NEW CYCLISATION REACTIONS OF 3-AMINOPYRAZOLE DERIVATIVES

by

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DECLARATION

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

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. Hamish McNab, since October 1st, 1989, the date of my admission as a research student.

DEDICATION

This thesis is dedicated to my family, and to the memory of Dr. B.C. Uff, late of Loughborough University.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. Hamish McNab for his encouragement, advice, and enthusiasm over the last three years.

I would also like to thank Dr. David Clarke of Kodak for his help during my three months industrial placement at Kodak Ltd and for his advice during the past three years.

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LECTURE COURSES

The following lecture courses were attended during the period of research:-

Organic Research Seminars and Colloquia, Edinburgh University Department of Chemistry (3 years attendance).

Current Developments in Organic Chemistry - Professor R. Ramage *et al.* (1 year attendance).

Aspects and Applications of NMR Spectroscopy - Dr. I.H. Sadler, Dr. D. Reed, and Dr. J. Parkinson (5 lectures).

Strategy of Synthesis - Dr. I. Gosney (5 lectures).

Pesticides - Dr. H. McNab (5 lectures).

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Postgraduate Symposia (3 years attendance)

Autumn Meetings (3 years attendance)

Joint Meeting with Società Chimica Italiana, Sciacca, 1992.

Recent Advances in the Synthesis and Activity of Agrochemicals - Schering Agrochemicals (5 lectures).

Discovery, Development and Pharmacology of Zoladex for Treatment of Prostate Cancer - I.C.I. Pharmaceuticals (5 lectures).

Medicinal Chemistry - Merck, Sharpe and Dohme (2 years attendance).

ABSTRACT

Three synthetic routes to cyclised pyrazole derivatives were investigated:- The first route was based on the chemistry of 2,3-diaminopyrazoles. Reactions with various electrophiles were carried out and some cyclised products were obtained. An important reaction with carbon disulphide was carried out and this resulted in the formation of the photographically important pyrazolo[1,5-*b*]1,2,4-triazole ring system.

The second route explored the chemistry of 3-acetamidopyrazoles. Monoacylation of 3-aminopyrazoles was found to give a mixture of 1- and 2-acylated aminopyrazoles. The mixture surprisingly underwent a solid state rearrangement to the required 3-acetamidopyrazole derivative over a period of a few days. The mechanism and kinetics of this reaction were investigated by solid state and traditional NMR methods.

The third route involved the preparation and pyrolysis of pyrazol-3-yl-1,2,3-triazoles to give carbene intermediates which could cyclise. These carbenes were found to undergo a rearrangement to give the pyrazolo[1,5-*b*]pyrimidin-7-one ring system. The mechanism of this reaction was extensively investigated by isotopic labelling methods.

CONTENTS

		Page No.
	INTRODUCTION	1
A.	**THE PHOTOGRAPHIC PROCESS**	1
B.	**IMIDAZO[1,2-*b*]PYRAZOLES**	8
1.	**Synthesis of Imidazo[1,2-*b*]pyrazoles**	8
(i)	Two Ring Synthesis of Imidazo[1,2-*b*]pyrazoles	8
(ii)	Imidazo[1,2-*b*]pyrazoles Derived From 3-Aminopyrazoles	14
(iii)	Rearrangement of 1-Oxo-3,4,8-triaza-2,4,6,7-octatetraenes to Imidazo[1,2-*b*]pyrazoles	17
2.	**Physical Properties of Imidazo[1,2-*b*]pyrazoles**	19
(i)	Infrared	19
(ii)	Ultraviolet	19
(iii)	^{1}H NMR	19
(iv)	^{13}C NMR	21
3.	**Chemical Reactions of Imidazo[1,2-*b*]pyrazoles**	22
(i)	Electrophiles	22
(ii)	Nucleophilic Reactions	26
(iii)	Oxidative Coupling Reactions	26

		Page No.
C.	**PYRAZOLO[5,1-*c*]1,2,4-TRIAZOLES**	**27**
1.	**Synthesis of Pyrazolo[5,1-*c*]1,2,4-triazoles**	**28**
(i)	Pyrazolo[5,1-*c*]1,2,4-triazoles Derived From Pyrazoledianium Salts	**28**
(II)	Pyrazolo[5,1-*c*]1,2,4-triazoles From Aminoazoles	**32**
(iii)	Pyrazolo[5,1-*c*]1,2,4-triazoles From Hydrazines	**34**
(iv)	Pyrazolo[5,1-*c*]1,2,4-triazoles *via* Ring Contractions	**36**
2.	**Physical Properties of Pyrazolo[5,1-*c*]1,2,4-triazoles**	**41**
(i)	Infrared	**41**
(ii)	Ultraviolet	**41**
(iii)	^{1}H NMR	**41**
(iv)	^{13}C NMR	**42**
3.	**Chemistry of Pyrazolo[5,1-*c*]1,2,4-triazoles**	**43**
(i)	Electrophiles	**43**
(ii)	Nucleophiles	**44**
(iii)	Oxidative Coupling Reactions	**45**
D.	**PYRAZOLO[1,5-*b*]1,2,4-TRIAZOLES**	**46**
1.	**Synthesis of Pyrazolo[1,5-*b*]1,2,4-Triazoles**	**47**
(i)	Pyrazolo[1,5-*b*]1,2,4-triazoles From 1,2,4-Triazoles	**47**
(ii)	Pyrazolo[1,5-*b*]1,2,4-triazoles From 3-Aminopyrazoles	**48**
(iii)	Pyrazolo[1,5-*b*]1,2,4-triazoles From 3,4-Diaminopyrazoles	**51**

		Page No.
2.	**Physical Properties of Pyrazolo[1,5-*b*]1,2,4-triazoles**	**51**
(i)	^{1}H NMR	**51**
3.	**Chemical Properties of Pyrazolo[1,5-*b*]1,2,4-triazoles**	**52**
(i)	Electrophiles	**52**
(ii)	Nucleophiles	**53**
(iii)	Oxidative Coupling Reactions	**53**
E.	**PHOTOGRAPHIC APPLICATIONS OF AZAPENTALENE DYES**	**54**
1.	**Effect of Functional Groups**	**56**
	DISCUSSION	**59**
A.	**SYNTHESIS AND CHEMISTRY OF 2,3-DIAMINOPYRAZOLES**	**59**
1.	**Preamble**	**59**
2.	***N*-Amination Reactions of Pyrazoles**	**60**
3.	**Synthesis of 2,3-Diaminopyrazoles**	**63**
4.	**Cyclisation Reactions of 2,3-Diaminopyrazoles**	**75**
5.	**Attempted Amination of Protected 3-Aminopyrazoles**	**90**
B.	**ACYLATION REACTIONS OF AMINOPYRAZOLES**	**93**
1.	**Solid State Reactions**	**97**
2.	**Preparation of Intermediates for Cyclisation Studies**	**113**

		Page No.
C.	SYNTHESIS AND PYROLYSIS OF PYRAZOL-3-YL-1,2,3-TRIAZOLES	118
1.	Cyclisation of Nitrenes	118
2.	Cyclisation of Carbenes	119
3.	Flash Vacuum Pyrolysis	120
	EXPERIMENTAL	146
	ABBREVIATIONS	146
	INSTRUMENTATION AND GENERAL TECHNIQUES	147
	SYNTHESIS AND CHEMISTRY OF 2,3-DIAMINOPYRAZOLES	151
	Preparation of Aminopyrazoles	151
	N-Amination of 3-Aminopyrazoles	152
	Reactions of 2,3-Diaminopyrazoles:-	153
(i)	With Butanedione	153
(ii)	With Benzil	154
(iii)	With Dimethylformamide Dimethyl Acetal	154
(iv)	With Benzaldehyde	155
(v)	With Triethyl Orthoformate	155
(vi)	With Acetic Anhydride	156
(viii)	With 5-Methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione	156

		Page No.
	Cyclisation Reactions of 2,3-Diaminopyrazoles:-	**157**
(I)	With Pyruvates	**157**
(ii)	With β-Ketoesters	**158**
(iii)	With Diethylmalonate	**160**
(iv)	With Acetylacetone	**160**
(v)	With Dimethyl Carbonate	**161**
(vi)	With Carbon Disulphide	**162**
	Synthesis of Protected 3-Aminopyrazoles	**163**
(i)	Synthesis and Reaction of Imines	**163**
(ii)	Trialkyl Oxonium Tetrafluoroborates	**165**
(iii)	Reaction of Trialkyl Oxonium Salts with Dimethylformamide	**165**
(iv)	Amidines	**166**
(v)	Reaction of Amidines with Hydroxylamine-*O*-sulphonic Acid	**167**
	ACYLATION REACTIONS OF AMINOPYRAZOLES	**168**
	Substituted Acetyl Chlorides	**168**
	Mono Acylation Reactions : A General Method	**168**
	Solid State NMR Methods	**170**
	1-Chloroacetyl-3-aminopyrazole	**170**
	Di-acyl Derivatives	**171**
	Reactions of Mono Acyl Pyrazoles	**173**
(i)	With Sodium Hydride	**173**
(ii)	With Trimethyl Oxonium Tetrafluoroborate	**173**
	Acylmorpholines	**173**
(i)	Reactions with Trimethyl Oxonium Tetrafluoroborate	**174**

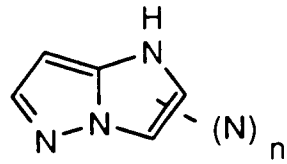
		Page No.
	SYNTHESIS AND PYROLYSIS OF PYRAZOL-3-YL-1,2,3-TRIAZOLES	**176**
	3-Amino-5-methyl-2-phenylpyrazole	**176**
	3-Azido-5-methyl-2-phenylpyrazole	**176**
(i)	Pyrolysis of 3-Azido-5-methyl-2-phenylpyrazoles	**177**
	Preparation of Azides : A General Method	**177**
(i)	Reaction of Azides with Methyl Propiolate	**178**
(ii)	Reaction of Azides with Dimethyl Acetylene Dicarboxylate	**180**
(iii)	Reaction of Azides with Other Acetylenes	**181**
	***N,N*-Dimethylchloromethylene Ammonium Chloride**	**181**
	Ethyl α-Formyldiazoacetate	**182**
	Reactions of Ethyl α-Formyldiazoacetate	**183**
(i)	With Aniline	**183**
(ii)	With 3-Amino-5-t-butylpyrazole	**183**
	Pyrolysis of Pyrazol-3-yl-1,2,3-triazole-4-carboxylates	**184**
	5-[Methylthio(*N*-5-t-butylpyrazol-3-ylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione	**186**
(i)	Pyrolysis Reaction	**186**
	Reactions of 5-Methoxymethylene-2,3-dimethyl-1,3-dioxane-4,6-dione	**186**
(i)	With 3-Amino-5-methylpyrazole	**186**
(ii)	With 3-Aminopyrazole	**187**
(iii)	With 3-Amino-1,2,4-triazole	**187**
(iv)	Pyrolysis Reactions	**188**

	Page No.
^{13}C Isotopic Labelling Experiment	189
REFERENCES	190

INTRODUCTION

PREAMBLE

This thesis is concerned with the exploration of potential new routes to the azapentalene ring systems **1**.



1

Compounds of this type have important applications in colour photography as magenta couplers.[1] In this introduction this aspect of the photographic process will be considered, followed by a detailed survey of the syntheses, physical and chemical properties of the ring systems.

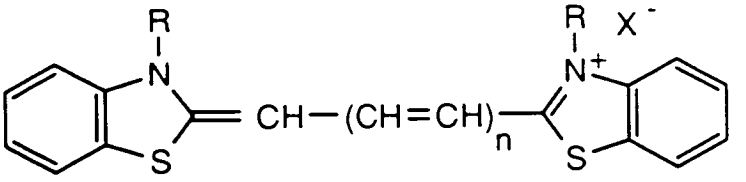
A. THE PHOTOGRAPHIC PROCESS

The majority of photographic processes are based on the use of silver halides[2,3] - usually silver bromide is employed.

The silver halides are present, as small crystals, in layers of gelatin. This gelatin/halide mixture is referred to as the photographic emulsion. Normally the gelatin is hardened using crosslinkers such as oxiranes.[2,3] This is necessary to make the coated layer more resistant to abrasions and possible damage from hot developing solutions.

The silver halides are either colourless or yellow and this makes them only sensitive towards blue or violet light. To overcome this classes of dyes known as sensitizers have been developed. These dyes extend the sensitivity range of silver halides throughout the visible spectrum. The best known examples are the cyanines and related merocyanines. The cyanines

are mono-acid salts in which two nitrogen containing heterocycles are linked by a conjugated, odd numbered carbon chain. Typical examples, **2 a-c**, are shown below.



2 **a** n = 0 yellow

b n = 1 magenta

c n = 2 cyan

Various other heterocycles such as benzoselenazole, quinoline and *N*-ethylbenzimidazole can also be used.

Modern colour photography incorporates all the above features but also requires the presence of colour forming dyes.[1,2,3] Three different colours are employed, these are yellow (blue absorbing), magenta (green absorbing), and cyan (red absorbing). Combinations of these dyes will give various colours: for example a 1:1 mixture of cyan plus magenta will give blue, and varying the proportions of the two will vary the colour obtained. Similarly cyan plus yellow gives green and yellow plus magenta gives red. Usually colour photographic materials are prepared by coating three sensitized silver halide layers on to a suitable base such as film or paper (Fig. 1).

Representation of a cross section of a colour photographic coating.

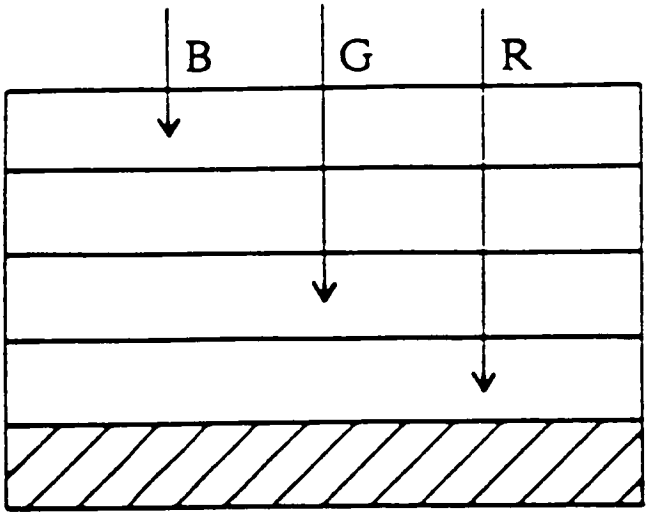


Figure 1

The yellow filter serves to screen out blue light which could otherwise affect the underlying green and red sensitive layers. When the film is developed the filter layer is bleached.

In the development process the exposed silver halide oxidises a reagent, the colour developer, to give a species which in turn reacts with various other reagents, the colour couplers to produce dyes.

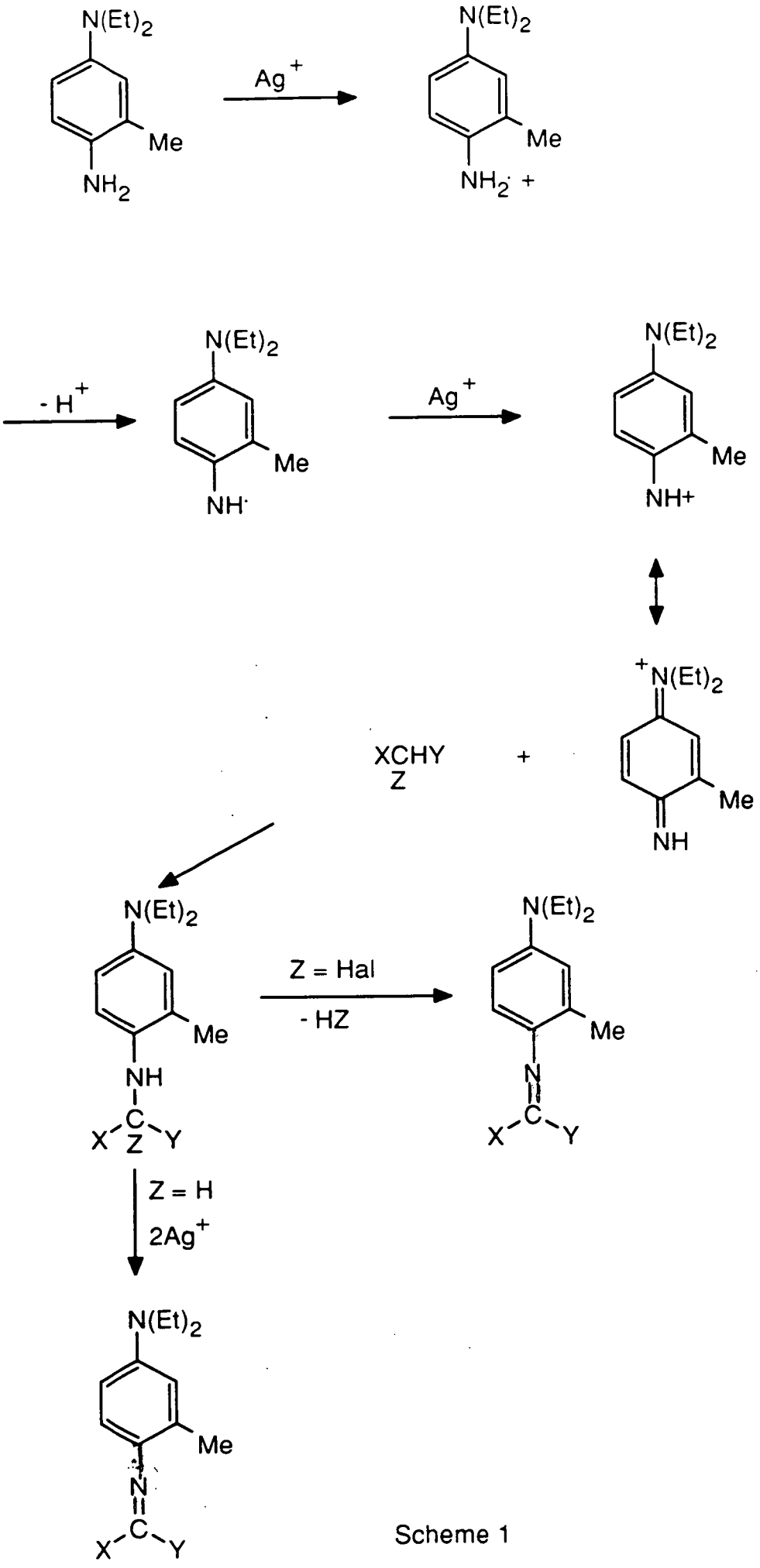
One version of the process requires the use of three different solutions each containing a developer and a coupler. The development sequence is performed in the following order: first the film is treated with a hydroquinone developer which forms silver from the silver halide which was originally exposed. The film is then exposed to red light through the base to yield a latent image where silver halide remains in the red sensitive layer. Processing with developer and coupler gives a cyan dye which is deposited

in the red sensitive layer. The film is then exposed to blue light from above, treatment with developer and a different coupler yields a yellow dye in the blue sensitive layer. Magenta dye is formed in the green layer by treatment with developer, coupler and an agent which renders the remaining silver halide developable. Bleaching of silver to silver bromide and removal of the silver salts by a thiosulphate solution completes the process.

A variation of this process employs three layers as before but this time non-wandering couplers are already incorporated in the film. This means that only one developing solution is required.

The couplers are rendered non-wandering by two methods. The first method involves attaching a long carbon chain or ballast group to the coupling moiety. An acid solubilizing group such as SO_3H is also incorporated, the coupler is then dissolved in alkali and added to its emulsion, interactions with the gelatin hold the coupler firmly in place. The other, more modern, method uses an oil solubilizing group. The coupler is dissolved in a small amount of suitable solvent (e.g. dibutyl phthalate) and is dispersed with the aid of a suitable wetting agent in the appropriate silver halide emulsion. This means the coupler is dispersed oil in water fashion and the final dye will be formed in the oil phase.

Colour developers are based on two species, these are *p*-phenylenediamines and *p*-aminophenols. A typical mechanism of reaction between the developer and the coupler is given below:(Scheme 1).

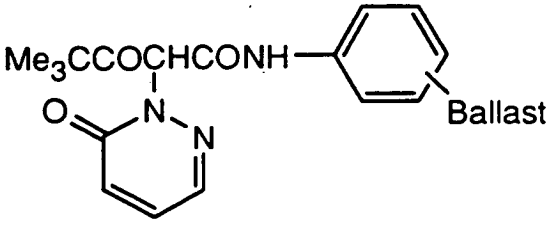


Scheme 1

X and Y are substituents which complete the coupler, and activate the carbon atom to attack by the oxidised developer. Z is a substituent lost during the coupling; it can be either a hydrogen atom or a halogen or another leaving group. The halogen is a more desirable substituent since it requires only *two* equivalents of silver halide to form the dye. When Z=H four equivalents are needed.

Colour couplers are generally small aromatic systems. It is essential they do not absorb visible light until the dye is formed. It is also important they remain in their respective layers; this is achieved, as described previously, by the use of long carbon chain ballast groups.

Yellow couplers are mainly benzoylacetanilides and pivaloyl-acetanilides **3.** The latter forms dyes with better light stability but are formed more slowly.



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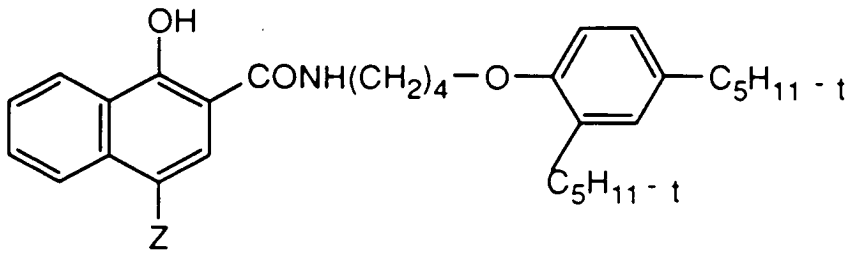
Cyan dyes are obtained from phenols and naphthols. Some of these also contain heterocyclic leaving groups (Z) and this is claimed to improve their performance.[3]

An example is the naphthol derivative **4** below.



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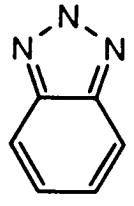
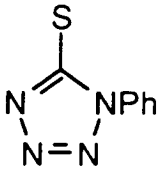
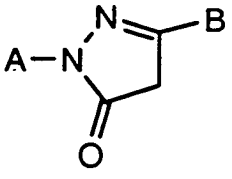
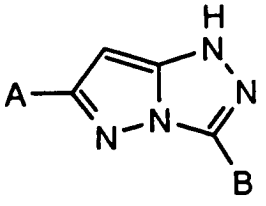
Z=  or 

Traditional magenta dyes are generally derived from 2-pyrazolin-5-ones **5**.



5

This class of magenta couplers have a troublesome secondary blue absorption which limits their effectiveness. To overcome this various azapentalene derivatives such as pyrazolo[5,1-*c*]1,2,4-triazoles, **6**, which give low blue absorption, have been developed.[4]



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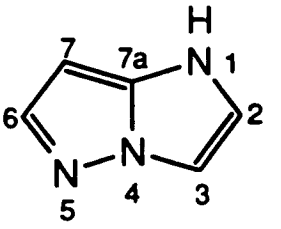
It is the synthesis and chemistry of these compounds and their analogues which form the basis of this introduction.

B. IMIDAZO[1,2-*b*]PYRAZOLES

The synthesis and chemistry of this class of compounds have been the subject of two reviews.[4,5] The parent ring system **7** and its numbering scheme is given below.



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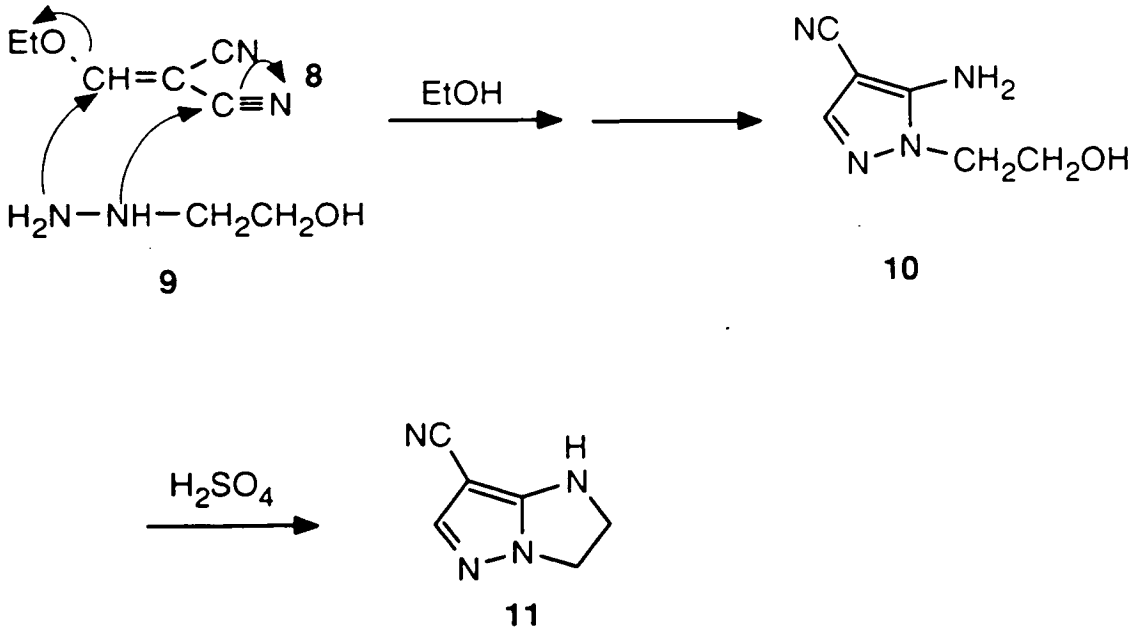
1. Synthesis of Imidazo[1,2-*b*]pyrazoles

Two main synthetic routes have been utilised to obtain imidazo[1,2-*b*]pyrazoles. The first is based on the sequential synthesis of the pyrazole component followed by ring closure to give the final product. The second route involves the use of aminopyrazoles as the starting material. A third route has also been reported and this involves the rearrangement of 1-oxo-3,4,8-triaza-2,4,6,7-octatetraenes.

(i) Two Ring Synthesis of Imidazo[1.2-*b*]pyrazoles

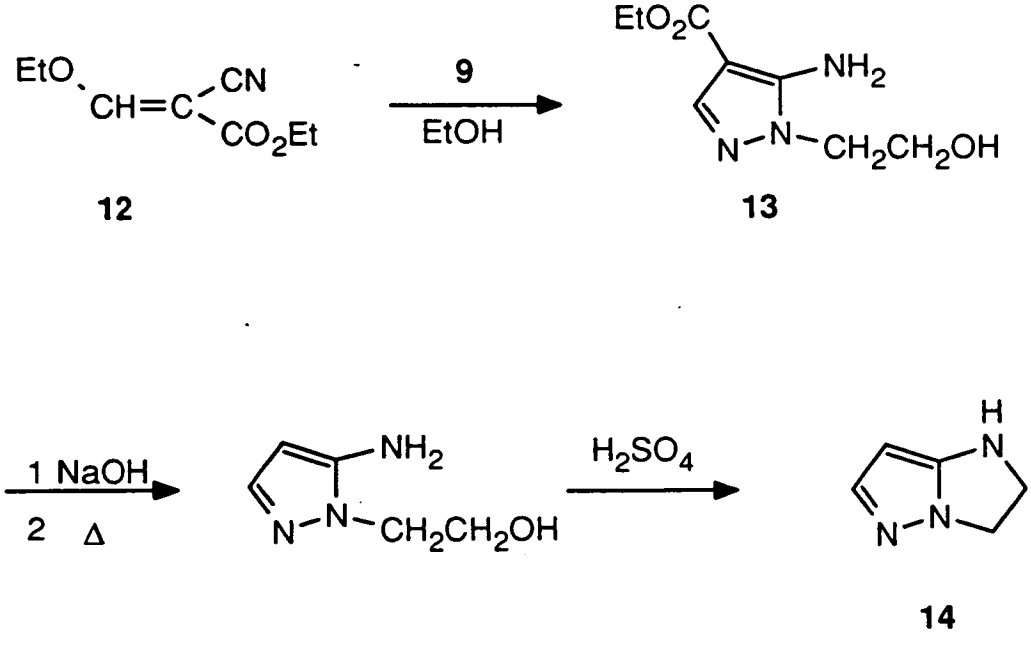
The first synthesis of imidazo[1,2-*b*]pyrazoles, albeit of 2,3-dihydro derivatives, was reported in 1961.[6] This involved the initial formation of the pyrazole ring by way of a substitution/addition reaction between ethoxymethylenemalononitrile **8** and 2-(hydroxyethyl)hydrazine **9**, to give **10**.

Cyclisation of **10** to **11** was achieved using sulphuric acid (Scheme 2).



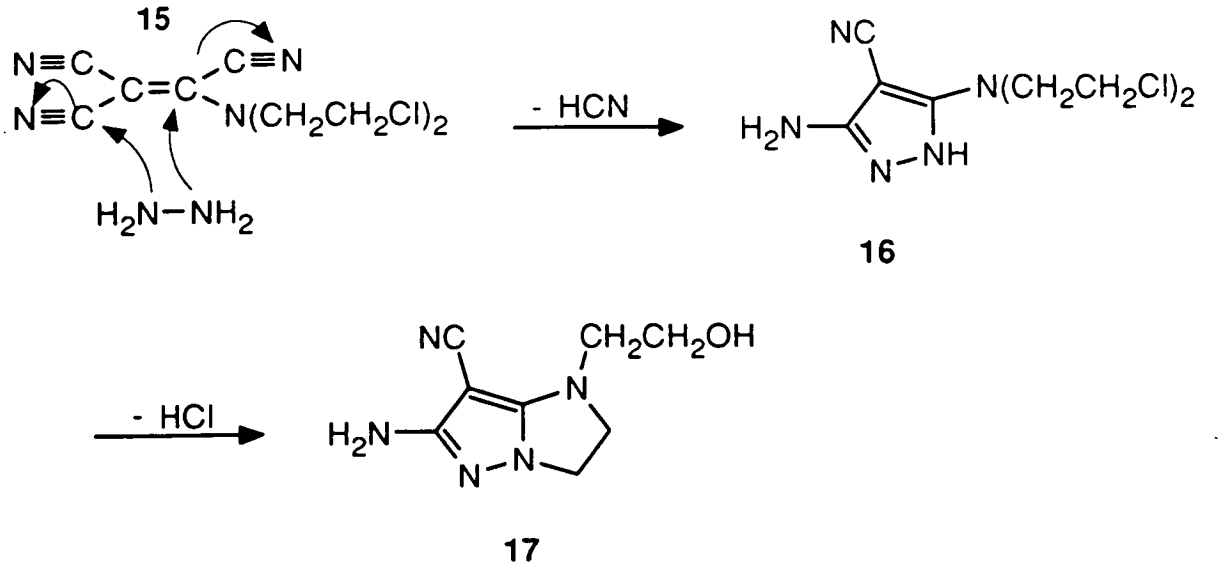
Scheme 2

The parent ring system could be prepared in an analogous fashion[6] starting from **9** and ethoxymethylenecyanacetic acid ethyl ester, **12**. The intermediate pyrazole carboxy ester **13** was first hydrolysed to the acid and subsequently thermally decarboxylated. Cyclisation under acid conditions afforded **14** (Scheme 3).



Scheme 3

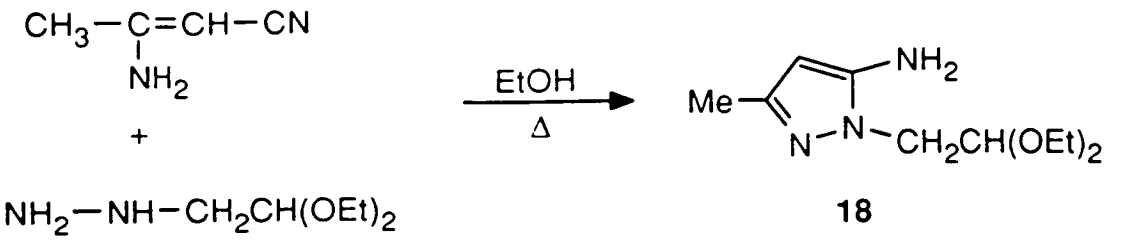
In a similar reaction Schulze *et al.*[7] reacted bis-(2-chloroethyl)-tricyanovinylamine **15**, with hydrazine to obtain the intermediate pyrazole, **16**, which was cyclised with the elimination of HCl to give **17** (Scheme 4).



Scheme 4

The presence of cyano and amino groups on the pyrazole ring should give much scope for functional group modification, although this does not appear to have been carried out in this case.

The first synthesis of the fully unsaturated imidazo[1,2-*b*]pyrazole ring system was reported in 1973 by Elguero *et al.*[8]. This reaction also follows similar methodology as previously described. In this reaction 3-aminocrotononitrile is reacted with hydrazinoacetaldehyde diethyl acetal to obtain the pyrazole **18**. This pyrazole, under acid catalysis and with the elimination of two moles of ethanol, gives 6-methylimidazo[1,2-*b*]pyrazole, **19**, in 40% yield (Scheme 5).



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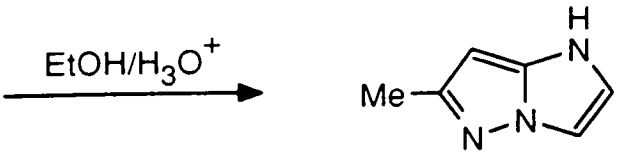

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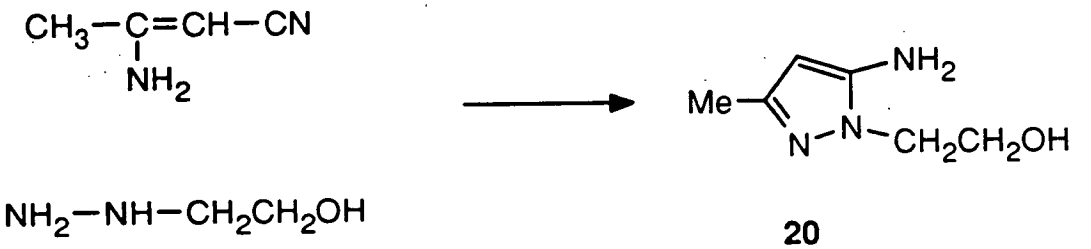
Scheme 5

In an analogous fashion Elguero[9] and co-workers also were able to synthesise a 2,3-dihydro derivative using 3-aminocrotononitrile and 2-(hydroxyethyl)hydrazine. Ring closure of the pyrazole, **20**, was effected by the use of phosphoric acid to give **21** (Scheme 6).



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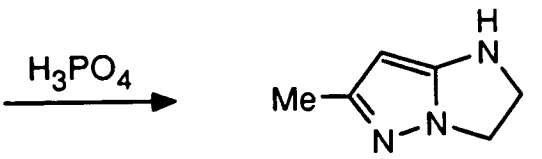
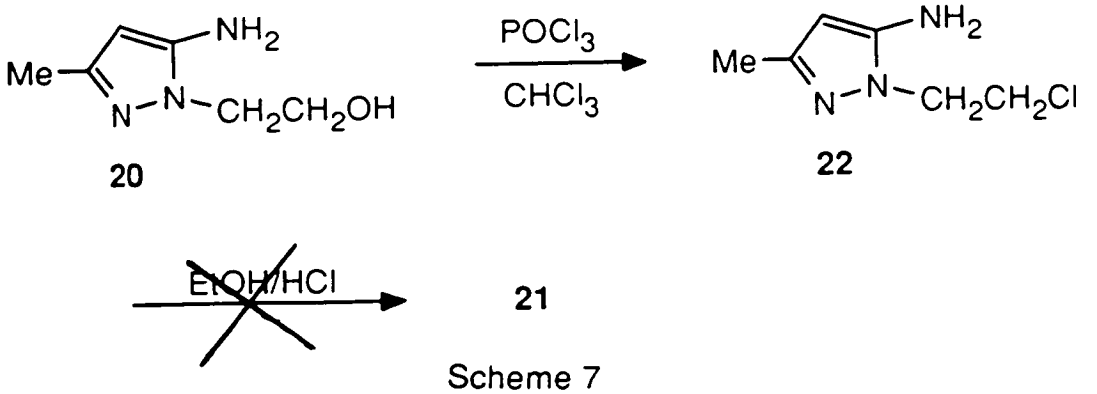


21

Scheme 6

Interestingly, **20** can be converted to the chloro derivative **22** which does not apparently cyclise.[9] Surprisingly this was carried out under acid conditions (Scheme 7).



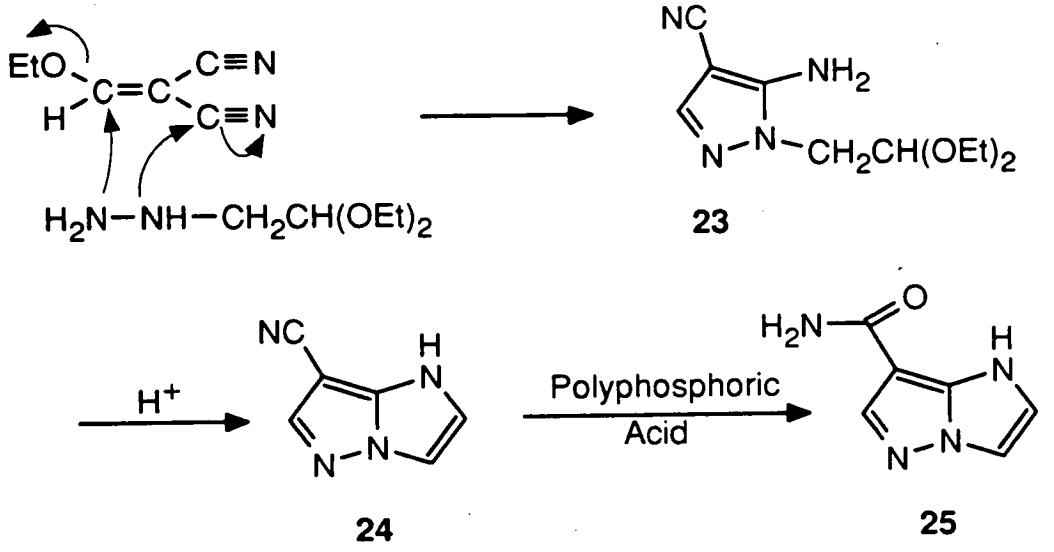
20 **22** **21**

Scheme 7

This is in direct contrast to the synthetic scheme reported by Schulze[7] (Scheme 4) which was carried out under basic or neutral conditions.

A further variation on Elguero's work reported by Revankar and co-workers[10] resulted in the introduction of a cyano group in position 7. The reaction involved the condensation of 2-hydrazinoacetaldehyde diethyl acetal and ethoxymethylenemalononitrile to give the intermediate pyrazole, **23**, which ring closed under acid catalysis to give imidazo[1,2-*b*]pyrazole-7-carbononitrile.

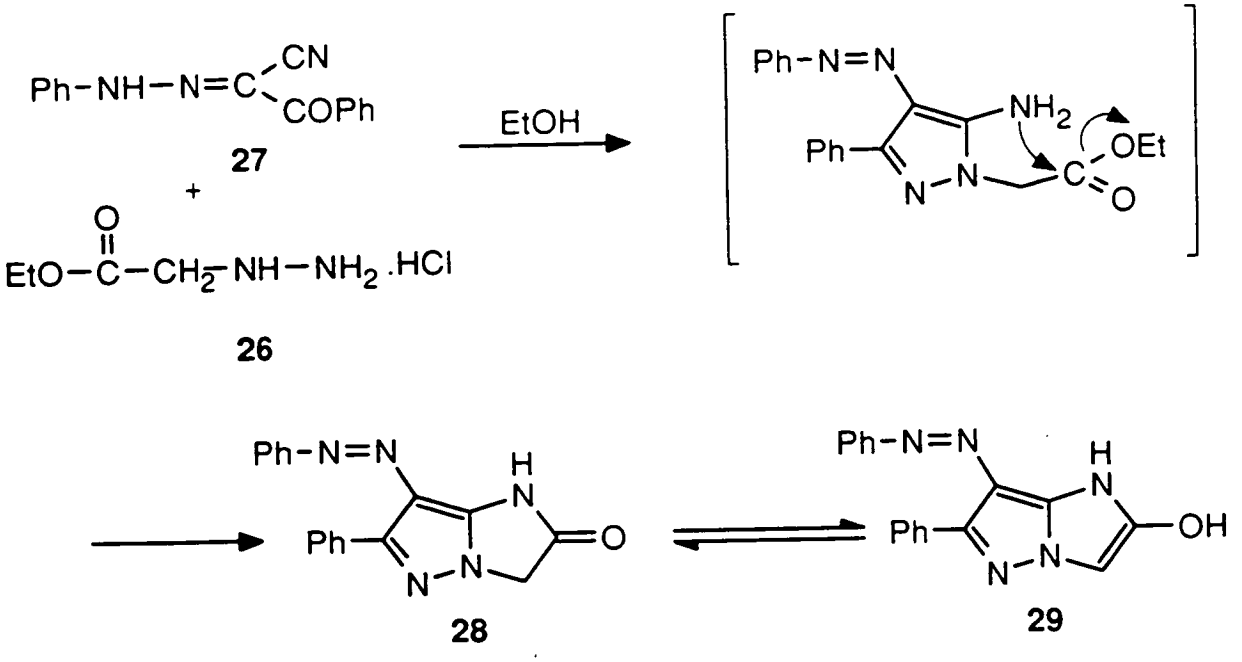
Further hydrolysis with polyphosphoric acid resulted in the formation of imidazo[1,2-*b*]pyrazole-7-carboxamide, **25** (Scheme 8).



24 **25**

Scheme 8

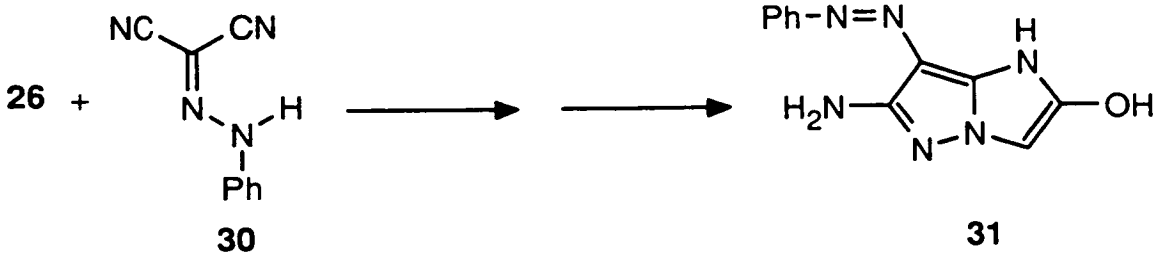
Elnagdi and co-workers[11] have reported two syntheses of the imidazopyrazole ring system based on reactions of ethyl hydrazinoacetate hydrochloride, **26**. The first reaction involves **26** and the hydrazone **27** (Scheme 9).



Scheme 9

The intermediate pyrazole is apparently not isolated here. The absence of a reported carbonyl stretch in the i.r. spectrum seems to indicate that tautomer **29** is almost exclusively formed in preference to **28**.

The second reaction is similar to the first and employs **26** and phenyl hydrazonomesoxanitrile **30** to give the imidazo[1,2-*b*]pyrazole **31**, (Scheme 10).

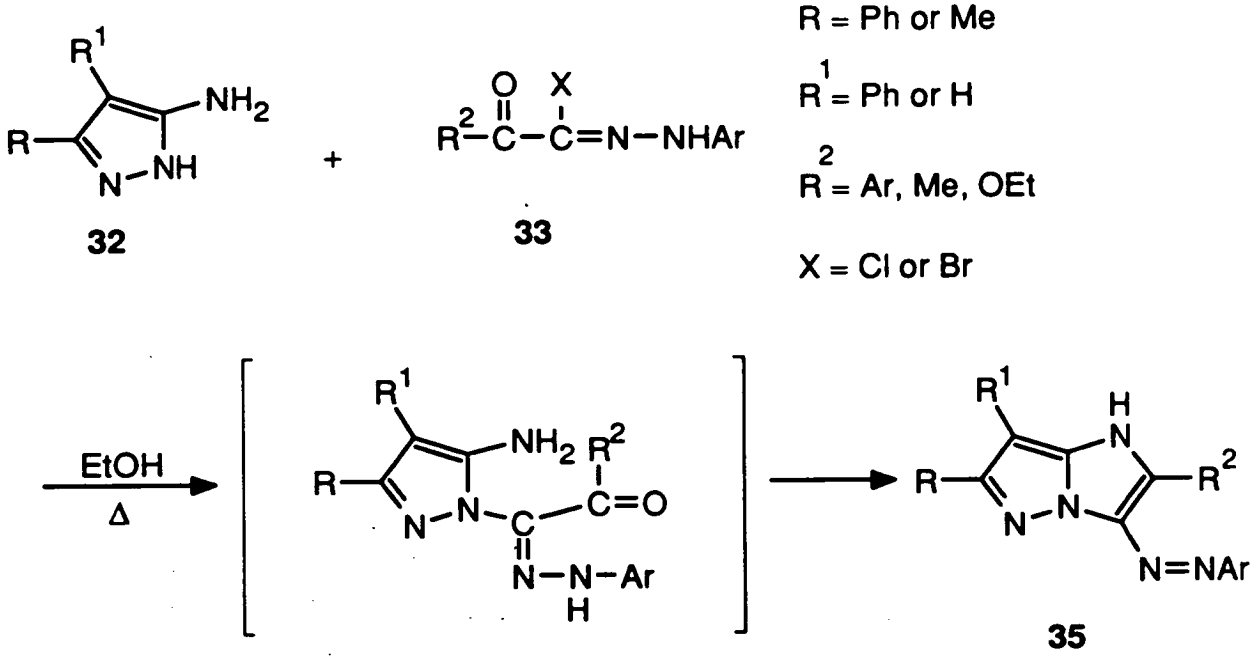


Scheme 10

The structures of **29** and **31** are based exclusively on i.r. and microanalyses.

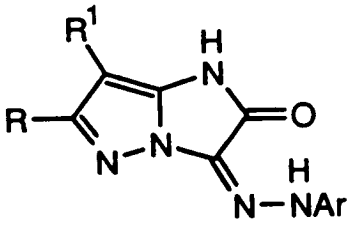
(ii) Imidazo[1,2-*b*]pyrazoles Derived From 3-Aminopyrazoles

There have been several reports in recent years of reactions between 3-aminopyrazoles **32** and *N*-arylhydrazones **33**[12,13,14,15] (Scheme 11).



Scheme 11

When R^2 = OEt the final product is **36**.



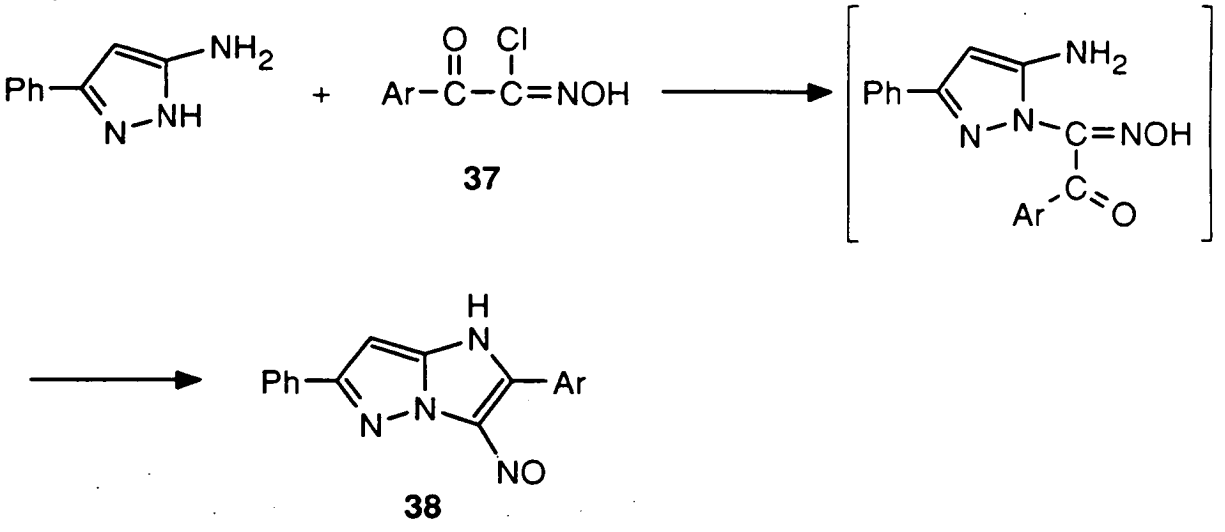
36

The reaction appears to involve displacement of a halogen by the pyrazole ring. The intermediate **34** is not isolated, and proceeds directly to the ring closed product **35**. It is interesting that no reaction at position 1 has been observed in these reactions. Two possible explanations are as follows:

Either 1) The two nitrogens on the ring are of variable reactivity and substitution at position 2 is favourable with respect to position 1.

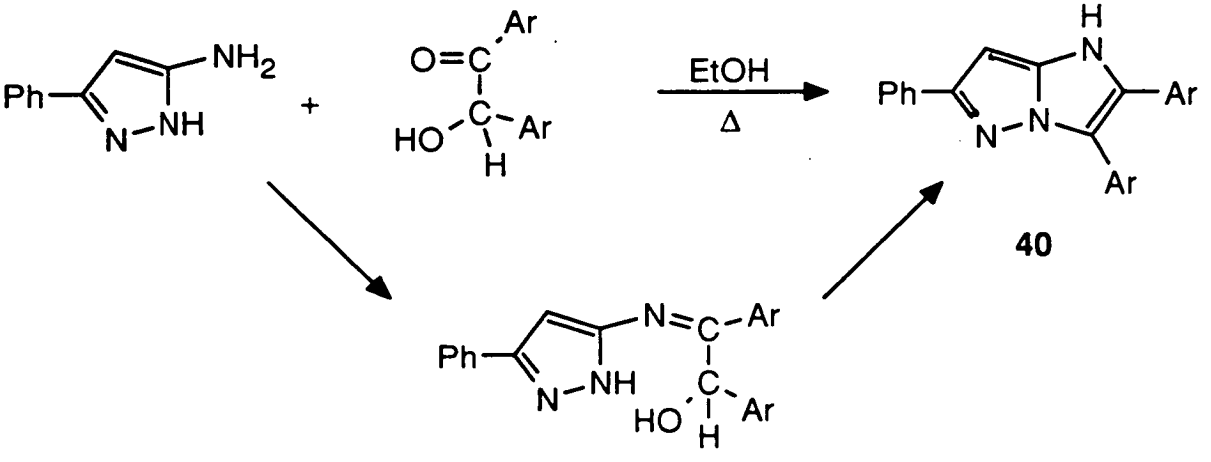
Or 2) The reaction between the pyrazole and the hydrazone is reversible and only the formation of the cyclised product drives the reaction forward.

In a similar reaction[16] α-ketohydroximoyl chlorides, **37**, react with aminopyrazoles to give 2-aryl-3-nitroso-6-phenyl-1*H*-imidazo[1,2-*b*]pyrazoles, **38** (Scheme 12).



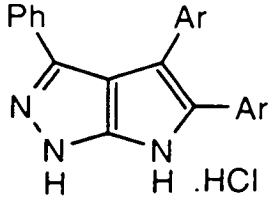
Scheme 12

Aminopyrazoles have also been shown to react with benzoin or anisoin[17] to give the product **40**, *via* the intermediate **39** (Scheme 13).



Scheme 13

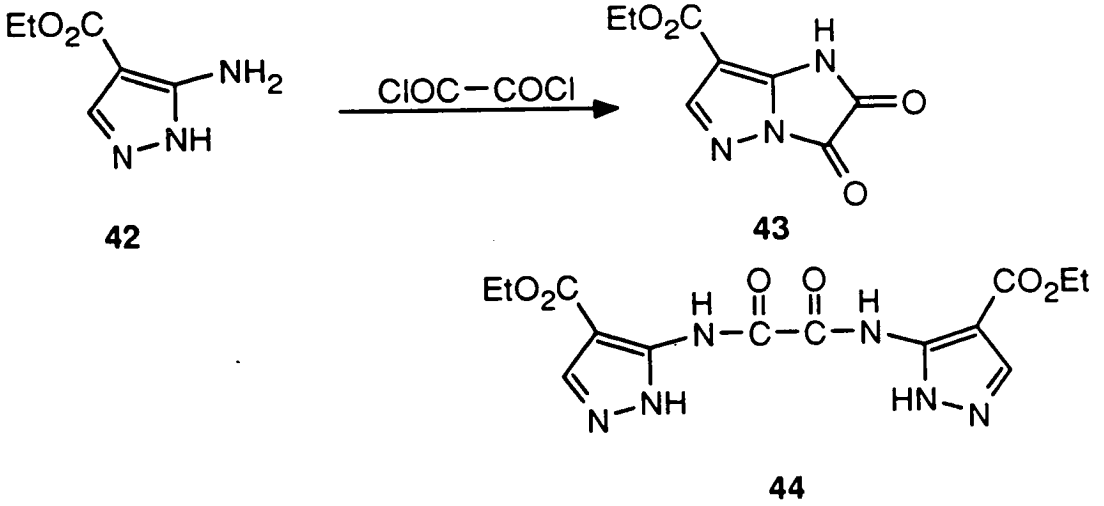
If HCl is added to the starting mixture the product isolated is now the pyrazolo pyrrole, **41**, in its hydrochloride form. The structure was deduced from its ^1H NMR spectrum which only showed resonances for aromatic and NH protons.



41

A possible reason for this change in orientation of the reaction is due to the decreased reactivity of position 2, with respect to position 4, under acid conditions.

Another synthesis reported by Gelt *et al.*[18] involves the reaction of the aminopyrazole **42** and oxalyl chloride to give products **43** and **44** which could be separated by chromatography (Scheme 14).

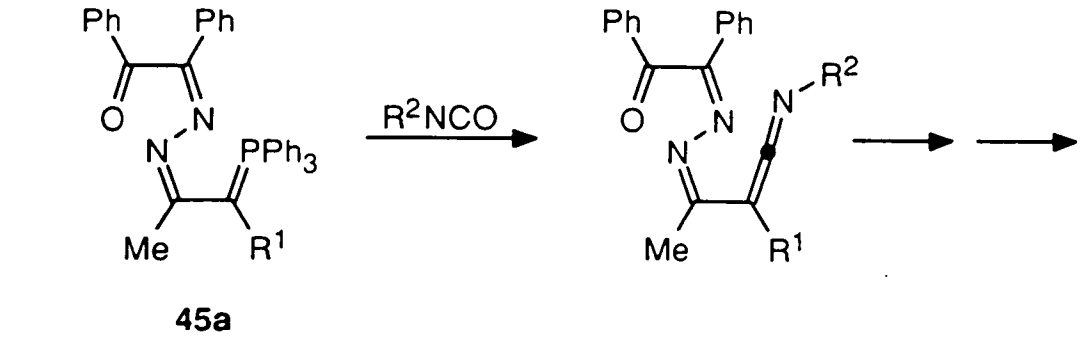


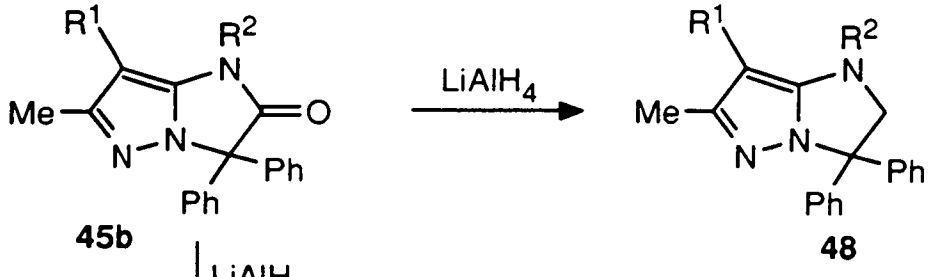
42 **43** **44**

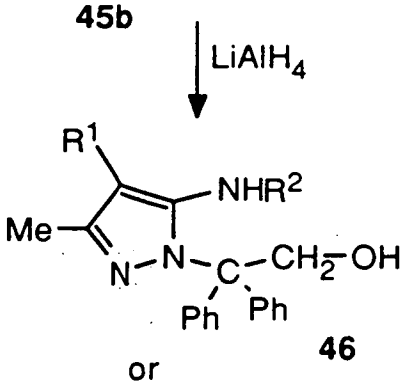
Scheme 14

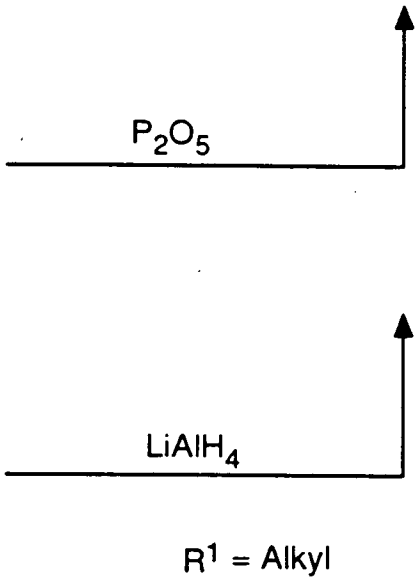
(iii) Rearrangement of 1-Oxo-3,4,8-triaza-2,4,6,7-octatetraenes to Imidazo[1,2-*b*]pyrazoles

A third type of reaction to generate the imidazo[1,2-*b*]pyrazole ring system has been reported.[19a,b] The synthesis first involves the reaction of a phosphorane, **45a**, with an isocyanate to give the 1-oxo-3,4,8-triaza-2,4,6,7-octatetraene[19a] which rearranges to the 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-one **45b** (Scheme 15). These 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-ones were reacted with lithium aluminium hydride in an attempt to bring about their direct reduction to the corresponding 2,3-dihydroimidazo[1,2-*b*]pyrazoles,[19b] **48**. This direct reduction did not occur; instead two reaction pathways were followed according to the nature of R^2. When R^2 is aryl, amino alcohols, **46**, are isolated and these could be cyclised to the desired 2,3-dihydroimidazo[1,2-*b*]pyrazoles, **48**, using phosphorus pentoxide. When R^2 is an alkyl group a different product, the formamide, **47**, was isolated. This is believed to be the first example of a carbonyl/α-carbon cleavage. The formamide was reacted with further lithium aluminium hydride to afford **48** (Scheme 15).









R^1 = Alkyl

46 R^2 = Aryl

47 R^2 = Alkyl

Scheme 15

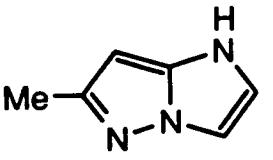
2. Physical Properties of Imidazo[1,2-*b*]pyrazoles

(i) Infrared

No detailed study of the infrared spectra of imidazo[1,2-*b*]pyrazoles has been undertaken. Experimental observations show the most intensive bands are at 3500-3200 (N-H) and 1620-1595 (C=N).[8]

(ii) Ultraviolet

Ultraviolet spectra of imidazo[1,2-*b*]pyrazoles do not show many features. For example 6-methylimidazo[1,2-*b*]pyrazole **49** has been studied in a range of solvents, e.g. water, ether, methanol *etc.* and shows λ_{max} at approximately 247 nm.[8]

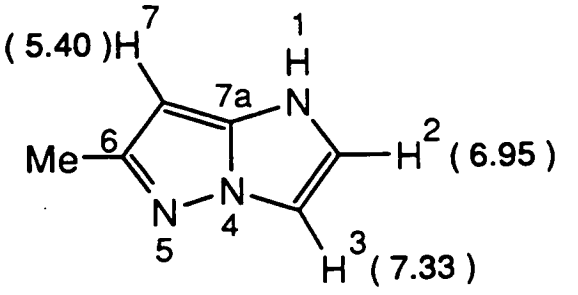


49

The presence of other substituents around the ring does not greatly affect λ_{max}. Although a bathochromic shift does occur at pHII, this must be due to partial deprotonation of the molecule.[10]

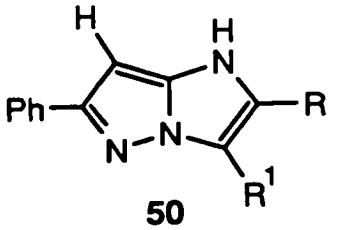
(iii) ^{1}H NMR

6-Methylimidazo[1,2-*b*]pyrazole, **49**, has been extensively studied by proton NMR (d_6-DMSO).[8,20]



49

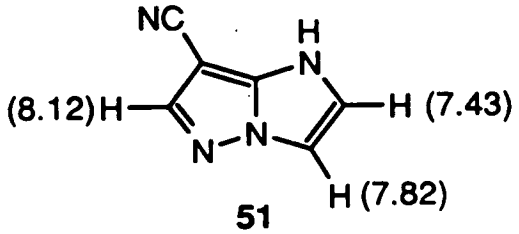
This reveals a pair of doublets at δ_H 7.33 and 6.95 which are 3-H and 2-H respectively. 7-H occurs at δ_H 5.40. The proton spectrum also reveals cross ring coupling between 3-H and 7-H. This is similar to cross ring coupling reported for indolizines.[21] If Me is replaced by Ph to give **50** we see a change in the chemical shift of 7-H to δ_H 5.9-6.3[13,17] due to the deshielding effect of the phenyl ring.



50

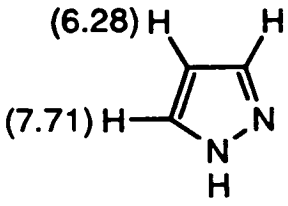
R = Alkyl or Aryl.
R^1 = NNAr or Aryl.

