (quat), 148.46 (quat), 133.03 (CH), 122.31 (2 × CH), 110.39 (2 × CH), 104.83 (quat), 59.53 (CH_2), 51.53 (CH_3) and 14.30 (CH_3).

1-Methyl-3-(pyrrol-1-yl)-4-hydroxymethylenepyrazole 231a and 2-methyl-3-(pyrrol-1-yl)-4-hydroxymethylenepyrazole 231b



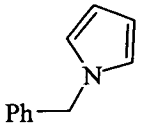
A solution of the *N*-methylated pyrazoles **230a/230b** (4.0 g, 0.018 mol) in dry THF (20 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of lithium aluminium hydride (1.37 g, 0.036 mol) in dry THF (30 cm^3). The mixture was then heated under reflux under nitrogen for 2 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (30 cm^3) followed by water (30 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected. The aqueous layer was extracted with ether (3 × 40 cm^3), and the combined organic layers dried ($MgSO_4$), then concentrated *in vacuo* to give a yellow oil, which was distilled to give the product (as a 5:1 **231a**:**231b** mixture of isomers from the ^{1}H-NMR spectrum) as a colorless oil, (1.71 g, 53%), bp 170 °C (3 Torr). (Found, M^+ 177.0906. $C_9H_{11}N_3O$ requires *M* 177.0902); *m/z* 177 (M^+, 100 %), 148 (80), 123 (28), 83 (73) and 39 (78).

231a: δ_H 7.20 (1H, s), 7.18 (2H, d, *J* 4.5 Hz), 6.27 (2H, d, *J* 4.5 Hz), 4.47 (2H, s) and 3.73 (3H, s); δ_C 147.01 (quat), 131.54 (CH), 120.22 (2 × CH), 111.01 (quat), 109.52 (2 × CH), 54.12 (CH_2) and 38.74 (CH_3).

231b: δ_H 7.63 (1H, s), 6.74 (2H, d, *J* 4.5 Hz), 6.34 (2H, d, *J* 4.5 Hz), 4.31 (2H, s) and 3.56 (3H, s); δ_C 147.01 (quat), 138.17 (CH), 122.38 (2 × CH), 111.01 (quat), 110.41 (2 × CH), 54.24 (CH_2) and 35.33 (CH_3).

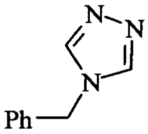
b) Development and applications of nitrogen based radical precursors

1-Benzyl-1*H*-pyrrole 234



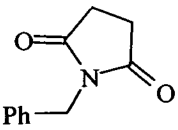
Benzylamine **232** (1.07 g, 0.01 mol), 2,5-DMT (1.28 g, 0.01 mol) and acetic acid (20 cm^3) were heated under reflux for 15 min. The mixture was concentrated *in vacuo* to give a brown oil, which was washed with water (30 cm^3) then extracted with DCM (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give 1-benzyl-1*H*-pyrrole **234** as a pale yellow oil, (1.3 g, 83%). δ_H 7.27 (3H, m), 7.01 (2H, m), 6.59 (2H, t, *J* 2.1 Hz), 6.13 (2H, t, *J* 2.1 Hz) and 4.95 (2H, s). (Spectral data consistent with literature). [58]

4-Benzyl-4*H*-[1,2,4]triazole 235



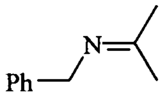
Benzylamine **232** (1.11 g, 0.01 mol), DMF azine **242** (1.42 g, 0.01 mol), toluene-*p*-sulfonic acid (0.4 g) and toluene (20 cm^3) were heated under reflux for 24 h. The solvent was removed *in vacuo* to give 4-benzyl-4*H*-[1,2,4]triazole **235** as a white solid (1.11 g, 70%), mp 113-114 °C (lit., [61] 112 °C). δ_H 8.12 (2H, s), 7.19 (3H, m), 7.07 (2H, m) and 5.04 (2H, s). (Spectral data consistent with literature). [61]

1-Benzylpyrrolidine-2,5-dione 236



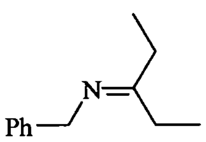
A solution of succinic anhydride (1.0 g, 0.01 mol) and benzylamine **232** (1.07 g, 0.01 mol) in toluene (30 cm^3) was heated under reflux for 24 h. The solvent was removed *in vacuo* to give the product as a white solid 1.22 g, 65%), mp 99-101 °C (hexane) (lit., [65] 102.5-103.5 °C). δ_H 7.24 (5H, m), 4.59 (2H, s) and 2.63 (4H, s). (Spectral data consistent with literature). [65]

Benzyl-isopropylidene-amine 238



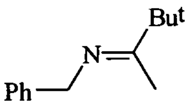
A solution of benzylamine **232** (1.07 g, 0.01 mol) and acetone (1.16 g, 0.02 mol) in toluene (20 cm^3) containing 4 Å molecular sieves (4 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave benzyl-isopropylidene-amine **238** as a yellow oil (0.99 g, 67%). δ_H 7.30 (5H, m), 4.41 (2H, s), 2.05 (3H, s) and 1.84 (3H, s). (Spectral data consistent with literature). [96]

Benzyl-(1-ethyl-propylidene)-amine 239



A solution of benzylamine **232** (1.07 g, 0.01 mol) and diethyl ketone (1.72 g, 0.02 mol) in toluene (20 cm^3) containing 4 Å molecular sieves (4 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave benzyl-(1-ethyl-propylidene)-amine **239** as a yellow oil (1.28 g, 73%). δ_H 7.31 (5H, m), 4.57 (2H, s), 2.35 (4H, m) and 1.10 (6H, m). (Spectral data consistent with literature). [96]

Benzyl-(1,2,2-trimethyl-propylidene)-amine 252

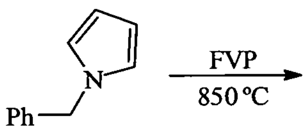


A solution of benzylamine **232** (1.07 g, 0.01 mol) and pinacolone **253** (2.0 g, 0.02 mol) in toluene (25 cm^3) containing 4 Å molecular sieves (5 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave *benzyl-(1,2,2-trimethyl-propylidene)-amine* **252** as a pale yellow oil (1.32 g, 70%), bp 80 °C (1.0 Torr). (Found, M$^+$ 189.1514. $C_{13}H_{19}N$ requires *M* 189.1518); δ_H 7.38 (5H, m), 4.58 (2H, s), 1.93 (3H, s) and 1.27 (9H, s); δ_C 175.88 (quat), 140.80 (quat), 127.92 (2 × CH), 127.00 (2 × CH), 125.92 (CH), 54.05 (CH_2), 40.45 (quat), 27.54 (3 × CH_3) and 13.20 (CH_3); *m/z* 189 (M$^+$, 22%), 132 (29), 91 (100), 65 (26) and 41 (29).

Pyrolysis of potential radical generators

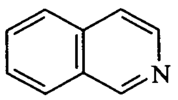
The radical precursors **234-239**, **252** were distilled at a pressure of *ca.* 1 × 10^{-2} Torr into an empty silica furnace tube maintained at the stated temperature (T_f) by an electrically heated furnace. The products were trapped in a U-tube cooled with liquid nitrogen, and were washed from the trap with deuteriated chloroform at the end of the pyrolysis. The products obtained were identified from the $^{1}H/^{13}C$-NMR spectra unless stated otherwise.

Pyrolsis of 1-benzyl-1*H*-pyrrole 234



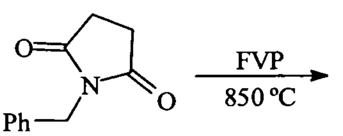
The starting material (0.10 g, 0.64 mmol) was pyrolysed, T_f = 850 °C, T_{in} = 180 °C, t_{FVP} = 1 h. The pyrolysate was collected in $CDCl_3$, and the following products identified from comparison with ^{1}H-NMR data quoted for the CH_2 protons in the literature [59]: 2-benzylpyrrole **240** [δ_H 3.78 (2H, s)], 3-benzylpyrrole **241** [δ_H 3.72 (2H, s)] and 1-benzylpyrrole **234** [δ_H 4.94 (2H, s)] in a ratio of *ca.* 2:1:1.

Pyrolysis of 4-benzyl-4*H*-[1,2,4]triazole 235



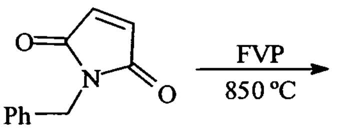
The starting material (0.30 g, 1.9 mmol) was pyrolysed, T_f = 850 °C, T_{in} = 100 °C, t_{FVP} = 1 h. The pyrolysate was collected in DCM, and the reaction mixture separated by dry flash chromatography (silica) using hexane as eluent to give isoquinoline **243** (0.056 g, 23%). δ_H 8.51 (1H, s), 7.92 (1H, d, *J* 7.4 Hz), 7.75 (1H, d, *J* 7.4 Hz) and 7.70-7.52 (4H, m). (Spectral data consistent with literature). [62]

Pyrolysis of 1-benzylpyrrolidine-2,5-dione 236



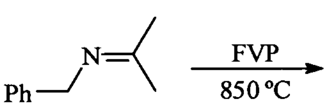
The starting material (0.10 g, 0.53 mmol) was pyrolysed, $T_f = 850$ °C , $T_{in} = 100$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in $CDCl_3$ with the ^{1}H-NMR spectrum shown to be comparable to that quoted for the starting material **236**, δ_H 7.29 (5H, m), 4.55 (2H, s) and 2.58 (4H, s).[65]

Pyrolysis of 1-benzylmaleamide 237



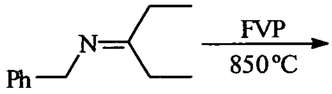
The starting material (0.05 g, 0.28 mmol) was pyrolysed, $T_f = 850$ °C , $T_{in} = 90$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in $CDCl_3$ with the ^{1}H-NMR spectrum shown to be comparable to that quoted for the starting material **237** in the literature,[65] δ_H 7.21 (5H, m), 6.59 (2H, s) and 4.56 (2H, s).

Pyrolysis of benzyl-isopropylidene-amine 238



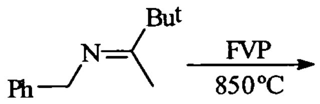
The starting material (0.10 g, 0.68 mmol) was pyrolysed, $T_f = 850$ °C , $T_{in} = 45$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in $CDCl_3$, and the following products identified from comparison with ^{1}H/^{13}C-NMR data quoted for the CH_2 groups in the literature: ethylbenzene **251** [δ_H 2.74 (2H, q, *J* 7.5 Hz) and 1.16 (3H, t, *J* 7.5 Hz); δ_C 28.67 (CH_2) and 15.43 (CH_3)][97] and bibenzyl **233** [δ_H 2.88 (4H, s); δ_C 37.28 (2 × CH_2)][97] in a ratio of *ca.* 5:1.

Pyrolysis of benzyl-(1-ethyl-propylidene)-amine 239



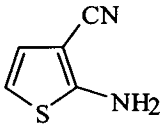
The starting material (0.10 g, 0.56 mmol) was pyrolysed, $T_f = 850$ °C , $T_{in} = 90$ °C, $t_{FVP} = 1$ h, and the pyrolysate collected in $CDCl_3$. No products could be identified from the $^1H/^{13}C$-NMR spectra.

