SYNTHESIS AND STUDIES OF PYRAZOLOBENZIMIDAZOLE AND HETEROAROYLACETANILIDE COLOUR COUPLERS

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 high degree.

This thesis describes the results of research carried out in the Department of Chemistry, The University of Edinburgh, under the supervision of Dr. Hamish McNab, since October 1st, 1992, the date of my admission as a research student.

DEDICATION

This thesis is dedicated to my Family.

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Current Developments in Organic Chemistry - Prof. R. Ramage *et al.*
(3 years attendance).

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ABSTRACT

Gas-phase pyrolysis of 1-(2-azidophenyl)pyrazoles leads to pyrazolobenzimidazoles, pyrazolobenzotriazoles and quinoxalines in good overall yield, in contrast to earlier solution-phase work. At low furnace temperatures the mechanism is thought to involve generation of a mixture of singlet and triplet nitrenes which collapse to the pyrazolobenzotriazole and pyrazolobenzimidazole respectively. At high furnace temperatures, the formation of high energy singlet nitrene products is favoured. In addition quinoxaline is formed at the expense of pyrazolobenzotriazole, as was proved by independent pyrolysis of the pyrazolobenzotriazole. Introduction of a conjugating electron donating methoxy group *para* to the incipient nitrene results in a vast increase in pyrazolobenzimidazole. The pyrolysis of 1-(2-azidophenyl)imidazole resulted in unexpected regiospecific nitrene insertion to give 9*H*-imidazo[1,2-*a*]benzimidazole whose structure was established by X-ray crystallography. The ^{1}H and ^{13}C spectroscopic properties of pyrazolobenzimidazoles, pyrazolobenzotriazoles and imidazobenzimidazoles are reported in detail.

Pyrolysis of imidazolyl propenoic acid esters yielded pyrroloimidazol-5-ones which, on reductive ring-opening, gave the unknown 3-(imidazolyl)propen-1-ols. Novel routes to the 5*H*-pyrrolo[1,2-*a*]imidazole and 5*H*-pyrrolo[1,2-*c*]imidazole systems *via* flash vacuum pyrolysis of the appropriate 3-imidazolyl-2-propen-1-ol are reported.

A number of new heteroaroylacetanilides have been synthesized as potential yellow colour couplers. Photographic properties were controlled by incorporating a range of electron-donating heterocyclic moieties. The optimum synthetic strategy involved acetylation of the heterocycle, followed by β-ketoester formation using diethyl carbonate in the presence of sodium hydride. The amide group was introduced by heating the β-ketoester with an appropriate amine in boiling *p*-xylene. For photographic application the heteroaroylacetanilides were modified by the introduction of hydantoin "coupling-off groups" and long chain saturated hydrocarbon "ballast" groups. Photographic evaluation results are presented with an explanation of the effects induced by certain substituents.

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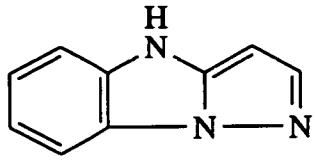
INTRODUCTION

PREAMBLE

Part of this thesis is devoted to the exploration of new routes to the [5,5,6]azapentalene ring systems, 4*H*-pyrazolo[1,5-*a*]benzimidazole **1**, 4*H*-imidazo[1,5-*a*]benzimidazole **2** and 9*H*-imidazo[1,2-*a*]benzimidazole **3**.



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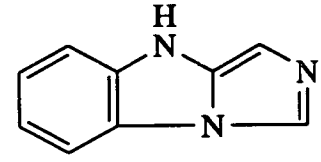

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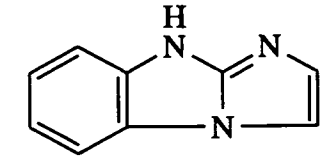

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These type of compounds have significant applications in colour photography as magenta couplers.[1] This introductory review will describe the photographic process and then outline the synthesis, physical and chemical properties of the ring systems **1-3**.

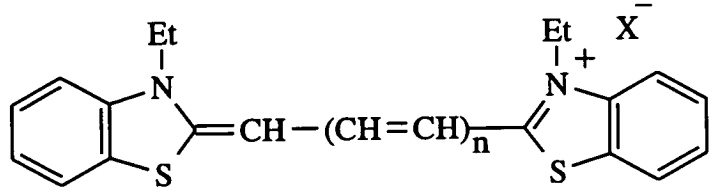
A. THE PHOTOGRAPHIC PROCESS

The significant modern dye-forming processes employ the use of light sensitive silver halides[2,3] which are especially suitable for short exposure times.

These silver halides are introduced into layers of gelatin to form the photographic emulsion, a transparent carrier for the dye-formation process. The amount of dye produced is directly proportional to the degree of light exposure received by the silver halide.

The silver halides are colourless or yellow thus rendering them naturally sensitive to ultraviolet and blue light only. The sensitivity of silver halides has been extended into all regions of the visible light spectrum through the use of sensitizers. These are dyes which absorb light thereby imparting sensitivity to the silver halide. The most effective of these compounds are the cyanines, mono-acid salts in which two

heterocyclic nitrogen-containing nuclei are linked by a conjugated odd-numbered carbon chain. A typical example of a series of dyes, **4 a-c**, is shown below.



4	**a**	n = 0	blue light sensitive
	b	n = 1	green light sensitive
	c	n = 2	red light sensitive

In addition to the compounds already discussed there is a requirement for colour forming dyes.[1,2,3] Modern colour photography makes use of the three subtractive primary colours, yellow (blue absorbing), magenta (green absorbing) and cyan (red absorbing). Each of these dyes absorb about one third of the visible light spectrum while transmitting the remaining two thirds. These dyes may be mixed to obtain various shades of colour, for example yellow plus magenta yields red, cyan plus yellow yields green and cyan plus magenta yields blue. When all three are combined then black is obtained.

Colour photographic materials are prepared by coating three sensitized silver halide layers onto a support such as film or paper (Figure 1).

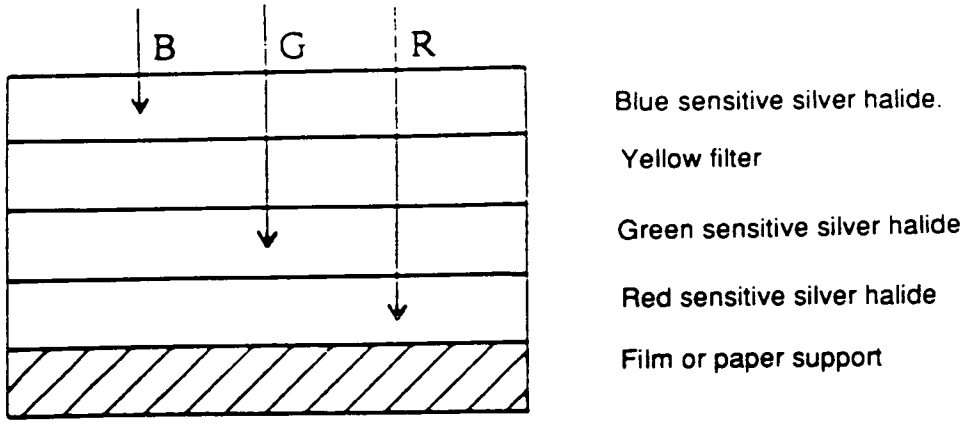


Figure 1

The yellow coloured layer absorbs any blue light which may otherwise affect the underlying layers, but is removed at a later stage in the developing process. Thus on exposure, each coloured component of a scene is recorded in the appropriate layer.

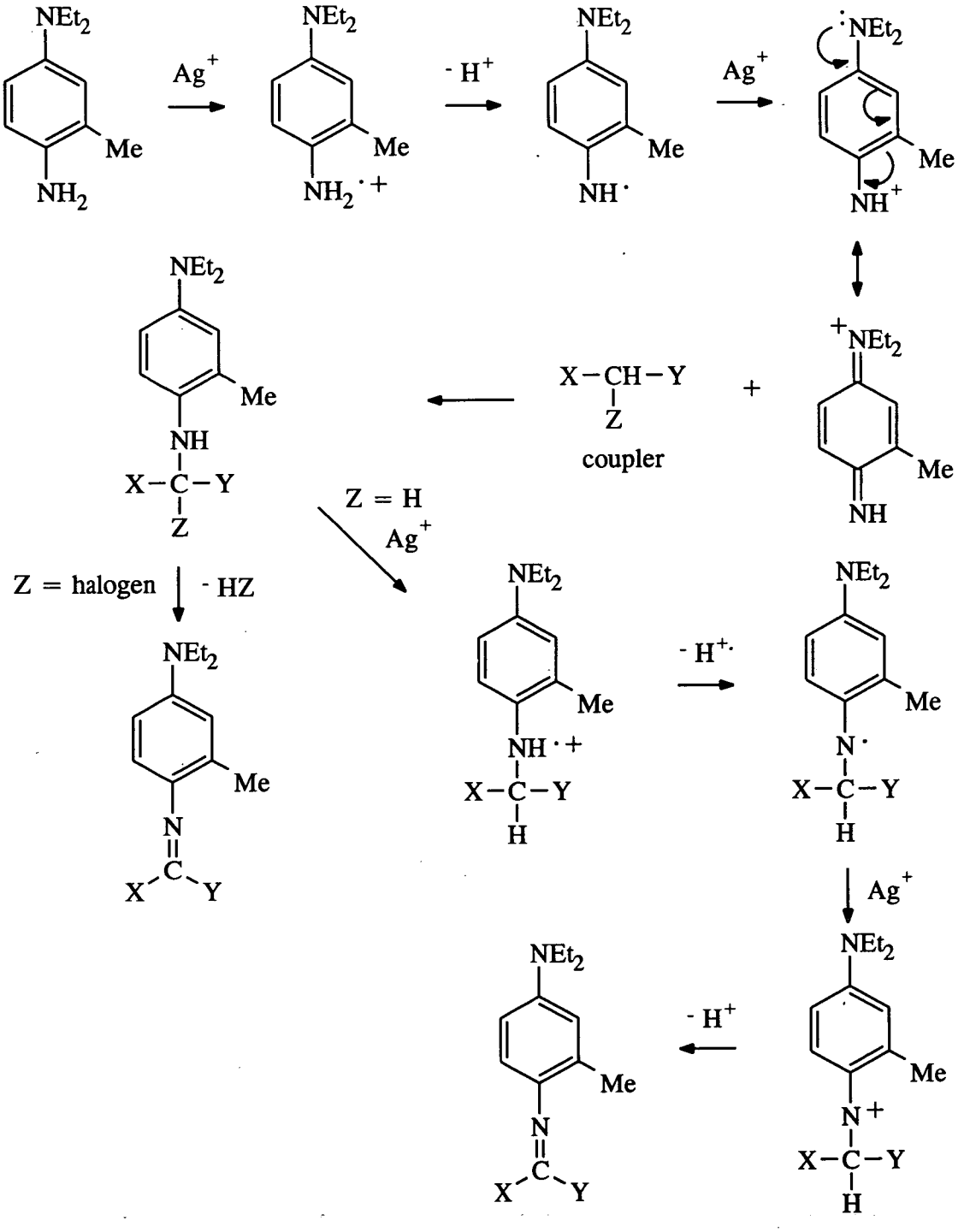
In the development process the exposed silver halide oxidises a reagent, the colour developer, to afford a species which is reactive to other reagents, colour couplers. Combination of these two species results in dye formation.

One version of the process requires the use of three separate solutions each containing a developer and a coupler. Initially the exposed film is treated with a hydroquinone developer which forms silver from the exposed silver halide. The film is then exposed to red light through the base to afford a latent image where silver halide remains in the red sensitive layer. Processing with developer and coupler affords a cyan dye which is present in the red sensitive layer. A further exposure to blue light from above results in a yellow dye after treatment with developer and a different coupler. Magenta dye is formed in the green sensitive layer on treatment with a developer, coupler and an agent which renders the remaining silver halide

developable. The developed silver is bleached to silver bromide and then all the silver salts are removed by treatment with thiosulfate solution. The final product after this is a coloured transparency.

A modification of this process includes non-wandering couplers already incorporated in the film. Thus only one developing solution is required to form the dyes in their individual layers. The couplers were designed to be non-diffusing by the inclusion of a long-chain hydrocarbon ballast group. The coupler is dissolved in a suitable solvent, typically di-*n*-butyl phthalate, then incorporated into the appropriate silver halide emulsion layer. As unreacted couplers remain in the layers, they must also satisfy a number of additional criteria; they must be colourless and stable to light, heat and moisture so that they do not show unless developed.

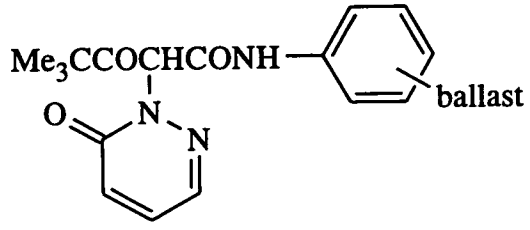
Colour developers have been known for over 70 years and include *p*-phenylenediamines and *p*-aminophenols. The generation of an azamethine dye from a *p*-phenylenediamine, a coupler and exposed silver halide is shown (Scheme 1). The coupler has substituents X and Y which provide activation, at the carbon atom, to attack by the oxidised developer. Z is a substituent which is eliminated in the oxidative coupling reaction, the nature of which determines the quantity of silver halide required to form the dye. When Z is a proton, the coupling reaction requires four equivalents of silver halide and the coupler is termed a four-equivalent coupler. If Z is a halogen or some other coupling-off (leaving) group then only two equivalents of silver halide are required for dye-formation. These two-equivalent couplers have the advantage of requiring less silver resulting in thinner layers, sharper images and increased reactivity.



Scheme 1

Yellow couplers are routinely derived from open-chain methylene compounds, for example the β-ketoamides, benzoylacetanilide or the pivaloylacetanilide **5**. Dyes

derived from pivaloylacetanilides have better light stability but are formed less rapidly.



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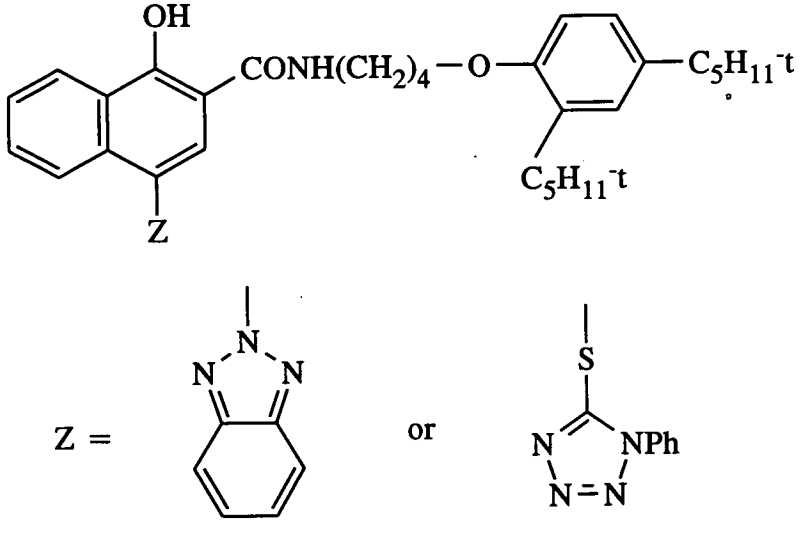
Cyan dyes are usually derived from phenols and naphthols, e.g. **6**, and may incorporate heterocyclic leaving groups Z to enhance their performance.[1]



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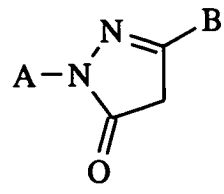
Typical magenta couplers are 2-pyrazolin-5-ones **7** where A is a substituted aryl and B may be an alkyl group or an amino group, however in certain instances these tend to absorb blue light in addition to green.



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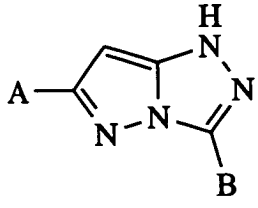
Other magenta couplers such as the azapentalenes pyrazolo[5,1-*c*]-1,2,4-triazoles[4] **8** and pyrazolo[1,5-*a*]benzimidazoles[5] **9** have shown more desirable dye-forming characteristics.



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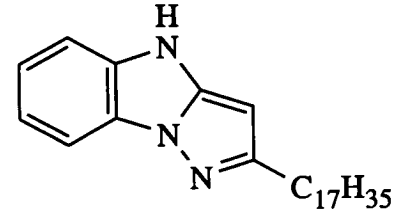

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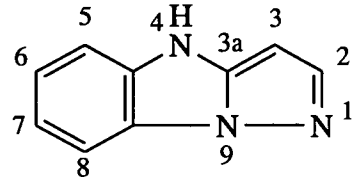
B. PYRAZOLO[1,5-*a*]BENZIMIDAZOLES

The synthesis and chemistry of this class of compounds has been the subject of a review.[6] The parent ring system **1** and its numbering scheme is shown.



1

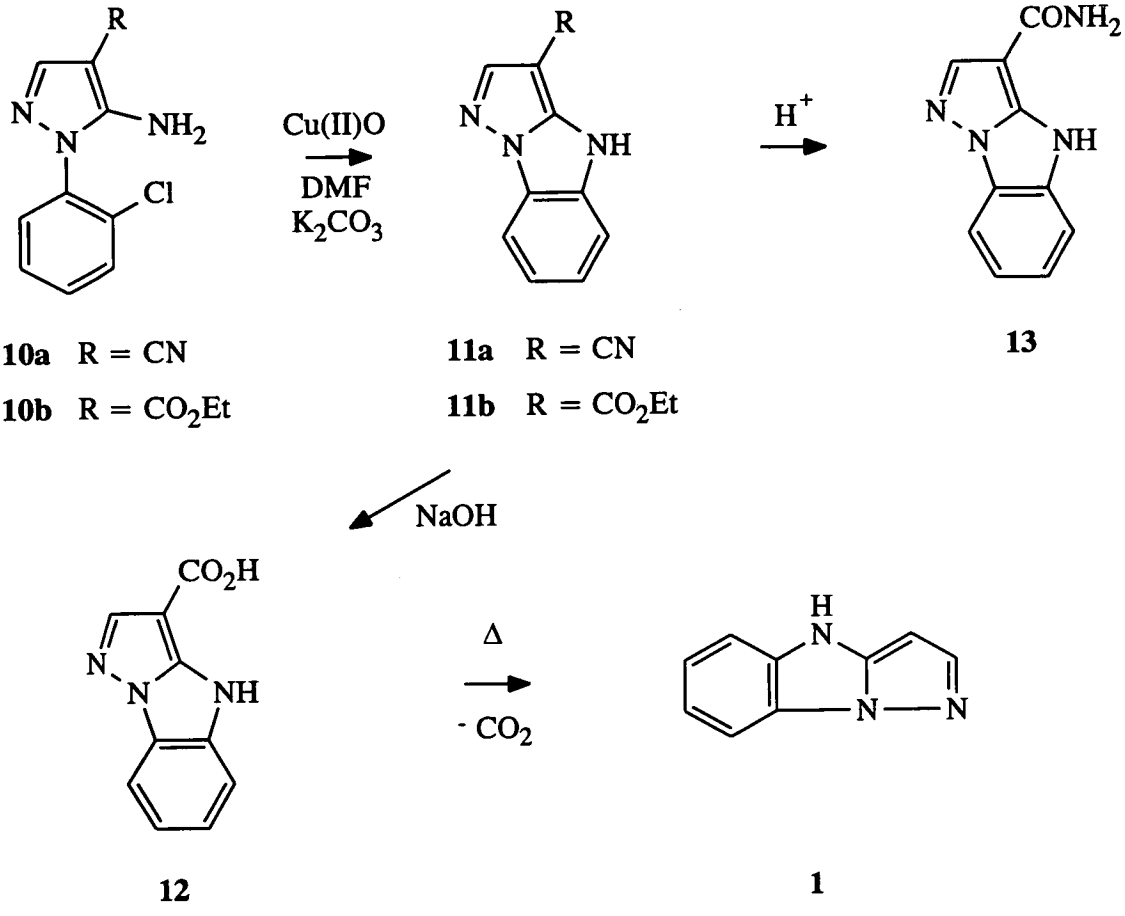
1. Synthesis of Pyrazolo[1,5-*a*]benzimidazoles

There are two principle routes to synthesize pyrazolo[1,5-*a*]benzimidazoles. The first involves initial formation of a substituted pyrazole or pyrazolone ring followed by ring closure to afford the final product. The second route involves the construction of only one ring by cyclisation to give the product. Recently a third route has emerged involving a ring contraction of 1,2,4-triazepino[2,3-*a*]benzimidazol-4-ones.

(i) Two Ring Synthesis of Pyrazolo[1,5-*a*]benzimidazoles

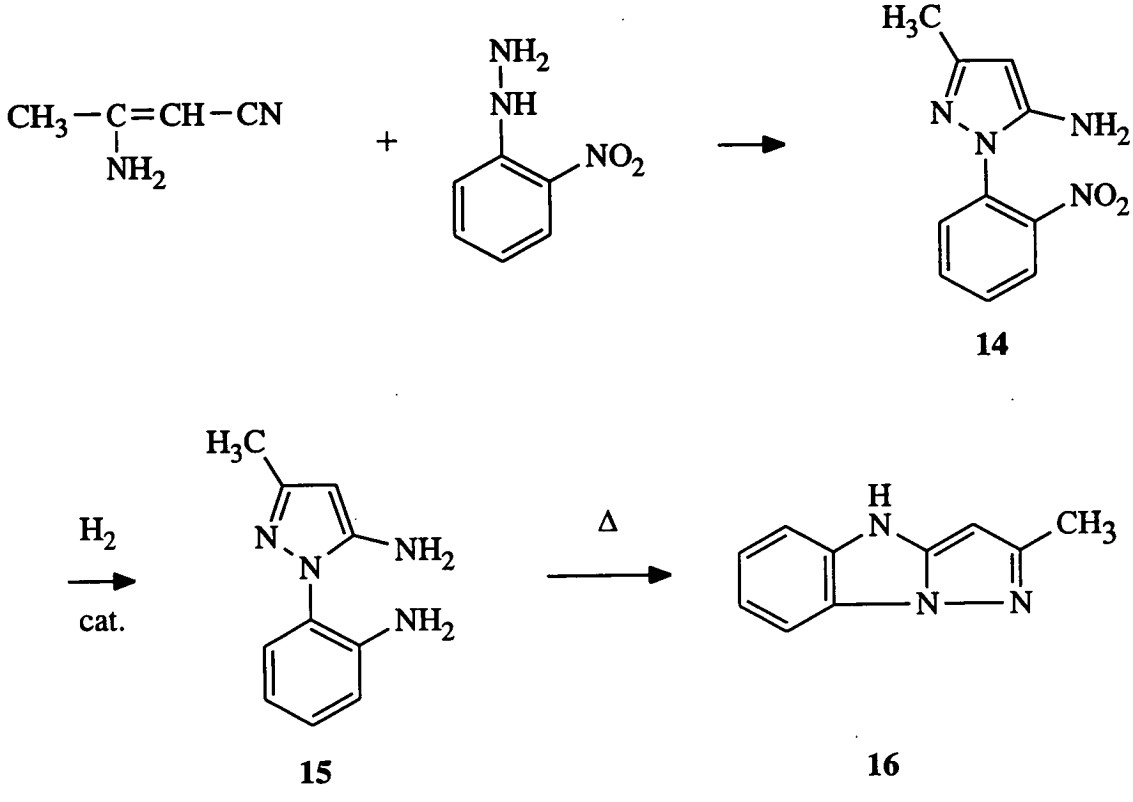
The first example of the parent 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** ring system was reported by Khan and co-workers[7] in 1977. The synthesis involves intramolecular cyclisation of aminopyrazoles **10a** and **10b** prepared from the reaction of *o*-chlorophenylhydrazine with ethoxymethylenemalononitrile[9] and ethyl ethoxymethylenecyanoacetate[8] respectively. Intramolecular cyclisation occurred on heating with copper (II) oxide in *N,N*-dimethylformamide in the presence of anhydrous potassium carbonate to give the corresponding pyrazolo[1,5-*a*]benzimidazole derivatives **11a** and **11b**. Hydrolysis of **11b** under basic conditions afforded the appropriate acid **12** which was decarboxylated on distillation to give the

unsubstituted 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** in 10% overall yield. Further hydrolysis of 3-cyano-4*H*-pyrazolo[1,5-*a*]benzimidazole **11a** with sulfuric acid resulted in the formation of 3-carboxamido-4*H*-pyrazolo[1,5-*a*]benzimidazole **13** (Scheme 2).



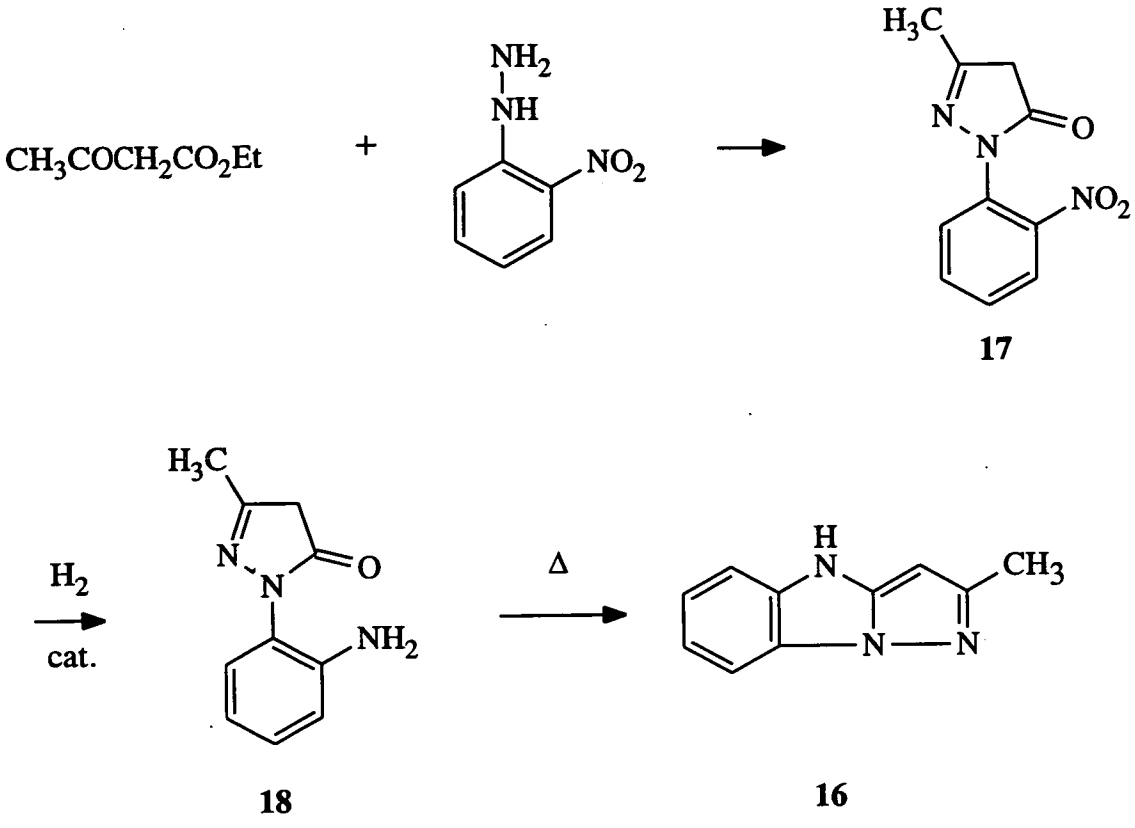
Scheme 2

In an analogous fashion, Elguero[10] and co-workers reported the synthesis of 2-methyl-4*H*-pyrazolo[1,5-*a*]benzimidazole **16** utilising the condensation of 3-aminocrotonitrile and *o*-nitrophenylhydrazine. The aminopyrazole **14** generated was hydrogenated to the diamino compound **15** and the final product **16** was obtained with elimination of ammonia on heating (Scheme 3).



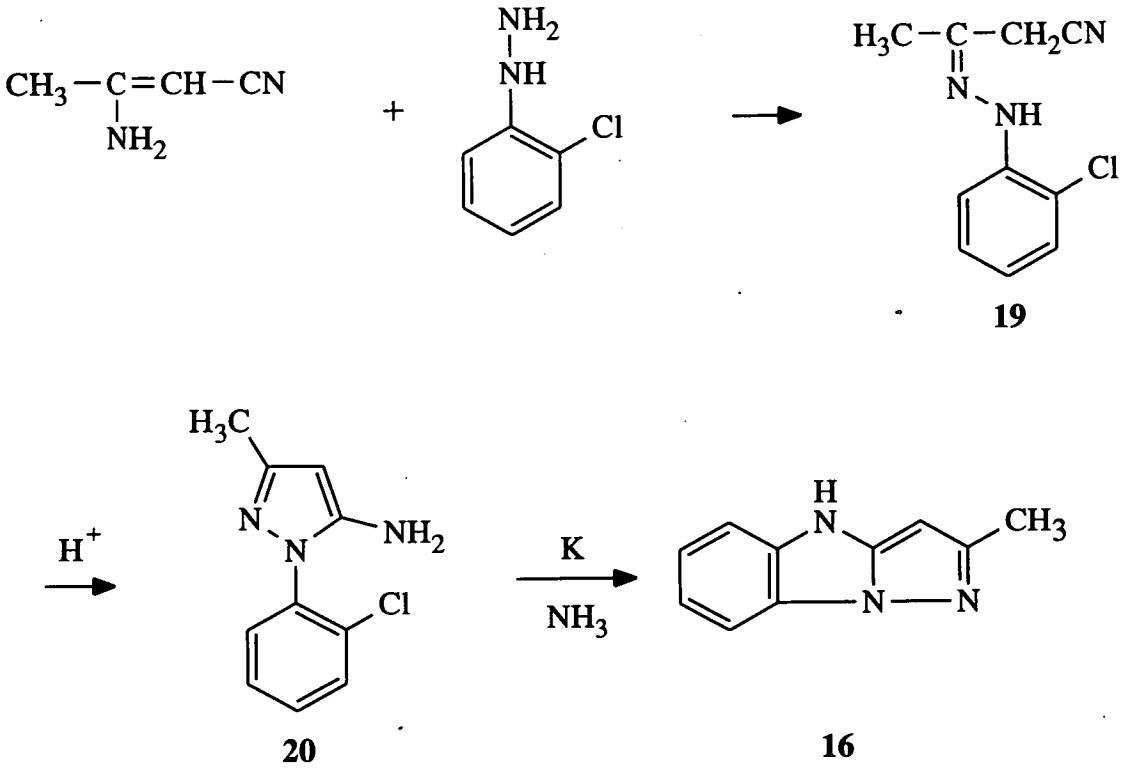
Scheme 3

Similarly, the reaction of ethyl acetoacetate with *o*-nitrophenylhydrazine generates the pyrazolone **17** which was then transformed by hydrogenation to the amine **18**. Heating results in intramolecular cyclisation with elimination of water to give 3-methyl-4*H*-pyrazolo[1,5-*a*]benzimidazole **16** again (Scheme 4).



Scheme 4

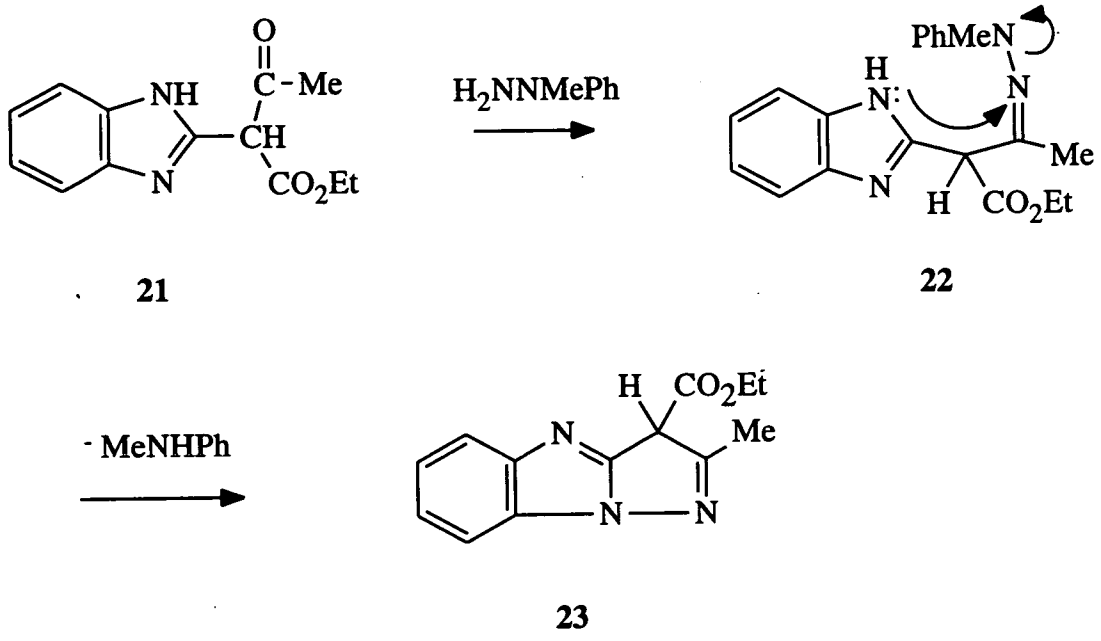
In the same paper,[10] another route to the aforementioned product **16** is described, namely intramolecular cyclisation of benzyne intermediates. In this case 3-aminocrotonitrile was condensed with *o*-chlorophenylhydrazine to afford the hydrazone **19** in 80% yield. Cyclisation on heating under reflux with acid catalysis gave the aminopyrazole **20** in 80% yield. Potassium amide in liquid ammonia was used to generate the benzyne intermediate which then cyclised, in 70% yield, to 2-methyl-4*H*-pyrazolo[1,5-*a*]benzimidazole **16** (Scheme 5).



Scheme 5

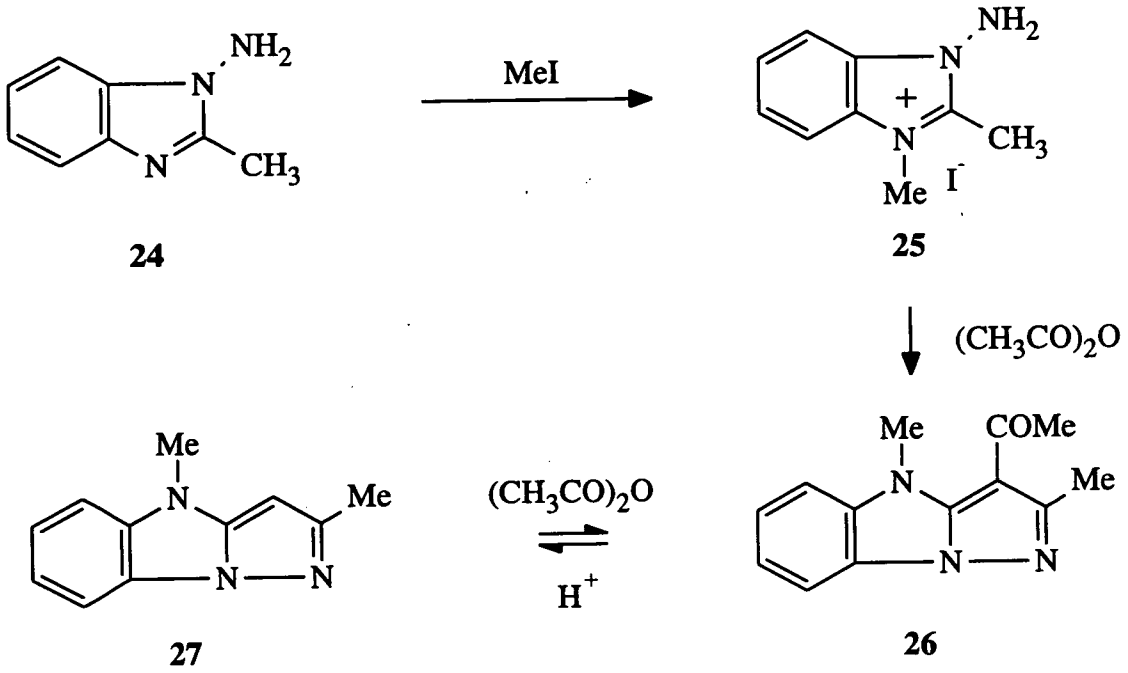
(ii) <u>One Ring Synthesis of Pyrazolo[1,5-*a*]benzimidazoles</u>

The first synthesis of the pyrazolo[1,5-*a*]benzimidazole ring system was reported in 1939.[11] Condensation of the ethyl 2-(benzimidazo-2-yl)acetoacetate **21** with α-methyl-α-phenylhydrazine afforded the methylphenylhydrazone **22**. On heating in acidic conditions, displacement of methylaniline occurred with intramolecular cyclisation to give the product **23** (Scheme 6).



Scheme 6

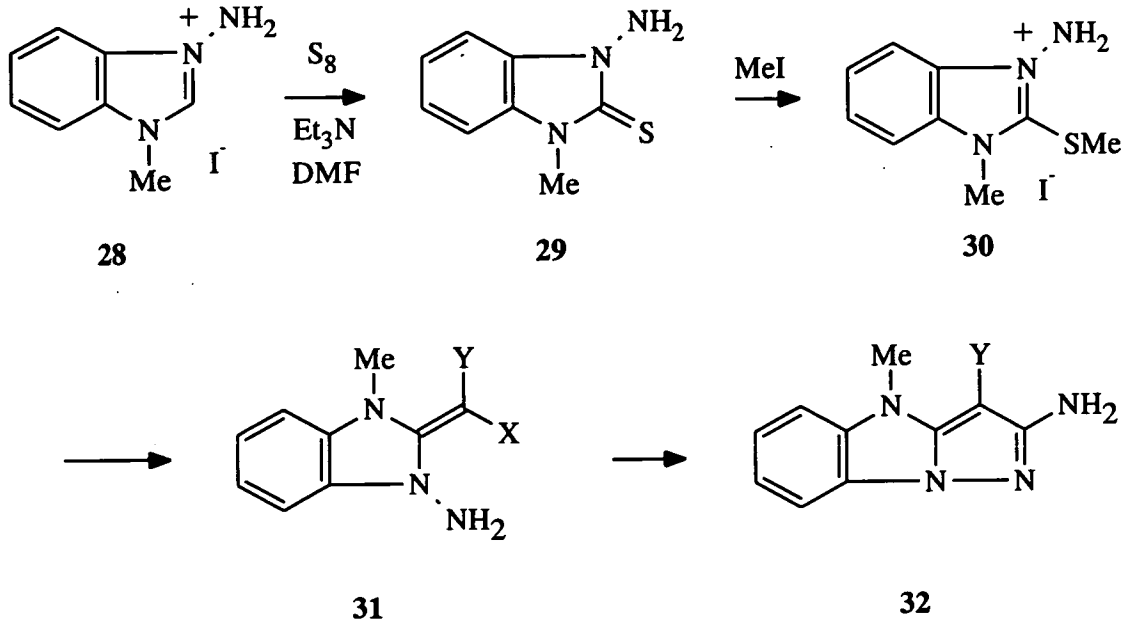
Kuz'menko *et al.*[12] reported in 1980 a new route to 2,4-disubstituted pyrazolo[1,5-*a*]benzimidazoles which were obtained by the action of carboxylic acid anhydrides on 1-amino-2-methyl-3-alkylbenzimidazolium salts **25**. The benzimidazolium salt **25** was isolated in 90% yield after heating 1-amino-2-methylbenzimidazole **24** with excess methyl iodide. Heating **25** under reflux with acetic anhydride in the presence of potassium carbonate results in the efficient formation of a pyrazole ring with simultaneous acetylation at position 3. The acetyl group may be removed under acid hydrolysis conditions to leave the 2,4-dimethylpyrazolo[1,5-*a*]benzimidazole **27** (Scheme 7).



24 **25** **26** **27**

Scheme 7

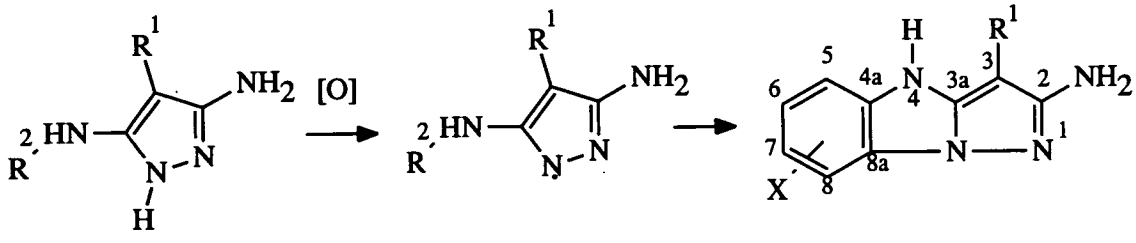
The preceding method was modified to facilitate the synthesis of pyrazolo[1,5-*a*]benzimidazole derivatives with amino groups in the 2-position by employing 1-amino-3-alkyl-2-(methylthio) benzimidazolium salts **30**.[13] 1-Amino-3-alkylbenzimidazolium salts **28** were heated under reflux with sulfur in *N,N*-dimethylformamide in the presence of triethylamine to give the thiones **29** in excellent yields. The salts **30** were afforded on reaction with methyl iodide, and this newly generated reactive site allowed nucleophilic substitution with a variety of CH-acid anions in the presence of triethylamine to give the methylene bases **31** in 60-90% yield. Cyclisation in acid conditions gave the 2-amino substituted pyrazolo[1,5-*a*]benzimidazoles **32** (Scheme 8).