An electron withdrawing group, such as nitrile or carboxamide, in position 7 exerts a deshielding effect on 7-H and to a lesser extent on 2-H and 3-H. An example **51** is shown below.[10]

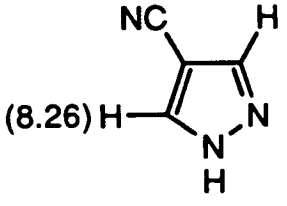


51

The actual value of the chemical shift of 6-H with no functional groups adjacent has not been reported. However, a cyano group in the corresponding position of pyrazole, **52, 53**, itself causes a high frequency shift of the adjacent proton of 0.5 ppm.[22,23]



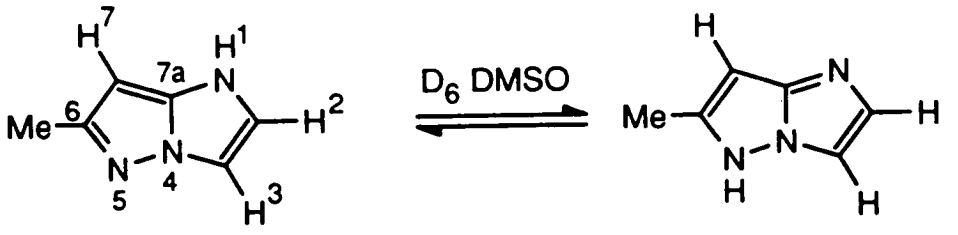
52



53

From this analogy we would expect 6-H to occur at about δ_H 7.7.

^{1}H NMR has been used to determine which of the two tautomers **54a** or **54b** is the most stable (Scheme 16).



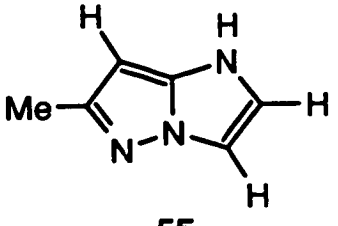
54a **54b**

Scheme 16

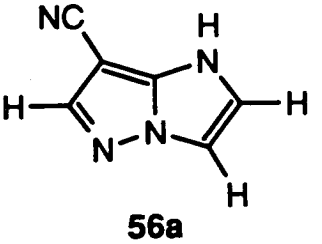
Observations by Elguero *et al.*[20] have shown that 2-H and 3-H couple to NH, also a long range coupling between Me and 7-H is not observed. These two observations clearly indicate tautomer **54a** is the more stable form.

(iv) ^{13}C NMR

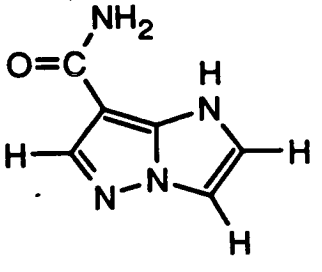
Only three ^{13}C NMR spectra have been reported.[10,24] These are the 6-methyl, 7-cyano and 7-carboxamide derivatives **55, 56a** and **56b.**



55



56a



56b

Assignments and effects of substituents are summarised in Table 1.

Table 1 **^{13}C spectra of imidazo[1,2-*b*]pyrazoles**

Compound	C-2	C-3	C-6	C-7	C-7a
55	116.5	107.2	151.1*	78.0	142.1*
56a	119.6	109.4	146.1	65.8	140.9
56b	119.6	108.5	141.9	93.6	139.9

* The initial assignments were transposed,[10] later work corrected this.[24]

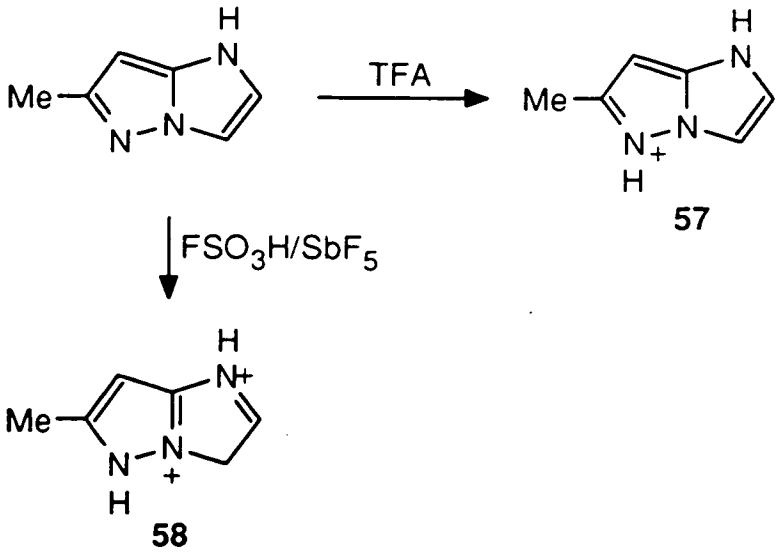
C-2, C-3 and C-6 were all assigned by selective irradiation of previously assigned protons. The presence of substituents should not greatly affect the chemical shift of the bridgehead carbon atom so this was assigned at ~ 141 ppm. The presence of a cyano group rather than H on C-7 exerts a shielding effect with respect to the 7-unsubstituted analogue. This effect is reversed when C-7 bears a carboxamide group.

3. Chemical Reactions of Imidazo[1,2-*b*]pyrazoles

Very few examples of chemical reactions of imidazo[1,2-*b*]pyrazoles are known.

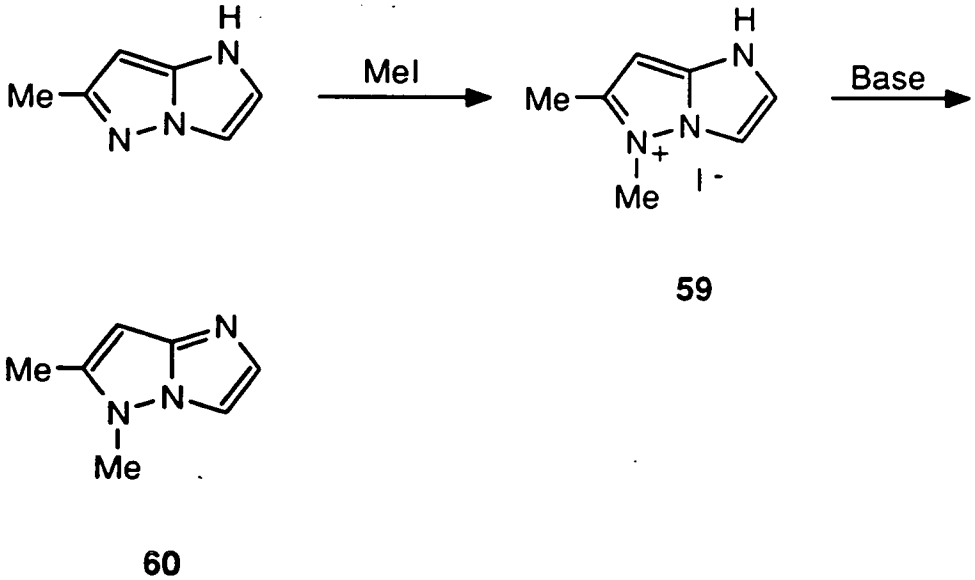
(i) Electrophiles

Imidazo[1,2-*b*]pyrazoles can either undergo electrophilic attack at nitrogen or an electron rich carbon such as position 3 or 7. Protonation initially occurs at nitrogen to give species **57**. This can be further protonated at C-3 to give **58**[25] (Scheme 17).



Scheme 17

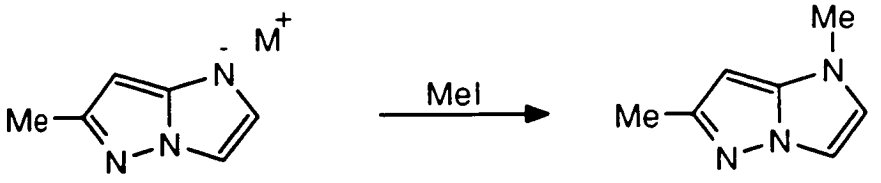
Methylation also occurs at nitrogen;[25] initially the salt, **59**, is formed which is then deprotonated to **60** (Scheme 18).



Scheme 18

The structure of **60** was confirmed by ^{1}H NMR; coupling between 7-H and the methyl group on C-6 was observed.

If the alkylation is carried out *via* the anion alkylation occurs on the imidazolic nitrogen, N-1, giving **61**[26] (Scheme 19).

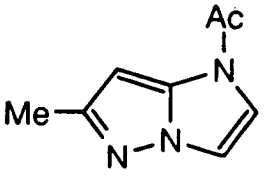


61

Scheme 19

The orientation of quaternisation in the first methylation reaction is apparently controlled by the predominant tautomer.[4]

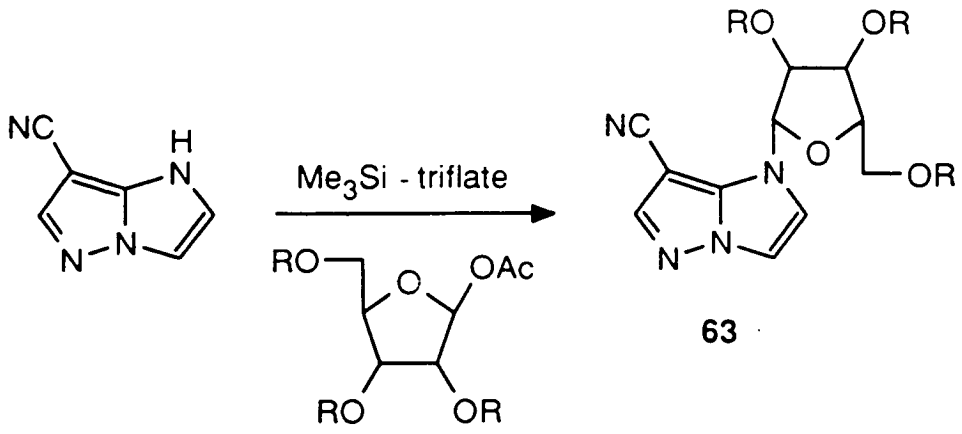
Acylation also occurs on the imidazolic nitrogen to give **62.**[20]



62

Acylation and methylation occur at different positions. The explanation is that acylation is thermodynamically controlled giving **62** while methylation occurs at the most nucleophilic nitrogen atom,[26] (Scheme 19).

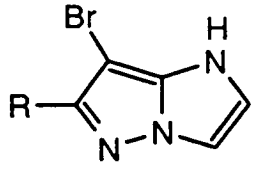
An interesting substitution at nitrogen puts a ribofuranose group on the imidazole portion of the bicyclic ring system. This product, **63**, could exhibit biological activity by acting as a purine nucleoside analogue[10] (Scheme 20).



63

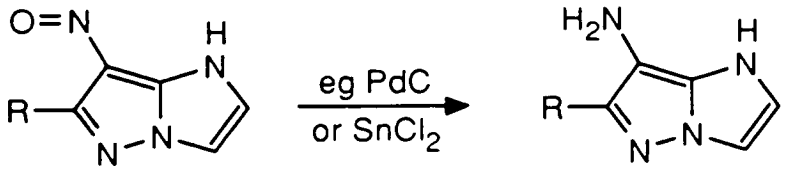
Scheme 20

Electrophilic substitutions at carbon seems to be limited to halogenation[4] and nitrosation reactions.[26] Chlorination and bromination occur at C-7 and can be brought about by direct halogenation, halogenosuccinimides or thionylhalides.[4] Halogenation is desirable because it aids the formation of photographic dyes (Section A). A typical product of halogenation is **64**.



64

Nitrosation also occurs at C-7 to give **65**. This reaction is of interest because the nitroso group may be reduced thus resulting in the introduction of an amino group at C-7. This has much potential for further modification[27] (Scheme 21).

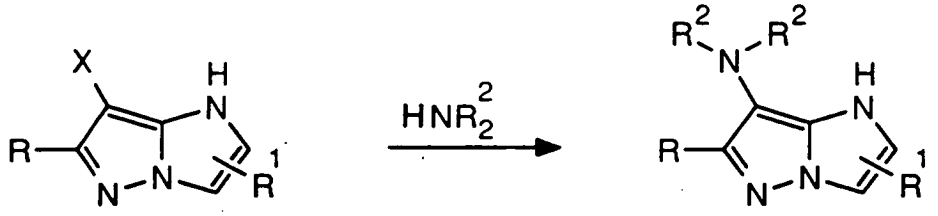


65

Scheme 21

(ii) Nucleophilic Reactions

Nucleophilic reactions are almost unknown; the only type reported for this system involves displacement of a halogen at C-7 by an amine, giving a product of general formula **66**[27] (Scheme 22).



66

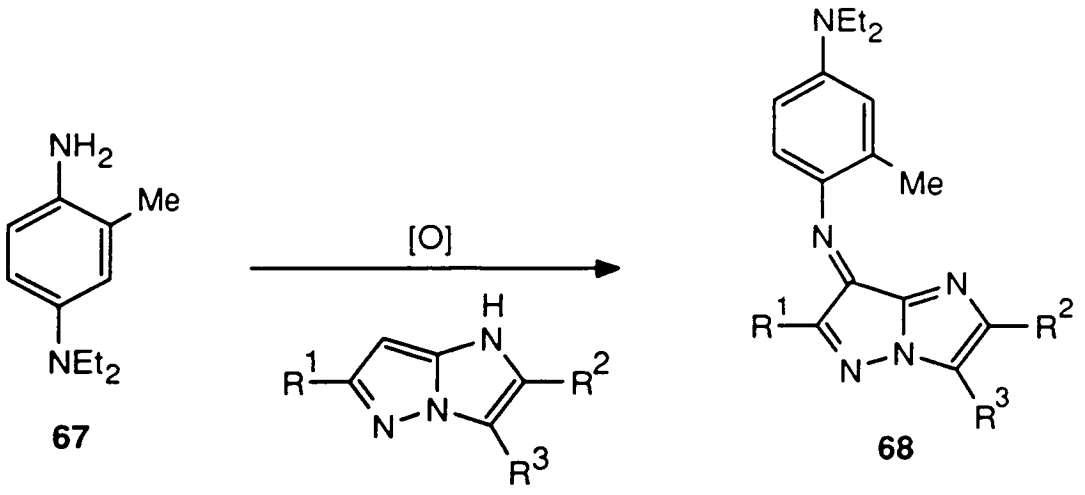
X = Cl or Br

R, R^1, R^2 = Alkyl or Aryl.

Scheme 22

(iii) Oxidative Coupling Reactions

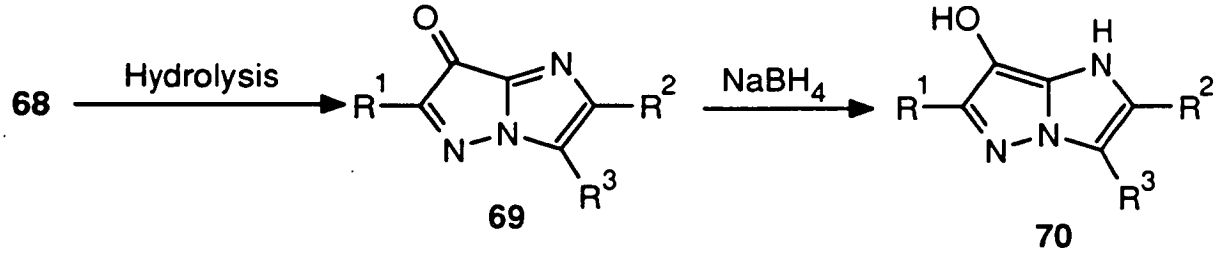
Imidazo[1,2-*b*]pyrazoles will react with p-phenylene diamines, e.g. **67** in the presence of an oxidising agent, silver halide or potassium persulphate, to give the coupled product **68**[27] (Scheme 23).



R^1, R^2, R^3 = H, Alkyl or Aryl.

Scheme 23

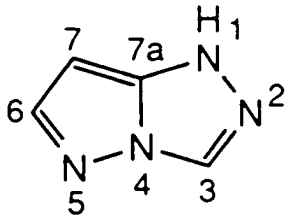
It is possible for **68** to be hydrolysed to give examples of imidazo[1,2-*b*]pyrazol-7-ones, **69**, further reduction of which with sodium borohydride gives 7-hydroxyimidazo[1,2-*b*]pyrazoles **70**[27] (Scheme 24).



Scheme 24

C. PYRAZOLO[5,1-*c*]1,2,4-TRIAZOLES

Extensive research into the synthesis and chemistry of this class of compounds has been carried out. Two reviews[4,5] and numerous papers deal with these compounds. The numbering scheme of the parent ring system, **71**, is illustrated below.



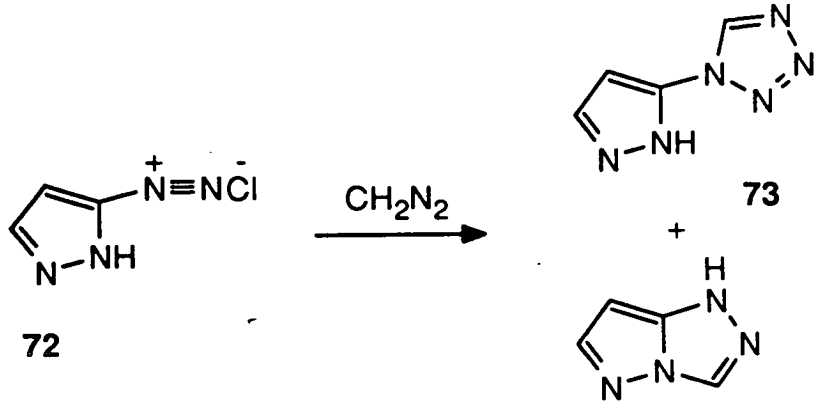
71

1. Synthesis of Pyrazolo[5,1-*c*]1,2,4-triazoles

Four synthetic routes to this system have been utilised. The first route is based on the use of pyrazolediazonium salts. The second employed aminoazoles (pyrazoles and 1,2,4-triazoles). The third route is derived from pyrazolehydrazines while the fourth involved ring contraction methodology.

(i) Pyrazolo[5,1-*c*]1,2,4-triazoles Derived from Pyrazolediazonium Salts

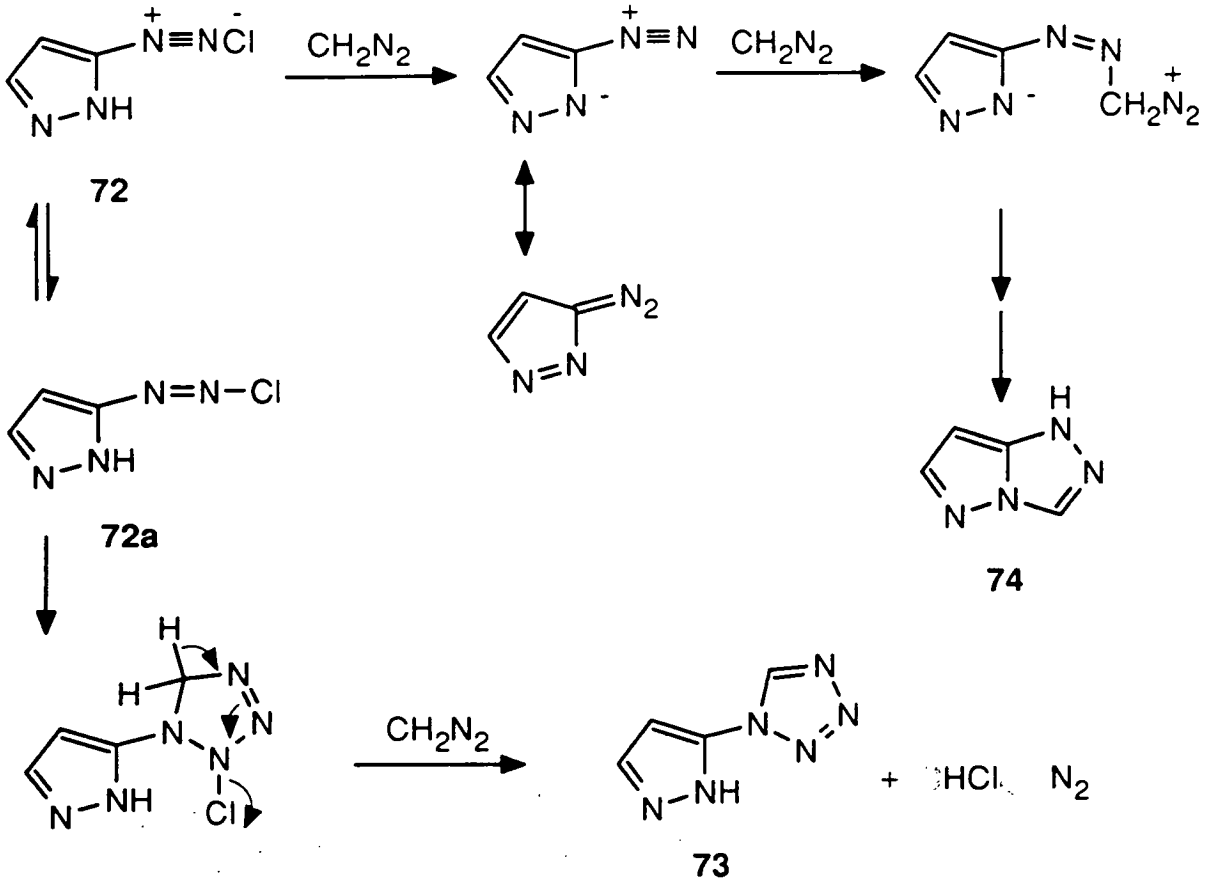
The first recorded synthesis of pyrazolo[5,1-*c*]1,2,4-triazoles appeared in 1970.[28] In this reaction diazomethane was allowed to react with pyrazole-3-diazonium chloride, **72**, to give two products. The major product was the tetrazole, **73**, but pyrazolo[5,1-*c*]1,2,4-triazole **74** was also isolated, albeit in low yield (Scheme 25).



72 **73** **74**

Scheme 25

To account for the formation of two products the following mechanistic scheme has been proposed[28] (Scheme 26).

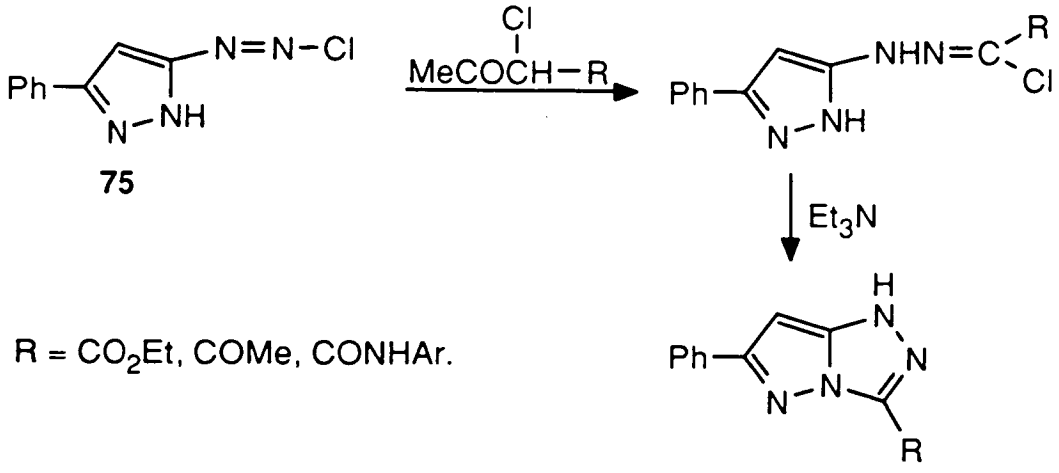


Scheme 26

It would seem the direction of the reaction is influenced by the relative reactivity of **72** and **72a**.

Pyrazole-3-diazonium salts have been found to react with ketones to give adducts which are subsequently cyclised.

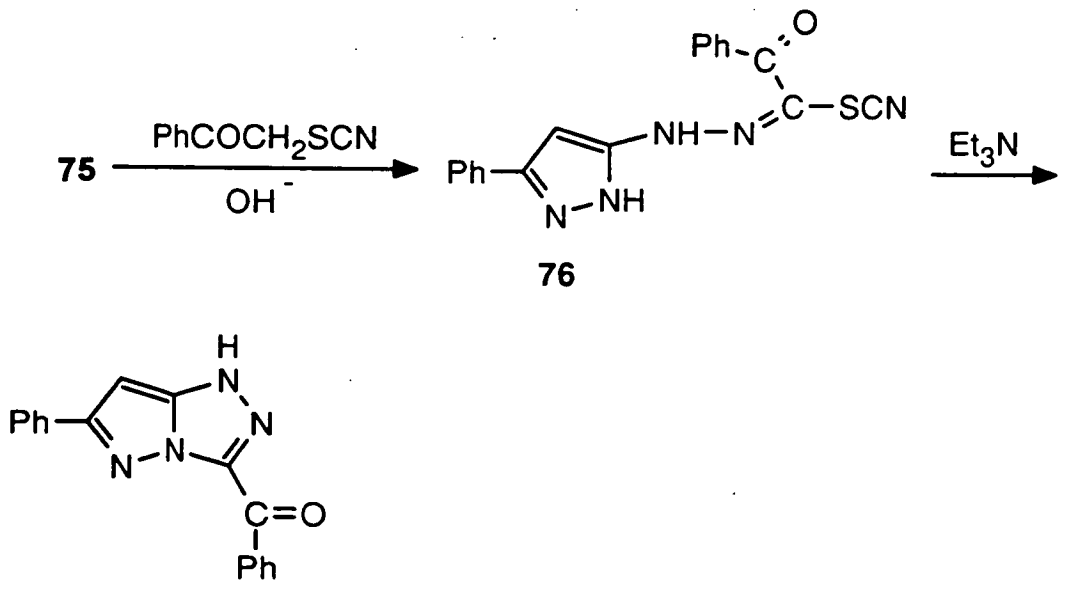
The first example of this was reported by Elnagdi[29,30] in 1977/80. This involved the reaction of α-chloroketones with the pyrazole-3-diazonium salts **75** to give the intermediate hydrazone. Subsequent treatment with triethylamine afforded the ring closed product, pyrazolo[5,1-*c*]1,2,4-triazole (Scheme 27).



75

Scheme 27

In a similar reaction[31] phenacyl thiocyanate in the presence of hydroxide reacts with **75** to give the intermediate **76**. This reaction involved coupling between the diazonium ion and an active methylene group. Cyclisation was again achieved with triethylamine (Scheme 28).

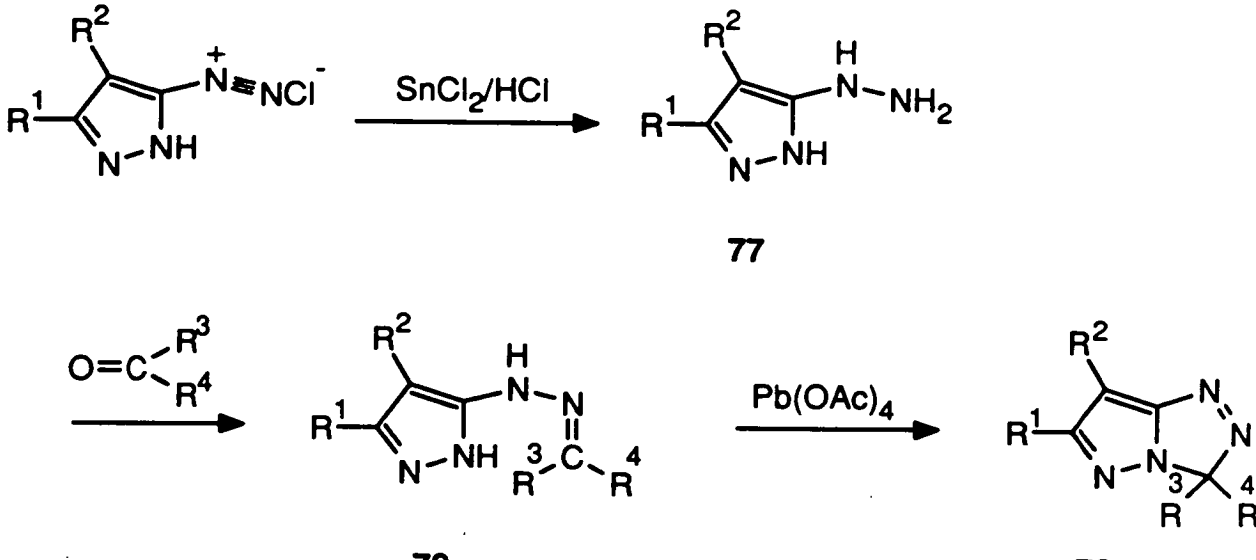


75 **76**

Scheme 28

However this observation must be considered questionable due to the absence of a signal attributable to 7-H in the proton NMR spectrum.

Pyrazole-3-diazonium salts can also be reduced by tin II chloride to the hydrazine **77**.[32] This may then be reacted with an appropriate ketone to give the hydrazone **78** which is then cyclised in the presence of lead tetracetate (Scheme 29).



77

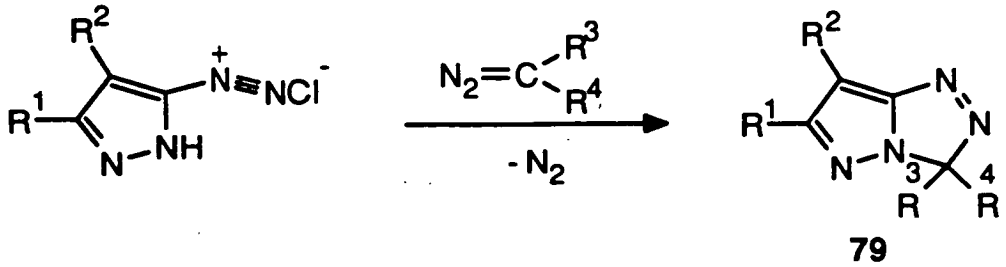
78

79

R^1 = Aryl, Alkyl, H. R^3 = Aryl, Alkyl.
R^2 = Aryl, H. R^4 = Aryl, Alkyl.

Scheme 29

Alternatively **79** could be synthesised *via* the reaction of pyrazole-3-diazonium salts and diazoalkanes[32] (Scheme 30).

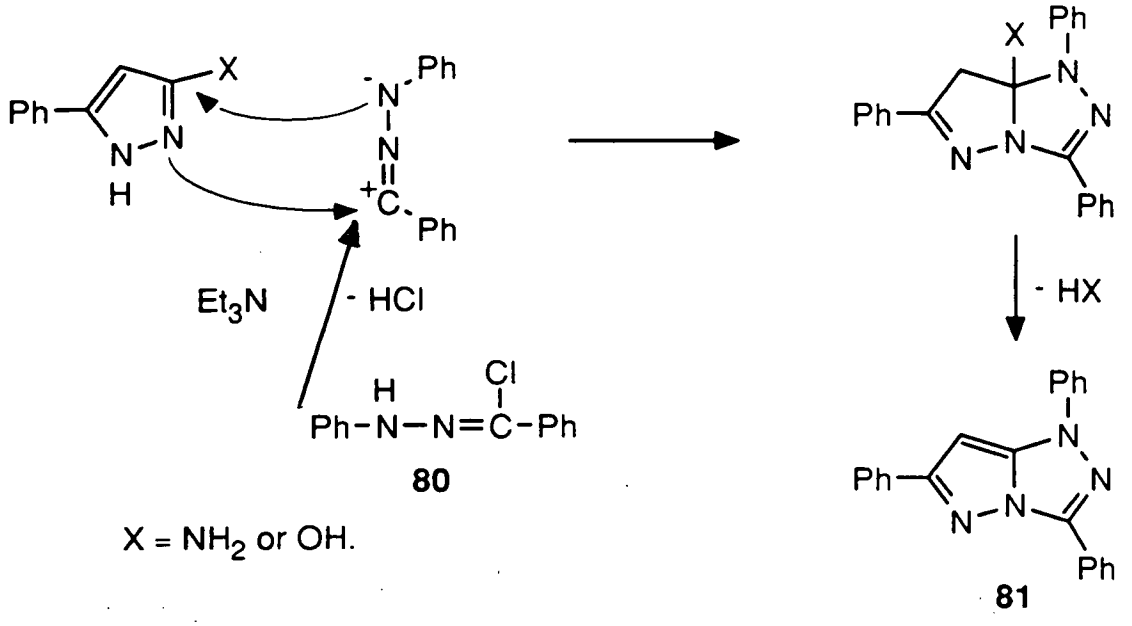


79

Scheme 30

(ii) Pyrazolo[5,1-*c*]1,2,4-triazoles From Aminoazoles

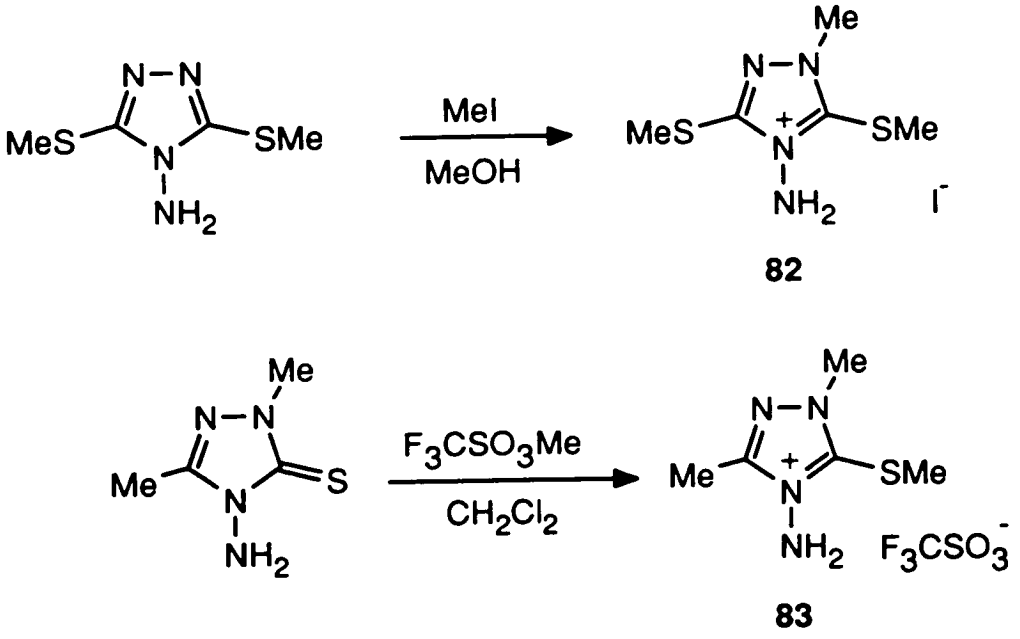
It has been reported by Elnagdi *et al.*[13,15,33] that nitrile imines can be used to synthesise pyrazolo[5,1-*c*]1,2,4-triazoles. The nitrile imines, which are obtained by base catalysed elimination of HCl from hydrazonyl chlorides, **80**, undergo a 2+3 dipolar cycloaddition reaction with 3-amino or 3-hydroxypyrazoles to afford **81** (Scheme 31).



Scheme 31

This reaction sequence has been developed into a more general method.[15]

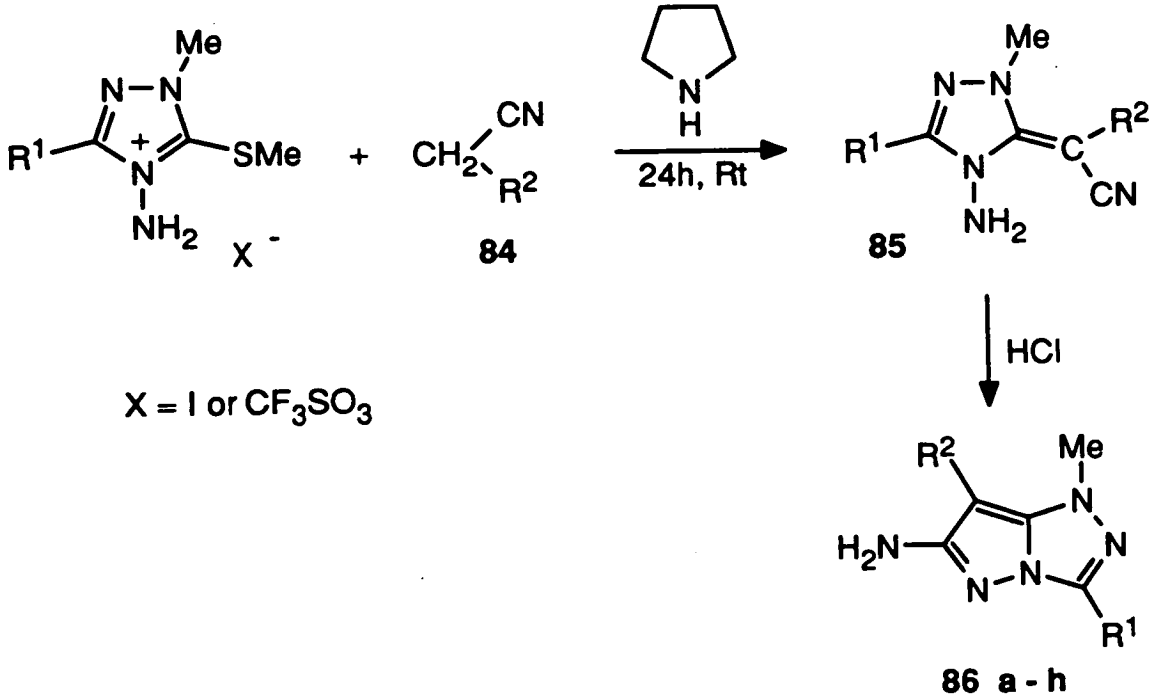
An interesting reaction that would appear to have reasonable scope has been reported by Molina.[34] This synthesis involved the reaction of the *N*-amino heterocycles **82** and **83** with activated acetonitriles (*i.e.* substituted with ester, amide, or a second nitrile group). 4-Amino-1-methyl-3,5-bis(methylthio)-1,2,4-triazolium iodide **82** is readily obtained from iodomethane and 4-amino-3,5-bis(methythio)-1,2,4-triazole.[35] **83** Is similarly synthesised from 4-amino-1,3-dimethyl-1,2,4-triazole-5*H*-thione and methyltrifluoromethylsulphonate[33] (Scheme 32).



Scheme 32

The two salts, **82** and **83**, then reacted with the activated acetonitriles **84** to give the adducts **85**. Yields of these were good for R^2 = CN or ester but only moderate for R^2 = $CONH_2$ or $CONHNH_2$.

The adducts **85** were cyclised, with varying success, with dry HCl (see Table 2) to give pyrazolo[5,1-c]1,2,4-triazoles, **86** (Scheme 33). Cyclisation by means of sodium methoxide was reported to decrease the yields.[34]



Scheme 33

Table 2

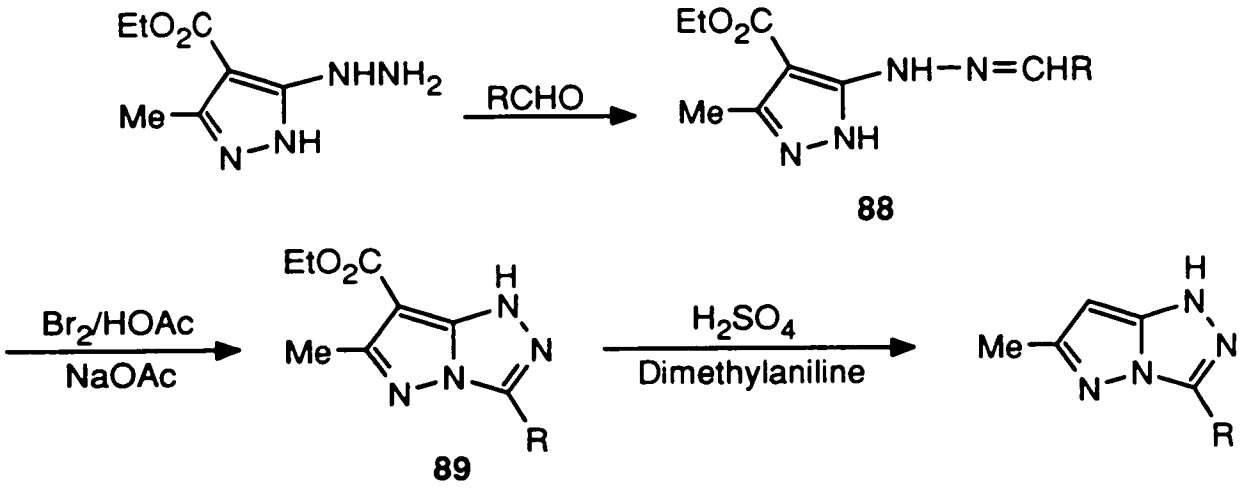
Percentage yields of 86 a - h

Entry 86	R^1	R^2	Yield
a	CH_3S	CN	80%
b	CH_3S	$CO_2CH_2CH_3$	73%
c	CH_3S	CO_2CH_3	74%
d	CH_3S	$CONH_2$	0
e	CH_3S	$CONHNH_2$	0
f	CH_3	CN	83%
g	CH_3	$CO_2CH_2CH_3$	83%
h	CH_3	CO_2CH_3	76%

(iii) Pyrazolo[5,1-*c*]1,2,4-triazoles From Hydrazines

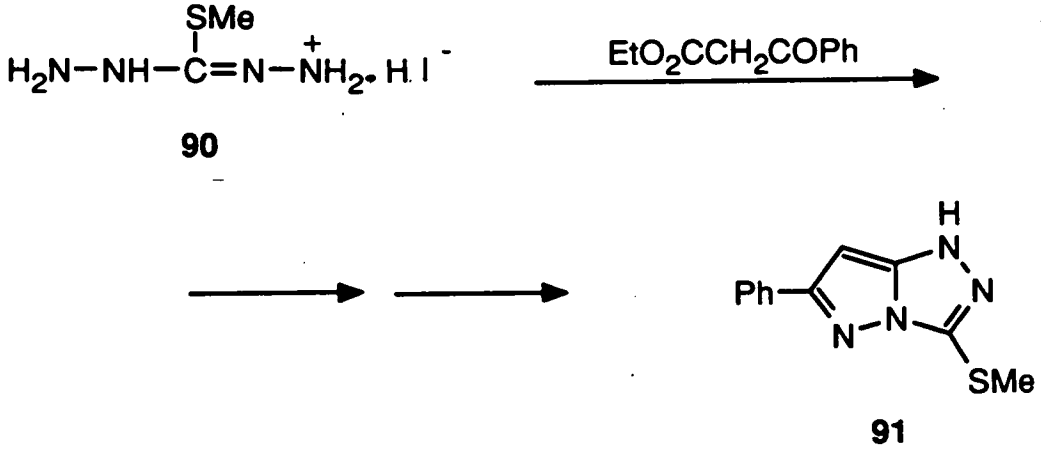
An important synthesis of pyrazolo[5,1-*c*]1,2,4-triazoles was reported in 1977 by Bailey.[36] The key starting material for this synthesis is the hydrazine **87**, which was first synthesised by Beyer.[37] The hydrazine was then reacted with various aldehydes to give the hydrazone **88**. Oxidative cyclisation in the presence of bromine, acetic acid and sodium acetate gave ethyl 1*H*-pyrazolo[5,1-*c*]1,2,4-triazole-7-carboxylates **89**.

These carboxylates could be hydrolysed in concentrated sulphuric acid to the corresponding acid which was then subsequently decarboxylated by heating with *N,N*-dimethylaniline[35] (Scheme 34).



Scheme 34

This preparation is rather lengthy and a simplified method was developed. This involved the condensation reaction of *S*-methylisothiocarbohydrazide hydroiodide, **90**, with, for example, ethyl benzoyl acetate. This yielded the pyrazolo[5,1-*c*]1,2,4-triazole **91** (Scheme 35).



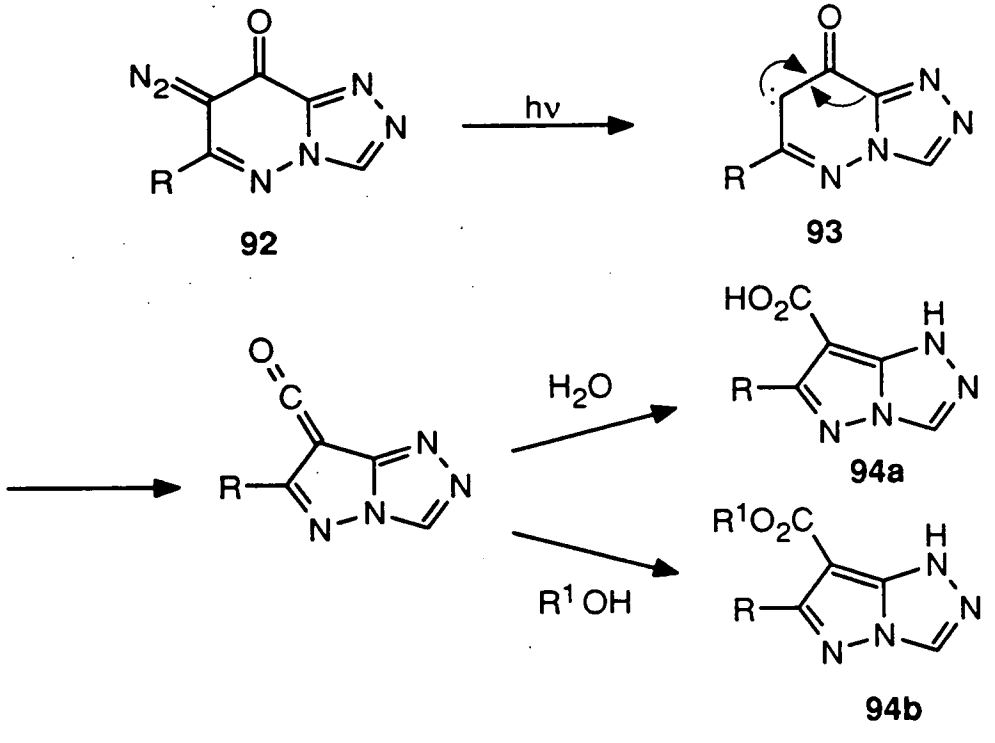
Scheme 35

Both these syntheses were applied to a wide range of compounds.[36]

(iv) Pyrazolo[5,1-*c*]1,2,4-Triazoles *via* Ring Contractions

Ring contractions of fused pyrazoles have been used on several occasions to generate pyrazolo[5,1-*c*]1,2,4-triazoles.[4,5] This can be achieved by thermal, chemical or photolytic methods.

There have been two reports in the literature concerning photolytic ring contractions to generate pyrazolo[5,1-*c*]1,2,4-triazoles.[38,39] Both reports are concerned with the photochemical Wolff rearrangement of 7-diazo-8-oxo-1,2,4-triazolo[4,3-*b*]pyridazines, **92**. The rearrangement generates a ketene, **93**, which is quenched using water or an alcohol to give examples of pyrazolo[5,1-*c*]1,2,4-triazole-7-carboxylates **94** (Scheme 36).



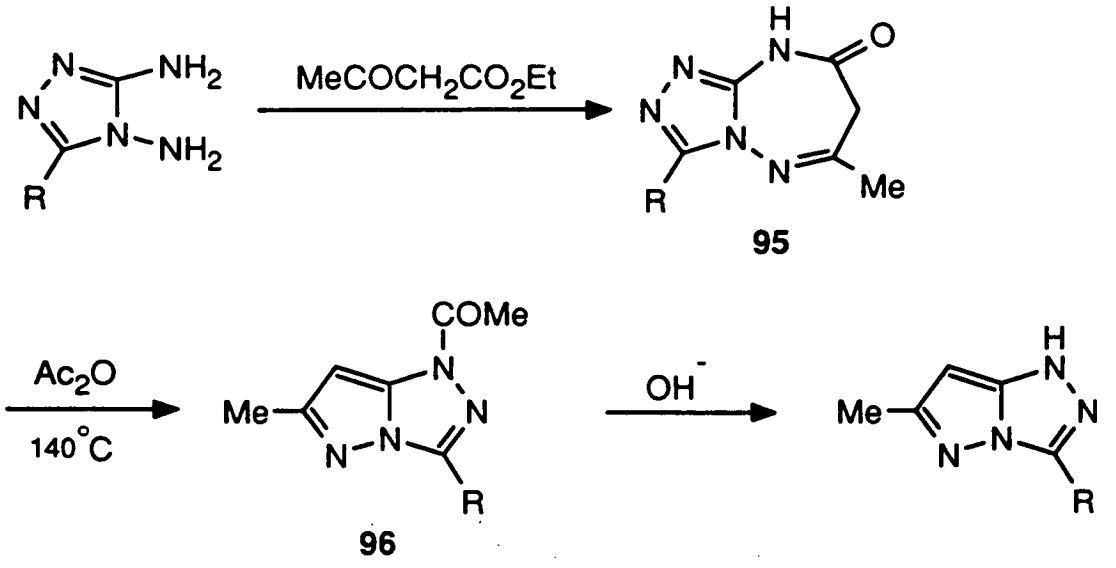
92 **93** **94a** **94b**

Scheme 36

Decarboxylation can be achieved by thermal methods.

Triazolotriazepinones, **95**, have been shown to undergo ring contraction on heating in acetic anhydride.[40] The triazepinones are first obtained by reaction of 3,4-diamino-1,2,4-triazoles and ethyl acetoacetate.[40]

The ring contraction gives the acetylated pyrazolo[5,1-*c*]1,2,4-triazole, **95**. This is readily deacetylated by treatment with base (Scheme 37).

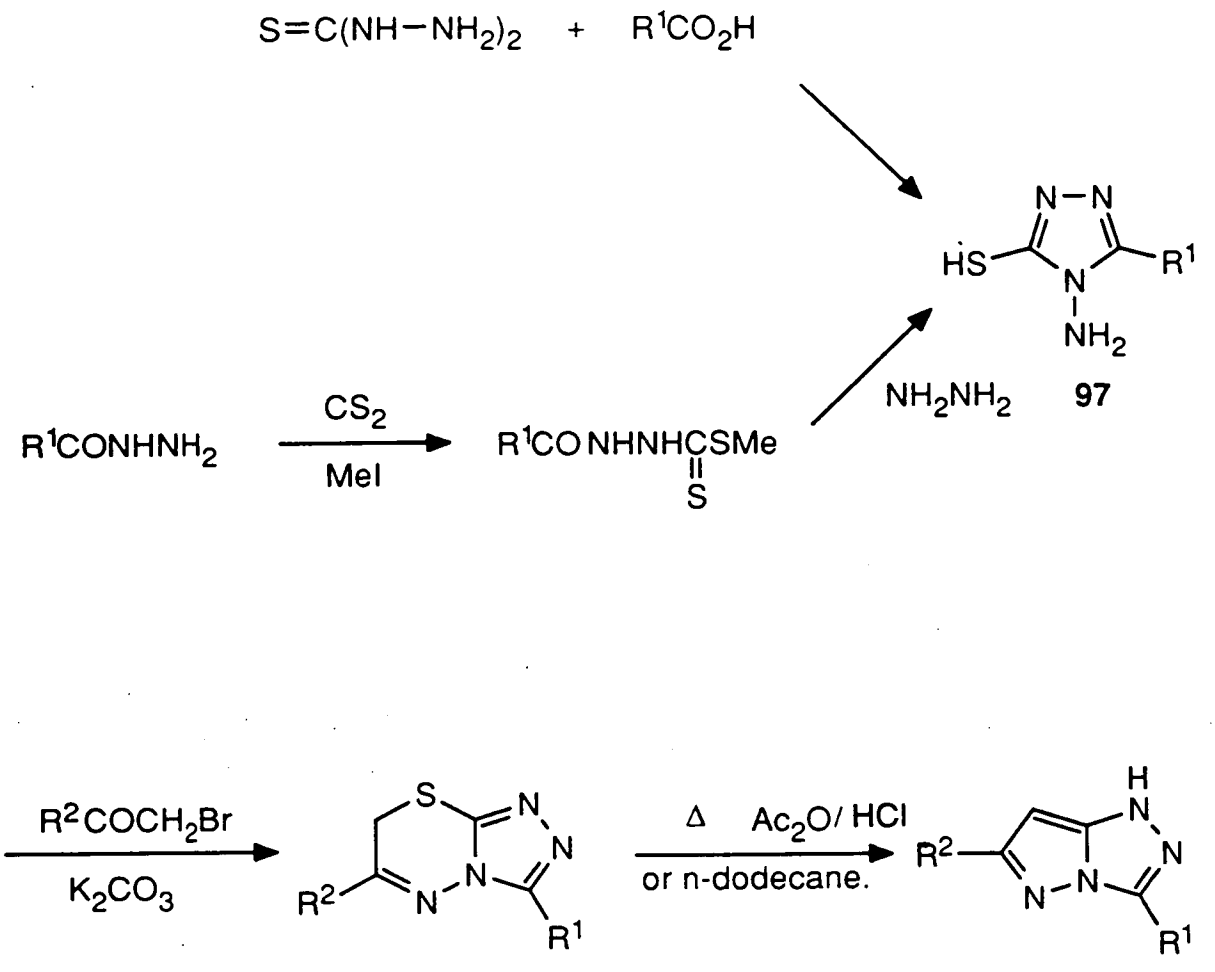


Scheme 37

Ring contraction to pyrazolo[5,1-*c*]1,2,4-triazoles may be brought about by sulphur extrusion from triazolothiadiazines.[41,42] The starting thiadiazines, **98**, can be synthesised by two different routes.[43,44]

The first involves the reaction of thiocarbazide with aliphatic carboxylic acids to give the triazole **97**.[43] The triazole is reacted with an α-halogenoketone, with base work up, to give the triazolothiadiazine **98**. Alternatively if R^1 is an aryl group an acid chloride is reacted with hydrazine to give the hydrazide. Treatment with carbon disulphide and iodomethane gives the dithiocarbazate ester which on reaction with hydrazine gives **97**.[44]

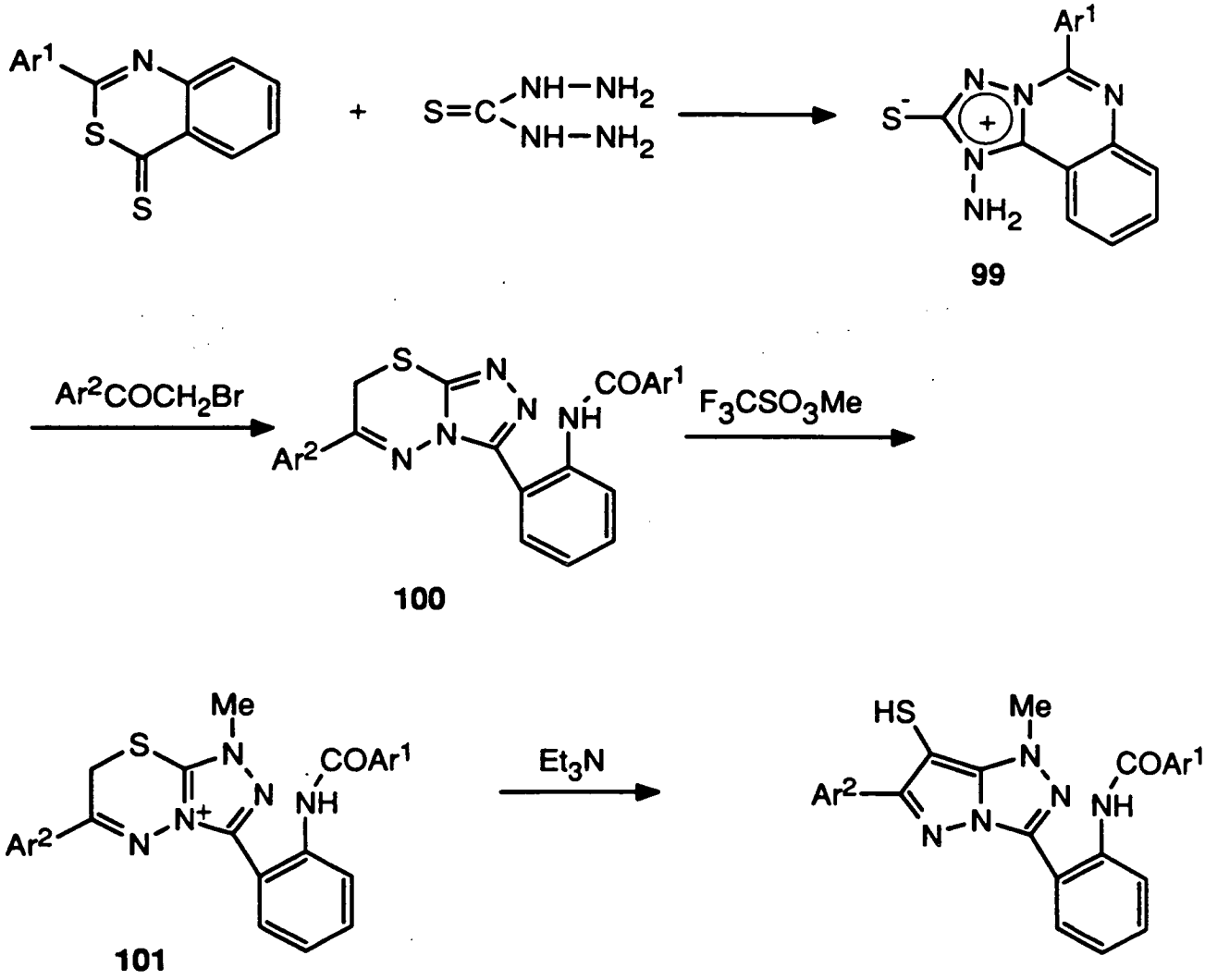
The ring contraction may be achieved by either heating the triazolothiadiazine in n-dodecane[41] or more conveniently under reflux in acetic anhydride[42] (Scheme 38).



Scheme 38

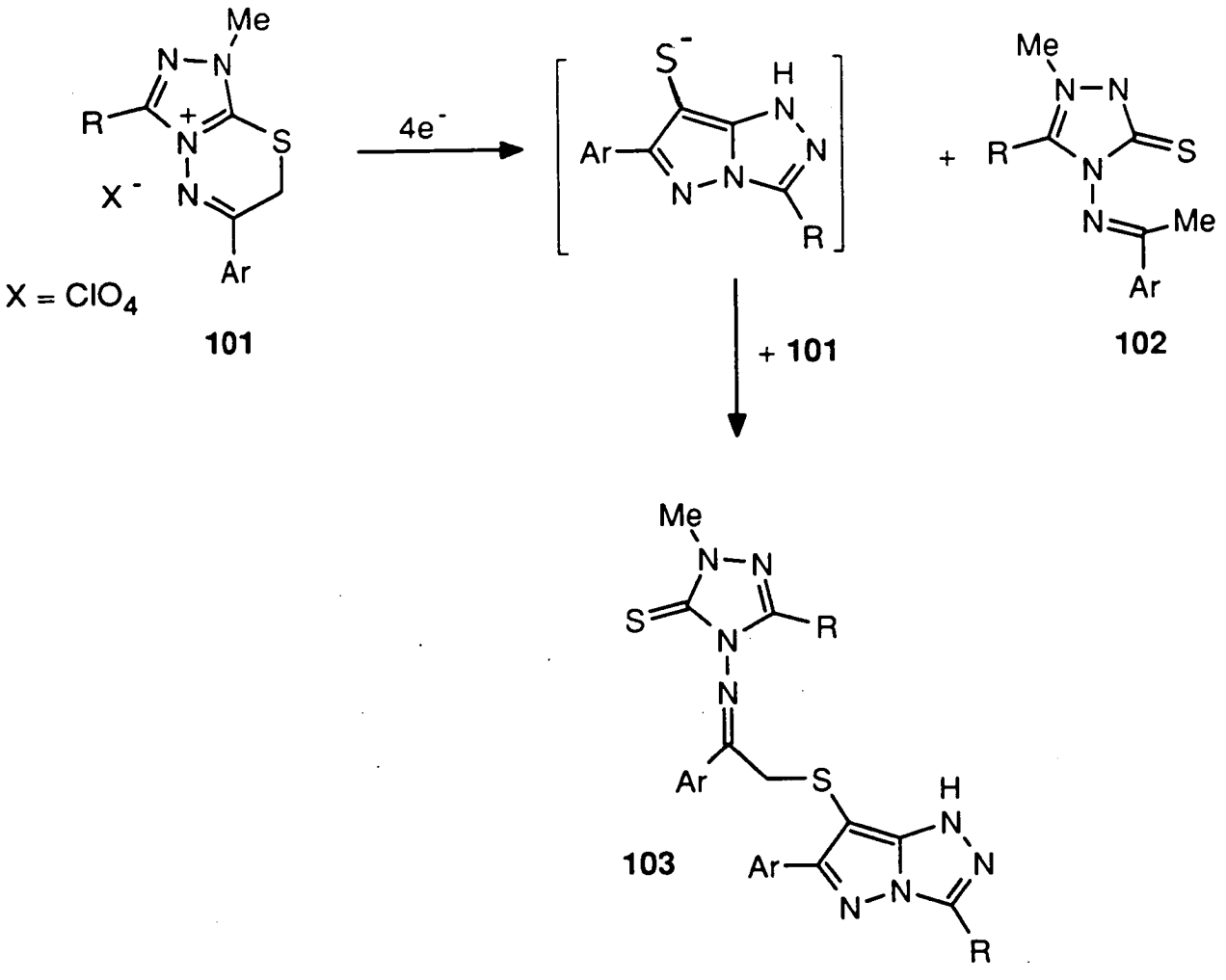
This reaction has very wide scope for attaching long chain groups R^1 and R^2 which will make the compounds potentially useful in colour photography.

Triazolothiadiazines, after quaternisation, may also undergo a base catalysed ring contraction to give pyrazolo[5,1-*c*]1,2,4-triazoles.[45] The overall reaction scheme is quite lengthy; initially it involved reaction between 2-aryl-1,3-benzothiazine-4-thiones and thiocarbazide to give the meso-ionic compound **99**. This in turn reacts with aryl acyl bromides to give the triazolothiadiazine **100**. Quaternisation with methyl trifluoromethylsulphonate followed by treatment with triethylamine afforded the pyrazolo[5,1-*c*]1,2,4-triazole (Scheme 39).