Pyrolysis of benzyl-(1,2,2-trimethyl-propylidene)-amine 252



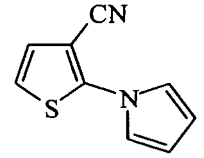
The starting material (0.10 g, 0.52 mmol) was pyrolysed, $T_f = 750$ °C, $T_{in} = 60$ °C, $t_{FVP} = 1$ h. The pyrolysate was collected in $CDCl_3$, with the $^1H/^{13}C$-NMR spectra showing the major product to be bibenzyl **233** (0.061 g, 74%). δ_H 7.21 (10H, m) and 2.92 (4H, s); δ_C 141.23 (quat), 128.38 (4 × CH), 128.31 (4 × CH), 125.49 (2 × CH) and 37.89 (2 × CH_2).[97]

2-Aminothiophene-3-carbonitrile 258



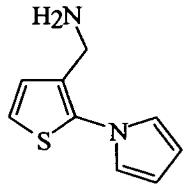
2,5-Dihydroxy-1,4-dithiane **256** (7.6 g, 0105 mol) was added to a solution of malonitrile **257** (6.6 g, 0.1 mol) in water (110 cm^3) at pH 3. The pH was then raised to pH 12 with 25 % NaOH $_{(aq)}$ at 10 °C over a period of 10 min, during which a brown precipitate was formed. The reaction mixture was extracted with ethyl acetate (3 × 50 cm^3), then the combined organics were dried ($MgSO_4$) then the solvent was removed *in vacuo* to give 2-aminothiophene-3-carbonitrile **258** as a pale gray solid, (10.23 g, 81 %), mp 105-106 °C (lit.,[98] 104-105 °C). δ_H ([^{2}H]$_6$ DMSO) 7.11 (2H, s), 6.72 (1H, d, 5.8 Hz) and 6.36 (1H, d, *J* 5.8 Hz); δ_C 165.28 (quat), 125.65 (CH), 116.65 (quat), 108.75 (CH) and 83.34 (quat).

2-(Pyrrol-1-yl)-thiophene-3-carbonitrile 260



The aminothiophene **258** (11.16 g, 0.09 mol), 2,5-DMT (11.58 g, 0.09 mol) and acetic acid (150 cm^3) were heated under reflux for 0.5 h. The mixture was concentrated *in vacuo* to give a dark brown oil, which was washed with water (150 cm^3) then extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), then the solvent was removed *in vacuo* to give *2-(pyrrol-1-yl)-thiophene-3-carbonitrile* **260** as a dark brown oil, (15.6 g, 99%), bp 140 °C (3.5 Torr). (Found, M$^+$ 174.0252. $C_9H_6N_2S$ requires *M* 174.0252); δ_H 7.18 (2H, t, *J* 2.1 Hz), 7.06 (1H, d, *J* 5.8 Hz), 6.97 (1H, d, *J* 5.8 Hz) and 2.45 (2H, t, *J* 2.1 Hz); δ_C 152.04 (quat), 127.66 (CH), 121.09 (2 × CH), 119.01 (2 × CH), 114.25 (quat), 112.07 (CH) and 97.62 (quat); *m/z* 174 (M$^+$, 100%), 147 (50), 103 (24), 64 (34) and 39 (37).

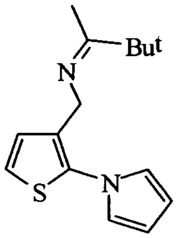
C-(2-Pyrrol-1-yl-thiophen-3-yl)-methylamine 261



A solution of 2-(pyrrol-1-yl)-thiophene-3-carbonitrile **260** (7.8 g, 0.045 mol) in dry THF (50 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of lithium aluminium hydride (4.4 g, 0.11 mol) in dry THF (50 cm^3). The mixture was then heated under reflux under nitrogen for 3 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (50 cm^3) followed by water (50 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected. The aqueous layer was extracted with DCM (3 × 50 cm^3), then the combined organic layers dried ($MgSO_4$). The solvent was removed *in vacuo* to give *C-(2-Pyrrol-1-yl-thiophen-3-yl)-methylamine* **261** as a brown oil (7.70 g, 96%), bp 150 °C (4 Torr). (Found, M$^+$ 178.0563. $C_9H_{10}N_2S$ requires *M* 178.0565); δ_H 7.04

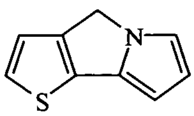
(1H, d, *J* 5.7 Hz), 6.96 (1H, d, *J* 5.7 Hz), 6.81 (2H, t, *J* 2.1Hz), 6.27 (2H, t, *J* 2.1Hz) and 3.69 (2H, s); δ_C 137.52 (quat), 135.81 (quat), 126.53 (CH), 123.10 (2 × CH), 120.91 (2 × CH), 109.56 (CH) and 38.32 (CH_2); *m/z* 178 (M^+, 100%), 161 (51), 137 (16), 110 (32) and 68 (11).

(2-Pyrrol-1-yl-thiophen-3-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine 262



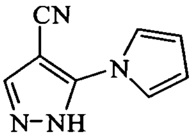
A solution of *C*-(2-pyrrol-1-yl-thiophen-3-yl)-methylamine **261** (3.0 g, 0.017 mol) and pinacolone **253** (1.69 g, 0.017 mol) in toluene (40 cm^3) containing 4 Å molecular sieves (6 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave *(2-pyrrol-1-yl-thiophen-3-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine* **262** as a pale brown oil, (2.90 g, 66%), bp 100 °C (0.01 Torr); δ_H 7.07 (2H, s), 6.90 (2H, t, *J* 2.1Hz), 6.31 (2H, t, *J* 2.1Hz), 4.30 (2H, s), 1.77 (3H, s) and 1.14 (9H, s); δ_C 176.29 (quat), 137.21 (quat), 133.95 (quat), 127.56 (CH), 123.25 (2 × CH), 120.31 (2 × CH), 109.40 (CH), 47.74 (CH_2), 40.42 (quat), 27.49 (3 × CH_3) and 13.26 (CH_3). (No mass spectrum data were collected due to hydrolysis of imine bond under sampling conditions).

7*H*-3-Thia-6*a*-aza-cyclopent[*a*]pentalene 265



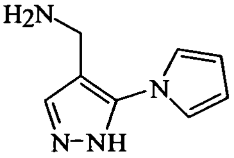
The FVP precursor, (2-pyrrol-1-yl-thiophen-3-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine **262** (0.75 g, 2 mmol) was pyrolysed, $T_f = 700$ °C, $T_{in} = 100$ °C, P = 0.01 Torr, $t_{FVP} = 0.5$ h. The pyrolysate was washed from the U-tube with DCM, then wet flash chromatographed (silica, hexane as eluent) to give *7H-3-thia-6a-aza-cyclopent[a]pentalene* **265** as a dark brown oil, (0.040 g, 12%). (Found, M^+161.0295. C_9H_7NS requires *M* 161.0299); δ_H 7.18 (1H, d, *J* 5.8 Hz), 7.01 (1H, d, *J* 5.8 Hz), 6.71 (1H, d, *J* 2.0 Hz), 6.29 (1H, t, *J* 2.0 Hz), 6.10 (1H, d, *J* 2.0 Hz) and 4.82 (2H, s); δ_C 141.02 (quat), 127.40 (quat), 126.52 (CH), 122.33 (CH), 118. 92 (CH), 118.61 (quat), 113.00 (CH), 97.08 (CH) and 49.60 (CH_2); *m/z* 161 (M^+, 100%), 134 (12), 117 (5), 80 (7) and 57 (8).

5-(Pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile 268



The aminopyrazole **267** (1.0 g, 9.2 mmol), 2,5-DMT (1.18 g, 9.2 mmol) and acetic acid (20 cm^3) were heated under reflux for 1 h. The mixture was concentrated *in vacuo* to give a brown oil, which was washed with water (50 cm^3) then extracted with DCM (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), then concentrated *in vacuo* to give *5-(pyrrol-1-yl)-1H-pyrazole-4-carbonitrile* **268** as a pale yellow solid, (1.14 g, 78%), mp 210-212 °C (from ethanol). (Found, M^+ 158.0559. $C_8H_6N_4$ requires *M* 158.0592); δ_H ($[^2H]_6$ DMSO) 8.66 (1H, s), 7.33 (2H, t, *J* 2.1 Hz) and 6.33 (2H, t, *J* 2.1 Hz); δ_C 149.06 (quat), 137.68 (CH), 119.14 (2 × CH), 113.95 (quat), 111.01 (2 × CH) and 80.84 (quat); *m/z* 158 (M^+, 100%), 131 (21), 104 (36), 77 (15), 51 (25) and 39 (15).

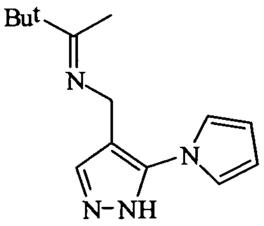
C-(5-Pyrrol-1-yl-1*H*-pyrazol-4-yl)-methylamine 269



A solution of 5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile **268** (0.40 g, 2.5 mmol) in dry THF (15 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of LAH (0.24 g, 6.2 mmol) in dry THF (15 cm^3). The mixture was then heated under reflux under nitrogen for 3 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (50 cm^3) followed by water (50 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected.

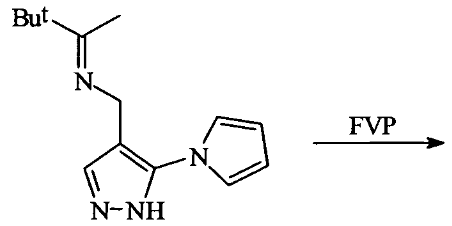
The aqueous layer was extracted with DCM (3 × 30 cm^3), and the combined organic layers dried ($MgSO_4$) then concentrated *in vacuo* to give *C-(5-pyrrol-1-yl-1H-pyrazol-4-yl)-methylamine* **269** as a pale yellow oil, (0.20 g, 49%), material not distilled due to thermal instability. (Found, M$^+$ 162.0908. $C_8H_{10}N_4$ requires *M* 162.0906); δ_H 7.37 (1H, s), 7.10 (2H, t, *J* 2.1 Hz), 6.32 (2H, t, *J* 2.1 Hz) and 3.82 (2H, s); δ_C 146.98 (quat), 128.82 (CH), 120.43 (2 × CH), 113.10 (quat), 109.77 (2 × CH) and 35.32 (CH_2); *m/z* 162 (M$^+$, 76%), 146 (55), 104 (48) and 39 (100).