Compound	X	Y	Compound	Y	Yield
31a	CO_2Et	CN	**32a**	CO_2Et	87%
31b	CN	CN	**32b**	CN	100%

Scheme 8

A recent report by Schultz[14] and co-workers describes the formation of substituted 2-aminopyrazolo[1,5-*a*]benzimidazoles *via* oxidative cyclisation of anilinopyrazoles. Oxidation of anilinopyrazoles **33** with either dibenzoylperoxide or lead(IV)oxide gave the appropriate pyrazolo[1,5-*a*]benzimidazoles **35**. The cyclisation reaction of intermediate pyrazolyl radicals **34** was favoured when donor substituents were incorporated into the aniline ring (Scheme 9).



33 34 35

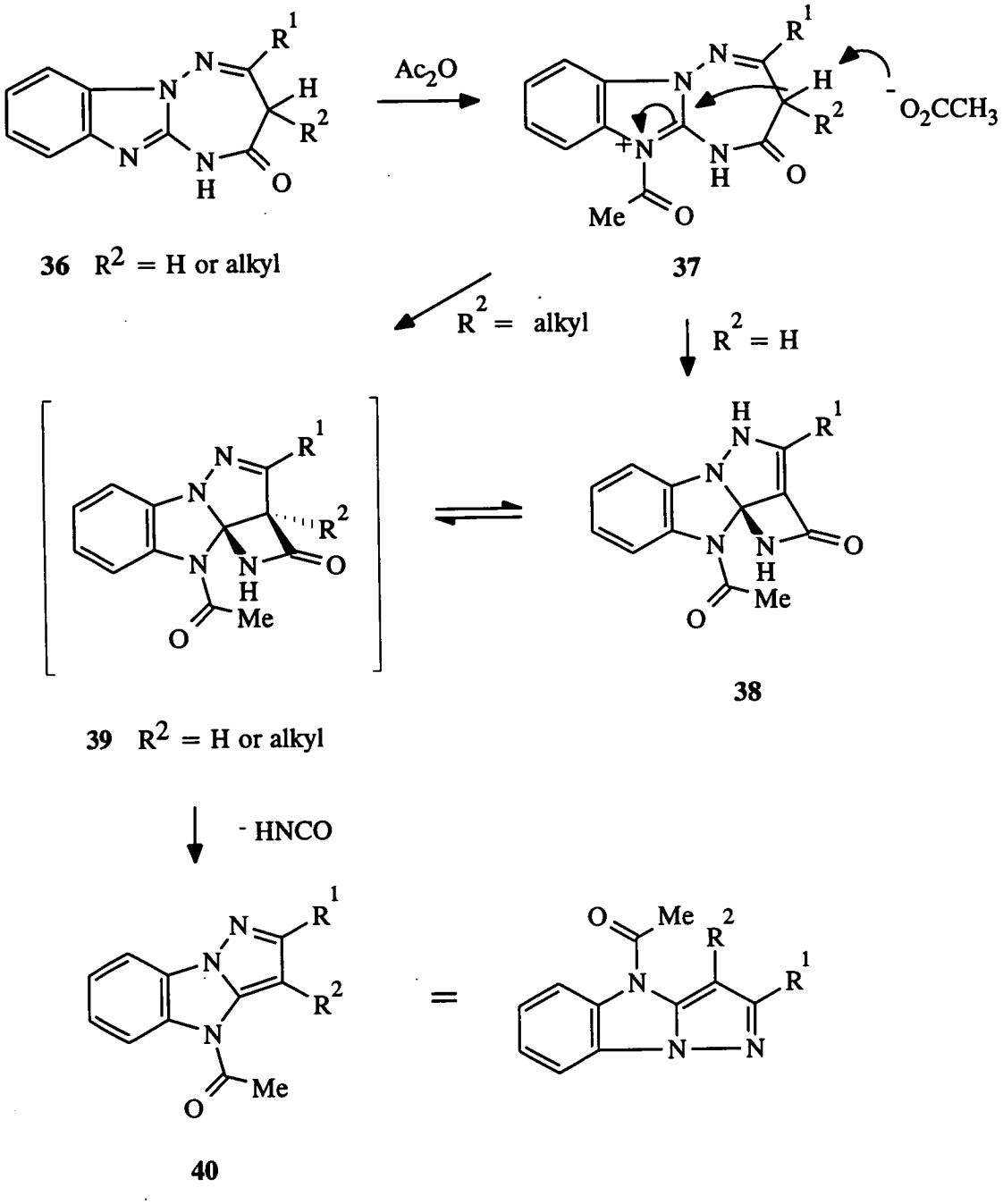
33	R^1	R^2
a	CO_2Et	C_6H_5
b	CO_2Et	4-MeO-C_6H_4
c	CN	C_6H_5
d	CN	4-MeO-C_6H_4

35	R^1	X	Yield
a	CO_2Et	H	54%
b	CO_2Et	7-MeO	62%
c	CN	H	40%
d	CN	7-MeO	45%

Scheme 9

(iii) Pyrazolo[1,5-*a*]benzimidazoles *via* ring contractions

A third type of synthesis of pyrazolo[1,5-*a*]benzimidazoles was reported by Avendano *et al.*[15] which involves the formation of the fused tetracyclic β-lactams **38** and **39** by the reaction of 1,2,4-triazepino[2,3-*a*]benzimidazol-4-ones **36** with acetic anhydride. Subsequent spontaneous ejection of cyanic acid affords the acetylated pyrazolo[1,5-*a*]benzimidazoles **40** in excellent yields. When the 3-position in the triazepinone **37** is unsubstituted (R^2 = H), β-lactam isolation is possible as a consequence of resonance stabilisation of the resulting conjugated enone **38**. This was confirmed by the low frequency value in the IR spectrum of the α,β-unsaturated β-lactam carbonyl group (Scheme 10).



36 R^2 = H or alkyl

37

38

39 R^2 = H or alkyl

40

Scheme 10

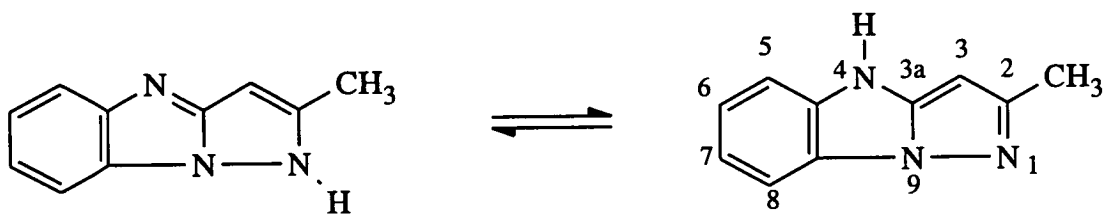
2. Physical Properties of Pyrazolo[1,5-*a*]benzimidazoles

(i) Infrared

No comprehensive study has been conducted on the infrared spectra of pyrazolo[1,5-*a*]benzimidazoles. Experimental observations reveal the most intense bands at 3210-2500 cm^{-1} (br. NH)[16] and 1630 cm^{-1} (C=N).[14]

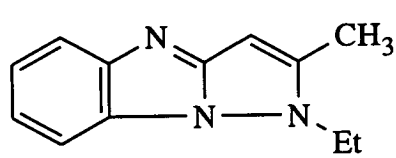
(ii) Ultraviolet

Ultraviolet spectra of pyrazolo[1,5-*a*]benzimidazoles generally show two absorption maxima at *ca.* 230 nm and 320-330 nm.[17] Lazaro and Elguero[17] used UV to give an indication as to the predominance of tautomerism in the 2-methylpyrazolo[1,5-*a*]benzimidazole **16 a** and **b** system shown.



16a **16b**

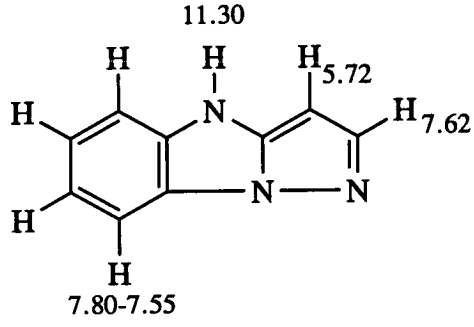
When N-1 of pyrazole was ethylated to yield **41**, an additional band was observed at 321 nm indicating a change in the electronic structure with respect to the starting material **16**. This fits with a tautomeric predominance of **16b**. The authors used the chemical shift and coupling pattern, in the ^1H NMR spectrum, of the proton at position 3 to determine the site of ethylation.



41

(iii) ^{1}H NMR

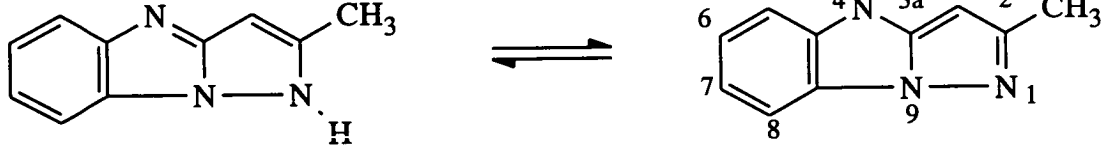
The ^{1}H NMR spectrum of the unsubstituted parent pyrazolo[1,5-*a*]benzimidazole **1** has not been fully assigned in the literature although certain characteristic resonances have been identified.[7] Full assignments are detailed later in the thesis.



1

When H-3 is replaced by an electron withdrawing group, for example carboxamide or nitrile, there is a high frequency shift of $\Delta\delta_H$ 0.5 ppm of the proton in position 2.[16] This is also accompanied by a slight deshielding effect on the benzenoid protons.

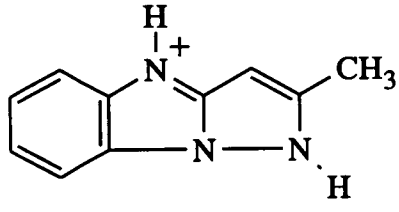
An extensive study into annular tautomerism using NMR has been conducted by Elguero and co-workers.[18] The system most commonly examined is 2-methylpyrazolo[1,5-*a*]benzimidazole **16** run in D_6-DMSO.



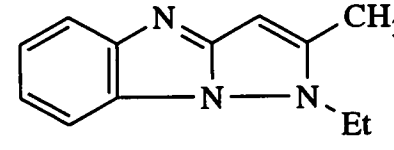
16a **16b**

The ^{1}H NMR spectrum shows transannular coupling between H-5 and H-8. There is no observed coupling between H-3 and the protons of the methyl group at C-2 in **16** however on protonation with TFA to afford cation **42**, a coupling of 0.75 Hz was

observed between those protons.[18] This indicates protonation at position 1 resulting in a shift in electronic structure thus facilitating coupling. This is also observed when N-1 is substituted with an ethyl moiety to give **41**.[17] The generation the cationic species **42** induces a large deshielding effect on both H-3 and the methyl protons at position 2. These results verify that the stable tautomer of 2-methylpyrazolo[1,5-*a*]benzimidazole is indeed **16b**.



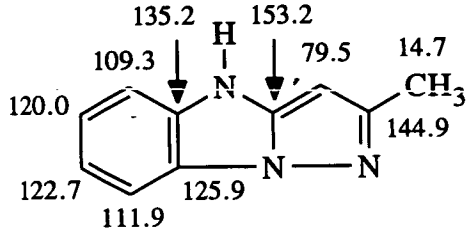
42



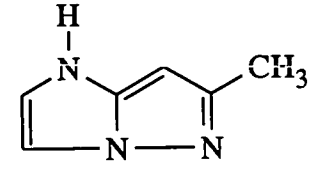
41

(iv) ^{13}C NMR

There have only been two reports of ^{13}C NMR spectra in the literature.[14,19] Elguero[19] assigned C-2, C-3 and C-3a of 2-methylpyrazolo[1,5-*a*]benzimidazole **16** by analogy with results obtained for 6-methylimidazo[1,2-*b*]pyrazole **43**. The benzenoid carbons were assigned by comparison with literature results for imidazole[18] and benzimidazole[20] which ascertain the effect of annelation on C-4 and C-5 of imidazole.

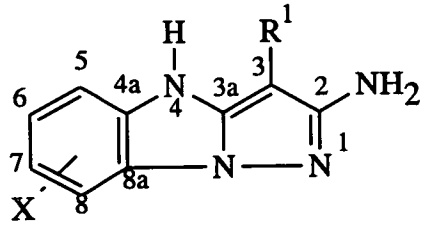


16



43

A more recent report[14] provides ^{13}C NMR data for a number of substituted pyrazolo[1,5-*a*]benzimidazoles **35a-d**.



35

35	R^1	X
a	CO_2Et	H
b	CO_2Et	7-MeO
c	CN	H
d	CN	7-MeO

Assignments are listed in Table 1.

Table 1:

^{13}C chemical shifts for substituted 4*H*-pyrazolo[1,5-*a*]benzimidazoles

Compound	C-2	C-3	C-3a	C-4a	C-5	C-6	C-7	C-8	C-8a
35a	159.2	77.3	143.2	133.5	112.5	122.4	121.5	109.1	125.4
35b	160.0	77.3	143.7	125.4	112.8	109.9	154.7	93.8	127.5
35c	161.4	55.4	144.6	133.1	112.3	122.6	121.6	109.0	125.6
35d	162.3	56.0	140.1	127.1	113.7	111.0	156.1	95.0	128.2

The presence of a conjugatively electron donating methoxy group at position 7 (**35b** and **35d**) results in substantial shielding of both adjacent carbons C-6 and C-8, for example $\Delta\delta_C$ 13-15 ppm for **35a** with respect to **35b**. A large deshielding, $\Delta\delta_C$ 33-35 ppm, at the site of substitution is observed. This is accompanied by deshielding of carbon 4a *para* to the methoxy group ($\Delta\delta_C$ 6-8 ppm) and slight deshielding ($\Delta\delta_C$ 1-2 ppm) of the benzenoid carbons *meta*. On substitution of the ethyl ester group at C-3 with a nitrile (**35a** to **35c**) there is a marked shielding effect, $\Delta\delta_C$ 22 ppm, at the

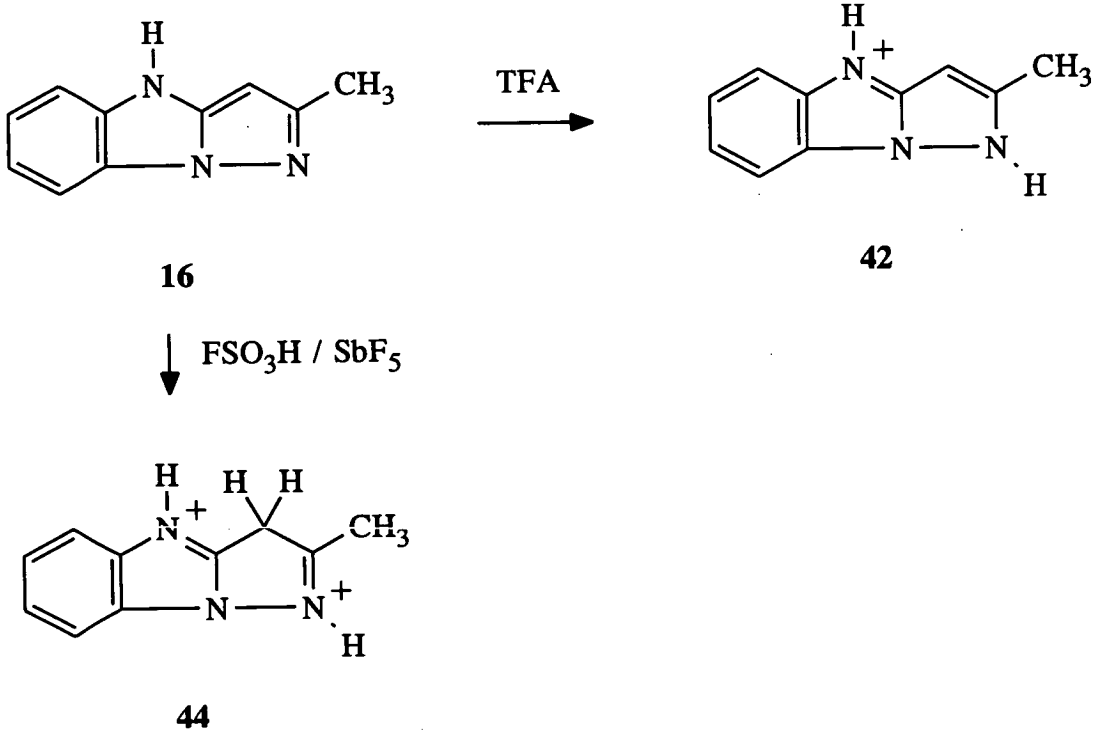
position of substitution accompanied by slight changes in the chemical shift of adjacent carbons.

3. Chemical Reactivity of Pyrazolo[1,5-*a*]benzimidazoles

There are relatively few examples of chemical reactions of pyrazolo[1,5-*a*]benzimidazoles in the literature.

(i) Electrophiles

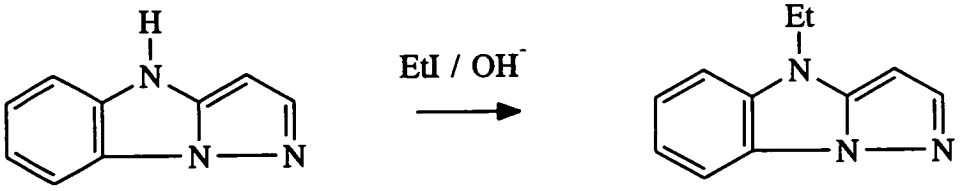
Pyrazolo[1,5-*a*]benzimidazoles can undergo electrophilic attack at a nitrogen atom or at an electron rich carbon atom such as C-3. Protonation of 2-methylpyrazolo[1,5-*a*]benzimidazole **16** with TFA occurs at nitrogen to give the monocation **42**. The electronic structure of this species was confirmed by ^1H NMR.[18] The dication **44** results from further protonation at C-3[17] (Scheme 11).



16 **42** **44**

Scheme 11

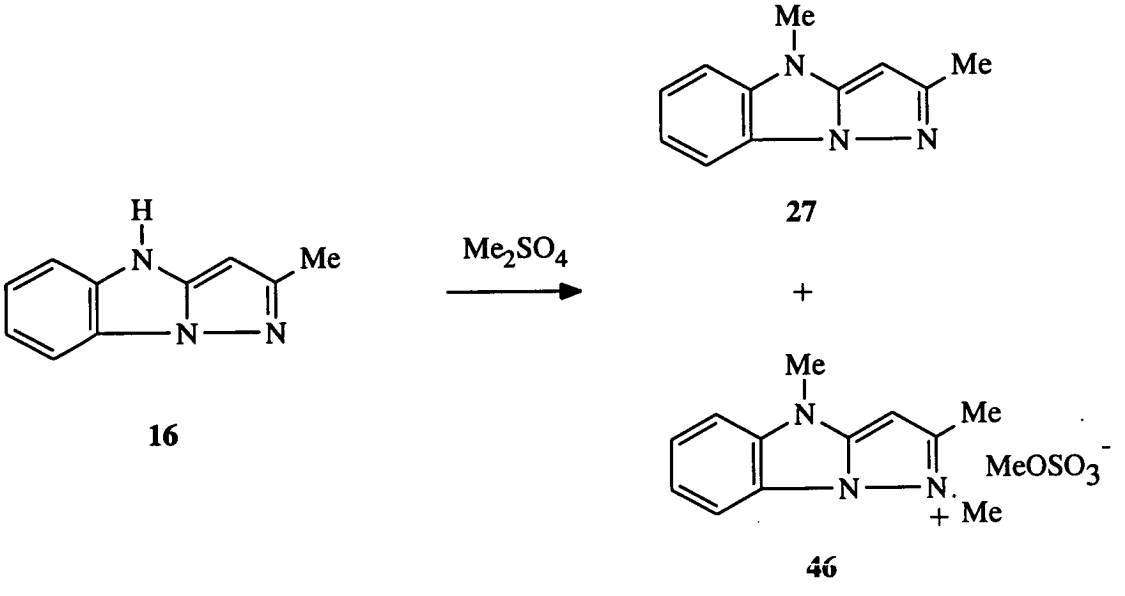
Alkylation of the parent pyrazolo[1,5-*a*]benzimidazole **1** with ethyl iodide in the presence of base occurs at N-4 *via* the anion to give the corresponding *N*-ethyl derivative **45** in 39% yield (Scheme 12).[16]



1 **45**

Scheme 12

Alkylation of **16** using dimethyl sulfate gave a mixture of *N*-methylated derivatives,[17] **27** and the salt **46** in 30% and 55% yields respectively (Scheme 13).

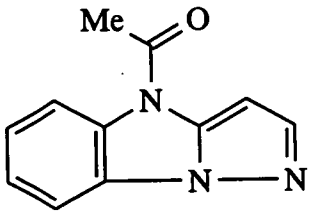


16 **27** + **46**

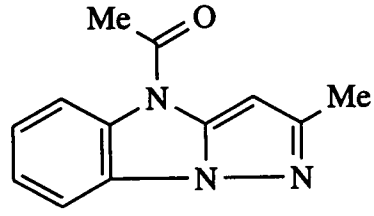
Scheme 13

The reaction of acetic anhydride with the parent heterocycle **1**[16] and the 2-methyl substituted analogue **16**[18] occurs on the imidazolic nitrogen atom to give *N*-acylated derivatives **47** and **48** respectively as verified by the chemical shift of proton H-3 in

the ^{1}H NMR spectrum. Reduction of **47** with lithium aluminium hydride regenerated the starting material **1**.[17]

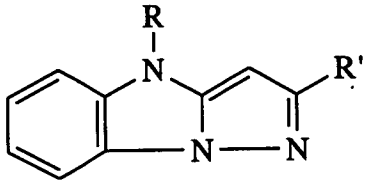


47



48

When N-4 is blocked, then acylation occurs at the electron rich C-3 position.[12]



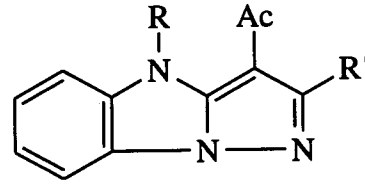
49

R,R' = alkyl

Ac_2O

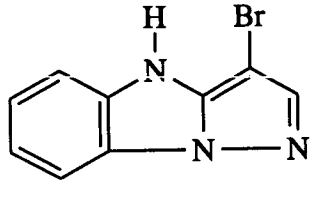
$\rightleftharpoons$

H^+



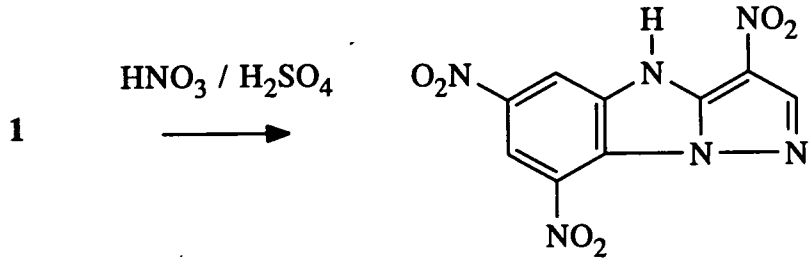
50

Bromination of unsubstituted pyrazolo[1,5-*a*]benzimidazole **1** with bromine[16] occurs at C-3 to afford the photographically desirable two-equivalent coupler **51** in 81% yield (Section A).



51

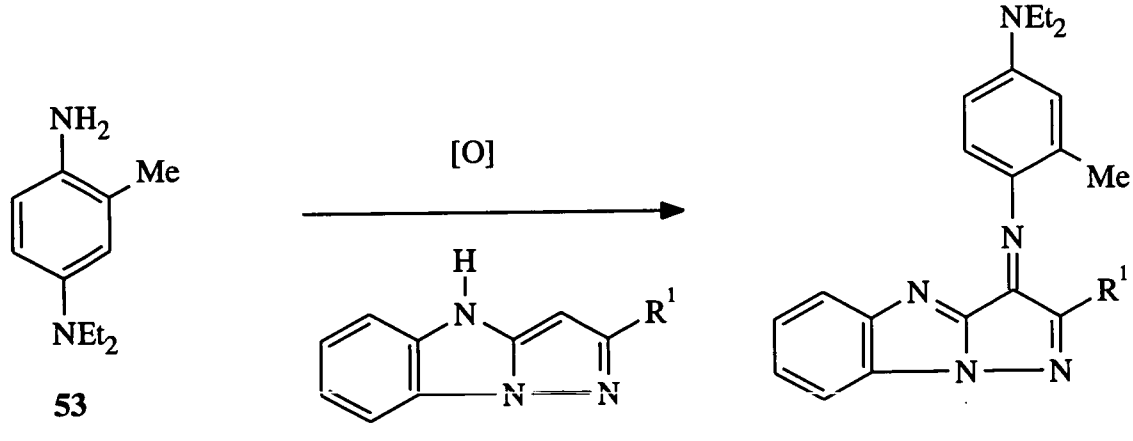
Nitration of the parent **1** with a mixture of nitric and sulfuric acids gave the trinitrated product **52**. Selective nitration at C-3 has been attempted with acetyl nitrate,[16] however only the *N*-acetyl compound **47** was isolated.



52

(ii) Oxidative coupling reactions

These type of reactions are utilised in the photographic dye forming process (Section A). Pyrazolo[1,5-*a*]benzimidazoles react with *p*-phenylenediamines,[21] for example **53**, in the presence of an oxidising agent, silver halide or potassium persulfate, to give the azamethine dye product **54** (Scheme 14).



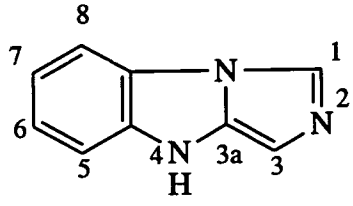
53 **54**

R^1 = H, Alkyl, Aryl.

Scheme 14

C. IMIDAZO[1,5-*a*]BENZIMIDAZOLES

The synthesis and chemistry of this class of compounds has formed part of a review,[6] however there are very few references to imidazo[1,5-*a*]benzimidazoles in the literature. The unknown parent ring system **2** and its numbering scheme is shown.



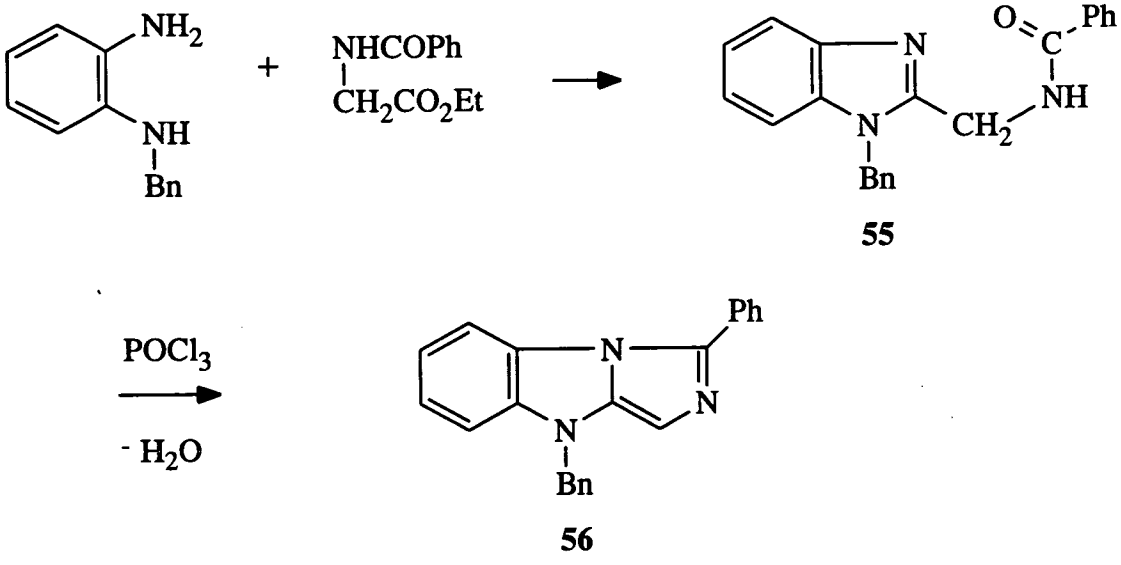
2

1. Synthesis of Imidazo[1,5-*a*]benzimidazoles

The synthesis of the rare imidazo[1,5-*a*]benzimidazole ring system has been achieved in a limited number of ways. The most common synthesis makes use of 2-aminomethylbenzimidazoles as starting materials. A more recent route utilises the aza-Wittig reaction of iminophosphoranes.

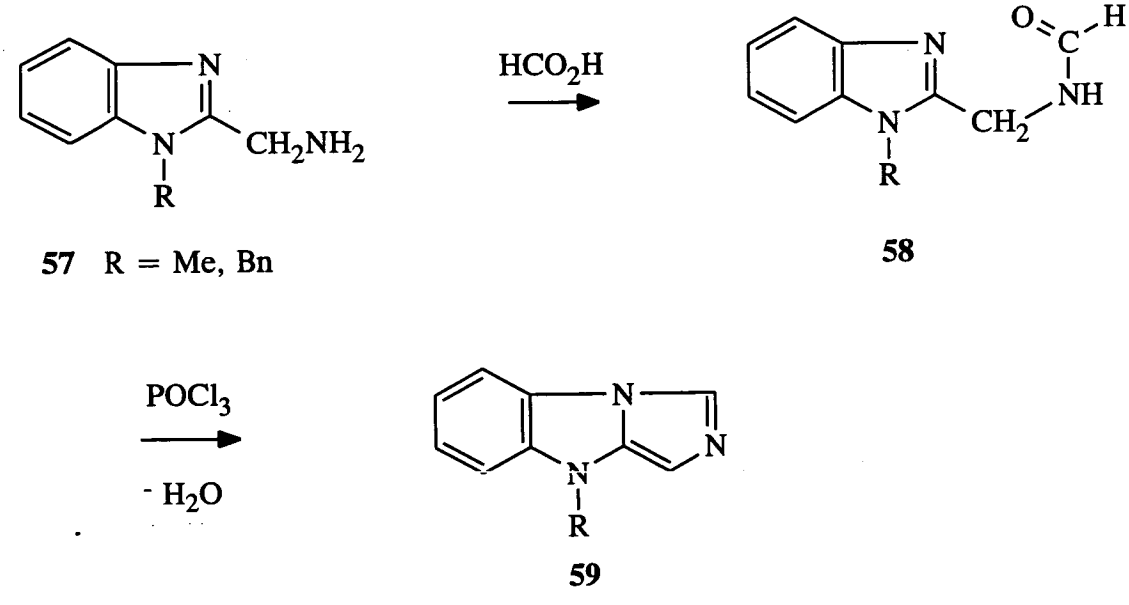
(i) Imidazo[1,5-*a*]benzimidazoles from 2-aminomethylbenzimidazoles

Aryuzina and Shchukina[22] have reported the synthesis of a number of substituted imidazo[1,5-*a*]benzimidazoles from the cyclic dehydration of acylated 2-aminomethylbenzimidazoles. For example the product **55** derived from the reaction of *N*-benzyl-*o*-phenylenediamine and ethyl hippurate undergoes cyclisation on treatment with phosphorus oxychloride to afford 1-phenyl-4-benzylimidazo[1,5-*a*]benzimidazole **56** in 52% overall yield (Scheme 15).



Scheme 15

Mono-substituted imidazo[1,5-*a*]benzimidazole derivatives **59** may be generated by the *N*-formylation and cyclodehydration of 1-substituted-2-aminomethylbenzimidazoles **58** (Scheme 16).

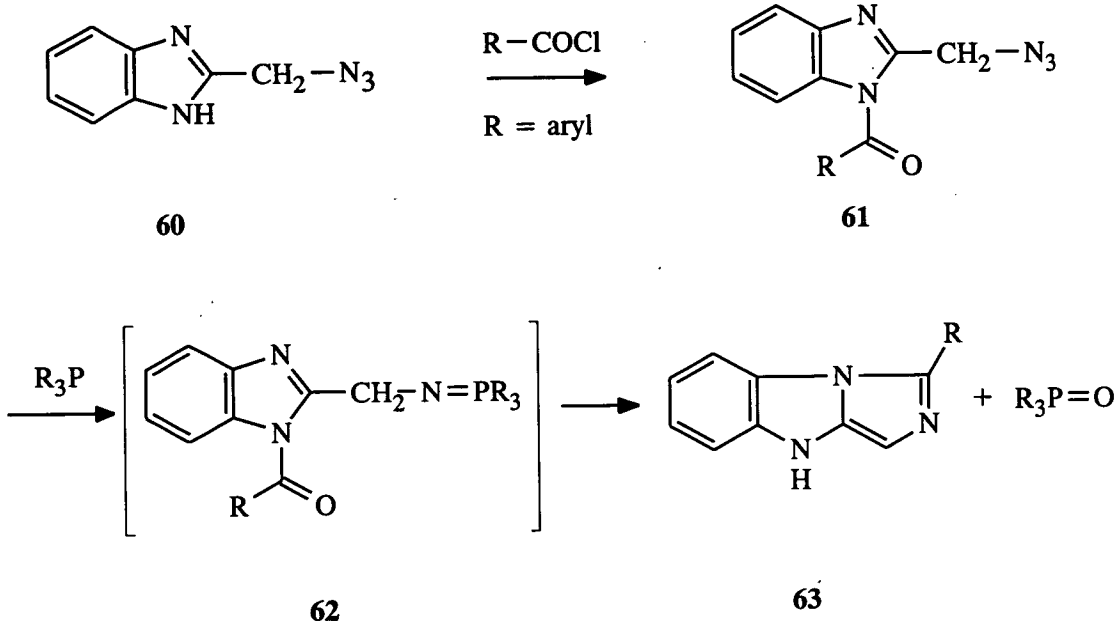


Scheme 16

(ii) Aza-Wittig reaction of Iminophosphoranes

Molina and co-workers[23] reported the synthesis of imidazo[1,5-*a*]benzimidazoles in reasonable yield (60-65%) *via* the intramolecular aza-Wittig reaction of iminophosphoranes **62** with the adjacent amide carbonyl moiety.

2-Azidomethylbenzimidazoles **60** may be acylated to the corresponding derivatives **61** with carboxylic acid chlorides in pyridine. The subsequent reaction with tertiary phosphines leads to the desired imidazo[1,5-*a*]benzimidazole **63** *via* the intermediate iminophosphorane derivative **62** (Scheme 17).



60 **61** **62** **63**

Scheme 17

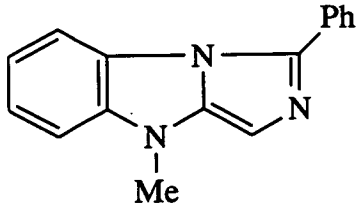
2. Physical Properties of Imidazo[1,5-*a*]benzimidazoles

(i) Infrared

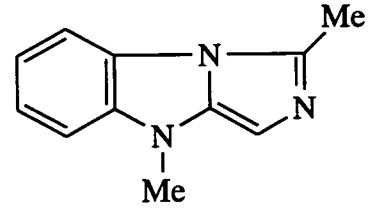
There is no detailed study on the infrared spectra of imidazo[1,5-*a*]benzimidazoles. Experimental observations show intense splitting of the absorption band at 1600-1620 cm^{-1} which is characteristic of these tricyclic compounds.[22]

(ii) Ultraviolet

Ultraviolet spectra of imidazo[1,5-*a*]benzimidazoles generally show three absorption maxima at *ca.* 230 nm, 280 and 350 nm.[22,24] Comparison of the ultraviolet spectra of 1,4-dimethylimidazo[1,5-*a*]benzimidazole **64** and 4-methyl-1-phenylimidazo[1,5-*a*]benzimidazole **65** reveals a bathochromic shift of 28 nm for **64** compared to **65**.[24]



64

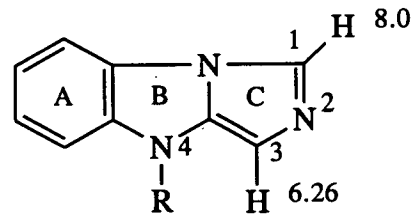


65

Electron withdrawing groups induce bathochromic shifts in the ultraviolet and visible spectrum thus the phenyl substituent is acting in this manner (see Results and Discussion, Section C.8). The additional absorption maxima at *ca.* 350 nm are indicative of these systems, and occur as a result of the creation of conjugated double bonds on dehydrative cyclisation of 2-aminomethylbenzimidazoles.[25]

(iii) ^{1}H NMR

Certain resonances of substitued imidazo[1,5-*a*]benzimidazoles have been identified, and a study has been conducted by Aryuzina and co-workers[26] relating π-electron densities and proton chemical shifts.



59 R = Bn

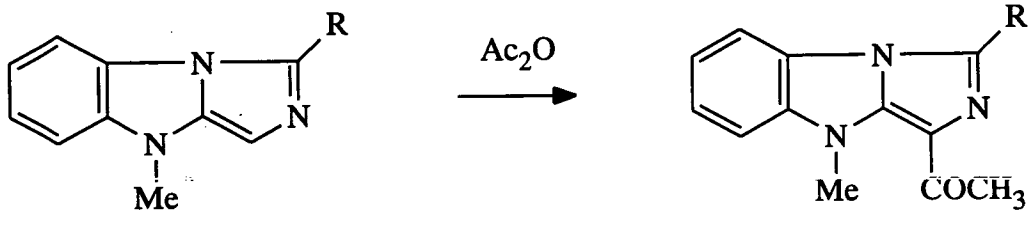
The greatest π-electron density is found at the C-3 atom, the singlet from the proton at this position is readily distinguished. Introduction of phenyl groups in either position 1 or 3 of 4-methylimidazo[1,5-*a*]benzimidazole **59** (R=Me) serves to slightly deshield the other proton by approximately 0.2 ppm[22] indicating that the phenyl substituent acts as an electron withdrawing group in this case.

3. Chemical Reactivity of Imidazo[1,5-*a*]benzimidazoles

(i) Electrophiles

Imidazo[1,5-*a*]benzimidazoles containing a substituent in position 1 or 3 readily undergo electrophilic substitution at the imidazole ring C.

Acetylation of 1-substituted-4-methylimidazo[1,5-*a*]benzimidazoles **66** with acetic anhydride in the presence of anhydrous sodium acetate gave high yields of the 3-acetylated derivatives[24] **67** (Scheme 18).



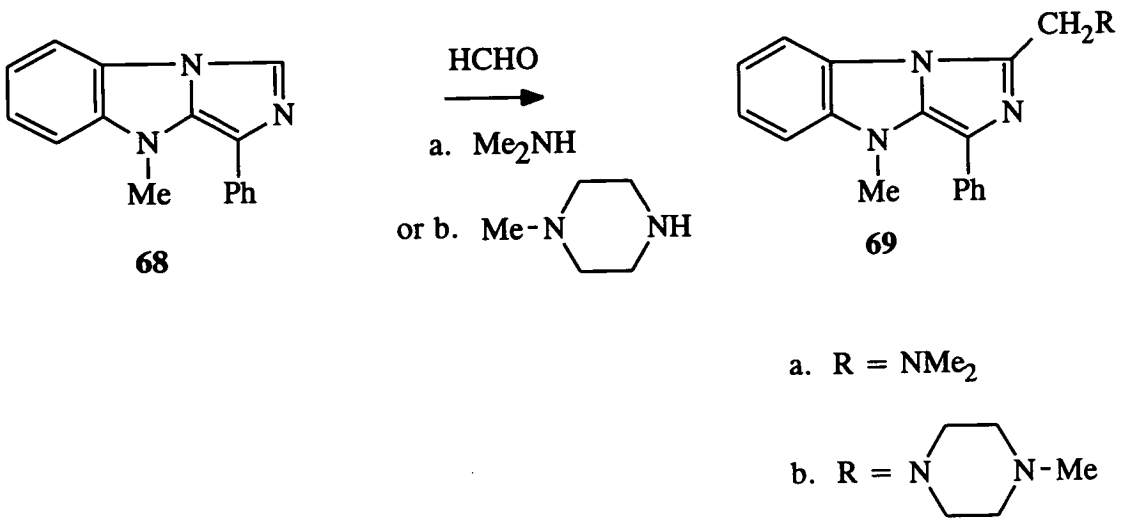
66 R = Me, Ph

67

Scheme 18

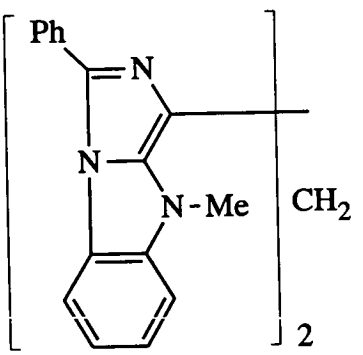
3-Phenyl-4-methylimidazo[1,5-*a*]benzimidazole **68** was found to undergo the Mannich reaction with formalin and aqueous dimethylamine to afford the

methylamino derivative **69a**.[27] The reaction was also carried out with another secondary amine, *N*-methylpiperazine, to afford the appropriate derivative **69b** in excellent yield (Scheme 19).