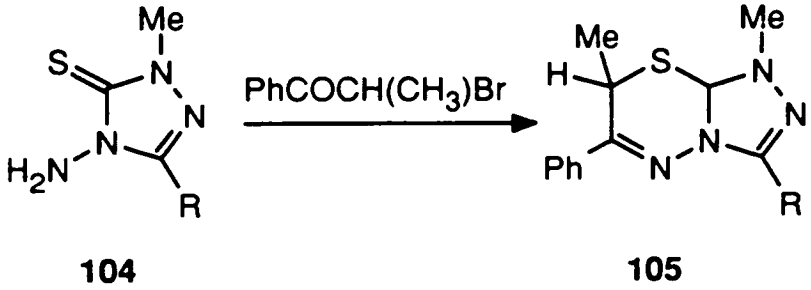
Scheme 39

It has also been reported[46] that the salt **101** can undergo cathodic reduction to give two products. These are the ketimine **102** and the pyrazolo[5,1-*c*]1,2,4-triazole **103**. The final product arises from the reaction of an intermediate with a further equivalent of the salt (Scheme 40).

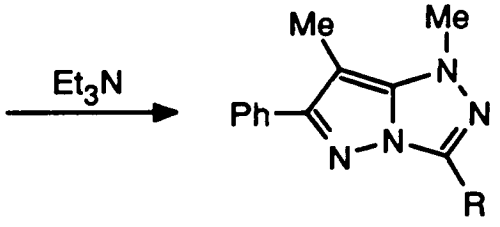


Scheme 40

One other sulphur extrusion reaction has been reported.[46] This synthesis initially requires the reaction of α-bromopropiophenone with the heterocycle **104**. This generates the salt **105**. Subsequent treatment with triethylamine brings about extrusion of sulphur to form the pyrazolo[5,1-*c*]1,2,4-triazole (Scheme 41).



104 **105**



Scheme 41

2. Physical Properties of Pyrazolo[5,1-*c*]1,2,4-Triazoles

(i) Infrared

The infrared spectra of these compounds does not greatly vary from those observed for imidazo[1,2-*b*]pyrazoles. Typical values recorded are 1640-1620 cm^{-1} (C=N) and 1610 (C=C).[29,30]

(ii) Ultraviolet

Pyrazolo[5,1-*c*]1,2,4-triazoles show similar uv spectra to imidazo[1,2-*b*]pyrazoles. Typical values of λ_{max} 253 nm have been quoted.[39]

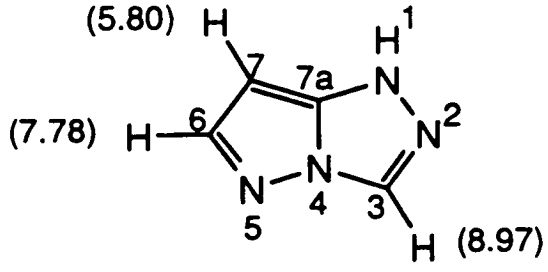
(iii) ^{1}H NMR

Proton NMR of pyrazolo[5,1-*c*]1,2,4-triazoles have been well documented.[13,28,40]

The proton NMR of the parent **106**[28] shows a pair of doublets at δ_H 5.80 and 7.78; these are 7-H and 6-H respectively. 7-H also exhibits finer

coupling which can be attributed to cross ring coupling to 3-H. This cross ring coupling has also been observed in imidazo[1,2-*b*]pyrazoles.

The chemical shifts of 6-H and 7-H are similar to observed (or calculated) values of the corresponding protons in imidazo[1,2-*b*]pyrazoles. In contrast to this a comparison of the chemical shifts of 3-H of the two ring systems shows that the presence of the extra nitrogen atom exhibits a strong deshielding effect upon 3-H. The variation is of the order of 2 ppm.

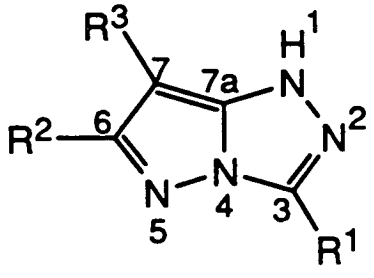


106

Replacement of 6-H with substituents such as Me or Ph have contrasting effects on the chemical shift of 7-H. The presence of a methyl group has a shielding effect, and a chemical shift for 7-H of δ_H 5.55 has been reported.[40] Phenyl groups on the other hand have a deshielding effect approximately 0.3 ppm, typical values for 7-H being ~ δ_H 6.1.[13]

(iv) ^{13}C NMR

^{13}C NMR spectra of pyrazolo[5,1-*c*]1,2,4-triazoles have been studied.[24] Chemical shifts and effects of ring substituents on compound **107** are given in Table 3.*



107

Table 3 ^{13}C Spectra of pyrazolo[5,1-*c*] 1,2,4- triazoles

R^1	R^2	R^3	C-3	C-6	C-7	C-7a
H	Me	H	128.7	157.1	76.4	147.4
Me	Me	H	136.4	156.8	76.9	147.7
H	Ph	H	129.0	158.7	74.3	147.5
Me	Ph	H	136.7	158.4	74.8	147.5
Me	Ph	Me	136.5	158.8	85.4	146.6

* The original assignments for C-7a and C-6 were reversed but this is not consistent with other data.

Alkyl and aryl substituents generally exert a deshielding effect of ~ 9-10 ppm on the carbon atom to which they are attached.[24]

A comparison with imidazo[1,2-*b*]pyrazoles show that C-6, C-7, C-7a have similar shifts in both systems. C-3 is however considerably deshielded in pyrazolo[5,1-*c*]1,2,4-triazoles due to the electron withdrawing effect of the extra nitrogen atom. The change in chemical shift is approximately 21 ppm.[24]

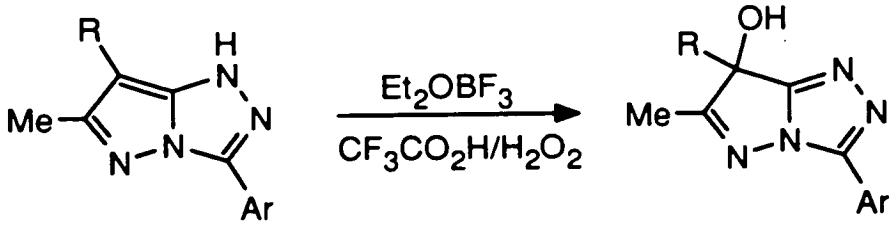
3. Chemistry of Pyrazolo[5,1-*c*]1,2,4-Triazoles

(i) Electrophiles

Simple electrophilic reactions such as methylation, bromination and acylation have not been reported in the open literature. Theoretical calculations[48] indicate bromination should take place at C-7, acetylation and methylation should occur at N-1 (this would be analogous to reactions reported for imidazo[1,2-*b*]pyrazoles).

An unusual electrophilic hydroxylation reaction has been reported by Goddard.[49] This reaction involved treatment of **108** with a mixture of trifluoroacetic acid, boron trifluoride diethyl etherate and hydrogen peroxide. When R=Br the bromo alcohol proved to be quite unstable though **108**

($R=CO_2Et$) gave a stable adduct which presumably could be hydrolysed and decarboxylated (Scheme 42).



108

R = Br, CO_2Et.

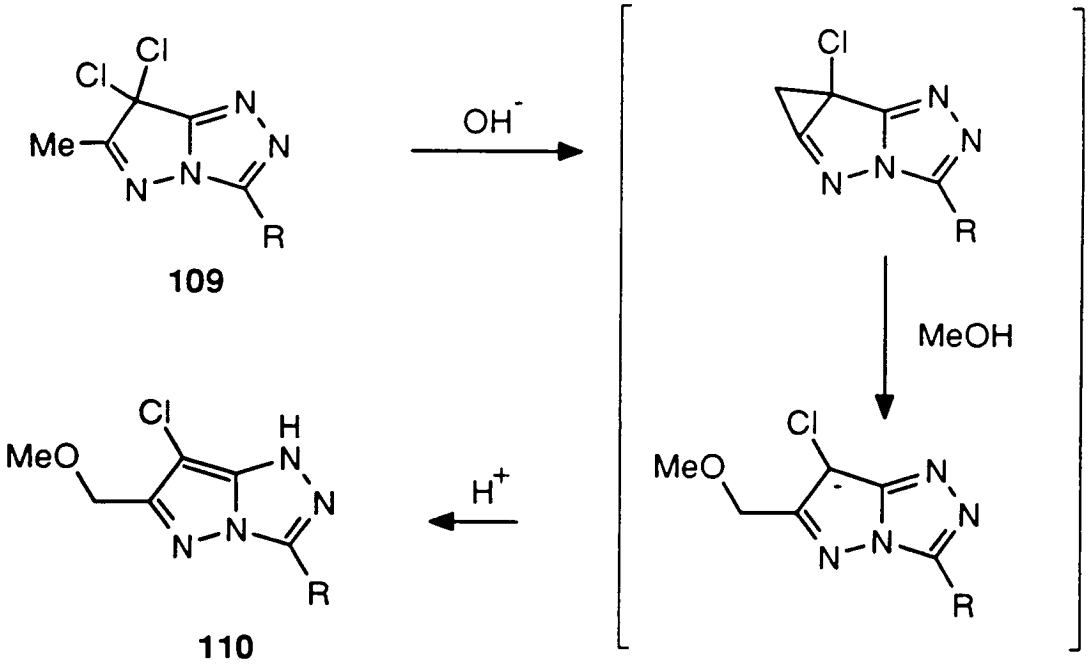
Scheme 42

An attempt to react the hydroxylating mixture with the 7-unsubstituted analogue **108** (R=H) was unsuccessful, possibly due to further oxidation of the hydroxy compound.

(ii) Nucleophiles

No simple nucleophilic reactions have been reported. The theoretical position for nucleophilic attack has been found to be position 3, which is electron deficient due to the presence of a neighbouring aza nitrogen atom.

An interesting reaction has been reported by Goddard.[49] The dichloropyrazolo[5,1-*c*]1,2,4-triazole **109** was reacted with methanolic potassium hydroxide. The expected hydroxyl derivative was not isolated, but instead the 6-methoxy methyl compound **110** was obtained. This observation can be rationalised by the following mechanism (Scheme 43).

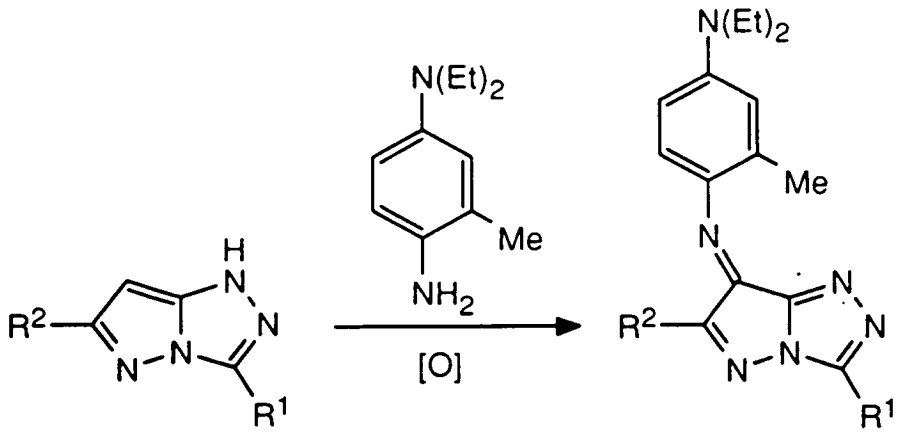


Scheme 43

It is reasonable to suppose that OH^- removes a proton from the relatively acidic methyl group to bring about formation of the cyclopropane. Attack by MeOH then ring opens the cyclopropane; protonation then results in the formation of **110**.

(iii) Oxidative Coupling Reactions

Pyrazolo[5,1-*c*]1,2,4-triazoles react with *p*-phenylenediamines such as 4-diethylamino-2-methylaniline[36] in the presence of oxidising agents (potassium persulphate or silver halides), and this leads to the formation of azomethine dyes **111** (Scheme 44).



111

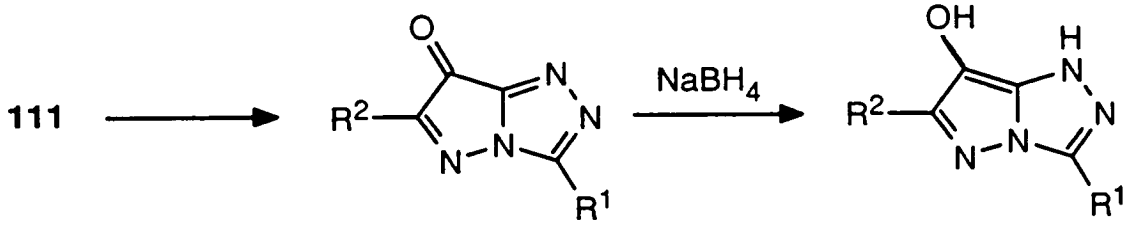
R^1 = Aryl, Alkyl.

R^2 = Aryl, Alkyl.

Scheme 44

The importance of these compounds will be discussed later.

These azamethine dyes can also be hydrolysed to the ketone which is then reduced to the 7-hydroxy compound (Scheme 45).

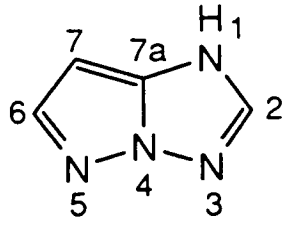


Scheme 45

D. PYRAZOLO[1,5-*b*]1,2,4-TRIAZOLES

This class of compounds was first synthesised in 1984.[50] Research into these compounds has been confined to patent literature although two

reviews have been published.[51,52] The parent ring system, **112**, and numbering scheme is depicted below.



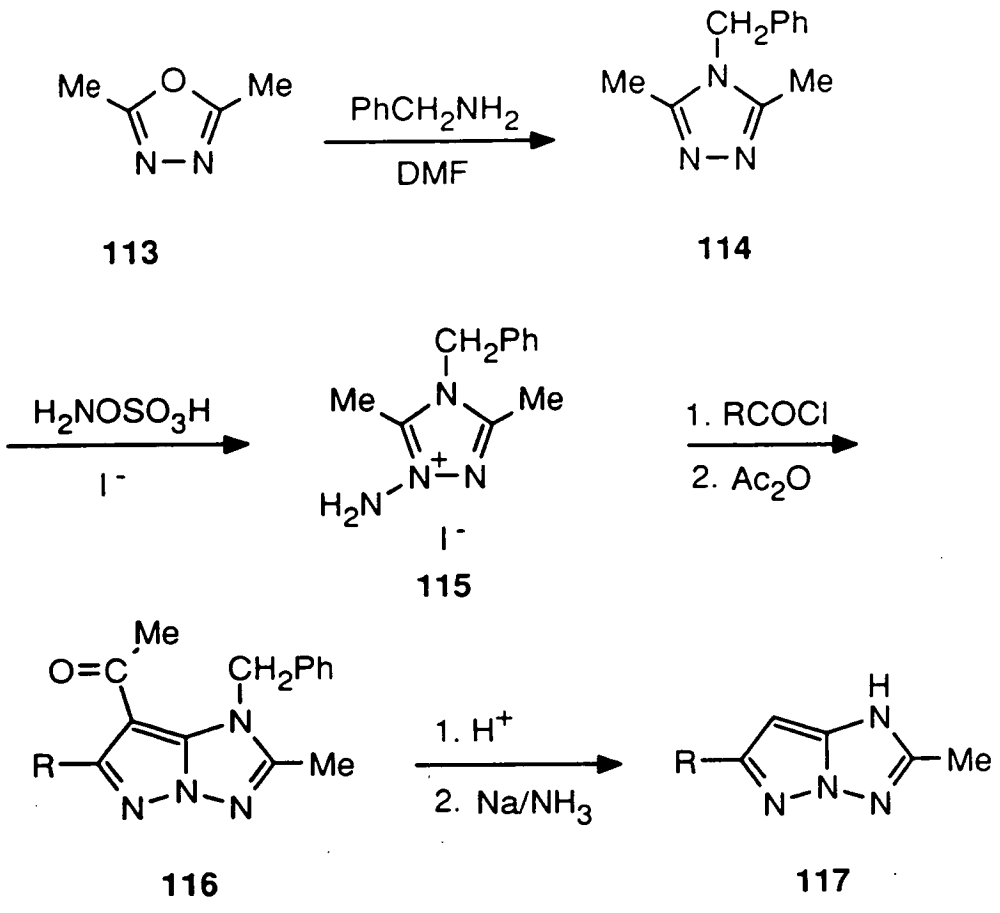
112

1. Synthesis of Pyrazolo[1,5-*b*]1,2,4-Triazoles

Three synthetic routes have been employed to obtain the target system. The first method is derived from 1,2,4-triazoles.[50] The second employs aminopyrazoles[50,53] as the key intermediates while the third uses diaminopyrazoles.[50]

(i) Pyrazolo[1,5-*b*]1,2,4-triazoles From 1,2,4-Triazoles

The first method initially involves the synthesis of a 1,2,4-triazole, **114**, from 1,3,4-oxadiazole, **113**, and benzylamine.[50] The triazole is then *N*-aminated using hydroxylamine-*O*-sulphonic acid to give the salt **115**. This is then treated with an acid chloride and acetic anhydride to afford the cyclised product **116**. Acid hydrolysis and debenzylation (Na/NH_3) afforded the final product **117** (Scheme 46).

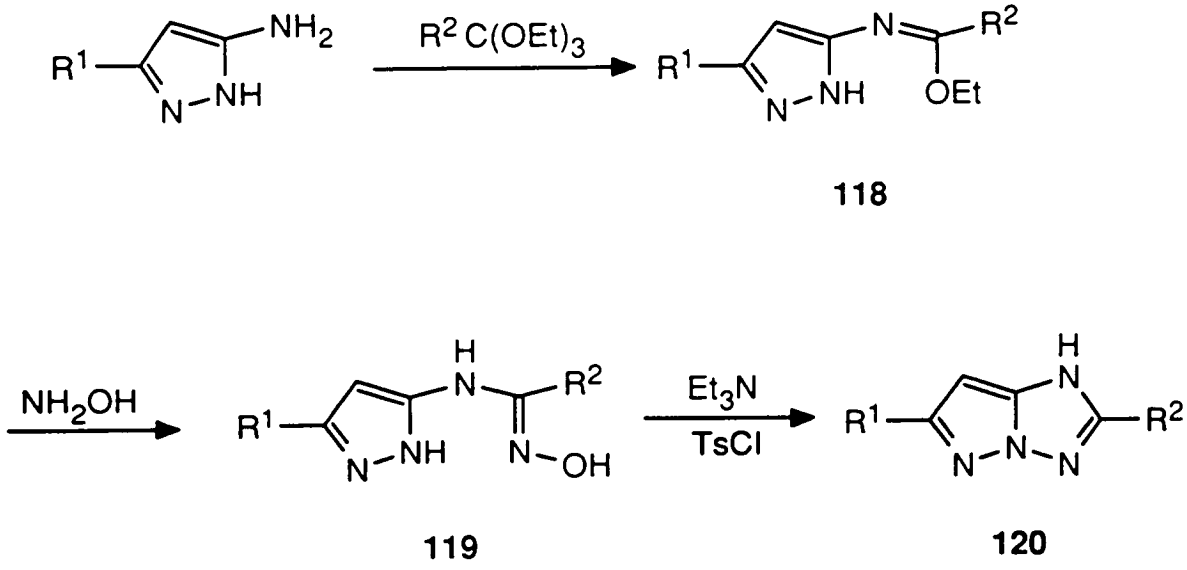


113 114 115 116 117

Scheme 46

(ii) Pyrazolo[1,5-*b*]1,2,4-triazoles From 3-Aminopyrazoles

3-Aminopyrazoles have been successfully used to synthesise pyrazolo[1,5-*b*]1,2,4-triazoles. The first route involves the reaction of a 3-aminopyrazole with a triethyl orthoester to give the imine, **118**. This is then reacted with hydroxylamine to give the oxime **119**, which is readily cyclised in the presence of triethylamine to the product pyrazolo[1,5-*b*]1,2,4-triazole **120**[50,52,53] (Scheme 47).

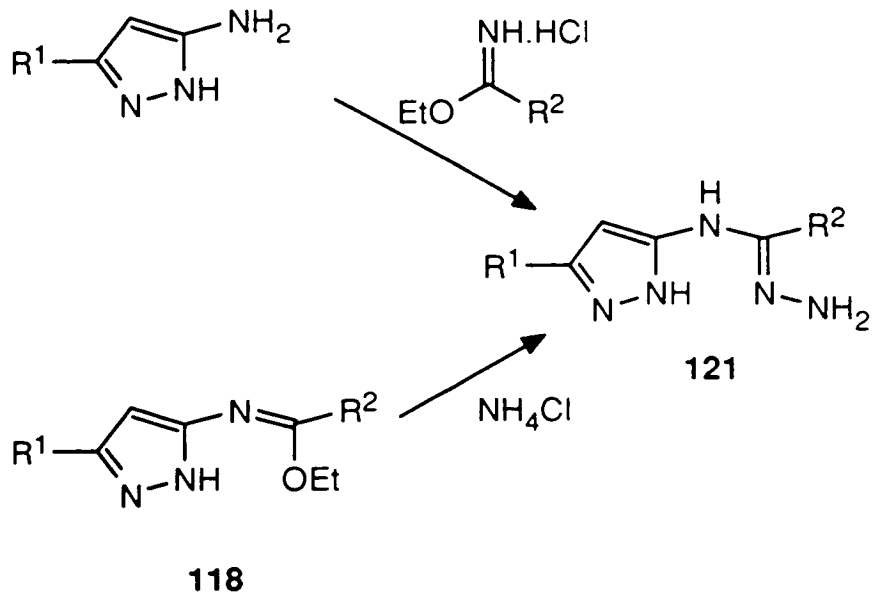


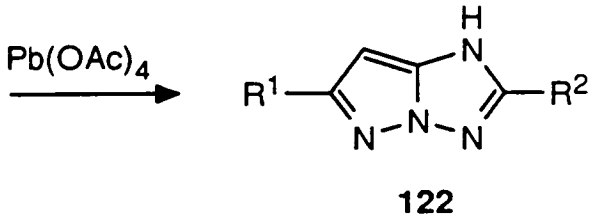
R^1 = Aryl, Alkyl.

R^2 = Aryl, Alkyl.

Scheme 47

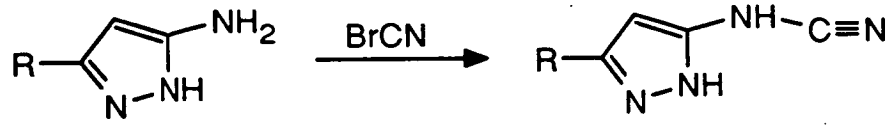
Pyrazolo[1,5-*b*]1,2,4-triazoles may also be obtained from oxidative cyclisation of the amidine **121**. The amidine itself may be prepared by two possible routes. The first route requires the reaction of a 3-aminopyrazole and an iminium hydrochloride. The second reaction uses intermediate **118** (from the previous scheme), and ammonium chloride to generate the amidine. Oxidative cyclisation using lead tetra-acetate gave the product **122**[50,52] (Scheme 48).

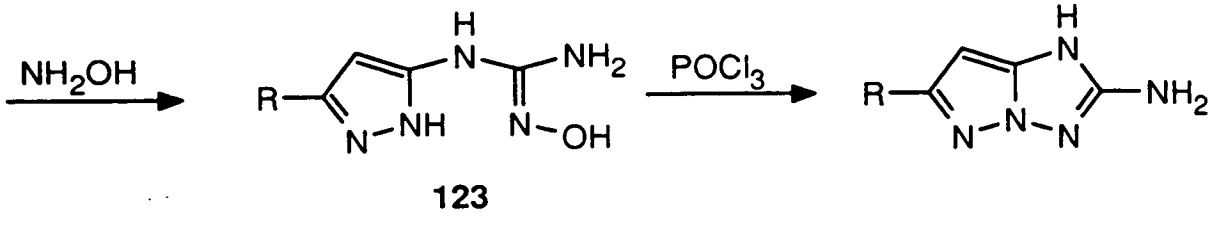




Scheme 48

Aminopyrazoles may also react with cyanogen bromide to give the corresponding cyano adduct.[50] This is in turn reacted with hydroxylamine to give the amino-oxime, **123**. This may then be cyclised in the presence of phosphorus oxychloride to give the pyrazolo[1,5-*b*]1,2,4-triazole (Scheme 49).



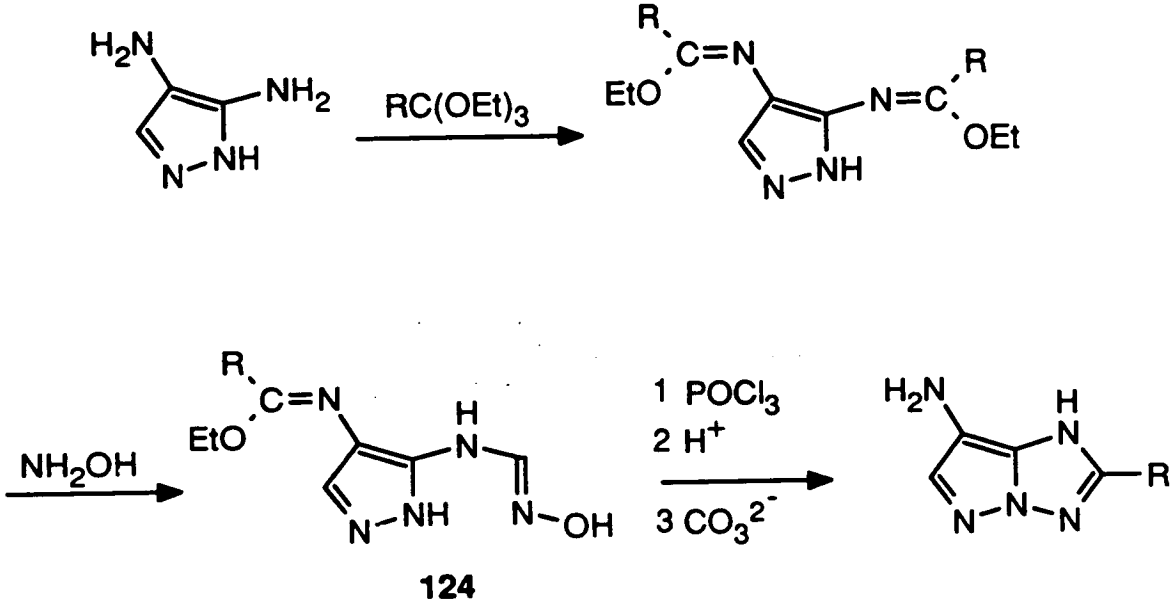


Scheme 49

The introduction of an amino group at position 2 is of importance as a "handle" for the attachment of long chain ballast groups.

(iii) Pyrazolo[1,5-*b*]1,2,4-Triazoles From 3,4-Diaminopyrazoles

3,4-Diaminopyrazoles may also be employed to synthesise pyrazolo[1,5-*b*]1,2,4-triazoles. This synthetic sequence involves the reaction of a triethyl orthoester with the diamine. The subsequent di-imine is then reacted with one equivalent of hydroxylamine which selectively forms the oxime, **124**. Ring closure and hydrolysis of the imine was achieved by phosphorus oxychloride and acid/base work up[50] (Scheme 50).



124

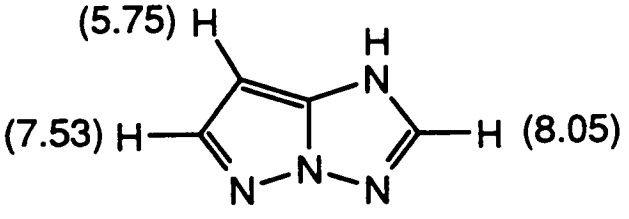
Scheme 50

2. Physical Properties of Pyrazolo[1,5-*b*]1,2,4-Triazoles

Only ^{1}H NMR has been extensively used to characterise these compounds, uv, ^{13}C NMR, and i.r. data have not been recorded. Mass spectrometry reports are limited to the mass ion and no breakdown patterns are given.

(i) ^{1}H NMR

The proton spectrum[50] of the parent, **125**, reveals two doublets at δ_H 5.75 (7-H) and 7.53 (6-H); these chemical shifts are similar to those observed for the pyrazole ring of imidazo[1,2-*b*]pyrazoles and pyrazolo[5,1-*c*)1,2,4-triazoles. A singlet at δ_H 8.05 is assigned to 2-H. This is somewhat deshielded with respect to 2-H of imidazo[1,2-*b*]pyrazoles and this must be due to the presence of the extra nitrogen atom.



125

Other ^{1}H NMR spectra have been recorded of 2,6-dialkylated examples. Chemical shifts for 7-H are δ_H 5.50-5.60.[50,52,53]

3. Chemical Properties of Pyrazolo[1,5-*b*]1,2,4-Triazoles

(i) Electrophiles

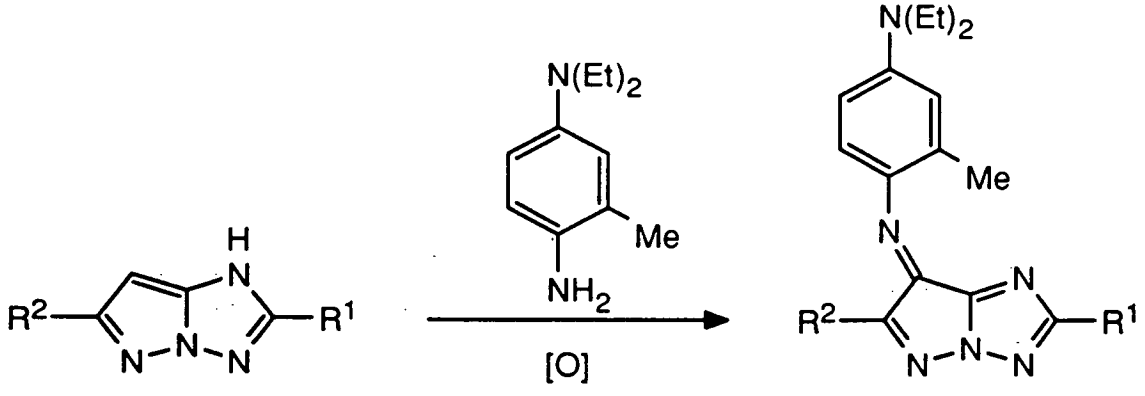
Electrophilic substitution has been predicted to occur at C-7.[48] Simple protonation, methylation and acylation reactions have apparently not been reported. Halogenation and nitrosation reactions have indeed been shown to occur at C-7.[50,53] These two reactions are of importance for the introduction of other functional groups.

(ii) Nucleophiles

Nucleophilic attack on the parent compound has been predicted to occur at C-2.[48] Such reactions have not been reported. However, halogen atoms attached to C-7 may be displaced by amino and thio-compounds.[50]

(iii) Oxidative Coupling Reactions

Pyrazolo[1,5-*b*]1,2,4-triazoles also form azamethine dyes with *p*-phenylene diamines.[50,51,52,53] The reaction is again carried out in the presence of oxidising agents (potassium persulphate or silver halides). Scheme 51 illustrates a typical example.

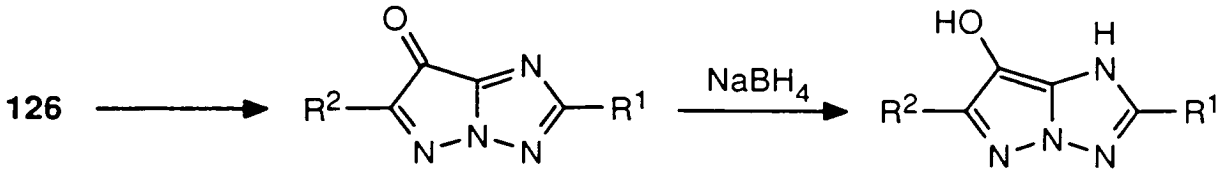


126

Scheme 51

The application and importance of these azamethine compounds will be discussed later.

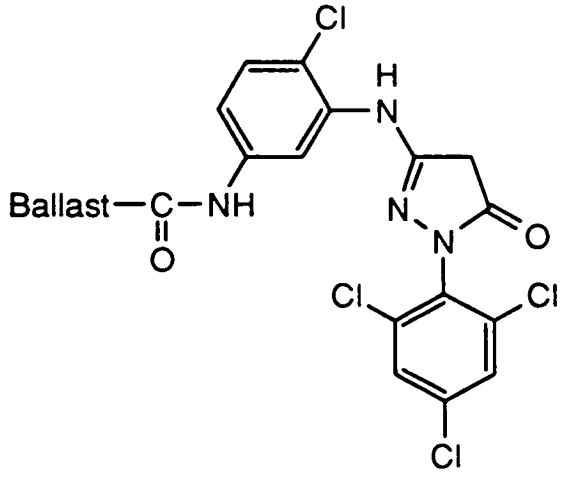
Compound **126** may also be hydrolysed to the ketone which may then be reduced. This provides a good route into the 7-hydroxy series[50] (Scheme 52), which is otherwise difficult to obtain.



Scheme 52

E. PHOTOGRAPHIC APPLICATIONS OF AZAPENTALENE DYES

The azamethine dyes derived from imidazo[1,2-*b*]-pyrazoles, pyrazolo[5,1-*c*]1,2,4-triazoles and pyrazole[1,5-*b*]1,2,4-triazoles are all of interest to the photographic industry. They are all magenta coloured which means they strongly absorb green light. They also minimise unwanted blue absorption at 430 nm which was a problem in the earlier pyrazolone couplers, e.g. **127**.

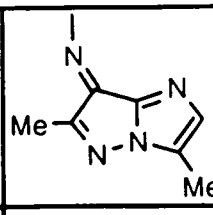
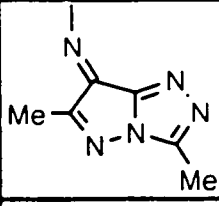
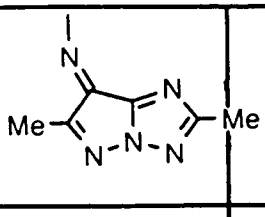


127

Values for λ_{max}, ε, and half band widths (W½) for the three azapentalenes and the pyrazolone have been obtained[54] (see Table 4).

Table 4

Visible light properties of photographic compounds

				**127**
Side Adsorption	-	-	-	430 nm
λ_{max} (EtOAc)	520	521	527	527
ε	NOT OBTAINED	5.3×10^4	5.5×10^4	6.0×10^4
$W_{½}$	78 nm	66 nm	66 nm	67 nm

From this table we can see that the dye from imidazo[1,2-*b*]pyrazole is the least satisfactory of the three azapentalenes. This is because its half band width ($W_{½}$) is too broad, and also it has been reported that its colour hue is inferior to the other azapentalenes.[54]

A comparison of the visible light absorption spectra of the two pyrazolotriazoles and the pyrazolone, **127**, emphasises the superiority of the former[54] (Fig. 2).

Electronic Spectra of Azamethine Dyes Derived From 71, 112, and 127 in EtOAc.

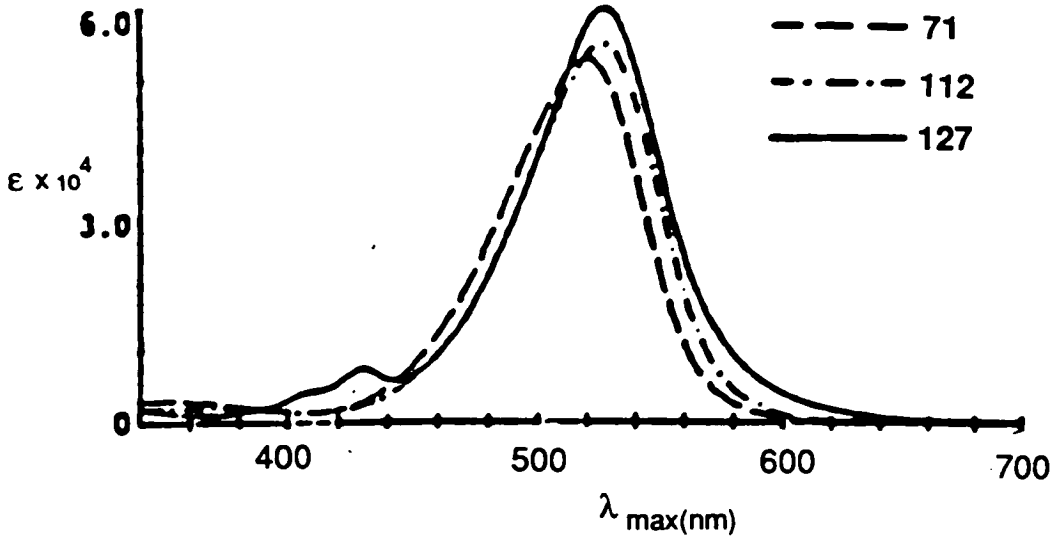


Figure 2

From this we can see that the two azapentalenes greatly reduce blue absorption. Furthermore they both have sharper cut off at the longer wavelengths which will minimise red light absorption.

(i) Effect of Functional Groups

Commercially used azapentalenes are heavily substituted, a typical example is **128**. The effect of the substituents is illustrated in (Fig. 3).[52]

Effect of substituents

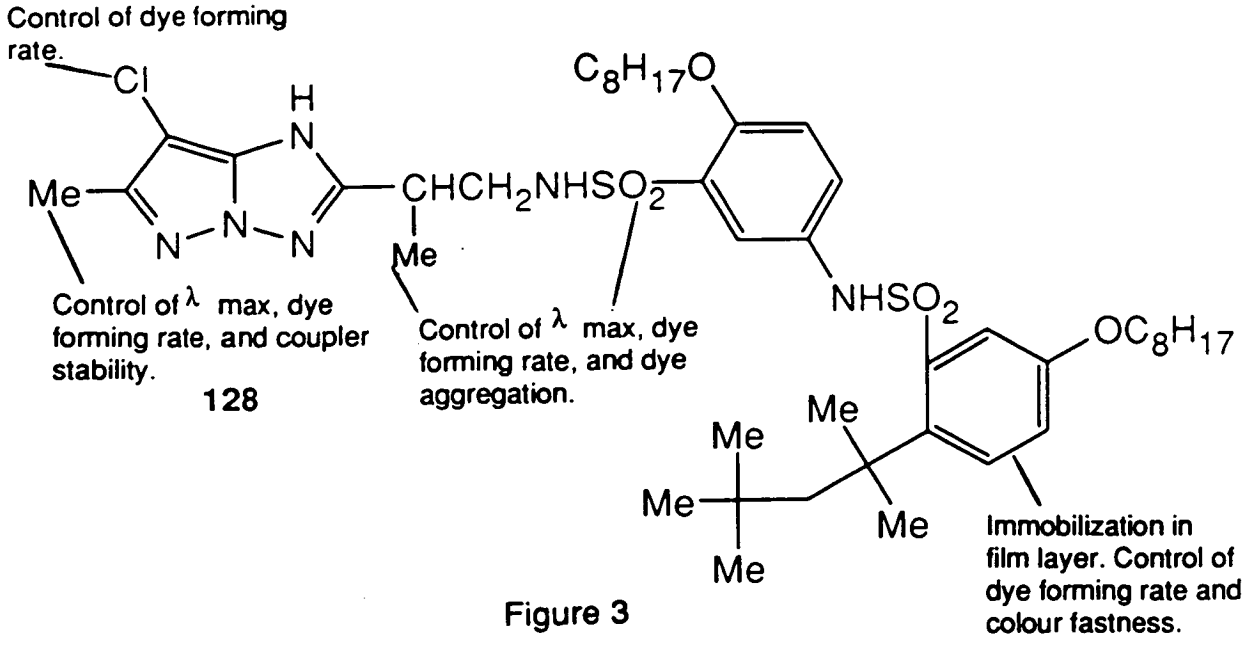


Figure 3

The effect of functional groups at position 6 on λ_{max} is illustrated by the following Hammett plot[52] (Fig. 4).

Substituent effects at position 6 of pyrazolo[1,5-*b*] 1,2,4 triazole dyes

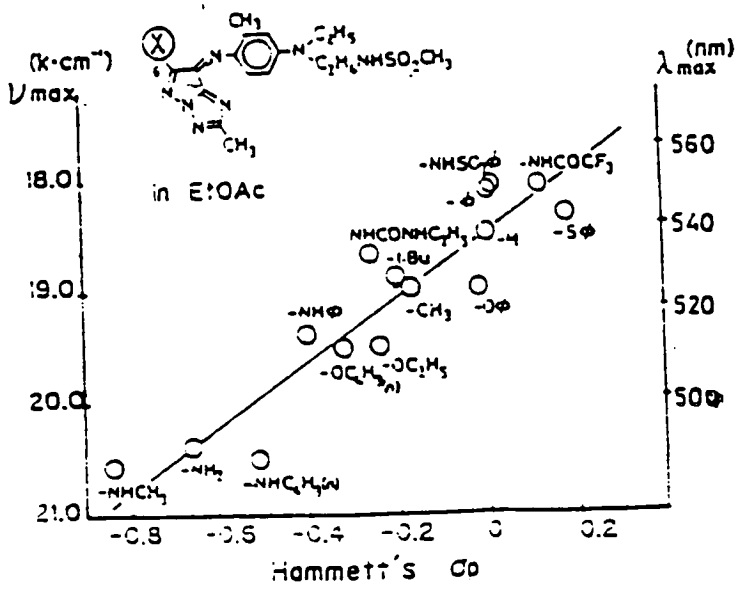


Figure 4

This reveals that λ_{max} decreases as X becomes more electron donating. For example λ_{max} decreases according to the following series:-

$$NH_2 < OEt < Me < H < Ar < NHSO_2Ar.^{52}$$

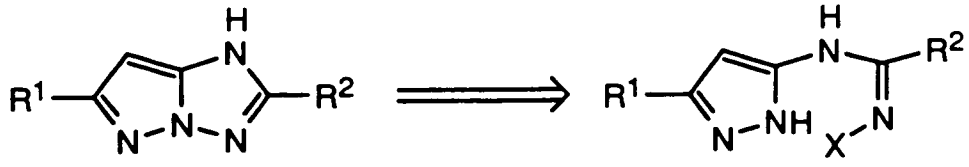
From the plot we can see X = Me or H gives the best value for λ_{max}.

DISCUSSION

A SYNTHESIS AND CHEMISTRY OF 2,3-DIAMINOPYRAZOLES

1. Preamble

Pyrazolo[1,5-*b*]1,2,4-triazoles, **129**, have not been studied outside patent literature.[51,52,53,54] All syntheses previously reported[51] have employed the following disconnection sequence (Scheme 53).

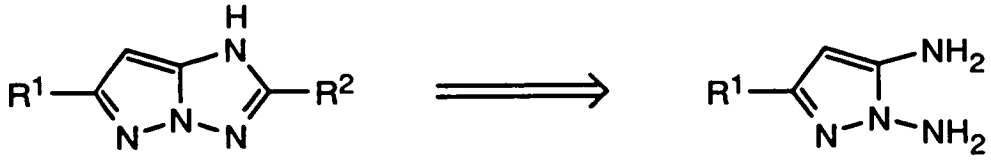


129

R^1, R^2 = alkyl, aryl. X = leaving group.

Scheme 53

We wished to investigate an alternative disconnection sequence (Scheme 54), and at the same time study the chemistry of the 2,3-diamine system **130**.



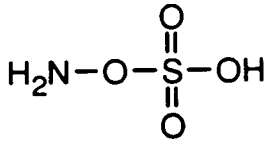
130

Scheme 54

The 2,3-diaminopyrazole, **130,** can potentially be synthesised by electrophilic *N*-amination of the corresponding 3-aminopyrazole.

2. *N*-Amination Reactions of Pyrazoles

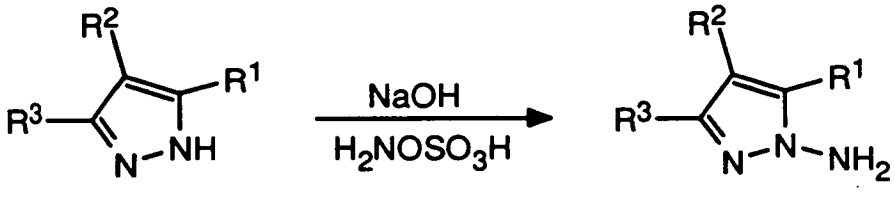
N-Amination of electron rich pyrazoles requires the use of a source of "electrophilic" NH_2. This is most commonly brought about by use of the reagent hydroxylamine-*O*-sulphonic acid,[54] **131**, in the presence of a strong base such as sodium or potassium hydroxide.



131

This reagent is a well-known source of "electrophilic" NH_2 and has been used in numerous *N*-amination reactions.[54]

N-Amination of symmetrical pyrazoles has been extensively carried out by Neunhoeffer and co-workers.[55] A typical reaction (Scheme 55) is shown below.



$R^1 = R^3$ = H or alkyl.

R^2 = H or alkyl.

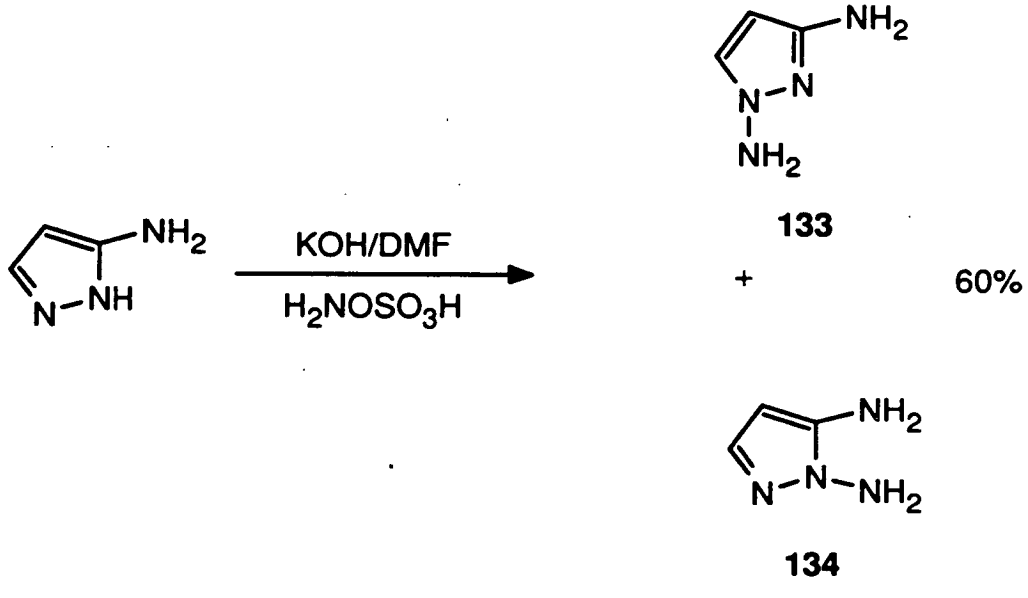
Scheme 55

Yields of up to 99% were reported for these reactions.

N-Amination of functionalised, unsymmetrical pyrazoles such as 3-aminopyrazole poses a greater problem. This is due to the fact that pyrazole anions exist in two resonance structures, *e.g.* **132a** and **132b**.

132a **132b**

This leads to the formation of two products 1,3-diaminopyrazole, **133,** and 2,3-diaminopyrazole, **134**, as a 1:1 mixture. This was carried out by Sliskovic and co-workers in 1986[56] according to the following reaction (Scheme 56).



133

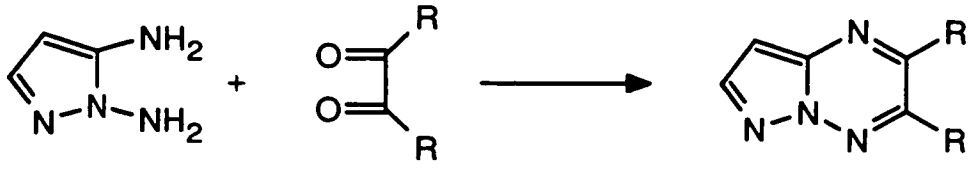
134

Scheme 56

They obtained a mixture of starting material and the two isomers which were separated by flash chromatography using an unusual eluant mixture (chloroform/methanol/triethylamine 94/3/3). Initially the two isomers were

separated from the starting material; the isomeric mixture was then rechromatographed to give the two isomers **133** and **134**. However, the isolated yields were only 10% and 13% respectively.

The 2,3-diaminopyrazole, **134**, was reacted with a series of diones such as glyoxal, butanedione, and benzil to yield the hitherto unknown pyrazolo[1,5-*b*]1,2,4-triazines, **135a-c** (Scheme 57).[56,57]



134

a R = H 90%

b R = Me 100%

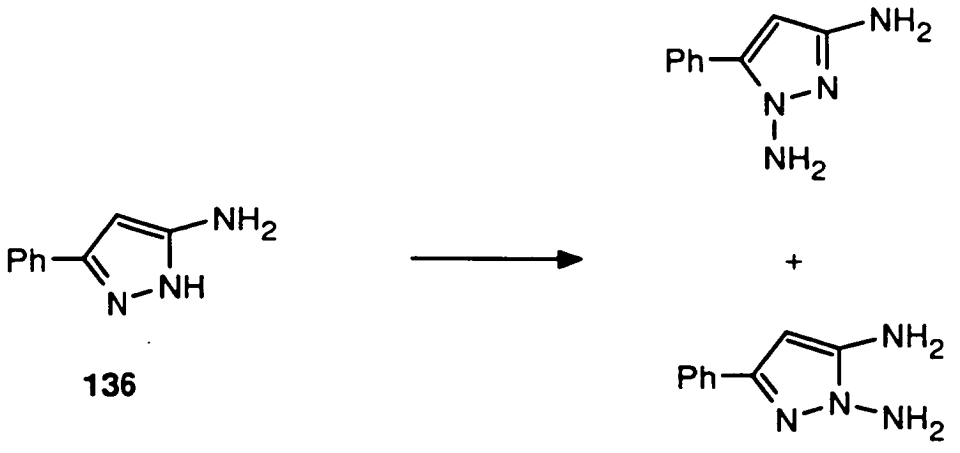
c R = Ph 36%

135a-c

Scheme 57

An attempt to increase the proportion of the 2,3-diaminopyrazole isomer with respect to the 1,3-diaminopyrazole isomer was also reported by Sliskovic.[56]

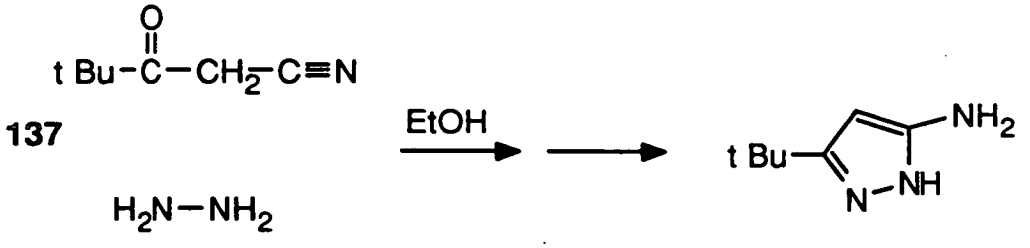
In this reaction 3-amino-5-phenylpyrazole, **136**, was aminated in the hope that the phenyl ring at position 5 would hinder attack at position 1. This was not found to be the case and in view of the planar nature of the phenyl group the result was not very surprising. In this reaction the two isomers proved to be inseparable by chromatography (Scheme 58).



Scheme 58

3. Synthesis of 2,3-Diaminopyrazoles

Three aminopyrazoles were used in these experiments; these were 3-aminopyrazole, 3-amino-5-methylpyrazole and 3-amino-5-t-butylpyrazole. The first two were commercially available compounds while 3-amino-5-t-butylpyrazole was synthesised from 4,4-dimethyl-3-oxopentanenitrile, **137**, and hydrazine (Scheme 59), by the method of Shechter *et al.*[58]



Scheme 59

3-Aminopyrazole was successfully *N*-aminated according to the method of Sliskovic[56] mentioned previously and as reported amination occurred at the 1 and 2 positions in a 1:1 ratio. A ^{1}H NMR spectroscopic study of the mixture revealed doublets at δ_H 7.25 and 5.58 (^3J = 2.2 Hz)

which were identified as 3-aminopyrazole. Two other pairs of doublets at δ_H 7.09, 5.40(^3J = 2.6 Hz) and 7.08, 5.31(^3J = 2.4 Hz) were also recorded, and these were assigned (from the literature) as 1,3-diaminopyrazole and 2,3-diaminopyrazole respectively. Sliskovic[56] reported ^3J values for both isomers of 1.5 Hz, and this would appear to be too low for the 1,3-isomer. Pyrazoles are known to show coupling constants of ~ 3.0 Hz across double bonds, and ~ 1.7 Hz across single bonds.[59] Our coupling constants seem to indicate some form of tautomerism although it is difficult to see how this may occur.

In view of the difficult separation of these isomers, some attempted *in situ* cyclisation reactions of the 2,3-diamino compound were carried out but these were completely unsuccessful. We therefore extended Sliskovic's study (Scheme 58) to the effect of a three dimensional 5-substituent on the regiochemistry of the *N*-amination process.

When 3-amino-5-methylpyrazole was *N*-aminated the formation of 2,3-diamino-5-methylpyrazole was found to be slightly favoured (approximately 60:40 ratio) presumably due to the steric effect of the methyl group. A ^{1}H NMR spectroscopic study of the mixture revealed singlets (pyrazole protons) at δ_H 5.50 (starting material) δ_H 5.39 and 5.28 which were assigned by analogy with the unsubstituted diaminopyrazoles as 1,3-diamino-5-methylpyrazole and 2,3-diamino-5-methylpyrazole respectively.

3-Amino-5-t-butylpyrazole was *N*-aminated under standard conditions and gave two identifiable products characterised by the resonances from their pyrazolic ring protons. These occurred at δ_H 5.31 which was identified as the starting aminopyrazole and δ_H 5.20 which was found to be 2,3-diamino-5-t-butylpyrazole, a peak at δ_H 5.26 could be assigned to 1,3-diamino-5-t-butylpyrazole but was less than 5% of the product formed. Clearly the t-butyl group has had the desired effect on the regiochemistry. The mixture was

about 40% starting material and 60% product so the reaction clearly was in need of optimisation.

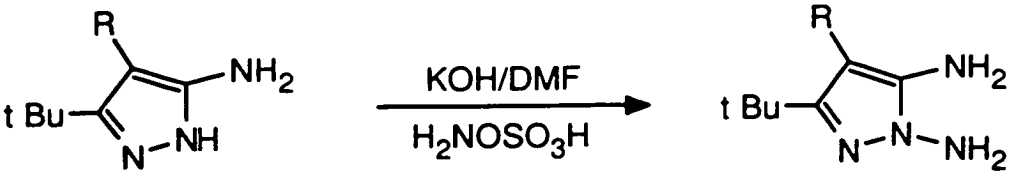
The synthesis was repeated with two equivalents of hydroxylamine-*O*-sulphonic acid and potassium hydroxide. This was found to increase the yield of product but not to push the reaction to completion. To try and accomplish this three and four equivalents of hydroxylamine-*O*-sulphonic acid were used. This, however, did not improve matters and indeed increased the levels of impurities in the final product. An attempt to separate the starting material and product by Kugelrohr distillation proved unsuccessful. Dry flash chromatography[60] (50% ethyl acetate/hexane) did manage to achieve some separation but yields were low and the technique proved to be very time consuming. The best method to maximise the yield was the reaction of 3-amino-5-t-butylpyrazole with the two equivalents of hydroxylamine-*O*-sulphonic acid and potassium hydroxide, isolation of the mixture followed by repetition of the whole reaction sequence. This yielded, after distillation, an oil which was pure enough for subsequent use. Yields of up to 70% based on 3-aminopyrazole were obtained, but were sometimes less, perhaps due to the quality of hydroxylamine-*O*-sulphonic acid. Mass spectrometry showed a mass ion at 154 which is correct for the desired product.

Following the successful synthesis of 2,3-diamino-5-t-butylpyrazole the sequence was extended to 2,3-diamino-5-t-butyl-4-chloropyrazole.

This is because the presence of a halogen in position 4 is beneficial for the formation of photographic dyes (see Introduction Section A). Direct chlorination of the 2,3-diaminopyrazole was unsuccessful and the *N*-amination, using the same conditions as previously, of 3-amino-5-t-butyl-4-chloropyrazole,[61] (synthesised from 3-aminopyrazole and *N*-chlorosuccinimide), brought about the synthesis of 2,3-diamino-5-t-butyl-4-chloropyrazole **139** in reasonable yield, 61%. The product was characterised

by mass spectrometry which showed mass ions at 190 and 188 (1:3 ratio) as expected. ^{13}C NMR spectroscopy showed peaks at δ_C 151.52(q), 141.84(q), 86.62(q), 32.62(q) and 28.37 which are attributable to a single compound and shows no sign of starting material.

The synthetic routes to both diaminopyrazoles are given below (Scheme 60).

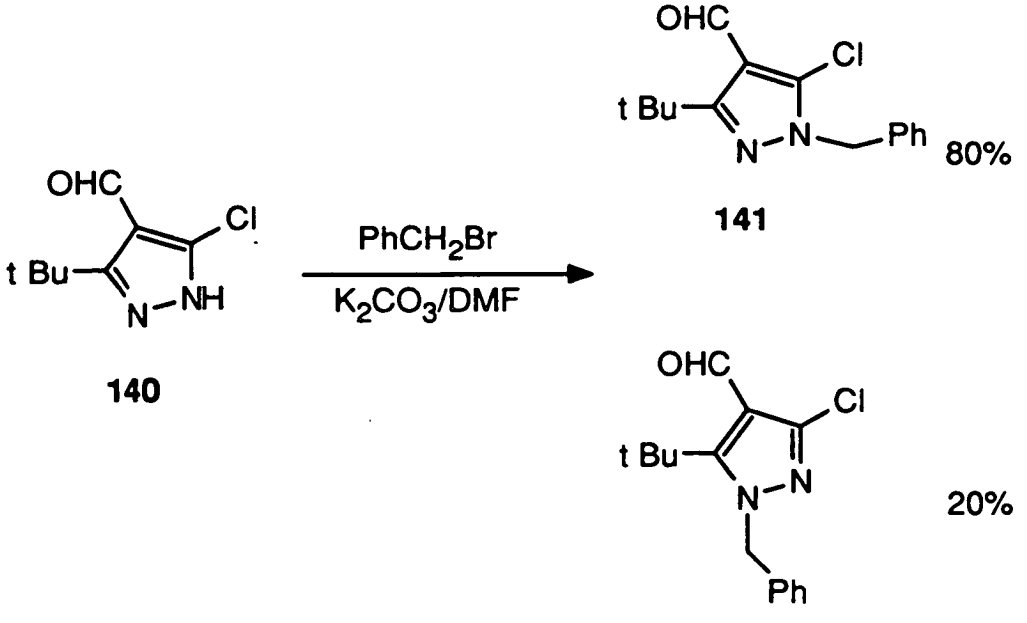


138 R = H

139 R = Cl

Scheme 60

While this work was in progress the steric effect of the t-butyl group in position 5 was reported for *N*-benzylation of pyrazoles.[62] Benzylation of the pyrazole, **140**, gave an 80:20 mixture of **141** and **142**. This selectivity is not as good as the *N*-aminations, and may be due to the relative steric effects of the 3-Cl and 3-NH_2 substituents. Alternatively a "looser" transition state with lesser steric demands may be expected for the *N*-benzylation (Scheme 61).



140

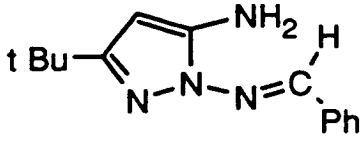
141

142

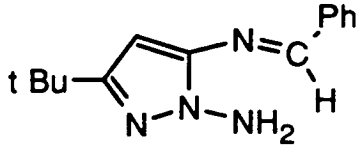
Scheme 61

The aim of the work described in this section was to study the relative reactivity of the two amino functions in 2,3-diamino-5-t-butylpyrazole, with a particular view to synthesise intermediates which might be used in cyclisation reactions.

Benzaldehyde was condensed with 2,3-diamino-5-t-butylpyrazole to yield a single imine. ^1H NMR spectroscopic investigation revealed a characteristic methine proton peak at δ_H 8.88. Mass spectrometry showed a mass ion at 242 which is also correct. This clearly shows that the two amino groups possess widely differing reactivities, and the two possible products, **143** and **144**, are shown below:-

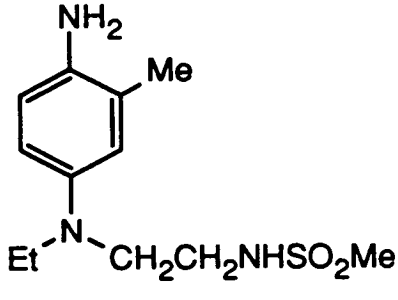


or



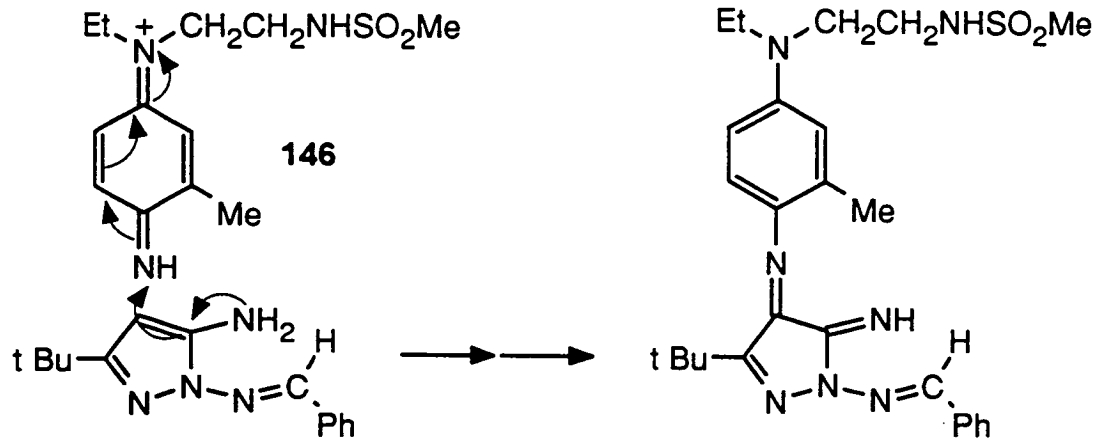
143 **144**

To confirm the regiochemistry it was necessary to use Colour Developing Spray 3 (CD3), **145**, and an oxidising agent ($K_2S_2O_8$).