(5-Pyrrol-1-yl-1*H*-pyrazol-4-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine 270



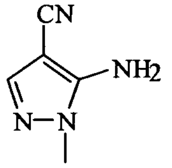
A solution of *C*-(5-pyrrol-1-yl-1*H*-pyrazol-4-yl)-methylamine **269** (0.15 g, 0.9 mmol) and pinacolone **253** (0.18 g, 1.8 mmol) in toluene:DCM (1:1) (20 cm^3) containing 4 Å molecular sieves (4 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave *(5-Pyrrol-1-yl-1H-pyrazol-4-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine* **270** as a pale brown oil (0.15 g, 69%), bp 165 °C (0.01 Torr). δ_H 7.37 (1H, s), 7.09 (2H, t, *J* 2.1 Hz), 6.24 (2H, t, *J* 2.1 Hz), 4.26 (2H, s), 1.76 (3H, s) and 1.06 (9H, s); δ_C 174.25 (quat), 147.25 (quat), 130.01 (CH), 120.65 (2 × CH), 114.03 (quat), 110.37 (2 × CH), 49.73 (CH_2) 40.39 (quat), 27.57 (3 × CH_3) and 13.52 (CH_3). (No mass spectrum data were collected due to hydrolysis of imine bond under sampling conditions).

Pyrolysis of (5-pyrrol-1-yl-1*H*-pyrazol-4-ylmethyl)-(1,2,2-trimethylpropylidene)-amine 270



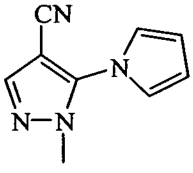
Pyrolysis of **270** at a furnace temperature of 750 °C, inlet temperature 150 °C gave a pyrolysate with no identifiable components.

5-Amino-1-methyl-1*H*-pyrazole-4-carbonitrile 273



Ethoxymethylenemalononitrile **271** (0.75 g, 6 mmol) and methylhydrazine **272** (0.86 g, 18 mmol) were mixed at such a rate as to bring about gentle reflux. The solution was then heated on a steam bath for 1h. Water (4 cm^3) was added, and the mixture cooled in a freezer overnight. The pale brown solid formed was collected by filtration and washed with ether to give the product **273** as a pale brown solid (0.56 g, 76%), mp 222-223 °C (from ethanol) (lit.,[75] 222-223 °C). δ_H ([^{2}H]$_6$ DMSO) 7.49 (1H, s), 6.54 (2H, s) and 3.34 (3H, s).[75]

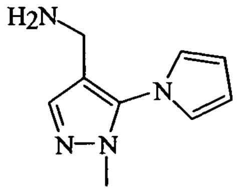
1-methyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile 275



The aminopyrazole **273** (1.22 g, 0.01 mol), 2,5-DMT (1.28 g, 0.01 mol) and acetic acid (20 cm^3) were heated under reflux for 0.5 h. The mixture was concentrated *in vacuo* to give a dark brown oil, which was washed with water (50 cm^3) then extracted with DCM (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), then the solvent removed *in vacuo* to give 1-methyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile **275** as a brown oil (1.51 g, 88%), bp 110-115 °C (1.5 Torr). (Found M$^+$ 172.0751. $C_9H_8N_4$ requires

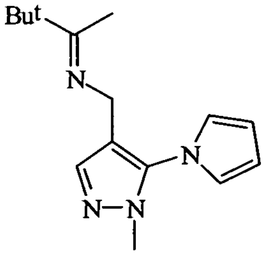
M 172.0749); δ_H ([^{2}H]$_6$ DMSO) 8.13 (1H, s), 7.20 (2H, t, *J* 2.2 Hz), 6.42 (2H, t, *J* 2.2 Hz) and 3.77 (3H, s); δ_C 143.24 (quat), 141.37 (CH), 122.42 (2 × CH), 112.82 (quat), 111.59 (2 × CH), 86.73 (quat) and 36.91 (CH_3); *m/z* 172 (M^+, 100%), 144 (26), 117 (27), 67 (29) and 43 (24). (All spectral data consistent with literature). [99]

_C_-(1-Methyl-5-pyrrol-1-yl-1_H_-pyrazol-4-yl)-methylamine 276



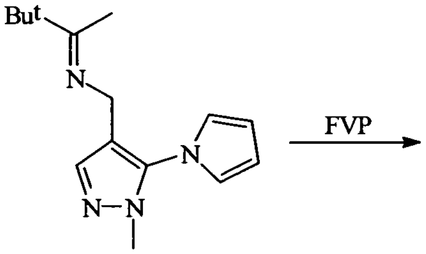
A solution of 1-methyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile **275** (0.95 g, 5.5 mmol) in dry THF (15 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of lithium aluminium hydride (0.43 g, 11 mmol) in dry THF (15 cm^3). The mixture was then heated under reflux under nitrogen for 3 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (50 cm^3) followed by water (50 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected. The aqueous layer was extracted with DCM (3 × 30 cm^3), and the combined organic layers dried ($MgSO_4$), then concentrated *in vacuo* to give C-(1-methyl-5-pyrrol-1-yl-1*H*-pyrazol-4-yl)-methylamine **276** as a pale brown oil, (0.62 g, 64%), material not distilled due to apparent thermal instability. δ_H 7.43 (1H, s), 6.67 (2H, t, *J* 2.2 Hz), 6.30 (2H, t, *J* 2.2 Hz), 3.68 (2H, s) and 3.54 (3H, s); δ_C 145.69 (quat), 131.74 (CH), 121.48 (2 × CH), 113.05 (quat), 110.43 (2 × CH), 37.08 (CH_2) and 36.82 (CH_3). (All spectral data consistent with literature). [99]

(1-Methyl-5-pyrrol-1-yl-1*H*-pyrazol-4-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine 277



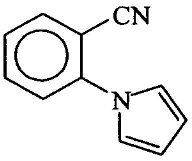
A solution of *C*-(1-Methyl-5-pyrrol-1-yl-1*H*-pyrazol-4-yl)-methylamine **276** (0.30 g, 1.7 mmol) and pinacolone **253** (0.34 g, 3.4 mmol) in toluene (15 cm^3) containing 4 Å molecular sieves (4 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave *(1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine* **277** as a pale yellow oil, (0.24 g, 54%), bp 100 °C (0.01 Torr). δ_H 7.43 (1H, s), 6.67 (2H, t, *J* 2.2 Hz), 6.30 (2H, t, *J* 2.2 Hz), 4.09 (2H, s), 3.54 (3H, s), 1.67 (3H, s) and 1.05 (9H, s); δ_C 173.46 (quat), 144.05 (quat), 131.25 (CH), 120.97 (2 × CH), 114.37 (quat), 109.97 (2 × CH), 48.33 (CH_2), 40.37 (quat), 36.85 (CH_3), 27.22 (3 × CH_3) and 13.42 (CH_3). (No mass spectrum data were collected due to hydrolysis of imine bond under sampling conditions).

Pyrolysis of (1-Methyl-5-pyrrol-1-yl-1*H*-pyrazol-4-ylmethyl)-(1,2,2-trimethyl-propylidene)-amine 277



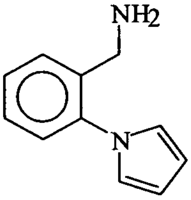
Pyrolysis of **277** at a furnace temperature of 750 °C, inlet temperature 120 °C gave a pyrolysate with no identifiable components.

2-(Pyrrol-1-yl)-benzonitrile 279



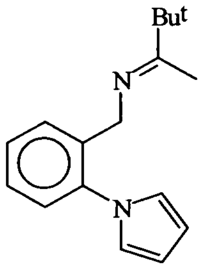
2-Aminobenzonitrile **278** (2.0 g, 0.017 mol), 2,5-DMT (2.17 g, 0.017 mol) and acetic acid (30 cm^3) were heated under reflux for 15 min. The mixture was concentrated *in vacuo* to give a brown oil, which was washed with water (50 cm^3) then extracted with DCM (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvents removed *in vacuo* to give 2-(pyrrol-1-yl)-benzonitrile **279** as pale yellow crystals, (1.65 g, 58%), mp 49-50 °C (from hexane) (lit.,[100] 48-50 °C). δ_H 7.69 (2H, m), 7.35 (2H, m). 7.11 (2H, t, *J* 2 Hz) and 6.40 (2H, t, *J* 2 Hz); δ_C 142.88 (quat), 134.35 (CH), 133.87 (CH), 126.40 (2 × CH), 120.96 (2 × CH), 116.80 (quat), 110.08 (2 × CH) and 106.68 (quat). (All spectral data consistent with literature). [100]

2-(Pyrrol-1-yl)-benzylamine 280



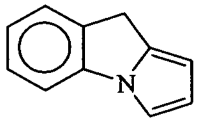
A solution of 2-(pyrrol-1-yl)-benzonitrile **279** (1.0 g, 6.0 mmol) in dry THF (15 cm^3) was added dropwise, with stirring under nitrogen, to a suspension of lithium aluminium hydride (0.46 g, 12 mmol) in dry THF (15 cm^3). The mixture was then heated under reflux under nitrogen for 3 h. Residual lithium aluminium hydride was destroyed through cautious addition of wet ether (30 cm^3) followed by water (50 cm^3). Insoluble inorganics were removed by filtration through celite, then the organic layer collected. The aqueous layer was extracted with ether (3 × 50 cm^3), and the combined organic layers dried ($MgSO_4$), then concentrated *in vacuo* to give 2-(pyrrol-1-yl)-benzylamine **280** as a brown liquid (0.83 g, 80%), bp 100 °C (2 Torr) [lit.,[100] 125-130 °C (2 Torr)]. δ_H 7.40 (4H, m), 6.82 (2H, t, *J* 2.1 Hz), 6.34 (2H, t, *J* 2.1 Hz) and 3.76 (2H, s). (All spectral data consistent with literature). [100]

(2-(Pyrrol-1-yl)-benzyl)-(1,2,2-trimethyl-propylidene)-amine 281



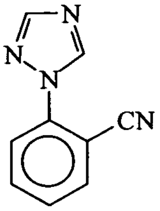
A solution of 2-(pyrrol-1-yl)-benzylamine **280** (0.17 g, 1 mmol) and pinacolone **253** (0.2 g, 2 mmol) in toluene (10 cm^3) containing 4 Å molecular sieves (4 g) was stirred at room temperature under nitrogen for 24 h. Removal of the solvent *in vacuo* gave *(2-pyrrol-1-yl-benzyl)-(1,2,2-trimethyl-propylidene)-amine* **281** as a pale brown oil (0.15 g, 60%), bp 80 °C (0.01 Torr). (Found, M$^+$ 254.1782. $C_{17}H_{22}N_2$ requires *M* 254.1783); δ_H 7.42 (4H, m), 6.82 (2H, t, *J* 2.1 Hz), 6.32 (2H, t, *J* 2.1 Hz), 4.25 (2H, s), 2.14 (3H, s) and 1.14 (9H, s); δ_C 176.42 (quat), 139.69 (quat), 136.91 (quat), 128.78 (CH), 127.87 (CH), 126.32 (2 × CH), 122.22 (2 × CH), 108.56 (2 × CH), 50.15 (CH_2), 40.60 (quat), 27.60 (3 × CH_3) and 13.53 (CH_3); *m/z* 254 (M$^+$, 17%), 197 (10), 156 (100), 128 (15), 100 (47) and 78 (19).