Scheme 19

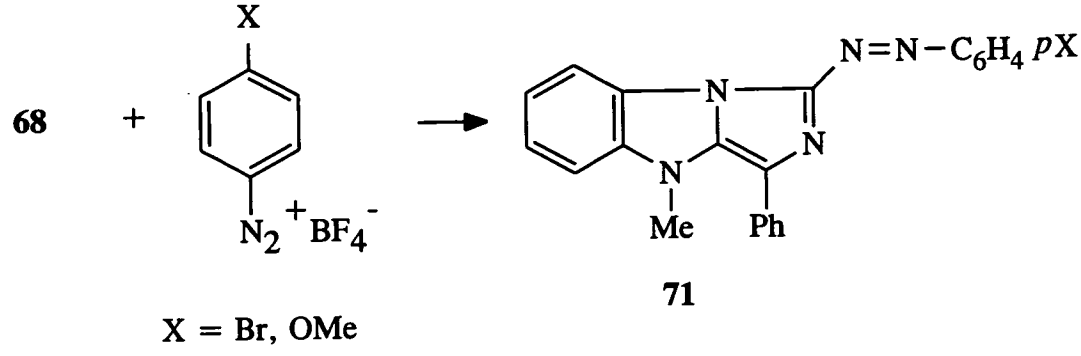
On attempting the reaction with 3-unsubstituted systems, however, the methylene bis derivative **70** was obtained.[24]



70

The azo-coupling reaction of 3-phenyl-4-methylimidazo[1,5-*a*]benzimidazole **68** was carried out with *p*-bromo- and *p*-methoxy-benzenediazonium tetrafluoroborates to

afford the corresponding 1-substituted azo-derivatives **71** in 50% and 43% yields respectively (Scheme 20).[27]

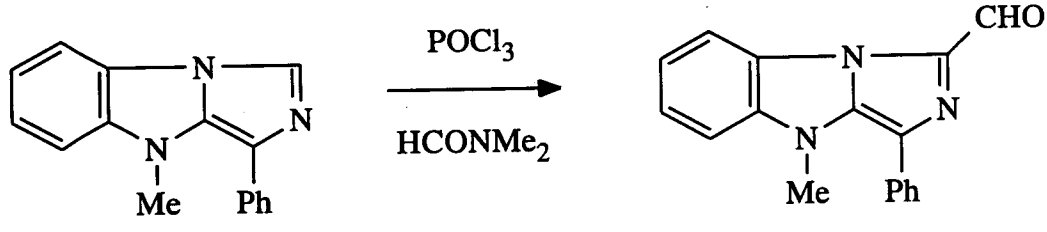


71

X = Br, OMe

Scheme 20

The Vilsmeier formylation reaction was carried out on 3-phenyl-4-methylimidazo[1,5-*a*]benzimidazole **68** with phosphorus oxychloride and *N,N*-dimethylformamide to give the aldehyde **72** in excellent yield[28] (Scheme 21).



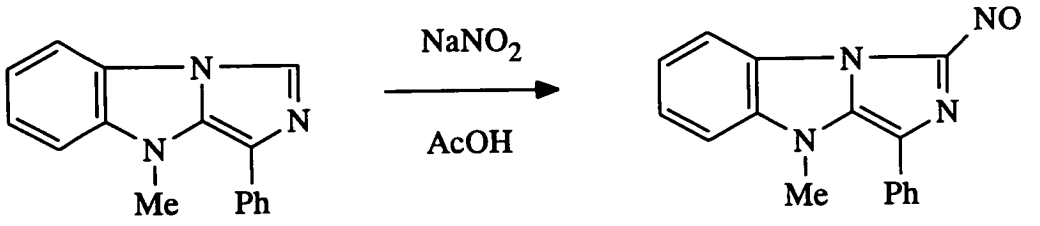
68 **72**

Scheme 21

The reaction was repeated using 1-phenyl-4-benzylimidazo[1,5-*a*]benzimidazole **56** to generate the 3-substituted aldehyde.[22]

The nitrosation of 3- or 1-substituted imidazo[1,5-*a*]benzimidazoles with sodium nitrite in acetic acid leads to 1- or 3-nitroso derivatives respectively.[24] One example of this reaction is the formation of 1-nitroso-3-phenyl-4-methylimidazo[1,5-

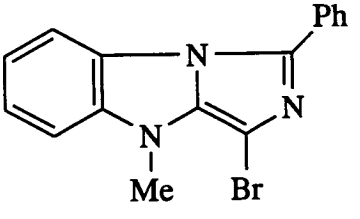
a]benzimidazole **73** from 3-phenyl-4-methylimidazo[1,5-*a*]benzimidazole **68** in 83% yield (Scheme 22).



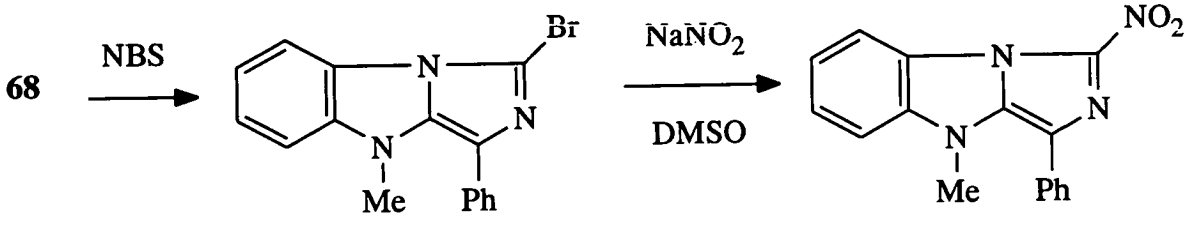
68 **73**

Scheme 22

Attempts to brominate 1- and 3-phenyl-4-methylimidazo[1,5-*a*]benzimidazoles **64** and **68** with molecular bromine proved unsuccessful, however on heating with *N*-bromosuccinimide the appropriate 3- and 1-bromosubstituted derivatives **74** and **75** were isolated in reasonable yield.[27] Further transformation of **75** to the nitro derivative **76** was effected in 72% yield by heating with sodium nitrite in DMSO (Scheme 23).



74

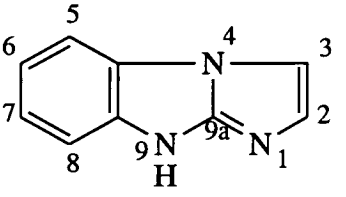


75 **76**

Scheme 23

D. IMIDAZO[1,2-*a*]BENZIMIDAZOLES

The synthesis and chemistry of this class of compounds has formed part of a review.[6] There has been considerable interest in imidazo[1,2-*a*]benzimidazole and its derivatives as a consequence of their potent analgesic activity.[29] These systems reduce acetic acid induced writhing and cause a taming effect in fighting mice. The parent ring system **3** and its numbering scheme is shown.



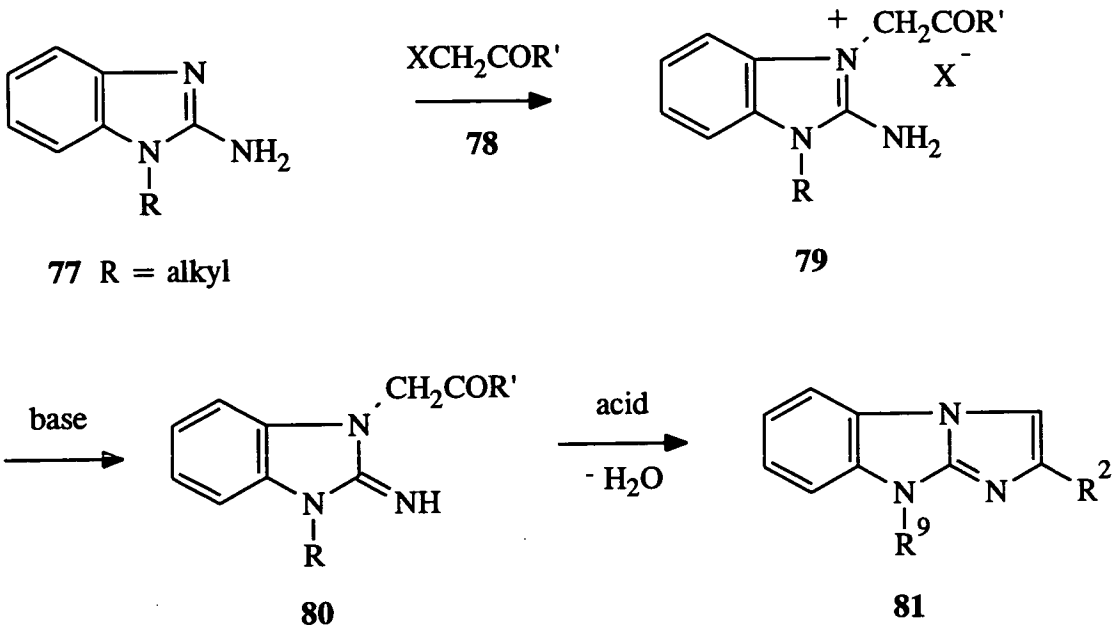
3

1. Synthesis of Imidazo[1,2-*a*]benzimidazoles

One principle route to synthesize imidazo[1,2-*a*]benzimidazoles has featured in the literature. This involves construction of the terminal imidazole ring *via* cyclisation to give the appropriate substituted imidazo[1,2-*a*]benzimidazole. A number of miscellaneous syntheses will also be discussed.

(i) One Ring Synthesis of Imidazo[1,2-*a*]benzimidazoles

Simonov and Kochergin[30] were the first to report the synthesis of substituted imidazo[1,2-*a*]benzimidazoles by the reaction of 1-alkyl-2-aminobenzimidazoles **77** with α-halocarbonyl compounds **78**. On treatment with dehydrating agents (mineral or organic acids) the intermediate 1,3-disubstituted 2-iminobenzimidazolines **80** cyclise to substituted imidazo[1,2-*a*]benzimidazoles **81** in good yields with the expulsion of water (Scheme 24)



Scheme 24

Depending on the nature of R and R', then a variety of 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles may be generated (Table 2).

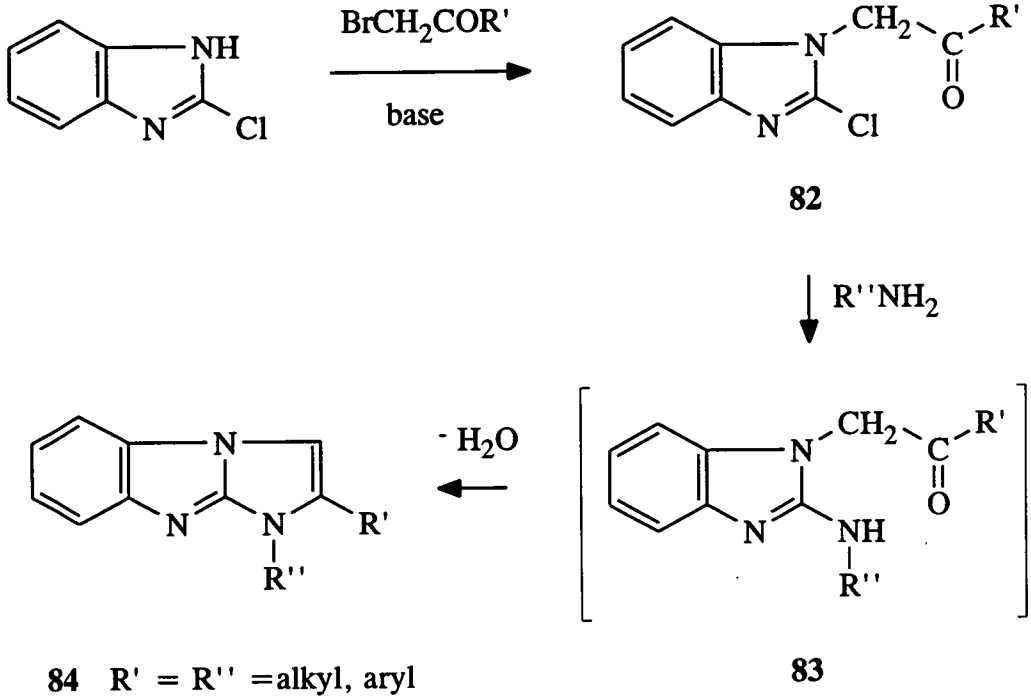
Table 2

80	R	X	R'	**81** R^9	**81** R^2	Yield	Ref.
a	H	Br	Ph	H	Ph	85%	29
b*	H	Br	Ph	CH_2COPh	Ph	100%	39
c	Me	Br	Me	Me	Me	88%	41
d**	Me	Cl	NHPh	Me	NHPh	-	42
e**	Me	Cl	N(Me)Ph	Me	N(Me)Ph	-	42
f	NH_2	Br	Ph	NH_2	Ph	80%	40
g	NH_2	Br	$C(CH_3)_3$	NH_2	$C(CH_3)_3$	77%	40

Notes: * 2 equivalents of phenacyl bromide required

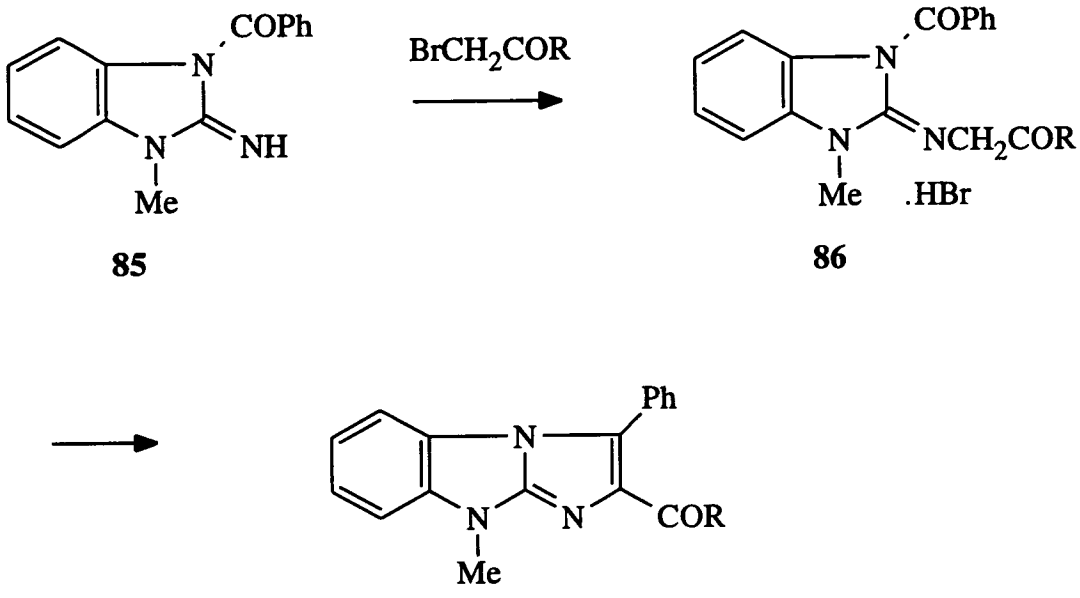
** isolated as hydrochloride salt

1,2-Disubstituted imidazo[1,2-*a*]benzimidazoles are formed in an analogous fashion starting from a prefunctionalised amino moiety. For example Kochergin[31] reported that 1-acylmethyl-2-chlorobenzimidazoles **82** were obtained in high yield by the reaction of 2-chlorobenzimidazole with α-haloketones in the presence of base. When **82** is heated with primary amines then the 1,2-disubstituted product **84** is formed by the simultaneous nucleophilic substitution and dehydration in 50-90% yields (Scheme 25).



Scheme 25

Synthesis of 2,3,9-trisubstituted imidazo[1,2-*a*]benzimidazoles from α-halocarbonyl compounds is also known.[32] Heating 3-benzoyl-2-imino-1-methylbenzimidazoline **85** with α-bromoketones in DMF gave the *N*-(acylmethyl)iminium salts **86**. Heating under dehydrating conditions gave the 2-acyl substituted imidazo[1,2-*a*]benzimidazole **87** in 60% yield (Scheme 26).

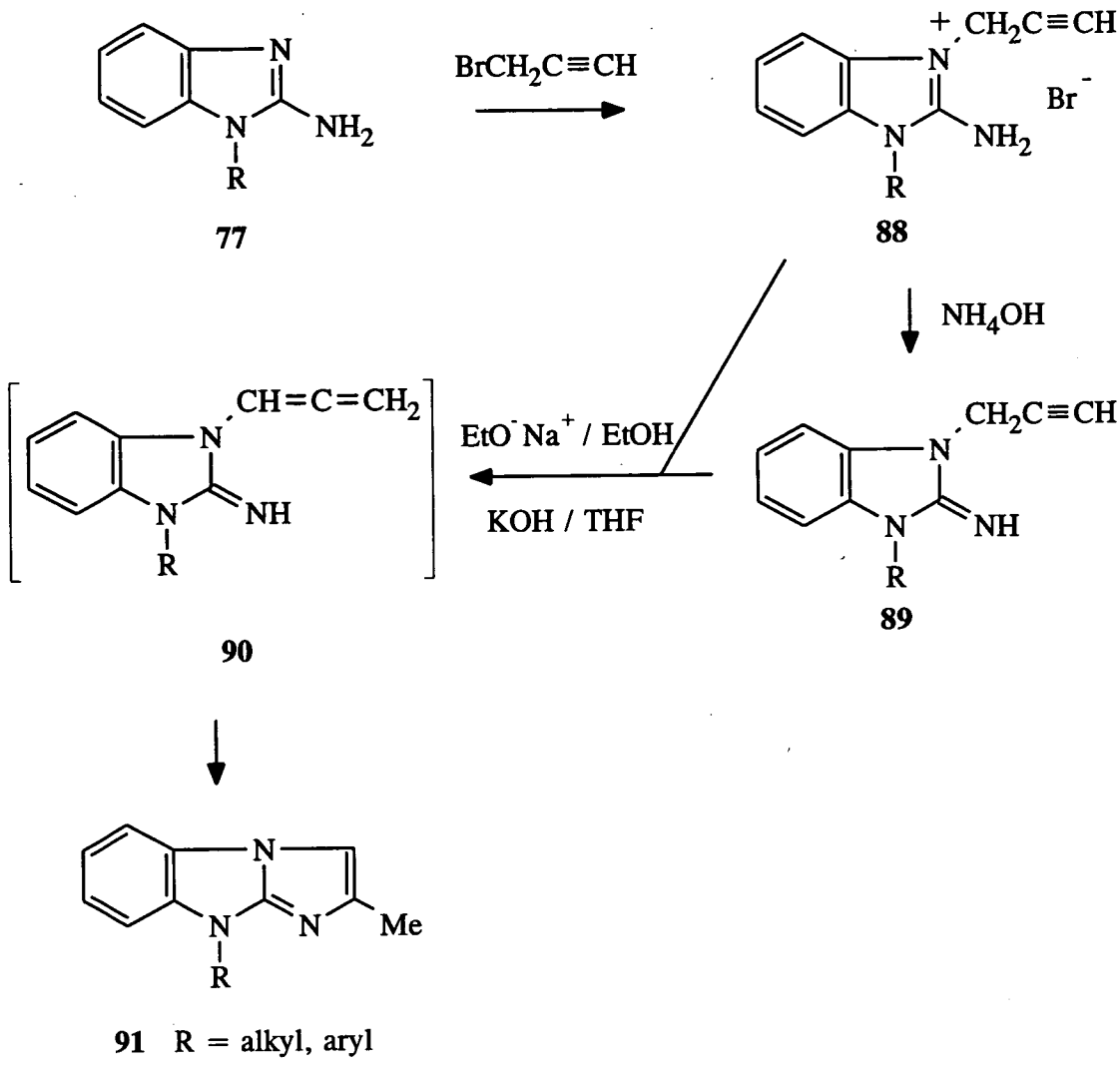


85 **86**

87 R = Me, Ph

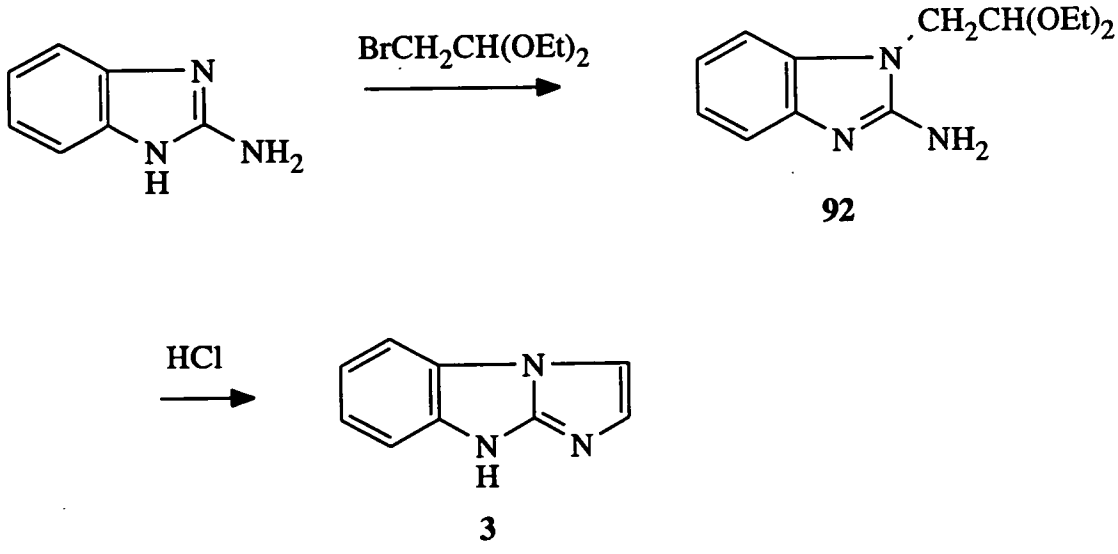
Scheme 26

Simonov and co-workers[33] reacted 1-alkyl-2-aminobenzimidazoles **77** with propargyl bromide to yield the salts **88**. These were readily converted to 1-alkyl-3-(2'-propargyl)-2-iminobenzimidazolines **89** by the action of concentrated ammonium hydroxide. When **88** and **89** are treated with either an alcoholic solution of sodium ethoxide or potassium hydroxide in THF, they undergo prototropic rearrangement to intermediate allenes **90**, which then cyclise to the substituted imidazo[1,2-*a*]benzimidazoles **91** in *ca.*70% overall yield (Scheme 27).



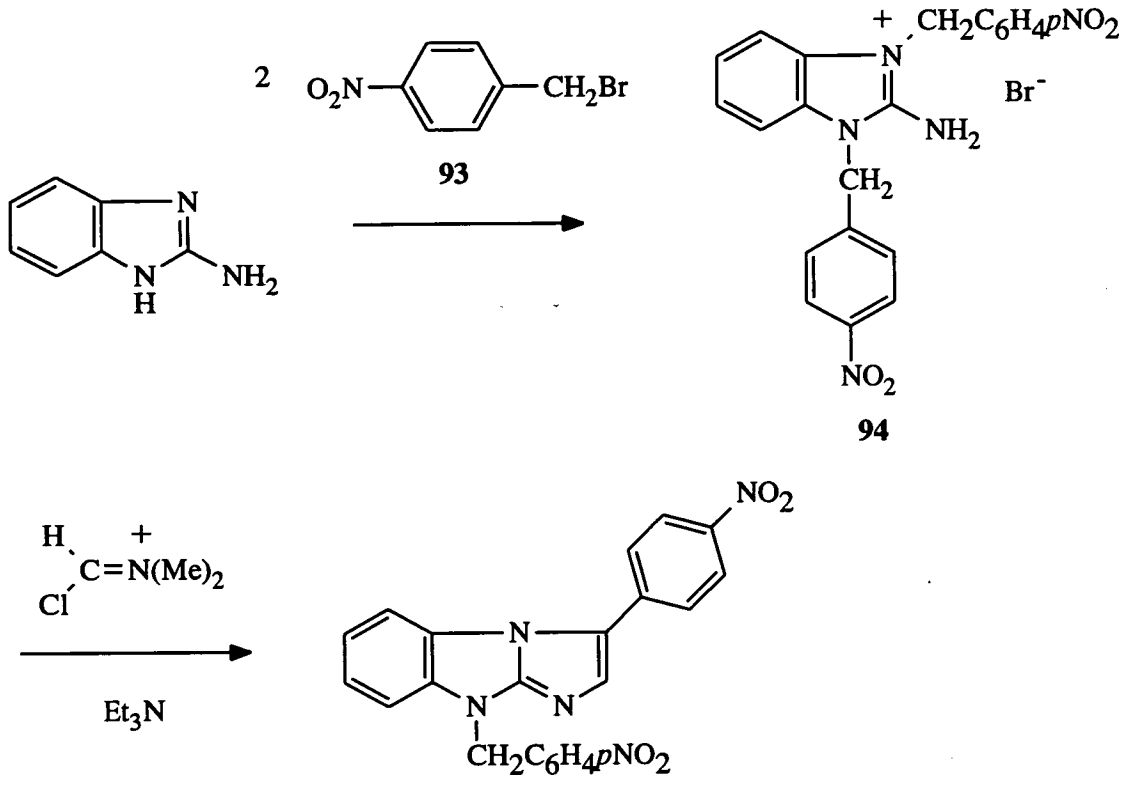
Scheme 27

The synthesis of unsubstituted imidazo[1,2-*a*]benzimidazole **3** was reported by Ogura and co-workers in 1972.[29] The reaction of 2-aminobenzimidazole with bromoacetal gave the intermediate **92** which cyclised under acidic conditions to give the parent **3** in 71% overall yield (Scheme 28).



Scheme 28

A more recent route[34] employs activated 2-aminobenzimidazoles as N-C-N-C synthons for the reaction with formamide chlorides. The reaction of 2-aminobenzimidazole with two equivalents of 4-nitrobenzyl bromide **93** gave the salt **94** in reasonable yield. The 4-nitrobenzyl group serves as a chemically inert but electron withdrawing substituent to acidify the CH_2 function. In the presence of triethylamine, the reaction of the free base of the salt with (chloromethylene)dimethylammonium chloride generated the 3,9-disubstituted imidazo[1,2-*a*]benzimidazole **95** in only 18% yield (Scheme 29).

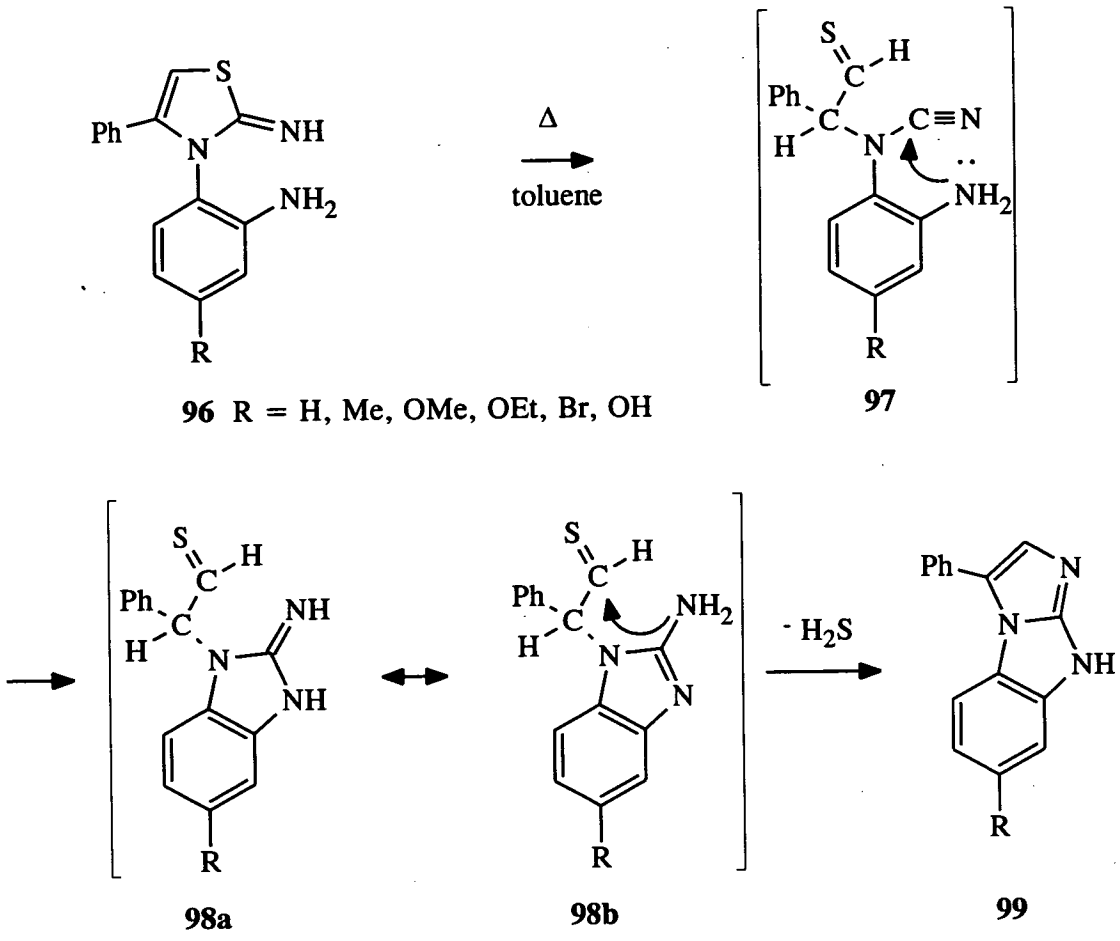


95

Scheme 29

(ii) Two Ring Synthesis of Imidazo[1,2-*a*]benzimidazoles

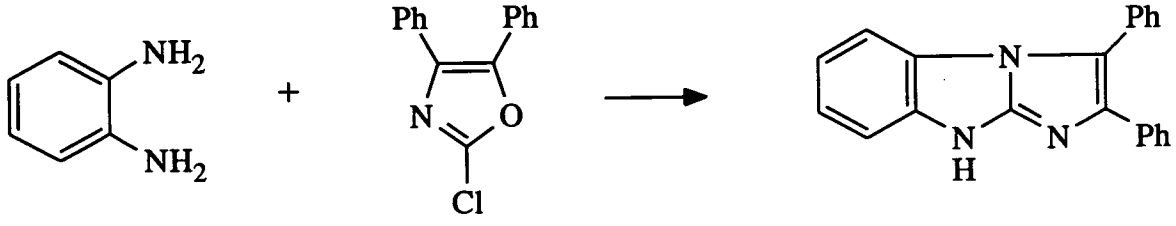
Soni[35] reported the synthesis of new 7-substituted 1*H*-imidazo[1,2-*a*]benzimidazoles **99**. The proposed thermal rearrangement of 3-(2-amino-4-substituted phenyl)-2-imino-4-phenyl-4-thiazoline **96** in toluene gave the intermediate ring-opened product **97**. Nucleophilic attack of the amino group gave the imine **98a.** Cyclisation of the tautomeric amine **98b** with extrusion of H_2S resulted in the formation of 3,7-disubstituted imidazo[1,2-*a*]benzimidazoles **99** in moderate yield (Scheme 30).



Scheme 30

(iii) Miscellaneous Syntheses

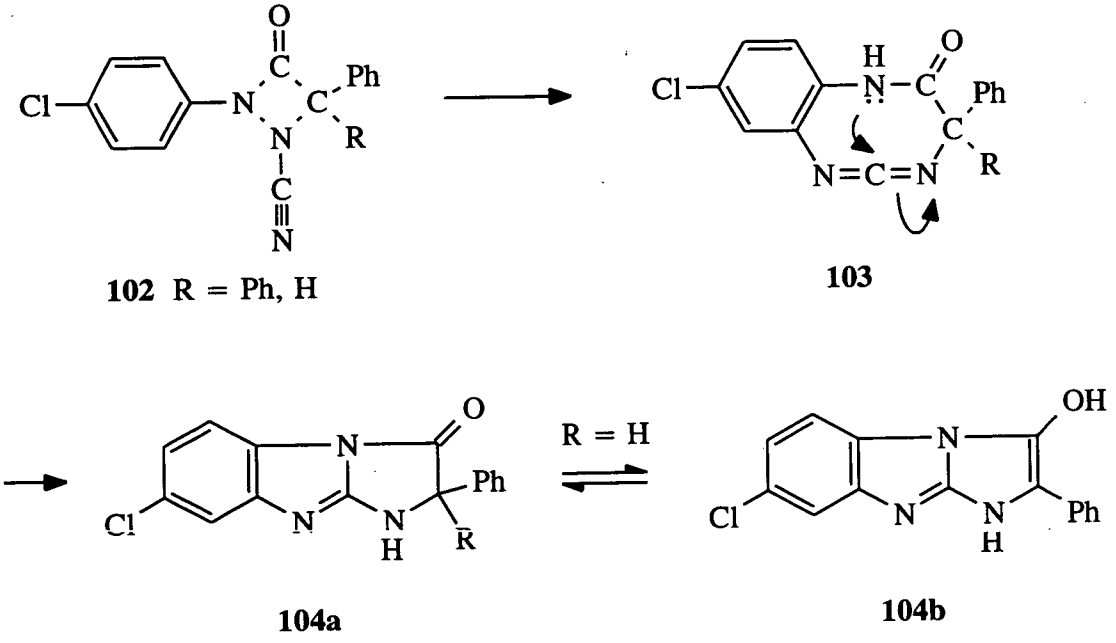
The first example of the imidazo[1,2-*a*]benzimidazole system appeared in the literature in 1959. Gompper and Effenberger[36] proposed the synthesis of 2,3-diphenylimidazo[1,2-*a*]benzimidazole **101** from the reaction of *o*-phenylenediamine with 2-chloro-4,5-diphenyloxazole **100** (Scheme 31).



100 **101**

Scheme 31

The generation of imidazo[1,2-*a*]benzimidazoles has been achieved *via* intramolecular cyclisation of cyclic carbodiimides.[37] In a study of the thermal rearrangement of 1-aryl-2-cyano-3,3-diphenyldiazetidin-4-ones **102**, Bird found that conversion to the cyclic carbodiimide **103** proceeds *via* a [3.3]-sigmatropic rearrangement. Intramolecular cyclisation occurred spontaneously to give the imidazo[1,2-*a*]benzimidazole product **104** (Scheme 32).

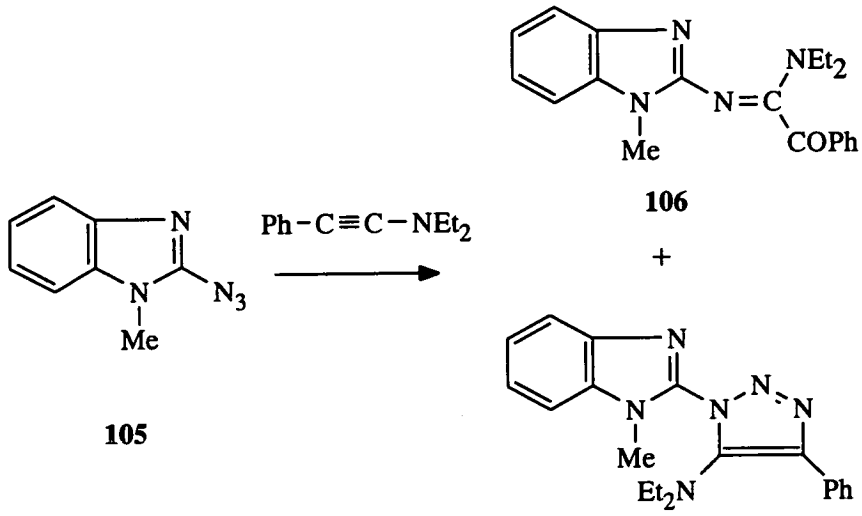


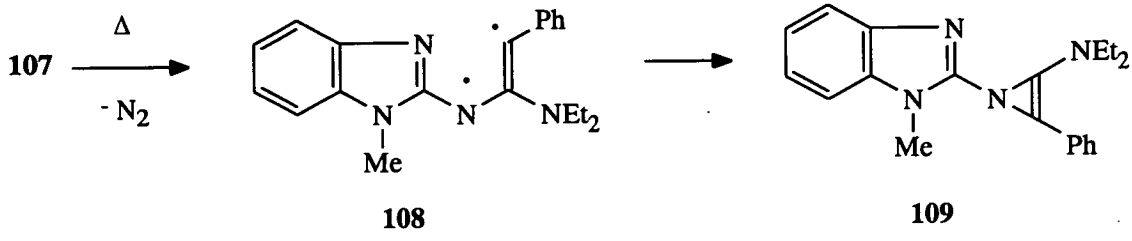
102 R = Ph, H **103**

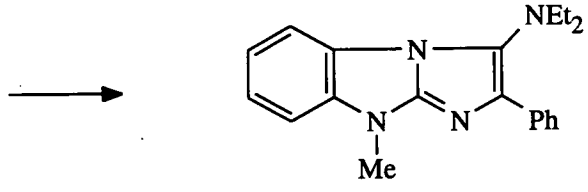
104a **104b**

Scheme 32

Shiokawa and Ohki[38] investigated cycloaddition reactions of 2-azido-1-methylbenzimidazole **105** with a variety of substrates. Reaction with *N,N*-diethylphenylethynylamine in boiling THF regioselectively gave the triazole **107** in 86% yield. The structure of **107** was deduced on the basis of spectroscopic data and the formation of amidine **106** on thermal decomposition. Formation of product **110** cannot occur through loss of a nitrogen molecule followed by recyclisation hence it is suggested that thermal decomposition, with elimination of nitrogen, leads to the biradical species **108**. Radical recombination generates the 1-azirine compound **109** which rearranges to **110** in 21% overall yield. The proposed structure was supported by spectral data and independent synthesis (Scheme 33).


Ph–C≡C–NEt2
Me
N3
NEt2
N=C
COPh
106
+
Et2N
Ph
105
107


107
Δ
- N2
Ph
NEt2
Me
108
109


NEt2
Ph
Me
110

Scheme 33

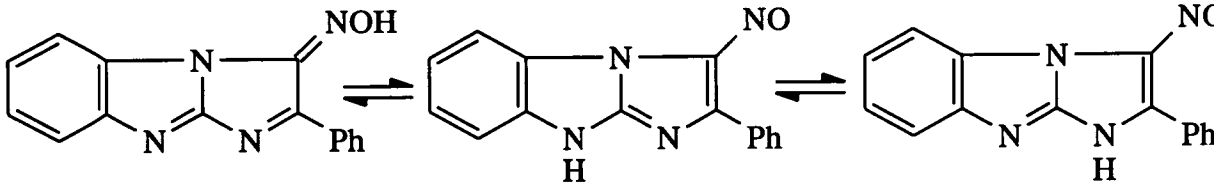
2. Physical Properties of Imidazo[1,2-*a*]benzimidazoles

(i) Infrared

Experimental observations reveal absorption maxima at 3200-2600 cm^{-1} (NH) [35] and 1640-1600 cm^{-1} (C=N).[29, 32, 39]

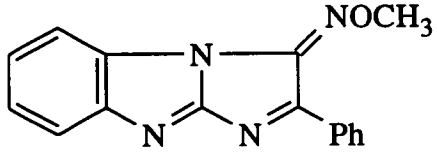
(ii) Ultraviolet

Ultraviolet spectra of imidazo[1,2-*a*]benzimidazoles generally show three absorption maxima at *ca.* 245 nm, 270 nm and 280 nm.[35] Kuz'menko and co-workers[40] used ultraviolet/visible spectra to determine the tautomeric predominance in the novel 3-nitroso-2-phenylimidazo[1,2-*a*]benzimidazole system **111a,b** and **c**.

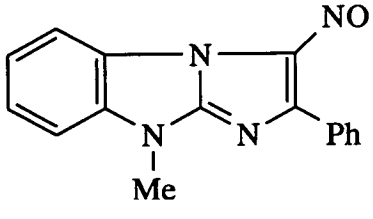


111a **111b** **111c**

Methylation of **111a** and **111b** results in fixed model structures **112** and **113** respectively as confirmed by ^1H NMR. **112** and **111** have similar UV/vis spectra indicating the predominance of the **111a** tautomer in the system.



112

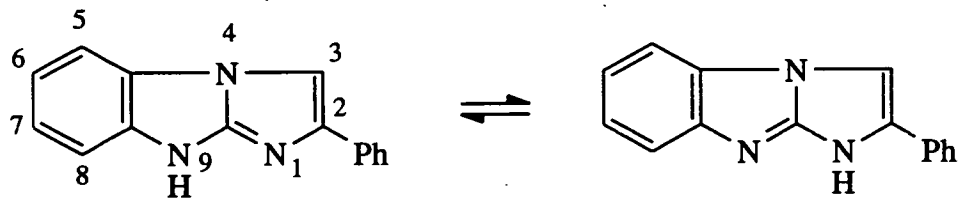


113

(iii) Quantum mechanical calculations

The π-electron density within both tautomers of 2-phenylimidazo[1,2-*a*]benzimidazole **81a** was calculated by the Hückel linear combination of atomic

orbitals molecular orbital method.[39] The greatest π-electron density was found to exist at the 2- and 3-positions of 9*H*-2-phenylimidazo[1,2-*a*]benzimidazole **81a(i)**. This is in agreement with experimental observations which show the high reactivity of the 3-position in electrophilic substitution reactions.



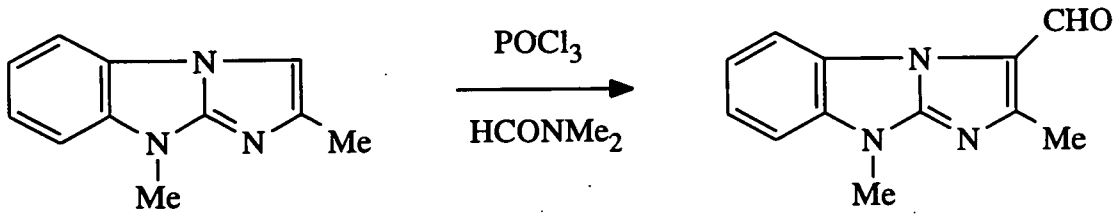
81a(i) **81a(ii)**

3. Chemical Reactivity of Imidazo[1,2-*a*]benzimidazoles

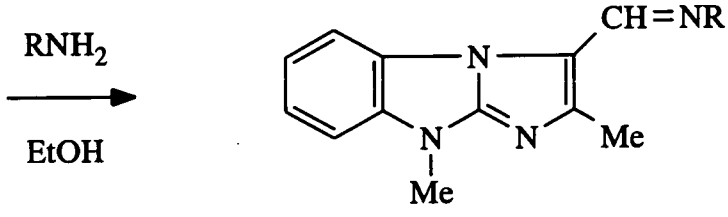
(i) Electrophiles

Imidazo[1,2-*a*]benzimidazoles tend to undergo electrophilic attack at nitrogen atom or at an electron rich carbon atom. Electrophilic substitution reactions occur more readily in the 9*H* tautomer system **81a(i)** than in the 1*H* tautomer system **81a(ii)** as a consequence of the donation of electron density from the middle imidazole ring to the terminal ring.[39]

The Vilsmeier formylation reaction may be carried out on 2,9-dimethylimidazo[1,2-*a*]benzimidazole **81c** with phosphorus oxychloride and *N,N*-dimethylformamide to give the aldehyde **114** in 70% yield.[41] Further reaction with appropriate amines gave a number of imines **115** in variable yield (Scheme 34).