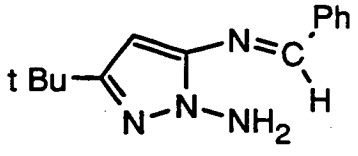
145

CD3 is oxidised to an entity **146** which can react with an activated species. Position 4 in the pyrazole ring of **143** would be susceptible to attack by **146** but **144** would not (Scheme 62).



146

143



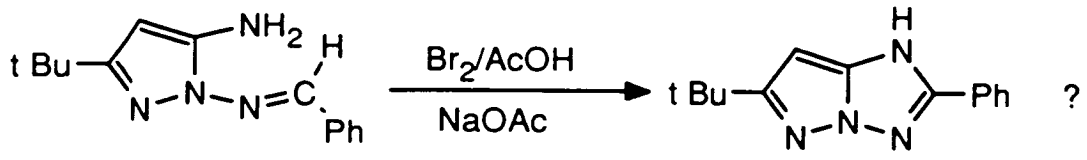
Cannot react.

144

Scheme 62

Development of the tlc plate duly showed a cyan coloured spot which confirmed isomer **143** is the correct structure. Furthermore this also shows that the *N*-amino group possesses much greater reactivity than the 3-amino group.

The imine **143** was subjected to oxidative cyclisation according to the method of Bailey (see Introduction p34-35).[36] This was an attempt to obtain the cyclised product **147** (Scheme 63).



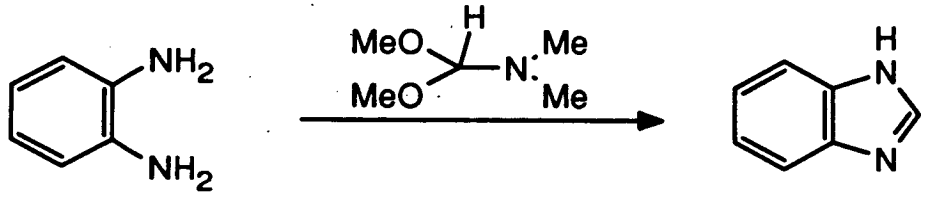
143 **147**

Scheme 63

A black tarry product was obtained which did not show any activity towards CD3. No useful peaks were identified in the ^{1}H NMR spectrum.

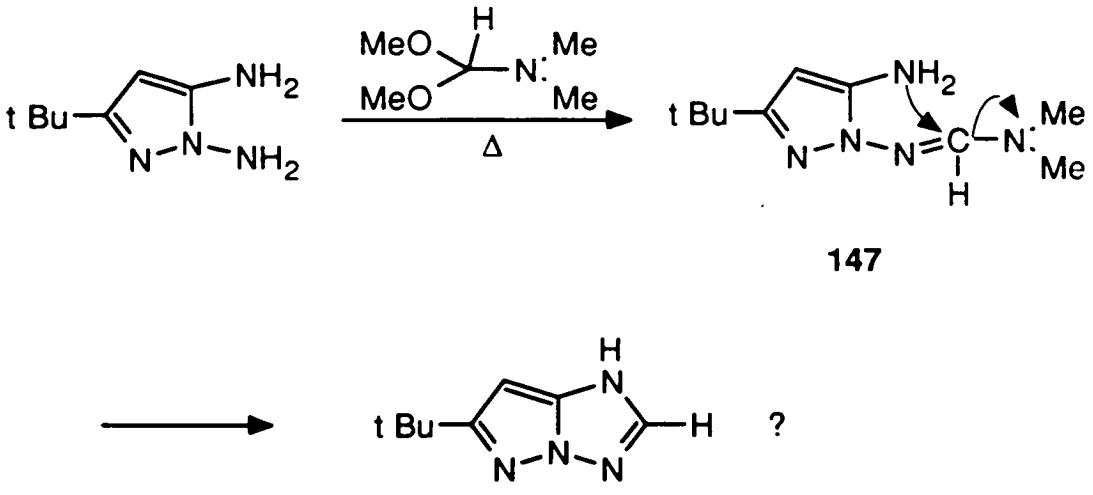
Since the oxidative cyclisation (Scheme 63) was unsuccessful, we then studied examples of trifunctional electrophiles which are at the correct oxidation level for direct cyclisation.

N,*N*-Dimethylformamide dimethyl acetal (DMF acetal) is known to react with *o*-phenylenediamine to give benzimidazole (Scheme 64).[63]



Scheme 64

Therefore 2,3-diamino-5-t-butylpyrazole was reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMF acetal) under a variety of conditions in an attempt to generate the pyrazolo[1,5-*b*]1,2,4-triazole ring system **148** (Scheme 65). By analogy with the benzaldehyde reaction, this process would be expected to take place *via* the mono-amidine **147**.

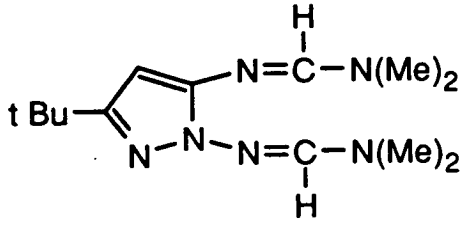


147

148

Scheme 65

The first attempt employed an excess of DMF acetal. The product isolated showed two proton shifts of δ_H 8.27 and δ_H 7.74 which were consistent with the methine protons of the bis-amidine, **149**.



149

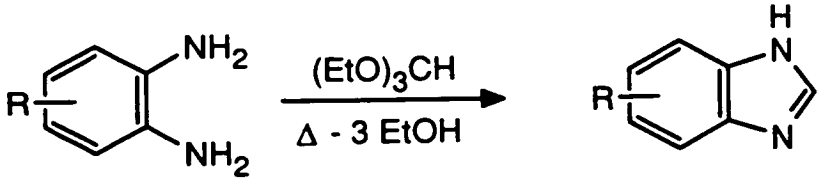
The ^{13}C NMR spectrum showed broadening of the peaks at δ_C 40.11, 37.62(2C) and 34.19 (all assigned to N-Me) which is indicative of restricted rotation about the N-C bond. Mass spectrometry also showed the correct mass ion (264) consistent with the bis-amidine, **149**.

Clearly an excess of DMF acetal was not satisfactory, so a 1:1 mixture of the two reactants was employed. This apparently yielded a mixture of bis-

amidine, some mono-amidine and starting diamine. The ^1H NMR spectrum of the mixture did not show any singlets at ~ δ_H 5.8-6.1 which would be typical for pyrazolo[1,5-*b*]1,2,4-triazoles (see Introduction, p52).[51] DMF acetal however is sufficiently reactive to react with both amino functions and this is in direct contrast to the result obtained with benzaldehyde.

The synthetic scheme then turned to the use of triethyl orthoformate which is less reactive than DMF acetal.

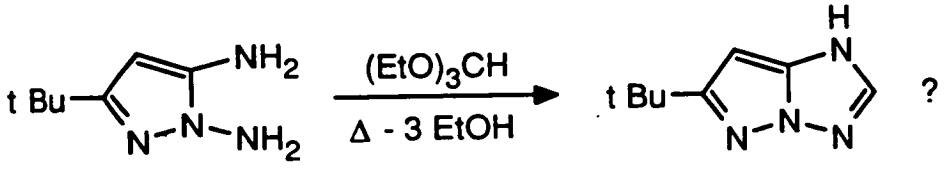
Triethyl orthoformate is known to react with *o*-phenylenediamines to give the corresponding benzimidazole,[64] (Scheme 66). This reaction was successfully repeated on a micro scale using Kugelrohr methodology.



R = H, Alkyl, etc.

Scheme 66

This methodology was then applied to 2,3-diamino-5-t-butylpyrazole in an attempt to obtain the pyrazolo[1,5-*b*]1,2,4-triazole, **148**, (Scheme 67).

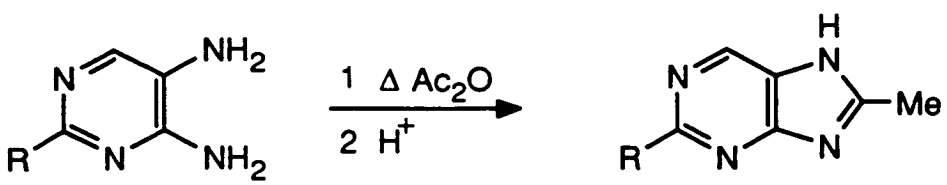


148

Scheme 67

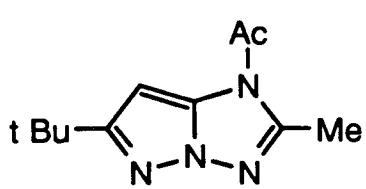
When the two reactants were heated in a Kugelrohr bulb evolution of ethanol was noted (confirmed by ^1H NMR) but the glass like product appeared to be polymeric material.

In view of the failure of triethyl orthoformate, acetic anhydride was chosen as another alternative electrophile which might be less reactive than DMF acetal. Acetic anhydride has been used to synthesise purines (Scheme 68).[65]



Scheme 68

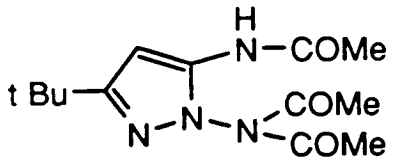
It was hoped the diamino pyrazole could react with acetic anhydride to give the monoacetylated pyrazole which would then undergo an acid catalysed ring closure to yield the acetylated pyrazolo[1,5-*b*]1,2,4-triazole, **150**.



150

The mixture was heated to reflux for 2 h. On cooling a white precipitate was isolated. Mass spectrometry showed a mass ion at 280, ^1H NMR spectroscopy revealed two broad peaks, also indicative of restricted

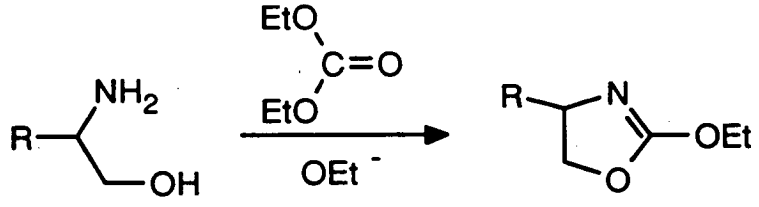
rotation, at δ_H 2.18 and 2.06 which were identified as three methyl groups. The compound was identified as the triacylated diamino pyrazole, **151**.



151

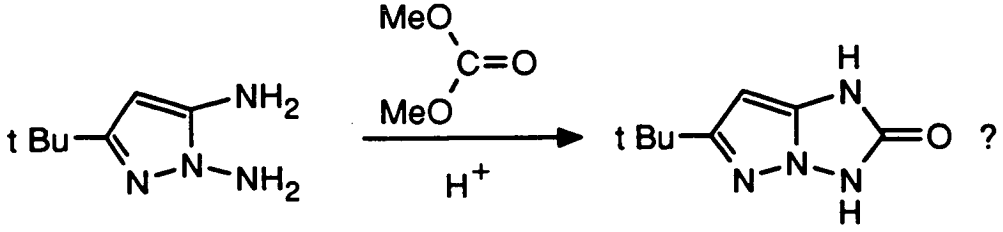
A yellow oil was also obtained, on removal of solvent, and this was identified by mass spectrometry (mass ions 280 and 238) as a mixture of di and triacetylated products.

Diethyl (or dimethyl) carbonate has been shown to react with amino alcohols to give oxazolines (Scheme 69).[66]



Scheme 69

We decided to adapt this methodology to 2,3-diamino-5-t-butylpyrazole in an attempt to synthesise the pyrazolo[1,5-*b*]1,2,4-triazol-2-ones, **152**, (Scheme 70).

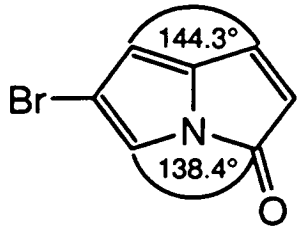


152

Scheme 70

No product was detected by t.l.c. and work up resulted in the recovery of starting material.

The failure of these syntheses could be due to a number of factors:- The first factor could be the differing reactivity of the two amino functional groups. The 3-amino group is much less reactive than the *N*-amino group and could inhibit cyclisation. The second factor could be due to the ring strain exhibited by these ring systems. A good example of a strained 5:5 ring system is 6-bromopyrrolizin-3-one, **153**.[67]

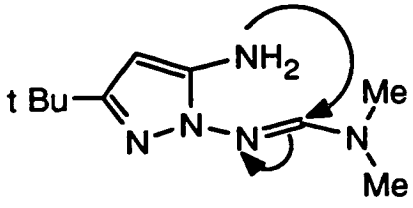


153

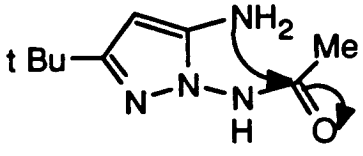
The compound **153** shows a high degree of deviation from the normal 120° associated with planar carbon systems. If this strain is inherent in pyrazolo[1,5-*b*]1,2,4-triazoles it could make cyclisation highly unfavourable.

In addition to this many of these cyclisations involve the *5-endo-trig* process which is predicted to be unfavourable by Baldwin's rules (Fig. 5).[68]

Illustration of Baldwin's Rules.



5 - endo - trig



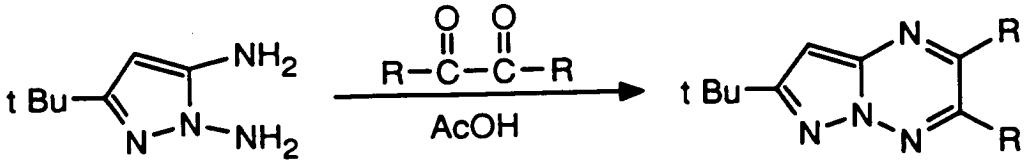
5 - exo - trig

figure 5

Presumably the *5-exo-trig* cyclisations are disfavoured because of the two factors mentioned previously.

4. Cyclisation Reactions of 2,3-Diaminopyrazoles

In an analogous fashion to Sliskovic's work mentioned previously[56,57] 2,3-diamino-5-t-butylpyrazole was found to react with butanedione and benzil to give the corresponding pyrazolo[1,5-*b*]1,2,4-triazines, **154** and **155**, which were identified by mass spectrometry; m/z(204) and (328) respectively (Scheme 71).



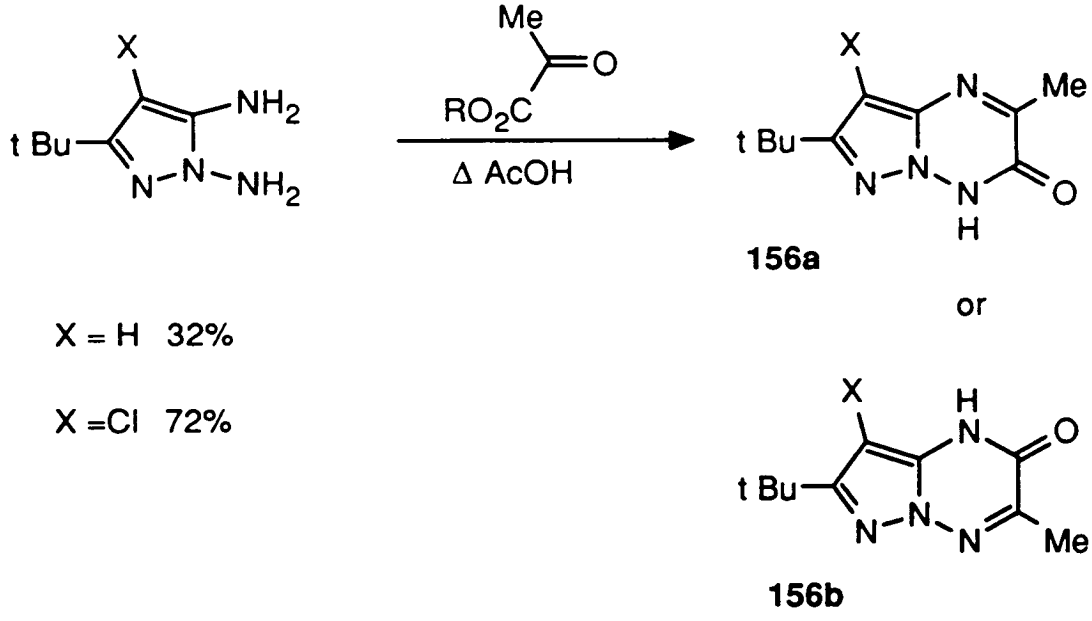
154 R = Me 54%

155 R = Ph 27%

Scheme 71

The lower yield from benzil, also found by Sliskovic, must be due to the lesser reactivity of a phenyl carbonyl group compared to a methyl carbonyl group.

Following these observations it was decided to react 2,3-diamino-5-t-butylpyrazole and its chloro analogue with α-keto esters such as methyl (or ethyl) pyruvate. This would provide a route into the novel pyrazolo[1,5-*b*]1,2,4-triazin-ones. Both 2,3-diamino-5-butylpyrazole and 2,3-diamino-5-t-butyl-4-chloropyrazole were found to react with these reagents in refluxing glacial acetic acid to give single solid products which from their mass spectra could be one of two regioisomers, **156a** and **156b** (Scheme 72).



X = H 32%

X =Cl 72%

Scheme 72

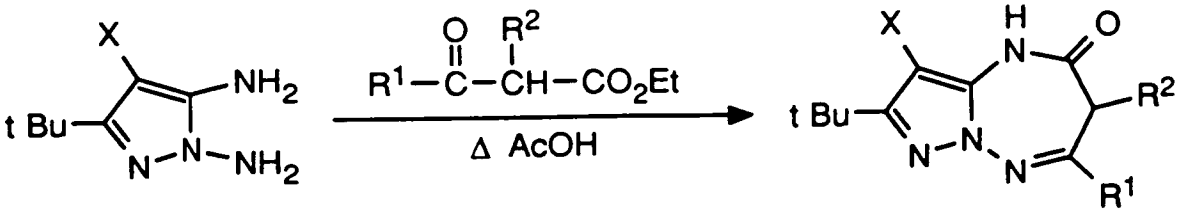
One and a half hours reaction time was found to be optimum: shorter reaction times decreased the yield and this was also the case for longer reaction time, presumably due to decomposition of starting materials or the product.

The presence of the chlorine atom at position 4 apparently increases the yield of cyclised product by a considerable amount: this could be, however, fortuitous.

The products (**156**, X = H and Cl) were both shown to be weakly active towards the coupler (CD3) and this was used to prove that the structure must be the pyrazolo[1,5-*b*]1,2,4-triazin-2-one, **156b**, since the alternative isomer, **156a**, would be inactive (cf. Scheme 62). The regiochemistry is therefore defined by reaction of the more reactive 2-amino function with the ketonic carbonyl group of the pyruvate.

Unfortunately these compounds were not active enough to synthesise the corresponding dye.

By analogy with pyruvates, β-ketoesters also react with 2,3-diaminopyrazoles in refluxing glacial acetic acid to give the novel pyrazolo[1,5-*b*]1,2,4-triazepin-2-ones, **157**, (Scheme 73). The cyclisation was unsuccessful when ethanol was used as solvent: clearly the acid catalysis is important.



157	R^1	R^2	X	
a	Me	H	H	44%
b	Me	Me	H	55%
c	n-Pr	H	H	42%
d	Ph	H	H	0
e	t-Bu	H	H	0
f	Me	H	Cl	81%

Scheme 73

^{1}H NMR spectroscopic studies of these compounds revealed the pyrazole ring protons (**a-c**) all occurred at δ_H 5.80. Mass spectrometry of **a**, **b**, **c** and **f** revealed the correct mass ions at 220, 234, 248 and 256/254 respectively.

The failure to obtain products **d** or **e** must be due to the reduced reactivity of aromatic keto groups (for **d**) and steric problems (a bulky t-butyl group) for **e**.

Compound **157a**, 1*H*-8-t-butyl-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one has been studied by X-ray crystallography (Fig. 6). This confirmed the regiochemistry as shown in Scheme 73. Again the 2-amino function has reacted with the ketone in the β-keto ester. The X-ray also revealed the planarity of the five membered ring and the highly distorted nature of the seven membered ring. The amide bond lengths were found to be 1.360(7) Å

X - Ray Crystal Structure of 157a.

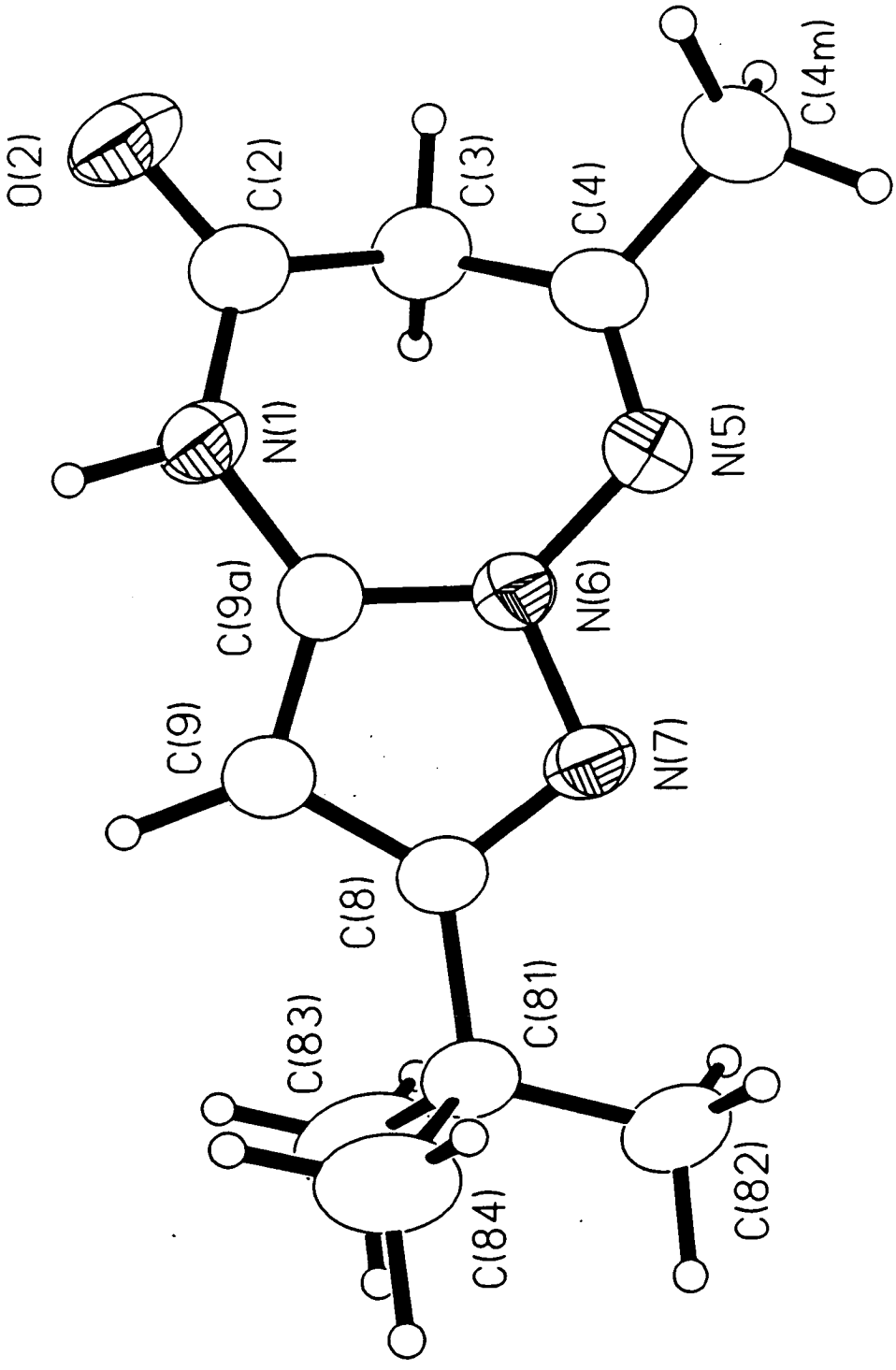


Figure 6

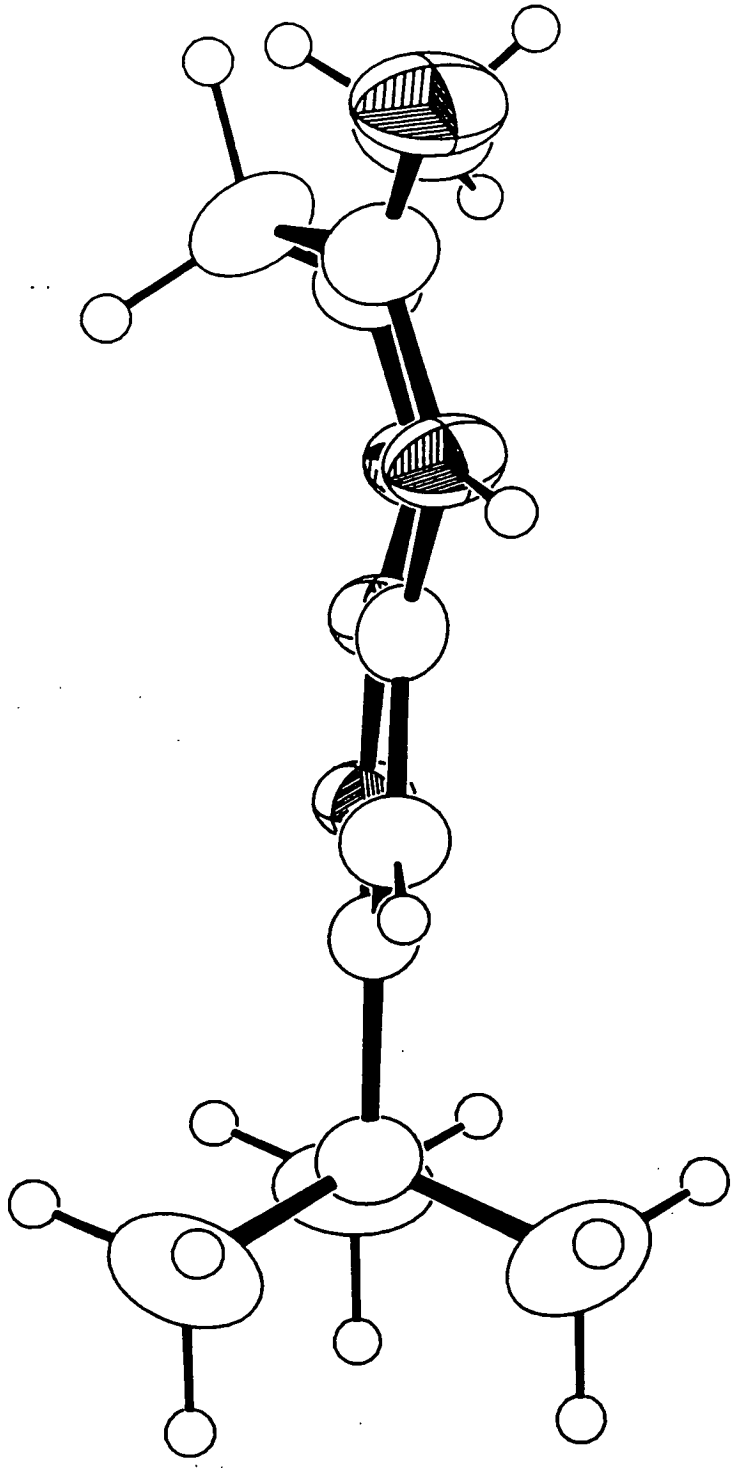


Table 1. Bond Lengths(Å) with standard deviations

N(1) - H(1)	0.998(6)	N(6) - N(7)	1.363(5)
N(1) - C(2)	1.360(7)	N(6) -C(9A)	1.350(6)
N(1) -C(9A)	1.389(6)	N(7) - C(8)	1.327(6)
C(2) - O(2)	1.211(7)	C(8) -C(81)	1.504(7)
C(2) - C(3)	1.500(8)	C(8) - C(9)	1.406(7)
C(3) - C(4)	1.496(8)	C(81) -C(82)	1.511(8)
C(4) -C(4M)	1.473(8)	C(81) -C(83)	1.515(9)
C(4) - N(5)	1.285(7)	C(81) -C(84)	1.535(9)
N(5) - N(6)	1.388(6)	C(9) -C(9A)	1.358(7)

Table 2. Angles(degrees) with standard deviations

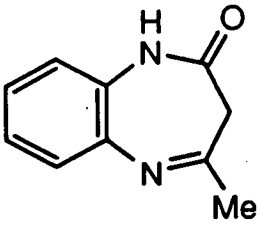
H(1) - N(1) - C(2)	122.7(5)	N(6) - N(7) - C(8)	104.8(4)
H(1) - N(1) -C(9A)	109.6(5)	N(7) - C(8) -C(81)	120.7(4)
C(2) - N(1) -C(9A)	126.9(4)	N(7) - C(8) - C(9)	111.1(4)
N(1) - C(2) - O(2)	121.3(5)	C(81) - C(8) - C(9)	128.2(4)
N(1) - C(2) - C(3)	115.3(5)	C(8) -C(81) -C(82)	112.0(4)
O(2) - C(2) - C(3)	123.3(5)	C(8) -C(81) -C(83)	110.7(5)
C(2) - C(3) - C(4)	114.3(5)	C(8) -C(81) -C(84)	106.9(4)
C(3) - C(4) -C(4M)	118.6(5)	C(82) -C(81) -C(83)	110.9(5)
C(3) - C(4) - N(5)	124.5(5)	C(82) -C(81) -C(84)	108.2(5)
C(4M) - C(4) - N(5)	116.9(5)	C(83) -C(81) -C(84)	108.0(5)
C(4) - N(5) - N(6)	116.8(4)	C(8) - C(9) -C(9A)	105.3(4)
N(5) - N(6) - N(7)	114.3(4)	N(1) -C(9A) - N(6)	124.4(4)
N(5) - N(6) -C(9A)	132.0(4)	N(1) -C(9A) - C(9)	128.1(4)
N(7) - N(6) -C(9A)	111.5(4)	N(6) -C(9A) - C(9)	107.3(4)

Table 3. Torsion angles(degrees) with standard deviations

H(1) - N(1) - C(2) - O(2)	10.9(9)	C(9A) - N(6) - N(7) - C(8)	0.7(5)
H(1) - N(1) - C(2) - C(3)	-168.4(5)	N(5) - N(6) -C(9A) - N(1)	11.5(8)
C(9A) - N(1) - C(2) - O(2)	-179.8(5)	N(5) - N(6) -C(9A) - C(9)	-163.8(5)
C(9A) - N(1) - C(2) - C(3)	0.9(8)	N(7) - N(6) -C(9A) - N(1)	173.6(4)
H(1) - N(1) -C(9A) - N(6)	-159.4(5)	N(7) - N(6) -C(9A) - C(9)	-1.7(5)
H(1) - N(1) -C(9A) - C(9)	14.9(7)	N(6) - N(7) - C(8) -C(81)	-178.4(4)
C(2) - N(1) -C(9A) - N(6)	30.1(8)	N(6) - N(7) - C(8) - C(9)	0.6(5)
C(2) - N(1) -C(9A) - C(9)	-155.6(5)	N(7) - C(8) -C(81) -C(82)	0.7(7)
N(1) - C(2) - C(3) - C(4)	-61.1(6)	N(7) - C(8) -C(81) -C(83)	-123.6(5)
O(2) - C(2) - C(3) - C(4)	119.6(6)	N(7) - C(8) -C(81) -C(84)	119.1(5)
C(2) - C(3) - C(4) -C(4M)	-112.9(6)	C(9) - C(8) -C(81) -C(82)	-178.1(5)
C(2) - C(3) - C(4) - N(5)	67.1(7)	C(9) - C(8) -C(81) -C(83)	57.6(7)
C(3) - C(4) - N(5) - N(6)	-4.0(7)	C(9) - C(8) -C(81) -C(84)	-59.7(7)
C(4M) - C(4) - N(5) - N(6)	176.0(4)	N(7) - C(8) - C(9) -C(9A)	-1.6(6)
C(4) - N(5) - N(6) - N(7)	156.9(4)	C(81) - C(8) - C(9) -C(9A)	177.3(5)
C(4) - N(5) - N(6) -C(9A)	-41.4(7)	C(8) - C(9) -C(9A) - N(1)	-173.1(5)
N(5) - N(6) - N(7) - C(8)	166.2(4)	C(8) - C(9) -C(9A) - N(6)	1.9(5)

(C-N) and 1.211(7) Å (C-O). These values are not significantly different to those obtained for δ lactams: 1.332(11) Å and 1.234(11) Å respectively.[69] The value obtained for the imine group, 1.285(7) Å is also typical (average values for imines 1.279(8) Å.[70]). The pyrazole ring in the molecule has values N-N 1.363(6) Å which also is not significantly different to the isolated pyrazole ring [1.336(19) Å].[70]

Despite the non-planarity of the 7-membered ring, the methylene group shows a singlet at δ_H 3.36 in ^1H NMR which implies a rapid ring inversion mechanism is taking place in solution at room temperature. The free energy of activation ($\Delta G^{\ddagger}$) for the ring inversion of 4-methyl-1*H*-1,5-benzodiazepin-2-one, **158**, has been reported.[71] At -60°C the methylene protons resolved into two doublets and $\Delta G^{\ddagger}$ was found to be 9.5 kcal/mol (39.8 kJ/mol).

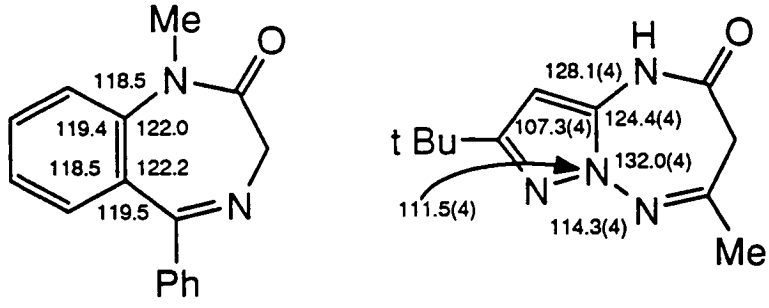


158

The pyrazolo[1,5-*b*]1,2,4-triazepin-2-one **157a** was cooled in $[^2H]_6$ acetone (to -80°C). The methylene singlet at δ_H 3.36 broadened slightly but did not coalesce; this implies the ring inversion process is still extremely rapid.

To try and account for this it is necessary to compare bond angles of **157a** at the ring junction with a well known structure, diazepam,[72] (X-ray data for **158** has not been obtained) (Fig. 7).

A Comparison of Bond Angles in Diazepam and 157a



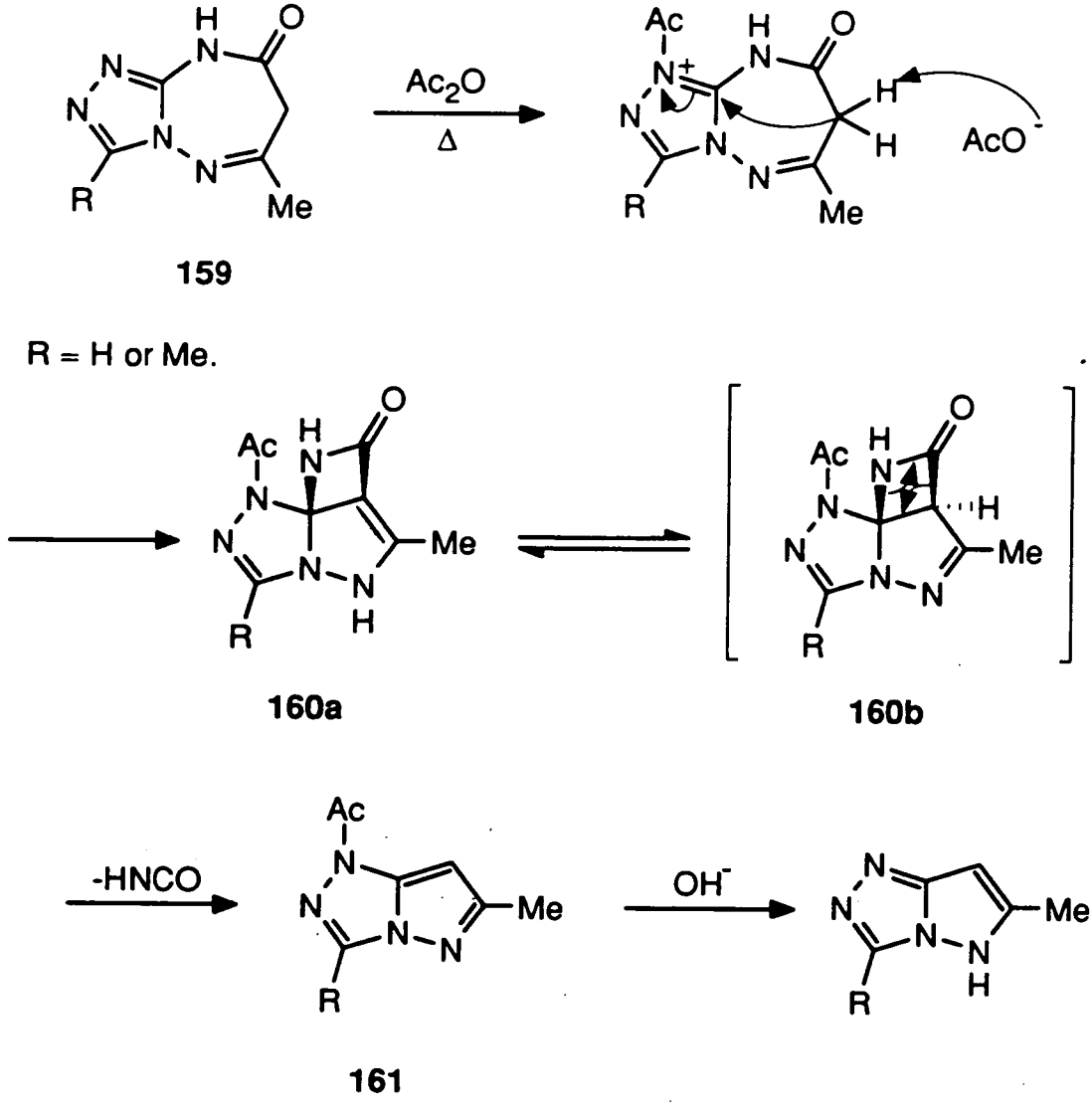
157a

figure 7

The inter-ring bond angles are wider in the 5:7 ring system leading to a more flexible ring structure which might account for the rapidity of the ring inversion process.

The pyrazolo[1,5-*b*]1,2,4-triazepin-2-ones synthesised were all shown to be weak yellow couplers. Coupling would be expected to occur at the methylene position but the result for **157b** was anomalous in this regard (**159b** has a blocked methylene position). Attempts to form the yellow dye, however, proved unsuccessful.

Elguero[40] has reported that analogous triazolo[4,3-*b*]1,2,4-triazepin-2-ones, **159**, can undergo an unusual ring contraction on heating in acetic anhydride to give the acetylated pyrazolo[5,1-*c*]1,2,4-triazole, **161**. This may be then deacylated by treatment with base. The mechanism of the reaction has also been studied,[73] and is believed to involve the formation of β-lactam intermediates **160a** and **160b**. Loss of isocyanate brings about the formation of **161** (Scheme 74).



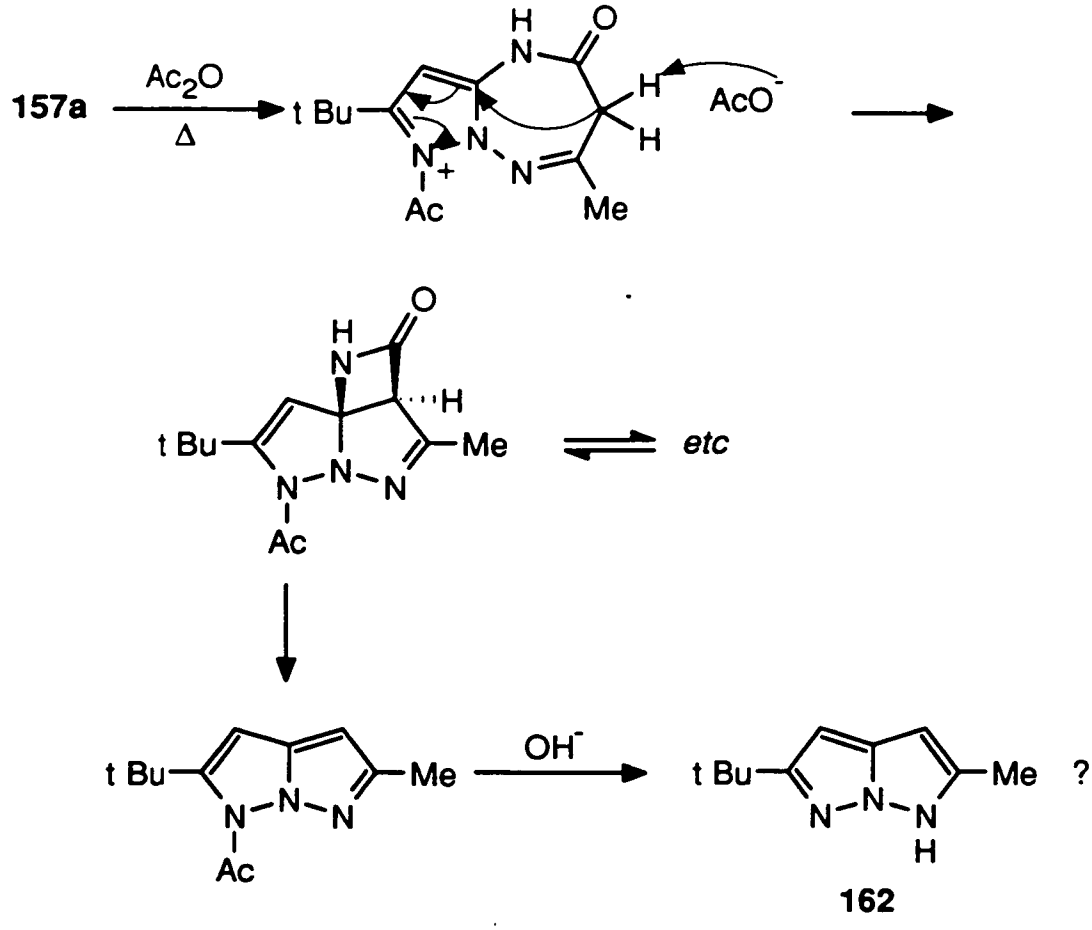
159

160a **160b**

161

Scheme 74

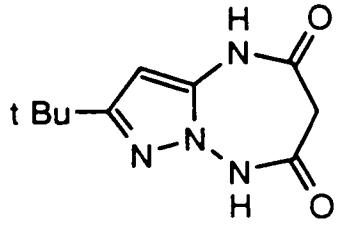
This methodology was applied to pyrazolo[1,5-*b*]1,2,4-triazepin-2-ones in an attempt to generate the poorly known pyrazolo[1,5-*b*]pyrazoles, **162**. The reaction would be expected to proceed *via* an analogous mechanism (Scheme 75).



Scheme 75

The ring contraction conditions and work up were carried out but no useful products were isolated. There are two possible explanations for this: (i) The position of the nitrogen atoms in the five membered ring may be important. This may mean that for the ring contraction to take place it is essential to have a nitrogen atom at position 9, or (ii) The presence of the t-butyl group sterically hinders position 7 and prevents acetylation thus preventing the ring contraction mechanism from operating.

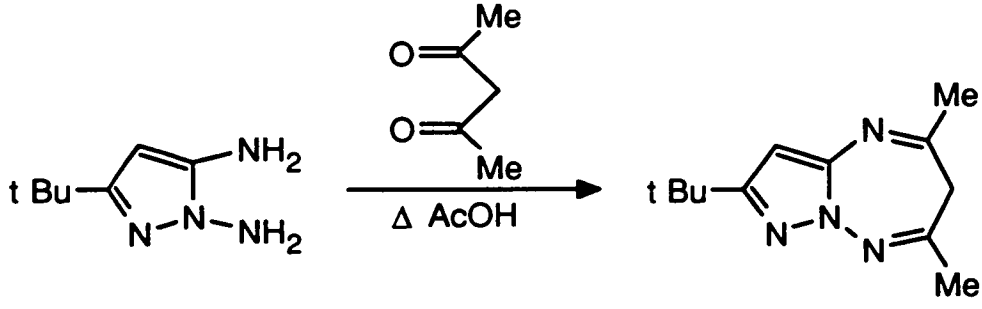
2,3-Diamino-5-t-butylpyrazole was reacted with diethyl malonate in an attempt to obtain the dicarbonyl derivative **163**.



163

However, the reduced reactivity of the di-ester was not sufficient to bring about the formation of any cyclised product.

Acetylacetone was the next reagent used to synthesise a 5:7 ring system. This would be the first example of the simple pyrazolo[1,5-*b*]1,2,4-triazepine ring system, **164**. The reaction was carried out using the standard conditions (refluxing glacial acetic acid). The final product proved difficult to purify at first as silica column chromatography resulted in its decomposition. This problem was overcome by use of deactivated alumina and the product was obtained as an oil (Scheme 76) in 39% yield.



164

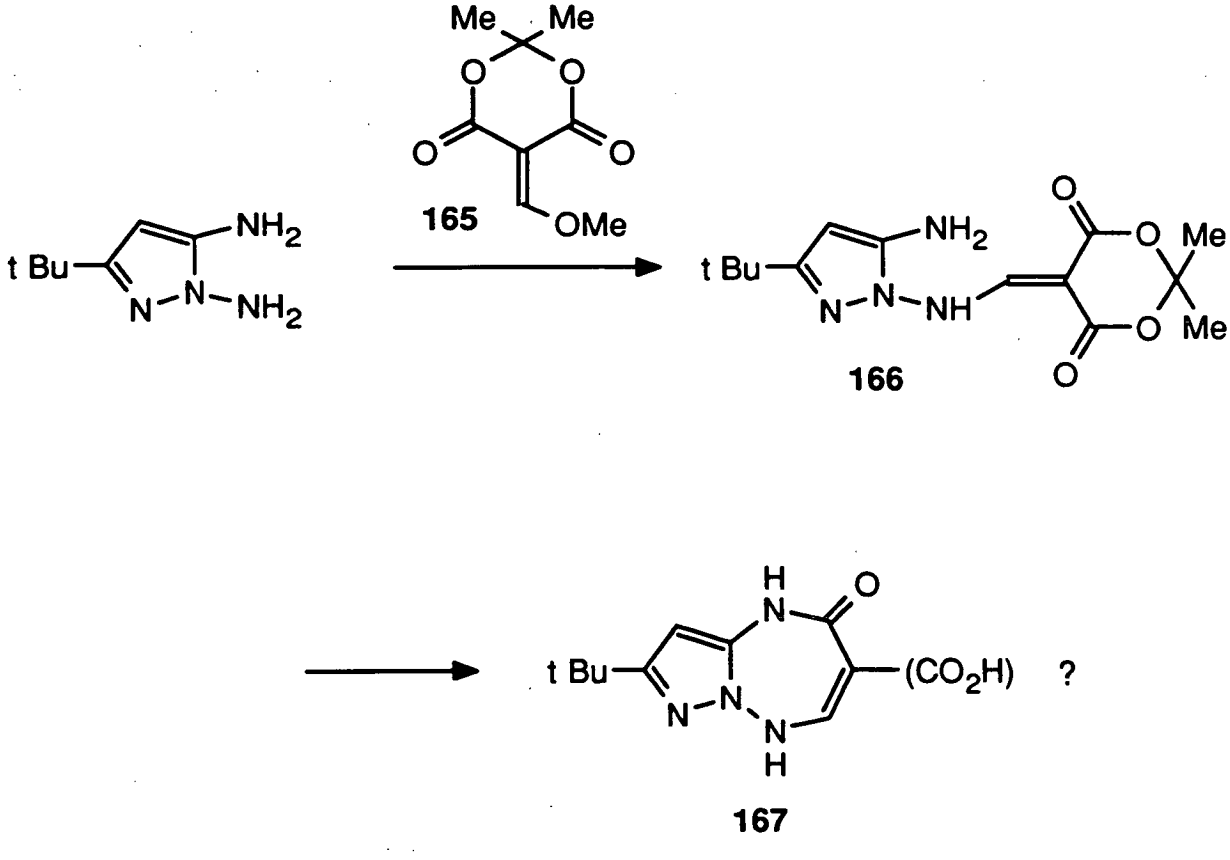
Scheme 76

The methylenic protons at δ_H 3.18 again appeared as a singlet. It was decided to investigate the value of $\Delta G^{\ddagger}$ for ring inversion since it would be reasonable to suppose that **164** would have greater rigidity that the

corresponding pyrazolo[1,5-*b*]1,2,4-triazepin-2-ones. Precedent for this hypothesis exists if we compare values obtained in the literature[71] for 1,5-benzodiazepines and 1,5-benzodiazepin-2-ones. The values are 11.9 Kcal/mol (49.8 KJ/mol) and 9.5 Kcal/mol (39.8 KJ/mol) respectively. Resolution of the methylenic protons occurred at -50°C for the former and -60°C for the latter.

The product **164** was cooled to *ca.* -100°C in $[^2H]_6$-acetone but the methylenic singlet only became slightly broadened; clearly, as previously, rapid ring inversion is still taking place.

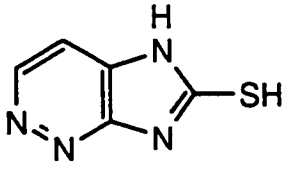
Methoxy methylene Meldrum's acid, **165**,[74] can be considered as a synthetic equivalent of ethyl acetoformate. This could be used as an alternative route into the pyrazolo[1,5-*b*]triazepin-2-one ring system, **167**, (Scheme 77).



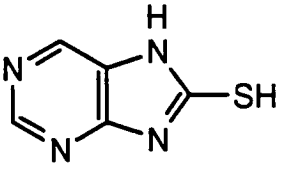
Scheme 77

The product was isolated as a white precipitate (37%). Mass spectrometry showed m/z(M^+ 308, 18%). ^1H NMR showed a methylenic proton at δ_H 8.58. These results indicate the formation of the adduct **166**. It is possible that the adduct could be cyclised to **167** but this was not attempted.

The reactions of carbon disulphide with diamines to give cyclised products are well known.[75] For example reactions of diaminopyridazines and diaminopyrimidines to give cyclised products such as **168a** and **168b** have been reported.[76,77]

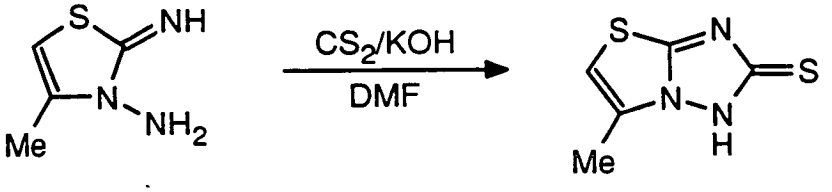


168a

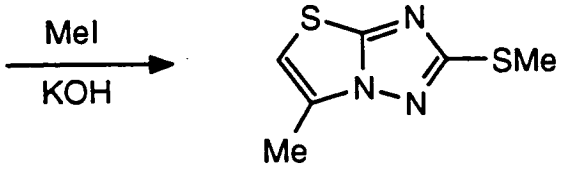


168b

Most importantly of all a synthesis of a strained 5:5 ring system has been reported by Pilgram and Pollard.[78] This synthesis involved the reaction of a 3-amino-2-imino-2-thiazoline, **169**, with carbon disulphide to give the thione **170**, which was then methylated with iodomethane to give **171** (Scheme 78).



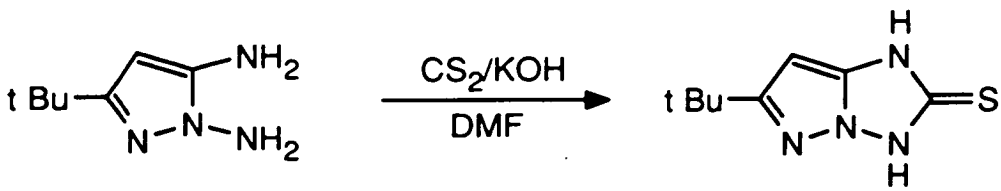
169 **170**



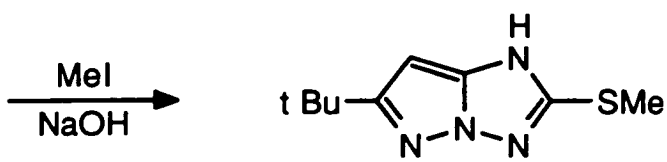
171

Scheme 78

By analogy, reaction of carbon disulphide with 2,3-diamino-5-t-butylpyrazole would generate the thione **172** and subsequent methylation to give **173** would complete the sequence (Scheme 79).



172

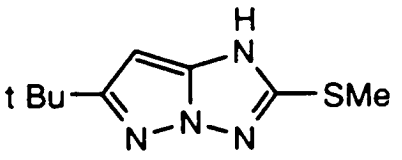


173

Scheme 79

This synthesis was carried out using the same method as Pilgram.[78] On work up of the thione a semi-solid was obtained. Tlc investigation showed many products were present including one which gave a purple spot on spraying with developer (CD3) and oxidiser. This was assumed to be the thione **172**. A ^{1}H NMR spectroscopic investigation of this mixture showed a singlet at δ_H 5.45 which could be attributed to the thione **172**. The mixture was not purified at this stage but was alkylated using iodomethane.

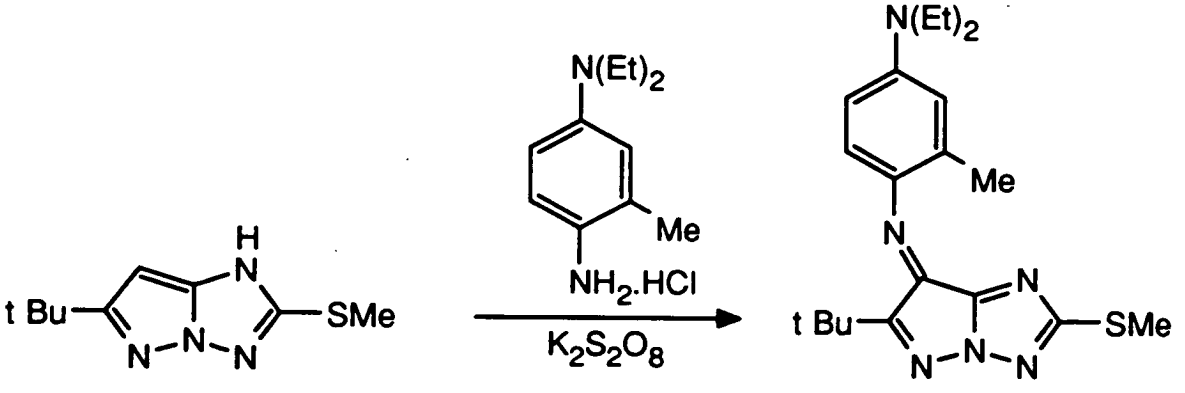
Tlc of the mixture again showed many spots including a product which showed purple on spraying with developer (CD3) and oxidiser. The product was isolated by column chromatography on silica, and was a yellow solid. ^{1}H NMR showed peaks at δ_H 5.61, 2.61 and 1.26 which were attributable to 6-t-butyl-2-methylmercaptopyrazolo[1,5-*b*]1,2,4-triazole, **173**, and this was confirmed by mass spectrometry (*m/z* 210, M^+, 81%).



173

Though overall yields were only in the range of 3-11% this could be explained particularly by the strain of ring closure to form the thione. Investigation of this reaction showed that the thione was only formed in low concentration which would lend support to this hypothesis.

The ring system, **173**, is of importance because of its ability to form magenta coloured dyes (see Introduction). Using methodology reported by Bailey[36] **173** was reacted with 4(*N,N*-diethylamino)-3-methylaminobenzene hydrochloride in the presence of potassium persulphate to give **174** as a purple solid (Scheme 80).

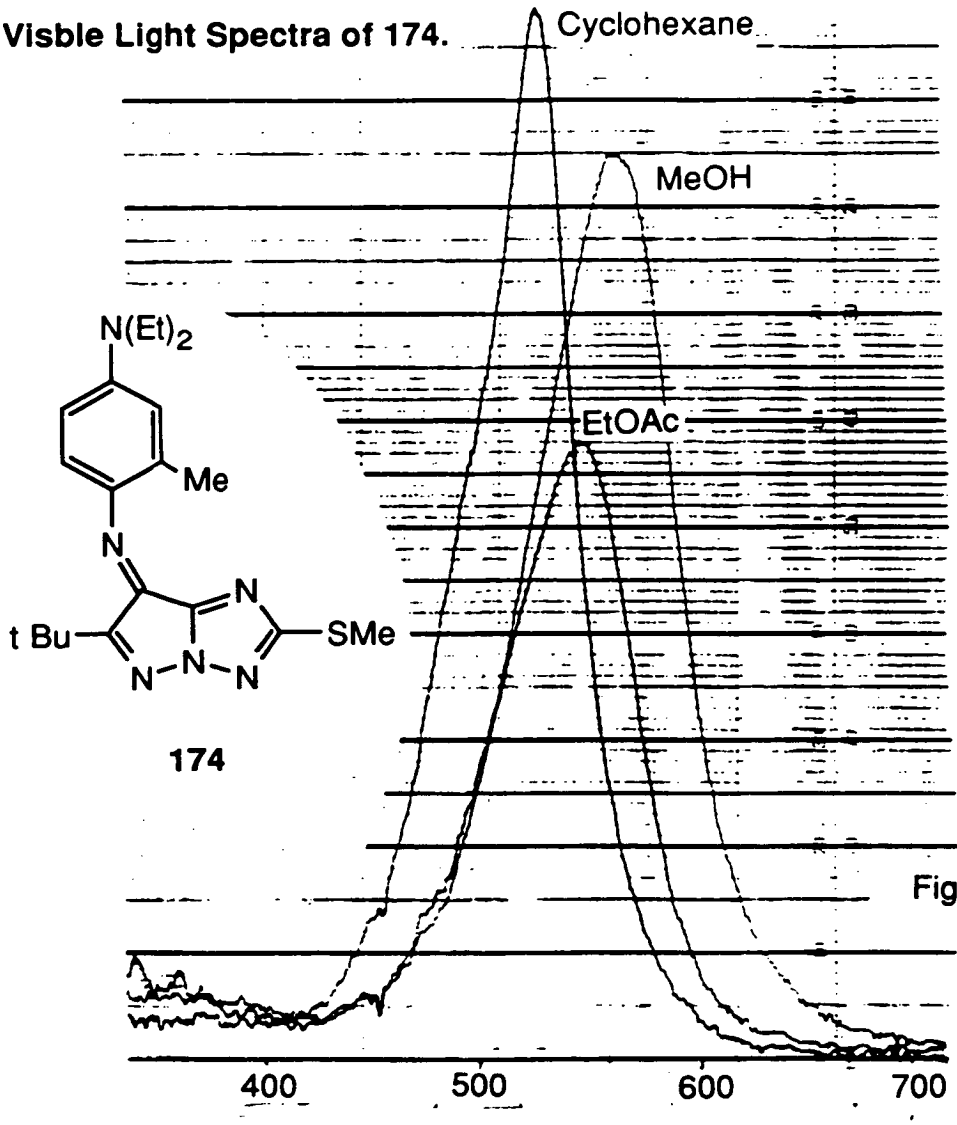


173 **174**

Scheme 80

The product was studied by visible spectroscopy in methanol, ethyl acetate and cyclohexane solvents. The spectra obtained are shown in Fig.8.

Visble Light Spectra of 174.

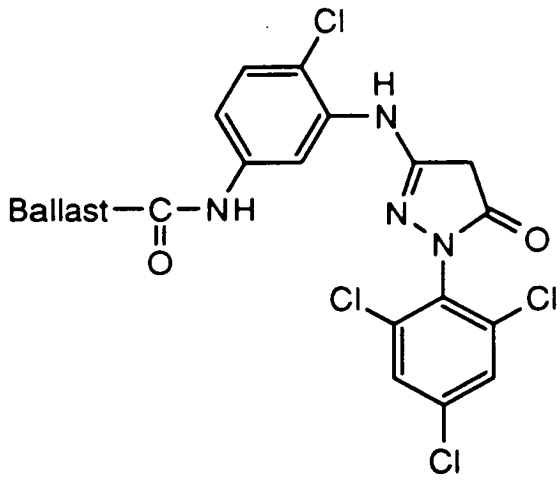


174

Figure 8

Dyes derived from pyrazolo[5,1-*c*]1,2,4-triazoles synthesised by Bailey[36] (see Introduction, Section C), have been shown to undergo bathochromic (red) shifts as the solvent polarity increases. The bathochromic shift was recorded for **174** and found to be 34 nm (cyclohexane → methanol). This observation can be explained by increasing ionisation of the dye as solvent polarity increases.[36]

The visible spectroscopic characteristics of **174** have been compared with the dye obtained from the pyrazolone **127**.[51]



127

Values for λ_{max}, ε, and half band widths ($W_{½}$)† are given in Table 5.