9*H*-Pyrrolo[1,2-*a*]indole 263



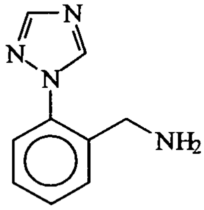
(2-Pyrrol-1-yl-benzyl)-(1,2,2-trimethyl-propylidene)-amine **281** (0.10 g, 0.4 mmol) was pyrolysed, T_f = 750 °C, T_{in} = 60 °C, t_{FVP} = 1 h, P = 0.01 Torr. The pyrolysate was washed from the U-tube with DCM, then the solvent removed *in vacuo* to give 9*H*-pyrrolo[1,2-*a*]indole **263** as a dark brown solid (0.045 g, 72%), mp 203-204 °C (from ether) (lit.,[69] 209-211 °C). δ_H 7.27 (1H, m), 7.16 (2H, m), 6.99 (2H, m), 6.30 (1H, m), 6.02 (1H, m) and 3.73 (2H, s). (All spectral data consistent with literature). [69]

2-[(1,2,4)Triazol-1-yl]-benzonitrile 285



A solution of 2-fluorobenzonitrile **284** (2.62 g, 0.02 mol) and 1,2,4-triazole (0.98 g, 0.02 mol) in DMSO (30 cm^3) containing K_2CO_3 (3.04 g, 0.022 mol) was heated at 100 °C with stirring for 3 h. The cooled reaction mixture was poured into water (150 cm^3) then extracted with DCM (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the product **285** as a white solid (2.42 g, 71%), mp 120-121 °C (from ethanol) (lit.,[76] 120-122 °C); δ_H 8.75 (1H, s), 8.17 (1H, s), 7.79 (3H, m) and 7.54 (1H, m); δ_C 152.95 (CH), 142.94 (CH), 138.42 (quat), 134.33 (CH), 134.21 (CH), 128.86 (CH), 124.67 (CH), 115.83 (quat) and 106.21 (quat). (^{1}H-nmr data consistent with literature).[76]

2-[1,2,4]Triazol-1-yl-benzylamine 286



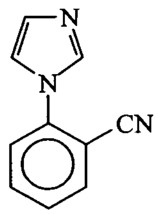
A solution of **285** (8.50 g, 0.05 mol) and cobaltous chloride hexahydrate (1.30 g, 5 mmol) in THF:H_2O (66:33 cm^3) was cooled and stirred. Sodium borohydride (7.60 g, 0.2 mol) was added in portions over a 15 min period. The mixture was then left stirring at room temperature for 2 h. The black precipitate was removed by filtration through a celite pad, and washed with DCM (30 cm^3). The filtrate was concentrated *in vacuo* to remove the organic solvent, then the aqueous layer made basic (sodium carbonate) and extracted with DCM (3 × 50 cm^3). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil, which solidified to give a sticky brown solid which was purified by column chromatography (silica, EtOH as eluent) to give *2-[(1,2,4)triazol-1-yl]-benzylamine* **286** as a pale brown oil, (1.30 g, 15%). (Found, M$^+$ 174.0900. $C_9H_{10}N_4$ requires *M*

174.0906); δ_H ([^{2}H]$_6$ DMSO) 8.89 (1H, s), 8.19 (1H, s), 7.51 (4H, m) and 3.51 (2H, s); δ_C 152.05 (CH), 145.22 (CH), 135.94 (quat), 135.31 (quat), 130.30 (CH), 129.33 (CH), 127.99 (CH), 126.03 (CH) and 48.18 (CH$_2$); *m/z* 174 (M$^+$, 31%), 173 (100), 156 (49), 131 (67), 91 (37), 77 (50), 45 (79) and 29 (91).

Attempted synthesis of 287

A solution of **286** (1.20 g, 6.9 mmol) and pinacolone **253** (1.99 g, 20.7 mmol) in toluene (50 cm^3) containing 4 Å mol. sieves (4 g) was stirred at room temperature under N$_2$ for 24 h. Standard work up conditions produced only materials with spectroscopic data identical to starting materials.

2-(Imidazol-1-yl)-benzonitrile 288

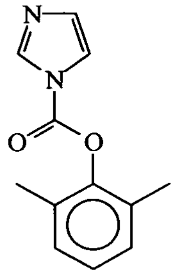


A solution of 2-fluorobenzonitrile **284** (3.28 g, 0.025 mol) and imidazole (1.6 g, 0.025 mol) in DMSO (30 cm^3) containing K$_2$CO$_3$ (3.75 g, 0.028 mol) was heated at 100 °C with stirring for 3 h. The cooled reaction mixture was poured into water (150 cm^3) then extracted with DCM (3 × 50 cm^3). The combined organic extracts were dried (MgSO$_4$) then concentrated *in vacuo* to give the product **288** as a white solid (2.32 g, 55%), mp 146-147 °C (from ethanol) (lit.,[76] 146-148 °C); δ_H 7.80 (1H, d, *J* 1.6 Hz), 7.72 (2H, m), 7.45 (2H, m), 7.30 (1H, s) and 7.21 (1H, d, *J* 1.6 Hz). (^{1}H-nmr data consistent with literature).[76]

Attempted synthesis of 289

A solution of **288** (0.4 g, 2.25 mmol) and cobaltous chloride hexahydrate (0.06 g, 0.23 mmol) in THF:H$_2$O (15:8 cm^3) was cooled and stirred. Sodium borohydride (0.2 g, 4.5 mmol) was added in portions over a 5 min period. The mixture was then left stirring at room temperature for 2 h. Work up as in synthesis of **286** gave no identifiable products.

Imidazole-1-carboxylic acid 2,6-dimethylphenyl ester 293



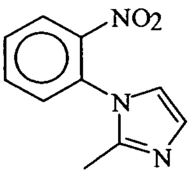
A solution of 2,6-dimethylphenol **291** (1.23 g, 0.01 mol) and CDI **292** (2.11 g, 0.013 mol) in acetonitrile (20 cm^3) was heated under reflux with stirring for 3 h. The solvent was removed *in vacuo* to give imidazole-1-carboxylic acid 2,6-dimethylphenyl ester **293**, (2.01 g, 93%). (Found, M$^+$ 216.0897. $C_{12}H_{12}N_2O_2$ requires *M* 216.0899); δ_H 8.32 (1H, s), 7.58 (1H, s), 7.15 (1H, s), 7.11 (3H, s) and 2.20 (6H, s); δ_C 146.93 (quat), 146.18 (quat), 137.18 (CH), 130.85 (CH), 129.77 (2 × quat), 128.81 (2 × CH), 126.79 (CH), 117.25 (CH) and 15.91 (2 × CH_3); ir 1772.4 cm^{-1} (CO); *m/z* 216 (M$^+$, 54%), 144 (22), 122 (100), 105 (48), 68 (57) and 41 (41). (All spectral data consistent with literature).[79]

Repeating the above reaction with a reaction time of 24 h gave a product with identical spectroscopic properties to that of compound **293**.

c. Use of the nitro group as a radical precursor

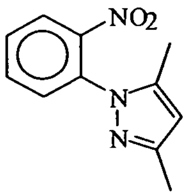
The pyrolysis precursors **318**, **324** - **326** were prepared *via* the reaction between the stated aromatic nitro-compound (0.02 mol) and the appropriate heterocycle (0.02 mol) in DMF (25 cm^3) containing K_2CO_3 (2.76 g, 0.02 mol) at the stated temperature, with stirring, for the stated time. The reaction mixture was then poured into water (150 cm^3), and then extracted with ether (3 × 50 cm^3). The combined organics were dried ($MgSO_4$), then concentrated *in vacuo* to give the products which were purified by recrystallisation (unless stated otherwise).

2-Methyl-1-(2-nitrophenyl)-1*H*-imidazole 318



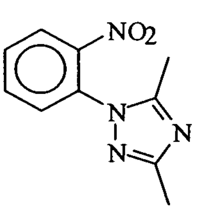
2-Fluoronitrobenzene **316** (2.82 g, 0.02 mol) and 2-methylimidazole **317** (1.62 g, 0.02 mol) gave, after 24 h at 125 °C, *2-methyl-1-(2-nitrophenyl)-1H-imidazole* **318** as an orange solid, (2.10 g, 52%), mp 91-92 °C (from toluene). (Found, M$^+$ 203.0694. $C_{10}H_9N_3O_2$ requires *M* 203.0695); δ_H 8.00 (1H, d, *J* 8 Hz), 7.65 (2H, m), 7.37 (1H, d, *J* 8 Hz), 6.98 (1H, d, *J* 1.5 Hz), 6.85 (1H, d, *J* 1.5 Hz) and 2.16 (3H, s); δ_c 146.00 (quat), 145.31 (quat), 133.67 (CH), 130.84 (quat), 129.98 (CH), 129.84 (CH), 128.21 (CH), 125.07 (CH), 120.33 (CH) and 12.77 (CH_3); *m/z* 203 (M$^+$, 19%), 161 (28), 134 (21), 90 (14), 77 (28) and 43 (100).

3,5-Dimethyl-1-(2-nitrophenyl)-1*H*-pyrazole 324



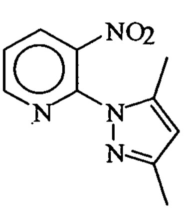
2-Fluoronitrobenzene **316** (2.82 g, 0.02 mol) and 3,5-dimethylpyrazole **322** (1.92 g, 0.02 mol) gave, after 24 h at 125 °C, *3,5-dimethyl-1-(2-nitrophenyl)-1H-pyrazole* **324** as a yellow solid (3.20 g, 74%), mp 105-107 °C (from toluene). (Found C, 60.8; H, 5.1; N, 19.35. $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.35%. Found, M^+ 217.0845. $C_{11}H_{11}N_3O_2$ requires *M* 217.0851); δ_H 7.92 (1H, dd, *J* 1.3 Hz, 8 Hz), 7.56 (3H, m), 5.98 (1H, s), 2.14 (3H, s) and 2.13 (3H, s); δ_C (one quaternary not apparent) 150.25 (quat), 146.20 (quat), 140.75 (quat), 132.99 (CH), 129.27 (CH), 129.03 (CH), 124.87 (CH), 106.63 (CH), 13.27 (CH_3) and 11.13 (CH_3); *m/z* 217 (M^+, 74%), 200 (43), 170 (21), 129 (29), 95 (86), 77 (63), 65 (34) and 43 (100).

3,5-Dimethyl-1-(2-nitrophenyl)-1*H*-[1,2,4]triazole 325



2-Fluoronitrobenzene **316** (2.82 g, 0.02 mol) and 2,5-dimethyl[1,2,4]triazole **323** (1.93 g, 0.02 mol) gave, after 40 h at 125 °C, *3,5-dimethyl-1-(2-nitrophenyl)-1H-[1,2,4]triazole* **325** as an orange solid, (2.88 g, 66%), mp 89-90 °C (from toluene). (Found, M^+ 218.0803. $C_{10}H_{10}N_4O_2$ requires *M* 218.0804); δ_H 8.03 (1H, dd, *J* 1.7, 8.0 Hz), 7.68 (2H, m), 7.45 (1H, dd, *J* 1.7, 8.0 Hz), 2.32 (3H, s) and 2.31 (3H, s); δ_C (one quaternary not apparent) 161.58 (quat), 154.43 (quat), 145.97 (quat), 134.30 (CH), 131.09 (CH), 129.77 (CH), 125.96 (CH), 14.13 (CH_3) and 12.58 (CH_3); *m/z* 218 (M^+, 20%), 166 (13), 91 (61), 78 (45) and 43 (100).