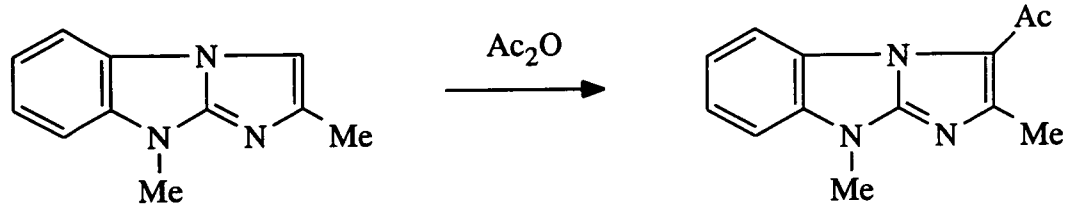
81c **114**



115 R = aryl

Scheme 34

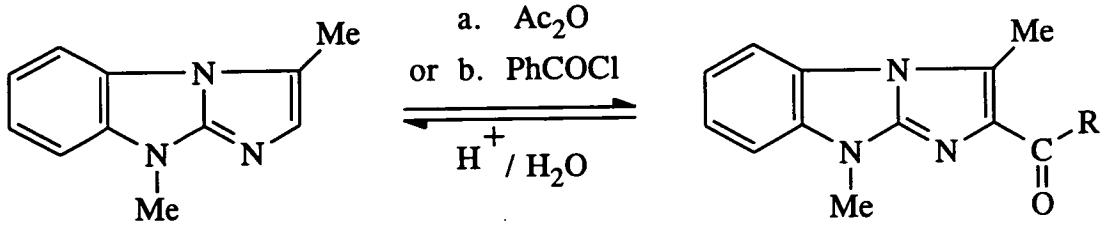
Acetylation of 2,9-dimethylimidazo[1,2-a]benzimidazole **81c** with acetic anhydride in the presence of anhydrous sodium acetate gave rise to the 3-acetylated derivative **116** (Scheme 35).[34]



81c **116**

Scheme 35

Similarly, acylation of 3,9-dimethylimidazo[1,2-a]benzimidazole **117** under the same conditions or with benzoyl chloride in the presence of pyridine affords the corresponding acylated derivatives **118** both of which are cleaved by acid hydrolysis (Scheme 36).[32]

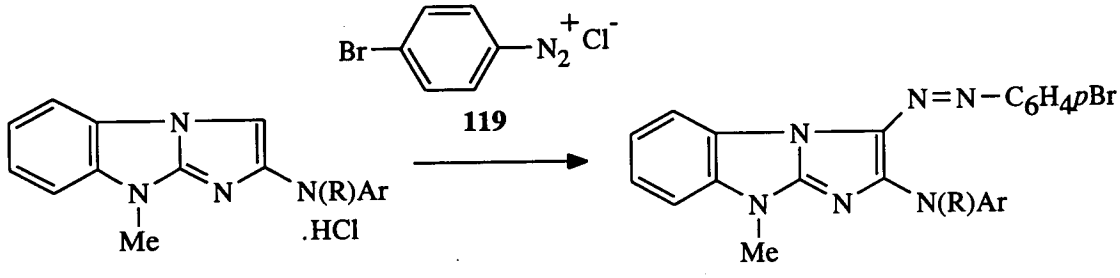


117 **118** a. R = Me

b. R = Ph

Scheme 36

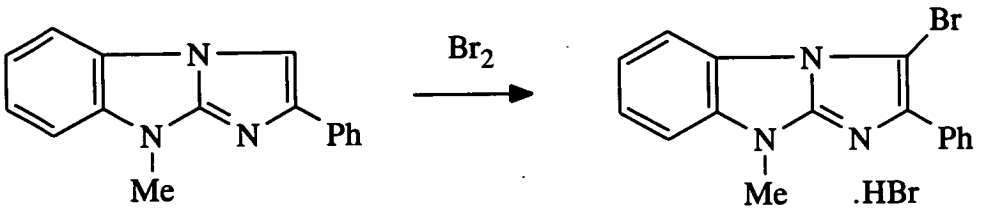
As is typical for imidazo[1,2-*a*]benzimidazole systems, the amines **81d** and **81e** undergo diazo coupling with the diazonium salt of *p*-bromoaniline **119** at the C-3 position to give good yields of azo derivatives **120** (Scheme 37).[42]



81 R = H, Me **120**

Scheme 37

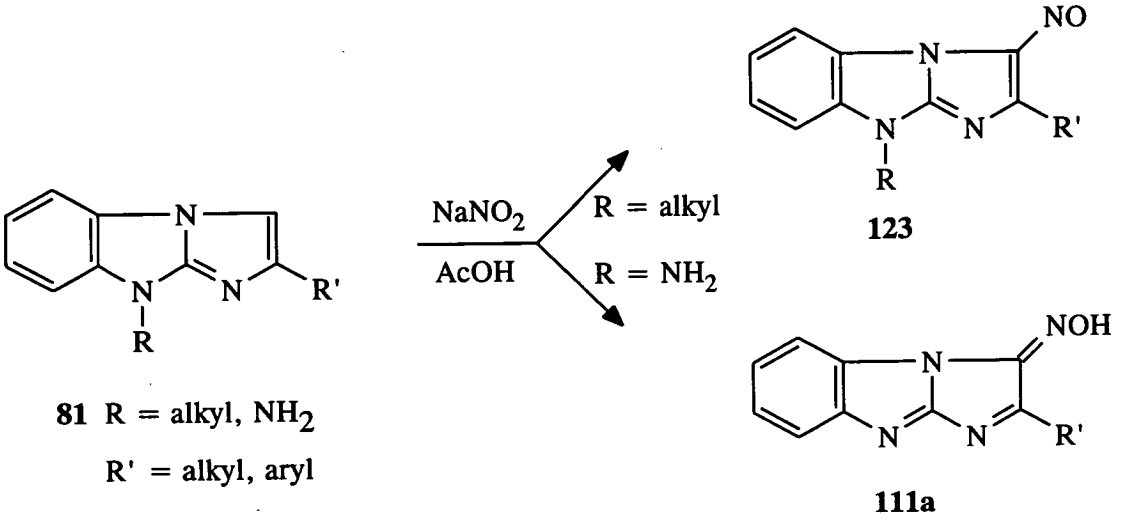
Bromination of 2-phenyl-9-methylimidazo[1,2-a]benzimidazole **121** was effected with molecular bromine in dry chloroform to give a quantitative yield of the salt **122** (Scheme 38).[43]



121 **122**

Scheme 38

The nitrosation of 2,9-disubstituted imidazo[1,2-a]benzimidazoles **81** with sodium nitrite in acetic acid leads to the 3-nitroso derivatives **123**.[44] If the 9-position is substituted with an amino group, then deamination occurs in addition to nitrosation, and the 3-hydroxyimino derivative **111a** is obtained (Scheme 39). The tautomeric predominance was confirmed by UV/vis spectra [section D.2].[40]



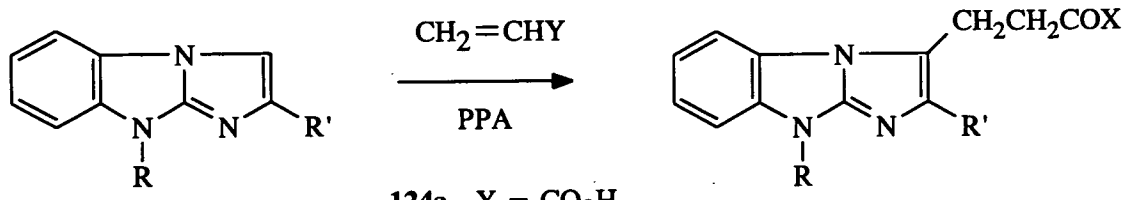
81 R = alkyl, NH_2
R' = alkyl, aryl

123

111a

Scheme 39

The addition reaction of acrylic acid, its ester and nitrile **124a-c** to 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles **81** in polyphosphoric acid (PPA) leads to imidazo[1,2-*a*]benzimidazol-3-ylpropionic acid and derivatives **125a-c** (Scheme 40).[45]



81 R = alkyl
R' = alkyl, aryl

124a. Y = CO_2H
124b. Y = CO_2Me
124c. Y = CN

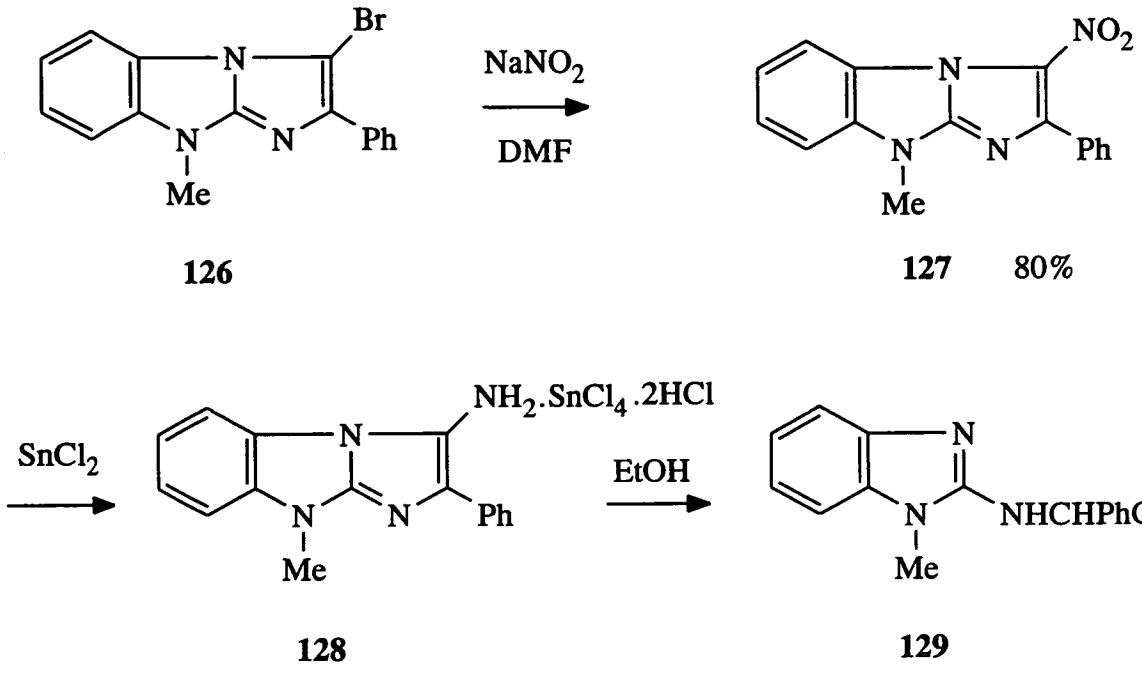
125a. X = OH
125b. X = OMe
125c. X = NH_2

Scheme 40

Simultaneous saponification of the nitrile to the amide **125c** is observed.

(ii) Nucleophiles

Treatment of 3-bromo-9-methyl-2-phenylimidazo[1,2-*a*]benzimidazole **126** with sodium nitrite in DMF resulted in nucleophilic displacement to give the nitro derivative **127** in 80% yield.[43] A following report[46] by the same authors outlined the reaction of **127** with stannous chloride to give the complex **128** which, on heating in ethanol, ring opened to give the acid **129** (Scheme 41).

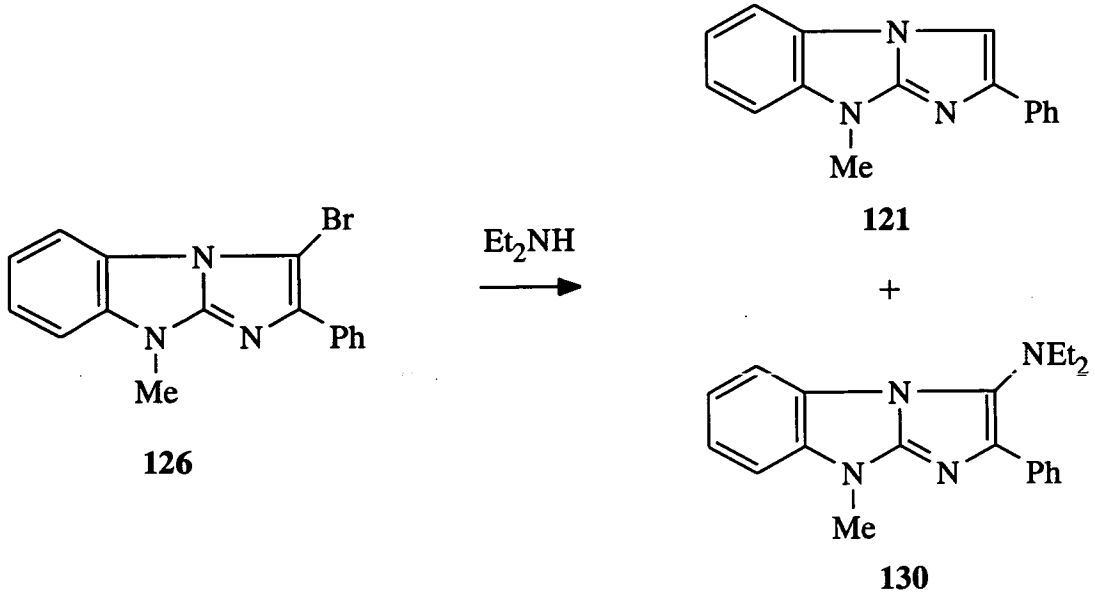


126 **127** 80%

128 **129**

Scheme 41

Reaction of **126** with diethylamine in a sealed tube gave a mixture of the debrominated product **121** and the amine **130** in very low yield (Scheme 42).[38]



Scheme 42

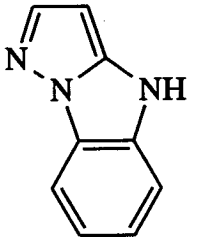
RESULTS AND DISCUSSION

A. NOVEL ROUTES TO [5,5,6]AZAPENTALENE SYSTEMS

1. 4*H*-Pyrazolo[1,5-*a*]benzimidazoles

a. INTRODUCTION

Derivatives of 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** are known to be magenta couplers in colour photography,[1] although there are relatively few references to the parent system in the literature. The main thrust of the project was to synthesize 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** and its derivatives using alternative gas phase methodology to the solution phase routes already reported.[7]



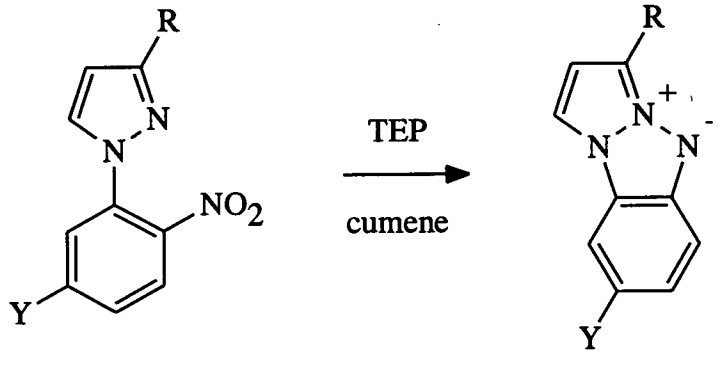
1

The work described centres on the generation of nitrenes *via* flash vacuum pyrolysis of azides. Thermolysis and photolysis studies have been conducted previously[47] in the solution phase, however work in the gas phase is unreported.

Aromatic nitrenes are uncharged, electron deficient reactive intermediates with six electrons in their outer shell. Two of these electrons contribute to a formal carbon-nitrogen single bond, two are present in a lone-pair orbital, and the remaining two may exist either as a pair in a non-bonding orbital yielding an electrophilic singlet nitrene, or they may exist unpaired in separate orbitals giving the biradical triplet nitrene. Aryl nitrenes have a triplet ground state, however thermolysis of an aromatic azide affords the high energy singlet species which may then undergo intersystem

crossing to generate the triplet ground state. Photochemical decomposition has been researched more extensively[48-51] due to the differing reactivities of the singlet and triplet states which may be selected through the use of sensitizers and solvents.

Meth-Cohn and co-workers[48] elaborated on studies by Lynch and Hung[52] relating to the deoxygenative cyclisation of 1-(2-nitrophenyl)pyrazole **131** with triethyl phosphite (TEP) to give pyrazolobenzotriazole **132** albeit in low yield. They demonstrated the electrophilic character of the singlet nitrene by its willingness to attack nitrogen nucleophiles. Enhancement of the electrophilicity of the nitrene by the introduction of a *p*-chloro substituent and/or increasing the nucleophilicity of the pyrazole N-2 with the inclusion of a methyl group in position 3 resulted in an increase in the yield of singlet derived product **132** (Scheme 43).



131 **132**

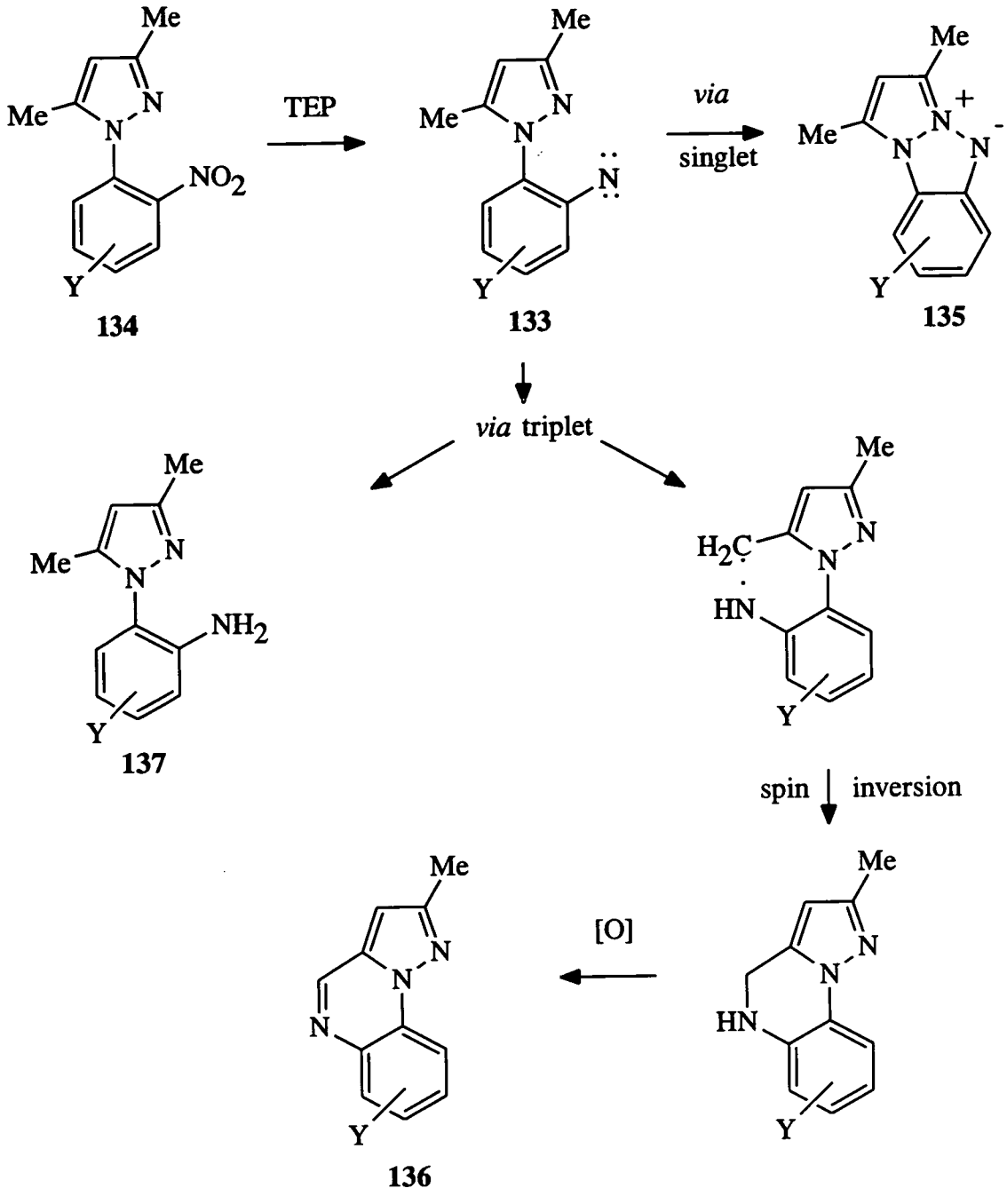
131	Y	R	Yield of **132**
a	H	H	15%
b	Cl	H	21%
c	H	Me	29%
d	Cl	Me	65%

Scheme 43

The work on substituent effects was extended to include studies on competitive cyclisation reactions of singlet and triplet nitrenes for the substituted 1-(2-nitrenophenyl)-3,5-dimethylpyrazole system **133**.[49] Generation of the nitrene was again effected by deoxygenation of the nitro precursor **134** with TEP. The system was chosen to enable singlet attack at pyrazole N-2 or reaction of the triplet at the methyl in position 5. In these cases the products are pyrazolobenzotriazoles **135** and pyrazoloquinoxalines **136** respectively. Other products isolated were the aminophenylpyrazoles **137**, generated by intermolecular H-atom abstraction *via* the triplet nitrene. A variety of substituents *para* and *meta* to the incipient nitrene were incorporated to alter the singlet/triplet nitrene ratio (Scheme 44). Electron-withdrawing groups, Cl or Br, *para* to the nitrene increase its electrophilicity resulting in enhanced singlet derived pyrazolobenzotriazole **135** yields. Electron-releasing substituents, *p*-NMe_2 or *p*-OMe, conjugate with and stabilise the nitrene which may then undergo spin inversion to the ground state triplet nitrene. In this case increased yields of triplet derived pyrazoloquinoxalines **136** and amines **137** are observed.

Substituents of all types *meta* to the nitrene were shown to enhance the proportion of singlet products to the exclusion of triplet products for both types of substituents but this effect was less easily rationalised.

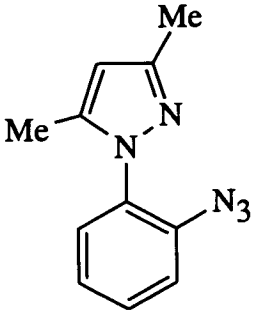
Additional deoxygenations carried out in solvents containing a heavy atom, for example bromobenzene, showed a slight increase in the ratio of triplet derived products through collisional deactivation.



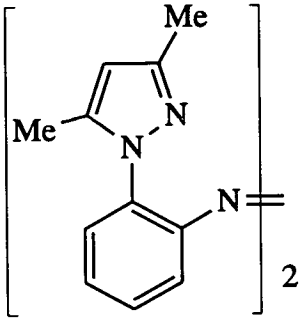
Scheme 44

Further investigations into the nitrene **133** generated by steady-state irradiation of substituted pyrazolobenzotriazoles **135**, and also thermal or photochemical decompostion of the azide **138** have been recently published.[50,53] These concur with

the results reported previously and elaborate on possible other nitrene reaction pathways. Photocleavage of 1,3-dimethylpyrazolobenzotriazole **135** (Y = H) was achieved by prolonged irradiation to yield the azo-derivative **139** in addition to the pyrazoloquinoxaline **136** and the amine **137** already mentioned.



138

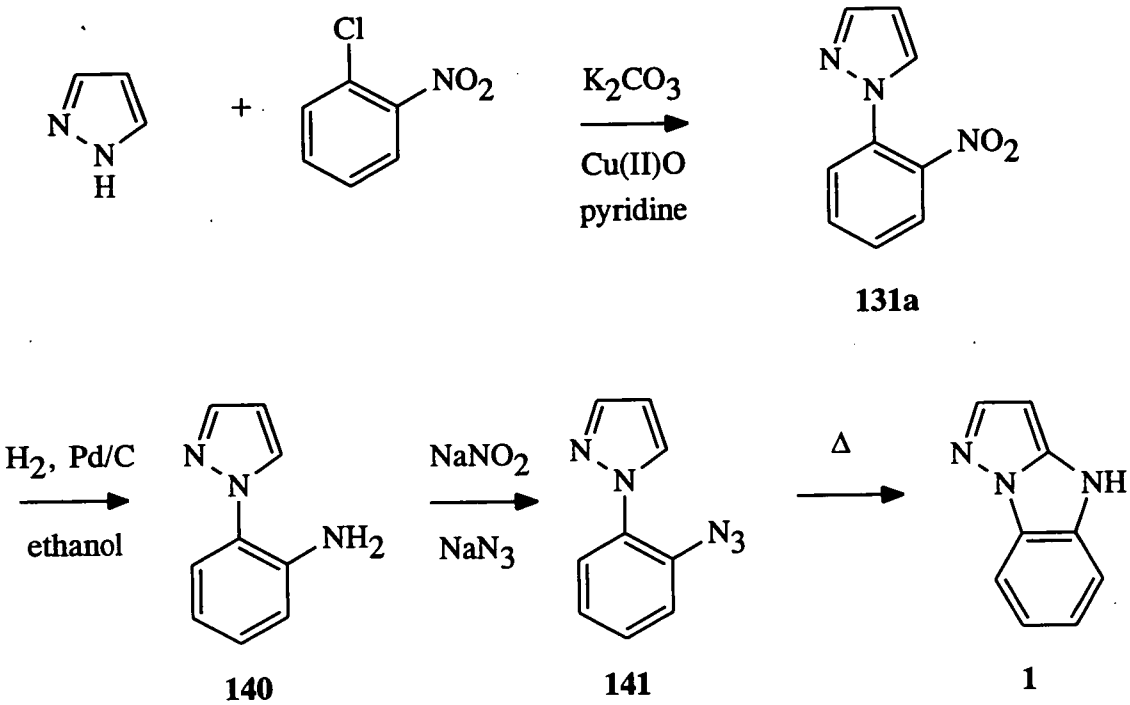


139

Products from photolysis of the azide **138** may also be influenced by the use of sensitizers and solvents. The inclusion of acetophenone, a triplet sensitizer, results in enhanced formation of triplet derived products whereas the use of pyrene, a well known triplet quencher and singlet photosensitizer,[54] leads to vastly increased singlet derived product ratios.

b. SYNTHESIS OF 4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE

The reaction scheme for the synthesis of 1-(2-azidophenyl)pyrazole **141** is similar to that reported in the literature (Scheme 45).[47]

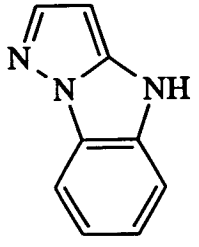


Scheme 45

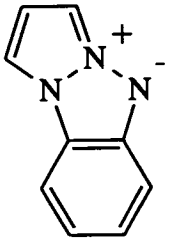
The generation of nitro compound **131a** was effected in 66% yield by the copper-mediated Ullmann condensation of pyrazole and *o*-chloronitrobenzene in pyridine. The amine **140** was obtained in almost quantitative yield by medium pressure hydrogenation (45 p.s.i.) of the nitro compound **131a**. Diazotisation of the amine **140** with sodium nitrite followed by reaction with sodium azide afforded the azide precursor **141** in good yield as reported by Suschitzky and co-workers.[47]

Flash vacuum pyrolysis, at 400-550°C, of the azide **141** gave three products; the desired pyrazolobenzimidazole **1**, pyrazolobenzotriazole **132a** and quinoxaline **143**. Formation of pyrazolobenzimidazole **1** from nitrene insertion into the C(5)-H bond

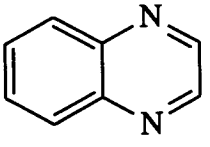
has never been achieved in the solution phase and the formation of quinoxaline was totally unexpected. The three products all show characteristic peaks in their ^{1}H nmr spectra which were used for identification purposes. Proton H-3 of pyrazolobenzimidazole **1** is shielded since this position is in conjugation with lone pair electrons on nitrogen, and appears as a doublet at δ_H 5.8. Quinoxaline **143** has a singlet at δ_H 8.9 corresponding to protons H-2 and H-3 whereas the spectrum of pyrazolobenzotriazole (PBT) **132a** reveals a characteristic multiplet at δ_H 6.9.



1



132a



143

The pyrolysis of **141** was carried out at various temperatures to determine the effect of temperature on the proportions of components of the pyrolysate. Thus by comparison of the characteristic integrals the optimum temperature for generation of desired pyrazolobenzimidazole (PBI) **1** could be obtained (Table 3).

Table 3: Relative proportions of pyrolysate components at various temperatures

Temp./ °C	PBI **1**	PBT **132a**	quinoxaline **143**
300	22%	78%	0%
400	23%	76%	1%
425	23%	75%	2%
450	27%	61%	13%
475	29%	51%	20%
500	30%	30%	40%
525	23%	17%	60%
600	17%	-	83%
700	-	-	100%

At low temperatures pyrazolobenzotriazole **132a** formation dominates and at higher pyrolysis temperatures quinoxaline **143** formation dominates with a relatively constant background of pyrazolobenzimidazole **1** until 600°C (Figure 2).

These observations may be explained by invoking the singlet/triplet nitrene theory introduced previously. The desired target pyrazolobenzimidazole **1** is formed presumably *via* triplet nitrene insertion into the C(5)-H bond of the pyrazole. The isomeric pyrazolobenzotriazole **132a** may be a product from electrophilic singlet nitrene attack on the N(2) lone pair electrons. Quinoxaline **143**, the sole product at high temperatures, is formed *via* a secondary process involving loss of HCN and not directly from the azide generated nitrene.

Singlet nitrenes have greater energy than triplet nitrenes and thus at higher furnace temperatures, high energy singlet nitrene derived products might be expected to dominate. It may therefore be assumed that quinoxaline **143** formation is the

ultimate result of a singlet nitrene initiated process. At higher temperatures the formation of triplet derived pyrazolobenzimidazole **1** is inhibited indicating that the opportunity for intersystem crossing has been reduced. The stability of pyrazolobenzimidazole **1** was independently verified by its pyrolysis at high temperatures (600°C and 700°C) giving only unreacted starting material, hence it may be assumed that the desired product **1** and the nitrene **142** are not in equilibrium.

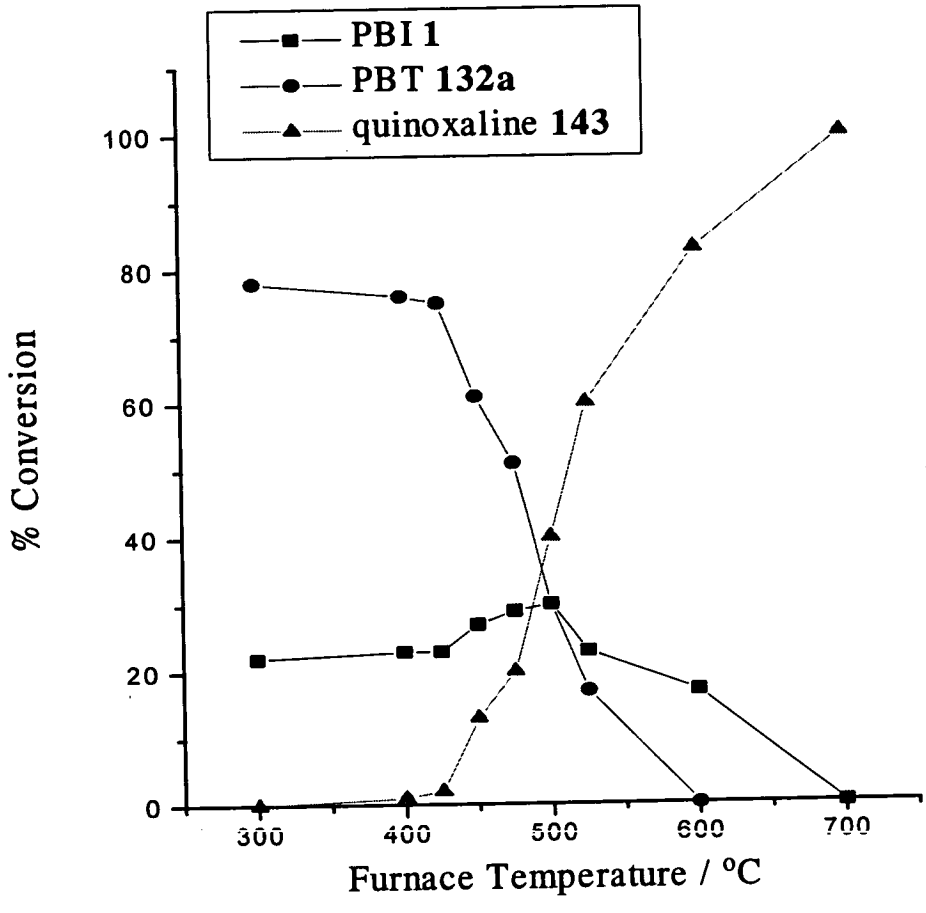


Figure 2: Conversion of Azide **141** to PBI **1**, PBT **132a** and quinoxaline **143** as a Function of Pyrolysis Temperature.

From Figure 2, the optimum temperature to obtain a 3:1 mixture of pyrazolobenzotriazole **132a** and desired pyrazolobenzimidazole **1** with no quinoxaline **143** is 400°C. Pyrolysis of azides required the use of a metal inlet oven for safety reasons but no other precautions were taken. Preparative pyrolysis (8.5 mmol) of the azide **141** gave pyrazolobenzotriazole **132a** in 51% yield and pyrazolobenzimidazole **1** in 21% yield after column chromatography. Flash vacuum pyrolysis has provided a novel route to pyrazolobenzimidazole **1**, not accessible *via* the solution phase. In addition, the yield of pyrazolobenzotriazole **132a** is much improved in comparison with the yield of only 15% in the solution phase.[48] These observations indicate the synthetic utility of this technique for a number of systems. Once isolated, the products **1** and **132a** were fully characterised using NMR.

c. INVESTIGATION OF THE MECHANISM AND SCOPE OF 4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE FORMATION

It was initially thought that, once isolated, pyrazolobenzotriazole **132a** could be re-pyrolysed to maximise the yield of the target pyrazolobenzimidazole **1**. Under the conditions of flash vacuum pyrolysis the nitrene could be regenerated and the opportunity for intersystem crossing to triplet nitrene would be made available. This was the case for the photocleavage of substituted and unsubstituted pyrazolobenzotriazole, **135** and **132a** respectively, leading to triplet derived products (Section A.1.a.).[50] Variable temperature pyrolyses of pyrazolobenzotriazole **132a** were carried out to ascertain the effect of furnace temperature on product ratios. Pyrolysis of pyrazolobenzotriazole **132a** gave only unreacted starting material and quinoxaline **143** with no trace of desired pyrazolobenzimidazole **1** (Table 4). It is therefore likely that the quinoxaline **143** generated in the pyrolysis of azide **141** is formed by secondary decomposition of pyrazolobenzotriazole **132a**.

Table 4: Relative proportions of pyrolysate components at various temperatures

Temp./ °C	PBT **132a**	quinoxaline **143**
400	97%	3%
450	97%	3%
500	93%	7%
550	68%	32%
600	34%	66%

The temperature profile is shown in figure 3.

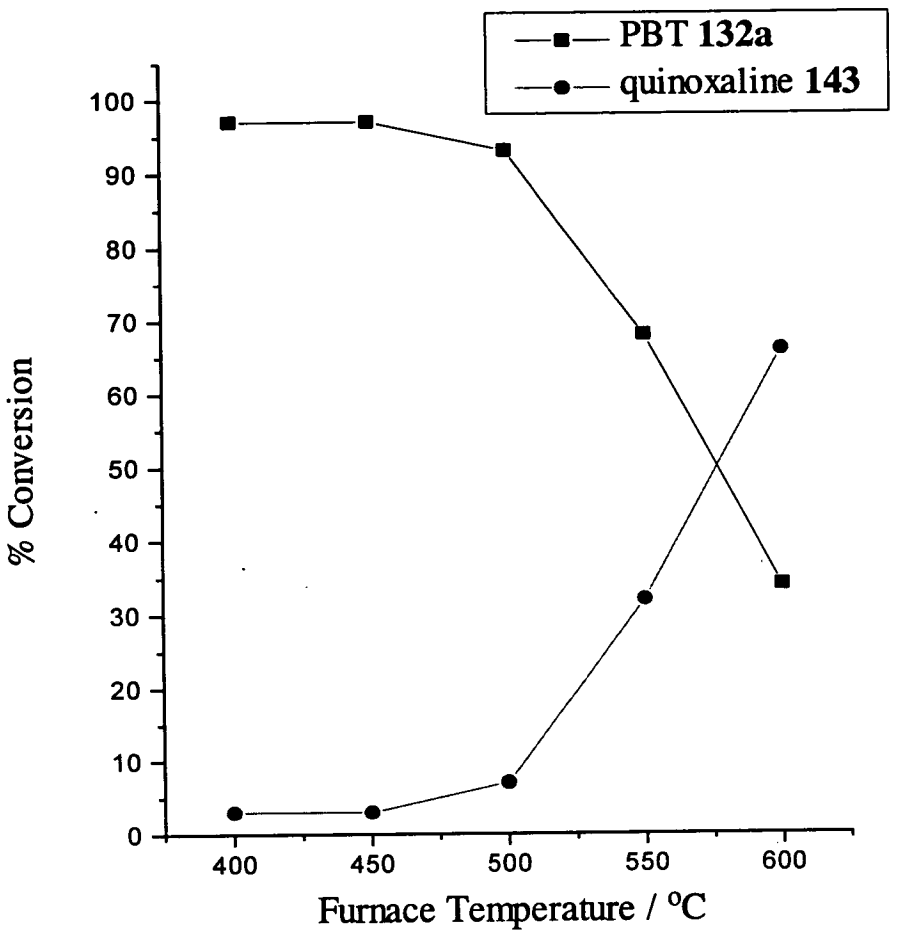
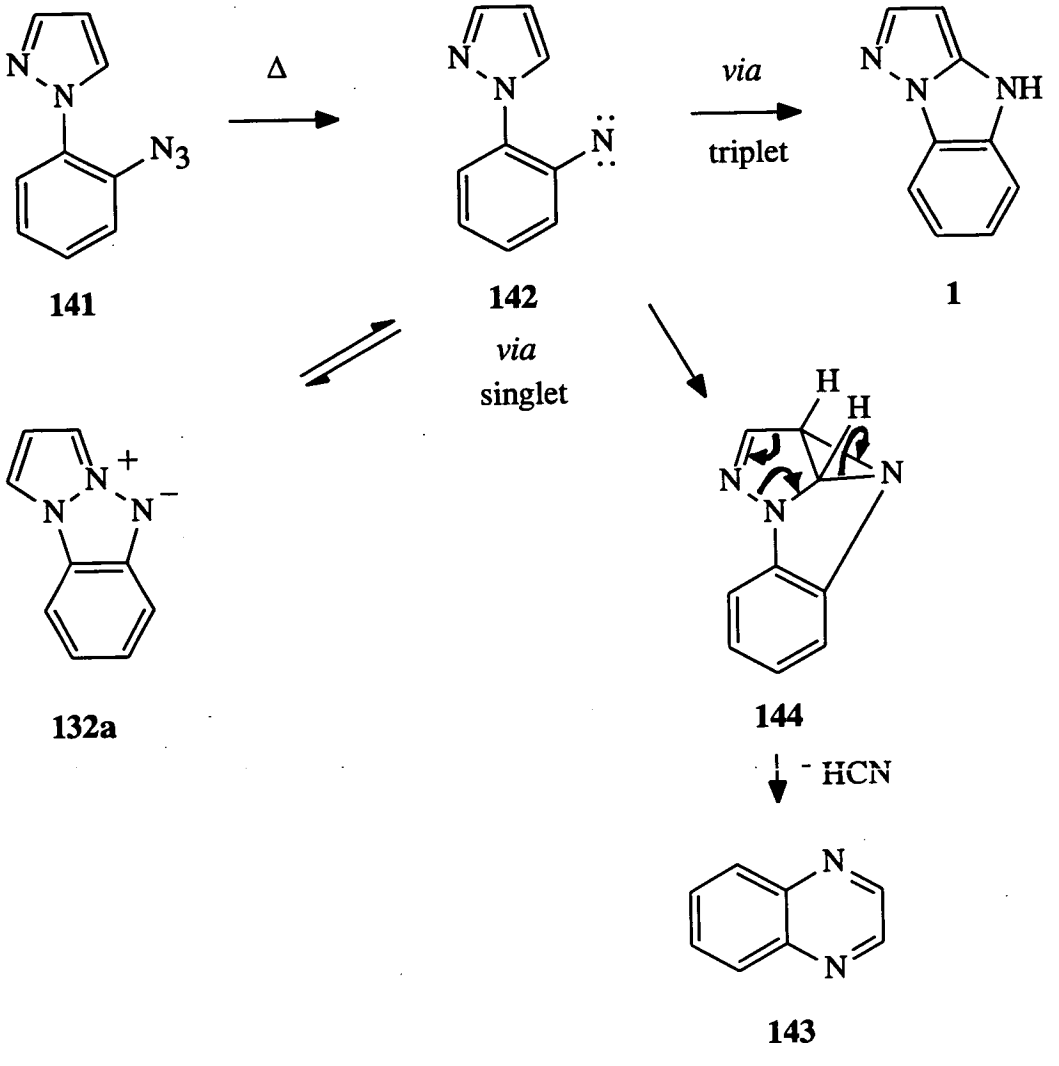


Figure 3: Conversion of PBT **132a** to quinoxaline **143** as a Function of Pyrolysis Temperature

As before, at low temperatures pyrazolobenzotriazole **132a** dominates and at higher temperatures the route to quinoxaline **143** becomes accessible, once there is enough energy in the system, by regeneration of the singlet nitrene. No apparent opportunity for intersystem crossing to triplet nitrene is available. Comparison of the temperature profiles of azide **141** and pyrazolobenzotriazole **132a** pyrolyses reveals a difference in the ease with which the nitrene **142** is converted to quinoxaline **143**. For example,

at 500°C there is 35% formation of quinoxaline **143** from the azide **141** however from pyrazolobenzotriazole **132a** there is only 7% conversion. This may be attributed to chemical activation whereby the nitrene generated from the azide is more vibrationally excited and forms quinoxaline with greater ease.