Table 5

Visible Light Properties of 127 and 174

	127	**174**
Side Absorption	430 nm	-
λ_{max} (EtOAc)	527 nm	546 nm
ε	6.0×10^{-4}	5.8×10^{-4}
$W_{½}$	67 nm	66 nm

† (A narrow half band width is essential to avoid absorbance of other parts of the visible spectrum, *i.e.* blue and red).

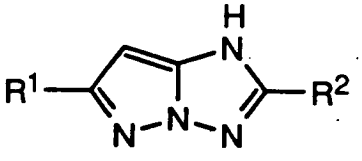
It can be seen from the above table that **174** avoids the troublesome secondary blue absorption of **127**; it also has a comparable vlaue for ε. The band width $W_{½}$ is slightly better and the value for λ_{max} shows good green absorption.

A comparison of the effect of SMe λ_{max} *vs.* other functional groups on **173b** and **173c** has been made (Table 6).

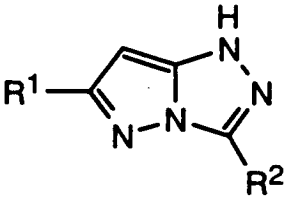
Table 6

Substituent Effects on Ring Systems 173b and 173c

Compound	R^1	R^2	λ_{max} (EtOAc)
173b	t Bu	SMe	546
173b	t Bu	Me	530[51]
173b	Me	Me	527[51]
173c	Me	Me	521[36]
173c	Me	Ph	551[36]
173c	Me	*p*-NO_2-ϕ	570[36]



173b



173c

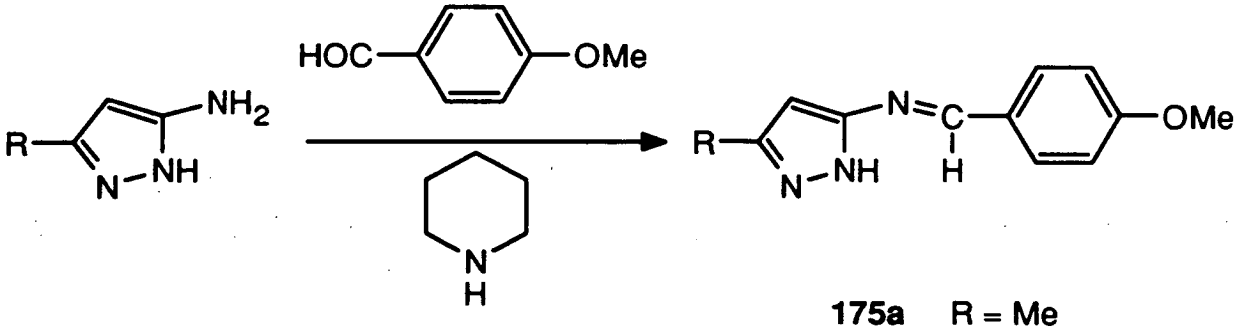
The table shows the two ring systems have very similar properties so a direct comparison of the effect of functional groups is possible. R^1 = t-Bu or Me also shows very little variation. R^1 = Me *vs.* R^1 = SMe (**173b**) shows a bathochromic shift of 16 nm (increased electron withdrawal). This effect is more marked for phenyl and *p*-NO_2-ϕ. To summarise, as electron withdrawing effects become stronger the bathochromic shift becomes more pronounced.

5. Attempted Amination of Protected 3-Aminopyrazoles

It has been shown that simple cyclisation reactions of diaminopyrazoles are often ineffective, probably due to the low reactivity of the 3-amino group. In an attempt to overcome the problem, preliminary work was carried out by protecting the 3-amino position with a group which could potentially cyclise after *N*-amination.

The first route envisaged the *N*-amination of imines although it was recognised that possible hydrolysis could occur.

Two imines were synthesised using methodology reported by Mann.[79] This involved the condensation of *p*-anisaldehyde with the appropriate aminopyrazole (Scheme 81).



175a R = Me

175b R = t Bu

Scheme 81

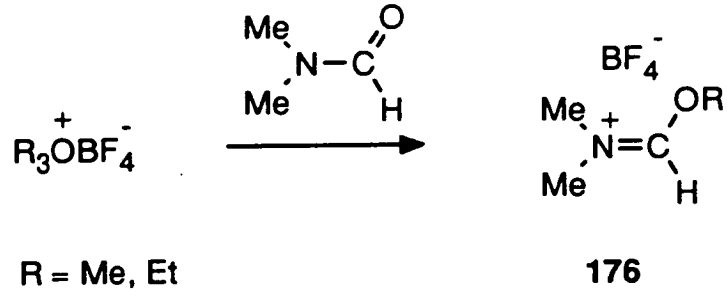
The ^{1}H NMR spectra of these two compounds showed resonances δ_H 8.63 and 8.67 which are attributable to the imine protons. For **175b** the pyrazolic proton occurred at δ_H 6.10 deshielded by 0.8 ppm with respect to 3-amino-5-t-butylpyrazole.

The *N*-amination of **175b** was carried out using the same conditions as before. The resulting product showed a pyrazole resonance at δ_H 5.31 which was identified as coming from the starting aminopyrazole; clearly hydrolysis had taken place.

N-Amination of amidines was the next strategy attempted. Two routes to the starting amidines were developed.

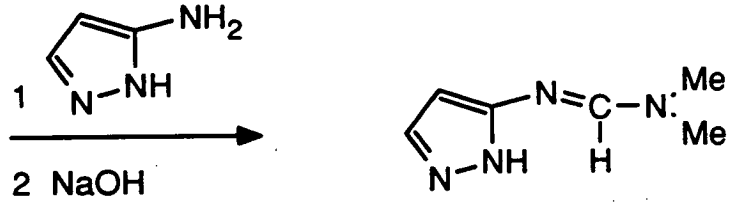
The first route was a preliminary investigation into the use of salts formed from DMF as intermediates to form amidines.

The salts **176** were formed as oils from the reaction of DMF and trialkyl oxonium tetrafluoroborates.[80] The salts were then reacted with 3-aminopyrazole to give the amidine **177** (Scheme 82).



R = Me, Et

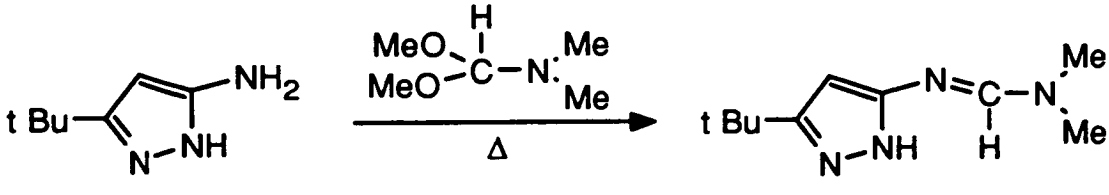
176



177

Scheme 82

This method was not pursued further due to its supersession by a more convenient one step synthetic route. Dimethyl formamide dimethyl acetal has been found to react with 2,3-diamino-5-t-butylpyrazole to give a bis-amidine (see Page 71). Accordingly 3-amino-5-t-butylpyrazole was reacted under the same conditions to give the mono-amidine **178** (Scheme 83).

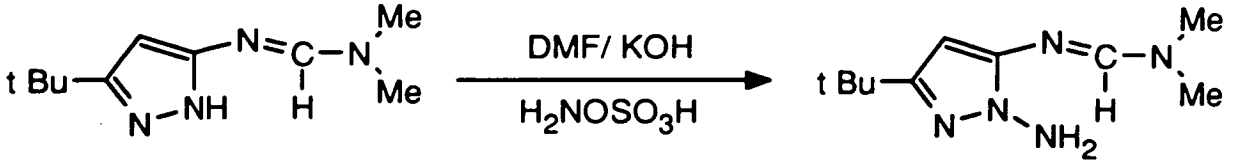


178

Scheme 83

The amidine showed a signal (in ^1H NMR) at δ_H 7.85 which was attributable to the methine proton, and the mass spectrum showed the correct parent ion (*m/z* 194).

The amidine **178** was *N*-aminated under standard conditions (Scheme 84).



178 **179**

Scheme 84

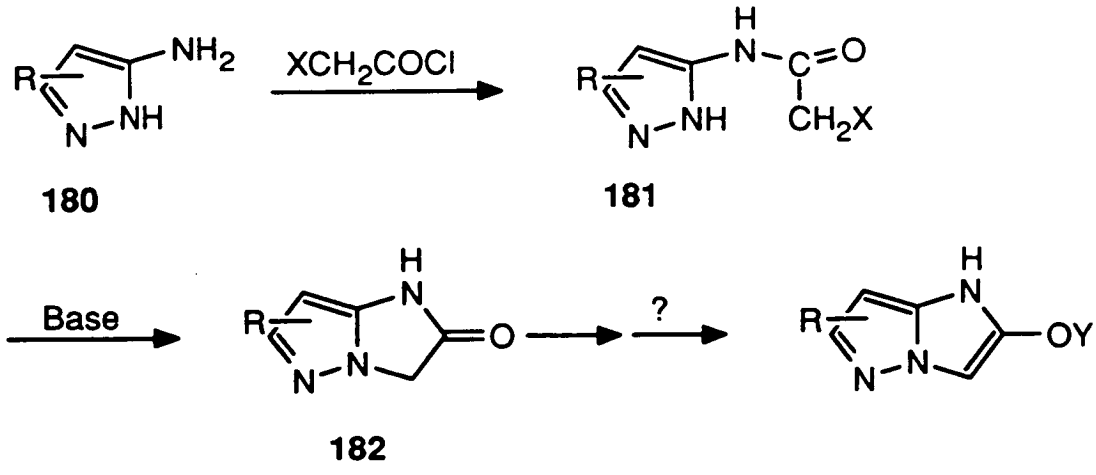
The reaction gave two products; one was starting material while the other was identified as **179**. This was confirmed by mass spectrometry which showed a peak at 209 which is attributable to the molecular ion of **179**; a peak at 194 was also detected which was starting material.

Attempts were made to optimise the reaction by increasing the amount of hydroxylamine-*O*-sulphonic acid but without success.

No cyclisation products were detected in the reaction mixture. The increased reactivity of the 2-amino function should aid cyclisation, however, since this is a *5-endo-trig* process this is disfavoured by Baldwin's rules.[68]

B. ACYLATION REACTIONS OF AMINOPYRAZOLES

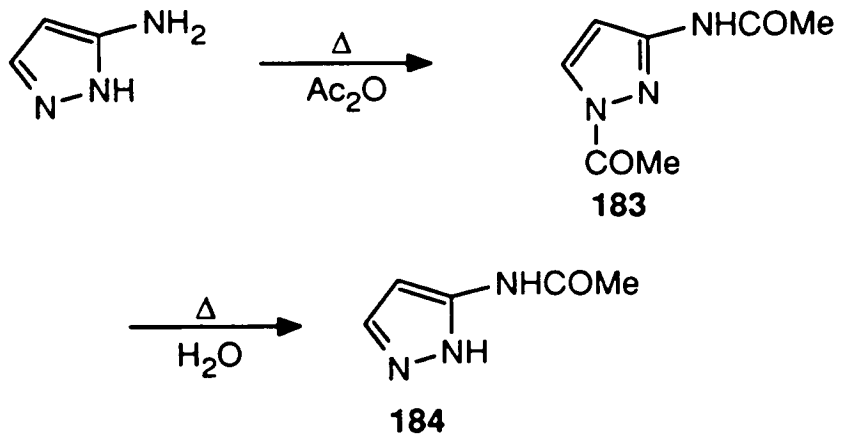
Preliminary investigations were carried out into the following synthetic route (Scheme 85).



Scheme 85

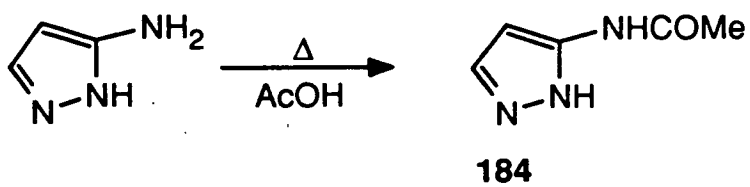
The route envisaged acylation of the 3-aminopyrazole **180** to give the derivative **181**; ring closure to the imidazo[1,2-*b*]pyrazol-2-one **182** would complete the first sequence and reactions of the lactam carbonyl group would then be explored.

Little is known about acylation reactions of 3-aminopyrazoles. The first synthesis of 3-acetamidopyrazole was reported in 1962 by Makisumi.[81] This was achieved by two synthetic routes. The first route involved a di-acetylation with acetic anhydride to give **183** which was initially reported as the isomeric 2-acetyl compound. This synthetic step was also reported by Parrick in 1979[82] who confirmed structure **183** by NMR methods (see later). The diacetyl derivative was heated in water to give 3-acetamidopyrazole, **184**, (Scheme 86).



Scheme 86

The second route involved heating 3-aminopyrazole in acetic acid to give 3-acetamidopyrazole, **184**, directly (Scheme 87).



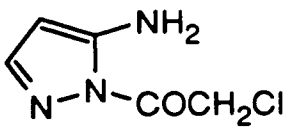
Scheme 87

We first decided to explore mono-acylation reactions using acid chlorides for potential cyclisation reactions. The acid chlorides required a leaving group at the 2 position. Chloroacetyl chloride was commercially available while methoxyacetyl chloride was synthesised from methoxy acetic acid using thionyl chloride.[83]

3-Aminopyrazole was treated with chloroacetyl chloride in the presence of triethylamine.

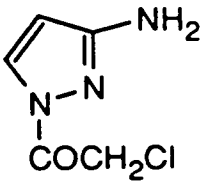
The product was readily isolated and was investigated by ^{1}H NMR. This showed two sets of pyrazolic proton peaks at δ_H 8.02, 6.08 (^3J 3.0 Hz), and 7.39 and 5.40 (^3J 1.7 Hz). It also showed two methylene peaks at

δ_H 4.99 and 4.85. This is consistent with the formation of two mono-acylated products, though the ratio of the two sets of pyrazole peaks was variable. Three possible products could have formed here; these are **185**, **186** and **187**.



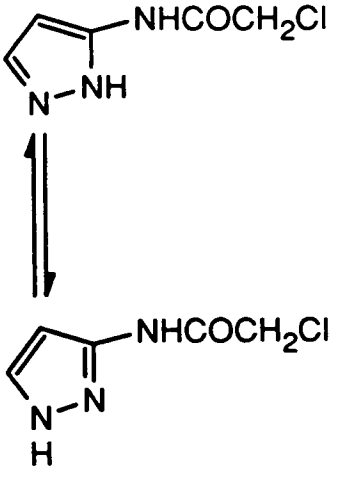
185

A



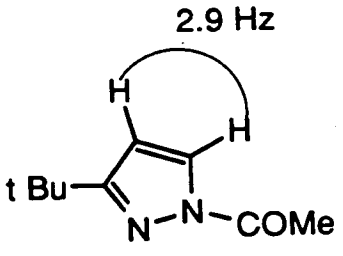
186

B

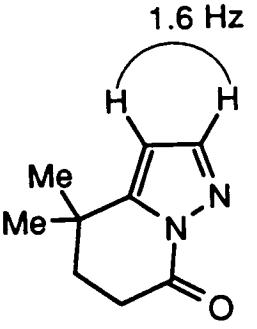


C **187**

To determine which products had been formed the pyrazole proton coupling constants were examined. A comparison was made of the coupling constants reported above with those obtained by Williams[59] for substituted pyrazoles, **188**, and **189**.



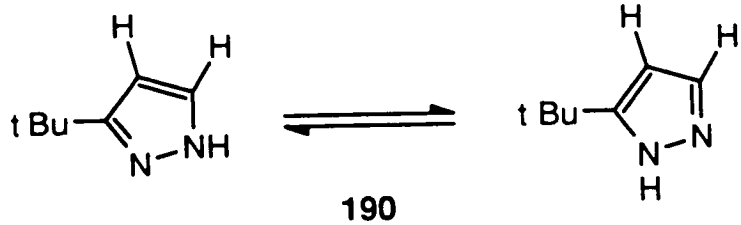
188



189

The coupling constants from these compounds imply that **185** and **186** are the correct structures. Williams also studied the coupling constants for ring protons of 3-t-butylpyrazole, **190**. This showed a coupling constant of

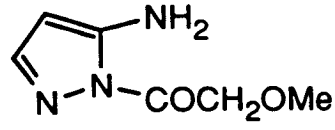
2.0 Hz for all the protons, and this must be an average based on the relative amounts of the two possible rapidly exchanging tautomers. Compound **187** can also adopt two tautomeric forms, and would be expected to have a similar value of ^3J.



190

The two isomers **185** and **186** were formed in varying proportions (from 1:4 to *ca.* 1:1 respectively). However, it was noted that rapid rate of addition of the acid chloride apparently favoured the formation of 1-chloroacetyl-3-aminopyrazole **186**. This reaction must be exhibiting some form of kinetic control.

The reaction of 3-aminopyrazole with methoxyacetyl chloride also gave a similar mixture; the formation of isomers **191** and **192** was confirmed as above by their ^3J values.



191

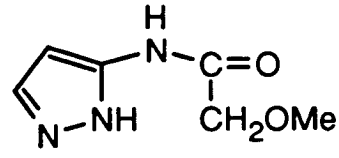
192

Remarkably, the isomeric mixture of 1-chloroacetyl-3-aminopyrazole and 2-chloroacetyl-3-aminopyrazole was found to be unstable at room temperature and underwent a clean *solid state* rearrangement over a period of days to a single product. The ^{1}H NMR spectrum of this product showed peaks attributable to pyrazole ring protons at δ_H 7.63 and 6.67; the coupling constant ^3J was the intermediate value of 2.3 Hz, which would suggest that

the pyrazole ring component was undergoing tautomerism. Mass spectrometry showed molecular ion peaks at 161 and 159 which was consistent with another chloroacetyl isomer.

The structure of the rearranged product was therefore 3-(chloroacetamido)pyrazole **187**.

The mixture of 1-methoxyacetyl-3-aminopyrazole and 2-methoxyacetyl-3-aminopyrazole was also found to undergo a solid state rearrangement, over a similar period, to 3-(methoxyacetamido)pyrazole, **193**.



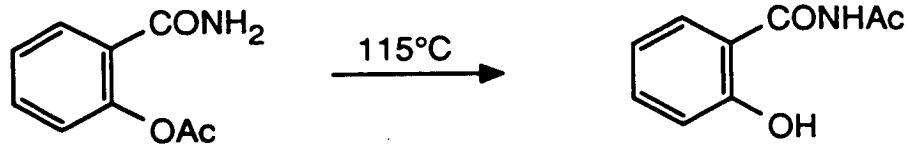
193

1. Solid State Reactions

Reactions in the solid state are well known but often not fully investigated processes. Examples of solid state chemistry include racemizations, proton transfer, Diels-Alder and other electrocyclic reactions, E-Z isomerisations of alkenes, acyl or alkyl migrations *etc.*[84,86]

Acyl and alkyl migration are the most important reactions because they may be able to provide parallels to our rearrangement.

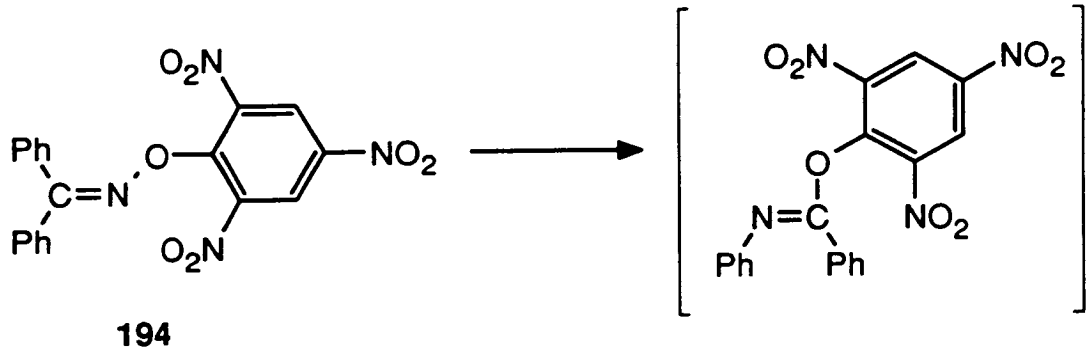
Rearrangement of *O*-acetylsalicylamide has been extensively studied by Gordon[86] (Scheme 88).



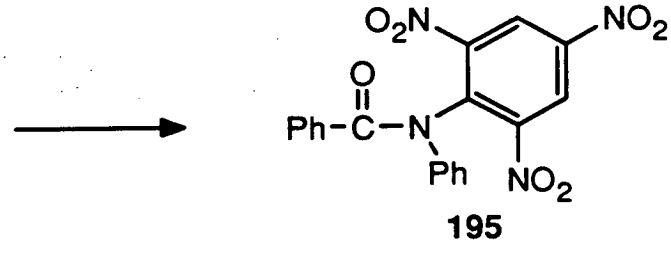
Scheme 88

This rearrangement takes place at 25 degrees below the melting point (140-142°C) which is in direct contrast to our rearrangement which occurs at 100 degrees below the melting point!

Some solid state reactions are known to have induction periods. A good example is the Beckmann-Chapman rearrangement of the picrylether, **194,** to the corresponding *N*-picrylbenzamide, **195,** (Scheme 89). Induction periods of a few hours were reported.[84]



194

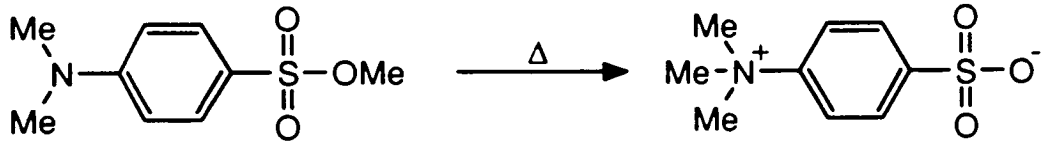


195

Scheme 89

This rearrangement takes place after the development of cracks in the initial crystal; it is possible that this process is occurring in our rearrangement giving rise to the induction periods observed (see later).

An important solid state rearrangement which occurs at room temperature has been reported by Bergmann.[87] This reaction involves the rearrangement of a methyl sulphonate ester **196** to the zwitterion, **197**, (Scheme 90).



196 197

Scheme 90

The kinetic and mechanistic properties of this reaction were extensively investigated. Kinetic studies revealed that Ea = *ca.* 89 kJ mol^{-1}.

X-ray crystallography of **196** was employed to study the reaction mechanism. This revealed that the individual molecules were stacked with alternating dimethylamino and sulphonate groups. This means that the methyl migration takes place *via* an intermolecular cascade mechanism.

All these rearrangements are single starting material to single product reactions. Our solid state rearrangement consists of two starting materials going to a single product. This means that either we have a series process A→B→C or a parallel process A→C and B→C.

The effect of functional groups on the solid state rearrangement was studied first. Four acid chlorides, XCH_2COCl, where X = H, Ph, Cl or OMe were used to determine qualitatively the effect of various functional groups on the rate of rearrangement.

The results obtained are summarised in Table 7.

Table 7

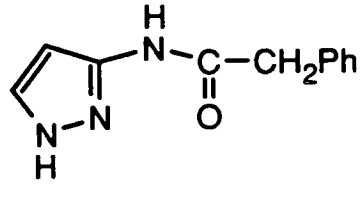
Relative Rates of Rearrangement

X	Time (Days)
H	>21 Incomplete
Ph	16
OMe	9
Cl	8

From these results it can be seen that the solid state rearrangement is assisted by electron withdrawing functional groups.

In an analogous fashion to Bergmann[87] X-ray crystallography was used in an attempt to provide a mechanistic explanation for the solid state rearrangement. Unfortunately the starting material mixture could not be crystallised, but crystals of 3(phenylacetamido)pyrazole, **198**, were suitable for analysis.

The results (Fig. 9) showed an intricate three dimensional array of pyrazoles linked by intermolecular hydrogen bonding from 0-7 to NH-1, but it was not possible to determine the course of the rearrangement from this isolated result. Nevertheless the results showed that in the solid state the NH of the pyrazole ring is at position one and has the structure **198**.



198

X - Ray Crystal Structure of 198.

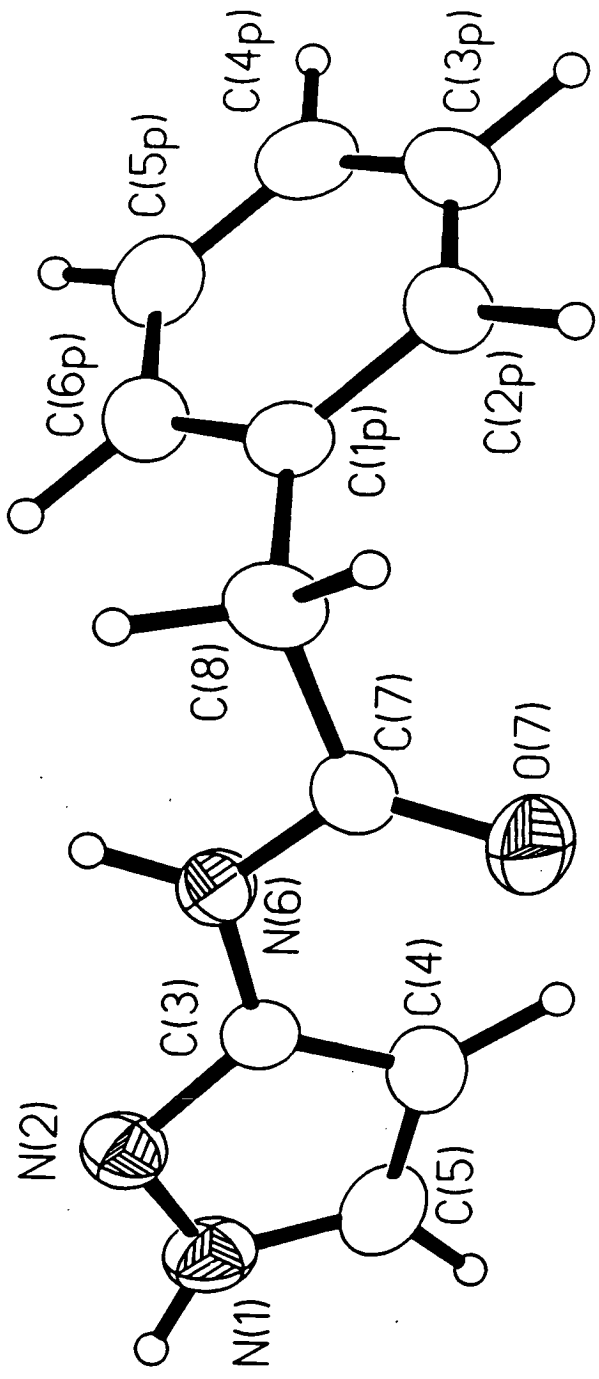


Figure 9

C 11 H 11 N 3 O SSPROD #582 for RWM:HMN Z 0.0-0.5

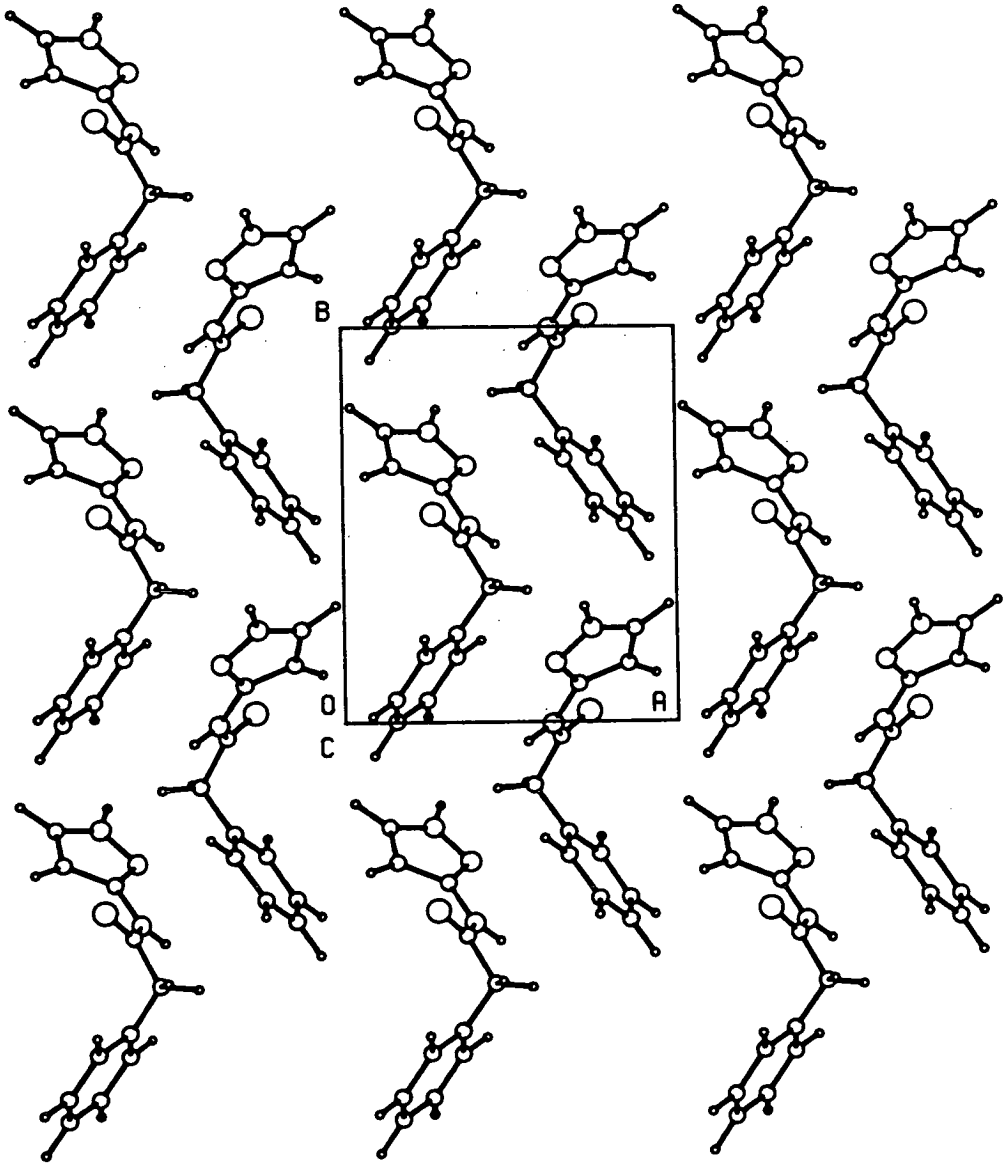


Table 1. Bond Lengths(Å), angles(degrees) and torsion angles(degrees) with standard deviations

N(1) - H(1)	0.922(23)	C(7) - O(7)	1.2207(22)
N(1) - N(2)	1.3572(21)	C(7) - C(8)	1.5148(25)
N(1) - C(5)	1.328(3)	C(8) -C(1P)	1.5161(24)
N(2) - C(3)	1.3280(22)	C(1P) -C(2P)	1.3885(24)
C(3) - C(4)	1.3915(25)	C(1P) -C(6P)	1.3918(24)
C(3) - N(6)	1.4005(22)	C(2P) -C(3P)	1.388(3)
C(4) - C(5)	1.365(3)	C(3P) -C(4P)	1.378(3)
N(6) - H(6)	0.909(24)	C(4P) -C(5P)	1.388(3)
N(6) - C(7)	1.3545(23)	C(5P) -C(6P)	1.387(3)

H(1) - N(1) - N(2)	121.4(14)	N(6) - C(7) - O(7)	123.18(16)
H(1) - N(1) - C(5)	126.0(14)	N(6) - C(7) - C(8)	114.68(15)
N(2) - N(1) - C(5)	112.35(16)	O(7) - C(7) - C(8)	122.12(16)
N(1) - N(2) - C(3)	103.45(14)	C(7) - C(8) -C(1P)	111.10(14)
N(2) - C(3) - C(4)	112.44(15)	C(8) -C(1P) -C(2P)	121.07(15)
N(2) - C(3) - N(6)	118.61(15)	C(8) -C(1P) -C(6P)	120.31(15)
C(4) - C(3) - N(6)	128.88(16)	C(2P) -C(1P) -C(6P)	118.62(15)
C(3) - C(4) - C(5)	103.99(17)	C(1P) -C(2P) -C(3P)	120.38(16)
N(1) - C(5) - C(4)	107.77(18)	C(2P) -C(3P) -C(4P)	120.54(18)
C(3) - N(6) - H(6)	118.1(15)	C(3P) -C(4P) -C(5P)	119.78(18)
C(3) - N(6) - C(7)	124.14(15)	C(4P) -C(5P) -C(6P)	119.58(18)
H(6) - N(6) - C(7)	117.7(15)	C(1P) -C(6P) -C(5P)	121.09(16)

H(1) - N(1) - N(2) - C(3)	174.7(17)	H(6) - N(6) - C(7) - O(7)	172.0(17)
C(5) - N(1) - N(2) - C(3)	0.47(20)	H(6) - N(6) - C(7) - C(8)	-9.6(17)
H(1) - N(1) - C(5) - C(4)	-174.1(18)	N(6) - C(7) - C(8) -C(1P)	-86.63(18)
N(2) - N(1) - C(5) - C(4)	-0.18(22)	O(7) - C(7) - C(8) -C(1P)	91.82(20)
N(1) - N(2) - C(3) - C(4)	-0.62(19)	C(7) - C(8) -C(1P) -C(2P)	-97.78(19)
N(1) - N(2) - C(3) - N(6)	176.58(14)	C(7) - C(8) -C(1P) -C(6P)	82.51(19)
N(2) - C(3) - C(4) - C(5)	0.53(21)	C(8) -C(1P) -C(2P) -C(3P)	-178.64(16)
N(6) - C(3) - C(4) - C(5)	-176.30(17)	C(6P) -C(1P) -C(2P) -C(3P)	1.1(3)
N(2) - C(3) - N(6) - H(6)	-21.8(17)	C(8) -C(1P) -C(6P) -C(5P)	179.22(17)
N(2) - C(3) - N(6) - C(7)	155.59(16)	C(2P) -C(1P) -C(6P) -C(5P)	-0.5(3)
C(4) - C(3) - N(6) - H(6)	154.8(17)	C(1P) -C(2P) -C(3P) -C(4P)	-0.9(3)
C(4) - C(3) - N(6) - C(7)	-27.8(3)	C(2P) -C(3P) -C(4P) -C(5P)	0.1(3)
C(3) - C(4) - C(5) - N(1)	-0.22(21)	C(3P) -C(4P) -C(5P) -C(6P)	0.5(3)
C(3) - N(6) - C(7) - O(7)	-5.5(3)	C(4P) -C(5P) -C(6P) -C(1P)	-0.3(3)
C(3) - N(6) - C(7) - C(8)	172.96(15)		

The X-ray showed the molecular is highly twisted and the pyrazole and phenyl rings are not in the same plane. The bond angles around the carbonyl group are shown in Fig. 10.

Carbonyl Group Bond Angles of 198.

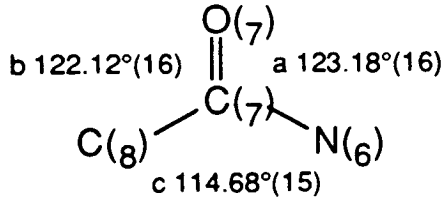


Figure 10

The bond angles for a typical secondary amide[69] are a = 122.8(12), b = 116.1(13), and c = 121.1(13), which is slightly different but not significant.

The bond length of the amide carbonyl group is 1.2207(22) Å which is typical (non-cyclic secondary amides have bond lengths of 1.231(11) Å).[69] The bond length of C-7-N-6 is 1.3545(23) Å, which is again similar to non-cyclic secondary amides (1.332(11) Å).

The progress of the solid state reaction was monitored directly by allowing the rearrangement to proceed in the probe of a solid state NMR spectrometer,[88] at 306 K and 310 K. The sample was enriched in the major isomer, **186**, which showed, amongst others, peaks at δ_C 163.5 and 105.4. The kinetic plots were obtained by monitoring the disappearance of these peaks and the appearance of peaks at δ_C 165.7, 148.0 and 100.3 (product **187**). No significant amounts of any stable intermediate were detected under these conditions.

Solid State ^{13}C Spectrum of the Decay of A and B.

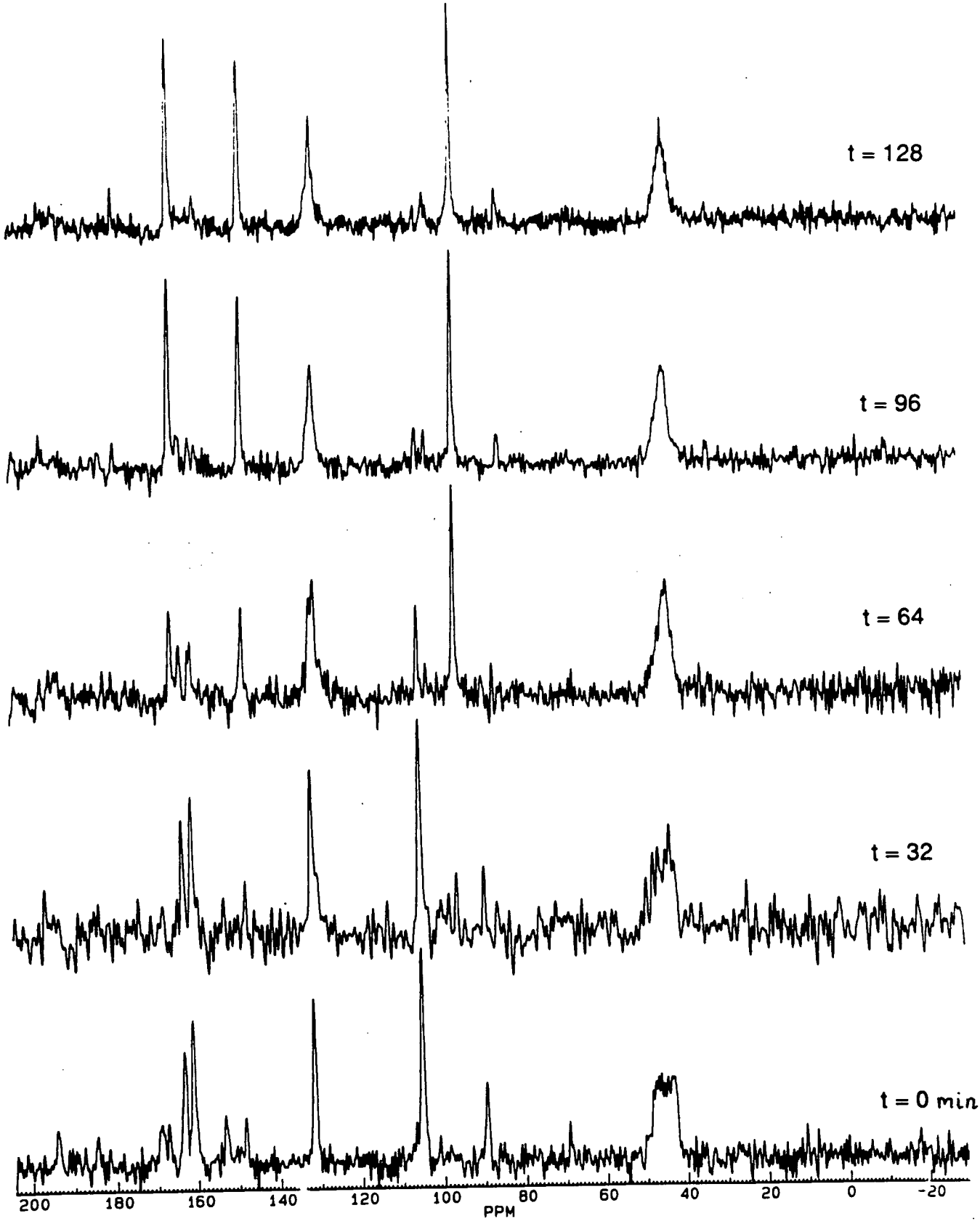


Figure 11

From the series of spectra (Fig. 11) it was possible to obtain approximate kinetic plots, *e.g.* Fig. 12, assuming the reaction was first order (solid state reactions are often assumed to be first order[84]).

Representative Kinetic Plot Obtained at 306K for the Solid State Rearrangement of A and B.

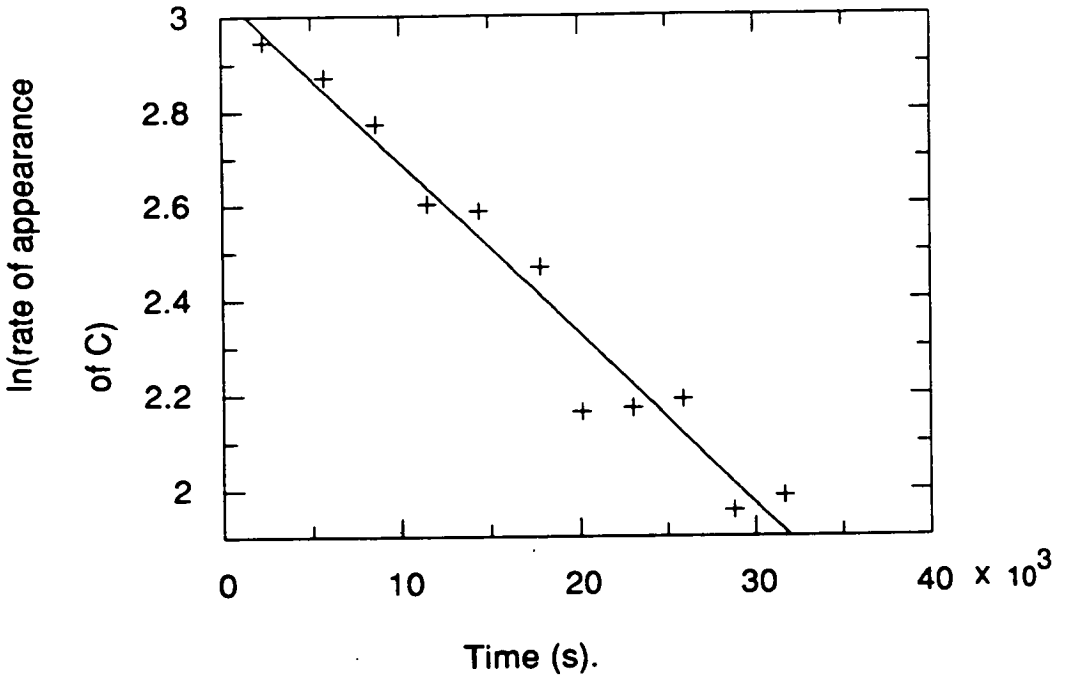


Figure 12

The rate constants obtained were k_{306} 3.58 ± 0.34 x 10^{-5} s^{-1} and k_{310} 7.32 ± 3.35 x 10^{-5} s^{-1}.

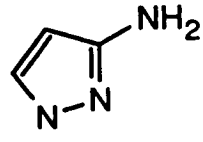
Solid state NMR was successful but gave noisy spectra with few data points which accounts for the large errors obtained. It was therefore necessary to obtain more data by means of a slower reaction. The reaction mixture was kept at a constant temperature (299 K) in a thermostatted water

bath. Samples were withdrawn at fairly regular intervals and examined by ^1H NMR spectroscopy using $[^2H]_6$ acetone.

2-Chloroacetyl-3-aminopyrazole (A) showed a short induction period (*ca.* 15 h) and then its decay followed good first order kinetics for ~ 4 half-lives. 1-Chloroacetyl-3-aminopyrazole (B), however, showed a much longer induction period (*ca.* 50 h) before it too decayed also following first order kinetics. Induction periods in solid state reactions have been reported previously.[84]

Some minor components, D, E, F, and G, were found during the rearrangement, but it is not clear if they are formed by side equilibrium reactions or are true intermediates lying on the reaction coordinate. Although for all of these certain structural features are well defined, it has not been possible to assign their overall structure. All must be relatively stable both in the solid state and in solution.

For example product D shows coupling constants of 2.9 Hz which indicates it must contain a pyrazole ring such as **199**.



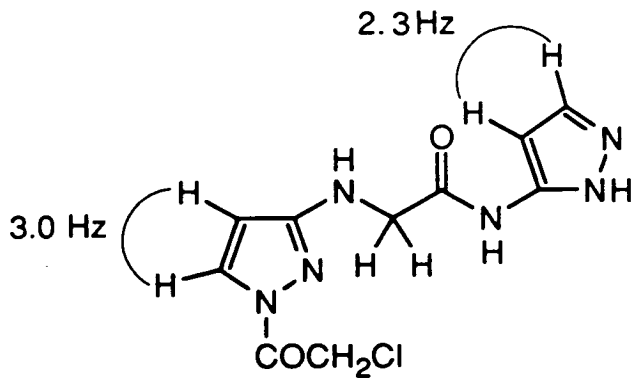
199

It is not likely to be a diacyl compound because the chemical shifts of its pyrazole ring protons (δ_H 8.26 and 6.24) do not correspond with those observed for 1-chloroacetyl-3(chloroacetamido)pyrazole (δ_H 8.30 and 7.06).

Products E and F, which always appear in the same proportions, are probably only one intermediate containing two different pyrazole rings. The formation of this intermediate requires reaction at the CH_2Cl function. Future work with CH_2Ph (for example) could show if this is viable. The coupling

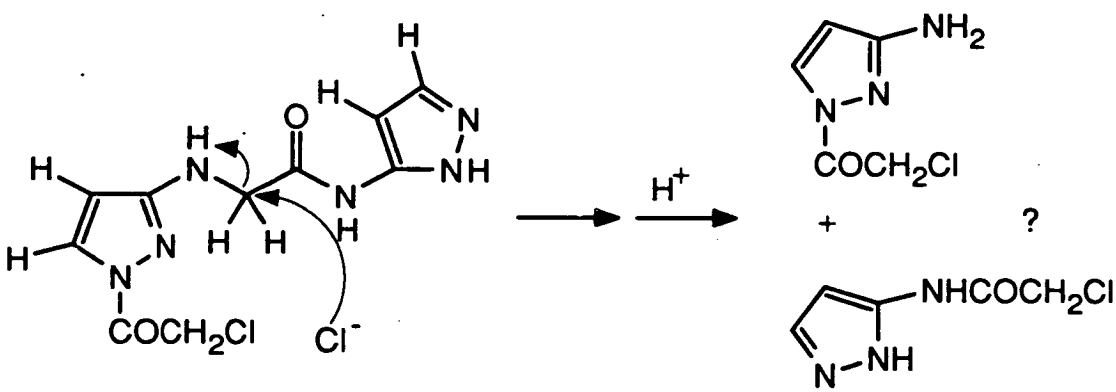
constant for E pyrazole protons is 3.0 Hz whilst the coupling constant for F is 2.3 Hz.

A possible partial structure, **200**, is shown.



200

The right hand portion of this structure is able to tautomerise giving rise to the observed coupling constant. The structure must be able to break up into two fragments 1-chloroacetyl-3-aminopyrazole and 3-(chloroacetamido)pyrazole; this could be brought about by attack of a chloride ion (Scheme 91).



Scheme 91

Product G shows coupling constants of 2.5 Hz, indicating a tautomerising pyrazole ring. The product was initially thought to be 3-aminopyrazole but this was disproved by a comparison of chemical shifts (3-

aminopyrazole δ_H 7.32 and 5.52; product G δ_H 7.75 and 6.56). Since G and C are usually in the same proportions the most plausible explanation is that G is merely a geometrical isomer.

The results and percentages of the reaction components are given in Table 8.

Table 8

Results Obtained for the Decay of A and B→C

Time (s)	% A	% B	% C	% D	% E	% F	% G
0	40.4%	57.4%	2.2%	0	0	0	0
11,400	42.2%	50.9%	1.8%	1.5%	1.8%	1.8%	0
70,500	38.6%	45.3%	5.8%	1.7%	4.3%	4.3%	0
97,200	22.5%	48.9%	14.6%	1.6%	5.6%	5.6%	1.2%
156,900	13.7%	45.3%	25.4%	1.2%	6.6%	6.6%	1.2%
180,000	10.4%	44.8%	24.0%	1.2%	8.8%	8.8%	2.0%
245,100	3.7%	33.2%	42.3%	0	8.7%	8.7%	3.4%
280,200	3.1%	30.4%	52.2%	0	4.0%	4.0%	6.3%
329,100	0	20.6%	65.9%	0	5.0%	5.0%	3.5%
352,800	0	14.6%	66.5%	0	6.4%	6.4%	6.1%
421,200	0	6.7%	79.2%	0	4.1%	4.1%	5.9%
509,400	0	2.5%	85.4%	0	2.4%	2.4%	7.3%
∞	0	0	92.6%	0	0	0	7.4%

Simple plots of ln (concentration) against time gave the rate constants k_A, k_B, k_C (for example Fig. 13), assuming first order kinetics apply.

Representative Kinetic Plot Obtained at 299K

for the Solid State Rearrangement of A and B.

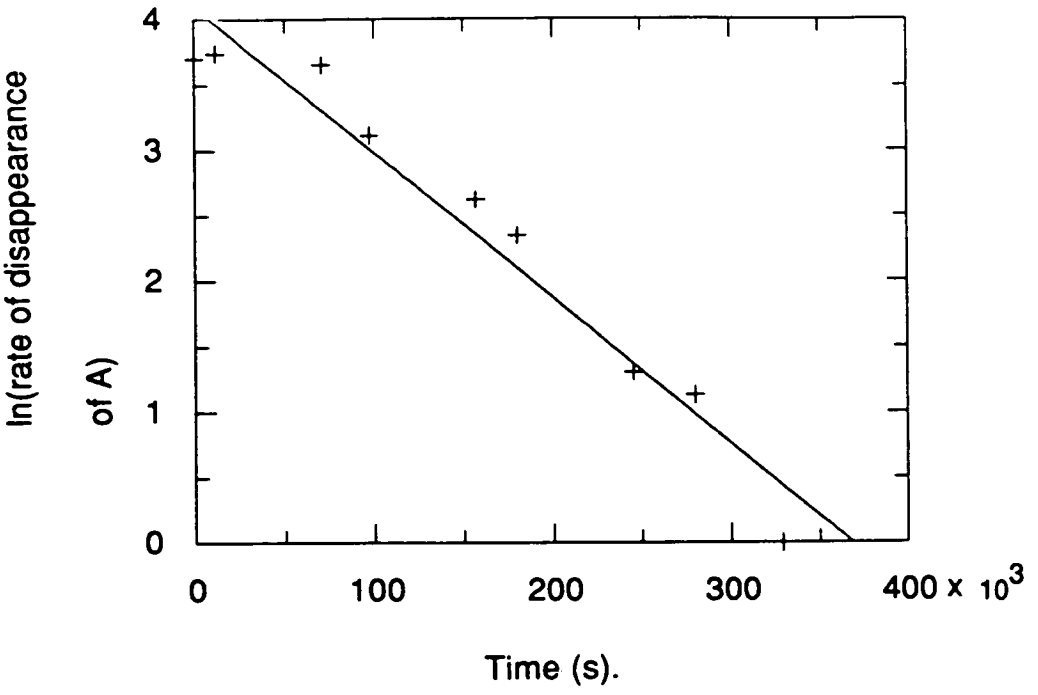


Figure 13

k_A was found to be 1.1 ± 0.1 x 10^{-5} s^{-1}, k_B = 5.4 ± 0.8 x 10^{-6} s^{-1}, and k_C = 3.8 ± 0.3 x 10^{-6} s^{-1}.

The kinetic data k_B is not wholly reliable due to the long induction period before B starts to decay *via* first order kinetics. The data also does not show which mechanism is operation, *i.e.* A→C and B→C or A→B→C which would require B is replenished by A and doesn't decay until all A is used up.

To determine which mechanism is operating it was necessary to obtain a pure sample of B. This was accomplished by low temperature crystallisation, from acetone, of the isomeric mixture (high temperature would bring about rearrangement). The solid state rearrangement of pure B (1-

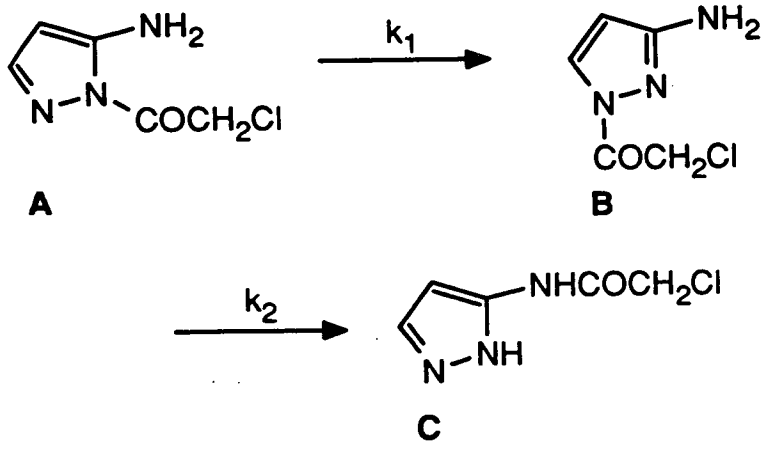
chloroacetyl-3-aminopyrazole), was also studied at 299 K. The results obtained are shown in Table 9.

Table 9

Results Obtained for the Decay of B→C

Time (s)	% B	% C	% D	% E	% F	% G
0	100%	0	0	0	0	0
61,200	78.6%	6.4%	5%	5%	5%	0
82,000	61.7%	19.8%	2.4%	7.2%	7.2%	1.7%
147,600	41.1%	38.4%	1.8%	7.6%	7.6%	3.5%
172.800	27.7%	58.4%	0	4.0%	4.0%	5.9%
241,200	21.6%	68.3%	0	2.9%	2.9%	4.3%
410,000	7.8%	86.7%	0	0	0	5.5%

It was first noted that no A was formed, and that the induction time for B to start rearranging was shorter than for the mixture of A+B. This suggests that A does not rearrange directly to C but actually rearranges to B and that A and B are not in equilibrium. This is not the obvious route for the rearrangement, one would expect B→A→C to be more logical. The reason why B (in the A, B mixture) decays so slowly at first is that it is indeed being replenished by A. The reaction is shown below (Scheme 92).



Scheme 92

It was also noted that the intermediates D, E/F and G were again formed; this shows they must be intermediates between B and C. The overall value of k_2 B→C only was obtained (Fig. 14) and was found to be 6.1 ± 0.5 x 10^{-6} s^{-1} which is not significantly different to the value obtained for k_2 when both A and B are present (5.4 ± 0.8 x 10^{-6} s^{-1}).

Representative Kinetic Plot Obtained at 299K for the Solid State Rearrangement of B.

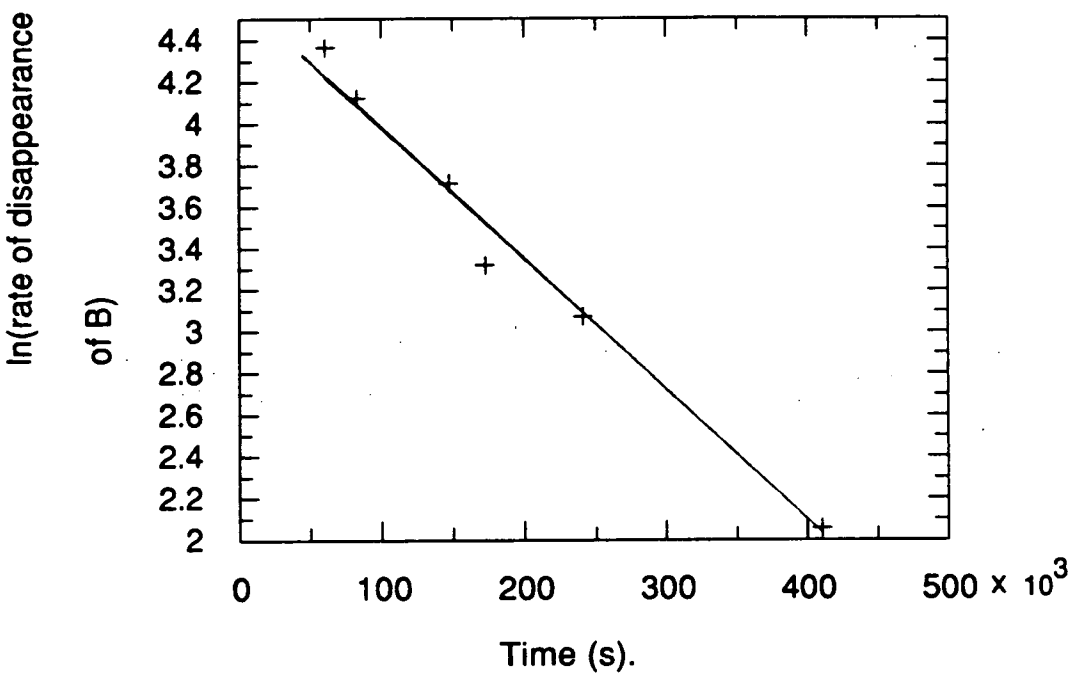


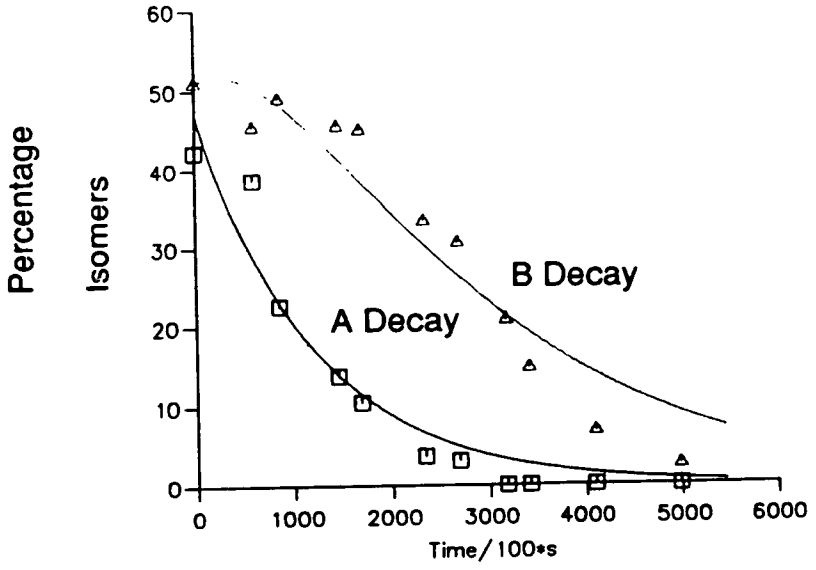
Figure 14

If the above mechanism holds (Scheme 92) then the kinetic equation for the formation of C is as follows:[89]

$$[B] = [B]_0 e^{-k_2 t} + \frac{k_1[A]_0}{(k_2-k_1)} (e^{-k_1 t} - e^{-k_2 t})$$

This was tested by fitting the data of the decay of B alone, and the decay of A and B together to exponential plots (Fig. 15).

Exponential Plot of the Decay of A and B.



Exponential Plot of the Decay of Pure B.

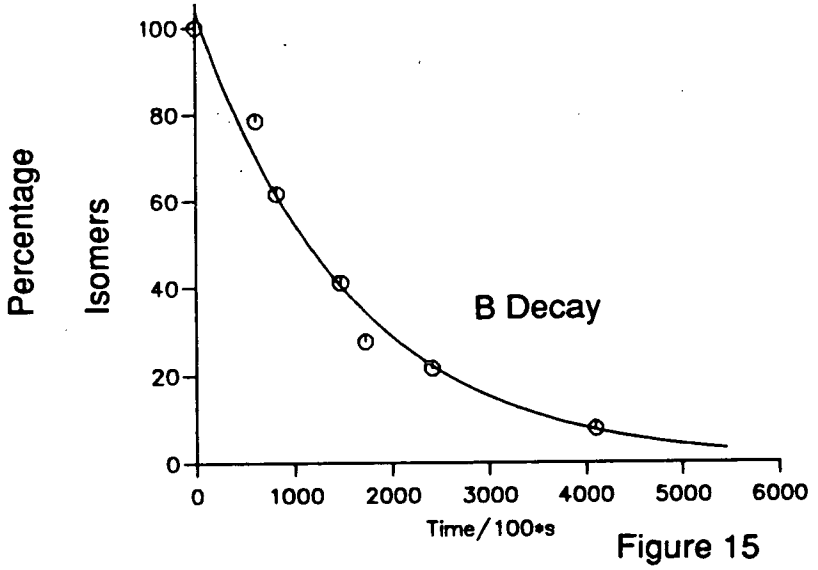


Figure 15

The decay of A was found to be first order and gave a good fit; the value of k_1 was found to be 8.37×10^{-6} s^{-1}. The decay of pure B was also found to be first order to a reasonable accuracy ($k_2 = 6.39 \times 10^{-6}$ s^{-1}). The decay of B in the presence of A did not give such a good fit but the value for k_2 was calculated to be 5.58×10^{-6} s^{-1} which is within 14% of the value

obtained for pure B decay. Although the fit for B in the presence of A was reasonable the points were found to be above and below the theoretical line. This shows there is a systematic error in this treatment and this is consistent with there being an intermediate which is not taken into account in the kinetic scheme. However, taking into account the uncertainties in interpreting the kinetic data in the solid state the results are very satisfactory.

The energy of activation, E_a, of the solid state reaction was estimated by an Arrhenius plot of the log of the rate constants obtained at 299, 306 and 310 K (Fig. 16) using kinetic data obtained from solid state NMR and ^1H NMR methods.

Arrhenius Plot of Kinetic Data Obtained at 299, 306, and 310K.