2-(3,5-Dimethylpyrazol-1-yl)-3-nitropyridine 326

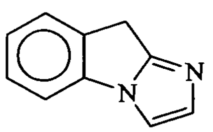


2-Chloro-3-nitropyridine **321** (3.44 g, 0.02 mol) and 3,5-dimethylpyrazole **322** (1.92 g, 0.02 mol) were heated at 125 °C for 48 h. The mixture obtained after ether work up was purified by dry flash chromatography (silica, hexane as eluent), to give *2-(3,5-dimethylpyrazol-1-yl)-3-nitropyridine* **326** as a pale yellow solid, (1.40 g, 32%), mp 110-112 °C (from ethanol). (Found, M^+ 218.0804. $C_{10}H_{10}N_4O_2$ requires *M* 218.0804); δ_H 8.61 (1H, dd, *J* 1.6, 2.9 Hz), 8.14 (1H, dd, *J* 1.6, 6.3 Hz), 7.38 (1H, m), 6.02 (1H, s), 2.49 (3H, s) and 2.20 (3H, s); δ_C 151.48 (quat), 150.38 (CH), 144.56 (quat), 141.31 (quat), 140.86 (quat), 133.58 (CH), 121.82 (CH), 108.82 (CH), 13.35 (CH_3) and 12.30 (CH_3); *m/z* 218 (M^+, 9%), 201 (13), 188 (7), 139 (64), 93 (45), 66 (62) and 39 (100).

Pyrolysis of nitro precursors 318, 324 - 326

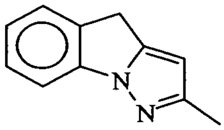
The nitro-compounds **318, 324 – 326** were distilled at a pressure of 0.02 Torr into an empty silica furnace tube maintained at a temperature of 850 °C. Instead of using a U-tube cooled with liquid nitrogen to condense the pyrolysate, a cold finger trap cooled with dry ice/acetone was employed. The cold finger joint with the furnace tube was pushed as far into the furnace as possible, and both this joint and the inlet tube joint insulated with tin foil. This gave two advantages over the standard set up. Firstly, the desired product was condensed directly onto a surface cooled to -80 °C as opposed to the warmer surface of the furnace tube exit. Secondly, the reactive co-products did not condense at -80 °C, but were trapped in a liquid nitrogen cooled U-tube connected to the cold finger in series. These two factors minimise the possibility of product decomposition. Once the pyrolysis was complete, nitrogen gas was released through the system, which was dismantled before the U-tube could warm to room temperature. This allowed the co-products to be removed from the system before they were in the gaseous state, so that they had no further contact with the product. The cold finger was then dismantled whilst still cold, and the product washed off immediately with acetone and stored at -18 °C until required.

9*H*-Imidazo[1,2-*a*]indole 319



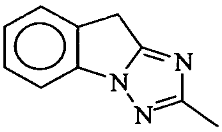
2-Methyl-1-(2-nitrophenyl)-1*H*-imidazole **318** (0.27 g, 1.3 mmol) was pyrolysed, T_{in} = 120 °C, t_{FVP} = 1 h. The pyrolysate was collected in acetone then distilled to give *9H-imidazo[1,2-a]indole* **319** as a pale yellow liquid, (0.09 g, 44%), bp 60 °C (0.02 Torr). (Found, M^+ 156.0687. $C_{10}H_8N_2$ requires *M* 156.0688); δ_H 7.31 (6H, m) and 3.90 (2H, s); δ_C 153.60 (quat), 133.93 (quat), 133.52 (quat), 133.28 (CH), 128.33 (CH), 126.65 (CH), 125.08 (CH), 111.34 (CH), 111.01 (CH) and 29.23 (CH_2); *m/z* 156 (M^+, 100%), 117 (43), 102 (23), 90 (23), 77 (25) and 51 (29).

2-Methyl-4*H*-pyrazolo[1,5-*a*]indole 327



3,5-Dimethyl-1-(2-nitrophenyl)-1*H*-pyrazole **324** (0.62 g, 2.9 mmol) was pyrolysed, T_{in} = 90 °C, t_{FVP} = 1 h. The pyrolysate was collected in acetone then distilled to give 2-methyl-4*H*-pyrazolo[1,5-a]indole **327** as a pale brown oil, (0.21 g, 43%), bp 150-160 °C (2 Torr). δ_H 7.34 (4H, m), 6.05 (1H, s), 3.79 (2H, s) and 2.40 (3H, s); δ_C 153.70 (quat), 145.27 (quat), 140.76 (quat), 132.89 (quat), 127.83 (CH), 125.61 (CH), 123.62 (CH), 109.74 (CH), 100.39 (CH), 28.09 (CH_2) and 14.21 (CH_3); *m/z* 170 (M^+, 94%), 155 (49), 143 (20), 129 (100) and 102 (76). (^{1}H-nmr data consistent with literature).[92]

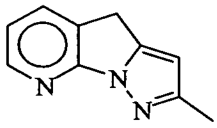
2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 328



3,5-Dimethyl-1-(2-nitrophenyl)-1H-[1,2,4]triazole **325** (0.15 g, 0.69 mmol) was pyrolysed, T_{in} = 90 °C, t_{FVP} = 1 h. The pyrolysate was collected in acetone then distilled to give *2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **328** as a pale yellow oil, (0.07 g, 59%), bp 60-70 °C (0.2 Torr). (Found, M^+ 171.0793. $C_{10}H_9N_3$ requires *M* 171.0797); δ_H 7.46

(4H, m), 3.83 (2H, s) and 2.49 (3H, s); δ_C 165.32 (quat), 160.34 (quat), 138.01 (quat), 131.78 (quat), 128.21 (CH), 126.01 (CH), 125.11 (CH), 110.65 (CH), 27.45 (CH_2) and 14.54 (CH_3); *m/z* 171 (M^+, 79%), 128 (78), 102 (100), 76 (68) and 51 (61).

2-Methyl-8*H*-3,3a,4-triaza-cyclopenta[*a*]indene 329



2-(3,5-Dimethyl-pyrazol-1-yl)-3-nitropyridine **326** (0.15 g, 0.69 mmol) was pyrolysed, T_{in} = 60 °C, t_{FVP} = 1 h. The pyrolsate was collected in acetone then distilled to give *2-methyl-8H-3,3a,4-triaza-cyclopenta[a]indene* **329** as a brown oil, (0.05 g, 42%), bp 110 °C (2 Torr). (Found, M^+ 171.0796. $C_{10}H_9N_3$ requires *M* 171.0797); δ_H 8.34 (1H, d, *J* 5.2 Hz), 7.72 (1H, m), 7.09 (1H, m), 6.14 (1H, s), 3.85 (2H, s) and 2.45 (3H, s); δ_C 156.07 (quat), 153.2 (quat), 147.72 (CH), 145.87 (quat), 134.12 (CH), 127.09 (quat), 119.40 (CH), 102.03 (CH), 26.87 (CH_2) and 14.90 (CH_3); *m/z* 171 (M^+, 100%), 130 (66), 103 (38), 92 (25), 63 (37), 51 (45) and 39 (86).

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E. APPENDIX

Gas-phase pyrolysis of 4-amino-3-allylthio-1,2,4-triazoles: a new route to [1,3]thiazolo[3,2-*b*][1,2,4]triazoles

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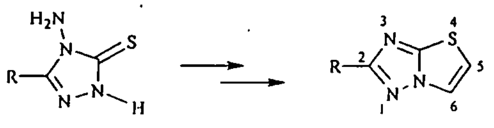
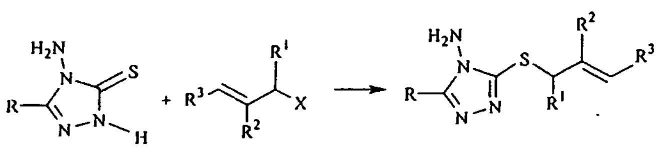
Flash vacuum pyrolysis of the 3-allylthio derivatives of 4-amino-4*H*-1,2,4-triazoles **10–13** and **15–17** at 750–850 °C (10^{-2}–10^{-3} Torr) gives [1,3]thiazolo[3,2-*b*][1,2,4]triazoles **19** and **24–29** in *ca.* 50% yield. The mechanism is thought to involve initial [3,3]sigmatropic shift of the allyl group, followed by cleavage of the N–N bond to generate a thiaza-allyl radical, which then undergoes cyclisation, rearrangement and alkyl group extrusion.

In previous work we have used the flash vacuum pyrolysis (FVP) reactions of aromatic allylthio compounds to generate thiophenoxyl radicals which can take part in rearrangement and cyclisation reactions.[1–3] In attempting to extend this methodology into the heterocyclic series we have discovered in one case an unusual sequence involving a [3,3]sigmatropic shift, thiaza-allyl radical generation, cyclisation, rearrangement and alkyl group extrusion, all of which leads to a convenient synthesis of the [1,3]thiazolo[3,2-*b*][1,2,4]triazole ring system[4] **1** in two steps from readily available *N*-amino-1,2,4-triazoles **2** (Scheme 1).


2
1

Scheme 1


3 R = H
4 R = Me
5 R = Ph

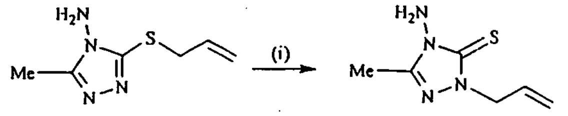
6 $R^1 = R^2 = R^3 = H$, X = Br
7 $R^1 = R^3 = H$, $R^2 = Me$, X = Cl
8 $R^1 = R^2 = H$, $R^3 = Me$, X = Cl
9 $R^1 = Me$, $R^2 = R^3 = H$, X = Cl

10 $R = R^1 = R^2 = R^3 = H$
11 $R = Me$, $R^1 = R^2 = R^3 = H$
12 $R = Me$, $R^1 = R^3 = H$, $R^2 = Me$
13 $R = Me$, $R^1 = R^2 = H$, $R^3 = Me$
14 $R = Me$, $R^2 = R^3 = H$, $R^1 = Me$
15 $R = Ph$, $R^1 = R^2 = R^3 = H$
16 $R = Ph$, $R^1 = R^3 = H$, $R^2 = Me$
17 $R = Ph$, $R^1 = R^2 = H$, $R^3 = Me$

Scheme 2

The triazole precursors **3–5** (Scheme 2) were readily obtained by literature methods as described briefly in the Experimental section.[5–7] Allylation of the triazoles **4** and **5** using allyl bromide **6** or methallyl chloride **7**[†] in *N*,*N*-dimethylformamide containing anhydrous potassium carbonate gave products which were obtained as single isomers in 54–81% yield. The product obtained from the 5-unsubstituted compound **3** decomposed on work-up under these conditions, but a product was obtained in satisfactory yield (79%) when the reaction was carried out using acetonitrile as the solvent. The assignment of the products as the *S*-allyl compounds **10–12**, **15** and **16** followed in particular from their ^{13}C NMR spectra. Thus *N*-alkylation (either at the exocyclic amino group or at the ring N2 atom) would give a product which has a thione group. These are known to show signals in the range δ_C 166–167 in triazole-3-thiones,[8] whereas the spectra of **10–12**, **15** and **16** show no peaks at δ_C >155 ppm. The corresponding reaction of **4** with either crotyl chloride **8** or 3-chlorobut-1-ene **9** gave a mixture of *S*-allylated isomers in 6:1 and 13:1 ratio respectively. The ^{13}C NMR DEPT spectrum of the mixture confirmed that both isomers had a CH_2 group adjacent to the sulfur atom (δ_C 35.65) and therefore they are likely to be the *E* and *Z* isomers of **13**. Recrystallisation from toluene gave a single compound which is likely to be the *E*-isomer. No trace of the regioisomer **14** was apparent from the crude spectra. Similarly the butenyl compound **17** was obtained by reaction of the phenyl-substituted precursor **5** with crotyl chloride.[‡]

FVP of the *S*-allyl compound **11** at 650 °C (0.01 Torr) gave a mixture of two products in 9:1 ratio from which the major compound could be isolated by chromatography on silica. This product was clearly isomeric with the starting material and was identified as the *N*-allyl compound **18** by its spectra (Scheme 3).