Pyrazolobenzotriazole **132a** cannot be converted to quinoxaline in one step, hence another intermediate must exist which is derived from the nitrene **142**. If the nitrene adds across the pyrazolic C(4)-C(5) double bond to give the semibullvalene-type structure **144** proposed, then elimination of HCN can occur to afford quinoxaline **143** (Scheme 46).



Scheme 46

Our studies on the $C_9H_7N_3$ energy surface are also summarised in Scheme 46. Pyrolysis of the azide **141** generates a temperature dependent mixture of singlet and triplet nitrenes. At low furnace temperatures the triplet nitrene inserts into the neighbouring C-H bond to give pyrazolobenzimidazole **1** whereas the singlet nitrene is quenched by the adjacent lone pair to give the pyrazolobenzotriazole **132a**. This latter process can be reversed at higher temperatures and under these conditions the singlet nitrene can add to give the intermediate **144** which collapses to quinoxaline **143**. The absence of pyrazolobenzimidazole **1** at 700°C, a temperature at which it is stable, may be a direct consequence of singlet nitrene generation to the exclusion of triplet nitrene formation.

d. NMR SPECTRA

The ^{1}H and ^{13}C spectra of pyrazolobenzimidazole **1** and pyrazolobenzotriazole **132a** have not been recorded in detail and were assigned using Nuclear Overhauser enhancement experiments, decoupling experiments, fully coupled ^{13}C-^{1}H spectra and ^{1}H / ^{13}C correlation spectra.

(i) 4*H*-Pyrazolo[1,5-*a*]benzimidazole 1

Tables 5 and 6 detail ^{1}H and ^{13}C data which have never been reported previously.

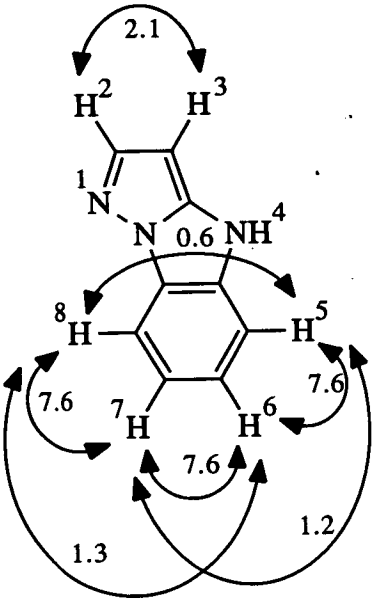
Table 5: ^{1}H NMR Parameters for 4*H*-Pyrazolo[1,5-*a*]benzimidazole **1** in $[^{2}H_6]$ acetone

δ_H / ppm	Coupling Constants / Hz	Assignment	Pattern
10.44	-	NH	br. s
7.76	^{3}J 7.6, ^{4}J 1.3, ^{5}J 0.6	H-8	ddd
7.69	^{3}J 2.1	H-2	d
7.46	^{3}J 7.6, ^{4}J 1.2, ^{5}J 0.6	H-5	ddd
7.28	^{3}J 7.6, ^{4}J 1.3	H-6	td
7.21	^{3}J 7.6, ^{4}J 1.2	H-7	td
5.77	^{3}J 2.1	H-3	d

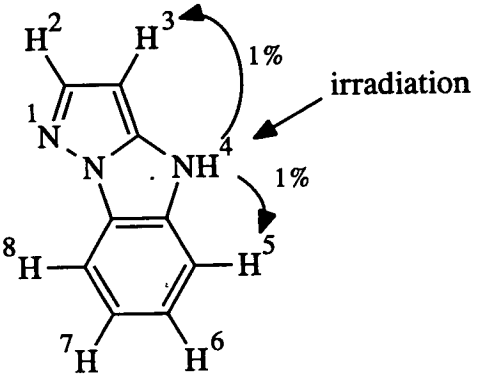
Nuclear Overhauser enhancement experiments showed that irradiation of the NH at δ_H 10.44 resulted in a 1% increase in intensity of the resonances at δ_H 5.77 and δ_H 7.46 corresponding to protons H-3 and H-5 respectively. H-2, at δ_H 7.69, was assigned by comparison of coupling constants. When H-5 was decoupled, the large *ortho* coupling (^{3}J 7.6 Hz) to H-6 at δ_H 7.28 was observed to disappear in addition to

the *meta* coupling (^4J 1.2 Hz) to H-7 at δ_H 7.21. H-8 at δ_H 7.76 was assigned by inspection.

Figure 4: **a.** ^{1}H-^{1}H Coupling Constants (Hz)
and **b.** Nuclear Overhauser Enhancements for
4*H*-Pyrazolo[1,5-*a*]benzimidazole **1**.



a

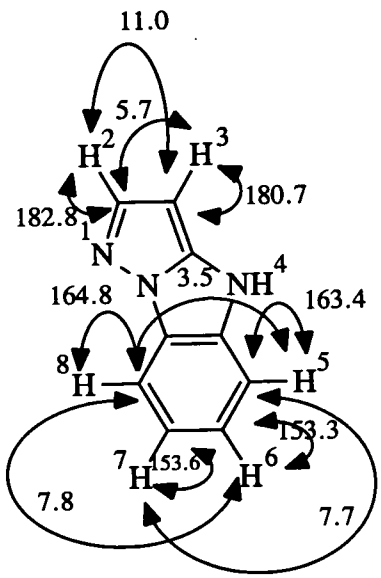


b

Table 6: ^{13}C NMR Parameters for 4*H*-Pyrazolo[1,5-*a*]benzimidazole **1** in $[^2H_6]$ acetone

δ_C / ppm	Coupling Constants / Hz	Assignment	Pattern
143.03	$^1J_{CH}$ 182.8, $^2J_{CH}$ 5.7	C-2	dd
122.43	$^1J_{CH}$ 153.3, $^3J_{CH}$ 7.8	C-6	dd
119.39	$^1J_{CH}$ 153.6, $^3J_{CH}$ 8.0	C-7	dd
111.09	$^1J_{CH}$ 163.4, $^3J_{CH}$ 7.7	C-5	dd
108.94	$^1J_{CH}$ 164.8, $^3J_{CH}$ 7.6, $^4J_{CH}$ 3.5	C-8	ddd
78.76	$^1J_{CH}$ 180.7, $^2J_{CH}$ 11.0	C-3	dd

Figure 5: ^{13}C-^1H NMR Coupling Constants (Hz) for 4*H*-Pyrazolo[1,5-*a*]benzimidazole **1**



The ^{13}C spectrum was assigned using 2D ^1H / ^{13}C correlation experiments. A fully coupled ^{13}C-^1H spectrum allowed assignment of all long range couplings by inspection.

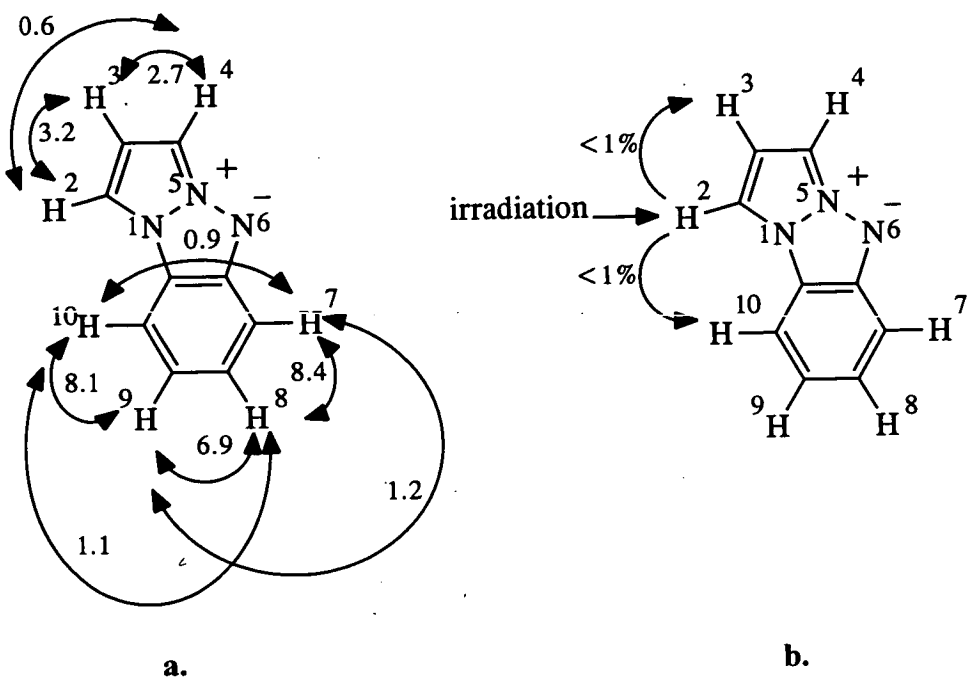
(ii) **Pyrazolo[1,2-*a*]benzotriazole 132a**

Tables 7 and 8 detail ^{1}H and ^{13}C data.

Table 7: ^{1}H NMR Parameters for Pyrazolo[1,2-*a*]benzotriazole **132a** in $[^{2}H_6]$ acetone

δ_H / ppm	Coupling Constants / Hz	Assignment	Pattern
8.14	^{3}J 3.2, ^{4}J 0.6	H-2	dd
7.86	^{3}J 8.1, ^{4}J 1.1, ^{5}J 0.9	H-10	dt
7.77	^{3}J 2.7, ^{4}J 0.6	H-4	dd
7.38	^{3}J 8.4, ^{4}J 1.2, ^{5}J 0.9	H-7	ddd
7.33	^{3}J 8.4, ^{3}J 6.9, ^{4}J 1.1	H-8	ddd
6.930	^{3}J 3.2, 2.7	H-3	dd
6.926	^{3}J 8.1, ^{3}J 6.9, ^{4}J 1.2	H-9	ddd

Figure 6: **a.** ^{1}H-^{1}H Coupling Constants (Hz) and **b.** Nuclear Overhauser Enhancements for Pyrazolo[1,2-*a*]benzotriazole **132a**



a. **b.**

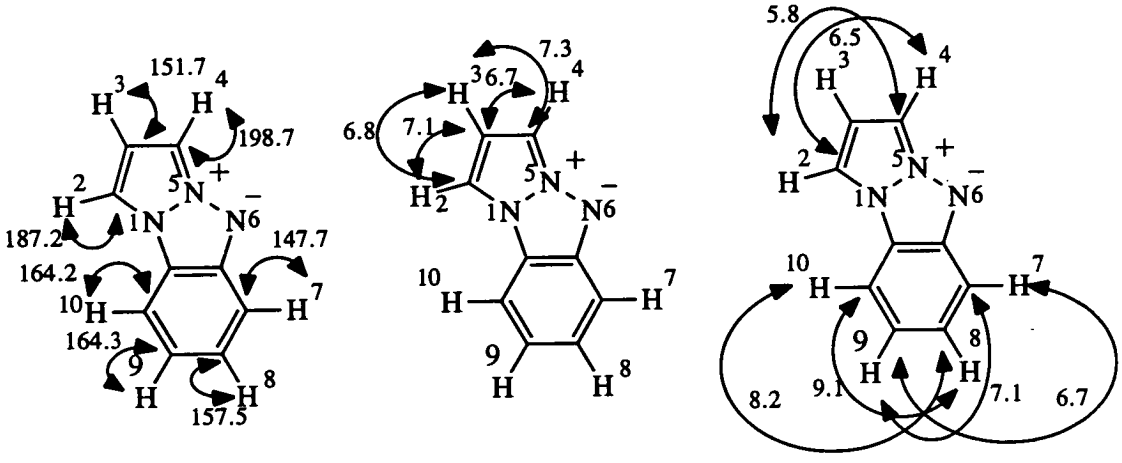
Irradiation of the proton at δ_H 8.14 showed small but detectable enhancements of less than 1% at H-3 and a benzenoid proton at δ_H 7.86 corresponding to H-10, thus the irradiated proton must be H-2. Decoupling of H-2 resulted in the loss of a large coupling (^3J 3.2 Hz) to H-3 and a small coupling (^4J 0.6 Hz) to H-4 at δ_H 7.77. Decoupling experiments on the benzenoid protons resulted in full assignment of all protons.

The ^{13}C spectrum was assigned using 2D ^1H / ^{13}C correlation experiments and the fully coupled ^{13}C-^1H spectrum allowed assignment of all long range couplings by inspection.

Table 8: ^{13}C NMR Parameters for Pyrazolo[1,2-*a*]benzotriazole **132a** in [$^2H_6$] acetone

δ_C / ppm	Coupling Constants / Hz	Assignment	Pattern
125.14	$^1J_{CH}$ 157.5, $^3J_{CH}$ 8.2	C-8	dd
114.70	$^1J_{CH}$ 164.3, $^3J_{CH}$ 6.7	C-9	dd
111.41	$^1J_{CH}$ 147.7, $^3J_{CH}$ 7.1	C-7	dd
109.53	$^1J_{CH}$ 164.2, $^3J_{CH}$ 9.1	C-10	dd
108.30	$^1J_{CH}$ 151.7, $^2J_{CH}$ 6.7, 7.1	C-3	dd
104.79	$^1J_{CH}$ 187.2, $^2J_{CH}$ 6.8, $^3J_{CH}$ 6.5	C-2	dt
102.65	$^1J_{CH}$ 198.7, $^2J_{CH}$ 7.3, $^3J_{CH}$ 5.8	C-4	dt

Figure 7: **a.** $^{1}J_{CH}$ - **b.** $^{2}J_{CH}$ and **c.** $^{3}J_{CH}$-^{13}C-^{1}H NMR Coupling Constants (Hz) for Pyrazolo[1,2-*a*]benzotriazole **132a**



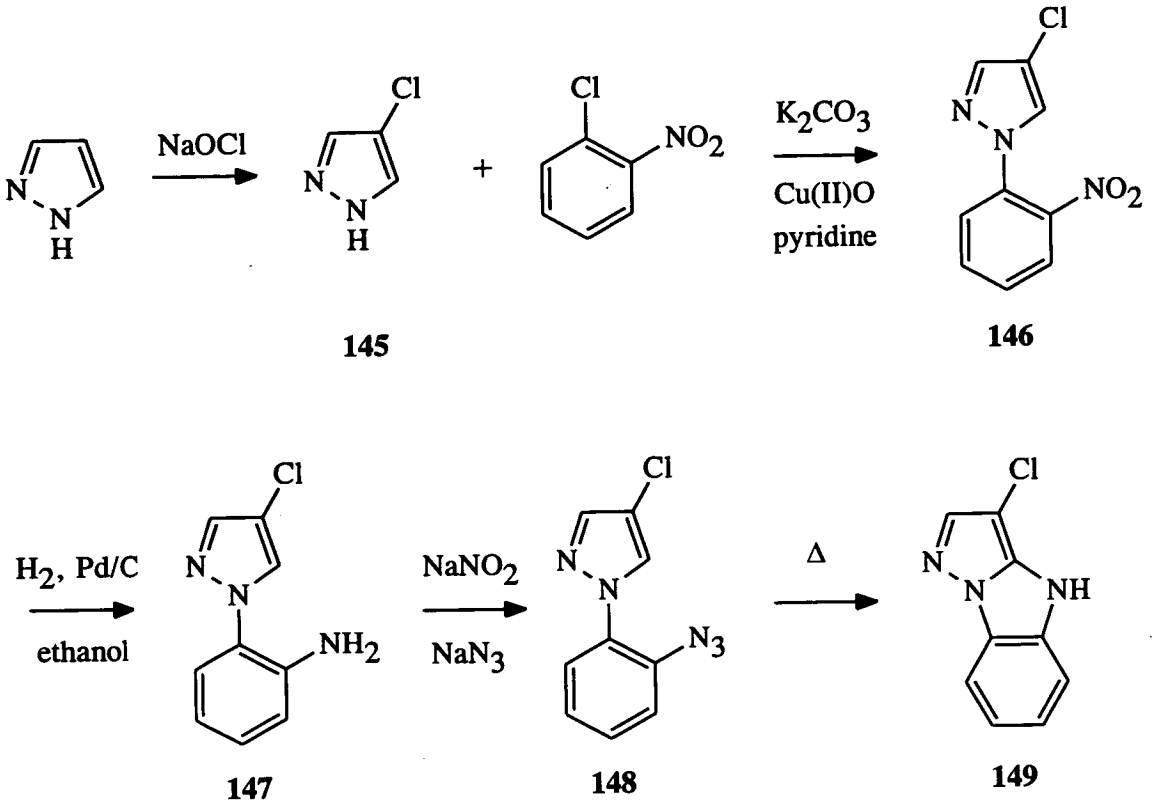
a **b** **c**

e. SYNTHESIS OF 3-HALOGENO-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLES

Pyrolysis of the azide **141** gave pyrazolobenzimidazole **1** with an optimised yield of 30% (Figure 2). The route to quinoxaline competes with the required nitrene insertion reaction at C(5)-H in pyrazole, thus a method of inhibiting nitrene addition across the C(4)-C(5) double bond might be desirable for maximising the yield of chloro-substituted pyrazolobenzimidazole. It was thought that the introduction of an electronegative halogen substituent at position 4 of the azide precursor might remove electron density from the double bond and thus disfavour quinoxaline formation. Conversely, lone pair conjugative donation may also occur to render the double bond more electron rich and therefore increase quinoxaline formation. These halogenopyrazolobenzimidazole analogues have the added advantage of being two-equivalent photographic couplers (see Introduction, section A).

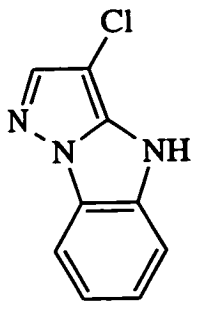
(i) Synthesis of 3-chloro-4*H*-pyrazolo[1,5-*a*]benzimidazole

Incorporation of a chloro substituent in the 4-position of the pyrazole was attempted by treatment of 1-(2-nitrophenyl)pyrazole **131a** with either *N*-chlorosuccinimide or sulfuryl chloride[55] however both reactions afforded only recovered starting material. However chlorination of pyrazole with sodium hypochlorite solution[56] to give 4-chloropyrazole **145** in 62% yield was the best method of introducing a chloro group. The nitro compound **146** was synthesized in 73% yield after column chromatography by the Ullmann condensation of **145** with *o*-chloronitrobenzene. Hydrogenation, diazotisation and subsequent reaction with sodium azide under the same conditions as previously described gave the amine **147** and azide **148** respectively, both in excellent yield (Scheme 47).

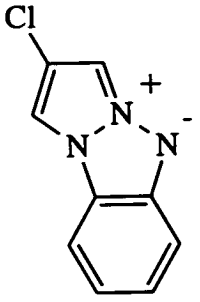


Scheme 47

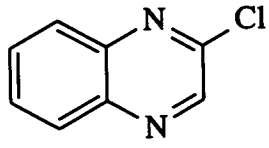
The azide **148** was pyrolysed at various temperatures as before. By analogy with the parent system **141** there were three possible products: 3-chloropyrazolobenzimidazole **149**, 2-chloropyrazolobenzotriazole **150** and 2-chloroquinoxaline **151**. The ^{1}H NMR spectra show a mixture of all three compounds as indicated by their characteristic peaks. Proton H-2 of 3-chloropyrazolobenzimidazole **149** appears as a singlet at δ_H 7.78. 2-Chloroquinoxaline **151** has a singlet at δ_H 8.9 corresponding to proton H-3 and the spectrum of 2-chloropyrazolobenzotriazole (PBT) **149** reveals a characteristic multiplet at δ_H 6.9.



149



150



151

Comparison of the characteristic integrals gave the percentage of components at each temperature (Table 9).

Table 9: Relative proportions of pyrolysate components at various temperatures

Temp./°C	Cl-PBI **149**	Cl-PBT **150**	Cl-quin. **151**
400	28%	53%	18%
450	33%	11%	54%
550	16%	-	83%

The temperature profile is shown in figure 8.

As the furnace temperature increases, the percentage of 2-chloroquinoxaline **151** increases to a greater extent than for the unsubstituted system *only* to the detriment of 2-chloropyrazolobenzotriazole **150** yields. There remains a background of 3-chloropyrazolobenzimidazole **149** between 16% and 33%, slightly improved in comparison with the unsubstituted case.

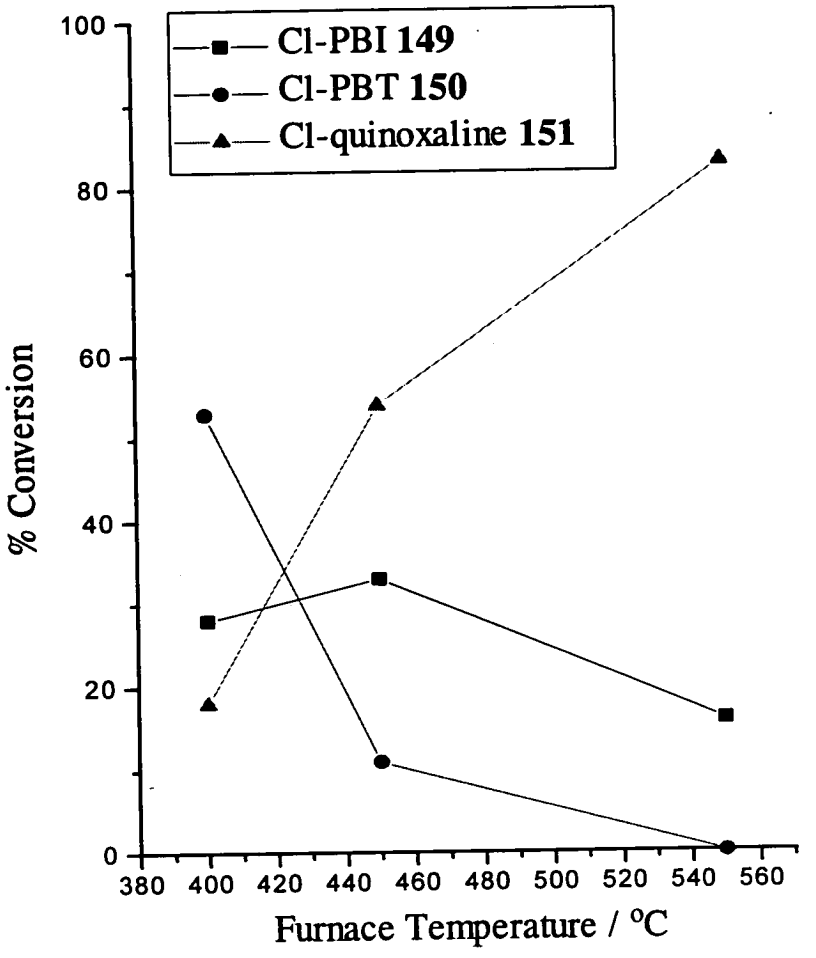
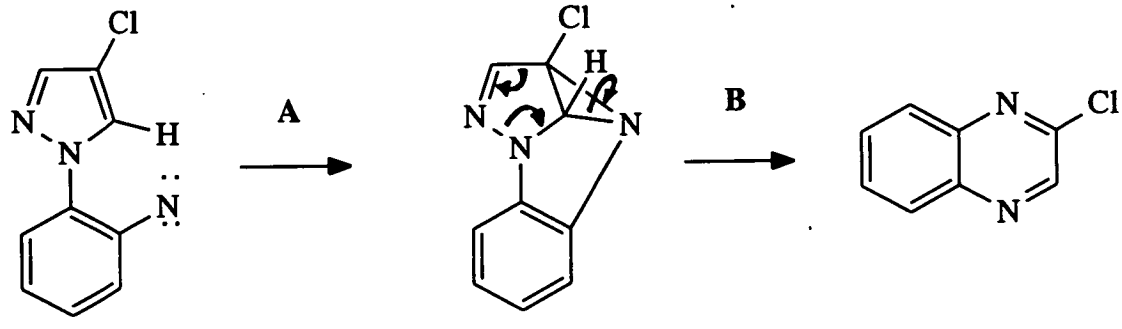


Figure 8: Conversion of Azide **148** to **149**, **150** and **151** as a Function of Furnace Temperature

The same degree of 2-chloroquinoxaline formation occurs at a lower temperature than quinoxaline formation previously, for example 50% formation of 2-chloroquinoxaline **151** occurs at furnace temperatures of *ca.* 450°C compared with a required furnace temperature of *ca.* 510°C for 50% quinoxaline **143** in the unsubstituted pyrolysis. The chlorine atom has made the double bond more electron rich which has the consequence of either making the electrophilic singlet nitrene **152**

more susceptible to addition across the double bond (step A) or allowing more facile collapse of intermediate **153** to quinoxaline (step B, Scheme 47).



152 **153** **151**

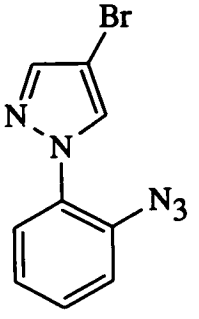
Scheme 47

At low temperatures, the presence of the chloro group appears not to have influenced the partition between singlet and triplet nitrenes. The drop in yield of 3-chloropyrazolobenzimidazole **149** at higher temperatures may be a consequence of the increase in singlet/triplet nitrene ratio leading to the formation of singlet derived products.

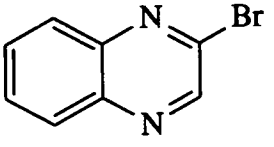
(ii) Attempted synthesis of 3-bromo-4*H*-pyrazolo[1,5-*a*]benzimidazole

Bromination of 1-(2-nitrophenyl)pyrazole **131a** with a solution of bromine in methanol gave the required 4-bromo derivative, but subsequent hydrogenation to the amine gave a complex mixture. However it proved possible to brominate 1-(2-azidophenyl)pyrazole **141** directly using a solution of bromine in methanol to afford 4-bromo-1-(2-azidophenyl)pyazole **154** in quantitative yield. Pyrolysis was carried out at a number of temperatures however, unlike the preceding unsubstituted azide **141** and chloro-substituted azide **148** pyrolyses, the products were not completely soluble in the standard NMR solvent [$^2H_6$] acetone, thus requiring the use of [$^2H_6$] DMSO. In addition, the pyrolyses did not proceed smoothly especially on a larger

(*ca.* 4 mmol) scale as indicated by charring on the inside surface of the furnace tube. ^{1}H NMR showed a complex mixture of products including 2-bromoquinoxaline **155.** This, at least, indicated that the reaction had proceeded in a similar manner to the chloro-substituted system.



154



155

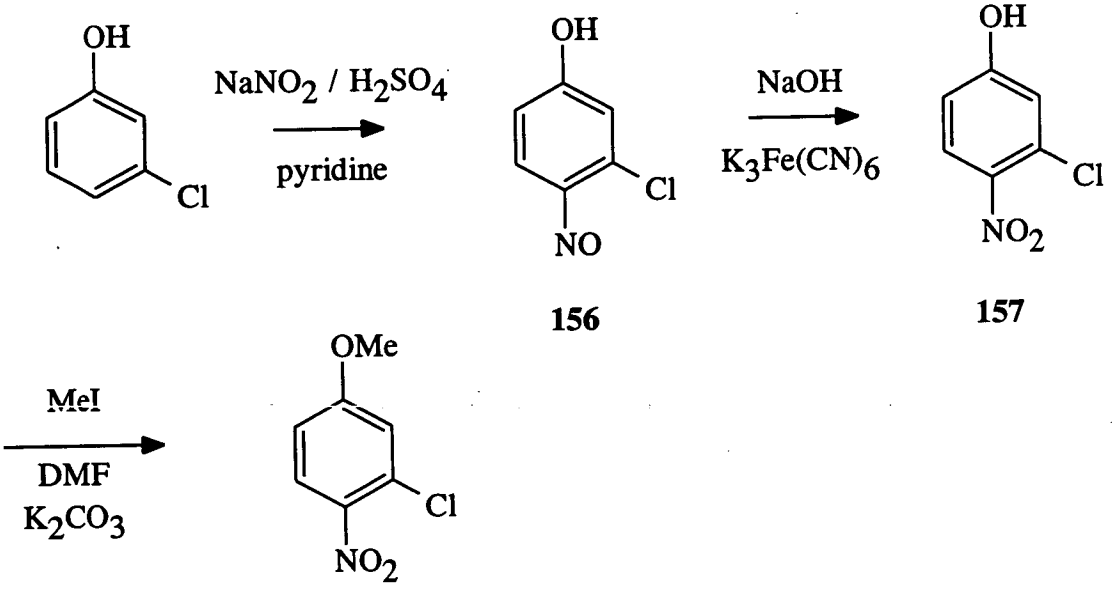
The route was discarded as a result of the problems of decompositon in the furnace tube.

f. SYNTHESIS OF PYRAZOLOBENZIMIDAZOLES WITH CONJUGATIVE ELECTRON DONATING SUBSTITUENTS

The highest yield for pyrazolobenzimidazole **1** from flash vacuum pyrolysis of 1-(2-azidophenyl)pyrazole **141** was 30%. Solution phase work reported by Meth-Cohn and co-workers[49] on analogous systems showed that the spin state of the incipient nitrene was influenced by substituents. Literature reports[48,49] suggest that an electron donating group *para* to the azide moiety would conjugate with and stabilise the nitrene. Thus the spin state of the longer lived nitrene would change from high energy singlet to triplet ground state, thereby yielding an increased proportion of triplet derived products. This would augment the previous theory relating to singlet/triplet reactivities.

(i). Synthesis of 7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole

A synthesis of the azide **141** with a methoxy group para to the azide function was required. The best synthetic route to 3-choro-4-nitroanisole **158** was found in the literature (Scheme 48).



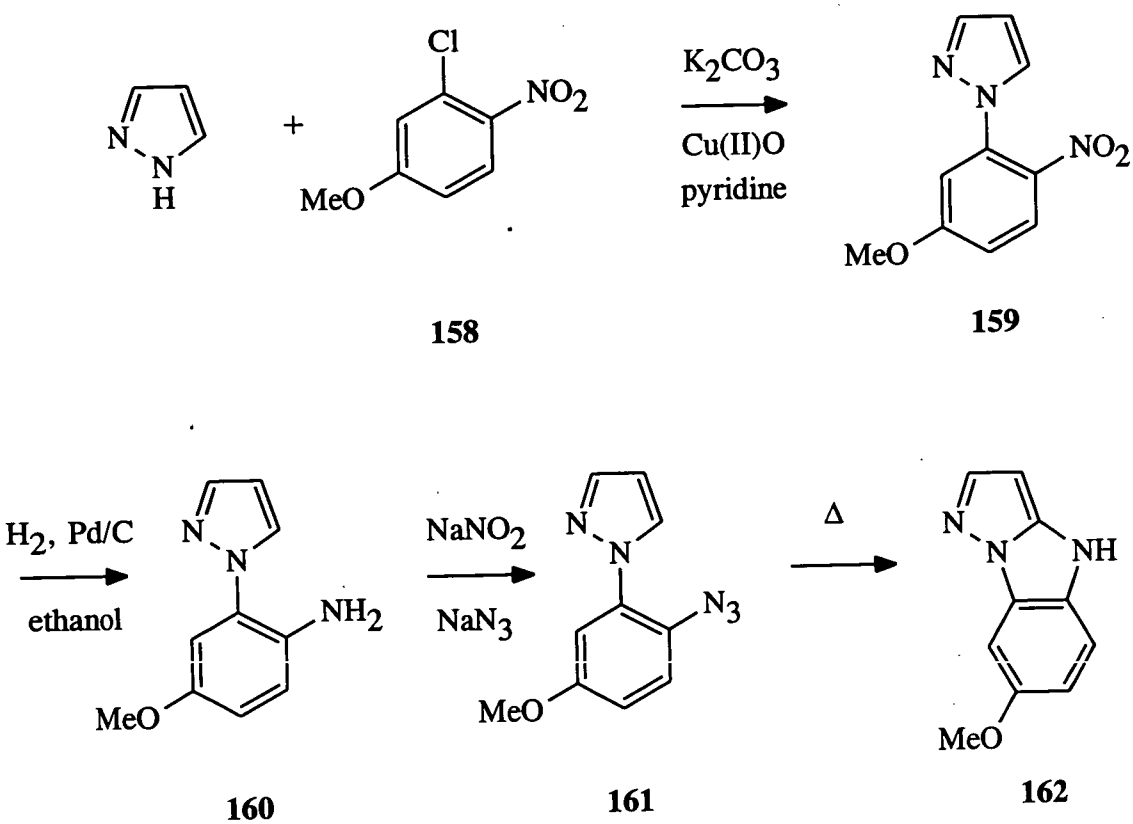
156 **157**

158

Scheme 48

The nitrosation of 3-chlorophenol[57] was effected in 69% yield by the action of sodium nitrite and sulfuric acid in pyridine. The subsequent oxidation to the nitro species **157** occurred in 68% yield with sodium hydroxide and potassium ferricyanide.[58] *O*-Methylation of the hydroxy function with methyl iodide in dimethylformamide in the presence of potassium carbonate was carried out in 93% yield to the required Ullmann condensation starting material **158**.

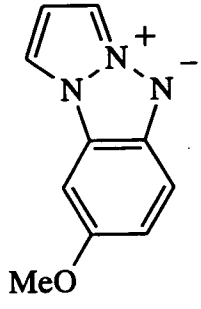
The Ullmann condensation of 3-chloro-4-nitroanisole **158** and pyrazole afforded the required nitro compound **159** in 79% yield after column chromatography. The amine **160** was again obtained in quantitative yield after medium pressure hydrogenation, and the azide **161** obtained in 100% crude yield also after diazotisation and reaction with sodium azide (Scheme 49).



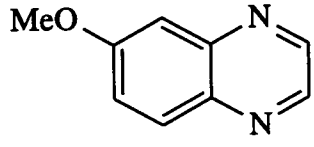
158 **159** **160** **161** **162**

Scheme 49

By analogy with the unsubstituted system, there were three possible products, the desired 7-methoxypyrazolobenzimidazole **162**, 7-methoxypyrazolobenzotriazole **163** and 6-methoxyquinoxaline **164**. Each of the products was identified by characteristic resonances in their ^1H NMR spectra. Proton H-3 of 7-methoxypyrazolobenzimidazole **162** appeared as a doublet at δ_H 5.74. 6-Methoxyquinoxaline **164** was identified by two doublets at δ_H 8.74 and δ_H 8.83 corresponding to protons H-2 and H-3. 7-Methoxypyrazolobenzotriazole **163** appeared showed a characteristic multiplet at δ_H 7.99.



163



164

Pyrolysis of 1-(2-azido-5-methoxyphenyl)pyrazole **162** was carried out at various furnace temperatures (Table 10).

Table 10: Relative proportions of pyrolysate components at various temperatures

Temp./ °C	Meo-PBI **162**	MeO-PBT **163**	MeO-quinox. **164**
400	88%	12%	-
450	87%	9%	4%
500	89%	-	11%
550	87%	-	13%

As anticipated, the methoxy substituent induced an effect on the partition of singlet/triplet nitrenes, although the magnitude of the effect was extremely surprising. Consistently high yields of the required triplet nitrene derived pyrazolobenzimidazole **162** were obtained on pyrolysis at all furnace temperatures (Figure 9).

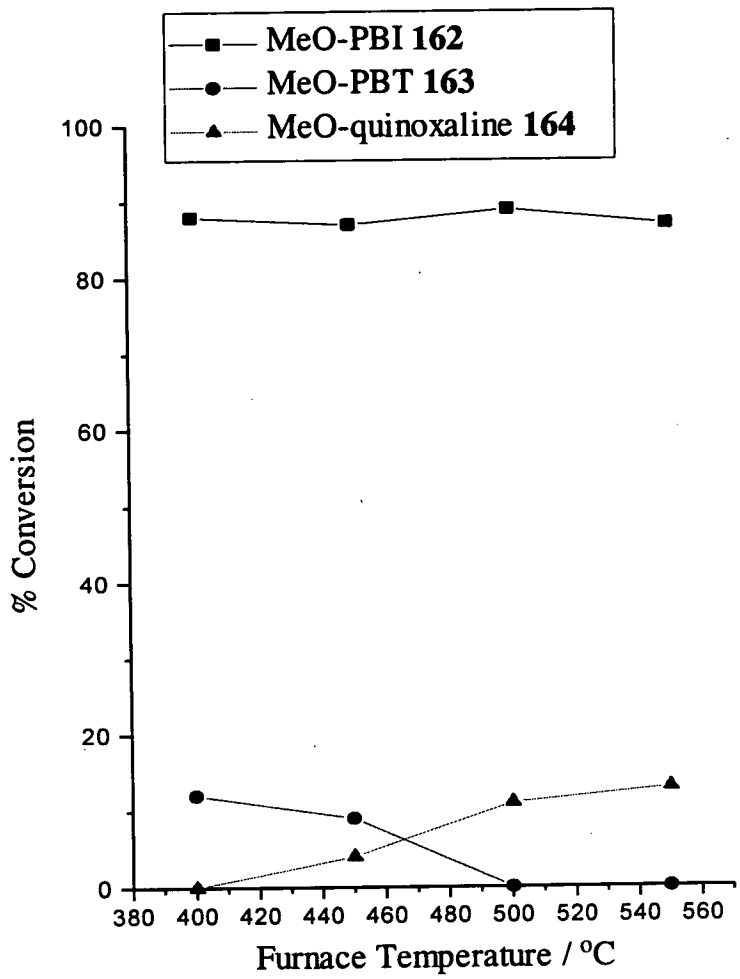
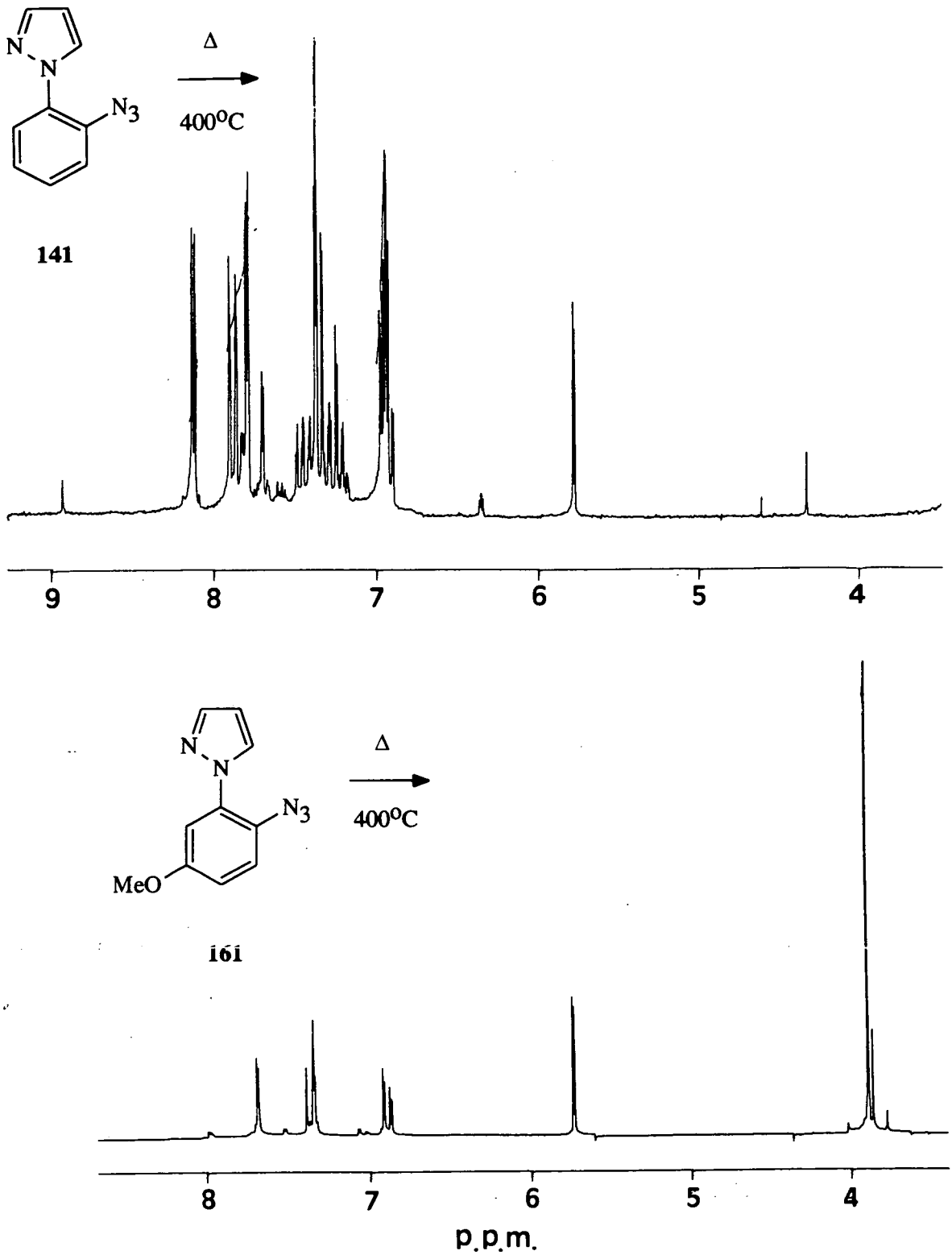


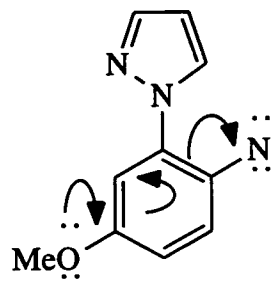
Figure 9: Conversion of Azide **161** to **162**, **163** and **164** as a Function of Furnace Temperature

The ^{1}H NMR spectra of the crude pyrolysis products of the *para*-methoxy substituted azide **161** and the unsubstituted azide **141** at 400°C are shown (Figure 10).