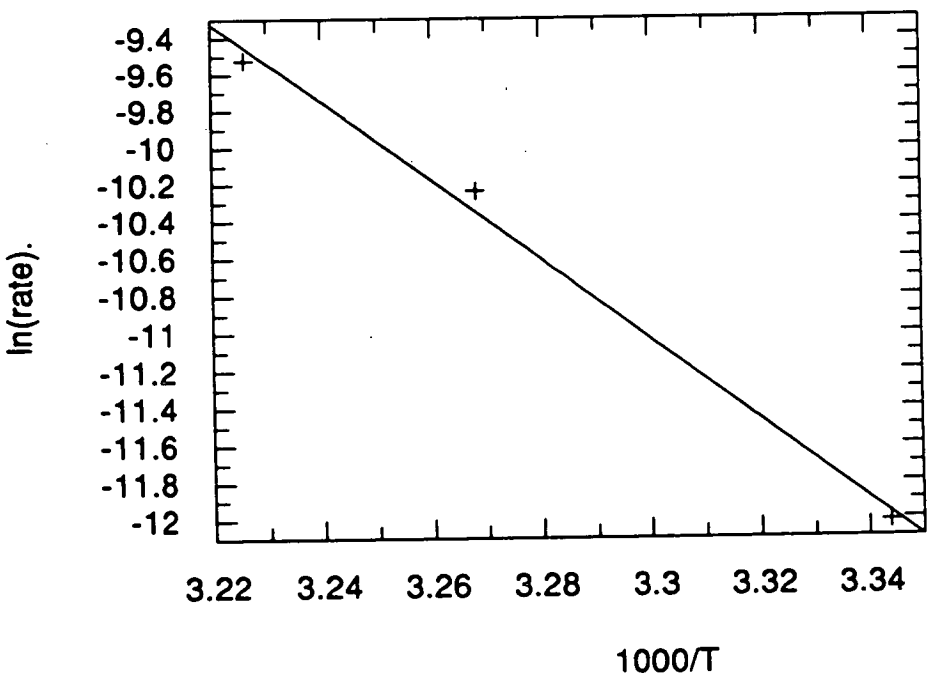
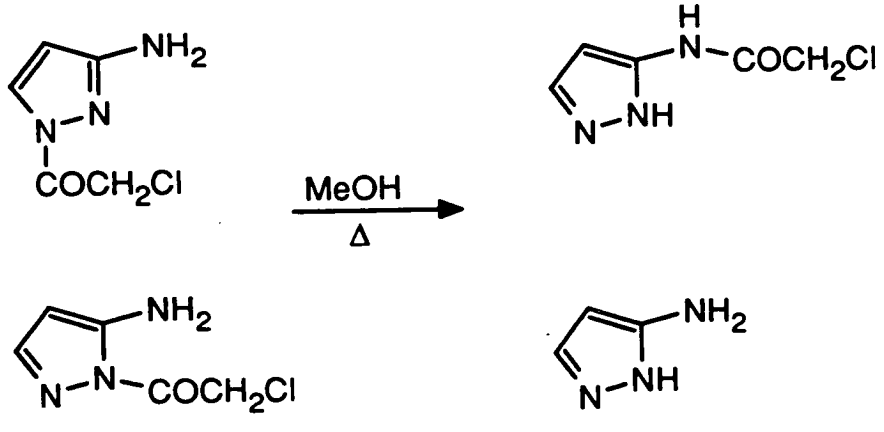


Figure 16

The value of E_a was estimated as 177.9 ± 13.6 kJ mol^{-1}. This is a very high value as expected of a reaction showing a strong temperature dependence. However, the intrinsic errors in the treatment could make E_a too high. Kinetic treatment of Bergmann's solid state reaction (see Scheme 90) gave a value of 89 kJ mol^{-1}.[87]

The rearrangement of A and B to C was also monitored in solution ($[^2H]_6$ acetone) under the same controlled conditions (299 K, thermostatted water bath). The sample was examined at regular intervals for a period of two weeks but no rearrangement was detected. The sample showed the formation of decomposition products.

The rearrangement was also studied at 323 K in $[^2H]_4$ methanol for 2 h. Removal of solvent yielded two products. Characterisation by ^1H NMR spectroscopy revealed the first product was the rearrangement product 3-(chloroacetamido)pyrazole while the second (major) product showed resonances at δ_H 7.32 and 5.52 which indicates 3-aminopyrazole. It can be inferred that two competing processes are taking place here; these are the rearrangement previously noted and a nucleophilic deacylation process (Scheme 93).



Scheme 93

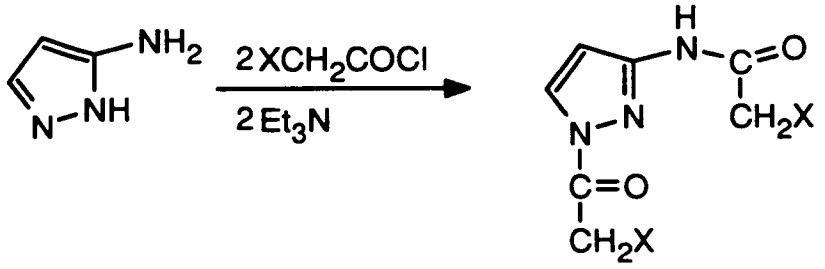
The mechanism of A→B→C is clearly an intermolecular process and a molecular cascade as reported by Bergmann[87] (see Scheme 90 *etc*). To

prove this it will be necessary to obtain the X-ray crystallographic structure of A and B and this will be of crucial importance in the future.

2. Preparation of Intermediates for Cyclisation Studies

Since mono-acylation reactions of 3-aminopyrazole give mixtures it was decided to diacylate 3-aminopyrazole and remove one acyl group as described by Makisumi[81] (see Scheme 85).

Two diacyl derivatives were synthesised these were 1-chloroacetyl-3-(chloroacetamido)pyrazole **201** and 1-methoxyacetyl-3-(methoxyacetamido)pyrazole **202** (Scheme 94).



201 X = Cl

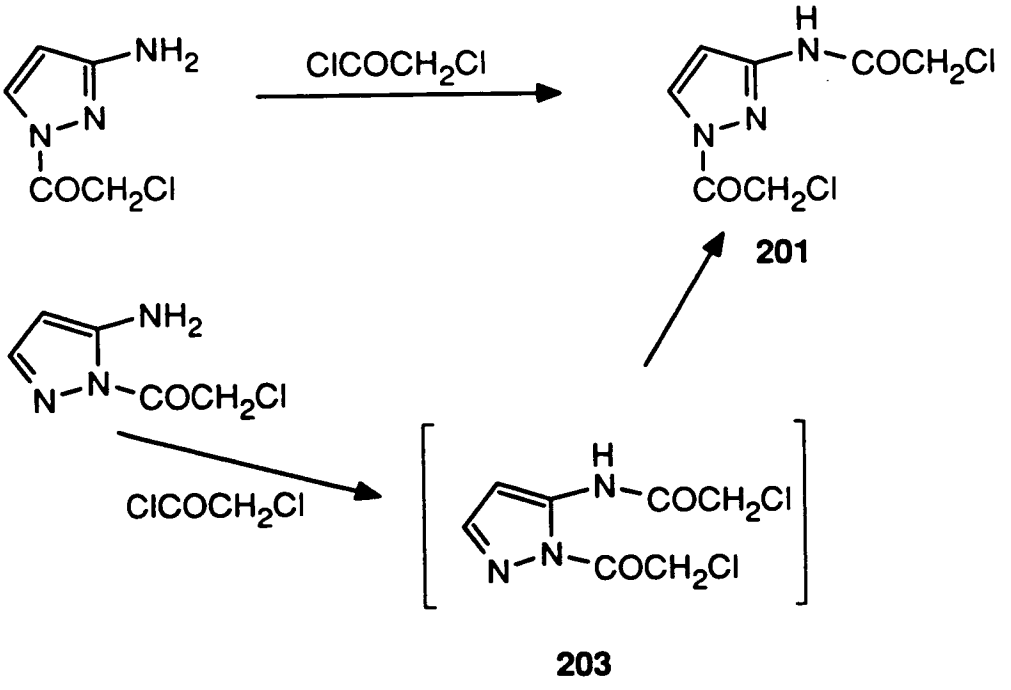
202 X = OMe

Scheme 94

The regiochemistry was proved by measuring the coupling constants of the pyrazole ring protons. The values were found to be 2.9 Hz which (as mentioned previously)[59] confirms structures **201** and **202** to be correct.

The mixture of 1-chloroacetyl-3-aminopyrazole and 2-chloroacetyl-3-aminopyrazole was also treated with another equivalent of chloroacetyl chloride. On work up a single product was isolated and this was identified as **201**. ^{1}H NMR spectra and mass spectrometry were identical to those of the original sample; surprisingly 2-chloroacetyl-3-(chloroacetamido)pyrazole **203** was not identified. The reason for this could be due to steric factors; **203** could be initially formed from 2-chloroacetyl-3-aminopyrazole but

nucleophile-induced deacylation due to steric crowding drives the rearrangement forward to **201** (Scheme 95).

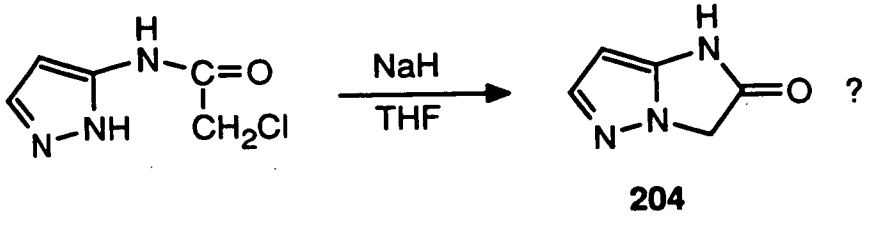


Scheme 95

Both **201** and **202** were cleanly deacylated to 3-(chloroacetamido)pyrazole and 3-(methoxyacetamido)pyrazole by heating in methanol.

The two mono-acyl compounds were identical with the products obtained in the solid-state rearrangement.

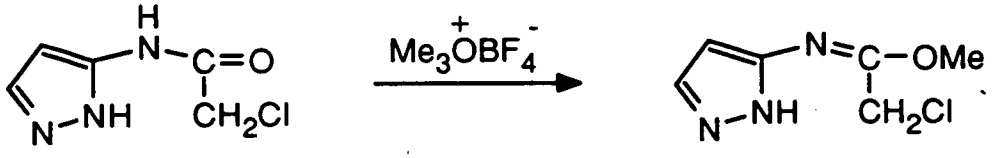
3-(Chloroacetamido)pyrazole was treated with sodium hydride in an attempt to bring about cyclisation to **204** (Scheme 96).



Scheme 96

The material isolated did not show peaks at ~ δ_H 5.5 or 7.7 which is approximately where we would expect the pyrazole ring protons to occur.[8] Furthermore, no colour was detected on spraying with CD3; possibly we had obtained polymeric material. This reaction may have failed due to the presence of two ionisable protons (pyrazole NH and amide NH).

In an attempt to try and circumvent this problem it was decided to try and alkylate the amide **187** with trimethyl oxonium tetrafluoroborate.[90] The use of trimethyl oxonium tetrafluoroborate as an alkylating agent for amide carbonyl groups is well known.[80] The reaction was hoped to proceed as shown below (Scheme 97).



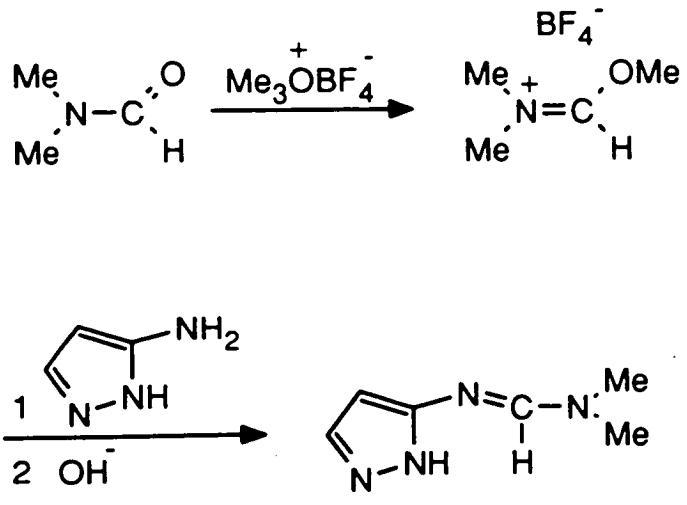
187 **205**

Scheme 97

The product **205** should be more readily cyclisable.

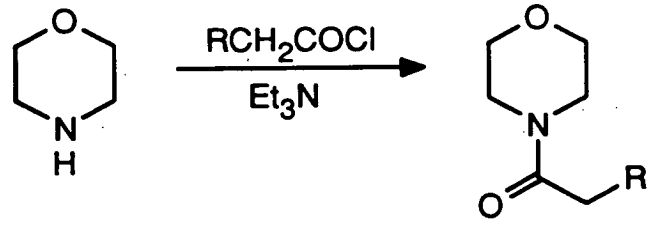
When the reaction was carried out t.l.c. showed many products and this could be explained by alkylation at the various nitrogen atoms present.

Another synthetic approach to imidazo[1,2-*b*]pyrazoles envisaged the use of trimethyl oxonium tetrafluoroborate as a route into substituted amidines. A model reaction (Scheme 98) has been previously described in the preceding chapter (see Scheme 82).



Scheme 98

The approach initially required the synthesis of acyl morpholines **206** and **207**. These were made using conditions previously described (Scheme 99).



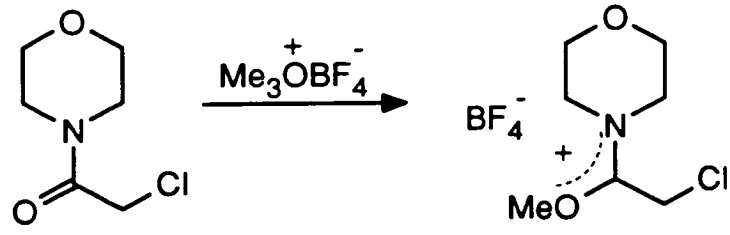
206 R = Cl

207 R = OMe

Scheme 99

The two products were confirmed by their mass spectra: **206** showed two mass ion peaks at 165 and 163 in a 3:1 ratio which is typical for a compound containing a single chlorine atom. Compound **207** showed the correct mass ion peak at *m/z* 159.

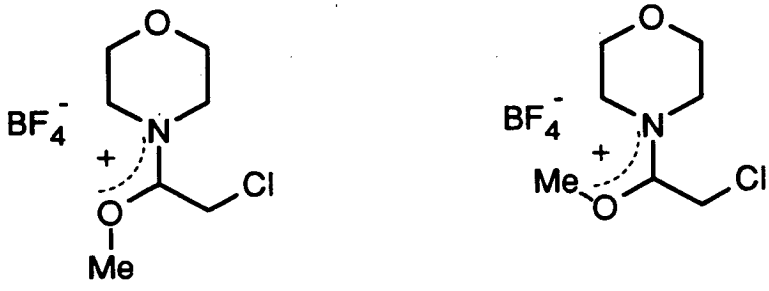
The two products **206** and **207** were then reacted with trimethyl oxonium tetrafluoroborate to give salts. The methoxy derivative was too hygroscopic for easy isolation but the chloro derivative **208** was obtained as a white solid (Scheme 100).



208

Scheme 100

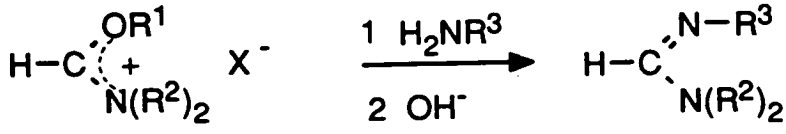
The ^1H NMR spectrum of this compound showed two sets of peaks at δ_H 4.30, 4.19, 4.18 and 3.96 and also, 4.26, 3.75, 3.61 and 3.41. This observation can be explained by assuming the molecule exists as two geometrical isomers **208a** and **208b**.



208a **208b**

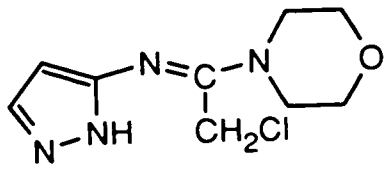
The FAB mass spectrum showed molecular ion peaks (cation) at 180 and 178 (1:3 ratio) which would be expected.

Imidinium salts are known to react with primary amines to give (after treatment with base) the corresponding amidines[91] (Scheme 101).



Scheme 101

This methodology was extended to the reaction of 3-aminopyrazole with **208** in an attempt to obtain **209**.



209

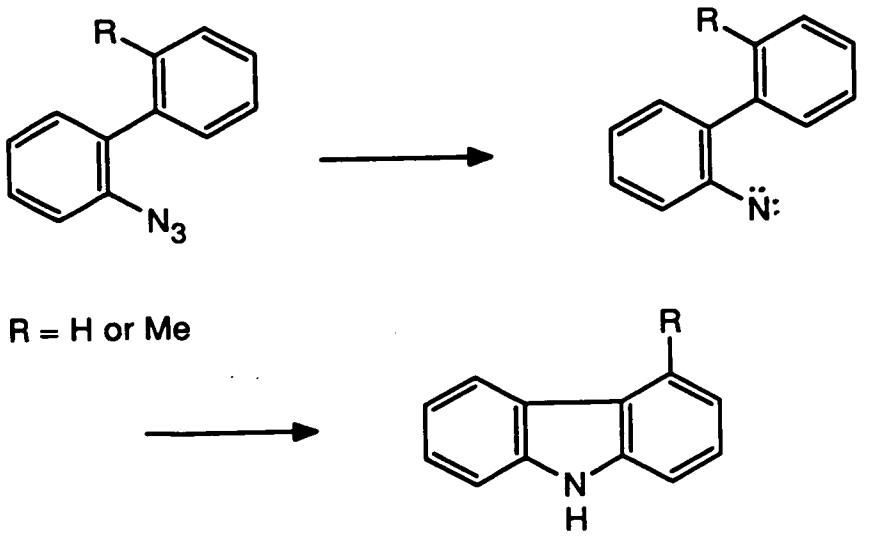
A solid product was obtained, mass spectrometry of which revealed starting material had been recovered.

C. SYNTHESIS AND PYROLYSIS OF PYRAZOL-3-YL-1,2,3-TRIAZOLES

Carbenes and Nitrenes are electron deficient species and are normally generated by photolytic and thermal means. Both species have been used in cyclisation reactions of which some examples are given below.[92]

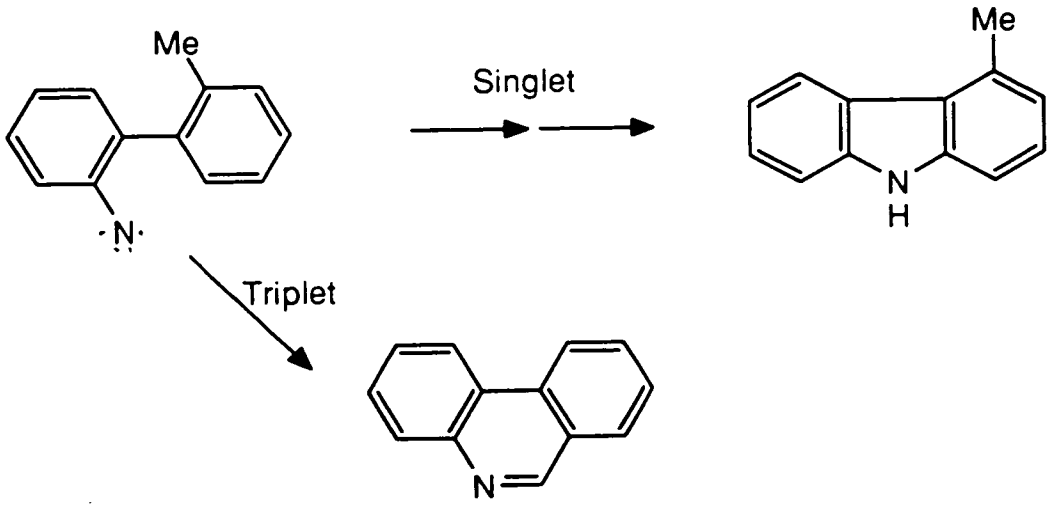
1. Cyclisation of Nitrenes

Aromatic nitrenes may undergo cyclisation *via* the singlet or triplet state. Singlet nitrenes can insert into neighbouring rings to give carbazoles (Scheme 102).[93]



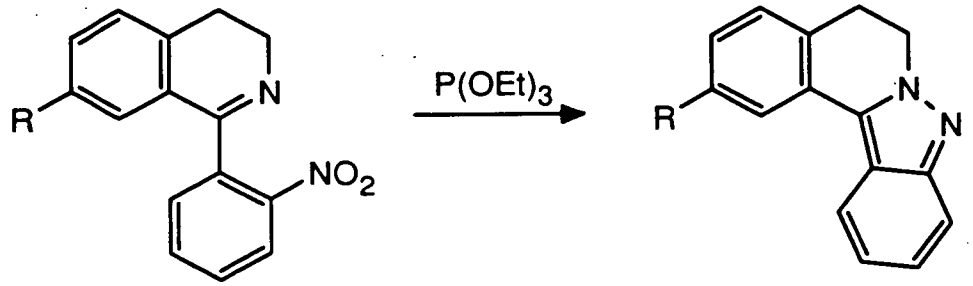
Scheme 102

Triplet nitrenes on the other hand can insert into methyl groups to give phenanthridines (Scheme 103).[94]



Scheme 103

Aryl nitrenes may also cyclise onto heterocyclic rings, examples of this include the formation of **210** (Scheme 104).[95]

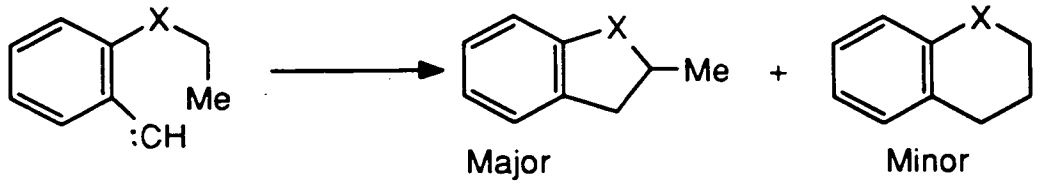


210

Scheme 104

2. Cyclisation of Carbenes

Insertion of aryl carbenes into side chains to form dihydrobenzofurans and dihydroindoles has been described (Scheme 105).[96]

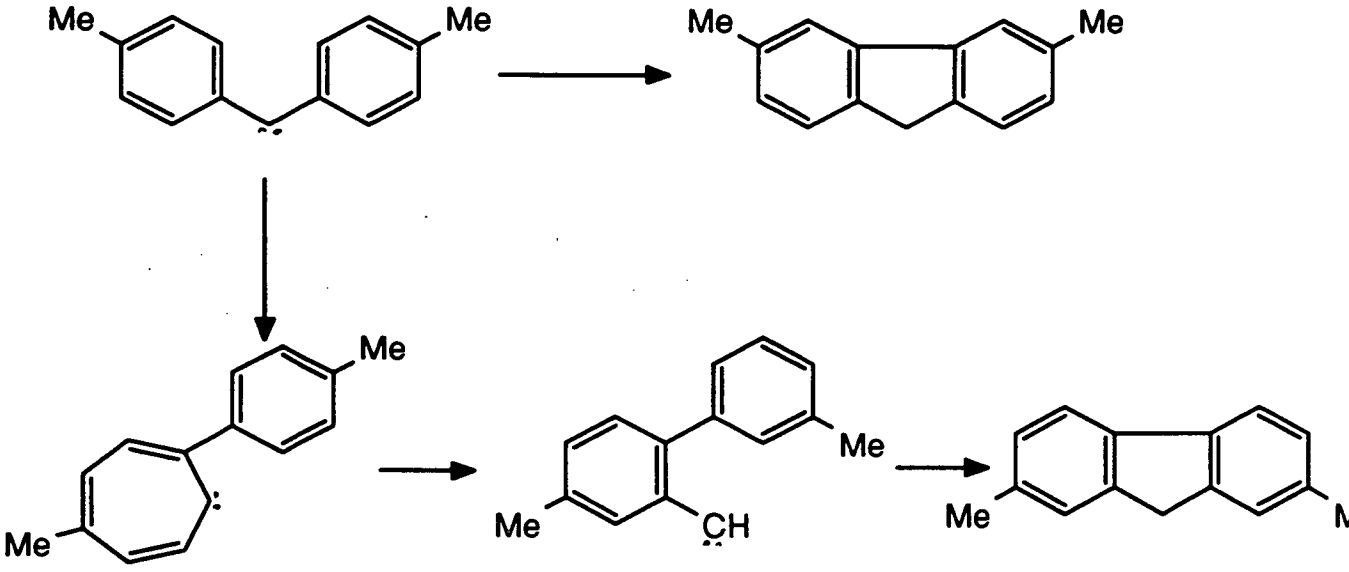


X = O, NEt.

Scheme 105

The minor product is formed by insertion of the carbene function into the methyl group.

Fluorenes may be generated from carbenes in an analogous fashion to carbazoles. The process is not direct and the carbene is found to rearrange *via* the 7-membered ring **211** (Scheme 106).[97]



211

Scheme 106

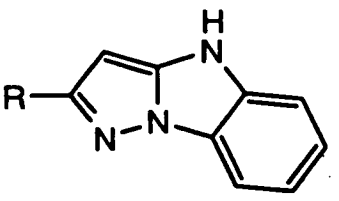
3. Flash Vacuum Pyrolysis

The technique of Flash Vacuum Pyrolysis (F.V.P.),[98] involves vaporisation of a substrate from an inlet system into a silica furnace tube which can be maintained at temperatures up to 1000°C. The apparatus is evacuated to a pressure of 10^{-2}-10^{-3} mbar and the products are collected in a

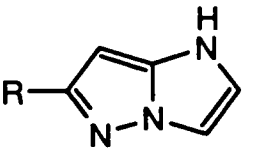
liquid nitrogen trap situated at the exit point of the furnace (a diagram can be found in the Experimental section).

Although the molecules are subjected to high temperatures most functional groups survive unchanged due to the very short contact time in the hot zone (10-100 ms). The technique is of importance because of its ability to bring about extrusion of small molecules (*e.g.* N_2, CO_2 *etc.*), to give highly reactive intermediates which can then undergo intra-molecular cyclisation reactions. Many examples of these reactions occur in this chapter.

Investigations into the use of nitrenes and carbenes as key intermediates in the synthesis of photographic compounds such as pyrazolo[1,5-*b*]benzimidazoles, **212**, and imidazo[1,2-*b*]pyrazoles, **213**, were carried out.

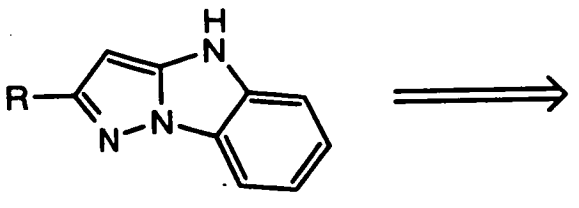


212

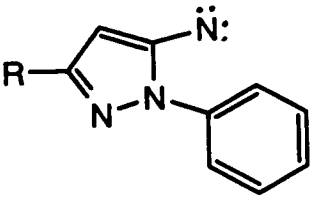


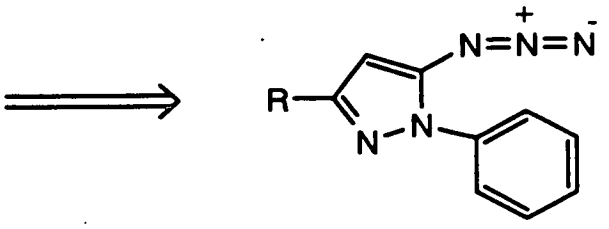
213

Approaches to **212** could follow the disconnection sequence below (Scheme 107).



212



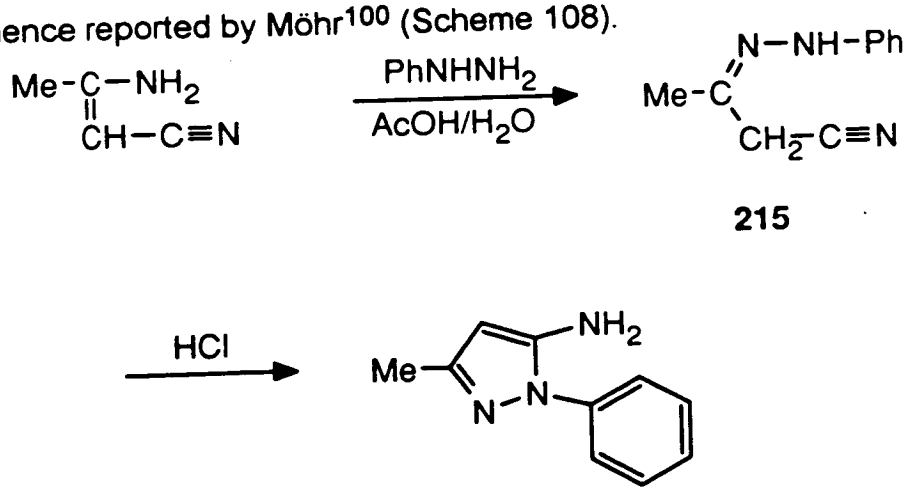


214

Scheme 107

The azide **217** can be synthesised from the corresponding aminopyrazole using standard methodology.[99]

3-Amino-5-methyl-2-phenylpyrazole, **216**, was synthesised using the sequence reported by Möhr[100] (Scheme 108).



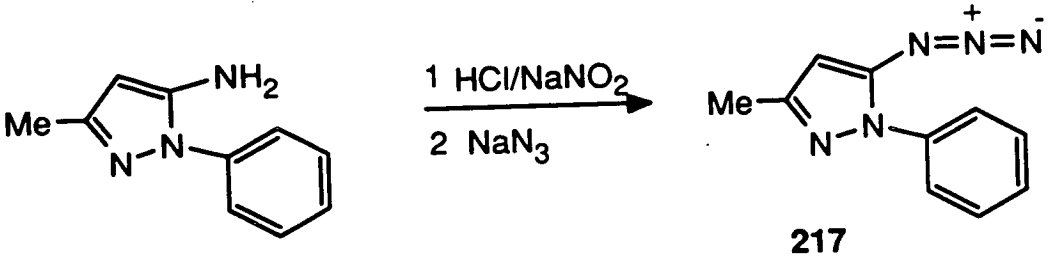
215

216

Scheme 108

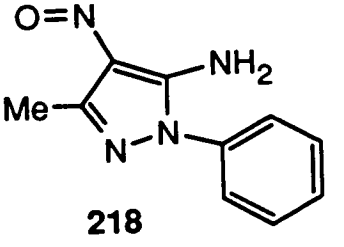
The intermediate **215** was isolated and was found to contain some **216**. This mixture was completely cyclised to **216** under acid conditions. ^{1}H NMR spectroscopy of **214** showed all the correct peaks including a singlet at δ_H 5.37 which is typical for 3-aminopyrazoles.

The 3-aminopyrazole **216** was converted into the corresponding azide **217** by diazotisation followed by treatment with sodium azide.[101] The azide was found to be contaminated with another product. Smith reported this to be 3-amino-5-methyl-4-nitroso-2-phenylpyrazole, **218**,[101] (Scheme 109).



216 **217**

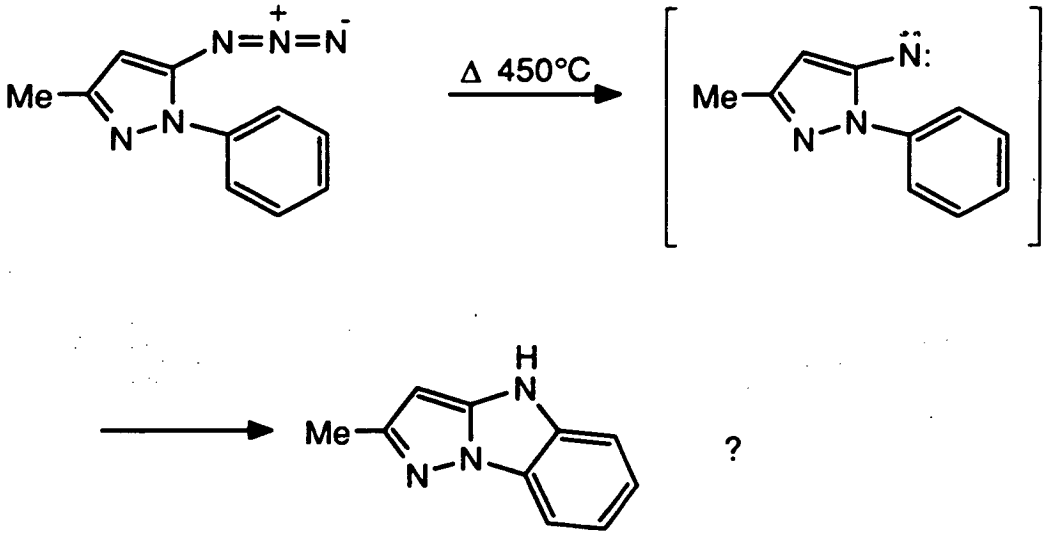
Scheme 109



218

The azide was purified by column chromatography. The ^{1}H NMR spectrum of the azide showed the resonance for the pyrazole proton had been displaced to δ_H 6.06 presumably due to the presence of an electron withdrawing azide group. Absolute confirmation of the structure was obtained from its ir spectrum which showed ν_{max} 2113 cm^{-1} which is diagnostic for azides.[102]

Although solution-phase thermolysis does not lead to cyclisation[101] the azide was nevertheless subjected to flash vacuum pyrolysis[98] in an attempt to generate the pyrazolo[1,5-*b*]benzimidazole **212** (Scheme 110).

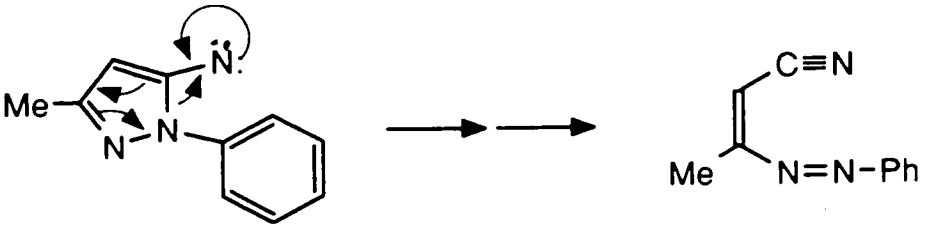


212

Scheme 110

At 450°C the sole product was a red solid which had a m.p. of 59-60°C. Its ^{1}H NMR spectrum showed peaks at δ_H 8.05-7.60 (aromatic), 6.35 (1H) and 2.35 (methyl group). Mann *et al.* in 1984[103] gave the m.p. of **212** to be 239-240°C also the ^{1}H NMR spectrum was δ_H 7.5-7.1 (aromatic), 5.64 (1H) and 2.35 (methyl group). This shows that our product is not **212**.

The proposed structure was **219** which could be formed by the following mechanism (Scheme 111).

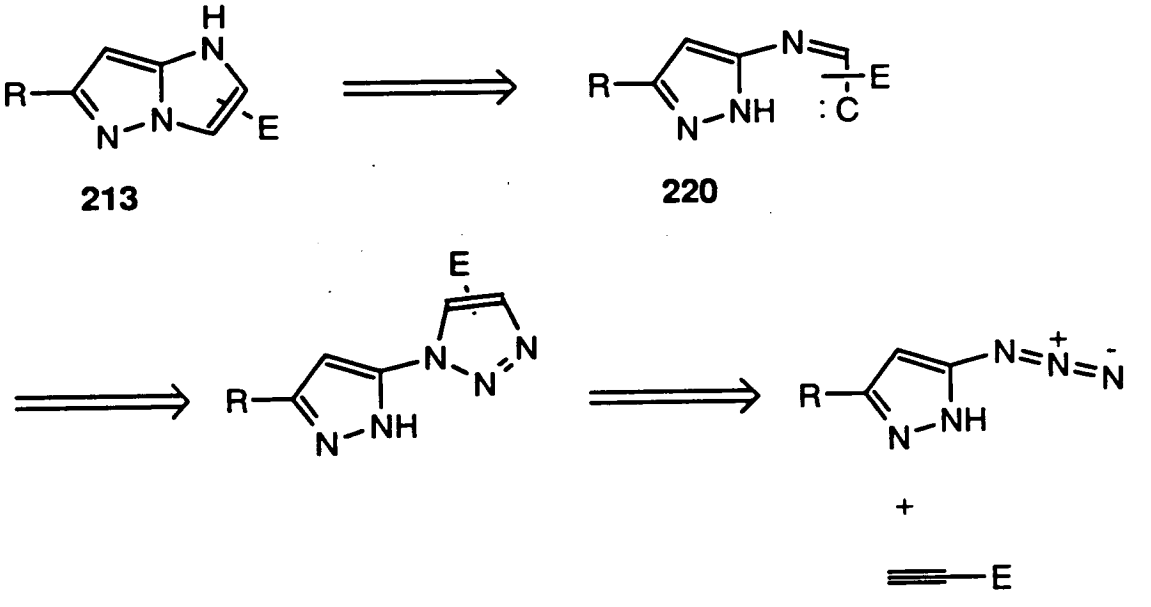


219

Scheme 111

This compound, **219**, was first reported by Smith who obtained it by thermolysis of the azide in refluxing bromobenzene.[101]

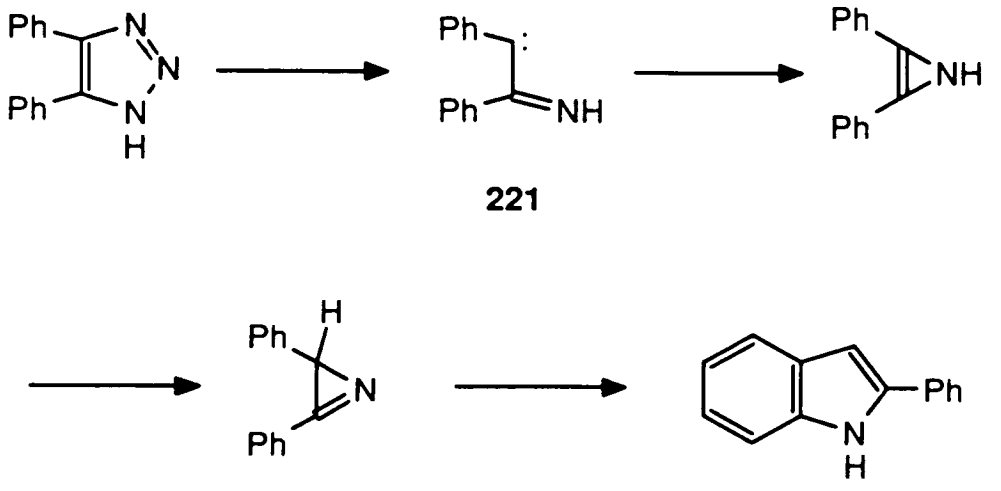
Synthetic approaches to imidazo[1,2-*b*]pyrazoles, **213**, could be envisaged *via* carbene intermediates such as **220** (Scheme 112).



213 **220**

Scheme 112

Gilchrist *et al.*[104] have shown that indoles may be generated from 1,2,3-triazoles by flash vacuum pyrolysis (Scheme 113).

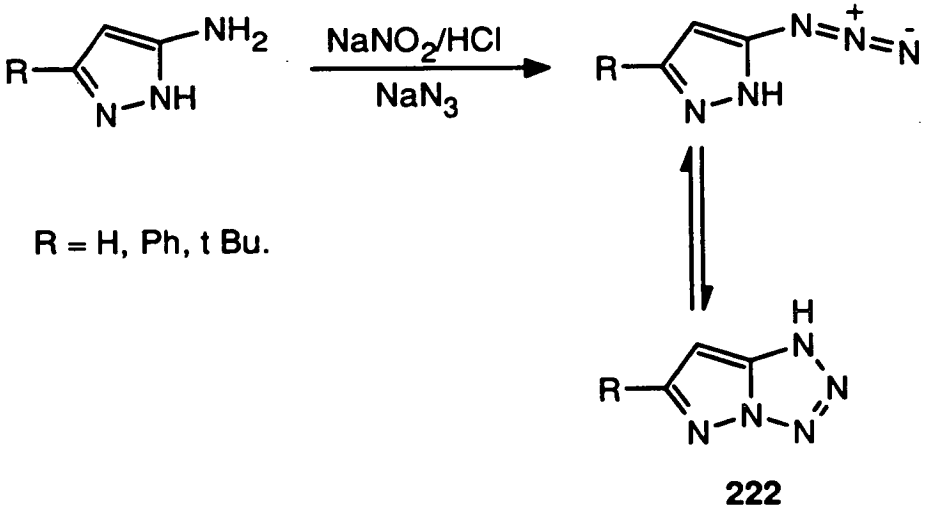


221

Scheme 113

It is also possible for the intermediate **221** to undergo a Wolff rearrangement to give diphenylacetonitrile.

Azides were synthesised in 46-96% yield from the corresponding 3-aminopyrazoles using standard methodology.[99] 3-Azidopyrazoles are also known to be in equilibrium with pyrazolo[1,5-*b*]tetrazoles **222** (Scheme 114).[99]



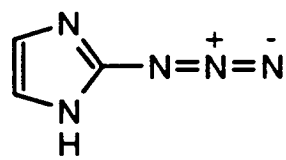
R = H, Ph, t Bu.

222

Scheme 114

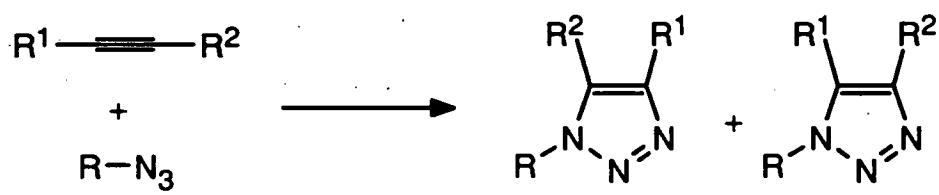
As before, the ^1H NMR spectra of these compounds showed the pyrazolic ring protons to be deshielded with respect to their aminopyrazole precursors. Ir showed ν_{max} at 2130 cm^{-1} (R=H), 2120 (R=Ph) and 2125 (R=t-Bu) which is typical for azides[102] and this agrees with the observation made by Elguero *et al.*[99] that the tetrazole tautomer is not favoured under neutral (or acid) conditions.

Also synthesised by this method was 2-azidoimidazole, **223**.[105]



223

Cycloaddition reactions of azides and alkynes are well known.[106] Normally regio-selectivity is low resulting in the formation of two isomers (Scheme 115).



Scheme 115

The addition of electron deficient alkynes to azides is a finely balanced process.[107] The relative energies are shown in Fig. 17.

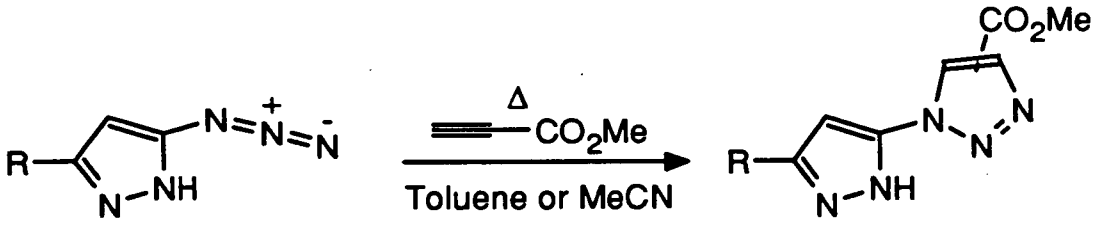
Relative Energies of 1 - 3 Cycloaddition Reactions of Azides.

Figure 17

Only a small change in the nature of the dipolarophile (*e.g.* addition of an α-methyl group) can completely alter the regiochemistry.[107]

We hoped to maximise regio-selectivity by use of ester substituted alkynes with the 3-azidopyrazoles.

3-Azidopyrazole, **224**, 3-azido-5-t-butylpyrazole, **225**, and 3-azido-5-phenylpyrazole, **226**, were all treated with methyl propiolate. The first two were reacted using refluxing toluene as solvent but 3-azido-5-phenylpyrazole, **226**, proved to decompose at this temperature and acetonitrile was used instead (Scheme 116).



224 R = H

225 R = t Bu

226 R = Ph

Scheme 116

It was found that **224** and **225** gave isomeric mixtures while **226** gave only one product possibly due to the lower reaction temperature. The ratios and yields are summarised in Table 10.

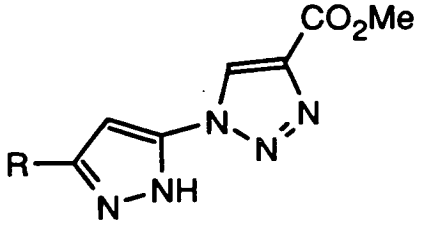
Table 10

Percentage Yields and Isomeric Ratios of Pyrazol-3-yl-1,2,3-triazolecarboxylates

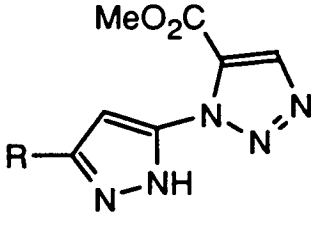
R	Yield (%)	Isomeric Ratio
H	86%*	4.6:1
t-Bu	79%	5.3:1
Ph	45%	-

* Both regioisomers.

It is likely that the major 1,2,3-triazoles formed in these reactions are 1,4-cyclo-adducts **227a-c** since it has been reported that alkynes with electron withdrawing functional groups favour this regiochemistry.[106,107]



227



228

a R = H

b R = t Bu

c R = Ph

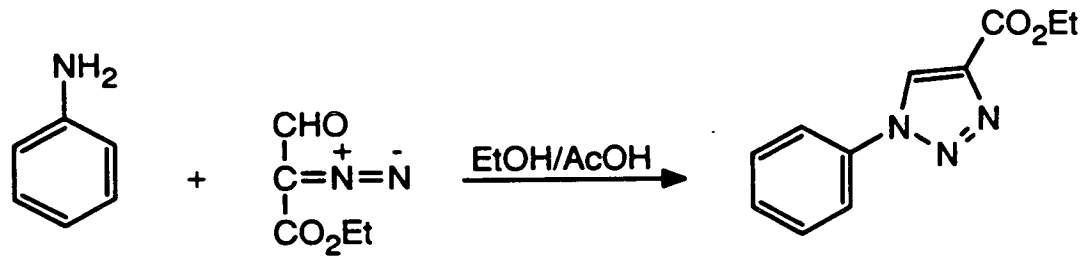
The ^{1}H NMR spectrum of **227a** shows a singlet at δ_H 9.18 (1,2,3-triazole ring proton) whereas the ^{1}H NMR spectrum of **228** shows the 1,2,3-

triazole ring proton at δ_H 8.44. The pyrazole ring protons show similar chemical shifts for both regio-isomers (**227a**, δ_H 7.99 and 6.79; **228**, δ_H 7.96 and 6.6). The value of ^3J for both isomers is 1.9 Hz which shows the pyrazole rings are mostly adopting the tautomers shown above, this may indicate intramolecular hydrogen bonding which is in direct contract to 3-acetamidopyrazoles. For R = t-Bu the 1,2,3-triazole proton occurred at δ_H 10.17 and the pyrazole proton at δ_H 6.64, and for R = Ph it was δ_H 9.22 and δ_H 7.27. All of the pyrazole ring protons were considerably deshielded with respect to the corresponding azide; for example R = t-Bu the azide pyrazole ring proton occurred at δ_H 5.84 and on going to the triazole a deshielding effect, due to the combined effects of electronegativity and ring current effect, of 0.8 ppm was observed.

An attempted n.O.e. experiment to prove the regiochemistry was unsuccessful.

To confirm the regiochemistry it was necessary to find an unambiguous synthetic route which would give only one regioisomer.

Such a route was reported in 1967 by Arnold.[108] This involved the reaction of ethyl α-formyldiazoacetate, **229**, with aniline to give ethyl 1-phenyl-1,2,3-triazole-4-carboxylate, **230**, (Scheme 117).

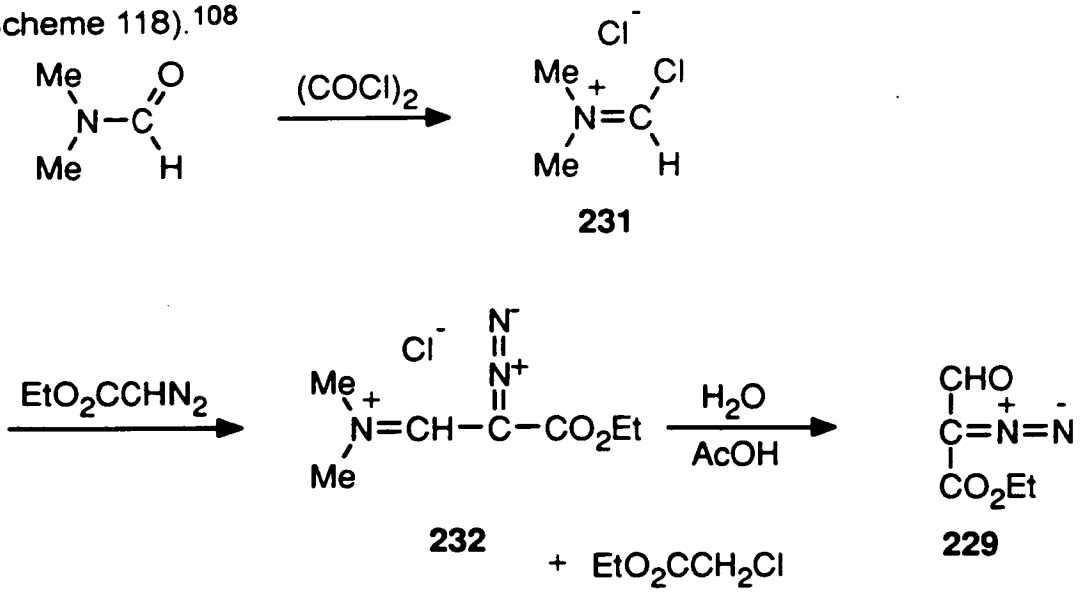


229 **230**

Scheme 117

It was decided to react **229** with 3-amino-5-t-butylpyrazole to obtain the corresponding 1,2,3-triazole which would unambiguously determine the regiochemistry of the previous synthetic route.

Ethyl α-formyl diazoacetate was synthesised by the following route (Scheme 118).[108]

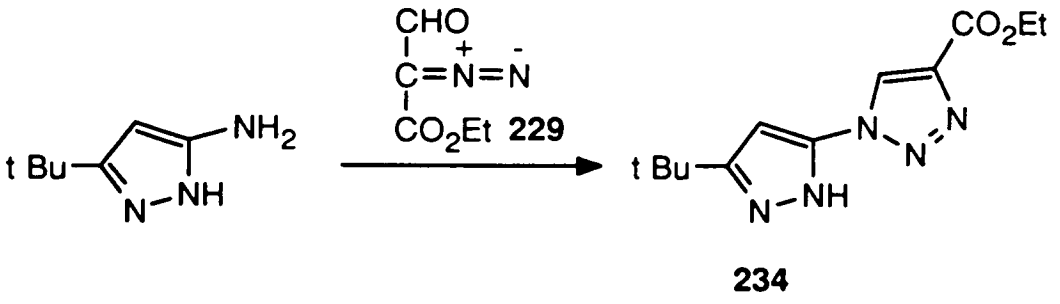


Scheme 118

N,N-Dimethylchloromethylene ammonium chloride, **231**, was synthesised according to the method described by Sato.[109] The salt, **231**, reacted with ethyl diazoacetate to give **232** and **233** (as a by-product). Hydrolysis of **232** gave ethyl α-formyl diazoacetate, **229**, as a yellow oil.

Ethyl α-formyl diazoacetate was first reacted with aniline in a repeat of Arnold's original work.[108] The white, crystalline, solid was found to be ethyl 1-phenyl-1,2,3-triazole-4-carboxylate by a comparison of melting points (86-87°C, lit. 88°C[108]).

Ethyl α-formyl diazoacetate, **229**, was reacted with 3-amino-5-t-butylpyrazole to give ethyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate, **234**, (Scheme 119) in 81% yield.

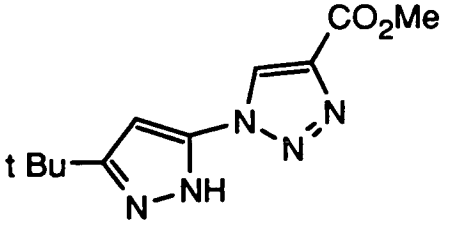


234

Scheme 119

The ^{1}H NMR spectrum of this compound showed the 1,2,3-triazole proton at δ_H 10.12 and the pyrazole proton at δ_H 6.63. This clearly indicates that 1,4-cycloaddition is the major process taking place in the reaction of 3-azidopyrazoles and methyl propiolate.

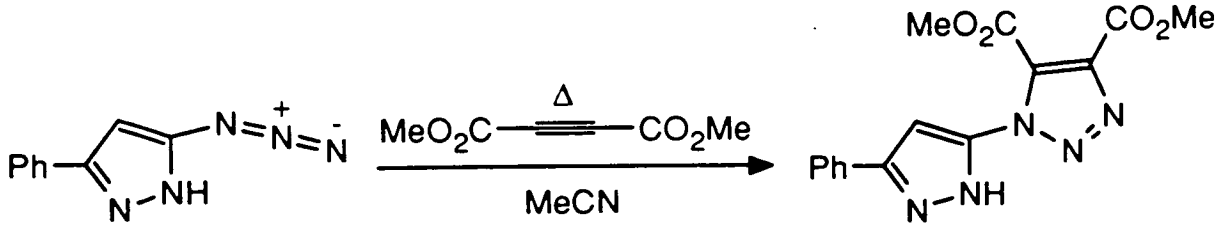
As further proof **234** was treated with sodium methoxide in methanol to bring about ester exchange to give **235**.



235

The ^{1}H NMR spectrum was identical in every way to that obtained for **227b**.

Other alkynes were also reacted with the azides. Dimethyl acetylenedicarboxylate was found to react with 3-azido-5-phenylpyrazole to give **236** (Scheme 120).



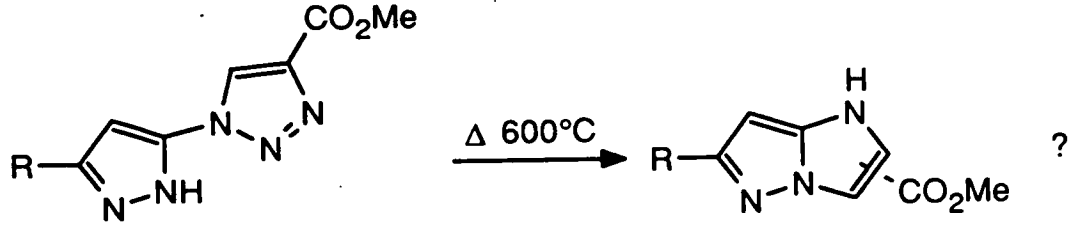
236

Scheme 120

The pyrazole ring proton in **236** was also found to be deshielded *versus* its parent azide (δ_H 7.33 and 6.64 respectively).

Other alkynes reacted with the azides included ethyl phenylpropiolate, phenyl acetylene, phenyl vinyl sulphoxide (ethyne precursor)[110] and ethyl (trimethylsilyl) propynoate. It was found that all of these were of insufficient reactivity and the azide decomposed. Similarly 2-azidoimidazole, **223** was also reacted with methyl propiolate but only yielded polymeric products.

The 1,2,3-triazoles, **227a-c**, were pyrolysed at 600°C under FVP conditions in an attempt to obtain the imidazo[1,2-*b*]pyrazoles, **237**, (Scheme 121).



227

a = H

b = t Bu

c = Ph

237

Scheme 121

The pyrolyses were relatively clean, and gave a single major product at the exit point of the furnace.

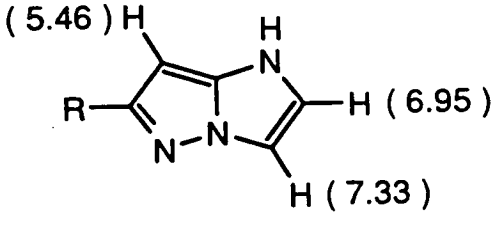
The compounds were glassy in appearance and mass spectrometry showed the expected masses for **237a-c** (*m/z* 165, 221 and 241 respectively). ^{1}H NMR spectroscopy showed the presence of the correct number of ring protons and the chemical shifts are given in Table 11.

Table 11

Chemical Shifts of Pyrolysates 237a-c

R=H	R=t-Bu	R=Ph
5.26	5.20	5.31
5.98	5.86	6.45
7.78	-	-

Surprisingly, the ir spectra of these compounds revealed the absence of an ester carbonyl stretch (aromatic esters occur between 1800-1750 cm^{-1}) [111]. Comparison of the chemical shifts of the ring protons of these compounds and 6-methylimidazo[1,2-*b*]pyrazole,[8] **238**, clearly shows that the pyrolysate products are not imidazo[1,2-*b*]pyrazoles.



238

To identify the pyrolysate products n.O.e. experiments were carried out on the phenyl derivative (Fig. 18).

n.O.e. Spectrum of the Pyrolysate Derived From 227c

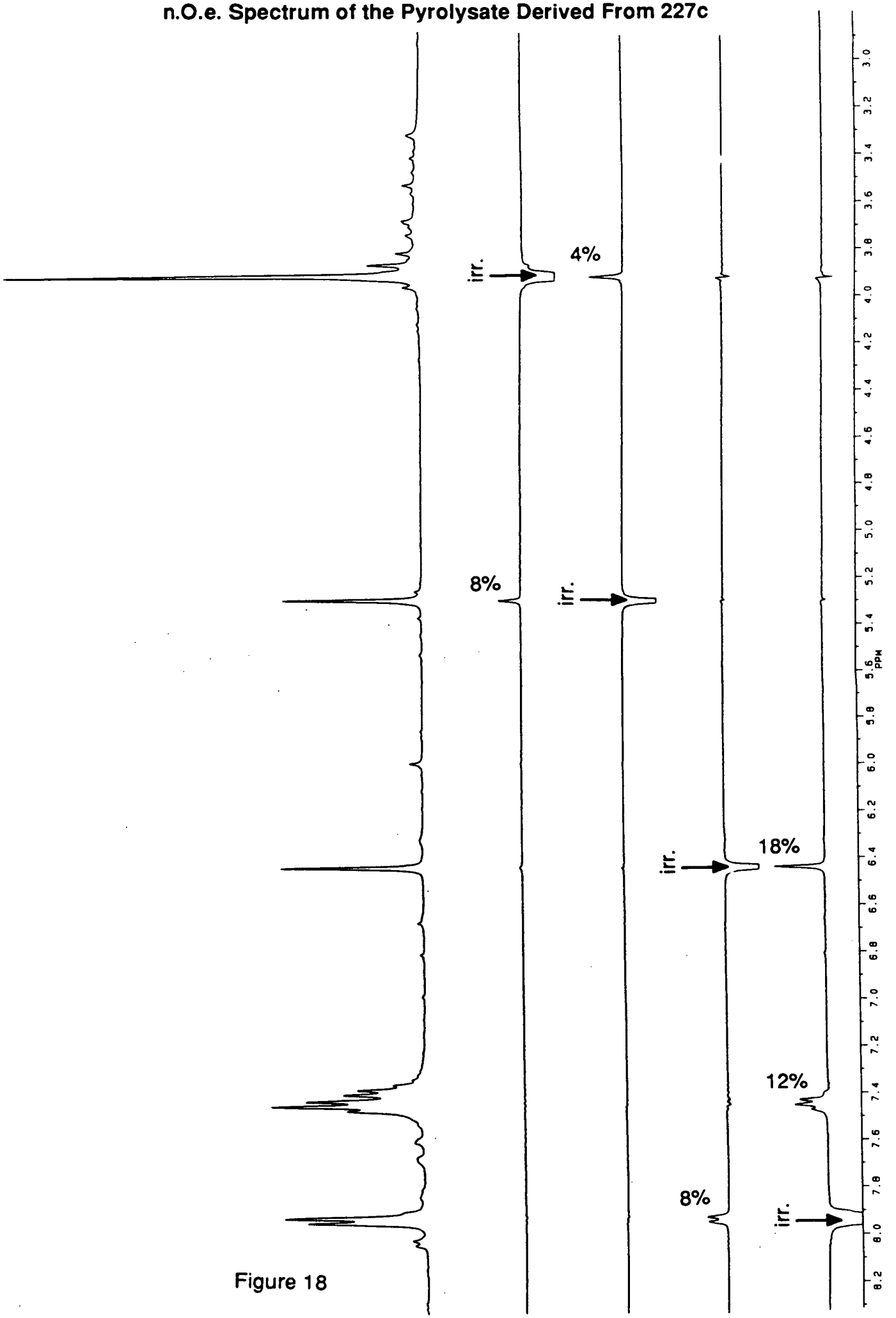
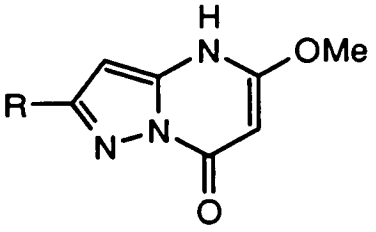


Figure 18

Irradiation of the ring proton at δ_H 5.31 resulted in the enhancement of the methoxy protons at δ_H 3.92. The effect was also observed on irradiation of the methoxy protons. Irradiation of the *meta* protons enhanced the signal at δ_H 6.45 (ring proton) and the *ortho/para* protons. This shows that the proton at δ_H 5.31 is in close proximity to the methoxy group and the proton at δ_H 6.45 is on the pyrazole ring.

The pyrazolo[1,5-*b*]pyrimidin-7-one structure, **239**, is consistent with these observations: a skeletal rearrangement of the non-pyrazolic portion of the molecule has clearly occurred.



R = H, t Bu, or Ph.