11
18

Scheme 3 *Reagents and conditions*: (i) 650 °C (0.01 Torr).

For example, the thione function is apparent from the signal at δ_C 165.99 in the ^{13}C NMR spectrum (see above). [3,3]Sigmatropic rearrangements of this type have been previously reported in the triazole series[8] and in the present example may take place to some extent during the sublimation stage of the pyrolysis.

[†] The IUPAC name for methallyl is 2-methylprop-2-enyl.

[‡] The IUPAC name for crotyl is but-2-enyl.

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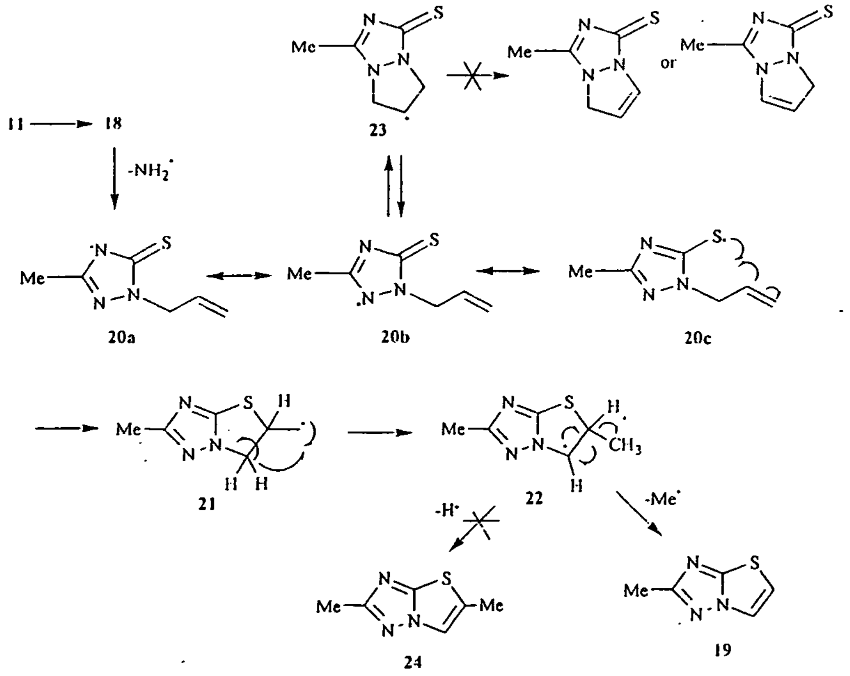
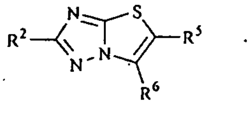


Scheme 4

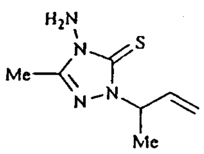
At higher furnace temperatures, FVP of **11** gave a single major product (identical with the minor product obtained in the 650 °C pyrolysis described above) which was purified by distillation. The mass spectrum of this material showed a molecular ion at *m/z* 139 corresponding to loss of 31 Daltons (= CH_5N) from the starting material. The assignment of the structure of the product as the known[9] 2-methyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **19** (54%) followed by comparison of its spectra with those in the literature. For example the ^1H NMR spectrum shows three signals in 1 : 1 : 3 ratio [δ_H 7.69 (*J* 4.5 Hz), 6.91 (*J* 4.5 Hz) and 2.50] which correspond closely with the reported data for **19** [δ_H 7.69 (*J* 5 Hz), 6.91 (*J* 5 Hz) and 2.47].[9] In addition the mass spectrum of our product (see Experimental section) shows the same initial breakdown peaks as previously reported.[9]



19 $R^2 = Me, R^5 = R^6 = H$
24 $R^2 = R^5 = Me, R^6 = H$
25 $R^2 = R^5 = R^6 = H$
26 $R^2 = R^6 = Me, R^5 = H$
27 $R^2 = Ph, R^5 = R^6 = H$
28 $R^2 = Ph, R^5 = Me, R^6 = H$
29 $R^2 = Ph, R^5 = H, R^6 = Me$

A possible mechanism for this unexpected transformation is shown in Scheme 4. After the initial [3,3]sigmatropic shift to give **18**, cleavage of the N–N bond apparently takes place to generate the resonance-stabilised radical **20**. This species then adds exclusively from its sulfur centre **20c** in 5-*exo-trig* fashion to the double bond of the allyl group. The primary radical **21** thus generated can achieve more stability by hydrogen shift from the site adjacent to the bridgehead nitrogen atom to give **22**. Aromatisation by C–C cleavage (and ejection of a methyl radical) gives the product **19**. Two instances of high selectivity in the chemistry of these radicals are apparent in this sequence. First, no products were obtained from an alternative cyclisation route which formally involves the nitrogen-centred canonical form **20b** (to give the secondary radical intermediate **23**). This suggests either that formation of **23** is reversible or that thiyl radicals are more reactive than aminyl radicals in such competitive cyclisation situations. Alternatively, the 5-*exo-trig* mode of cyclisation (to give **21**) may be inherently favoured over the 5-*endo-trig* to give **23**. Second, no trace of the dimethylthiazolo[3,2-*b*][1,2,4]triazole **24** (see below) which might have been formed by loss of a hydrogen atom from **22**, was observed in the crude pyrolysate; C–C cleavage is normally observed in preference to C–H cleavage under competitive conditions in the gas-phase.[10]

The synthetic potential of this two step sequence from 4-amino-1,2,4-triazole-3-thiones to [1,3]thiazolo[3,2-*b*][1,2,4]triazoles was then investigated using the 5-unsubstituted compound **10**, the 5-methyltriazoles **12** and **13**, and the 5-phenyl compounds **15–17** as model substrates. In all cases the pyrolysis step was carried out in the range 750–850 °C (10^{-2}–10^{-3} Torr) and the products were purified by Kugelrohr distillation; in general, chromatography was not required. Pyrolysis of **10** (850 °C) gave the unsubstituted [1,3]thiazolo[3,2-*b*][1,2,4]triazole **25** (45%) and that of the methallyl derivative **12** gave the expected 2,5-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole **24** in 48% yield. In the case of the butenyl precursor **13**, the initial sigmatropic shift produces **30** and hence leads to the 2,6-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole skeleton **26** (54%). Pyrolysis of the phenyl-substituted triazoles **15–17** proceeded normally and the [1,3]thiazolo[3,2-*b*][1,2,4]triazoles **27–29** were obtained in 23, 48 and 54% yields respectively, though chromatography was required to purify **29**. In general, the



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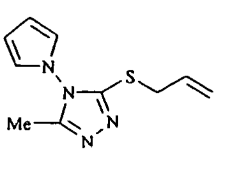

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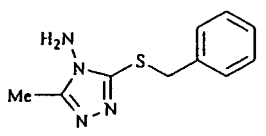

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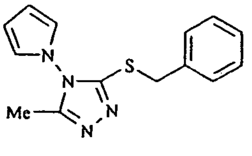

33

2,6-disubstituted products were obtained in a less pure state than the other derivatives. 2,5-Disubstitution in the [1,3]thiazolo[3,2-*b*][1,2,4]triazole ring system is apparently a rare substituent pattern[4] and both **24** and **28** are new compounds.

In the pyrolyses of the phenyl-substituted substrates **15–17**, some benzonitrile was detected in the crude pyrolysate, presumably due to breakdown of the heterocycle at the high temperatures required for the initial N–N bond cleavage. Since pyrolysis of **16** or **17** at 750 °C (rather than 850 °C) did not significantly reduce the level of benzonitrile, an attempt was made to design a substrate in which the co-formed aminyl radical was stabilised. Thus condensation of **4** with 2,5-dimethoxytetrahydrofuran gave the pyrrolyltriazole **31** (87%), which on FVP at 750 °C (10^{-2} Torr) gave a mixture of the [1,3]thiazolo[3,2-*b*][1,2,4]triazole **19** (15%) and pyrrole, which were separated by chromatography. Since the yield of product was much lower than that obtained from the pyrolysis of **11** and a chromatographic separation was required, this strategy was not pursued further.

Finally, in an attempt to induce cyclisation without an initial sigmatropic shift, the benzyl compounds **32** and **33** were synthesised by standard methods and subjected to FVP, but no cyclisation products were obtained (see Experimental section).

Although many spectroscopic studies of the [1,3]thiazolo-[3,2-*b*][1,2,4]triazole system have been carried out, no systematic study of their ^{13}C NMR spectra has been reported.[4] The parent compound of the system **25** apparently shows only three signals in the proton decoupled spectrum, at δ_C 156.34, 119.86 and 113.85. However, a ^{1}H coupled spectrum revealed the bridgehead quaternary signal (C-3a), also at δ_C 156.34, and the following coupling constants: C-2, $^1J_{CH}$ 208.7; C-5, $^1J_{CH}$ 195.2, $^2J_{CH}$ 10.2; C-6 $^1J_{CH}$ 198.2, $^2J_{CH}$ 7.2 Hz. The 2-methyl compound **19** shows 4 signals due to the ring carbon atoms, quaternaries at δ_C 166.52 (C-2) and 156.84 (C-3a) and methine resonances at δ_C 119.66 and 112.14. Because methyl substitution at an adjacent position is likely to cause a high frequency shift of that signal (*cf.* data for thiazoles[11,12]) comparison of the spectra of **19**, **24** and **26** allow the assignment of the resonances of C5 (δ_C 112–114) and C6 (δ_C 119–120) in compounds **19** and **24**. Further assignments are given in the Experimental section.

In conclusion we have shown that an unusual pyrolysis sequence has provided a short route to the [1,3]thiazolo[3,2-*b*]-[1,2,4]triazole ring system in moderate overall yield. The carbon atoms in the fused triazole and thiazole rings are derived initially from a 4-aminotriazole-3-thione unit and an allyl group respectively. The sequence is compatible with substituents at all three possible positions on the rings and complements traditional condensation routes from triazoles to the [1,3]thiazolo[3,2-*b*][1,2,4]triazole system.[4]

Experimental

Unless otherwise stated ^{1}H and ^{13}C NMR spectra were recorded in [^{2}H]chloroform at 250 (or 200) and 63 (or 50) MHz respectively and mass spectra were recorded under electron impact (EI) conditions. Coupling constants are quoted in Hz. Dry-flash chromatography was carried out on silica gel (GF_{254}) using a hexane–ethyl acetate gradient as eluent.