Figure 10: ^{1}H NMR spectra of crude pyrolysis products of **161** and **141** at 400°C



The inclusion of the *para*-methoxy substituent has dramatically altered the ratio of singlet/triplet nitrene **165** in favour of the triplet state. Conjugation of lone pairs appears to have resulted in intersystem crossing from the higher energy singlet state to the ground triplet state allowing almost exclusive formation of triplet derived 7-methoxypyrazolobenzimidazole **162**.

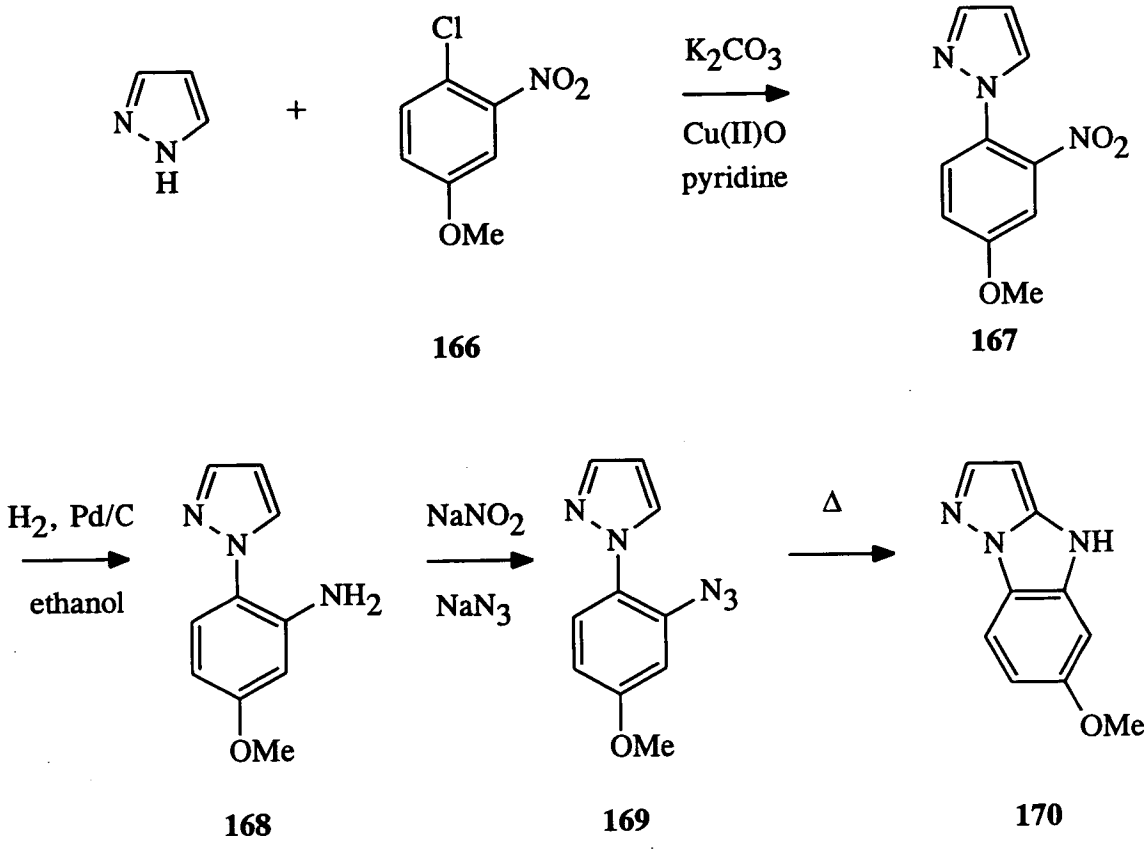


165

When a larger scale pyrolysis (*ca.* 400mg) was attempted, the azide substrate **161** underwent partial decomposition in the inlet leading to lower yields, although the same trends found in the small scale pyrolyses were observed.

(ii). Synthesis of 6-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole

The example in which the methoxy group was *meta* to the incipient nitrene was also studied. The Ullmann condensation of 4-chloro-3-nitroanisole **166** with pyrazole gave the nitro compound **167** in only 15% yield after chromatography. The low yield may have been predicted because of conjugation of the *para*-methoxy group to the site of substitution reducing its electrophilicity. Conversion to the amine **168** and azide **169** was effected as previously described in 96% and 63% yields respectively (Scheme 50).



166 **167** **168** **169** **170**

Scheme 50

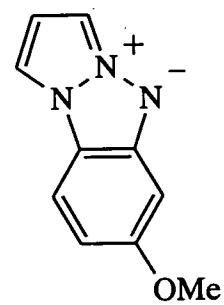
Pyrolysis of **169** at 500°C gave a mixture of three products as observed by ^{1}H NMR. Proton H-3 of 6-methoxypyrazolobenzimidazole **162** appears at δ_H 5.75, 6-methoxyquinoxaline **164** was identified by two doublets at δ_H 8.74 and δ_H 8.81 corresponding to protons H-2 and H-3. Proton H-7 of 6-methoxypyrazolobenzotriazole **171** appeared as a doublet of doublets at δ_H 6.53.

A comparison of product ratios for the unsubstituted, the *para*-methoxy substituted and the *meta*-methoxy substituted azide pyrolyses at 500°C is shown (Table 11).

Table 11: Product Ratios for Azide Pyrolysis at 500°C

Product	unsubstituted	*para*-methoxy	*meta*-methoxy
PBI **1**, **162** or **170**	30% (**1**)	89% (**162**)	31% (**170**)
PBT **132a**, **163** or **171**	30% (**132a**)	-	22% (**171**)
quinoxaline **143** or **164**	40% (**143**)	11% (**164**)	47% (**164**)

In comparison with the unsubstituted example, the *meta*-methoxy group had no effect on the overall yield of 6-methoxypyrazolobenzimidazole **170**, although a slight increase in the yield of 7-methoxyquinoxaline **164** compared to quinoxaline **143** was noted possibly due to an inductive effect to the nitrene. This substitution has had the same effect as introduction of a chloro group in the 4-position of the pyrazole azide precursor, that is an increase in the yield of quinoxaline products to the detriment of pyrazolobenzotriazole.

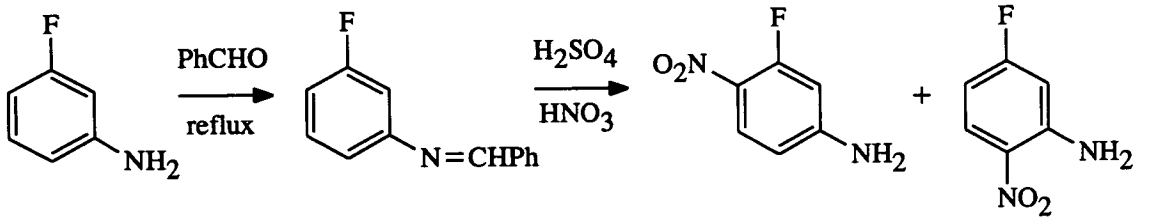


171

(iii). <u>Attempted synthesis of 7-*N*-substituted amino-4*H*-pyrazolo[1,5-*a*]benzimidazoles</u>

The synthesis of a number of *para*-*N*-substituted amino azide precursors was embarked upon to augment the preceding arguments relating to substituent effects.

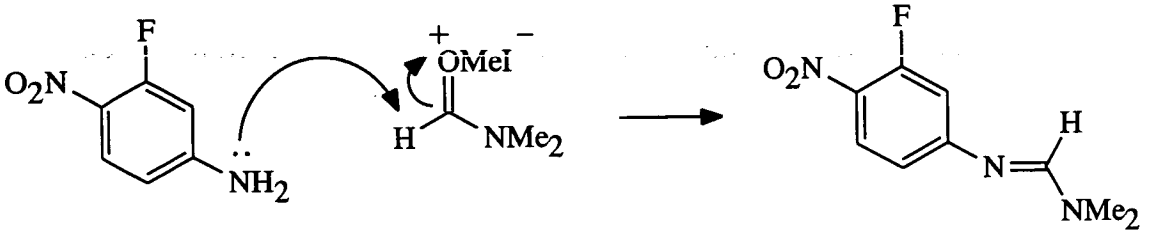
The synthesis of 3-fluoro-4-nitroaniline **173** was achieved according to the method of Hodgson and Nicholson.[59] Protection of 3-fluoroaniline with benzaldehyde followed by nitration with a mixture of concentrated nitric and sulfuric acids afforded a mixture of isomers **173** and **174**. The literature method stated that steam distillation separated the volatile impurities, **174** and benzaldehyde, both of which were present in 1% yield. Contrary to this, however, **173** and **174** were isolated in 45% and 40% yields respectively after dry-flash column chromatography (Scheme 51).



172 **173** **174**

Scheme 51

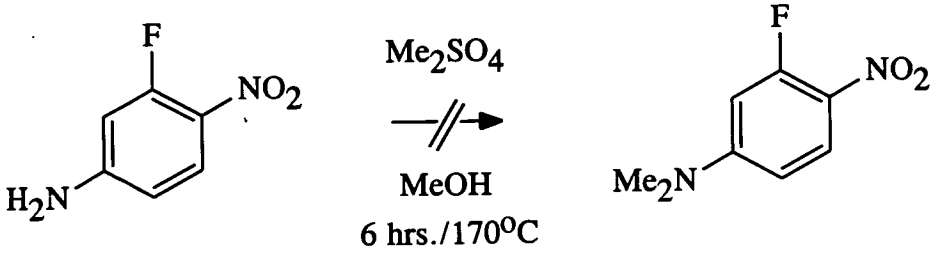
Methylation of the amine **173** was attempted utilising methyl iodide, DMF and potassium carbonate. Contrary to expectations, the amidine **175** was isolated in 29% yield. The *para*-nitro group has served to reduce the nucleophilicity of the amino function and as a result of this reduction in reactivity, methyl iodide instead reacts with DMF solvent to form a salt. The amine may then attack to afford the amidine **175** (Scheme 52).



173 **175**

Scheme 52

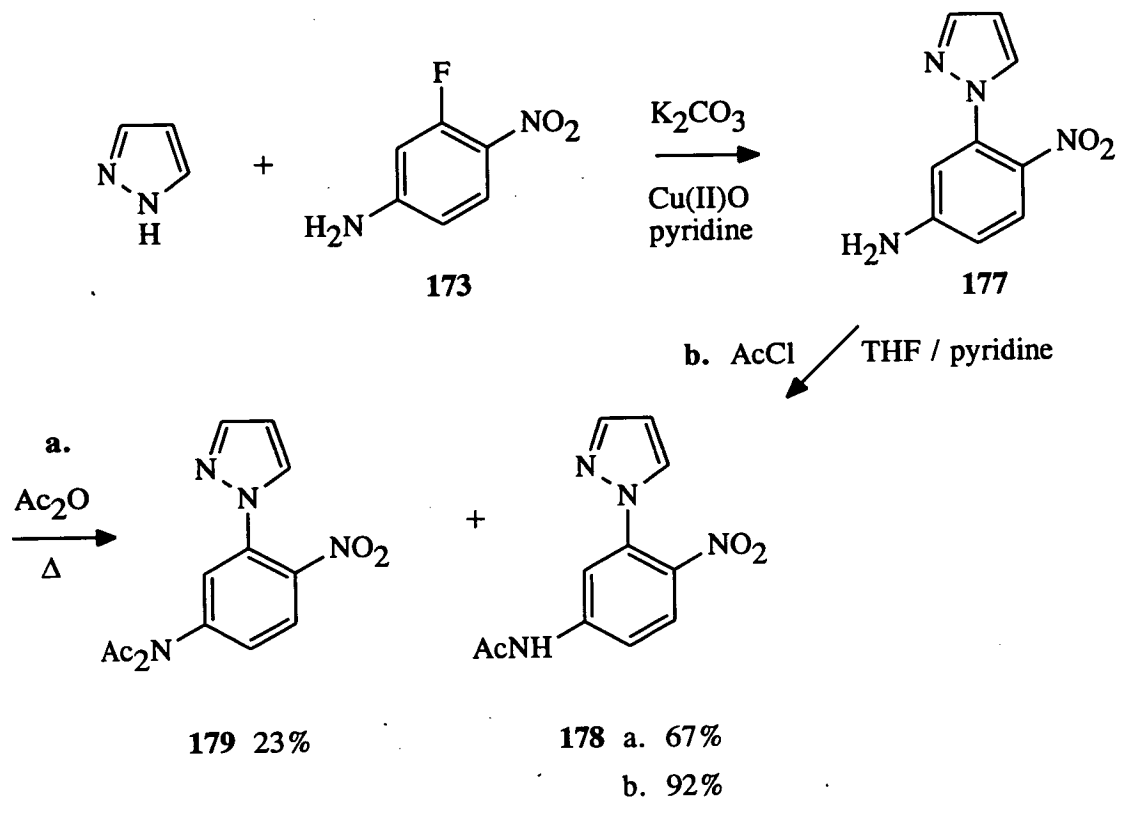
An alternative route to the dimethylated species **176** was attempted by reaction of the amine **173** with dimethyl sulfate in a sealed tube at high temperature.[59] On work-up, only a black tar residue was isolated (Scheme 53).



173 **176**

Scheme 53

An alternative strategy was employed by carrying out the condensation of 3-fluoro-4-nitroaniline **173** with pyrazole to give the nitro species **177** in 40% yield. Protection of the *para*-amino moiety before the diazotisation reaction would be required. This was effected by heating under reflux with acetic anhydride to give the monoacetylated amine **178** in 67% yield and the diacetylated amine **179** in 23% yield (route **a**). Selective monoacetylation was also carried out by stirring with acetyl chloride and pyridine in THF at room temperature to give the product **178** in 92% yield (route **b**, Scheme 54).

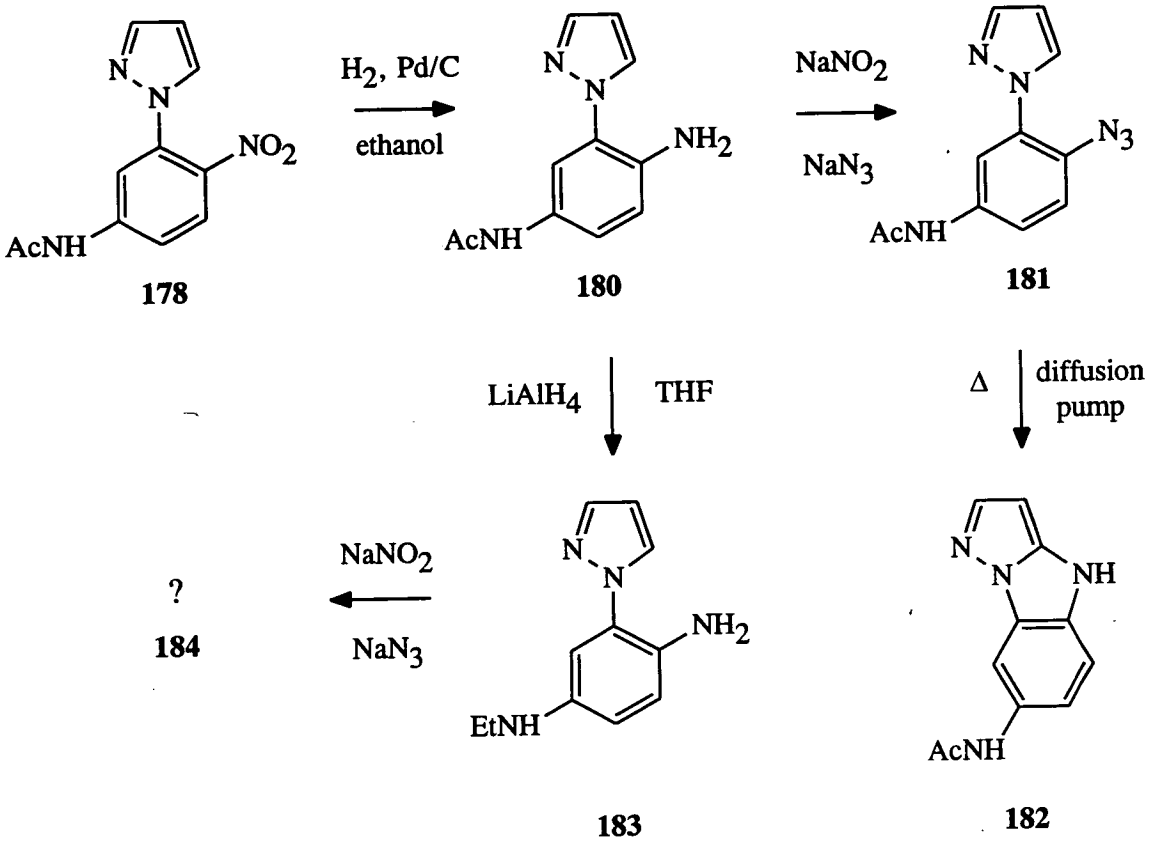


Scheme 54

Hydrogenation of the monoacetylated nitro compound **178** gave the amine **180** in quantitative yield. Subsequent diazotisation and reaction with sodium azide generated the azide **181** in 92% yield. Pyrolysis of the azide **181** was hampered by decomposition in the inlet. This was reduced to some extent by lowering the pressure using a diffusion pump, thus requiring lower inlet temperatures for substrate volatilisation. Pyrolysis afforded a complicated mixture of products among which the desired 7-*N*-acetylamino-4*H*-pyrazolo[1,5-*a*]benzimidazole **182** was observed from the ^{1}H NMR spectrum. The characteristic resonance of H-3, as in all such systems, at δ_H 5.73 was noted, however the negligible integral showed that the desired product was a minor component of the total pyrolysis.

Reduction of the monoacetylated amine **180** with lithium aluminium hydride gave the *N*-ethyl derivative **183** in 72% yield. Diazotisation with sodium nitrite followed

by reaction with sodium azide generated a product which was not the desired azide but a dimer **184** as indicated by ^{1}H and ^{13}C NMR after chromatography. An especially high proportion of nitrogen was indicated by microanalysis, however all attempts to characterise the dimer **184** failed (Scheme 55).

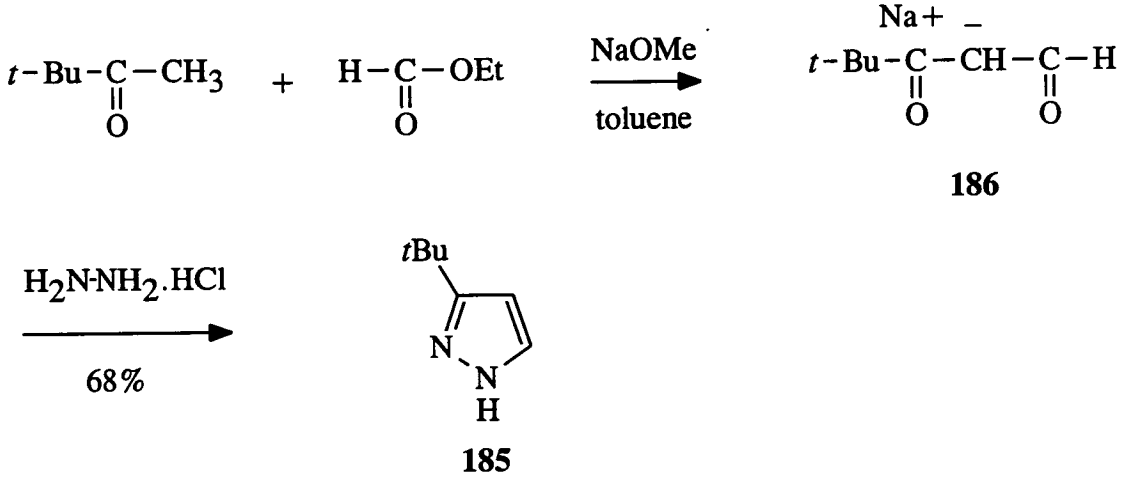


Scheme 55

g. SYNTHESIS OF 2-*t*-Bu-4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE

Introduction of a *tertiary*-butyl substituent in position 2 of pyrazolobenzimidazole **1** was attempted for two reasons. The size of the *t*-Bu group is thought to inhibit aggregation in the dye-forming process thereby facilitating more even coverage on film. In addition, the appearance of tertiary butyl cyanide in the ^{1}H NMR spectrum would serve to validate the theory suggested earlier with regard to the breakdown to quinoxaline.

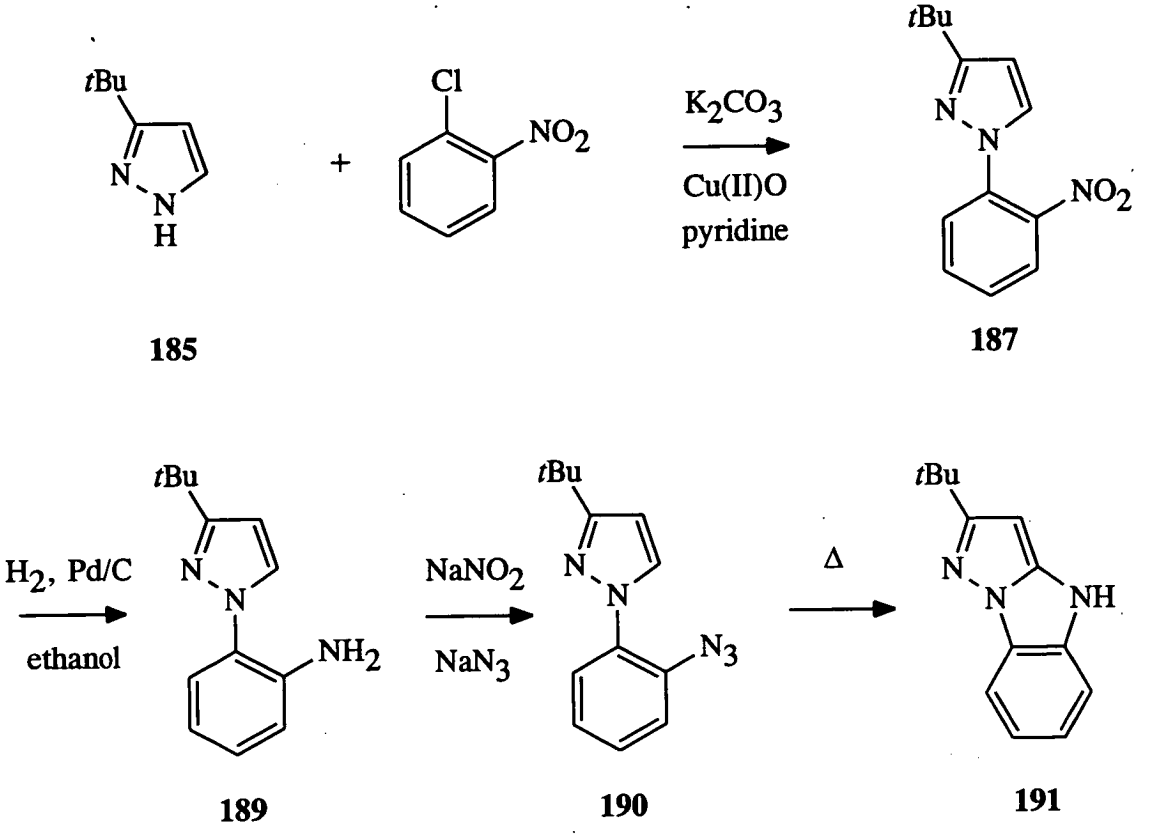
The synthesis of 3-*t*-Bu-pyrazole **185** was effected in 68% yield following the method of Trofimenko.[60] The reaction of pinacolone and ethyl formate in the presence of sodium methoxide gave the resonance stabilised species **186** which gave the product **185** on reaction with hydrazine monohydrochloride (Scheme 56).



Scheme 56

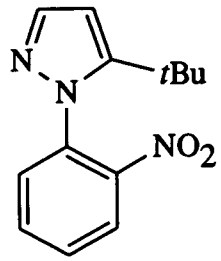
The standard scheme for the synthesis of the azide precursor was applied, although the Ullmann condensation of 3-*t*Bu-pyrazole **185** with *o*-choronitrobenzene gave the nitro product **187** in only 39% yield after 72 hours. Steric inhibition arguments may be employed to explain why the nitro compound was obtained regioselectively with no trace of isomeric product **188** from substitution at the N-2 position of pyrazole.

Conversion to the amine **189** by medium pressure hydrogenation and subsequent diazotisation and reaction with sodium azide to give the azide precursor **190** both occurred in quantitative yield (Scheme 57).

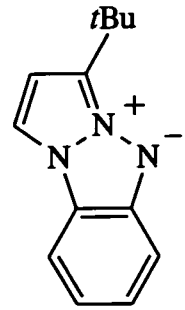


Scheme 57

The azide **190** was pyrolysed at a number of furnace temperatures to give, in each case, a mixture of the three expected products; 2-*t*Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191**, 3-*t*Bu-pyrazolo[1,2-*a*]benzotriazole **192**, quinoxaline **142**. *t*-Butyl cyanide was tentatively assigned in the ^{1}H NMR spectrum of the 400°C pyrolysis at δ_H 1.64. Proton H-3 of 2-*t*Bu-pyrazolobenzimidazole **191** appears as a doublet at δ_H 5.68. Protons H-2 and H-3 of quinoxaline appear as a singlet at δ_H 8.93 and the spectrum of 3-*t*Bu-pyrazolobenzotriazole **192** has a doublet arising from H-2 at δ_H 6.78.



188



192

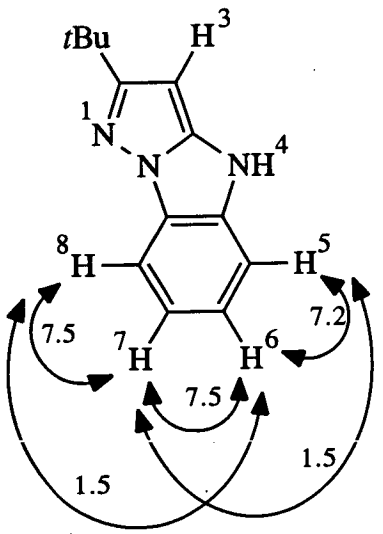
Pyrolysis of **190** at 400°C gave a complicated mixture of products, however at 500°C, 2-*t*Bu-pyrazolobenzimidazole **191** was present in 34% yield, 3-*t*Bu-pyrazolobenzotriazole **192** in 9% yield and quinoxaline in 57% yield. At 600°C, there was no trace of 3-*t*Bu-pyrazolobenzotriazole **192** with quinoxaline present as the major product (71%) and 2-*t*Bu-pyrazolobenzimidazole **191** in 29% yield. In comparison with the pyrolysis of the unsubstituted compound **141**, there are slightly increased yields of 2-*t*Bu-pyrazolobenzimidazole **191** and much increased yields of quinoxaline, again at the expense of 3-*t*Bu-pyrazolobenzotriazole **192** formation. This may be attributed to the steric hinderance to quenching of the nitrene by the N-2 lone pair.

Once isolated, ^{1}H NMR analysis using nuclear Overhauser enhancements and decoupling experiments fully assigned 2-*t*Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191** (Table 12).

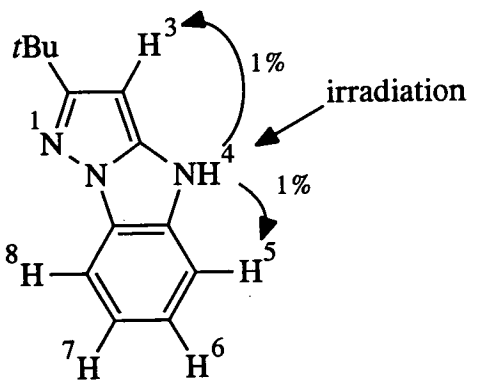
Table 12: ^{1}H NMR Parameters for 2-*t*Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole**191** in [$^2H_6$] acetone

δ_H / ppm	Coupling Constants / Hz	Assignment	Pattern
10.23	-	NH	br. s
7.70	^3J 7.5, ^4J 1.5	H-8	dd
7.41	^3J 7.2, ^4J 1.5	H-5	dd
7.23	^3J 7.5 and 7.2, ^4J 1.5	H-6	td
7.17	^3J 7.5, ^4J 1.5	H-7	td
5.67	-	H-3	s
1.41	-	*t*-Bu	s

Figure 11: **a.** ^{1}H-^{1}H Coupling Constants (Hz)
and **b.** Nuclear Overhauser Enhancements for
2-*t*Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191**



a

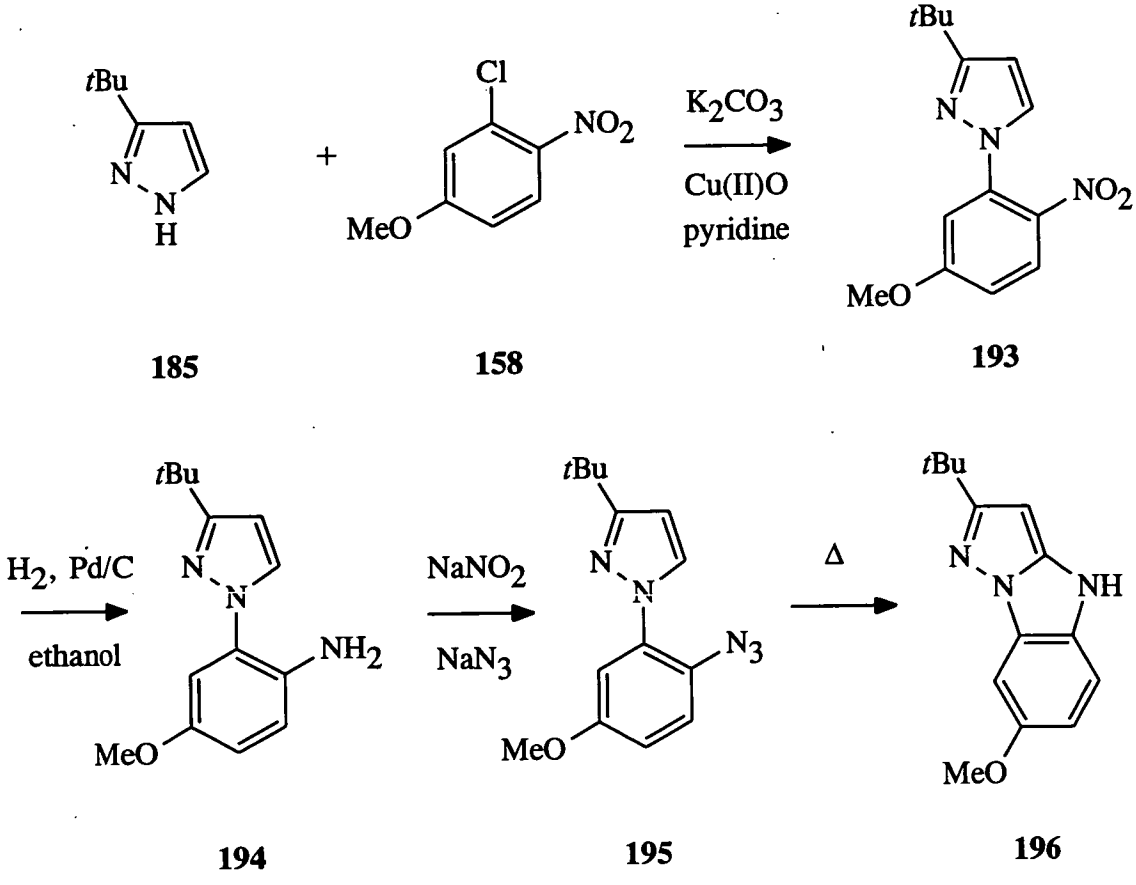


b

Irradiation of the NH at δ_H 10.23 resulted in 1% enhancements in the signals from H-3 at δ_H 5.67 and H-5 at δ_H 7.41. Decoupling experiments subsequently allowed full assignment of the benzenoid protons.

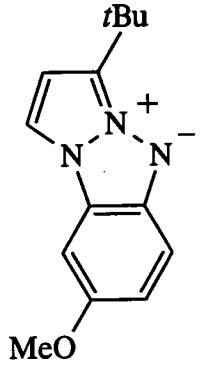
h. SYNTHESIS OF 2-*t*-Bu-7-METHOXY-4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE

The work was further extended to include the condensation of 3-*t*-Bu-pyrazole **185** and 3-chloro-4-nitroanisole **158** which occured in 33% yield. Conversion to the amine **194** and azide **195** by the methods previously described was effected in 97% and 84% yields respectively. Pyrolysis at 500°C gave the desired substituted pyrazolobenzimidazole **196** in 59% yield after purification by preparative t.l.c. (Scheme 58).



Scheme 58

As with the *para*-methoxy 2-unsubstituted azide **161** pyrolysis, the desired 2-*t*Bu-7-methoxy-pyrazolo[1,5-*a*]benzimidazole **196** was the major component in the pyrolysis due to the increase in the triplet/singlet nitrene ratio induced by the conjugating methoxy function. In the ^{1}H NMR spectrum, proton H-3 of 2-*t*Bu-7-methoxy-pyrazolo[1,5-*a*]benzimidazole **196** appears as a singlet at δ_H 5.74 and protons H-2 and H-3 of 6-methoxyquinoxaline **164** appear as two doublets at δ_H 8.85 and δ_H 8.93. No trace of 3-*t*Bu-7-methoxy-pyrazolo[1,5-*a*]benzotriazole **197** is detected in the ^{1}H NMR spectrum.



197

A comparison of product ratios for the unsubstituted, the *para*-methoxy substituted, *tertiary* butyl and *para*-methoxy *tertiary* butyl azide pyrolyses all at 500°C is shown (Table 13).

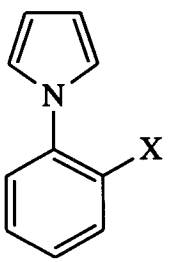
Table 13: Product Ratios for Azide Pyrolysis at 500°C

Compound	unsubstituted	*para*-methoxy	*t*-Bu	*t*-Bu *para*-methoxy
PBI **1**, **162**, **191** or **196**	30% (**1**)	89% (**162**)	34% (**191**)	84% (**196**)
PBT **132a**, **163**, **192** or **197**	30% (**163**)	-	9% (**192**)	-
quinoxaline **143** or **164**	40% (**143**)	11% (**164**)	57% (**143**)	16% (**164**)

The presence of the *tertiary* butyl substituent in both cases has not affected the ratio of the desired substituted pyrazolobenzimidazole to any significant extent, the major influence is obviously the methoxy group. No 3-*t*Bu-7-methoxy-pyrazolo[1,5-*a*]benzotriazole **197** is observed at 500°C, again possibly due to steric hinderance of the *tertiary* butyl group inhibiting attack of the N-2 lone pair by the already disfavoured singlet nitrene.

i. SYNTHESIS OF 4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE *via* RADICAL CYCLISATION

Previous studies have been conducted into the generation and intramolecular cyclisation of phenoxyl, aminyl, benzyl and thiophenoxyl radicals **198a-d**. The attempted intramolecular cyclisation to the *ortho*-pyrrolyl heterocyclic moiety lead to mixed results.[61]



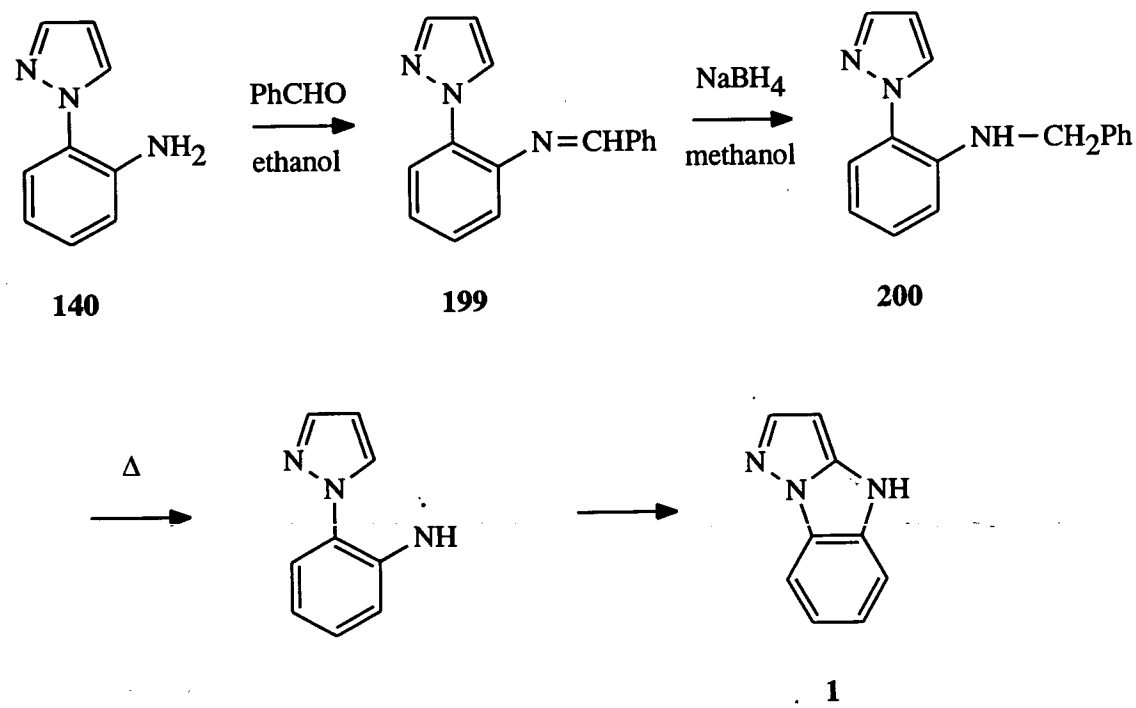
198 **a** = O· **c** = CH_2·

b = NH· **d** = S·

Highly efficient cyclisation reactions took place for carbon- and sulfur-centred radicals, **198c** and **198d** respectively, to give the appropriate condensed heterocycle. The desired cyclisation reaction of nitrogen and oxygen-centred radicals, **198b** and **198a** respectively, was not observed to take place possibly because of the sensitivity of the expected products. In these cases, a mixture of rearrangement and hydrogen capture products was generated. On the basis of this work, an alternative route to

unsubstituted pyrazolobenzimidazole **1** can be proposed. Synthesis of the the *N*-benzyl derivative of the 1-(2-aminophenyl)pyrazole **140** followed by pyrolysis will generate the appropriate aminyl radical. The formation of pyrazolobenzimidazole **1** would show the ability of aminyl radicals to insert into CH bonds under conditions where the product is known to be stable.

Condensation of the amine **140** with benzaldehyde followed by bulb-to-bulb distillation gave pure imine **199** in 80% yield. Reduction with sodium borohydride afforded the *N*-benzyl derivative **200** in 67% yield as a yellow crystalline solid. Pyrolysis at 750°C gave a number of products from which the desired compound **1** was isolated in only 20% yield, bibenzyl was generated in 47% yield and the starting amine **140** was reformed in low yield. The bibenzyl is the product formed by coupling of the co-formed benzyl radicals and hydrogen capture leading to **140** is a well known reaction of aminyl radicals under FVP conditions (Scheme 59).[61]



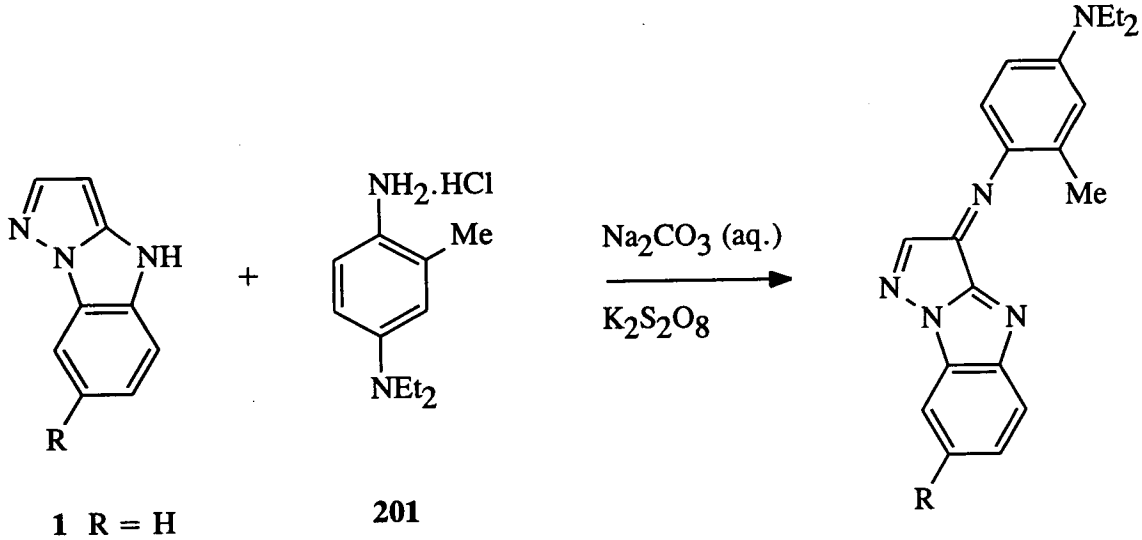
140 **199** **200** **1**

Scheme 59

Thus, the cyclisation of aminyl radicals to the *ortho*-pyrazole ring has been shown to work, in contrast to the results obtained for cyclisation to an *ortho*-pyrrole ring. This project was not elaborated on, however, due to low yields of the desired product **1**.

j. SYNTHESIS OF 3-(4-DIETHYLAMINO-2-METHYLPHENYLIMINO) -3*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLES

Azamethine dye formation is the result of an oxidative addition reaction of a suitable coupler with a developer, typically a *p*-phenylenediamine. The dye forming reaction was carried out for pyrazolobenzimidazoles with 4-(*N,N*-diethylamino)-3-methylaminobenzene hydrochloride **201** in the presence of base, essentially as described by Bailey.[4] The resulting solution was oxidised with potassium persulfate to generate the intense magenta dye in excellent yields (Scheme 60).