239

In agreement with the proposed structure, the ^{13}C NMR spectrum of the phenyl derivative shows the presence of 5 quaternary carbon signals at δ_C 160.80, 157.20, 152.72, 140.41 and 132.67. It was important to assign the quaternaries for further confirmation of the structure and also in preparation for a ^{13}C labelling experiment (see below). To assign these it was necessary to obtain the proton coupled spectrum (Fig. 19).

Proton Coupled Spectrum of 239c.

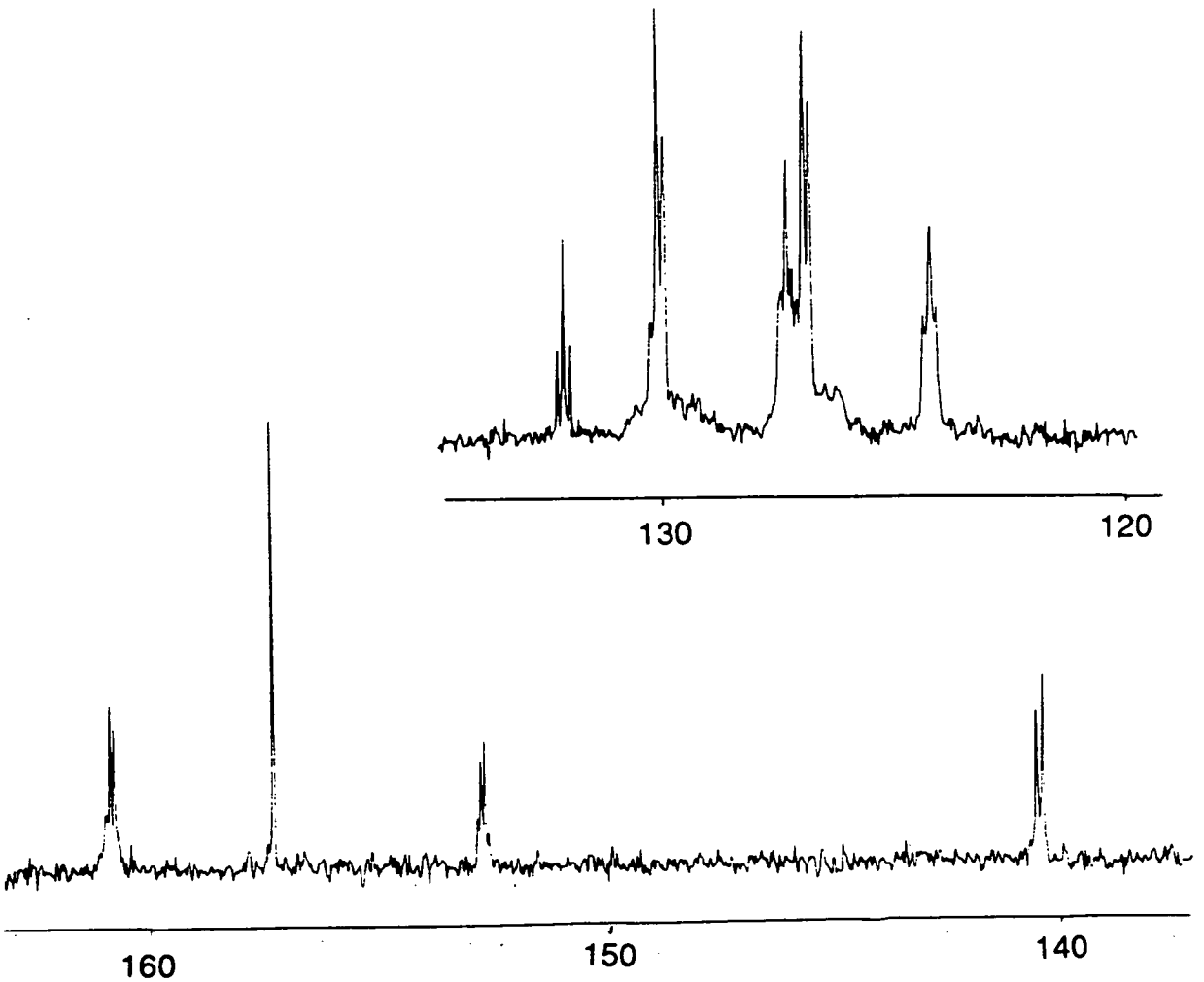
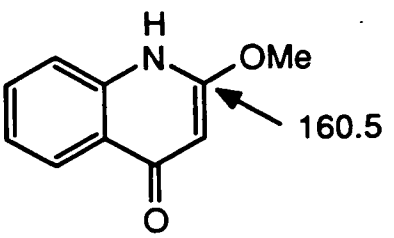


Figure 19

The quaternary at δ_C 160.80 is split into a doublet which indicates long-range coupling to a single proton and is likely to be the carbon bearing the methoxy group. This observation is reinforced if we compare the chemical shift of a methoxy group on a known quinolone, **240**.[112]



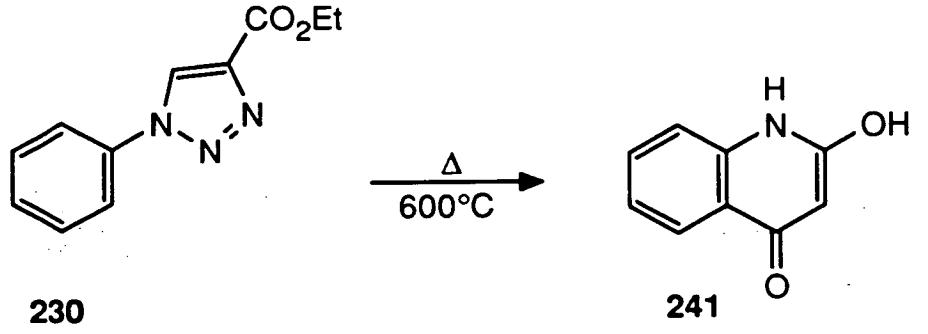
240

The carbonyl group of **239b** should not couple significantly to any proton and should appear as a singlet; the singlet occurs at δ_C 157.20.

The bridgehead carbon should also appear as a doublet and this is the case at δ_C 140.41.

The quaternary at δ_C 132.67 is on the phenyl ring while the quaternary (multiplet, coupling to aromatic protons), at δ_C 152.72 is where the pyrazole ring is joined to the phenyl ring. If the phenyl ring is replaced by t-Bu we see a deshielding effect of ~ 11 ppm, [e.g. a comparison of biphenyl (δ_C 141.50) and t-butylbenzene (δ_C 150.5)],[112] confirms this assignment.

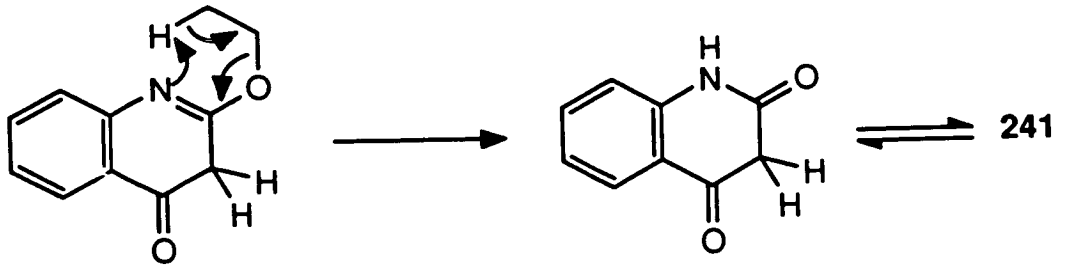
To further prove the ring system of the suggested structure, **239**, ethyl 1-phenyl-1,2,3-triazole-4-carboxylate, **230**, was pyrolysed. This gave the quinoline, **241**, (Scheme 122) which was identical with an authentic sample.



230 **241**

Scheme 122

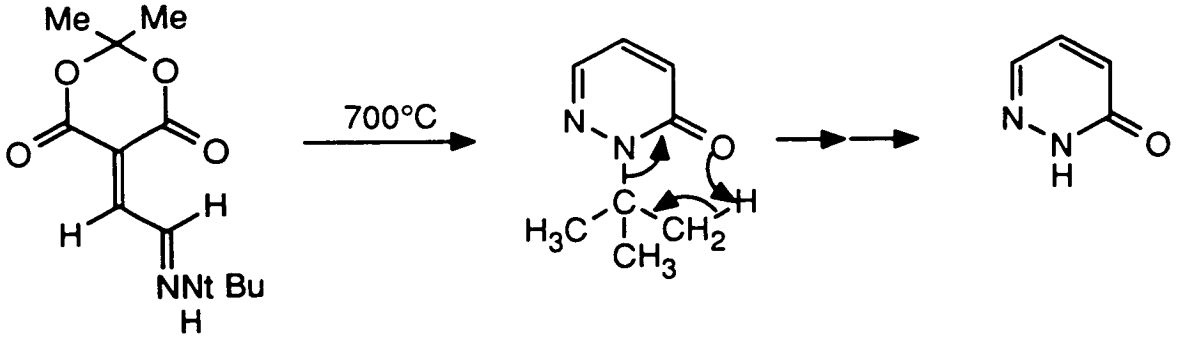
To account for the loss of ethene the pyrolysis must pass *via* an intermediate **242** (Scheme 123).



242

Scheme 123

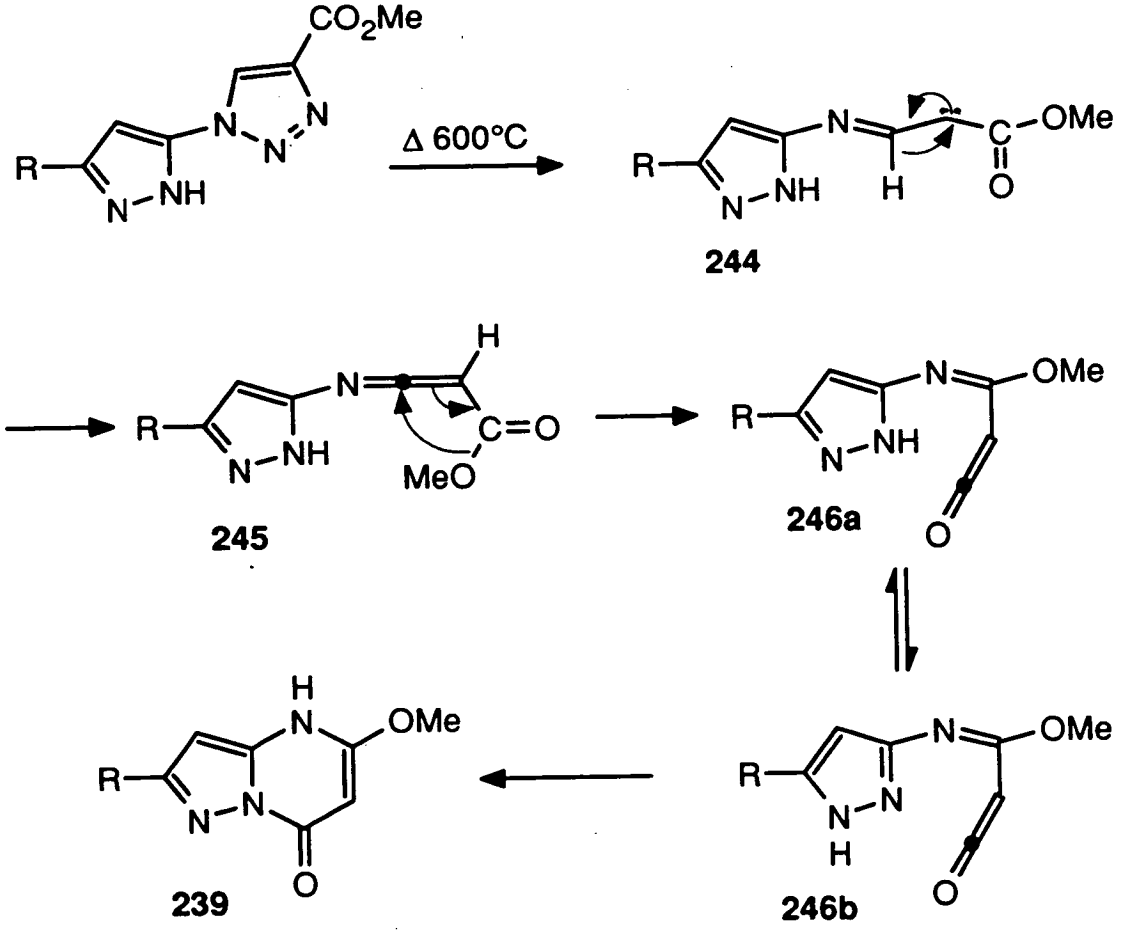
Precedent for the loss of ethene has been established by McNab[113] in the pyrolysis of **243** to initially give the t-butylpyridazin-2-one which is able to lose isobutene by the same mechanism (Scheme 124) to give the unsubstituted pyridazin-2-one.



243

Scheme 124

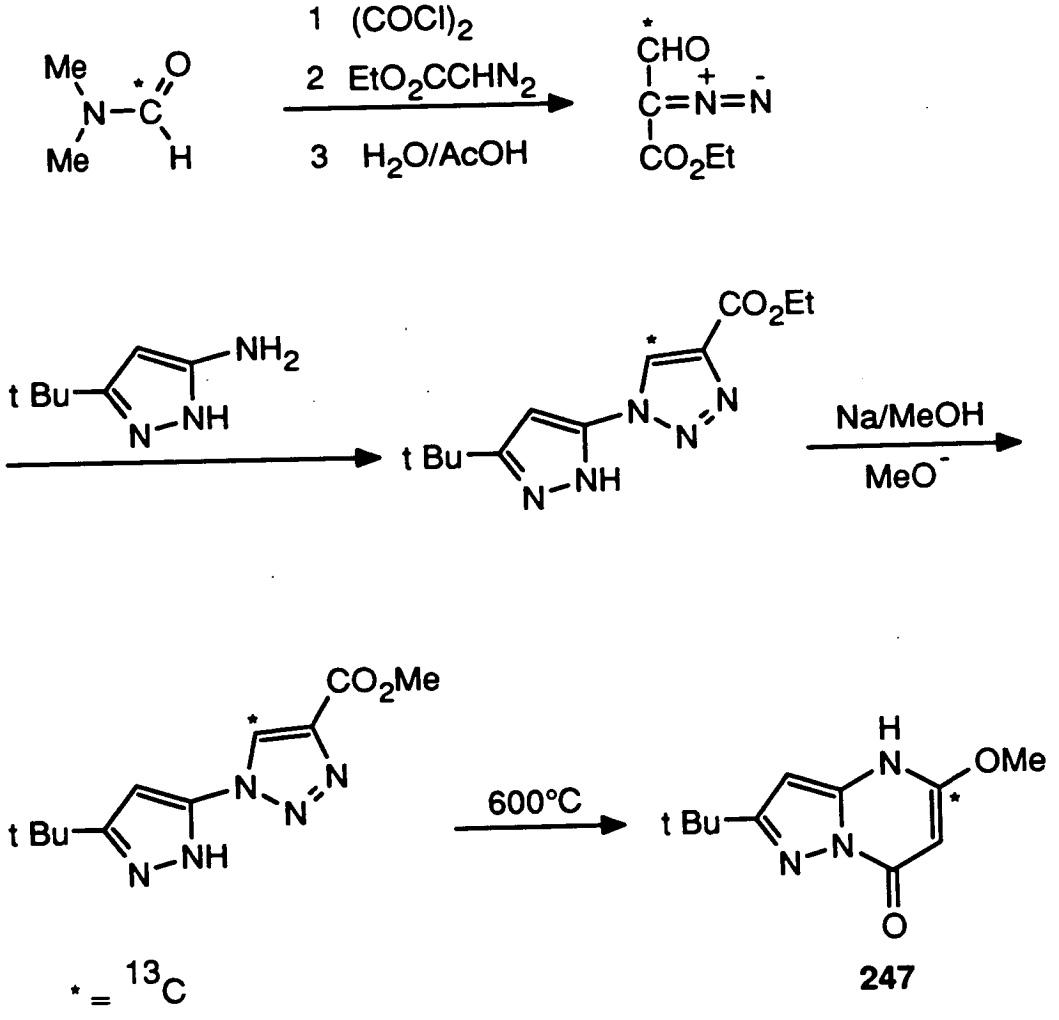
To account for the formation of **239** and **241** the following mechanism was proposed (Scheme 125).



Scheme 125

The mechanism postulates the formation of a carbene, **244**, which inserts into the α C-H bond[96] to give **245**, migration of OMe to give the ketene, **246**, and the sequence is completed by cyclisation of the ketene tautomer, **246b**.

To prove the mechanism in Scheme 125 it was decided to introduce a ^{13}C label into the molecules. This could be accomplished from a commercially available ^{13}C source, ^{13}C DMF and employing Arnold's methodology,[108] (Scheme 126) for the synthesis of 1,2,3-triazoles.

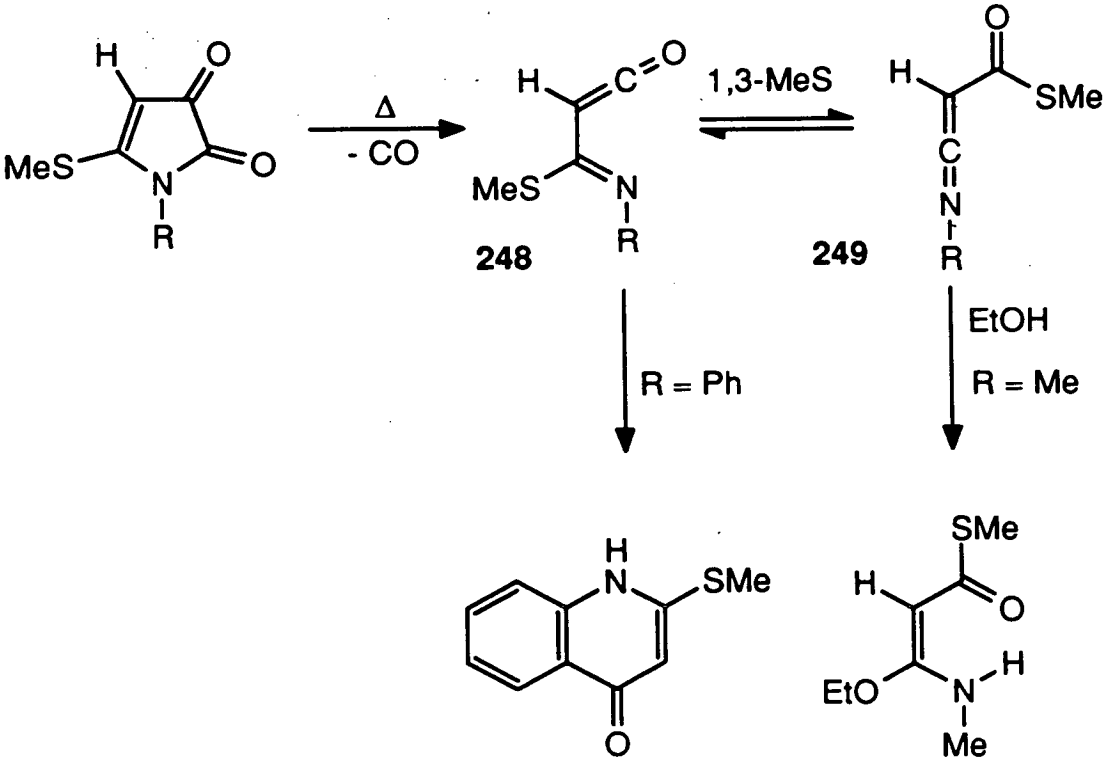


247

Scheme 126

If the preceding scheme is correct we would expect the isotopic label only to appear at the placed marked *. The ^{13}C NMR of **247** showed strong enhancement of the peak at δ_C 160.92 (Fig. 20) which in the original compound occurred at δ_C 160.88 and was the OMe bearing quaternary, thus confirming the proposed mechanism. A minor peak at δ_C 165.01 is not present in the pyrazolo[1,5-*b*]pyrimidin-2-one spectrum and must belong to a minor product which was not identified in the pyrolysates from the unlabelled precursors.

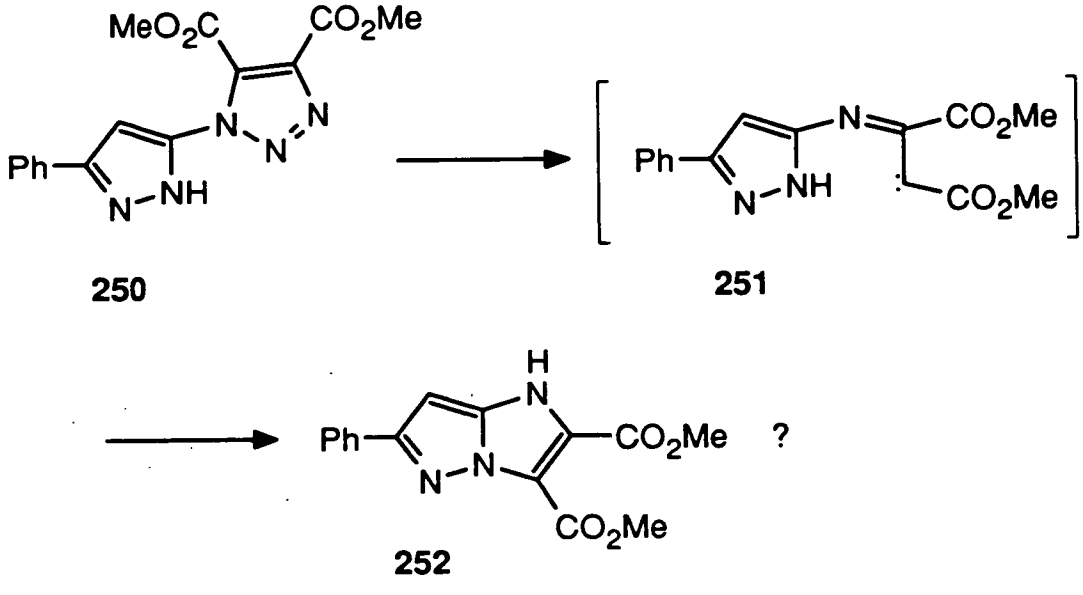
Precedent for the migration of OMe from the oxoketenimine, **244**, to form the imidoylketene, **245**, has been recorded by Wentrup.[114,115] He also shows that there is an equilibrium between the two intermediates, **248** and **249**, and the position of this equilibrium is determined by the nature of R (Scheme 127).



Scheme 127

Our reaction provides entry into the ketenimine-imidoylketene from the opposite side to Wentrup and the equilibrium lies over the left in the presence of an intramolecular trapping group, in agreement with his observation.

In an attempt to prevent this rearrangement from taking place it was decided to pyrolyse dimethyl 1-(1*H*)-(5-phenyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4,5-dicarboxylate, **250**. The intermediate carbene, **251**, formed should not be able to insert into the double bond and should therefore provide a route to the desired imidazo[1,2-*b*]pyrazole, **252**, (Scheme 128).



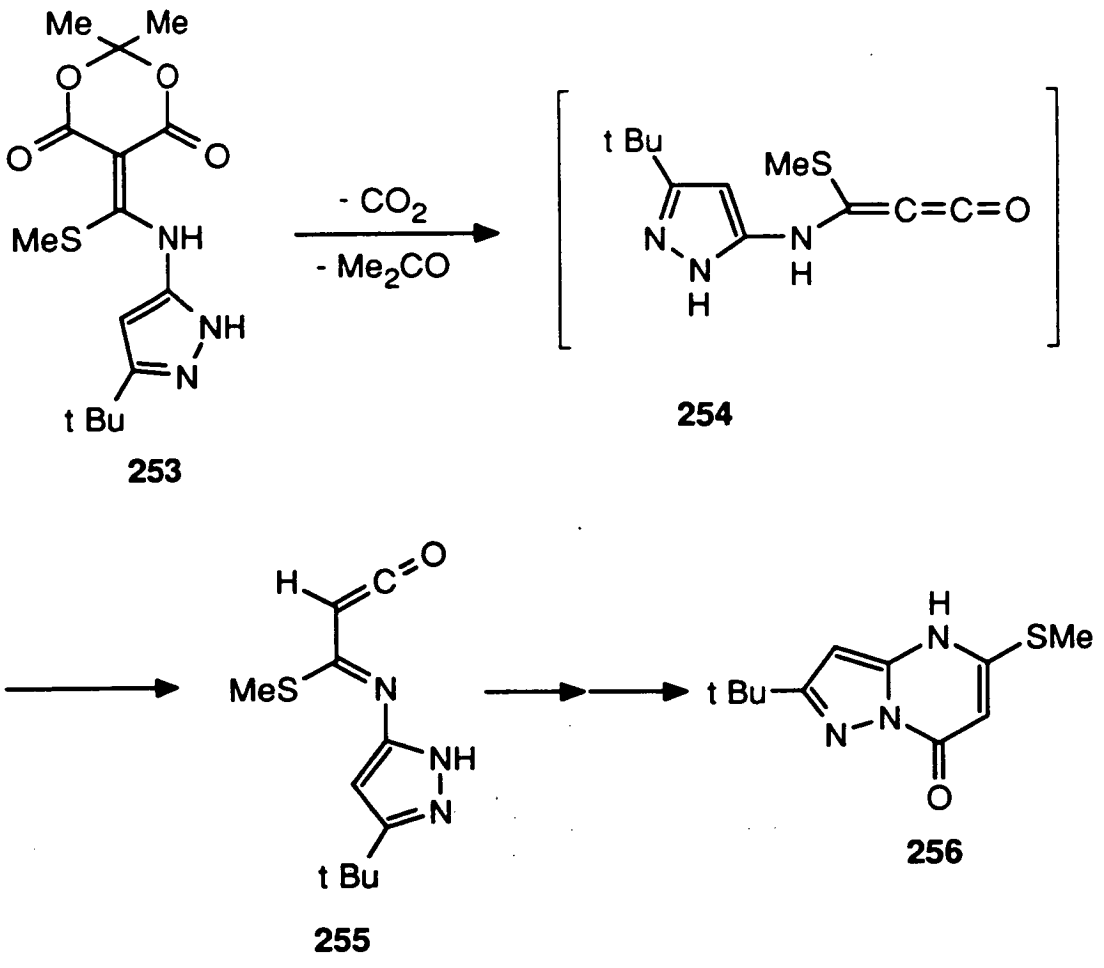
250 **251** **252**

Scheme 128

Although extrusion of nitrogen (rise in pressure) was noted no useful products were identified.

Another route into the imidoylketene-oxoketimine energy surface is obtained by the pyrolysis of Meldrum's acid derivatives such as **253** which is prepared from *bis* methylthiomethylene Meldrum's acid[116] and 3-amino-5-t-butylpyrazole. This reaction proceeds *via* the elimination of CO_2 and acetone to give the methylenekətene, **254**, which undergoes a 1,3-hydrogen shift to

give the imidoylketene, **255**, which cyclises to the pyrazolo[1,5-*b*]pyrimidin-7-one, **256**.



Scheme 129

A reaction of this type has also been reported by Wentrup.[114]

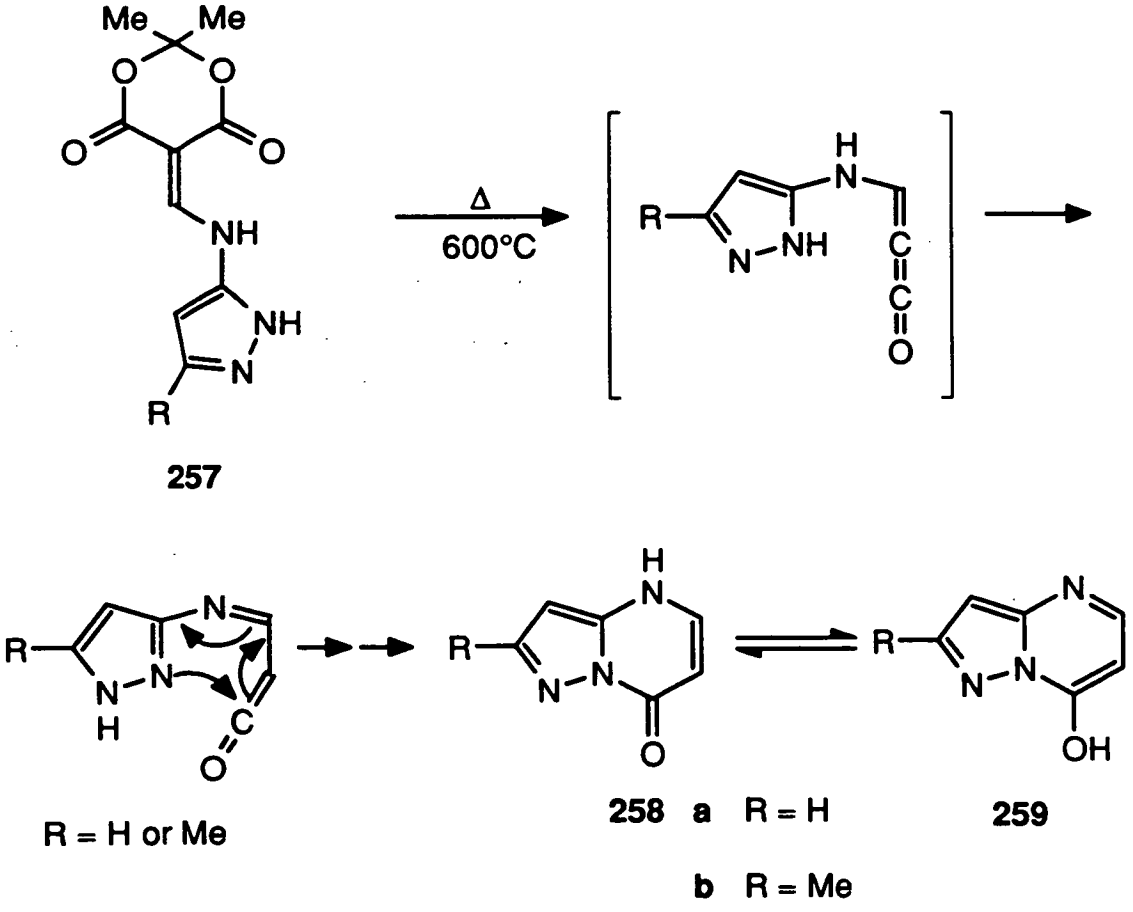
A comparison of the effects of SMe and OMe on a carbon atom C-6 was made. This revealed its greater deshielding effect of OMe *vs.* SMe as the chemical shifts were δ_C 160.88 and 152.70 respectively.

The mass spectrum of the thio derivative, **256,** shows a breakdown pattern 237→222→190 which requires the elimination of SMe. This is in direct

contrast to the breakdown patterns exhibited by 2-t-butyl -2-phenyl-6-methoxypyrazolo[1,5-*b*]pyrimidin-7-one, which do not show breakdown peaks for the loss of OMe but only show the loss of Me.

Meldrum's acid derivatives can also be used to synthesise the unsubstituted examples of pyrazolo[1,5-*b*]pyrimidin-7-ones. These compounds are of interest as potential antiinflammatory drugs.[117]

The synthetic scheme is as follows and proceeds *via* an imidoylketene intermediate as mentioned previously (Scheme 130). The starting materials, **257**, are prepared from methoxymethylene Meldrum's acid[74] in >90% yields.



257

R = H or Me

258 **a** R = H

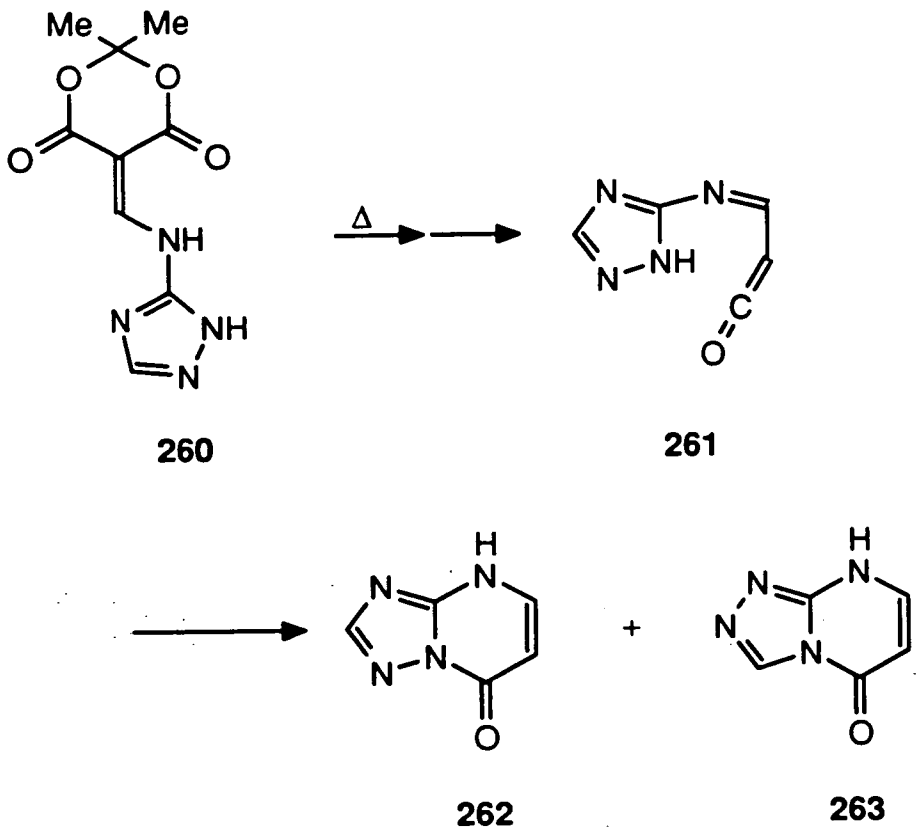
b R = Me

259

Scheme 130

The ^1H NMR spectrum of **258a** (R=H) shows doublets at δ_H 7.88 and 5.69 which have a ^3J value of 7.3 Hz. This shows that tautomer **258** is the favoured structure.

The 1,2,4-triazole derivative, **259**, prepared in an analogous fashion to **257**, was also pyrolysed at 600°C. This resulted in the formation of two products, which can be explained by the following mechanism (Scheme 131).



260 **261**

262 **263**

Scheme 131

The intermediate, **261**, may cyclise at two sites to give **262** and **263**. It was not possible to identify which isomer was the major product, however it was found that varying the pyrolysis temperature altered the product ratio (Fig. 20). The relative proportions were determined from the integrals of the peaks at δ_H 5.94 and 5.77. The percentages of each isomer are shown in Table 12.

Graph Showing the Relative Proportions of A and B.

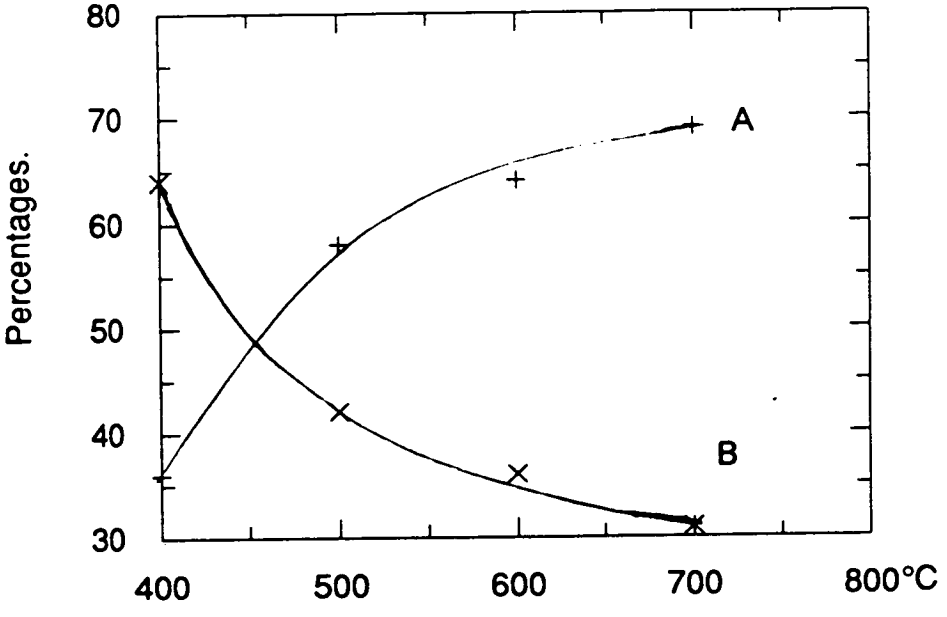


Figure 20

Table 12

Percentages of Isomers A and B at Variable Temperatures

Temperature	%A	%B
400°C	36%	64%
500°C	58%	42%
600°C	64%	36%
700°C	69%	31%

This data shows that B must be the kinetic product while A is the thermodynamic product.

EXPERIMENTAL

ABBREVIATIONS

NMR	Nuclear Magnetic Resonance
δ	chemical shift
s	singlet
d	doublet
t	triplet
q	quartet (in ^{1}H NMR spectroscopy)
q	quaternary (in ^{13}C NMR spectroscopy)
m	multiplet
br	broad
M^{+}	mass of molecular ion
m/z	mass to charge ratio
t.l.c.	thin layer chromatography
m.p.	melting point
i.r.	Infrared
u.v.	Ultraviolet
ε	Extinction coefficient
h.	hours
min.	minutes
mol.	moles
mmol.	millimoles

INSTRUMENTATION AND GENERAL TECHNIQUES

Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were recorded on Bruker WH360, WP200 or WP80 spectrometers.

^{13}C NMR spectra were obtained from a Bruker WP200 (50 MHz) instrument.

The WH360 was operated by Dr. D. Reed; the WP200 by Dr. H. McNab, Mr. J.R.A. Millar, and Miss H. Grant, and the WP80 was operated by Miss H. Grant.

Spectra were obtained in deuteriochloroform solutions unless otherwise stated. Chemical shifts (δ_H and δ_C) were measured in parts per million (p.p.m.), relative to tetramethylsilane.

Mass Spectrometry

Mass spectra were recorded by Miss E. Stevenson on an A.E.I. MS902 spectrometer and by Mr. A. Taylor on a Kratos MS50TC instrument.

Structure Determination

X-ray crystal structural data were collected and solved by Dr. A.J. Blake on a Stoë STADI-4 four circle diffractometer, with graphite monochromator.

Melting Points

Melting points were recorded on a Gallenkamp Melting point apparatus and are uncorrected.

Infrared Spectroscopy

I.r. spectra were obtained on a Perkin-Elmer 781 spectrometer in the form of liquid films or nujol mulls.

Ultraviolet and Visible Spectroscopy

U.v. and visible spectra were obtained on a Unicam SP800A spectrometer; the solvent used is indicated.

Elemental Analysis

Microanalyses were carried out on a Carlo-Erba 1106 microanalyser and a Perkin-Elmer 2400 microanalyser by Mrs. E. McDougall. Further analyses were carried out by the Kodak analytical service.

Chromatography

Thin-layer chromatography was carried out using pre-coated aluminium sheets (0.2 mm silica gel, or 0.2 mm alumina), impregnated with a u.v. fluorescent indicator from Merck.

Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å) by the method of Harwood.[60] Ethyl acetate and n-hexane were used as the solvent system, with 10% increments in the more polar component per fraction.

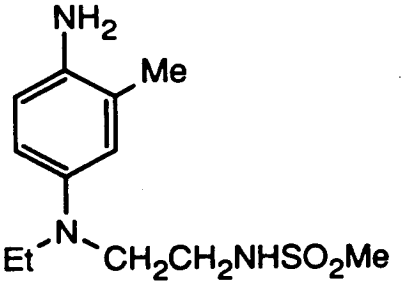
Wet flash[118] and gravity chromatography were carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å) or type H alumina deactivated by 6% water supplied by Laporte Industries.

Solvents

Solvents used for chromatography were normally distilled through a rotary evaporator. Most commercially available solvents were used without further purification. Dimethyl sulphoxide, dimethylformamide, dichloromethane and acetonitrile were dried over an A4 molecular sieve. Chloroform was dried over phosphorus pentoxide.

The T.l.c. Development Spray

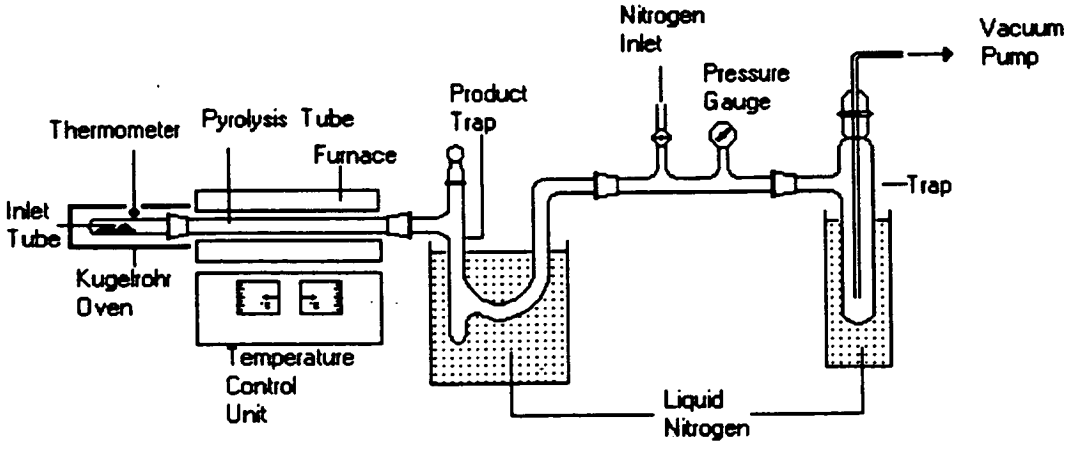
The colour developer, **145**, (CD3) *ca.* (1 g) was dissolved in a 1:1 mixture of ethanol/water (150 ml). A small amount of sodium dithionite was added to preserve the solution. The t.l.c. plates were sprayed with CD3 followed by an oxidising solution (potassium persulphate). Potential couplers showed up as coloured spots.



145

Pyrolysis Apparatus and General Methods

Flash vacuum pyrolysis (F.V.P.)[98] was carried out using apparatus based on the design of W.D. Crow, Australian National University. The important features of the apparatus are shown below:-



Experiments involved the volatilisation of substrates from a horizontal tube, heated by a Büchi Kugelrohr oven, into a hot silica glass tube (30 x 2.5 cm). The temperature of the tube is monitored by a platinum/platinum 13% rhodium thermocouple situated at the centre of the furnace. The temperature is maintained (450-850°C) by a Stanton-Redcroft Laboratory Tube Furnace LM8100. Products were collected in a U-shaped trap cooled in liquid nitrogen at the exit point of the furnace. The system is evacuated to 10^{-2}-10^{-3} mbar by an Edwards Model ED100 high capacity oil pump. Less volatile samples were volatilised using a mercury diffusion pump in conjunction with the oil pump. Pressures of 10^{-4}-10^{-5} mbar are obtained. These pressures are measured using an Edwards High Vacuum Vacustat (1-10^{-3} mbar) or an Edwards Penning Type 8 gauge (10^{-2}-10^{-8} mbar). The latter is only used in conjunction with the mercury diffusion pump. Products obtained are generally of high purity and are washed from the trap with solvent or scraped out.

Synthesis and Chemistry of 2,3-Diaminopyrazoles

Preparation of Aminopyrazoles

3-Aminopyrazole was commercially available.

3-Amino-5-methylpyrazole was obtained from Kodak Ltd.

3-Amino-5-t-butylpyrazole[58] - Hydrazine hydrate (15 g, 15 ml, 0.28 mol) was cooled to 0°C. With continuous stirring 4,4-dimethyl-3-oxo-pentanenitrile (18.5 g, 0.15 mol) in ethanol (200 mol) was added dropwise keeping the temperature close to 0°C. After addition was complete the solution was left to stir at 0°C and was then heated under reflux conditions for 1 h. The reaction mixture was then poured into water (300 ml) and extracted with three portions of ether (3 x 150 ml). The combined ether extracts were washed with water (2 x 200 ml) and dried over anhydrous magnesium sulphate. The solvent was then removed *in vacuo* to give a yellow oil which crystallised slowly on prolonged standing.

The crude compound was recrystallised from benzene/cyclohexane as reported.[58] The yield of the pyrazole was 16.80 g (74%), m.p. 78-79°C (lit.[58] 80°C). δ_H 5.31(1H, s), 3.89(2H, br, s) and 1.19(9H, s); δ_C 155.18(q), 153.62(q), 88.93, 30.86(q), and 29.88.

3-Amino-5-t-butyl-4-chloropyrazole.[61] - 3-Amino-5-t-butylpyrazole (1.39 g, 10 mmol) was dissolved in dichloromethane (30 ml) and cooled to 0°C. *N*-chlorosuccinimide (1.335 g, 10 mmol) was added slowly in small portions. The mixture was then stirred at room temperature for 1 h. The reaction mixture was washed with saturated sodium bicarbonate solution (3 x 50 ml) and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* to give a dark coloured solid which was recrystallised from

cyclohexane to give 3-amino-5-t-butyl-4-chloropyrazole as orange/red crystals, 1.25 g (72%), m.p. 122-123°C (from cyclohexane). δ_H 6.10(2H, br, s) and 1.31(9H, s); δ_C 151.11(q), 147.54(q), 93.13(q), 31.72(q), and 27.80; *m/z* 175(M^+, 13%), 173(M^+, 40%), 160(33), 158(100), 132(5), 130(15), and 123(10). This compound has been previously reported in a Japanese patent.[61]

N-*Amination of 3-Aminopyrazoles : A General Method.* - The aminopyrazole (10 mmol) was dissolved in dry dimethylformamide (15 ml) and cooled to -10°C. Crushed potassium hydroxide (4.16 g) was added and the solution, at -10°C, was left to stir for 20 min. Hydroxylamine-O-sulphonic acid (2.26 g, 20 mmol) was added cautiously and in small portions. The resulting mixture was allowed to warm to room temperature and was left stirring for 2 h. The mixture was then filtered and the dimethylformamide was removed under reduced pressure. The resulting semi-solid was re-dissolved in dichloromethane, filtered, and dried over anhydrous magnesium sulphate. On removal of the solvent at reduced pressure oily products were obtained. These were found to be mixtures of diamines and starting materials. The mixtures were re-dissolved in dimethylformamide and the whole reaction sequence was repeated. The resulting products were distilled under vacuum (Kugelrohr); they could be further purified by dry flash chromatography (50:50 ethyl acetate/hexane), but were generally used after distillation. Two diamines were synthesised. The first example was *2,3-diamino-5-t-butylpyrazole*, 0.92-1.07 g (60-70%), b.p. 128-129°C/0.1 mm Hg. (Found: M^+ 154.1214. $C_7H_{14}N_4$ requires M^+ 154.1218); δ_H 5.20(1H, s), 4.50(4H, br, s), and 1.19(9H, s); δ_C 158.10(q), 144.43(q), 83.35, 31.87(q), and 31.10; *m/z* 154(M^+, 44%), 139(81), 124(100), 122(16), 112(22), 109(97), 95(12), and 94(18).

The second example was *2,3-diamino-5-t-butyl-4-chloropyrazole* 1.15 g (61%), b.p. 156-158°C/0.1 mm Hg. (Found: M^+ 188.0830. $C_7H_{13}{}^{35}ClN_4$ requires M^+ 188.0829); δ_H 5.08(2H, br, s), 4.08(2H, br, s), and 1.26 (9H, s); δ_C 151.52(q), 141.84(q), 86.62(q), 32.62(q), and 28.37; *m/z* 190(M^+, 8%), 188(M^+, 26%), 175(24), 173(79), 160(33), 158(100), 139(31), and 124(43).

3-Aminopyrazole as reported by Sliskovic[56] gave a 1:1 mixture of 1,3-diaminopyrazole and 2,3-diaminopyrazole. Efforts to separate the mixture were unsuccessful.

3-Amino-5-methylpyrazole gave a 2:3 mixture of 1,3-diamino-5-methylpyrazole and 2,3-diamino-5-methylpyrazole. The mixture was also inseparable.

7-t-Butyl-2,3-dimethylpyrazolo[1,5-b]1,2,4-triazine. - 2,3-Diamino-5-t-butylpyrazole (0.154 g, 1 mmol) was dissolved in acetic acid (5 ml). Butanedione (0.086 g, 1 mmol) was added and the mixture was heated under reflux conditions for 1 h. The solvent was removed *in vacuo* and the residue was partitioned between hexane (25 ml) and aqueous sodium bicarbonate (25 ml). The organic layer was dried ($MgSO_4$) and removed at reduced pressure to give *7-t-butyl-2,3-dimethylpyrazolo[1,5-b]-1,2,4-triazine*, 0.110 g, (54%), m.p. 144-145°C (from ethanol/cyclohexane). (Found: M^+ 204.1367. $C_{11}H_{16}N_4$ requires M^+ 204.1375); δ_H 6.37(1H, s), 2.50(3H, s), 2.48(3H, s) and 1.34(9H, s); δ_C 164.32(q), 150.62(q), 144.42(q), 140.57(q), 91.37, 32.60(q), 30.12, 22.52 and 19.44; *m/z* 204(M^+, 51%), 189(100), 162(28), 148(67), 109(11), and 77(13).

7-t-Butyl-2,3-diphenylpyrazolo[1,5-b]1,2,4-triazine. - 2,3-Diamino-5-t-butylpyrazole (0.154 g, 1 mmol) was reacted with benzil (0.5 g, 4.2 mmol) in acetic acid (5 ml). The resulting solution was heated to reflux for 4 h. The solvent was removed and the residue was purified by column chromatography, silica (toluene), to give a yellow solid, *7-t-butyl-2,3-diphenylpyrazolo[1,5-b]1,2,4-triazine*, 0.090 g (27%), m.p. 135-136°C (from hexane/ethanol). (Found: M^+ 328.1678. $C_{21}H_{20}N_4$ requires M^+ 328.1688); δ_H 7.43-7.25(10H, m), 6.67(1H, s) and 1.46(9H, s); δ_C 166.59(q), 149.98(q), 145.69(q), 140.67(q), 136.76(q), 134.67(q), 129.59, 129.42, 1129.33, 129.11, 128.10(2C), 92.93, 32.94(q) and 30.17; *m/z* 328(M^+, 100%), 313(65), 286(26), 211(12), 210(78), 178(12), 105(11) and 77(55).

Reaction of 2,3-Diamino-5-t-butylpyrazole with Dimethylformamide dimethylacetal. - 2,3-Diamino-5-t-butylpyrazole (0.154 g, 1 mmol) was heated on a steam bath, with dimethylformamide dimethylacetal (2 ml) for 1 h. On removal of solvent under reduced pressure a white solid was obtained which was identified as the bis-amidine, *2,3-bis-(3,3-dimethyl-1,3-diazapropenyl)pyrazole*, 0.254 g (96%), which could not be purified, m.p. *ca.* 92°C; (Found: M^+ 264.2068. $C_{13}H_{24}N_6$ requires M^+ 264.2062); δ_H 8.27(1H, s), 7.74(1H, s), 5.52(1H, s), 2.94-2.90(12H, m), and 1.21(9H, s); δ_C 155.88(q), 154.54, 154.10, 144.87(q), 84.42, 40.11, 37.96(2C), 34.19, 32.05(q), and 30.39; *m/z* 264(M^+, 100%), 249(10), 194(21), 193(12), 179(26), 152(14), and 138(24).

Reaction of 2,3-Diamino-5-t-butylpyrazole with Benzaldehyde. - 2,3-Diamino-5-t-butylpyrazole (0.167 g, 1.08 mmol) was condensed with benzaldehyde (0.115 g, 0.110 ml) in the presence of p-toluene sulphonic acid (cat.) in methanol (3 ml). The mixture was maintained at reflux temperature for 3 h. Removal of solvent gave a brown solid, *1-aza-1(3-amino-5-t-butylpyrazol-2-yl)-2-phenylethene*, 0.188 g (72%), m.p. *ca.* 136°C. (Found M^+ 242.1527. $C_{14}H_{18}N_4$ requires M^+ 242.1531); δ_H 8.88(1H, s), 7.79(2H, m), 7.39(3H, m), 5.41(1H, s), 4.24(2H, br, s), and 1.31(9H, s); δ_C 160.55(q), 144.82, 144.04(q), 133.9(q), 129.59, 128.53, 127.55, 84.85, 32.44(q), and 29.99; *m/z* 242(M^+, 20%), 227(7), 210(7), 138(4), and 124(9).

The imine (0.282 g, 1.17 mmol), without purification, was dissolved in acetic acid (8 ml). Sodium acetate (0.328 g) was added followed by bromine (0.1 ml) dissolved in acetic acid (1.6 ml). The mixture was left stirring for 1 h at room temperature and was subsequently heated on a steam bath for 20 mins. The mixture was poured into water (40 ml), this yielded a tarry product. Clean oxidative cyclisation *cf.*[36] had not taken place.

Reaction of 2,3-Diamino-5-t-butylpyrazole with Triethyl Orthoformate. - 2,3-Diamino-5-t-butylpyrazole (0.154 g, 1 mmol) was heated in a Kugelrohr oven to 80°C with triethyl orthoformate (0.25 ml). The by-product ethanol was distilled off, collected and identified by its ^1H NMR spectrum. The mixture was heated until ethanol ceased to evolve. A glassy solid was obtained which appeared to be polymeric material.

Reaction of 2,3-Diamino-5-t-butylpyrazole with Acetic Anhydride. - 2,3-Diamino-5-t-butylpyrazole (0.308 g, 2 mmol) was heated, under reflux conditions, in acetic anhydride (10 ml) for 2 h. On cooling a white precipitate was recovered and this was identified as *3-acetamido-2(*N,N-*diacetylamino)-5-t-butylpyrazole*, 0.140 g (25%), m.p. 220-221°C (from ethanol). (Found: M^+ 280.1540. $C_{13}H_{20}N_4O_3$ requires M^+ 280.1535); δ_H ($[^2H]_6Me_2SO$), 6.43(1H, s), 2.18(6H, s), 2.06(3H, s), and 1.21(9H, s); δ_C ($[^2H]_6Me_2SO$), 170.47(q), 167.33(q), 159.81(q), 137.85(q), 92.00, 32.21(q), 30.01, 24.56 and 23.29; *m/z* 280(M^+, 20%), 238(93), 196(100), 154(33), and 125(40).

Removal of solvent *in vacuo* yielded a yellow oil which was found to be a mixture of triacetylated and diacetylated products.

*5-(*N-*5-t-Butyl-3-aminopyrazol-2-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione.* - To a solution of 5-t-butyl-2,3-diaminopyrazole (0.154 g, 1 mmol) in acetonitrile (2 ml) was added 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (0.165 g, 0.89 mmol). The mixture was left stirring overnight. A white precipitate was isolated and was identified as *5-(*N-*5-t-butyl-3-aminopyrazol-2-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione*, 0.115 g (37%), m.p. 230-231°C (from acetonitrile). (Found: C, 54.25; H, 6.45; N, 17.9. $C_{14}H_{20}N_4O_4$ requires C, 54.55; H, 6.5; N, 18.2%); δ_H ($[^2H]_6Me_2SO$), 8.58(1H, d, $^3J_{H,NH}$ 13.9 Hz), 6.67(1H, s), 3.19(2H, br, s), 1.71(6H, s), and 1.29(9H, s); δ_C ($[^2H]_6Me_2SO$), 164.58(q), 162.29(q), 156.87(q), 152.22, 137.01(q), 104.69(q), 87.54(q), 87.11, 32.16(q), 30.22 and 26.58; *m/z* 308(M^+, 18%), 251(20), 250(100), 217(16), 205(15), 204(79), 191(20), and 123(11).

*7-t-Butyl-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one*. - 2,3-Diamino-5-t-butylpyrazole (1 g, 6.5 mmol) was reacted with ethyl (or methyl) pyruvate (1.5 g, 13 mmol) in acetic acid (10 ml). The mixture was heated to reflux for 1½ h. The solvent was then removed under reduced pressure. The residue was washed with ether and filtered to obtain *7-t-butyl-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one* as a white solid, 0.416 g (32%), m.p. 233-234°C (from ethanol/cyclohexane). (Found: C, 58.2; H, 6.85; N, 27.2. $C_{10}H_{14}N_4O$ requires C, 58.25; H, 6.85; N, 27.2%); δ_H 5.86(1H, s), 2.41(3H, s), and 1.33(9H, s); δ_C 162.87(q), 154.29(q), 145.95(q), 132.98(q), 84.17, 32.57(q), 29.89 and 16.92; *m/z* 206(M^+, 47%), 191(100), 164(26), and 150(53).

*7-t-Butyl-8-chloro-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one*. - 2,3-Diamino-5-t-butyl-4-chloropyrazole (0.8 g, 4.25 mmol) was reacted with ethyl pyruvate (0.5 g, 4.30 mmol) in acetic acid (7 ml). The mixture was heated to reflux for 1½ h. The solvent was then removed *in vacuo*, the residue was washed with light petroleum (b.p. 60-80°C) to yield a white solid *7-t-butyl-8-chloro-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one*, 0.736 g (72%), m.p. 174-175°C (from ethanol/cyclohexane). (Found: M^+ 240.0770. $C_{10}H_{13}{}^{35}ClN_4O$ requires M^+ 240.0778); δ_H 7.66(1H, br, s), 2.40(3H, s), and 1.14(9H, s); δ_C 156.42(q), 153.3335(q), 147.24(q), 130.60(q), 88.01(q), 33.40(q), 33.40 and 16.82; *m/z* 242(M^+, 20%), 240(M^+, 60%), 227(33), 225(100), 215(5), 200(15), 198(45), 186(25), 184(76), 163(25), and 156(40).

*1*H-*8-t-Butyl-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*. - 2,3-Diamino-5-t-butylpyrazole (0.822 g, 5.33 mmol) was dissolved in acetic acid (8 ml). Ethyl acetoacetate (0.70 g, 5.40 mmol) was added and the mixture was heated under reflux conditions for 1 h. The solvent was removed *in vacuo* and the residue was washed with ether, this yielded a pale buff coloured solid, *1*H-*8-t-butyl-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*, 0.509 g (44%), m.p. 221-222°C (from ethyl acetate). (Found: C, 59.6; H, 7.15; N, 24.85. $C_{11}H_{16}N_4O.0.1\ H_2O$ requires C, 59.5; H, 7.3; N, 25.25%); δ_H 9.96 (1H, br, s), 5.80(1H, s), 3.36(2H, s), 2.32(3H, s), and 1.28(9H, s); δ_C 165.66(q), 160.12(q), 157.53(q), 132.61(q), 90.56, 41.73, 32.17(q), 29.92 and 24.44; *m/z* 220(M^+, 51%), 205(100), 178(15), and 164(11).

*1*H-*8-t-Butyl-3,4-dimethylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*. - 5-t-Butyl-2,3-diaminopyrazole (0.171 g, 1.11 mmol) was reacted with ethyl 2-methylacetoacetate (0.160 g, 1.11 mmol) in acetic acid (3 ml). The mixture was heated to reflux for 1½ h. The solvent was removed *in vacuo* to yield initially an oil. Trituration with ether yielded a buff solid, *1*H-*8-t-Butyl-3,4-dimethylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*, 0.144 g (55%), m.p. 204-205°C (from ethanol/cyclohexane). (Found: M^+ 234.1487. $C_{12}H_{18}N_4O$ requires M^+ 234.1480); δ_H 5.80(1H, s), 3.45(1H, q, ^3J 6.9 Hz), 2.21(3H, s), 1.42(3H, d, ^3J 6.9 Hz), and 1.30(9H, s); δ_C 167.28(q), 162.00(q), 160.34(q), 132.91(q), 90.04, 42.49, 32.20(q), 29.95, 19.79, and 10.53; *m/z* 234(M^+, 42%), 219(100), 178(9), and 96(11).

*1*H-*8-t-Butyl-4-propylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*. - 5-t-Butyl-2,3-diaminopyrazole (184 mg, 1.2 mmol) was reacted with ethyl

butyrylacetate (0.189 g, 1.2 mmol) in acetic acid (5 ml). The mixture was heated to reflux for 1½ h. Removal of solvent *in vacuo* yielded a yellow oil. This crystallised slowly over a period of 2 days. The solid was washed with cyclohexane to give *1*H-*8-t-butyl-4-propylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*, 0.125 g (42%), m.p. 155-156°C (from ethanol/cyclohexane). (Found: M^+ 248.1648. $C_{13}H_{20}N_4O$ requires M^+ 248.1637); δ_H 5.80 (1H, s), 3.34(2H, s), 2.59-2.51(2H, m), 1.76-1.65(2H, m), 1.28(9H, s), and 0.98-0.91(3H, m); δ_C 165.84(q), 160.39(q), 160.16(q), 132.79(q), 90.52, 40.68, 40.05, 32.17(q), 29.93, 18.84, and 13.42; *m/z* 248(M^+, 46%), 233(100), 220(18), 206(10), 164(14), and 124(14).

*1*H-*8-t-Butyl-9-chloro-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*. - 2,3-Diamino-5-t-butyl-4-chloropyrazole (0.212 g, 1.12 mmol) was treated with ethyl acetoacetate (0.146 g, 1.12 mmol) in acetic acid (8 ml). The mixture was heated to reflux for 1 h. Removal of solvent gave an oil which crystallised on cooling in a salt-ice bath. The solid was washed with light petroleum (b.p. 60-80°C) and was identified as *1*H-*8-t-butyl-9-chloro-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2[3*H*]-one*, 0.232 g (81%), m.p. 224-225°C (from cyclohexane/ethanol). (Found: M^+ 254.0939. $C_{11}H_{15}{}^{35}ClN_4O$ requires M^+ 254.0934); δ_H 3.36(2H, s), 2.31(3H, s), and 1.35(9H, s); δ_C 164.71(q), 158.72(q), 153.65(q), 130.03(q), 94.20(q), 42.02, 33.00(q), 28.17, and 24.52; *m/z* 256(M^+, 20%), 254(M^+, 60%), 241(32), 239(100), 214(10), 212(30), 177(10), and 158(10).