4-Amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 3

Treatment of thiocarbohydrazide (5.3 g, 0.05 mol) with refluxing formic acid (10 cm^3)[5] gave the parent triazole **3** (3.2 g, 55%) mp 166–167 °C (lit.,[5] 166–167 °C); δ_H ([^{2}H]$_6$DMSO) 13.51 (1H, s), 8.41 (1H, s) and 5.62 (2H, s).

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 4

Prepared from thiocarbohydrazide (5.3 g, 0.05 mol) and acetic acid (15 cm^3) by the standard method[6] the product **4** was obtained as white crystals (6.31 g, 97%) mp 203–204 °C (lit.,[6] 205–206 °C); δ_H ([^{2}H]$_6$DMSO) 13.40 (1H, s), 5.50 (2H, s) and 2.22 (3H, s).

4-Amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 5

This compound was made by treatment of benzoic acid hydrazide (1.0 g, 7.4 mmol) with carbon disulfide (0.84 g, 0.011 mol) under basic conditions in ethanol followed by reaction with aqueous hydrazine hydrate (0.38 g, 0.012 mol).[7] The triazole **5** so obtained (0.49 g, 35%) had mp 204–206 °C (lit.,[6] 204–206 °C); δ_H ([^{2}H]$_6$DMSO) 7.60 (5H, m) and 5.83 (2H, s); *m*/*z* 192 (M$^+$, 100%) and 104 (45).

Allylation of 4-amino-3*H*-1,2,4-triazole-3-thione derivatives

The appropriate 1,2,4-triazole **3–5** (8 mmol) was added to *N*,*N*-dimethylformamide (50 cm^3) containing potassium carbonate (1.0 g, 8 mmol). The appropriate allyl halide **6–9** (8 mmol) was added dropwise with stirring, then the mixture was stirred at room temperature for 21–48 hours. The inorganic salts were removed by filtration, the filtrate was concentrated *in vacuo*, dichloromethane (20 cm^3) was added and the mixture was filtered once more. The product was obtained on removal of the solvent. The following preparations were carried out by this method:

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **4** (1.04 g, 8 mmol) and allyl bromide **6** (0.96 g, 8 mmol) gave, after 48 h, *4-amino-3-allylthio-5-methyl-4H-1,2,4-triazole* **11** as a pale pink solid (1.1 g, 81%), mp 77–80 °C (from toluene) [Found, MH$^+$ (FAB) 171.0710. $C_6H_{11}N_4S$ requires *MH* 171.0704]; δ_H 5.91 (1H, m), 5.15 (2H, m), 4.83 (2H, s), 3.68 (2H, m) and 2.37 (3H, s); δ_C 153.48 (quat), 150.31 (quat), 132.62 (CH), 118.80 (CH_2), 36.04 (CH_2) and 10.23 (CH_3); *m*/*z* (FAB) 171 (MH$^+$, 100%).

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **4** (1.04 g, 8 mmol) and 2-methylprop-2-enyl chloride **7** (0.72 g, 8 mmol) gave, after 21 h, *4-amino-3-(2-methylprop-2-enyl)thio-5-methyl-4H-1,2,4-triazole* **12** as a white solid, (0.6 g, 81%), mp 102–103 °C (from toluene) (Found, M$^+$ 184.0782. $C_7H_{12}N_4S$ requires *M* 184.0783); δ_H 4.86 (1H, m), 4.82 (1H, m), 4.64 (2H, s), 3.71 (2H, s), 2.39 (3H, s) and 1.86 (3H, m); δ_C 153.42 (quat), 150.62 (quat), 140.36 (quat), 115.03 (CH_2), 40.77 (CH_2), 20.99 (CH_3) and 10.24 (CH_3); *m*/*z* 184 (M$^+$, 55%), 169 (68), 130 (31), 102 (66) and 70 (100).

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **4** (1.04 g, 8 mmol) and but-2-enyl chloride **8** (0.72 g, 8 mmol) gave, after 21 h, a 6 : 1 mixture of *E* and *Z* isomers, from which *4-amino-3-(but-2-enylthio)-5-methyl-4H-1,2,4-triazole* **13** was obtained as a white solid after recrystallisation from toluene, (0.26 g, 50%) mp 105–107 °C (from toluene) (Found, C, 43.6; H, 6.3; N, 28.75. $C_7H_{12}N_4S\cdot0.5H_2O$ requires C, 43.5; H, 6.2; N, 29.0%. Found, M$^+$,184.0790. $C_7H_{12}N_4S$ requires *M* 184.0783); δ_H 5.55 (1H, m), 5.50 (1H, m), 4.82 (2H, s), 3.60 (2H, m), 2.33 (3H, s) and 1.58 (3H, d, *J* 4.8); δ_C 153.28 (quat), 150.57 (quat), 130.50 (CH), 125.13 (CH), 35.65 (CH_2), 17.56 (CH_3) and 10.15 (CH_3); *m*/*z* 184 (M$^+$, 19%), 169 (74), 143 (49), 130 (71) and 55 (100).

The corresponding reaction of 4-amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **4** (1.04 g, 8 mmol) and 3-chlorobut-1-ene **9** (0.72 g, 8 mmol) gave, after 21 h, a 13 : 1 mixture of the *E* and *Z* isomers of **13**, whose spectra were identical with those reported above.

4-Amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **5** (1.54 g, 8 mmol) and allyl bromide **6** (0.96 g, 8 mmol) gave, after 48 h, *4-amino-3-allylthio-5-phenyl-4H-1,2,4-triazole* **15** as a white solid, (0.74 g, 64%), mp 132–134 °C (from toluene) (Found, C, 55.75; H, 5.2; N, 23.3. $C_{11}H_{12}N_4S\cdot0.25H_2O$ requires C, 55.8; H, 5.3; N, 23.7%); δ_H 8.00 (2H, m), 7.44 (3H, m), 5.99 (1H, m), 5.19 (2H, m), 4.82 (2H, s) and 3.81 (2H, m); δ_C 154.04 (quat), 152.06 (quat), 132.61 (CH) 129.93 (CH), 128.44

(CH), 127.99 (CH), 126.32 (quat), 119.12 (CH_2) and 36.10 (CH_2); *m/z* 232 (M^+, 39%), 217 (36), 129 (47), 103 (80) and 41 (100).

4-Amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **5** (1.54 g, 8 mmol) and 2-methylprop-2-enyl chloride **7** (0.72 g, 8 mmol) gave, after 48 h, *4-amino-3-(2-methylprop-2-enyl)thio-5-phenyl-4H-1,2,4-triazole* **16** as a white solid, (0.66 g, 54%), mp 130–132 °C (from toluene) (Found, C, 58.3; H, 5.85; N, 22.5. $C_{12}H_{14}N_4S$ requires C, 58.5; H, 5.7; N, 22.8%); δ_H 8.00 (2H, m), 7.40 (3H, m), 4.92 (2H, m), 4.84 (2H, m), 3.78 (2H, s) and 1.87 (3H, s); δ_C 153.97 (quat), 152.44 (quat), 140.23 (quat), 129.94 (CH), 128.41 (CH), 128.00 (CH), 126.23 (quat), 115.23 (CH_2), 40.62 (CH_2) and 21.03 (CH_3); *m/z* 246 (M^+, 88%), 201 (52), 143 (30), 103 (56) and 70 (100).

4-Amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **5** (1.54 g, 8 mmol) and but-2-enyl chloride **8** (0.72 g, 8 mmol) gave, after 48 h, *4-amino-3-(but-2-enylthio)-5-phenyl-4H-1,2,4-triazole* **17** as a gummy yellow solid, which was recrystallised from toluene to give the product as pale yellow crystals (0.64 g, 33%), mp 145–147 °C (from toluene) [Found, MH^+ (FAB) 247.1016. $C_{12}H_{15}N_4S$ requires MH^+ 247.1017]; δ_H 7.99 (2H, m), 7.44 (3H, m), 5.66 (1H, m), 5.63 (1H, m), 4.78 (2H, s), 3.76 (2H, m) and 1.65 (3H, d, *J* 4.8); δ_C 153.94 (quat), 152.29 (quat), 130.89 (CH), 129.91 (CH), 128.43 (CH), 127.98 (CH), 126.36 (quat), 125.08 (CH), 35.78 (CH_2) and 17.67 (CH_3); *m/z* (FAB) 247 (MH^+, 100%).

A modified procedure was adopted for the preparation of the 5-unsubstituted derivative **10**. A solution of 4-amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **3** (0.25 g, 2.1 mmol) and allyl bromide **6** (0.23 g, 2.1 mmol) in acetonitrile (10 cm^3) containing anhydrous potassium carbonate (0.40 g, 2.5 mmol) was stirred at room temperature for 21 h. The inorganic salts were removed by filtration, the filtrate was concentrated *in vacuo* at room temperature or below, ethanol (10 cm^3) was added and the mixture was filtered once more. On removal of the solvent *4-amino-3-allylthio-4H-1,2,4-triazole* **10** (0.26 g, 79%), was obtained mp 83–85 °C (from ethanol) (Found, C, 37.9; H, 4.65; N, 34.8. $C_5H_8N_4S \cdot 0.2\ H_2O$ requires C, 37.6; H, 5.3; N, 35.1%. Found, M^+,156.0469. $C_5H_8N_4S$ requires *M* 156.0470); δ_H ([^{2}H]$_6$DMSO) 8.46 (1H, s), 6.08 (2H, s), 5.95 (1H, m), 5.24 (1H, m), 5.07 (1H, m) and 3.77 (2H, m); δ_C 150.40 (quat), 146.39 (CH), 133.72 (CH), 118.44 (CH_2) and 34.15 (CH_2); *m/z* 156 (M^+, 37%), 141 (25), 129 (20) 56 (80) and 41 (100).

Flash vacuum pyrolysis of 4-amino-3-allylthio-4*H*-1,2,4-triazoles 10–13 and 15–17

The aminotriazoles **10–13** and **15–17** were distilled at a pressure of *ca.* 1 × 10^{-2} Torr into an empty silica furnace tube which was maintained at the stated temperature by an electrically heated furnace. The products were trapped in a U-tube cooled with liquid nitrogen, and were washed from the trap with solvent at the end of the pyrolysis.

When 4-amino-3-allylthio-5-methyl-4*H*-1,2,4-triazole **11** (0.30 g, 1.8 mmol) was sublimed at 120 °C over a period of 1.5 h into the furnace tube at a temperature of 650 °C a mixture of products was obtained, which was separated by dry flash chromatography (silica), hexane–ethyl acetate (6 : 1), to give *2-allyl-4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione* **18** as a pale yellow liquid, (0.10 g, 33%) (Found, M^+ 170.0623. $C_6H_{10}N_4S$ requires *M* 170.0626); δ_H 5.85 (1H, m), 5.28 (2H, m), 4.72 (2H, m), 4.65 (2H, s) and 2.37 (3H, s); δ_C 165.99 (quat), 148.66 (quat), 130.53 (CH), 119.23 (CH_2), 51.55 (CH_2) and 10.37 (CH_3); *m/z* 170 (M^+, 80%), 155 (64), 102 (45), 74 (42) and 56 (100).