1 R = H
162 R = OMe

201

202 R = H
203 R = OMe

Scheme 60

The visible spectra of dyes **202** and **203** were run in various solvents (Table 14).

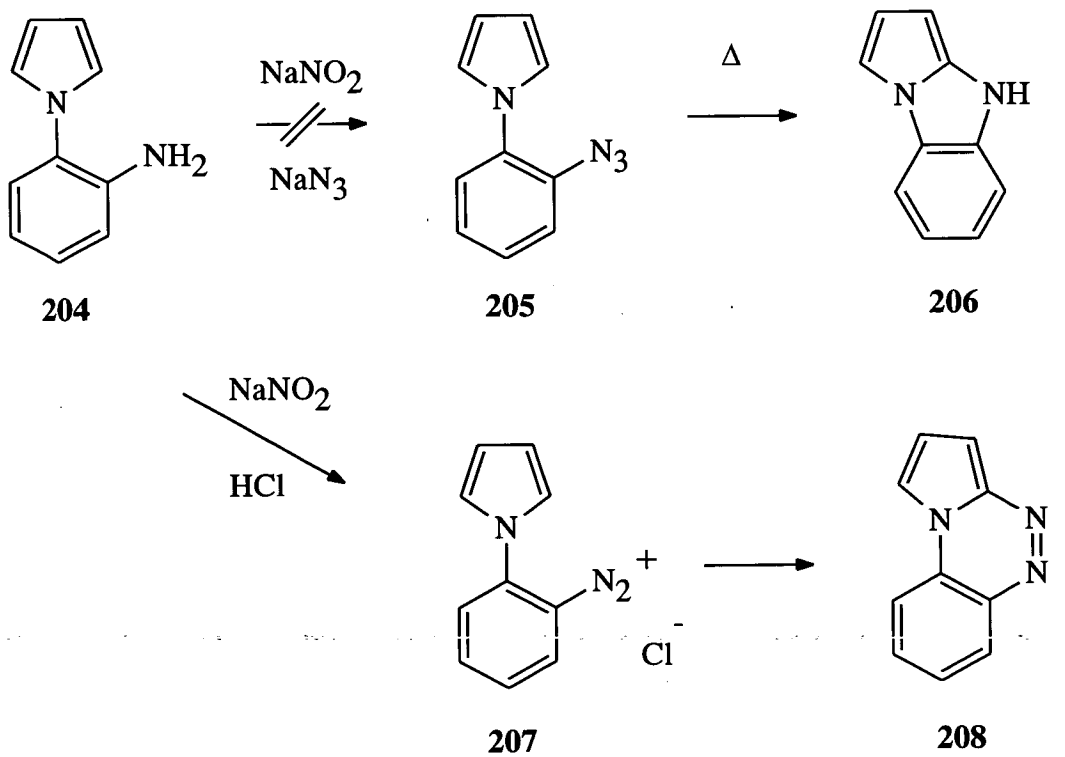
Table 14: Visible spectra data for dyes **202** and **203**.

Compound	solvent	λ_{max} / nm	1/2 band / nm
202	methanol	578	91
202	ethyl acetate	556	84
202	cyclohexane	529, 554 sh.	73
203	ethyl acetate	566	-

The absorption maxima are observed to undergo a bathochromic shift with increasing dielectric constant of the solvent. This is a consequence of the lowering of the energy of the excited state with increasing solvent polarity. In cyclohexane, the absorption band of **202** is resolved into a doublet. This fine structure is lost in the more polar solvents due to hydrogen bonding of the dye molecules with the solvent. A bathochromic shift was also observed in the dye on inclusion of the methoxy substituent.

2. 4*H*-Pyrrolo[1,5-*a*]benzimidazole

The inclusion of other heterocycles in the azapentalenes was desired for the purposes of comparison of spectroscopic and dye-forming properties. Thus the synthesis of pyrrolobenzimidazole **206** was attempted by initial formation of 1-(2-azidophenyl)pyrrole **205** followed by flash vacuum pyrolysis. 1-(2-Aminophenyl)pyrrole **204** was diazotised with sodium nitrite, however after sodium azide addition and work-up, the product was found not be the required azide **205** but pyrrolo[2,1-c][1,2,4]benzotriazine[62] **208** which resulted from the spontaneous intramolecular cyclisation of the diazonium salt **207** due to the π-excessive nature of pyrrole (Scheme 61).



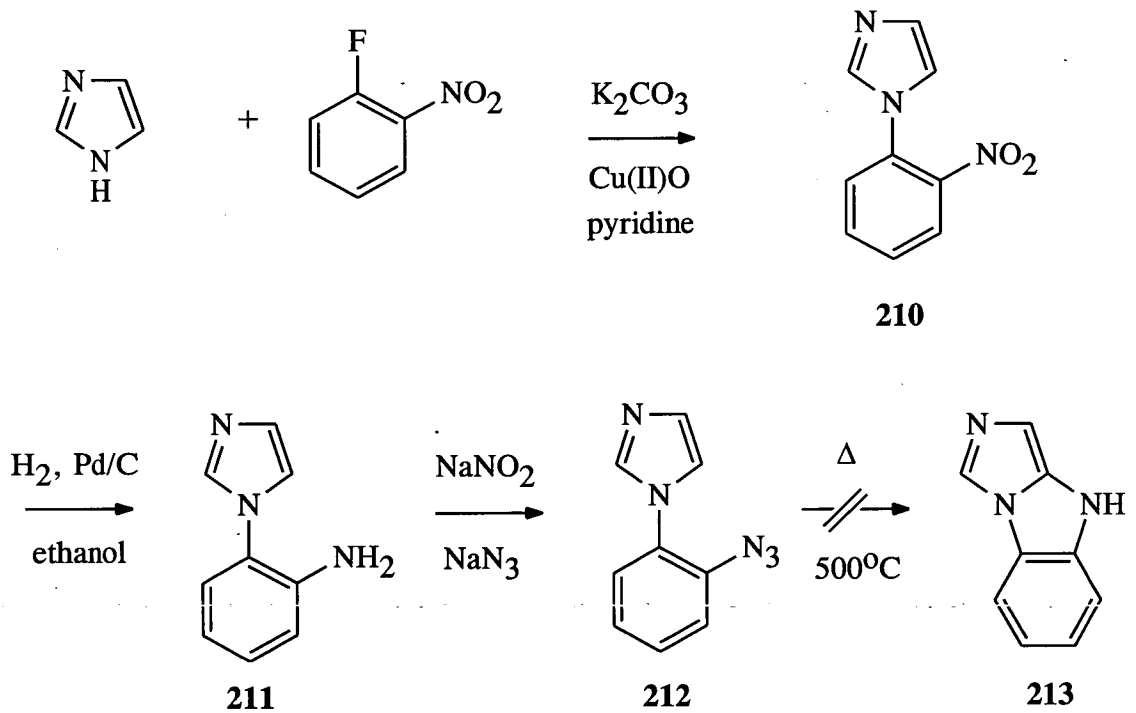
Scheme 61

3. 4*H*-Imidazo[1,5-*a*]benzimidazoles

a. SYNTHESIS AND PYROLYSIS OF 1-(2-AZIDOPHENYL)IMIDAZOLE

The title imidazobenzimidazole **213** was targeted as a potential new magenta coupler. A possible route into this system might utilise flash vacuum pyrolysis of the azide precursor 1-(2-azidophenyl)imidazole **212**. This compound has been synthesized by Meth-Cohn and co-workers,[47] however thermolysis in the solution phase lead only to *o*-nitroaniline in 29% yield.

Condensation of imidazole and *o*-fluoronitrobenzene afforded chromatographically pure 1-(2-nitrophenyl)imidazole **210** in 92% yield as an orange crystalline solid.[47] The corresponding amine **211** and azide **212** were obtained in 99% and 98% yields respectively by the methods described in previous sections of this thesis.

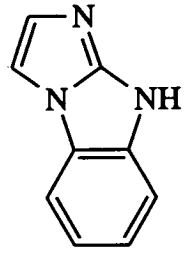


Scheme 62

Flash vacuum pyrolysis of the highly involatile azide **212** at 500°C resulted in extremely low yields of products accompanied by significant decomposition in the inlet. The problems of involatility were overcome to some extent with the use of a mercury diffusion pump. Pyrolyses were run for several hours at a time, without heating the inlet, until there was enough combined material for analysis (Scheme 62).

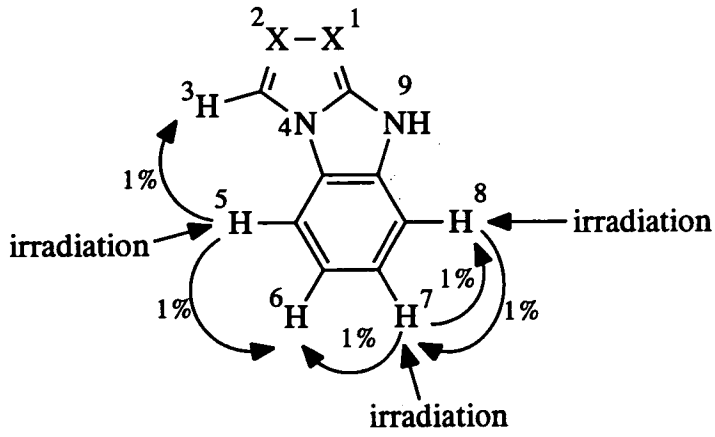
b. STRUCTURE DETERMINATION OF PYROLYSIS PRODUCTS

The product appeared as white crystals whose mass spectrum showed a molecular ion at *m/z* 157 indicating the formation of the desired product **213**, or its isomer, 9*H*-imidazo[1,2-*a*]benzimidazole **214**. The composition of the pyrolysate was expected to be a mixture of **213** and **214**.



214

^{13}C NMR of the crude pyrolysate surprisingly revealed the presence of only one regioisomer. Differentiation of the two possible regioisomers was not possible by analysis of the ^{1}H NMR spectrum as the $^{3}J_{HH}$ and $^{4}J_{HH}$ coupling constants in imidazole-like systems are small and of similar magnitude.[63] On conducting nuclear Overhauser enhancement experiments by irradiating the NH and the terminal imidazole protons, the results proved inconclusive and therefore unsuccessful in determining the identity of the isomer. However some signal enhancements were obtained on irradiation of the benzenoid protons (Figure 12).

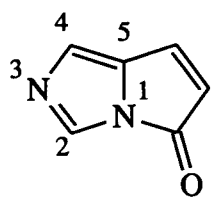


213 X^2 = N, X^1 = CH

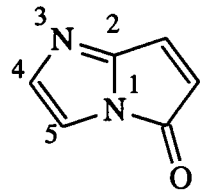
214 X^1 = N, X^2 = CH

Figure 12: Nuclear Overhauser Enhancements for Imidazobenzimidazole **213** or **214**.

In analogous systems,[64a,b] for example the azapyrrolizinones **215** and **216**, the C_2-H coupling constant in **215** is *ca.* 217 Hz and the C_4-H and C_5-H couplings are approximately 195 Hz.



215



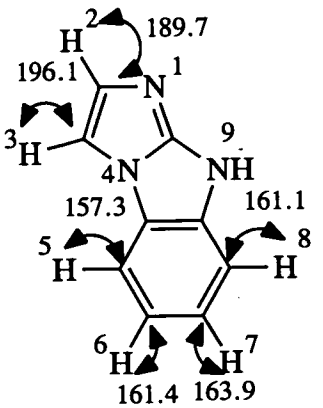
216

As the C_2-H coupling constant is significantly higher in magnitude than the C_4-H or C_5-H coupling constant, the presence or absence of this coupling will indicate whether or not the equivalent position in the imidazobenzimidazole system is substituted. With this in mind, a fully coupled ^1H-^{13}C spectrum was run (Table 15).

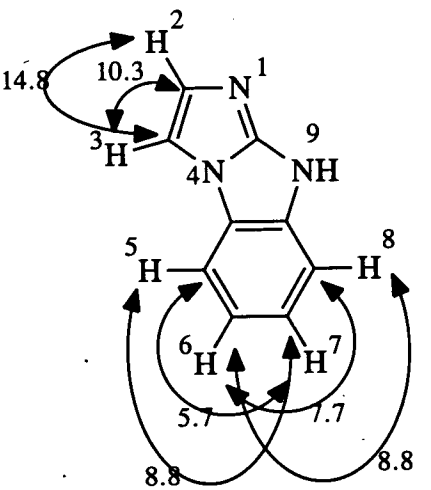
Table 15: ^{13}C NMR Parameters for Imidazobenzimidazole **213** or **214** in $[^2H_2]$ dichloromethane

δ_C / ppm	Coupling Constants / Hz	Assignment	Pattern
126.68	$^1J_{CH}$ 189.7, $^2J_{CH}$ 10.3	C-2	dd
123.36	$^1J_{CH}$ 157.3, $^3J_{CH}$ 5.7	C-5	dd
119.56	$^1J_{CH}$ 161.1, $^3J_{CH}$ 7.7	C-8	dd
113.55	$^1J_{CH}$ 163.9, $^3J_{CH}$ 8.8	C-7	dd
110.89	$^1J_{CH}$ 161.4, $^3J_{CH}$ 8.8	C-6	dd
105.74	$^1J_{CH}$ 196.1, $^2J_{CH}$ 14.8	C-3	dd

Figure 13: **a.** $^1J_{CH}$- and **b.** $^2J_{CH}$- and $^3J_{CH}$-^{13}C-^1H NMR Coupling Constants (Hz) for Imidazobenzimidazole



a



b

Form Figure 13, both $^1J_{CH}$ coupling constants for the imidazole system were approximately 190-196 Hz. As there is no imidazolic $^1J_{CH}$ coupling constant of

magnitude *ca.* 217 Hz for the imidazobenzimidazole system, then it may be assumed that the nitrene has inserted into the 2-position of imidazole to give the isomer **214**. The regiochemistry has been proved unequivocally by X-ray crystal structure analysis showing the formation of 9*H*-imidazo[1,2-*a*]benzimidazole **214**. A sample of **214** suitable for X-ray analysis was obtained by slow evaporation of the NMR solvent [$^2H_2$]-dichloromethane from the tube. The ORTEP plot with the crystallographic numbering system is shown in Figure 14, and the structural parameters are given in Figure 15 and Table 16.

Figure 14: ORTEP Plot of **214** with crystallographic numbering system

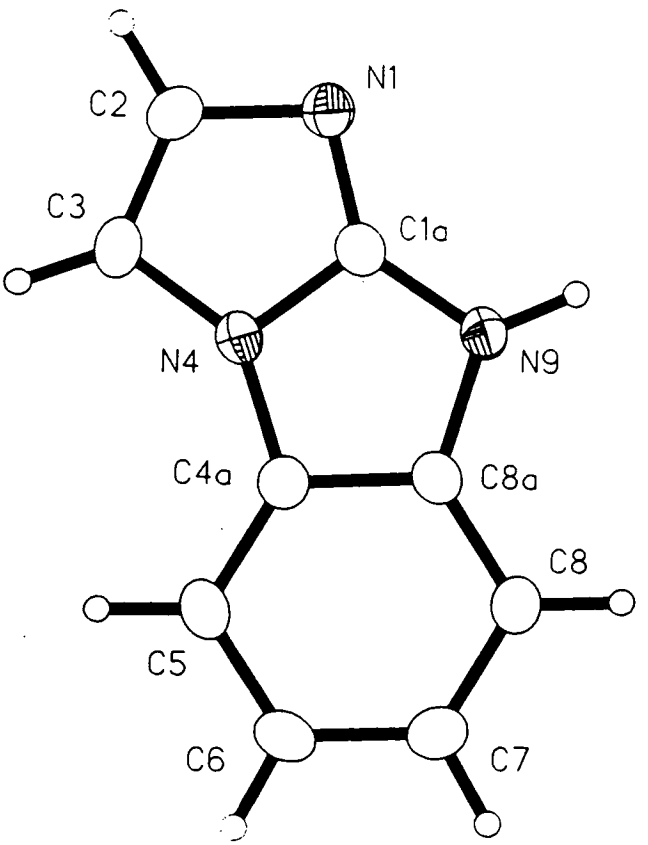
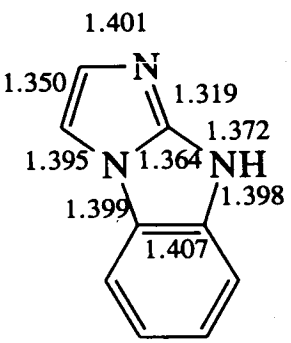
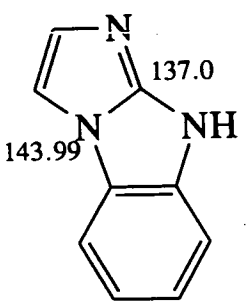


Figure 15: Selected structural parameters for 9*H*-imidazo[1,2-*a*]benzimidazole **214**



a. bond lengths (Å)

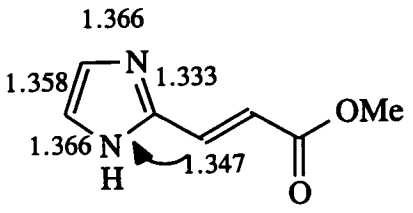


b. bond angles(°)

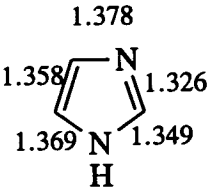
Table 16: Bond lengths (Å) and angles (°) of **214** with standard deviations

N(1)-C(1A)	1.319(2)
N(1)-C(2)	1.401(2)
C(2)-C(3)	1.350(2)
C(3)-N(4)	1.395(2)
N(4)-C(1A)	1.364(2)
N(4)-C(4A)	1.399(2)
C(4A)-C(5)	1.376(2)
C(4A)-C(8A)	1.407(2)
C(5)-C(6)	1.386(2)
C(6)-C(7)	1.392(2)
C(7)-C(8)	1.390(2)
C(8)-C(8A)	1.389(2)
C(8A)-N(9)	1.398(2)
N(9)-C(1A)	1.372(2)
C(1A)-N(1)-C(2)	102.22(13)
C(3)-C(2)-N(1)	113.17(14)
C(2)-C(3)-N(4)	104.3(2)
C(1A)-N(4)-C(3)	106.54(12)
C(1A)-N(4)-C(4A)	109.38(12)
C(3)-N(4)-C(4A)	143.99(14)
C(5)-C(4A)-N(4)	132.1(2)
C(5)-C(4A)-C(8A)	122.5(2)
N(4)-C(4A)-C(8A)	105.36(13)
C(4A)-C(5)-C(6)	117.1(2)
C(5)-C(6)-C(7)	121.2(2)
C(8)-C(7)-C(6)	121.7(2)
C(7)-C(8)-C(8A)	117.6(2)
C(8)-C(8A)-N(9)	131.2(2)
C(8)-C(8A)-C(4A)	119.84(14)
N(9)-C(8A)-C(4A)	108.94(13)
C(1A)-N(9)-C(8A)	106.90(13)
N(1)-C(1A)-N(4)	113.73(14)
N(1)-C(1A)-N(9)	137.0(2)
N(4)-C(1A)-N(9)	109.31(13)

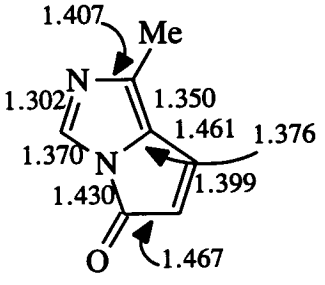
Figure 16: Selected bond lengths (Å) and angles (°) of model compounds



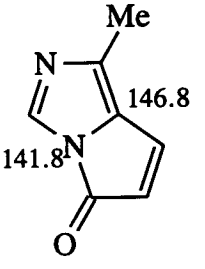
217



218



219 (bond lengths)



219 (bond angles)

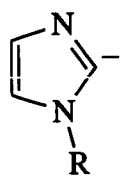
Bond alteration in the terminal imidazole ring is apparent in the fused systems compared with the *N*-unsubstituted imidazole analogues **217**[65] and **218**.[66a] The formal single bonds are longer for the fused systems **214** and **219**.[65] Double bonds C(1a)-N(1) and C(2)-C(3) are correspondingly slightly shorter in fused systems. The bond angle at the bridgehead nitrogen of **214** is slightly larger (*ca.* Δ 2°) than the corresponding C-N-C angle in **219**, whereas the difference between bridgehead carbon angles is more pronounced (*ca.* Δ 10°) in favour of the pyrroloimidazolone **219**.

c. REGIOSELECTIVITY OF NITRENE INSERTION REACTION

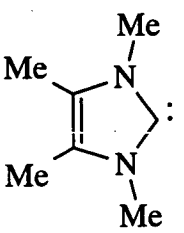
There are almost no examples of carbene or nitrene reactions with imidazole systems. Busby *et al.* reacted a number of imidazoles with dichlorocarbene and obtained ring expansion products, however there is no literature precedent for the observed regioselectivity.[66b]

Unlike the preceding pyrazole based systems, in imidazole there is no adjacent lone pair and thus there is no obvious reaction pathway for the singlet nitrene species. This may account for the presence of only very low yields of triplet derived insertion product **214**. In addition, the pyrolysis temperature of 500°C may not be enough to allow the singlet nitrene to form quinoxaline *via* the route proposed previously in the thesis.

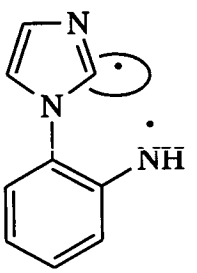
The triplet nitrene was expected to insert at both the 2- and the 5-positions of imidazole to give **214** and **213** respectively. The wholly regioselective insertion into the C_2-H bond may be rationalised by the fact that electrons in a sigma orbital at the imidazole 2-position endow the system with remarkable stability. Examples include the reactivity of the imidazole 2-position towards strong bases *via* the 2-carbanion **220a** and the isolation of the stable "carbene" **220b**.[66c] In the same way, the radical intermediate **220c** at position 2 in the triplet nitrene insertion reaction would be favoured.



220a



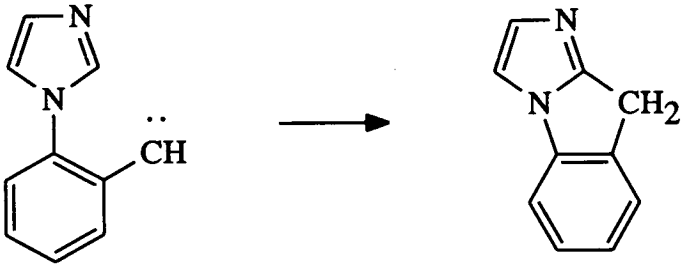
220b



220c

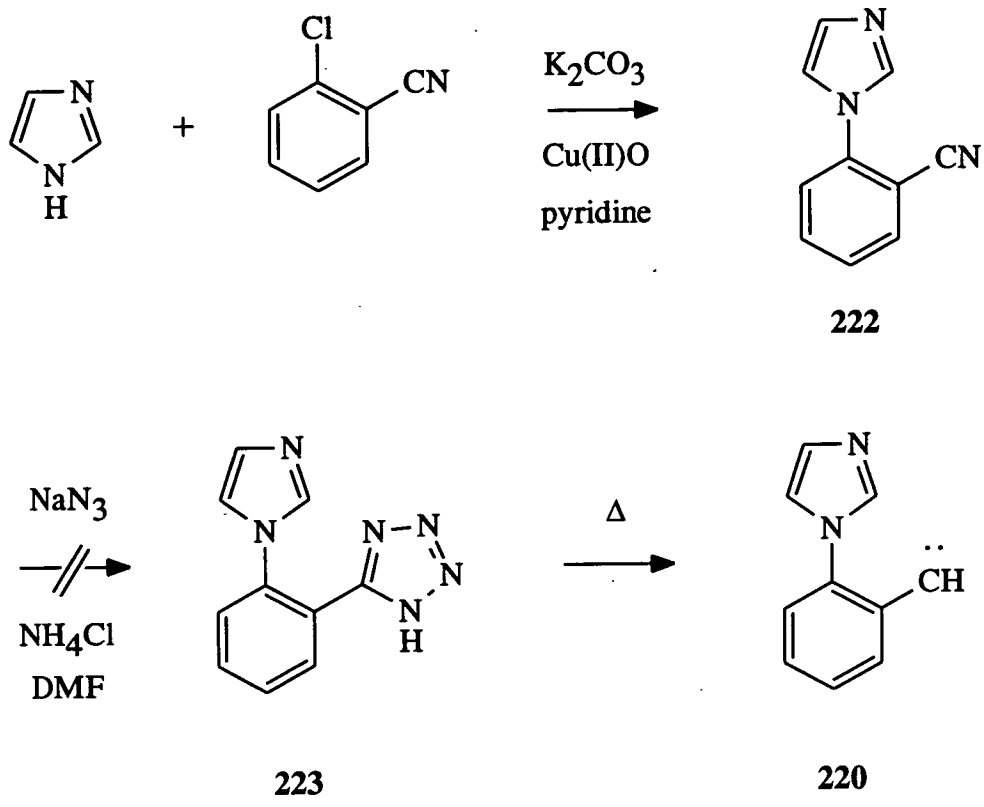
d. ATTEMPTED SYNTHESIS OF 9*H*-IMIDAZO[1,2-*a*]INDOLE

In order to augment the result in part b above, it was of interest to attempt to generate the corresponding carbene. If the carbene reacted in a similar manner to the nitrene then 9*H*-imidazo[1,2-*a*]indole **221** would be the only product obtained, *via* C_2-H insertion of the carbene.



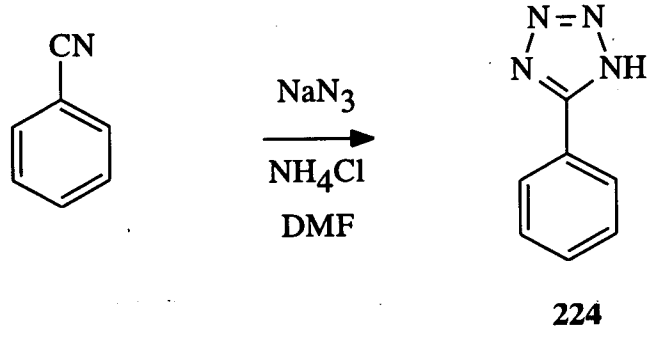
221

It is known that tetrazoles collapse to carbenes under the conditions of flash vacuum pyrolysis.[67] The Ullmann type condensation of pyrazole and 2-chlorobenzonitrile afforded the nitrile **222** in 21% yield after chromatography. Generation of the tetrazole **223** was attempted by heating **222** with sodium azide and ammonium chloride in DMF,[68] however only unreacted starting material was recovered (Scheme 63).



Scheme 63

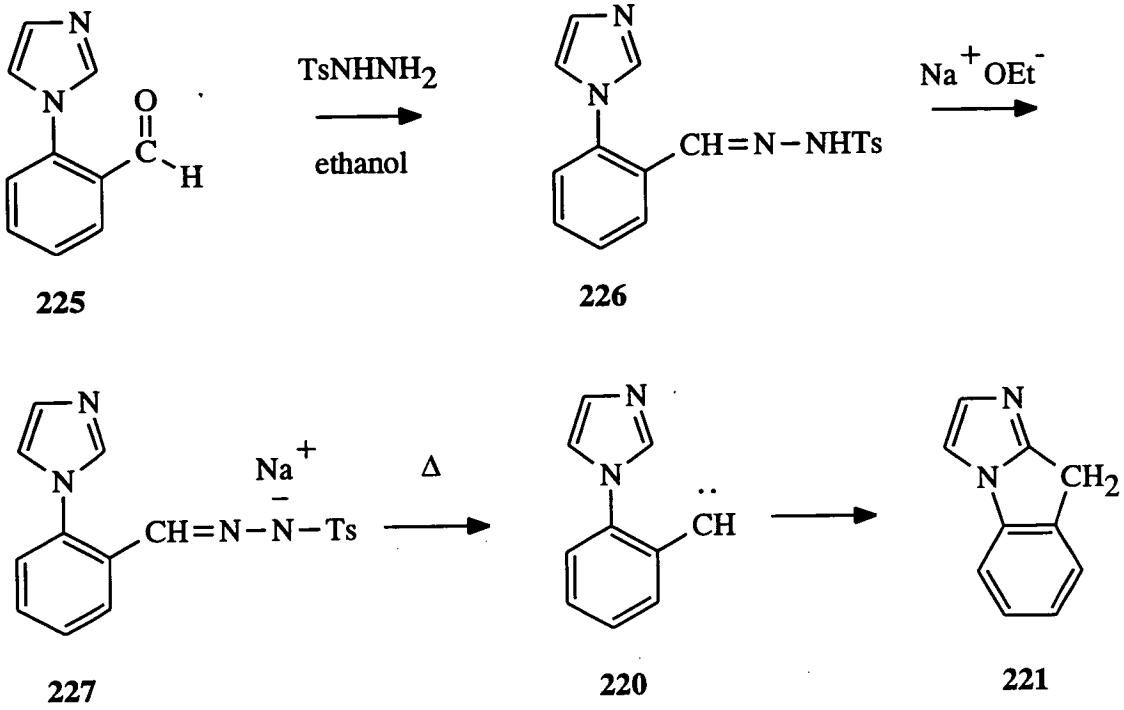
Under identical conditions phenyltetrazole **224** was obtained from benzonitrile (Scheme 64). Therefore it is possible the reaction of **222** failed due to steric reasons.



Scheme 64

Another possible route to carbenes involves flash vacuum pyrolysis of the sodium salt of the appropriate tosyl hydrazone. Treatment of the aldehyde **225** with *p*-

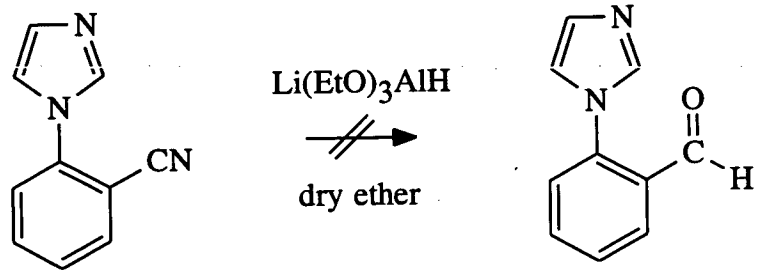
tosylhydrazide should give the tosyl hydrazone **226**, then subsequent displacement with sodium ethoxide should generate the sodium salt **227** (Scheme 65).



225 **226** **227** **220** **221**

Scheme 65

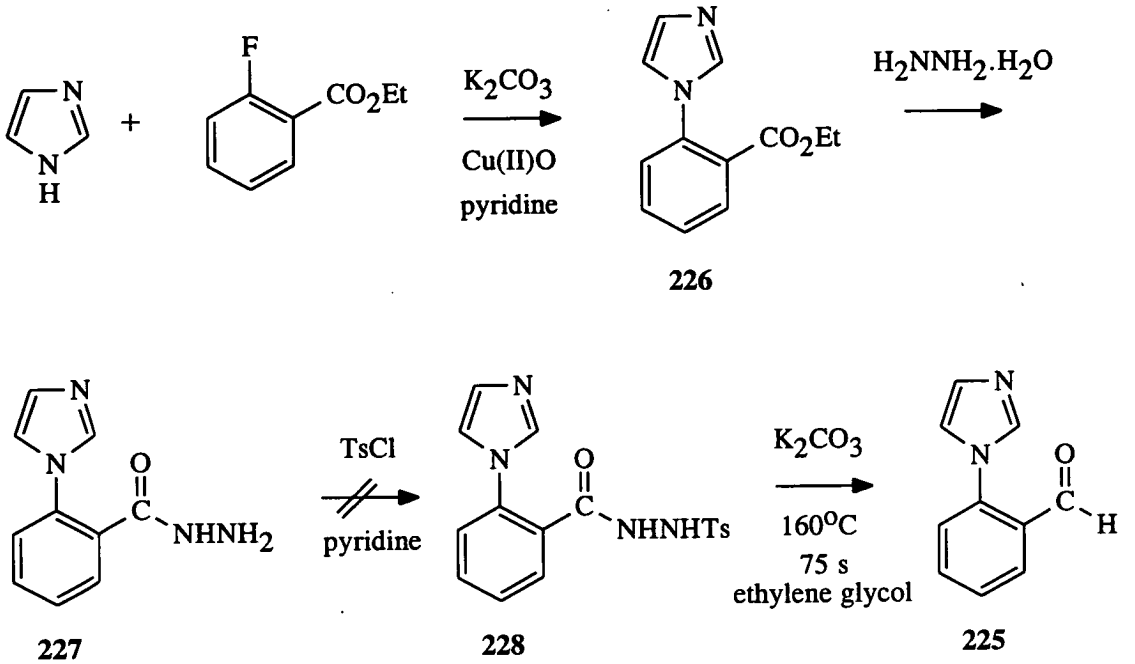
The initial route to the aldehyde **225** was based on a report by Brown[69] which utilised the reaction of reduced activity hydrides with nitriles. Lithium aluminium hydride was treated with anhydrous ethyl acetate to generate lithium triethoxyaluminium hydride. Reaction with the nitrile **222** failed to afford any trace of aldehyde product **225** (Scheme 66).



222 **225**

Scheme 66

The McFadyen-Stevens reaction for the conversion of esters to aldehydes was tried.[70] The ester **226** was obtained in 27% yield by the condensation of ethyl *o*-fluorobenzoate with imidazole. Hydrazide **227** formation was effected in 73% yield after heating **226** under reflux with an excess of hydrazine hydrate. Tosylation of the hydrazide **227** was attempted by the standard method of treatment with tosyl chloride in pyridine however no extractable product **228** was obtained (Scheme 67).



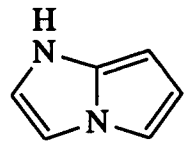
Scheme 67

Future efforts directed towards the key aldehyde **225** may involve other methods of reducing the readily obtained ester **226**.

B. SYNTHESIS AND STUDIES OF PYRROLOIMIDAZOLES

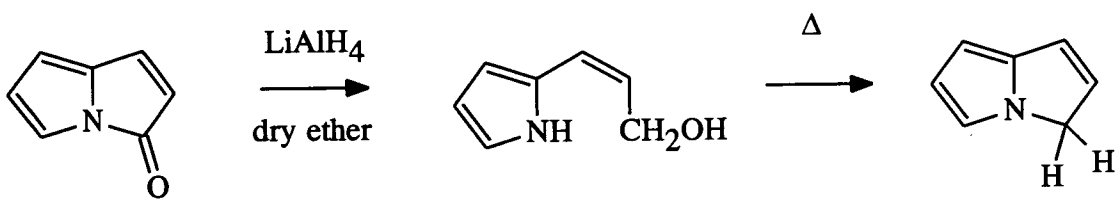
1. INTRODUCTION

1*H*-Pyrrolo[1,2-*a*]imidazole **229** has been identified as a possible magenta colour coupler.



229

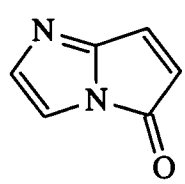
Early studies[71] had indicated that the analogous pyrrolizine system **232** could be obtained by the flash vacuum pyrolysis of allylic alcohol **231**. The route to the pyrolysis precursor **231** involved lithium aluminium hydride reductive ring-opening of the well known pyrrolizin-3-one system **230** (Scheme 68).



230 **231** **232**

Scheme 68

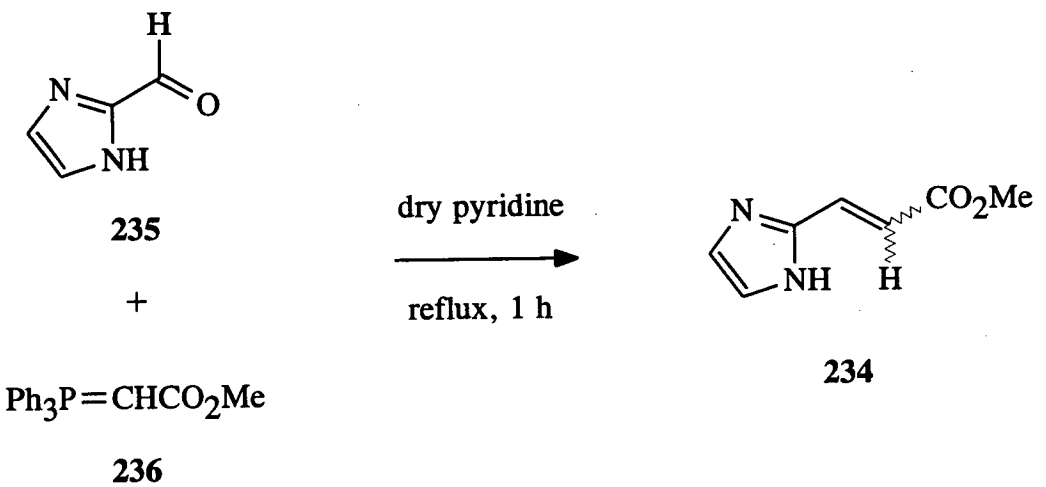
Extension of this work using pyrrolo[1,2-*a*]imidazol-5-one **233** could provide a new route to the desired title compound **229.**



233

2. SYNTHESIS OF PYRROLO[1,2-*a*]IMIDAZOLE

Previous work[65] on the synthesis of pyrroloimidazol-5-ones centred on the flash vacuum pyrolysis of 3-(imidazolyl)propenoic acid esters. The relevant ester in the proposed synthesis is methyl-3-(imidazol-2-yl)propenoate **234** which was prepared by the Wittig olefination of imidazole-2-carbaldehyde **235** with methyl (triphenylphosphoranylidene)acetate **236**. Imidazole-2-carbaldehyde **235** was prepared by the Organic Synthesis method of Godefroi and co-workers[72] however latterly the commercially available material was used. The Wittig reaction was carried out at reflux in pyridine and was monitored by t.l.c. (Scheme 69).



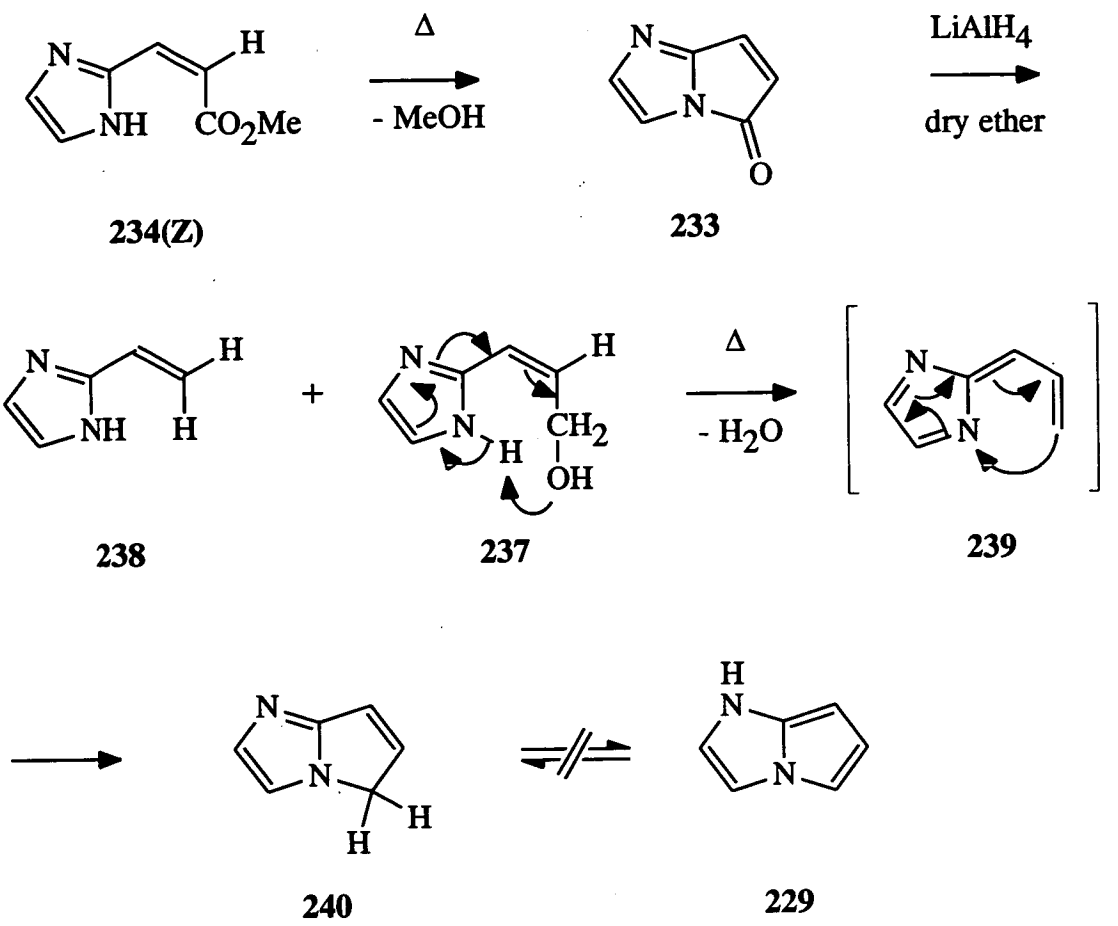
Scheme 69

The two stereoisomers of the product **234** were separated on the basis of the low solubility of the (*E*)-isomer in all but the most polar solvents, and also on the volatility of the (*Z*)-isomer which was obtained *via* vacuum subiimation. The reaction proceeded in 60% yield with an *E/Z* ratio of 2:1, the presence of the (*Z*)-isomer possibly a result of favourable intramolecular hydrogen bonding interactions.[65]

The temperature of flash vacuum pyrolysis of the ester **234** to afford pyrroloimidazol-5-one **233** is dependent on the configuration of the substrate.[65] There is evidence to

suggest that (*E*)/(*Z*)-isomerisation occurs in the gas phase as illustrated by required pyrolysis temperatures for the methyl 3-(imidazol-2-yl)propenoate **234** system. For quantitative conversion to product, the (*E*)-isomer requires temperatures *ca.* 150°C higher than the corresponding (*Z*)-isomer. Hence it may be assumed that the ring closure process requires the ester to be in the (*Z*)-configuration.