Reaction of 2,3-Diamino-5-t-butylpyrazole with Ethyl Benzoylacetate. - 2,3-Diamino-5-t-butylpyrazole (0.154 g, 1 mmol) was reacted with ethyl

benzoylacetate (0.192 g, 1 mmol) in acetic acid (3 ml). The mixture was heated to reflux for 1½ h and considerable darkening of the solution was observed. The solvent was removed under reduced pressure to give a dark oil which was identified as mostly starting material with some decomposition.

Reaction of 2,3-Diamino-5-t-butylpyrazole with Ethyl Pivaloylacetate. - Ethyl pivaloylacetate (0.136 g, 0.78 mmol) was heated with 2,3-diamino-5-t-butylpyrazole (0.120 g, 0.78 mmol) in acetic acid (3 ml) for 2 h. Removal of solvent gave an oil which was the starting diamine. Reaction for an extended time was attempted but brought about the decomposition of the β-keto ester.

Reaction of 2,3-Diamino-5-t-butylpyrazole with Diethyl Malonate. - 2,3-Diamino-5-t-butylpyrazole (0.106 g, 0.69 mmol) was reacted with diethyl malonate (0.173 g, 1.08 mmol) in acetic acid (3 ml). The mixture was heated to reflux for 2 h. On removal of solvent under reduced pressure a yellow oil was obtained which was identified as starting material.

1H-8-t-Butyl-2,4-dimethylpyrazolo[1,5-b]1,2,4-triazepine. - 2,3-Diamino-5-t-butylpyrazole (0.2 g, 1.3 mmol) was reacted with acetyl acetone (0.130 g, 1.3 mmol) in acetic acid (4 ml). The mixture was heated to reflux temperature for 2 h. The solvent was then removed *in vacuo* to yield a semi solid product. This was washed with aqueous sodium carbonate to remove the last traces of acetic acid. The mixture was purified by column chromatography (alumina)

using a 30/70 mixture of ethyl acetate/hexane as eluant. The dark red oily product obtained was identified as *1H-8-t-butyl-2,4-dimethylpyrazolo[1,5-b]1,2,4-triazepine*, 0.110 g (39%), b.p. 120-122°C (0.2 mm Hg). (Found: M^+ 218.1529. $C_{12}H_{18}N_4$ requires M^+ 218.1531); δ_H 6.12(1H, s), 3.18(2H, s), 2.30(3H, s), 2.26(3H, s), and 1.31(9H, s); δ_C 161.23(q), 160.07(q), 154.46(q), 135.70(q), 97.62, 42.33, 32.74(q), 30.76, 28.56, and 24.70; *m/z* 218(M^+, 57%), 217(17), 203(100), 189(6), 176(13), 164(14), 163(10), 162(13), and 148(14).

Reaction of 1H-8-t-Butyl-4-methylpyrazolo[1,5-b]1,2,4-triazepin-2[3H]-one with Acetic Anhydride. - 1*H*-8-t-Butyl-4-methylpyrazolo[1,5-*b*]triazepin-2[3*H*]-one (0.110 g, 0.5 mmol) was heated to reflux in acetic anhydride (5 ml) for 2 h. The solvent was removed *in vacuo* and the resulting product was stirred with a dilute solution of potassium hydroxide in methanol (3 ml) for 1 h. The solution was poured into water and extracted with ethyl acetate. Removal of ethyl acetate gave an oil which was an intractable mixture.

Reaction of 2,3-Diamino-5-t-butylpyrazole with Dimethyl Carbonate. - 2,3-Diamino-5-t-butylpyrazole (0.169 g, 1.1 mmol) was treated with dimethyl carbonate (0.099 g, 1.7 mmol) in ethanol (5 ml). A catalytic amount of hydrochloric acid was added and the mixture was heated to reflux for 2½ h. The solvent was then removed under reduced pressure to give a yellow oil which was identified as the starting diamine.

6-t-Butyl-2-methylmercaptopyrazolo[1,5-b]1,2,4-triazole. - 2,3-Diamino-5-t-butylpyrazole (0.6 g, 3.9 mmol) was dissolved in methanol (10 ml). Water (0.3 ml) was then added followed by potassium hydroxide (0.27 g, 4.82 mmol) and carbon disulphide (2.55 ml). The mixture was heated to reflux for 2-3 h during which time the solution became yellow and evolution of hydrogen sulphide was noted. The mixture was then neutralised with 5% hydrochloric acid and poured into water. The mixture was extracted with ethyl acetate (2 x 25 ml) and dried over anhydrous magnesium sulphate. On removal of solvent *in vacuo* a semi-solid product was obtained. T.l.c. showed many products had formed but NMR spectroscopy showed a peak at δ_H 5.45 which was attributable to 6-t-butylpyrazolo[1,5-*b*]1,2,4-triazole-2-thione which was used without further purification.

The solid mixture was dissolved in methanol (10 ml), iodomethane (0.22 ml, 3.53 mmol) was added followed by potassium hydroxide (0.2 g, 3.57 mmol). The mixture was then stirred at room temperature for 2 h. The mixture was then evaporated to dryness and partitioned between 5% hydrochloric acid and ethyl acetate. The organic layer was dried over magnesium sulphate to give an oily product. T.l.c. showed the presence of product as a purple spot on spraying with developer (CD3) and potassium persulphate (aq). The mixture was purified by column chromatography (silica), ethyl acetate/light petroleum (bp 60-80°C) (50:50) to give a yellow solid, *6-t-butyl-2-methylmercaptopyrazolo[1,5-b]1,2,4-triazole*, 0.045 g (5.5%), m.p. 226-227°C (from ethyl acetate). (Found: C, 50.05; H, 6.6; N, 25.6. $C_9H_{14}N_4S$ 0.33 H_2O requires C, 50.0; H, 6.8; N, 25.9%); δ_H ($[^2H]_6Me_2SO$), 12.77(1H, br, s), 5.61(1H, s), 2.61(3H, s) and 1.26(9H, s); δ_C ($[^2H]_6Me_2SO$), 161.43(q), 147.64(q), 138.01(q), 74.81, 32.49(q), 30.54 and 14.84; *m/z* 210(M^+, 81%), 195(100), 168(20), 148(32), and 127(23).

6-t-Butyl-2-methylthio-7-(4-diethylamino-2-methylphenylimino)-7H-pyrazolo[1,5-b]1,2,4-triazole. - 6-t-Butyl-2-methylmercaptopyrazolo[1,5-*b*]1,2,4-triazole (0.052 g, 0.25 mmol) was dissolved in a mixture of 5% aqueous sodium carbonate solution (5 ml) and methanol (2.5 ml). The developer, 4(*N,N*-diethylamino)-3-methylaminobenzene hydrochloride (0.062 g, 0.29 mmol) was added and the solution became purple. Potassium persulphate (0.15 g, 0.55 mmol) was added, the solution became intense purple and the resulting dye, *6-t-butyl-2-methylthio-7-(4-diethylamino-2-methylphenylimino)-7H-pyrazolo[1,5-b]1,2,4-triazole*, was formed as a purple precipitate. 0.077 g (81%), m.p. 133-134°C (crude). (Found: M^+ 384.2097. $C_{20}H_{28}N_6S$ requires 384.2096); λ_{max}(MeOH), 558 nm, λ_{max}(EtOAc), 546 nm, λ_{max}(cyclohexane), 524 nm; ε(EtOH) 58,368; δ_H 9.02(1H, d, ^3J 9.4 Hz), 6.73(1H, d, d, ^3J 9.4 Hz, and ^4J 2.9 Hz), 6.59(1H, d, ^4J 2.9 Hz), 3.49(4H, q, ^3J 7.1 Hz), 2.66(3H, s), 2.53(3H, s), 1.53(9H, s), and 1.25(6H, t, ^3J 7.1 Hz); δ_C 170.23(q), 162.30(q), 151.84(q), 146.70(q), 143.09(q), 135.21(q), 131.12(q), 127.10, 112.54, 110.39, 44.92, 35.38(q), 29.43, 20.42, 14.98, and 12.73; *m/z* 384(M^+, 100%), 369(33), and 258(24).

1-Aza-1(5-methylpyrazol-3-yl)-2(4-methoxyphenyl)ethene. - 3-Amino-5-methylpyrazole (0.97 g, 10 mmol) was dissolved in absolute ethanol (150 ml). *p*-Anisaldehyde (1.36 g, 1.21 ml, 10 mmol) was added together with piperidine (1 ml). The mixture was heated to reflux for 3 h. The solvent was removed *in vacuo* to give a white solid, *1-aza-1(5-methylpyrazole-3-yl)-2(4-methoxyphenyl)ethene*, 1.91 g (89%), m.p. 136-137°C (from ethanol). (Found: C, 67.0; H, 6.0; N, 19.7. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.1; N,

19.5%); δ_H 8.63(1H, s), 7.80(2H, d, ^3J 8.5 Hz), 6.91(2H, d, ^3J 8.5 Hz), 6.15(1H, s), 3.78(3H, s), and 2.30(3H, s); δ_C 161.99(q), 159.41, 157.87(q), 142.31(q), 130.28, 128.78(q), 113.90, 93.81, 55.13, and 11.67; *m/z* 215(M^+, 100%), 214(41), 200(7), 184(2), 172(4), and 146(6).

1-Aza-1(5-t-butylpyrazol-3-yl)-2(4-methoxyphenyl)ethene. - 3-Amino-5-t-butylpyrazole (1.39 g, 10 mmol) was dissolved in absolute ethanol (150 ml) and treated with piperidine (1 ml) and *p*-anisaldehyde (1.36 g, 1.21 ml, 10 mmol). The mixture was heated to reflux for 3 h. On removal of solvent a gummy product was obtained. This was redissolved in ether and removal of solvent gave a solid product identified as *1-aza-1(5-t-butylpyrazol-3-yl)-2(4-methoxyphenyl)ethene* 1.67 g (65%), m.p. 138-139°C (from cyclohexane). (Found: C, 67.85; H, 7.1; N, 15.9. $C_{15}H_{19}N_3O$. 0.5 H_2O requires C, 67.65; H, 7.1; N, 15.8%); δ_H 8.67(1H, s), 7.80(2H, d, ^3J 8.7 Hz), 6.89(2H, d, ^3J 8.7 Hz), 6.10(1H, s), 3.78(3H, s), and 1.32(9H, s); δ_C 161.88(q), 159.14, 157.31(q), 156.08(q), 130.24, 128.84(q), 113.79, 91.20, 55.04, 31.16(q), and 29.91; *m/z* 257(M^+, 100%), 256(31), 241(62), 215(36), 200(12), and 134(52).

Reaction of 1-Aza-1(5-t-butylpyrazole-3-yl)-2(4-methoxyphenyl)ethene with Hydroxylamine-O-sulphonic Acid. - 1-Aza-1(5-t-butylpyrazol-3-yl)-2(4-methoxyphenyl)ethene (0.257 g, 1 mmol) was dissolved in DMF (2 ml). Potassium hydroxide (0.416 g, 7.4 mmol) and hydroxylamine-*O*-sulphonic acid (0.226 g, 2 mmol) were added using the same conditions mentioned previously.

The mixture was left stirring for 2 h and DMF was removed *in vacuo*. After further work up with dichloromethane products were isolated which were found to be 5-t-butyl-3-aminopyrazole and anisaldehyde, i.e. hydrolysis of the imine had occurred.

Trimethyl oxonium tetrafluoroborate was commercially available.

Triethyl Oxonium Tetrafluoroborate.[90] - Boron trifluoride diethyletherate (28.4 g, 25.2 ml, 0.2 mol) was added to ether (50 ml, sodium dried) in a dry 3-necked flask. Epichlorohydrin (14 g, 11.9 ml, 0.15 mol) was added over the period of 1 h at such a rate to maintain vigorous boiling. The mixture was then heated to reflux for 1 h and was subsequently left stirring overnight. Ether was removed from the crystalline mass under a nitrogen atmosphere. The hygroscopic crystals were washed with dry ether (3 x 30 ml) and were collected by suction. The crystalline product was triethyl oxonium tetrafluoroborate 16.88 g (59%). This was used in subsequent reactions without further purification.

Reaction of Trialkyl Oxonium Salts with Dimethyl Formamide: A General Procedure. - Dimethyl formamide (0.365 g, 5 mmol) was dissolved in dry dichloromethane (20 ml). Trialkyl oxonium tetrafluoroborate $R_3O^+BF^-$ (R = Me, 0.74 g, 5 mmol, R = Et, 0.95 g, 5 mmol) was added and the mixture was left stirring at room temperature overnight. The mixture was then concentrated to 1/3 of its original volume and added to ether (35 ml). An oil separated out and the solvent was removed. The oils were reacted with a 5% excess of 3-aminopyrazole (0.435 g, 5.25 mmol) in ethanol (R = Et) or

methanol (R = Me). The mixture was left stirring for 3 days. The solvent was removed *in vacuo* and the residue was added to water. The mixture was made strongly alkaline with sodium hydroxide (5 M) and was extracted with ethyl acetate (3 x 20 ml). The organic extracts were dried over magnesium sulphate and on removal of solvent gave a whitish solid identified as the amidine, *3-(3,3-dimethyl-1,3-diazapropenyl)pyrazole*, R = Me, 0.685 g (99%) R = Et, 0.250 g (36%), m.p. 230°C (dec). (Found: M^+ 138.0912. $C_6H_{10}N_4$ requires M^+ 138.0905); δ_H ($[^2H]_6Me_2SO$) 7.95(1H, s), 7.30(1H, d, ^3J 1.9 Hz), 5.78(1H, d, ^3J 1.9 Hz), 2.97(3H, s), and 2.90(3H, s); δ_C ($[^2H]_6Me_2SO$) 154.95, 134.45, 91.81, 30.68, and 30.30 (1 quaternary absent); *m/z* 138(M^+, 100%), 123(13), 96(28), 94(35), and 83(14).

5-t-Butyl-3(3,3-dimethyl-1,3-diazapropenyl)pyrazole. - 5-t-Butyl-3-aminopyrazole (1.6 g, 1.21 mmol) was dissolved in dimethylformamide dimethyl acetal (7 ml) and heated to reflux for 2 h. The excess dimethylformamide dimethyl acetal was removed to give an oily product. The oil was dissolved in hot cyclohexane (10 ml) and on cooling white crystals of *5-t-butyl-3-(3,3-dimethyl-1,3-diazapropenyl)pyrazole* separated out, 0.930 g (42%), m.p. 126-127°C (from cyclohexane). (Found: C, 61.35; H, 9.15; N, 28.3. $C_{10}H_{18}N_4$. 0.1 H_2O requires C, 61.3; H, 9.3; N, 28.6%); δ_H 7.85(1H, s), 5.67(1H, s), 2.96(6H, s), and 1.26(9H, s); δ_C 157.48(q), 155.51(q), 154.27, 89.06, 39.91, 34.07, 31.22(q), and 29.93; *m/z* 194(M^+, 81%), 179(33), 152(38), and 138(26).

Reaction of 5-t-Butyl-3-(3,3-dimethyldiazapropenyl)pyrazole with Hydroxylamine-O-Sulphonic Acid. - 5-t-Butyl-3-(3,3-dimethyldiazapropenyl)-

pyrazole (0.194 g, 1 mmol) was dissolved in DMF (2 ml). The mixture was cooled to < 0°C in a salt ice bath. Potassium hydroxide (0.46 g) was added followed after a 20 min. interval by hydroxylamine-O-sulphonic acid (0.226 g, 2 mmol). The mixture was allowed to stir (at room temperature) for 2 h. The DMF was removed *in vacuo* and the residue was dissolved in dichloromethane (20 ml). The solution was filtered and dried over magnesium sulphate. Removal of dichloromethane under reduced pressure yielded an oily product. This was shown to be a mixture of starting material and *2-amino-5-t-butyl-3-(3,3-dimethyldiazapropenyl)pyrazole*, which was identified by its mass spectrum. *m/z* 209(M^+, 78%), 194(100), 193(20), 179(27), 152(32), 149(12), 139(22), 138(15) and 124(14). Attempts to optimise this reaction and to purify the products have so far been unsuccessful.

Acylation Reactions of Aminopyrazoles

Substituted Acetyl Chlorides : A General Method.[83] - The 2-substituted acetic acid was reacted with an excess of thionyl chloride. The mixture was heated to reflux for 2 h. The resulting mixture was distilled to obtain the acid chloride. Examples obtained this way were: Methoxy acetyl chloride (5.84 g, 72%), b.p. 110-111°C (lit.[83] 112-113°C) from methoxy acetic acid (6.75 g, 5.75 ml, 64 mmol), thionyl chloride (13.3 g, 9.7 ml, 110 mmol) and phenyl acetyl chloride (3.12 g, 68%) from phenylacetic acid (4.08 g, 30 mmol) and thionyl chloride (8.24 g, 6 ml, 69 mmol).

Mono-Acylation Reactions : A General Method.[119] - 3-Aminopyrazole (0.415 g or 0.83 g, 5 or 10 mmol) was dissolved in dry dichloromethane (40 ml, 80 ml). Triethylamine (0.7 ml or 1.4 ml 1 eq.) was added followed by a solution of the relevant acid chloride (1 eq.) in dichloromethane (10 or 20 ml). The solution was added dropwise (copious fumes of hydrogen chloride were evolved), and the mixture was left stirring at room temperature for 2 h. The solution was poured into water and the lower organic layer was collected. The aqueous layer was extracted with a further portion of dichloromethane and the combined organic layers were dried over magnesium sulphate. The solvent was removed *in vacuo* to give solid products which were mixtures of 1- and 2-acylated products. These were characterised by resonances from their pyrazolic protons which are specified below. Chloroacetyl chloride gave 1-chloroacetyl-3-aminopyrazole and 2-chloroacetyl-3-aminopyrazole (1.255 g, 79%, 10 mmol scale) in varying proportions, however rapid rates of addition apparently favour the formation

of the 1-isomer. δ_H ([^{2}H]$_6$ acetone), (1-isomer) 8.02(1H, d, ^3J 3.0 Hz), 6.08(1H, d, ^3J, 3.0 Hz); (2-isomer) 7.39(1H, d, ^3J 1.7 Hz) and 5.40(1H, d, ^3J 1.7 Hz). Methoxy acetyl chloride gave a mixture of 1-methoxyacetyl-3-amino pyrazole and 2-methoxyacetyl-3-aminopyrazole (0.400 g, 52%, 5 mmol scale). ([^{2}H]$_6$) acetone), (1-isomer) 8.29(1H, d, ^3J 3.0 Hz), 6.08(1H, d, ^3J 3.0 Hz); (2-isomer) 7.41(1H, d, ^3J 1.7 Hz), and 5.47(1H, d, ^3J 1.7 Hz). Acetyl chloride gave a mixture of 1-acetyl-3-aminopyrazole and 2-acetyl-3-aminopyrazole (0.529 g, 83%, 5 mmol scale). δ_H ([^{2}H]$_6$ acetone), (1-isomer) 7.97(1H, d, ^3J 2.9 Hz), 6.97(1H, d, ^3J 2.9 Hz); (2-isomer) 7.32(1H, d, ^3J 1.7 Hz), and 5.37(1H, d, ^3J 1.7 Hz). Phenyl acetyl chloride gave a mixture of 1(phenyl)acetyl-3-aminopyrazole and 2(phenyl)acetyl-3-aminopyrazole (1.74 g, 86%, 10 mmol scale).

The above mixtures were found undergo a facile rearrangement over a period of days at room temperature (see Table 7). CAUTION:- these compounds may cause skin irritation. The following derivatives were made: *3-(chloroacetamido)pyrazole*, m.p. 129-130°C (from toluene). (Found: C, 37.2; H, 3.8; N, 25.9. $C_5H_6ClN_3O$ requires C, 37.6; H, 3.75; N, 26.3%); δ_H ([^{2}H]$_6$ acetone), 7.63(1H, d, ^3J 2.3 Hz), 6.67(1H, d, ^3J 2.3 Hz), and 4.30(2H, s); δ_C ([^{2}H]$_6$ acetone) 162.88(q), 145.80(q), 128.29, 95.36 and 44.28; *m/z* 161(M^+, 10%), 159(M^+, 34%), 124(6), 110(10), 83(100), and 82(10). *3-(Methoxyacetamido)pyrazole*, m.p. 126-127°C (from toluene). (Found: C, 46.3; H, 5.75; N, 26.9. $C_6H_9N_3O_2$ requires C, 46.4; H, 5.8; N, 27.1%); δ_H ([^{2}H]$_6$ acetone) 7.62(1H, d, ^3J 2.1 Hz), 6.67(1H, d, ^3J 2.1 Hz), 4.04(2H, s), and 3.47(3H, s); δ_C ([^{2}H]$_6$ acetone) 166.11(q), 145.10(q), 128.41, 94.89, 70.72 and 57.64; *m/z* 155(M^+, 66%), 140(3), 125(20), 110(27), 96(70), 95(23), 83(23), and 82(12).

For acetamidopyrazole the rearrangement did not go to completion. *3-(Phenylacetamido)pyrazole* m.p. 159-161°C (from ethyl acetate). (Found: C, 64.95; H, 5.55; N, 20.4. $C_{11}H_{11}N_3O$. 0.1 H_2O requires C, 65.1; H, 5.55; N, 20.7%); δ_H ($[^2H]_6$ acetone) 7.57 (1H, d, ^3J 2.2 Hz), 7.41-7.23(5H, m), 6.65(1H, d, ^3J 2.2 Hz), and 3.74(2H, s); δ_C ($[^2H]_6$ acetone) 167.55(q), 146.45(q), 135.221(q), 128.48, 127.53, 125.81, 95.16, and 4.231; *m/z* 201(M^+, 57%), 118(43), 92(17), 91(94), and 83(100).

The solid state rearrangement of the mixture was monitored at 299 K (thermostatted water bath). Samples were withdrawn from the initial mixture on a twice daily basis for 7 days. Aliquots were removed and dissolved in ($[^2H]_6$ acetone); ^1H NMR spectra were recorded at 200 MHz. The rearrangement was also monitored directly in the solid state using CP/MAS solid state ^{13}C NMR spectroscopy. (Bruker 500 MHz). The solid state reaction was monitored at 306 and 310 K.

The mixture of the two isomers was dissolved in $[^2H]_6$ acetone and kept in a thermostatted water bath (299 K) for 7 days. No rearrangement was recorded but numerous decomposition products were noted.

1-Chloroacetyl-3-aminopyrazole. - 3-Aminopyrazole (0.83 g, 10 mmol) was dissolved in dichloromethane (40 ml). Triethylamine (1.4 ml, 10 mmol) was added followed by chloroacetyl chloride (0.74 ml, 10 mmol) in dichloromethane (10 ml). The solution was left stirring at room temperature for 2 h. The solution was washed with water (2 x 30 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield a 4:1 mixture of *1-chloroacetyl-3-aminopyrazole* and *2-chloroacetyl-3-aminopyrazole*. The mixture was dissolved in acetone (10 ml) and cooled to

-20°C. *1-Chloroacetyl-3-aminopyrazole* crystallised as white needles, 0.42 g (27%) m.p. 112-113°C (from acetone). (Found: C, 37.8; H, 3.9; N, 26.05. $C_5H_6ClN_3O$ requires C, 37.6; H, 3.75; N, 26.3%); δ_H ($[^2H]_6$ acetone) 8.02(1H, d, ^3J 3.0 Hz), 6.08(1H, d, ^3J 3.0 Hz), and 4.84(2H, s); δ_C ($[^2H]_6$ acetone) 162.57(q), 158.36(q), 128.76, 101.65 and 41.12; *m/z* 161(M^+, 19%), 159(M^+, 19%), 124(2), 110(2), 101(3), 86(12), and 83(100).

The solid state rearrangement of 1-chloroacetyl-3-aminopyrazole to 3-(chloroacetamido)pyrazole was monitored at 299 K (thermostatted water bath) on a twice daily basis for 5 days. Aliquots were withdrawn and dissolved in ($[^2H]_6$ acetone); ^1H NMR spectra were obtained at 200 MHz. The results and implications are fully explored in the discussion.

Di-Acyl Derivatives : A General Method. - 3-Aminopyrazole (0.83 g, 10 mmol) was dissolved in dry dichloromethane (80 ml). Triethylamine (2.8 ml, 20 mmol) was added followed by the relevant acid chloride (20 mmol) in dichloromethane (20 ml). The mixture was then left stirring at room temperature for 2 h. Work up was the same as used for the mono-acyl compounds. Di-acyl compounds obtained were: from chloroacetyl chloride, *1-chloroacetyl-3-(chloroacetamido)pyrazole* 2.15 g (91%) m.p. 107°C (from toluene decomp.). (Found: C, 35.4; H, 3.15; N, 17.8. $C_7H_7Cl_2N_3O_2$ requires C, 35.5; H, 3.0; N, 17.8%); δ_H ($[^2H]_6$ acetone) 8.30(1H, d, ^3J 2.9 Hz), 7.06(1H, d, ^3J 2.9 Hz), 4.97(2H, s), and 4.37(2H, s); δ_C ($[^2H]_6$ acetone) 164.21(q), 163.48(q), 150.25(q), 128.95, 103.10, 41.92, and 41.11; *m/z* 237(M^+, 4%), 235(M^+, 6%), 161(12), 159(40), 124(3), 110(9), 83(100), and 77(19). From methoxyacetyl chloride, *1-methoxyacetyl-3-(methoxyacetamido)pyrazole*, 1.76 g (77%) m.p. 70-71°C (from toluene). (Found: C, 47.2; H, 5.75; N, 18.5.

$C_9H_{13}N_3O_4$ requires C, 47.6; H, 5.75; N. 18.5%); δ_H ($[^2H]_6$ acetone) 8.23(1H, d, ^3J 2.9 Hz), 7.02(1H, d, ^3J 2.9 Hz), 4.75(2H, s), 4.08(2H, s), 3.51(3H, s), and 3.49(3H, s); δ_C ($[^2H]_6$ acetone) 167.36(q), 166.88(q), 149.71(q), 128.28, 102.25, 70.71, 69.01, and 59.80 (2C); *m/z* 227(M^+, 36%), 212(8), 197(14), 184(13), 168(13), 156(53), 152(14), 139(27), 122(16), 110(16), and 108(29).

The mixture of 1-chloroacetyl-3-aminopyrazole and 2-chloroacetyl-3-aminopyrazole (0.319 g, 2 mmol) was dissolved in dry dichloromethane (30 ml). Triethylamine (2 mmol) and chloroacetyl chloride (2 mmol) in dichloromethane (10 ml) were sequentially added and the reaction and work up were the same as mentioned previously. Removal of solvent gave a solid product which was identified as 1-chloroacetyl-3-(chloroacetamido)pyrazole (0.386 g, 82%); its ^1H NMR spectrum was identical with that described above.

De-acylation Reactions. - 1-Chloroacetyl-3-(chloroacetamido)pyrazole (0.75 g, 3.16 mmol) was dissolved in methanol (20 ml). The solution was heated to reflux for 3 h. On removal of solvent a solid product was isolated, this was identified from its ^1H NMR spectrum as 3-(chloroacetamido)pyrazole 0.47 g (93%). Similarly 1-methoxyacetyl-3-(methoxyacetamido)pyrazole (2.0 g, 8.81 mmol) yielded 3-(methoxyacetamido)pyrazole (1.37 g, 97%).

Treatment of Mono Acyl Compounds with Methanol. - The isomeric mixture of 1 and 2-chloroacetyl-3-aminopyrazole (0.5 g) was heated in refluxing methanol for 2 h. Removal of solvent gave a mixture of products which were identified as 3-(chloroacetamido)pyrazole and 3-aminopyrazole.

Attempted Cyclisation of 3-(Chloroacetamido)pyrazole. - 3-(Chloroacetamido)pyrazole (0.159 g, 1 mmol) was dissolved in dry THF (10 ml). Sodium hydride (0.024 g, 1 mmol) was added and the mixture was left stirring for 1 h. The mixture was poured into water and separated. The organic layer was dried over magnesium sulphate, on removal of solvent a dark solid was obtained which was an intractable mixture.

Reaction of 3-(Chloroacetamido)pyrazole with Trimethyloxonium tetrafluoroborate. - 3-(Chloroacetamido)pyrazole (0.800 g, 5 mmol) was dissolved in methanol (20 ml). Trimethyloxonium tetrafluoroborate (0.74 g, 5 mmol) was added and the mixture was left stirring at room temperature for 2 h. Removal of solvent yielded an oil which on investigation by tlc proved to be at least three products.

N-*(Chloroacetyl)morpholine* . - Morpholine (3.48 g, 40 mmol) was dissolved in dry dichloromethane (150 ml) in the presence of triethylamine (4.04 g, 40 mmol). Chloroacetyl chloride (4.52 g, 40 mmol) in dichloromethane (50 ml) was slowly added and the solution was left stirring for 2 h. The mixture was poured into water and separated. The organic layer was dried over magnesium sulphate, removal of solvent gave a pale yellow oil *N*-(chloroacetyl)morpholine (6.33 g, 97%). δ_H 3.98(2H, s) and 3.62-3.38(8H, m); δ_C 165.08(q), 66.30, 66.22, 46.42, 42.21 and 40.47; *m/z* 165(M^+, 16%), 163(M^+, 45%), 150(8), 148(23), 128(100), 114(59), 105(10), 98(31), 86(74), 79(26), and 77(67).

N-*(Methoxyacetyl)morpholine*. - Morpholine (5 g, 57 mmol) was reacted with methoxyacetyl chloride (6.24 g, 57 mmol) and triethylamine (5.8 g, 57 mmol) in an analogous fashion to the previous reaction. N-*(methoxyacetyl)morpholine* was obtained as a red liquid (4.37 g, 48%) b.p. 102-104°C, 0.1 mm Hg. (Found: C, 52.8; H, 8.45; N, 8.75. $C_7H_{13}NO_3$ requires C, 52.85; H, 8.2; N, 8.8%); δ_H 3.98(2H, s), 3.58-3.36(8H, m), and 3.30(3H, s); δ_C 167.47(q), 71.48, 66.56, 58.77, 45.24, and 41.84; *m/z* 159(M^+, 6%), 129(41), 114(61), 105(25), 86(14), 70(89), 56(31), and 45(100).

1-Chloromethyl-1-methoxy-1-morpholinomethinium Tetrafluoroborate. - *N*-(Chloroacetyl)morpholine (0.818 g, 5 mmol) was added to dry dichloromethane (25 ml). Trimethyloxonium tetrafluoroborate (0.74 g, 5 mmol) was added and the mixture was left stirring at room temperature for 3 days. The solution was then concentrated to approximately one third of its original volume and ether (20 ml) was added. A white hygroscopic precipitate formed which was isolated and identified as two geometrical isomers of *1-chloromethyl-1-methoxy-1-morpholinomethinium tetrafluoroborate* (0.780 g, 60%), m.p. 127-128°C. (Found: M^+ [FAB] [cation] 178.0629. $C_7H_{13}{}^{35}ClNO_2$ requires M^+ 178.0635); δ_H ($[^2H]_6$ acetone) 4.30(2H, s), 4.18(3H, s), 4.19(2H, m), 3.96(6H, m); 4.26(2H, s), 3.75(3H, s), 3.61(6H, m), and 3.41(2H, m); δ_C ($[^2H]_6$ acetone) 166.85(q), 164.13(q), 65.45, 64.67, 62.65, 62.04, 52.11, 51.46, 45.51, 43.19, 41.42, 40.47, and 39.79; *m/z* (FAB) 180(M^+, cation, 40%), 178(M^+, cation, 100%), 144(30), and 88(M+1, anion, 100%), other peaks were detected at higher masses and assigned as anion-cation combinations.

Reaction of 1-Chloromethyl-1-methoxy-1-morpholinomethinium Tetrafluoroborate with 3-Aminopyrazole. - 1-Chloromethyl-1-methoxy-1-morpholinomethinium tetrafluoroborate (0.531 g, 2 mmol) was dissolved in dry methanol (15 ml). A 5% excess of 3-aminopyrazole (0.174 g, 2.1 mmol) was added and the mixture was left stirring for 3 days. The mixture was poured into 5 M sodium hydroxide (20 ml) and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate. Removal of solvent gave a semi-solid product (0.406 g), this was found to be a mixture of unreacted starting materials.

Synthesis and Pyrolysis of Pyrazol-3-yl-1,2,3-triazoles

3-Amino-5-methyl-2-phenylpyrazole.[100] - Phenylhydrazine (10.81 g, 9.84 ml, 0.1 mol) was dissolved in water (70 ml) and acetic acid (5.7 ml). 3-Aminocrotononitrile (8.2 g, 0.1 mol) was added and the solution formed an emulsion. The mixture was then heated to reflux for 1 h. On cooling an oil separated which then solidified. The solid was then washed with water and allowed to dry. It was identified as cyanoacetophenylhydrazone with some 3-amino-5-methyl-2-phenylpyrazole. This was used without subsequent purification. Cyanoacetophenylhydrazone (5 g) was stirred in 2.2 M hydrochloric acid (50 ml) at 55°C until it had all dissolved (50 min). The solution was allowed to cool and was made alkaline with 2 M sodium hydroxide. The crystals which formed were isolated and identified as 3-amino-5-methyl-2-phenylpyrazole 3.2 g (64%), m.p. 113-114°C (lit.[100]) 115-116°C); δ_H 7.51-7.29 (5H, m), 5.37(1H, s), 3.80(2H, br, s), and 2.18(3H, s); δ_C 149.22(q), 145.32(q), 129.21, 126.83, 123.62, 90.49, and 13.72 (one quaternary absent).

3-Azido-5-methyl-2-phenylpyrazole.[101] - 3-Amino-5-methyl-2-phenylpyrazole (1.73 g, 10 mmol) was initially heated in hydrochloric acid (5 M, 15 ml) for 10 min. The mixture was then slowly cooled to <0°C. A solution of sodium nitrite (0.76 g, 11 mmol) in water (10 ml) was added followed, after 5 min, by a solution of sodium azide (0.98 g, 15 mmol) in water (5 ml). The solution was left stirring for 30 min and was then extracted with ether (3 x 20 ml). The combined extracts were dried over magnesium

sulphate. Removal of solvent gave a semi-solid which was a mixture of the desired azide and 3-amino-5-methyl-4-nitroso-2-phenylpyrazole. Column chromatography (silica) (2:1 light petroleum b.p. 40-60°C/ethyl acetate) gave the azide, 3-azido-5-methyl-2-phenylpyrazole as a dark oil, 0.60 g (30%). Ir (liquid film) ν_{max} 2113 cm^{-1}; δ_H 7.78-7.30 (5H, m), 6.06(1H, s), and 2.35(3H, s); δ_C 149.27(q), 137.81(q), 129.08(q), 128.54, 126.77, 122.80, 95.50, and 13.76.

Pyrolysis of 3-Azido-5-methyl-2-phenylpyrazole. - 0.063 g, inlet 70°C, 450°C, 1 x 10^{-3} mbar, 40 min. gave a red compound, phenylazocrotononitrile 0.045 g (83%), m.p. 59-60°C (lit.[101] 59.5-61°C). δ_H 8.05-7.60(5H, m), 6.35(1H, s), and 2.35(3H, s).

Preparation of Azides : A General Method.[99] - The appropriate amine (10 mmol) was dissolved in 5 M hydrochloric acid (15 ml) and cooled to <0°C. A solution of sodium nitrite (0.76 g, 11 mmol) dissolved in water (5 ml, cooled to <0°C) was added and the mixture was stirred for 5-10 min. A solution of sodium azide (0.98 g, 15 mmol) in 5 ml water was cautiously added and the mixture was left stirring (at <0°C) for a further 30 min; a precipitate usually formed in the reaction vessel. The mixture was extracted with dichloromethane (3 x 25 ml) and the precipitate dissolved in the organic layer. The organic extracts were dried over magnesium sulphate. The dichloromethane was removed *in vacuo* to give the azide as a solid product. The material isolated was pure enough for further use and characterisation. The following compounds were made by this method. 3-Amino-5-t-butylpyrazole gave *3-azido-5-t-butylpyrazole*, 1,63 g (99%) m.p. 94-95°C.

(Found: M^+ 165.1003. $C_7H_4N_5$ requires M^+ 165.1014); Ir (nujol) ν_{max} 2125 cm^{-1}; δ_H 12.54(1H, br, s), 5.84(1H, s), and 1.34(9H, s); δ_C 156.87(q), 146.26(q), 92.16, 31.55(q), and 29.70; *m/z* 165(M^+, 40%), 137(11), 108(30), 94(34), and 81(33). 3-Aminopyrazole gave *3*-azidopyrazole 0.504 g (46%), m.p. 57-58°C (lit.[99] 60°C). Ir (nujol) ν_{max} 2130 cm^{-1}. 3-Amino-5-phenylpyrazole gave *3-azido-5-phenylpyrazole*, 1.77 g (96%) m.p. 147-148°C. (Found: M^+ 185.0703. $C_9H_7N_5$ requires M^+ 185.0701); Ir (nujol) 2120 cm^{-1}; δ_H ($[^2H]_6$ acetone), 7.79-7.73(2H, m), 7.50-7.33(3H, m), and 6.64(1H, s); δ_C ($[^2H]_6$ acetone) 147.65(q), s144.15(q), 128.11, 127.72, 124.35, and 92.13, one quaternary absent; *m/z* 185(M^+, 48%), 159(4), 157(6), 129(20), s128(90), 102(100), and 77(43).

2-Azidoimidazole[105]. -2-Aminoimidazole sulphate (0.66 g, 5 mmol) was dissolved in 5 M hydrochloric acid (8 ml) and cooled to <0°C. Sodium nitrite (0.38 g, 5.5 mmol) and sodium azide (0.49 g, 7.5 mmol) were added under the same reaction conditions described in the previous section. The mixture was left stirring for 30 min. and was then neutralised with sodium carbonate (aq) and extracted with dichloromethane (3 x 20 ml). The combined extracts were dried over magnesium sulphate. Removal of solvent *in vacuo* gave 2-azidoimidazole as a white solid, 0.35 g (64%) m.p. 138°C dec. (lit.[105] 140°C dec). Ir (nujol) ν_{max} 2122 cm^{-1}.

Methyl 1-(1H)-(5-t-butyl-2H-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate. - 3-Azido-5-t-butylpyrazole (0.687 g, 4.16 mmol) was dissolved in toluene (5 ml). Methyl propiolate (0.70 g, 8.33 mmol) was added. The reaction mixture was heated to reflux for 3 h and kept under a nitrogen atmosphere.

The mixture was cooled and a yellow precipitate was isolated. The crude product was crystallised from ethyl acetate to give *methyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate*, 0.72 g (70%) m.p. 192-193°C (from ethylacetate). (Found: C, 53.0; H, 6.1; N, 28.1. $C_{11}H_{15}N_5$ requires C, 53.0; H, 6.05; N, 28.1%); δ_H 10.07(1H, s), 6.64(1H, s), 4.05(3H, s), and 1.41(9H, s); δ_C 162.65(q), 155.71(q), 145.78(q), 139.3(q), 126.59, 92.87, 52.56, 31.28(q), and 29.78; *m/z* 249(M^+, 51%), 220(40), 218(18), 206(100), 190(94), 179(32), 174(70), and 150(18).

*Methyl 1-(1*H*)-(2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate.* - 3-Azidopyrazole (1.42 g, 13 mmol)) was dissolved in toluene (7 ml). Methyl propiolate (1.7 g, 1.8 ml, 20 mmol). The mixture was heated to reflux under a nitrogen atmosphere for 2½ h. On cooling a brown precipitate was formed, this was found to be a 4.6:1 mixture of two isomers 2.155 g (86%, both isomers). Crystallisation from acetic acid isolated the major isomer *methyl 1-(1*H*)-(2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate* m.p. 254-255°C (from acetic acid). (Found: C, 43.4; H, 3.9; N, 35.3. $C_7H_7N_5O_2.0.1\ CH_3CO_2H$ requires C, 43.4; H, 3.6; N, 35.2%); δ_H ($[^2H]_6Me_2SO$) 13.38(1H, br, s), 9.18(1H, s), 7.99(1H, d, ^3J 1.9 Hz), 6.79(1H, d, ^3J 1.9 Hz), and 3.87(3H, s); δ_C ($[^2H]_6Me_2SO$) 160.37(q), 145.12(q), 138.92(q), 131.40, 126.68, 97.06, and 51.89; *m/z* 193(M^+, 17%), 164(11), 162(17), 135(12), 134(100), 133(21), 107(36), and 106(42). The minor isomer methyl *1-(1*H*)-(2*H*-pyrazol-3-yl)-1,2,3-triazole-5-carboxylate* was identified by NMR spectroscopy. δ_H ($[^2H]_6Me_2SO$) 8.44(1H, s), 7.96(1H, unresolved), 6.64(1H, d, ^3J 1.9 Hz), and 3.78(3H, s); δ_C($[^2H]_6Me_2SO$) 157.54(q), 143.93(q), 136.93, 130.43, 129.64(q), 101.54, and 52.54.

Methyl 1-(1H)-(5-phenyl-2H-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate. - 3-Azido-5-phenylpyrazole (0.37 g, 2 mmol) was dissolved in acetonitrile (6 ml). Methyl propiolate (0.351 g, 0.372 ml, 4.2 mmol) was added and the mixture was heated to reflux under a nitrogen atmosphere for 4 h. On cooling a white precipitate was obtained. This was identified as *methyl 1-(1H)-(5-phenyl-2H-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate*, 0.24 g (45%) m.p. 254-255°C (from ethanol). (Found: C, 57.2; H, 4.15; N, 25.0. $C_{13}H_{11}N_5O_2$. 0.25 H_2O requires C, 57.05; H, 4.2; N, 25.6%); δ_H ($[^2H]_6Me_2SO$), 13.85(1H, br, s), 9.22(1H, s), 7.87-7.42(5H, m), 7.27(1H, s), and 3.88(3H, s); δ_C ($[^2H]_6Me_2SO$) 160.35(q), 145.39(q), 144.37(q), 138.97(q), 129.09, 128.98, 128.12(q), 126.64, 125.33, 94.68 and 51.94; *m/z* 269(M^+, 46%), 240(62), 238(14), 210(100), 198(23), 183(37), and 170(17).

Dimethyl 1-(1H)-(5-Phenyl-2H-pyrazol-3-yl)-1,2,3-triazole-4,5-dicarboxylate. - 3-Azido-5-phenylpyrazole (0.37 g, 2 mmol) was dissolved in acetonitrile (5 ml). Dimethyl acetylenedicarboxylate (0.284 g, 0.246 ml, 2 mmol) was added and the mixture, under a nitrogen atmosphere, was heated to reflux for 8 h. On cooling a white precipitate formed which was *dimethyl 1-(1H)-(5-phenyl-2H-pyrazol-3-yl)-1,2,3-triazole-4,5-dicarboxylate*, 0.200 g (30%), m.p. 195-196°C (from acetic acid). (Found: C, 54.2; H, 4.1; N, 21.2. $C_{15}H_{13}N_5O_4$. 0.2 H_2O requires C, 54.45; H, 4.05; N, 21.2%); δ_H ($[^2H]_6Me_2SO$) 7.89-7.85(2H, m), 7.56-7.43(3H, m), 7.33(1H, s), 3.96(3H, s), and 3.91(3H, s); δ_C ($[^2H]_6Me_2SO$) 159.55(q), 159.39(q), 144.92(q), 144.82(q), 137.10(q), 131.37(q), 129.33, 128.09, 125.64, 95.74, 54.13, and 52.78 (1

quaternary absent); *m/z* 327(M^+, 21%), 268(29), 267(100), 224(12), 209(20), and 185(15).

Reactions of 3-Azido-5-t-butylpyrazole with Other Acetylenes. - 3-Azido-5-t-butylpyrazole (0.33 g, 2 mmol) was dissolved in toluene (5-10 ml) and reacted with the following acetylenes under various conditions. With ethyl phenylpropiolate (0.348 g, 2 mmol) the mixture was heated to reflux for 4 h. Removal of solvent *in vacuo* yielded only decomposition products. With phenyl acetylene (0.202 g, 2 mmol) the mixture was heated to reflux for 5 h. Reduced pressure evaporation of solvent only yielded starting material and decomposition products. With phenyl vinylsulphoxide (0.450 g, 3 mmol) the mixture was heated to reflux for 5 h. Removal of solvent *in vacuo* yielded decomposition products. With ethyl (trimethylsilyl) propynoate (0.485 g, 2.5 mmol) the mixture was heated to reflux for 12 h. Removal of solvent gave an intractable mixture.

Reaction of 2-Azidoimidazole and Methyl Propiolate. - 2-Azidoimidazole (0.350 g, 2 mmol) was reacted with methyl propiolate (0.566 g, 0.60 ml, 6.7 mmol) in toluene. The mixture was heated to reflux for 3 h during which time a brown precipitate formed. The precipitate was collected and analysed. It was found to be polymeric material. Removal of solvent yielded decomposition products.

N,N-*Dimethylchloromethylene Ammonium Chloride.*[109] - Dimethylformamide (3.07 g, 3.25 ml, 42 mmol) was dissolved in dry

dichloromethane (50 ml). The mixture was kept under a nitrogen atmosphere and was cooled to 0°C. Oxalyl chloride (7.64 g, 5.25 ml, 60 mmol) was slowly added and the mixture left stirring for 1 h. Much gas was evolved during this reaction and a white precipitate formed. The solvent was then removed *in vacuo* and the hygroscopic white solid was collected. This was *N,N*-dimethylchloromethylene ammonium chloride, 5.07 g (84%); it was used in subsequent reactions without further purification.

Ethyl α-Formyldiazoacetate.[108] - *N,N*-Dimethylchloromethylene ammonium chloride (4.18 g, 32.5 mmol) was dissolved in dry chloroform (12 ml). The solution was cooled to -8°C and was kept under a nitrogen atmosphere. Ethyl diazoacetate (3.74 g, 3.44 ml, 32.5 mmol) was added over a period of 15 min *via* a syringe pump and the solution was left stirring for 1 h. The solvent was removed *in vacuo* to give a residue. Addition of dry ether yielded a precipitate which was collected. The precipitate was dissolved in 10% acetic acid which was left to stand for 3 h, during which time an oil separated out. The mixture was extracted with ether (3 x 20 ml) and the combined extracts were washed with saturated sodium bicarbonate (15 ml), sodium chloride (saturated solution) and 10% sulphuric acid (10 ml). The ether layer was then dried over magnesium sulphate and the solvent was removed to give an oil, ethyl α-formyldiazoacetate (1.10 g, 30%) which was purified by kugelrohr distillation b.p. 81-82°C/10 mm Hg (lit.[108] 82-83°C/10 mm Hg). δ_H 9.54(1H, s), 4.22(2H, q, ^3J 7.1 Hz), and 1.22(3H, t, ^3J 7.1 Hz); δ_C 181.10, 160.83(q), 61.56, and 13.86 (one quaternary absent).

Ethyl 1-Phenyl-1,2,3-triazole-4-carboxylate.[108] - Ethyl α-formyl diazoacetate (0.426 g, 3 mmol) was dissolved in ethanol (3 ml). A solution of aniline (0.27 g, 2.9 mmol) in ethanol (1.8 ml) and acetic acid (0.6 ml) was added and the mixture was left stirring for 16 h. On removal of solvent a solid was obtained, and crystallisation from ethanol gave white needles of ethyl 1-phenyl1,2,3-triazole-4-carboxylate, 0.450 g(70%), m.p. 86-87°C (lit.[108] 88°C).

*Ethyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate.* - 3-Amino-5-t-butylpyrazole (0.278 g, 2 mmol) was dissolved in ethanol (1.2 ml) and acetic acid (0.4 ml). A solution of ethyl α-formyldiazoacetate (0.284 g, 2 mmol) in ethanol (2 ml) was added and the mixture was left stirring for 16 h. On removal of solvent, a yellow solid was obtained this was *ethyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate*, 0.427 g (81%), m.p. 155-156°C (from cyclohexane/ethyl acetate). (Found: C, 54.7; H, 6.35; N, 25.95. $C_{12}H_{17}N_5O_2$. 0.1 H_2O requires C, 54.5; H, 6.5; N, 26.4%); δ_H 10.12(1H, s), 6.63(1H, s), 4.55(2H, q, ^3J 7.1 Hz), 1.47(3H, t, ^3J 7.1 Hz), and 1.41(9H, s); δ_C 162.32(q), 155.64(q), 145.75(q), 139.61(q), 126.61, 92.78, 61.95, 31.28(q), 29.79, and 14.07; *m/z* 263(M^+, 44%), 220(84), 190(100), 174(59), 164(50), 163(86), and 148(79). Ethyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,3-triazole-4-carboxylate (0.263 g, 1 mmol) was treated with sodium methoxide (0.05 g sodium) and methanol (5 ml). The mixture was left stirring at room temperature for 3 h. It was then poured into water and neutralised with dilute hydrochloric acid. The solution was extracted with dichloromethane (3 x 10 ml) and the extracts were dried over magnesium sulphate. Removal of solvent gave methyl 1-(1*H*)-(5-t-butyl-2*H*-pyrazol-3-yl)-1,2,4-triazole-4-carboxylate (0.238 g, 98%).

Pyrolysis of Methyl-1-(1H)-(2H-pyrazol-3-yl)-1,2,3-triazole-4-carboxylates. - The triazoles were pyrolysed at 600°C and a pressure of 1 x 10^{-3} mbar. The products were formed at the mouth of the trap and were glassy in appearance; they could not be successfully purified by crystallisation. They were recovered from the trap by scraping with a spatula.

5-t-Butyl derivative

0.71 g, inlet 140°C, 3 h, gave *2-t-Butyl-6-methoxy-pyrazolo[1,5-a]pyrimidin-7-one*, 0.350 g (50%) m.p. 207-209°C. (Found: M^+ 221.1155. $C_{11}H_{15}N_3O_2$ requires M^+ 221.1164); δ_H ($[^2H]_6Me_2SO$) 5.86(1H, s), 5.20(1H, s), 3.88(3H, s), and 1.27(9H, s); δ_C ($[^2H]_6Me_2SO$) 163.79(q), 160.88(q), 157.25(q), 139.88(q), 85.15, 75.02, 56.55, 32.22(q), and 29.87; *m/z* 221(M^+, 50%), 220(21), 206(52), 179(21), and 174(16).

Parent System

0.170 g, inlet 130°C, 45 min., gave *6-methoxypyrazolo[1,5-a]pyrimidin-7-one*, 0.060 g (42%), m.p. 203-205°C. (Found: M^+ 165.0538 $C_7H_7N_3O_2$ requires M^+ 165.0538); δ_H ($[^2H]_6Me_2SO$) 7.78(1H, d, ^3J 1.8 Hz), 5.98(1H, d, ^3J 1.8 Hz), 5.26(1H, s), and 3.90(3H, s); δ_C ($[^2H]_6Me_2SO$) 161.19(q), 157.33(q), 142.16(q), 139.79(q), 88.50, 75.10, and 56.61, *m/z* 165(M^+, 100%), 164(22), 134(24), 122(13), 107(22), and 106(11).

5-Phenyl derivative

0.168 g, inlet 160°C, 2 h, gave *6-methoxy-2-phenylpyrazolo[1,5-a]pyrimidin-7-one*, 0.080 g (53%) m.p. 167-169°C. (Found: M^+ 241.0850. $C_{13}H_{11}N_3O_2$ requires M^+ 241.0851); δ_H ($[^2H]_6Me_2SO$) 7.97-7.92(2H, m), 7.51-7.38(3H, m), 6.45(1H, s), 5.31(1H, s), and 3.92(3H, s); δ_C ($[^2H]_6Me_2SO$) 160.80(q), 157.20(q), 152.72(q), 140.41(q), 132.67(q), 128.63(2C), 125.93, 85.45, 75.35, and 56.85; *m/z* 241(M^+, 100), 240(22), 227(9), 213(14), 212(13), 210(11), 198(15), 173(16), and 159(16).

Pyrolysis of Dimethyl 1-(1H)-[5-phenyl-2H-pyrazole-3-yl]1,2,3-triazole-4,5-dicarboxylate. - 0.051 g, inlet 155°C, 600°C, 1 x 10^{-3} mbar, 1 h 15 min gave a mixture which showed four spots from tlc. The mixture was identified as decomposition products from the absence of any useful ^1H NMR peaks.

Pyrolysis of Ethyl-1,2,3-triazole-4-carboxylate. - 0.083 g, 130°C, 600°C, 1 x 10^{-3} mbar, 1 h, gave a product which was identified as 2,4-quinolinediol (comparison with an authentic sample, δ_H values are in brackets after pyrolysate sample). δ_H ($[^2H]_6Me_2SO$) 11.22(1H, s), [11.24(1H, s)], 7.78(1H, d, ^3J 7.9 Hz), [7.78(1H, d, ^3J 8.0 Hz], 7.53-7.44(1H, m), [7.53-7.45(1H, m)], 7.28-7.09(2H, m), [7.29-7.09(2H, m)], and 5.75(1H, s), [5.76(1H, s)]; δ_C ($[^2H]_6Me_2SO$) 163.72(q), 162.58(q), 139.27(q), 130.95, 122.76, 121.19, 115.26, 115.22(q), and 98.32.

*5-[Methylthio(*N*-5-t-butylpyrazol-3-ylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione.* - 5-[Bis(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione[116] (0.496 g, 2 mmol) was reacted with 3-amino-5-t-butylpyrazole (0.278 g, 2 mmol) in acetonitrile (4 ml). The mixture was first heated to reflux for 2 h and then was stirred at room temperature for a further 16 h. On removal of solvent *in vacuo* an oil was obtained; this was purified by chromatography (silica, 50:50 ethylacetate/hexane) to give *5-[methylthio(*N*-5-t-butylpyrazol-3-ylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione*, 0.234 g (35%), m.p. 134-135°C]. (Found: M+1 [FAB] 340.1331. $C_{15}H_{22}N_3O_4S$ requires M+1 340.1331); δ_H 12.76(1H, br, s), 6.10(1H, s), 2.34(3H, s), 1.72(6H, s), and 1.32(9H, s); δ_C 177.88(q), 163.79(q) 155.01(q), 145.65(q), 103.00(q), 96.99, 86.13(q), 31.13(q), 29.83, 26.19, and 18.65; *m/z* 281 (M^+-58, 14%), 263(25), 248(20), 237(28), 222(16), 221(14), and 190(42).

*Pyrolysis of 5-[Methylthio(*N*-5-t-butylpyrazol-3-ylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione.* - 0.087 g, 180°C, 600°C, 1 x 10^{-4} mbar (mercury diffusion pump), 2 h, gave *2-t-butyl-6-methylthio-pyrazolo[1,5-a]pyrimidin-7-one*. 0.033 g (53%), m.p. 319-320°C. (Found: M^+ 237.0940. $C_{11}H_{15}N_3Os$ requires M^+ 237.0936); δ_H ($[^2H]_6Me_2SO$) 5.92(1H, s), 5.55(1H, s), 2.57(3H, s), and 1.29(9H, s); δ_C ($[^2H]_6Me_2SO$) 164.25(q), 154.82(q), 152.70(q), 141.76(q), 91.22, 84.76, 32.28(q), 29.90, and 13.94; *m/z* 237(M^+, 100%), 222(23), 190(60), and 174(13).

*5-(*N*-Methylpyrazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione.* - 3-Amino-5-methylpyrazole (0.485 g, 5 mmol) was dissolved in

acetonitrile (25 ml). 5-Methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione[74] (0.93 g, 5 mmol) was added and the mixture was stirred at room temperature for 15 min. A yellow precipitate formed, this was collected by filtration and was identified as *5-(N-methylpyrazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione*, 1.15 g (92%), m.p. 188-189°C (from ethanol). (Found: C, 52.7; H, 5.4; N, 16.8. $C_{11}H_{13}N_3O_4$ requires C, 52.6; H, 5.2; N, 16.75%); δ_H 11.28(1H, br, s), 8.68(1H, br, s), 5.95(1H, s), 2.31(3H, s), and 1.73(6H, s); δ_C 165.04(q), 163.67(q). 153.14, 148.29(q), 141.20(q), 104.89(q), 93.49, 86.62(q), 26.83, and 11.02; *m/z* 251(M^+, 15%), 193(31), 175(100), 149(4), and 121(12).

5-(N-Pyrazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione. - 3-Aminopyrazole (0.83 g, 10 mmol) was dissolved in acetonitrile (50 ml). 5-Methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione[74] (1.86 g, 10 mmol) was added and the mixture was left stirring at room temperature for 30 min.[121] A yellow-white precipitate was collected which was *5-(N-pyrazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione*, 2.35 g (95%), m.p. 195-196°C (from ethanol). (Found: C, 50.2; H, 4.6; N, 17.6 $C_{10}H_{11}N_3O_4$ requires C, 50.6; H, 4.65; N, 17.7%); δ_H 11.30(1H, br, s), 8.75(1H, s), 7.56(1H, d, ^3J 2.5 Hz), 6.23(1H, d, ^3J 2.5 Hz), and 1.74(6H, s); δ_C 165.11(q), 163.56(q), 153.31, 148.11(q), 130.33, 104.99(q), 94.43, 86.91(q), and 26.86; *m/z* 237(M^+. 12%), 179(29), 161(100), and 107(22).

5-(N-1,2,4-Triazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione. - 3-Amino-1,2,4-triazole (1.013 g, 12 mmol) was reacted with 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione[74] (2.24 g, 12 mmol) in acetonitrile (50 ml). The mixture was left stirring at room temperature for 30

min.[121] during which time a white precipitate was formed. This was collected and found to be *5-(N-1,2,4-triazol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione*, 2.490 g(86%), m.p. 208-209°C (decomp, from ethanol). (Found: C, 45.3; H, 4.35; N, 23.4. $C_9H_{10}N_4O_4$ requires C, 45.4; H, 4.2; N, 23.5%); δ_H ($[^2H]_6Me_2SO$) 14.11(1H, br, s), 11.20(1H, br, s), 8.75(1H, s), 8.55(1H, s), and 1.68(6H, s); δ_C ($[^2H]_6Me_2SO$) 163.88(q), 162.32(q), 156.28(q), 152.37, 144.74, 104.67(q), 87.91(q), and 26.45; *m/z* 238(M^+, 24%), 181(18), 180(93), 163(13), 136(35), 134(11), 108(100), and 81(15).

Pyrolysis Reactions of 5-(N-Azol-3-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-diones. - The compounds were pyrolysed at 600°C and a pressure of 0.001 mbar. The products were formed at the exit of the furnace tube and were recovered by scraping out with a spatula.

3-Amino-5-methylpyrazole Derivative. - 0.507 g, inlet 190°C, 1 h. 45 min., gave 2-methylpyrazolo[1,5-*a*]pyrimidin-7-one, 0.156 g (52%), m.p. 274-277°C (lit.[117] 275-280°C); δ_H ($[^2H]_6Me_2SO$) 7.79(1H, d, ^3J 7.3 Hz), 6.01(1H, s), 5.62(1H, d, ^3J 7.3 Hz), and 2.28(3H, s); δ_C ($[^2H]_6Me_2SO$) 156.29(q), 151.74(q), 142.20(q), 138.89, 95.25, 88.64, and 13.96.

3-Aminopyrazole Derivative. - 0.500 g, inlet 120°C, 2 h gave pyrazolo[1,5-*a*]pyrimidin-7-one, 0.136 g (48%), m.p. 238-240°C (lit.[122] 239-240°C); δ_H ($[^2H]_6Me_2SO$) 7.88(1h, d, ^3J 7.3 Hz), 7.87(1H, d, ^3J 2.0 Hz), 6.19(1H, d, ^3J 2.0 Hz), and 5.69(1H, d, ^3J 7.3 Hz); δ_C ($[^2H]_6Me_2SO$), 156.65(q), 142.58, 141.85(q), 139.53, 95.15, and 88.97.

3-Aminotriazole Derivative. - 0.93 g, inlet 140°C, 5 h gave an inseparable mixture of two indistinguishable isomers 1,2,4-triazolo[1,5-*a*]pyrimidin-7-one, and 1,2,4-triazolo[4,3-*c*]pyrimidin-7-one (0.400 g, 76%). (The minor product is in brackets). δ_H ($[^2H]_6Me_2SO$) [9.05(1H, s)], 8.23(1H, s), 7.98(1H, 1H, d, 7.4 Hz), 5.94(1H, d, ^3J 7.4 Hz), and [5.77(1H, d, ^3J 7.4 Hz)].

0.050 g, inlet 140°C, 400-700°C, 1 x 10^{-3} mbar gave varying proportions of the two products. The relative quantities were determined from the integral values obtained for the peaks at δ_H 5.94 and 5.77. The relative proportions of the two isomers are given in table 12.

^{13}C Isotopic Labelling Experiment. - [^{13}C]-Dimethylformamide (0.250 g) was reacted with oxalyl chloride (0.428 ml) to give [^{13}C]-*N,N*-dimethyl chloromethylene ammonium chloride (0.436 g) as previously described. The salt was then reacted with ethyl diazoacetate (0.710 ml) under conditions previously described to give [^{13}C] ethyl α-formyldiazoacetate (0.116 g). [^{13}C]-Ethyl α-formyldiazoacetate (0.071 g) was then reacted with 3-amino-t-5-butylpyrazole (0.069 g) to give after ester exchange (Na/MeOH) [^{13}C]-methyl 1-(1*H*)-[5-t-butyl-2*H*-pyrazol-3-yl]1,2,3-triazole-4-carboxylate (0.046 g, 41%), δ_C 126.59 (isotopically enhanced, value $[^2H]_6$ acetone 124.24).

Pyrolysis, 0.028 g, 140°C, 600°C, 1 h. returned [^{13}C]-2-t-butyl-6-methoxypyrazolo[1,5-*a*]pyrimidin-7-one. δ_C ($[^2H]_6Me_2SO$) 160.92(q), (isotopically enriched).

An unidentified impurity peak was recorded at δ165.01.

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