The triazole **11** (0.30 g, 1.8 mmol) was pyrolysed using the same conditions as above, but at a furnace temperature of 850 °C. The pyrolysate was distilled to give 2-methyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole[9] **19** as a golden liquid (0.14 g, 54%), bp 120 °C (2.5 Torr) (mp lit.,[9] 49.5–51 °C); δ_H 7.69 (1H, d, ^3J 4.5), 6.91 (1H, d, ^3J 4.5) and 2.50 (3H, s); δ_C 166.52 (quat), 156.84 (quat), 119.66 (CH), 112.14 (CH) and 14.79 (CH_3); *m/z* 139 (M^+, 100%), 98 (73), 71 (51) and 58 (57).

The triazole **10** (0.14 g, 1.0 mmol) was pyrolysed at 850 °C (0.01 Torr) (inlet temperature 120 °C). The pyrolysate was distilled to give [1,3]thiazolo[3,2-*b*][1,2,4]triazole[13] **25** as a pale yellow solid, (0.055 g, 55%), bp 50–55 °C (4 Torr) mp 96–98 °C (lit.,[13] 98–100 °C); δ_H 8.15 (1H, d, ^6J 1.4), 7.81 (1H, d, ^3J 4.4) and 6.91 (1H, dd, ^3J 4.4 and ^6J 1.4); δ_C 156.34 (CH and quat), 119.86 (CH) and 113.85 (CH); *m/z* 125 (M^+, 100%), 98 (49), 71 (53) and 45 (65).

4-Amino-3-(2-methylprop-2-enyl)thio-5-methyl-4*H*-1,2,4-triazole **12** (0.20 g, 1.1 mmol) was pyrolysed at an inlet temperature of 130 °C and furnace temperature of 850 °C over a period of 1 h. The pyrolysate was collected in DCM, and distilled to give *2,5-dimethyl[1,3]thiazolo[3,2-b][1,2,4]triazole* **24** as a pale yellow liquid (0.08 g, 48%), bp 85 °C (2 Torr) (Found, M^+ 153.0363. $C_6H_7N_3S$ requires *M* 153.0361); δ_H 7.41 (1H, q, ^4J 1.4), 2.48 (3H, s) and 2.45 (3H, d, ^4J 1.4); δ_C 165.13 (quat), 156.00 (quat), 126.40 (quat), 116.34 (CH), 14.68 (CH_3) and 13.94 (CH_3); *m/z* 153 (M^+, 100%), 112 (58) and 59 (95).

4-Amino-3-(but-2-enylthio)-5-methyl-4*H*-1,2,4-triazole **13** (0.20 g, 1.1 mmol) was pyrolysed at an inlet temperature of 135 °C and a furnace temperature of 850 °C over a period of 0.5 h. The pyrolysate was collected in DCM, and distilled to give 2,6-dimethyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole[14,15] **26** as a pale yellow liquid (0.09 g, 54%), bp 90 °C (2 Torr) [lit.,[14] 112–114 °C (5 Torr); mp[14] 62–64 °C] (Found, M^+ 153.0355. $C_6H_7N_3S$ requires *M* 153.0361); δ_H 6.50 (1H, q, ^4J 1.3), 2.53 (3H, s) and 2.50 (3H, d, ^4J 1.3); δ_C (quaternaries not reported) 106.11 (CH), 14.77 (CH_3) and 12.32 (CH_3); *m/z* 153 (M^+, 100%), 112 (48), 67 (98) and 42 (69).

4-Amino-3-allylthio-5-phenyl-4*H*-1,2,4-triazole **15** (0.10 g, 0.4 mmol) was pyrolysed at an inlet temperature of 135 °C and a furnace temperature of 850 °C over a period of 1 h. The pyrolysate was collected in DCM, and distilled to give 2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole[9] **27** as a pale yellow liquid (0.02 g, 23%), bp 75 °C (0.7 Torr) which crystallised, mp 114–116 °C (lit.,[9] 118–119 °C) (Found M^+ 201.0360. $C_{10}H_7N_3S$ requires *M* 201.0361); δ_H 8.15 (2H, m), 7.81 (1H, d, *J* 4.5), 7.44 (3H, m) and 6.99 (1H, d, *J* 4.5); δ_C 167.35 (quat), 157.40 (quat), 130.92 (quat), 129.66 (CH), 128.60 (CH), 126.53 (CH), 119.92 (CH) and 112.95 (CH); *m/z* 201 (M^+, 100%), 116 (26), 103 (41) and 76 (33).

4-Amino-3-(2-methylprop-2-enyl)thio-5-phenyl-4*H*-1,2,4-triazole **16** (0.20 g, 0.8 mmol) was pyrolysed at a furnace temperature of 750 °C with an inlet temperature of 130 °C over a period of 1 h. The pyrolysate was collected in DCM, and distilled to give *5-methyl-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole* **28** as a pale yellow liquid (0.08 g, 48%), bp 85 °C (2 Torr) mp 126–128 °C (Found, M^+ 215.0512. $C_{11}H_9N_3S$ requires *M* 215.0517); δ_H 8.37 (2H, m), 7.77 (1H, q, ^4J 1.4), 7.75 (3H, m) and 2.74 (3H, d, ^4J 1.4); δ_C (quaternary signals not quoted) 129.43 (CH), 128.55 (CH), 126.39 (CH), 116.56 (CH) and 14.10 (CH_3); *m/z* 215 (M^+, 31%), 169 (46), 128 (43), 104 (58), 77 (47) and 55 (100).

4-Amino-3-(but-2-enylthio)-5-phenyl-4*H*-1,2,4-triazole **17** (0.20 g, 0.8 mmol) was pyrolysed at an inlet temperature of 135 °C and a furnace temperature of 750 °C over a period of 0.5 h. The pyrolysate was collected in DCM, and distilled to give 6-methyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole[9,13] **29** as a pale yellow liquid which was contaminated with benzonitrile. Dry-flash chromatography on silica gave **29** (0.09 g, 54%), bp 90 °C (2 Torr) (mp lit.,[9] 125–126 °C) (Found, M^+ 215.0513. $C_{11}H_9N_3S$ requires *M* 215.0517); δ_H 8.16 (2H, m), 7.46 (3H, m), 6.57 (1H, q, ^4J 1.4) and 2.58 (3H, d; ^4J 1.4); δ_C (quaternary signals not reported) 129.56 (CH), 128.56 (CH), 126.56 (CH), 106.98 (CH) and 12.52 (CH_3); *m/z* 215 (M^+, 100%), 144 (25), 103 (50) and 72 (52).

5-Methyl-4-(pyrrol-1-yl)-3-allylthio-4*H*-1,2,4-triazole 31

The aminotriazole 11 (2.55 g, 0.015 mol), 2,5-dimethoxytetrahydrofuran (1.9 cm^3, 0.015 mol) and acetic acid (50 cm^3) were heated under reflux for 30 min. The solvent was removed *in vacuo* to give a dark brown liquid, which solidified overnight to give *5-methyl-4-(pyrrol-1-yl)-3-allylthio-4H-1,2,4-triazole* 31 as a brown solid (2.91 g, 87%), mp 61–62 °C (from hexane) (Found, C, 54.3; H, 5.4; N, 25.25. $C_{10}H_{12}N_4S$ requires C, 54.55; H, 5.45; N, 25.25%); δ_H 6.70 (2H, t, *J* 4.5), 6.33 (2H, t, *J* 4.5), 5.91 (1H, m), 5.14 (2H, m), 3.76 (2H, m) and 2.24 (3H, s); δ_C 152.38 (quat), 151.02 (quat), 132.04 (CH), 120.72 (CH), 119.16 (CH_2), 109.77 (CH), 34.99 (CH) and 9.31 (CH_3); *m/z* 220 (M$^+$, 56%), 173 (97) and 124 (100).

4-Amino-3-benzylthio-5-methyl-4*H*-1,2,4-triazole 32

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione 4 (1.95 g, 0.015 mol) was added to DMF (50 cm^3) containing potassium carbonate (1.88 g, 0.015 mol). Benzyl chloride (1.89 g, 0.015 mol) was added dropwise with stirring then the mixture was stirred at room temperature for 21 h. The insoluble potassium carbonate was removed by filtration, then the filtrate concentrated *in vacuo* to give a pink solid. The solid was treated with dichloromethane (20 cm^3), the mixture filtered once more and the solvent was removed *in vacuo* to give *4-amino-3-benzylthio-5-methyl-4H-1,2,4-triazole* 32 as an orange–brown solid (0.65 g, 20%), mp 149–150 °C (from toluene) (Found, M$^+$ 220.0785. $C_{10}H_{12}N_4S$ requires *M* 220.0783); δ_H 7.25 (5H, m), 4.20 (2H, s), 3.93 (2H, s) and 2.33 (3H, s); δ_C 153.58 (quat), 149.48 (quat), 137.27 (quat), 128.71 (CH), 128.67 (CH), 127.89 (CH), 38.97 (CH_2) and 10.32 (CH_3); *m/z* 220 (M$^+$, 21%), 106 (45) and 91 (100).

3-Benzylthio-5-methyl-4-(pyrrol-1-yl)-4*H*-1,2,4-triazole 33

4-Amino-3-benzylthio-5-methyl-4*H*-1,2,4-triazole 32 (0.16 g, 0.7 mmol), 2,5-dimethoxytetrahydrofuran (0.09 g, 0.7 mmol) and acetic acid (30 cm^3) were heated under reflux for 30 minutes. The solvent was removed *in vacuo* to give a brown oil, which was treated with water, then extracted with DCM (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), and concentrated to give a brown oil. The oil was distilled to give pure *3-benzylthio-5-methyl-4-(pyrrol-1-yl)-4H-1,2,4-triazole* 33 as a pale yellow oil (0.14 g, 75%), bp 160 °C (0.5 Torr) (Found, M$^+$ 270.0933. $C_{14}H_{14}N_4S$ requires *M* 270.0939); δ_H 7.25 (5H, m), 6.47 (2H, t, *J* 4.5), 6.57 (2H, t, *J* 4.5), 4.33 (2H, s) and 2.20 (3H, s); δ_C 152.31 (quat), 151.09 (quat), 135.86 (quat), 128.88 (CH), 128.43 (CH), 127.63 (CH), 120.56 (CH), 109.57 (CH), 36.92 (CH_2) and 9.13 (CH_3); *m/z* 270 (M$^+$, 11%), 156 (33) and 91 (100).

Flash vacuum pyrolysis of the 1,2,4-triazoles 31–33

The triazole 31 (0.20 g, 1 mmol) was sublimed at 160 °C (0.05 Torr) into the furnace tube which was maintained at a temperature of of 750 °C. The pyrolysate was dissolved in dichloromethane and subjected to dry-flash chromatography on silica (3 : 1 hexane–ethyl acetate) to give 2-methyl[1,3]thiazolo[3,2-*b*]-[1,2,4]triazole[9] 19 (0.02 g, 15%) whose spectra were compatible with those reported above.

Pyrolysis of 32 or 33 (inlet temperatures 180 °C) at 650–750 °C (0.004–0.008 Torr) gave complex pyrolysates from which the presence of bibenzyl could be inferred from their ^{1}H NMR spectra (δ_H 2.85). No cyclisation products could be detected.

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