Flash vacuum pyrolysis of **234** (*Z*) at 800°C gives the brightly orange coloured pyrrolo[1,2-*a*]imidazol-5-one **233** in 76% yield. In order to avoid polymerisation of the product, the crude pyrolysate was immediately dissolved in freshly distilled ether and the subsequent lithium aluminium hydride reduction was carried out. The ring-opening reduction reaction was judged to be complete when the characteristic orange colour of pyrroloimidazolone **233** disappeared. Product yields were optimised using continuous extraction with dichloromethane as a result of the low partition coefficient of the product **237** from aqueous into organic solvents. A yield of 59% was obtained for 3-imidazol-2-yl-2-propen-1-ol **237**. In addition a volatile impurity of 2-vinylimidazole **238** was observed during purification by kugelrohr distillation as confirmed by the concurrence of ^{1}H NMR data with published values.[73] It is not clear whether the formation of **238** is a result of the pyrolysis or reduction process. Pyrolysis of allylic alcohol **237** at 650°C resulted in formation of the 5*H*-tautomer **240** with no trace of the desired 1*H*-tautomer as shown by a characteristic resonance integrating to two protons at δ_H 4.4 in the ^{1}H NMR spectrum. Presumably on pyrolysis the pericyclic process occurs with the expulsion of water to give the intermediate diene **239**. Ring closure to the imidazole ring affords the product **240**, a known compound in the literature, in 66% yield (Scheme 70).[74]



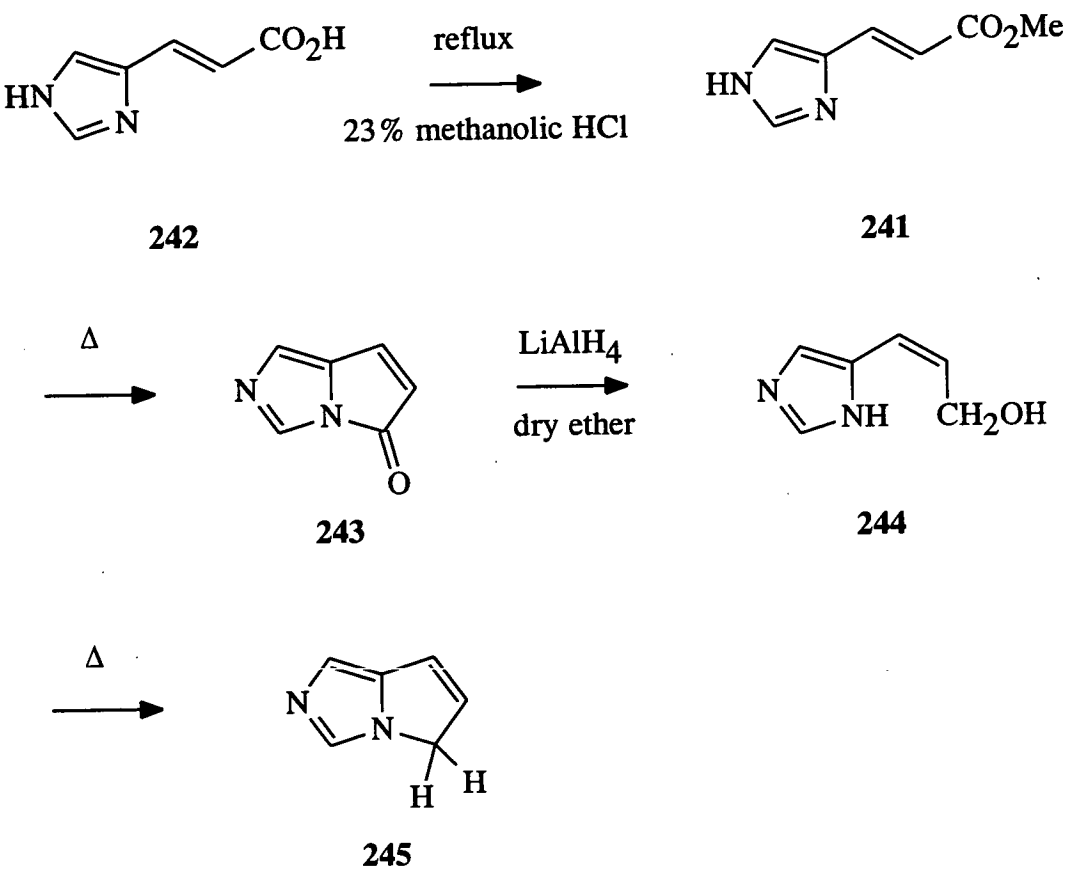
Scheme 70

Unfortunately, the product **240** had no photographic activity on treatment with suitable developer and oxidiser solutions.

3. SYNTHESIS OF PYRROLO[1,2-*c*]IMIDAZOLE

In view of the success of the previous methodology, extension to the isomeric pyrrolo[1,2-*c*]imidazole system was attempted. The pyrolysis precursor methyl 3-(imidazol-4-yl)propenoate **241** was conveniently prepared by esterification of the commercially available propenoic acid, urocanic acid **242** as outlined by Cohen.[75] In doing so, the requirement for isomeric separation at this stage was removed. Pyrolysis at 850°C resulted in the formation of the bright orange pyrrolo[1,2-

c]imidazol-5-one **243** product. However the pyrolysis also generated quantities of polymeric impurity so that the total pyrolysate was found to be only partially soluble in dry ether; this system appears to be more susceptible to polymerisation than the pyrrolo[1,2-*a*]imidazol-5-one **233** system. Decomposition of the substrate in the inlet was also observed, however this was reduced to a large extent through the use of the mercury diffusion pump. Immediately after pyrolysis, the product was dissolved in dry ether and subjected to lithium aluminium hydride reduction as previously described to afford the appropriate allylic alcohol **244** in 50% yield. Similar extraction problems were encountered as in the previous section. Pyrolysis of **244** at 650°C gave 71% yield of the 5*H*-tautomeric product **245** as confirmed by comparison with literature data (Scheme 71).[74,76]



Scheme 71

4. NMR SPECTRA

The ^{1}H and ^{13}C spectra of 5*H*-pyrrolo[1,2-*a*]imidazole **240** and 5*H*-pyrrolo[1,2-*c*]imidazole **245** were assigned using Nuclear Overhauser enhancement experiments and fully coupled ^{13}C-^{1}H spectra.

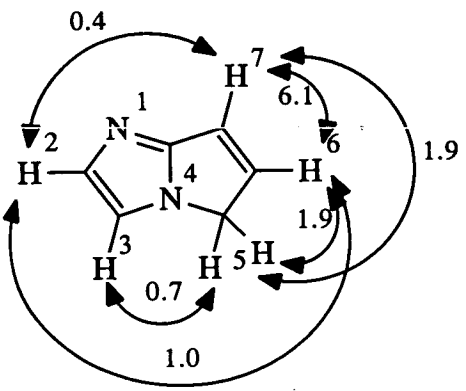
(i) 5*H*-pyrrolo[1,2-*a*]imidazole 240

Tables 17 and 18 detail ^{1}H and ^{13}C data which have never been reported previously.

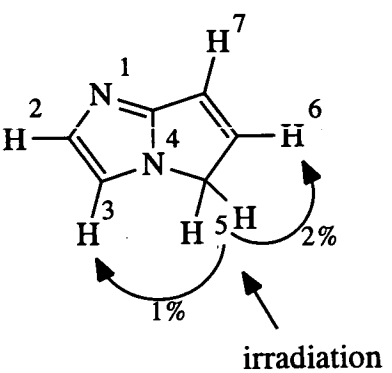
Table 17: ^{1}H NMR Parameters for 5*H*-pyrrolo[1,2-*a*]imidazole **240** in [^{2}H] chloroform

δ_H / ppm	Coupling Constants / Hz	Assignment	Pattern
7.14	-	H-3	m
7.11	-	H-2	m
6.72-6.69	^{3}J 6.1, ^{4}J 1.9, ^{5}J 0.4	H-7	dtd
6.66-6.63	^{3}J 6.1, ^{3}J 1.9, ^{6}J 1.0	H-6	dtd
4.39	^{3}J and ^{4}J 1.9, ^{4}J 0.7	H-5	td

Figure 18: **a.** ^{1}H-^{1}H Coupling Constants (Hz) and **b.** Nuclear Overhauser Enhancements for 5*H*-pyrrolo[1,2-*a*]imidazole **240**



a



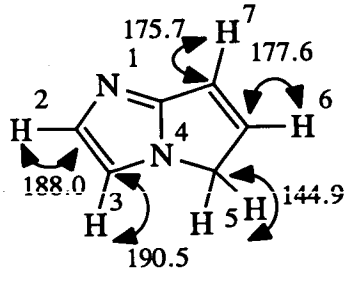
b

Nuclear Overhauser enhancement experiments showed that irradiation of the two H-5 protons at δ_H 4.39 resulted in a 2% increase in intensity of the resonance at δ_H 6.65 and a 1% increase in the intensity of the resonance at δ_H 7.14 corresponding to protons H-6 and H-3 respectively. All other protons and couplings were assigned by inspection and analogy with similar structures.[64a]

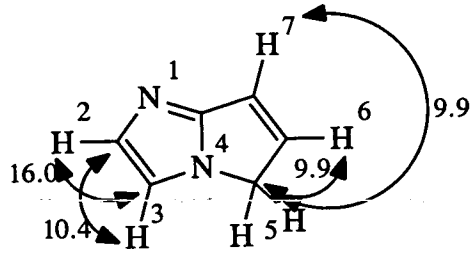
Table 18: ^{13}C NMR Parameters for 5*H*-pyrrolo[1,2-*a*]imidazole **240** in [^2H] chloroform

δ_C / ppm	Coupling Constants / Hz	Assignment	Pattern
134.52	$^1J_{CH}$ 175.7	C-7	d
132.66	$^1J_{CH}$ 188.0, $^2J_{CH}$ 10.4	C-2	dd
122.18	$^1J_{CH}$ 177.6	C-6	d
116.02	$^1J_{CH}$ 190.5, $^2J_{CH}$ 16.0	C-3	dd
50.35	$^1J_{CH}$ 144.9, $^2J_{CH}$ and $^3J_{CH}$ 9.9	C-5	tt

Figure 19: **a.** $^1J_{CH}$ - **b.** $^2J_{CH}$ - and $^3J_{CH}$ - ^{13}C-^1H NMR Coupling Constants (Hz) for 5*H*-pyrrolo[1,2-*a*]imidazole **240**



a



b

The ^{13}C spectrum was assigned by inspection and a fully coupled ^{13}C-^{1}H spectrum allowed assignment of all long and short range couplings by comparison with analogous systems.[64a]

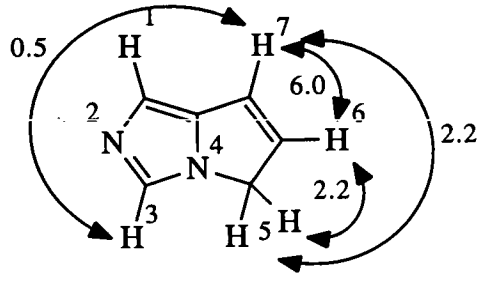
(ii) 5*H*-pyrrolo[1,2-*c*]imidazole 245

Tables 18 and 19 detail ^{1}H and ^{13}C data which have never been reported previously.

Table 18: ^{1}H NMR Parameters for 5*H*-pyrrolo[1,2-*c*]imidazole **245** in [^{2}H] chloroform

δ_H / ppm	Coupling Constants / Hz	Assignment	Pattern
7.66	-	H-3	s
6.82	-	H-1	s
6.63-6.60	^{3}J 6.0, ^{4}J 2.2, ^{5}J 0.5	H-7	dtd
6.29-6.26	^{3}J 6.0, ^{3}J 2.2	H-6	dt
4.51-4.50	^{3}J and ^{4}J 2.2	H-5	td

Figure 20: ^{1}H-^{1}H Coupling Constants (Hz) for 5*H*-pyrrolo[1,2-*c*]imidazole **245**

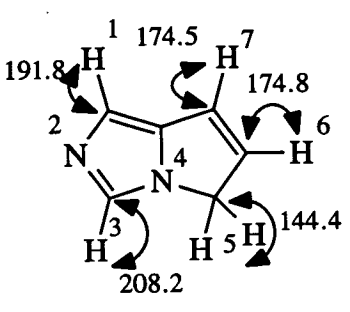


a

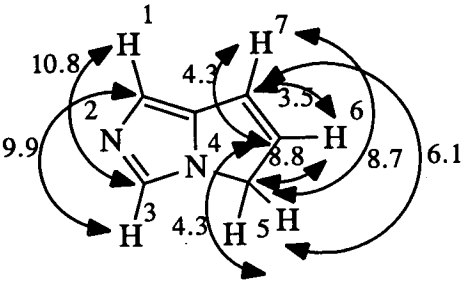
Table 19: ^{13}C NMR Parameters for 5*H*-pyrrolo[1,2-*c*]imidazole **245** in [^{2}H] chloroform

δ_C / ppm	Coupling Constants / Hz	Assignment	Pattern
132.38	$^{1}J_{CH}$ 208.2, $^{3}J_{CH}$ 10.8	C-3	dd
129.22	$^{1}J_{CH}$ 174.5, $^{2}J_{CH}$ 3.5, $^{3}J_{CH}$ 6.1	C-7	dtd
121.27	$^{1}J_{CH}$ 174.8, $^{2}J_{CH}$ 4.3	C-6	dq
116.74	$^{1}J_{CH}$ 191.8, $^{3}J_{CH}$ 9.9	C-1	dd
49.92	$^{1}J_{CH}$ 144.4, $^{2}J_{CH}$ 8.7, $^{3}J_{CH}$ 8.8	C-5	tdd

Figure 21: **a.** $^{1}J_{CH}$ - **b.** $^{2}J_{CH}$ and $^{3}J_{CH}$ - ^{13}C-^{1}H NMR Coupling Constants (Hz) for 5*H*-pyrrolo[1,2-*c*]imidazole **245**



a



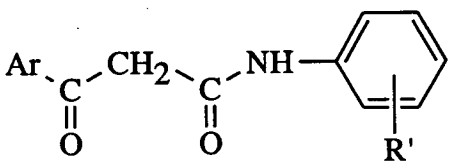
b

The ^{13}C spectrum was assigned on comparison with analogous systems[64a] and also by inspection. A fully coupled ^{13}C-^{1}H spectrum allowed assignment of all long and short range couplings.

C. SYNTHESIS AND PHOTOGRAPHIC EVALUATION OF NOVEL HETEROAROYLACETANILIDES

1. INTRODUCTION

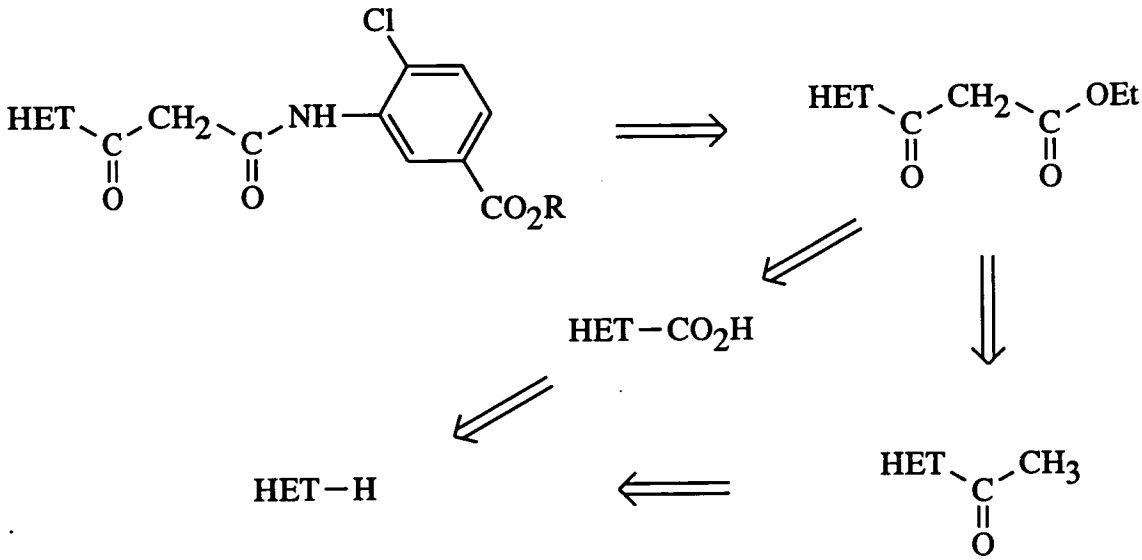
The heteroaroylacetanilides discussed in this chapter are open-chain active methylene compounds which are known to be yellow colour couplers in photography.[1] The general structure of these compounds is shown, where secondary substituents Ar and R' influence key properties such as the reactivity of the coupler towards the oxidised developer, the visible absorption spectrum of the image dye and its light and chemical stability.



246

Previous investigations into heteroaroylacetanilides with the aryl moiety based on furan and thiophene have been conducted, however the obvious alternative of pyrrole had not been considered. The aim of this project was to explore this area and also expand to include heterocycles with electron donating substituents which would alter the hue of the resultant azamethine dye. Suitable heterocyclic targets were methoxy- and methyl-substituted thiophenes in addition to *N*-phenyl and *N*-methyl pyrroles.

The optimum synthetic strategy for synthesis of these systems is shown by the retrosynthetic analysis (Scheme 72). Two routes to the key β-keto ester were considered using either methyl ketones or carboxylic acids as precursors.



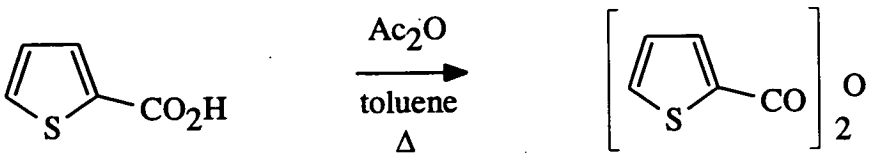
Scheme 72

2. β-KETO ESTER FORMATION (1)

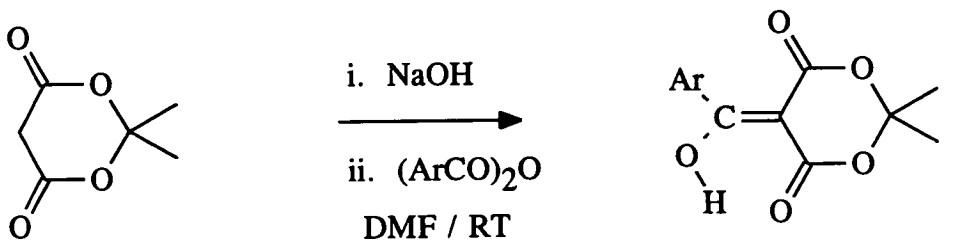
Preliminary studies towards a direct synthesis of β-keto esters were carried out for thiophene as the heterocyclic moiety. Thus establishment of a methodology would allow application to other targeted heterocyclic systems.

Initial methods of β-keto ester synthesis were based on work by Houghton and Lapham[77] involving treatment of the sodium salt of Meldrum's acid with carboxylic acid anhydrides. The sodium salt of Meldrum's acid was prepared in 88% yield by treatment with aqueous sodium hydroxide.

Thiophene carboxylic acid anhydride **247** was prepared in 52% yield by heating 2-thiophene carboxylic acid with acetic anhydride in toluene. In DMF, the sodium salt of Meldrum's acid is readily acylated by carboxylic anhydrides. The corresponding methyl keto ester should be generated by heating under reflux in methanol. Application of this procedure to thiophene carboxylic acid anhydride **247** failed to afford any extractable product **249**, however the method outlined does not include the synthesis of heteroaromatic containing β-keto esters (Scheme 73).

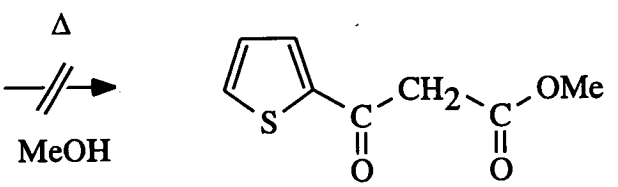


247



Ar = thiophene

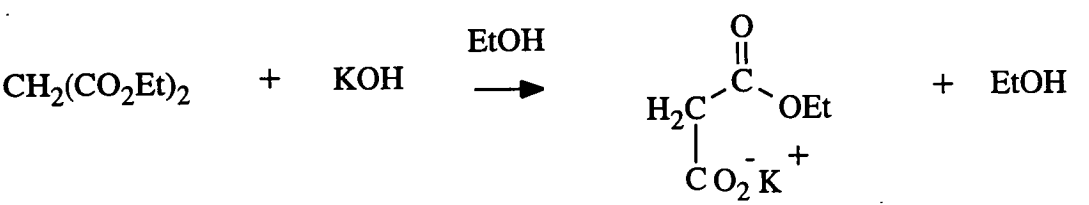
248



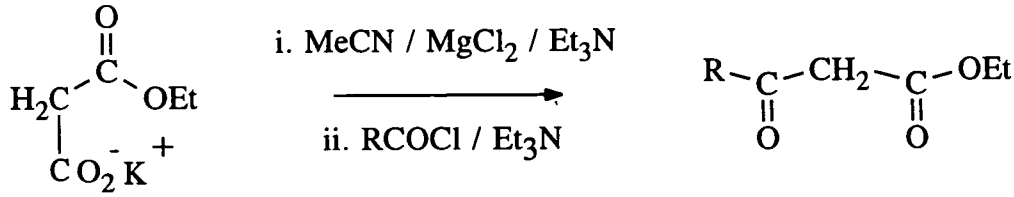
249

Scheme 73

Wemple and co-workers[78] have outlined a high yielding, economical method for the preparation of β-keto esters which employs the reaction of acid chlorides with potassium ethyl malonate **250** in the presence of magnesium chloride-triethylamine base system. Potassium ethyl malonate **250** was prepared 73% yield according to the method of Strube in Organic Synthesis (Scheme 74).[79]



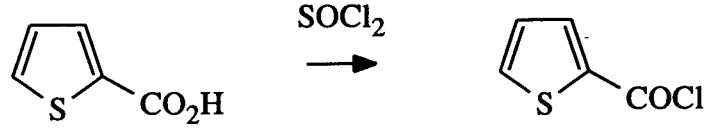
250



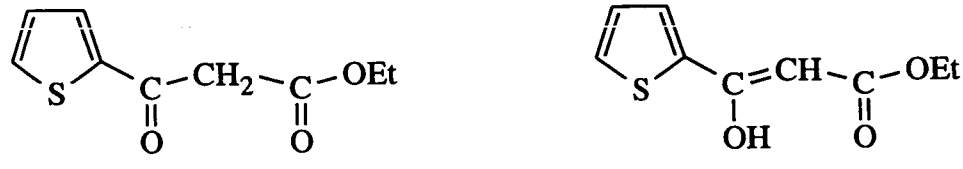
250 **251**

Scheme 74

The model compound 2-thiophene carboxylic acid chloride **252** was prepared in 91% yield by the reaction of 2-thiophenecarboxylic acid with thionyl chloride. The acid chloride **252** was added to potassium ethyl malonate **250** with the magnesium chloride-triethylamine base system in acetonitrile. Under these conditions the resulting magnesium malonate complex was readily acylated to afford the required β-keto ester **253** in 74% yield. The ^{1}H and ^{13}C NMR spectra reveal the existence of tautomerism with a 2 : 1 ratio of keto (δ_H 3.90 and δ_C 61.48) : enol (δ_H 5.86 and δ_C 102.13) tautomeric forms as indicated by the methylene and methine resonances respectively (Scheme 75).



252

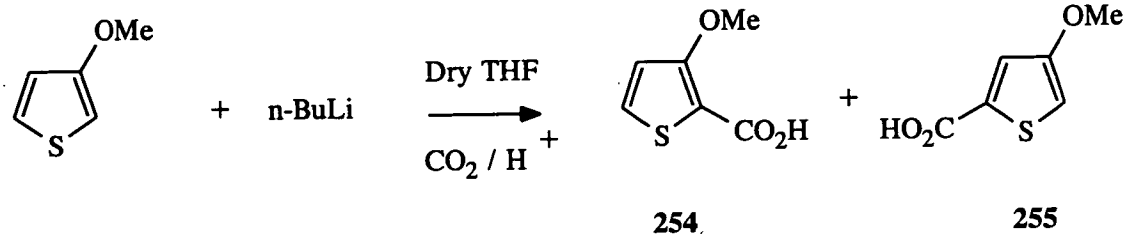


253 : **253**

2 : 1

Scheme 75

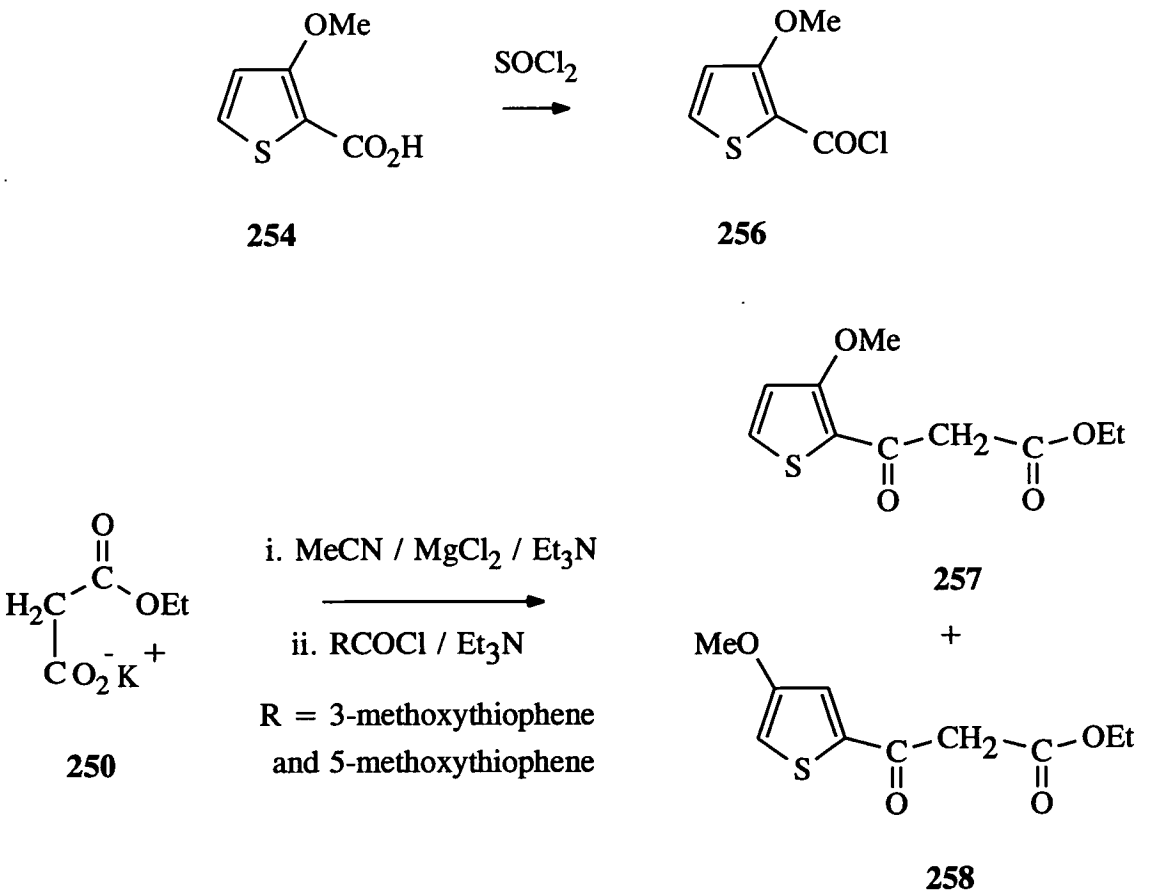
This method was applied to the commercially available 3-methoxythiophene system. 3-Methoxythiophene-2-carboxylic acid **254** was synthesized by room temperature metallation of 3-methoxythiophene with *n*-butyl lithium followed by quenching with solid CO_2 and acidic work-up. The desired product **254** was obtained in 74% yield (Scheme 76).



254 **255**

Scheme 76

The proton coupling constant for the 2,3-disubstituted thiophene **254** is 5.5 Hz. A 12% impurity of another isomer was observed in the ^1H NMR spectrum, as revealed by the smaller coupling constant of 1.9 Hz. This was deduced to be 3-methoxythiophene-5-carboxylic acid **255** from comparison of proton coupling constants with analogous 2,4-disubstituted thiophenes.[80] The conversion to the acid chloride **256** was effected as before in quantitative yield and the subsequent acylation was carried out to give the required β-keto ester **257** again existing in a tautomeric equilibrium as indicated by the ^1H and ^{13}C NMR spectra. The keto form shows methylene resonances at δ_H 3.84 and δ_C 60.68 and the enol form reveals peaks at δ_H 6.06 and δ_C 107.43 for the methine position. In addition, the product was contaminated with the 5-carboxylic acid isomer **258** which was carried through from the lithiation reaction (Scheme 77). The overall yield of the reaction was 85%.

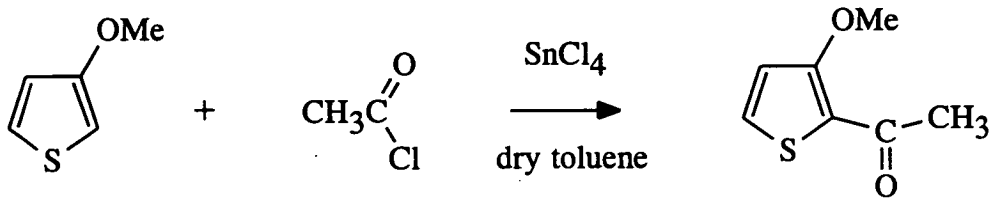


Scheme 77

The described route gives reasonable yields of required β-keto esters however an alternative route *via* acetylated heterocycles was investigated.

3. *C*-ACETYLATION REACTIONS OF THIOPHENES AND PYRROLES

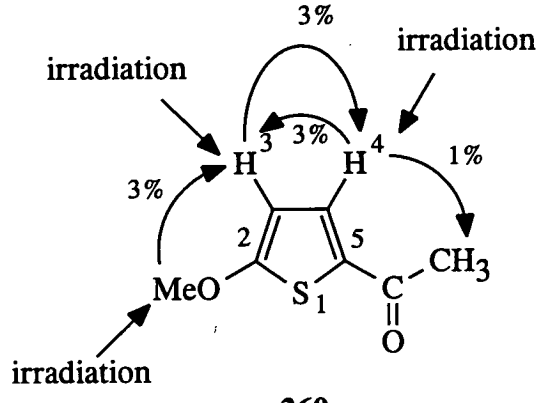
Friedel-Crafts acetylation of 3-methoxythiophene with acetyl chloride in the presence of stannic chloride, a weak Lewis acid, was effected in dry toluene at room temperature as described for the acylation of 3-methoxythiophene with cinnamic acid chlorides.[81] 2-Acetyl-3-methoxythiophene **259** was generated as orange crystals in 80% yield after recrystallisation or chromatography (Scheme 78). An X-ray crystal structure was also obtained (section 10).



259

Scheme 78

The same strategy was employed in the acetylation of 2-methoxythiophene, with desired product 2-acetyl-5-methoxythiophene **260** isolated in 30% yield after chromatography, a slight improvement on the literature yield of 24% obtained by acetylation at - 70°C.[82] The regiochemistry of the reaction was confirmed by nuclear Overhauser enhancement experiments (Figure 22).

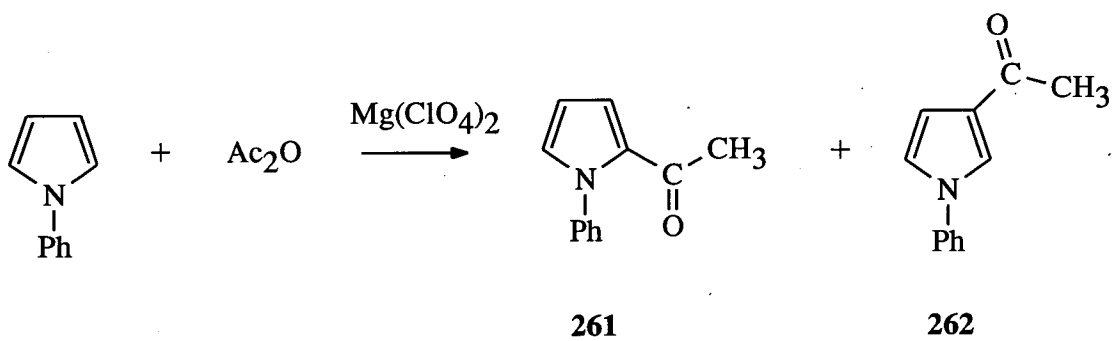


260

Figure 22 : Nuclear Overhauser Enhancements for **260**

Irradiation of the proton at δ_H 7.4 resulted in an enhancement of the resonance at δ_H 6.2 by 3%. The acetyl protons at δ_H 2.35 were enhanced by 1% indicating that the irradiated proton was H-4. Irradiation of H-3 gave a corresponding 3% increase in intensity of the signal for H-4 and on irradiation of the methoxy protons at δ_H 3.85 the signal for H-3 was enhanced by 3%.

The Friedel-Crafts acetylation of *N*-phenylpyrrole was similarly attempted, however both 2- and 3-acetylated isomers, **261** and **262** respectively, were afforded in addition to unreacted starting material. Conducting the reaction at -40°C and also using acetic anhydride instead of acetyl chloride failed to acetylate selectively in the 2-position. The literature method[83] for the preparation of 2-acetyl-*N*-phenylpyrrole **261** stated that the reaction proceeded in a selective manner using magnesium perchlorate catalyst in acetic anhydride. In our hands, however, both 2- and 3-acetylated *N*-phenylpyrroles, **261** and **262**, were isolated after column chromatography in 39% and 33% yields respectively by this method. Nevertheless the separation was efficient enough to be carried out on a 60 g scale and both isomers were used for β-keto ester formation. The regiochemistry of each isomer was determined by nuclear Overhauser enhancement using irradiation of the *ortho* protons of the phenyl group (Scheme 79).



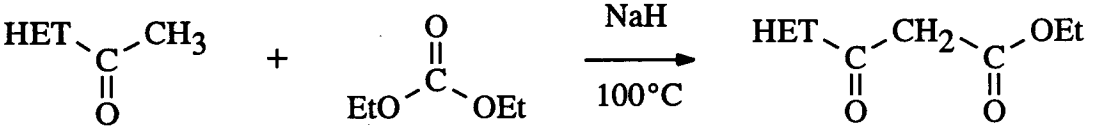
Scheme 79

It has been recently demonstrated by Jefford and co-workers[84] that the thermodynamically stable 2-acylated product may be formed regiospecifically from pyrrole by heating under reflux with an excess of acyl chloride in toluene in the absence of a catalyst. Reaction of *N*-phenylpyrrole with acetyl chloride was therefore attempted under these conditions. It transpired however that the major fraction after

264 hours was unreacted starting material (37%) with 2- and 3-acetylated products present in low yield, 8% and 9% respectively.

4. β-KETO ESTER FORMATION (2)

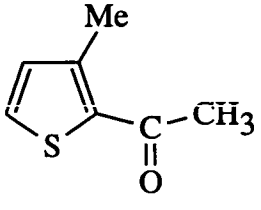
The Claisen condensation reaction was accomplished by heating appropriate acetyl compounds, **259 - 262**, with diethyl carbonate at 100°C in the presence of base and gave the required β-keto esters, **265 - 268**, in excellent yield. The use of potassium *tertiary* butoxide base met with limited success, although with sodium hydride, the reaction went to completion to give the required product as the keto tautomer exclusively (Scheme 80).



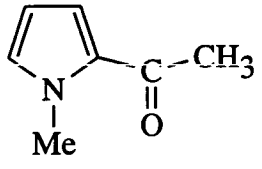
259 - 262 **265 - 268**

Scheme 80

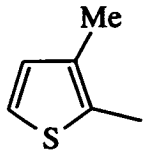
Two commercially available acetylated heterocycles, **263** and **264**, were also reacted in the above manner to give the appropriate β-keto esters, **269** and **270**, in excellent yield (Table 21).

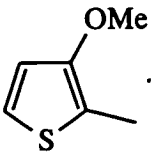


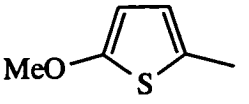
263

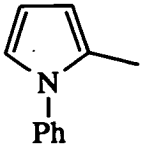


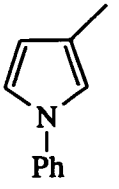
264

269 HET = 

265 HET = 

266 HET = 

267 HET = 

268 HET = 

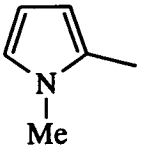
270 HET = 

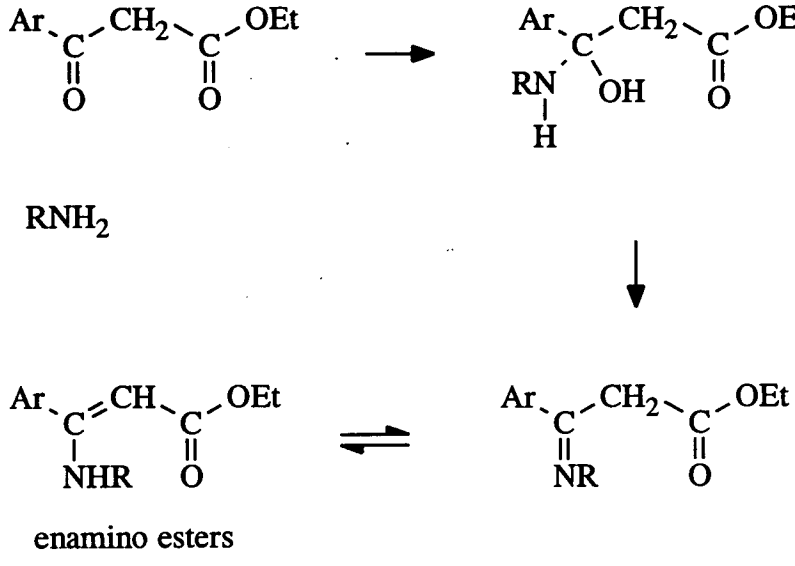
Table 21: Reaction yields for β-keto ester formation

Compound	Yield	Compound	Yield
269	100%	**267**	98%
265	99%	**268**	96%
266	91%	**270**	99%

5. β-KETO AMIDE FORMATION

The β-keto esters are difunctional compounds with the possibility of reaction of amines either at the aryl keto function yielding enamino esters (Scheme 81) or at the ester moiety to give the desired β-keto amide (Scheme 82).

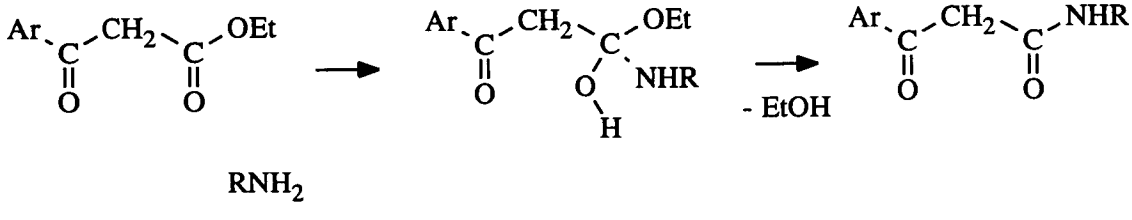
Reaction at keto



Scheme 81

Sano and co-workers[85] have shown that in the presence of acid catalysis the above route is favoured resulting in attack at the keto function. However in the absence of acid catalysis in high boiling solvents such as *para*-xylene then attack at the ester function occurs giving the desired β-keto amide (Scheme 82).

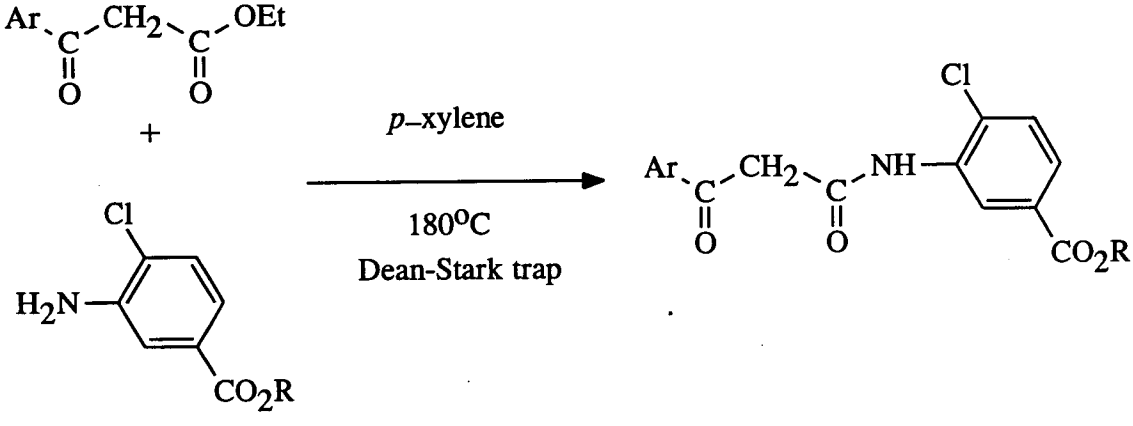
Reaction at ester



Scheme 82

In order to synthesize the desired acetanilides, the aforementioned β-keto esters were reacted with anilines **271** or **272** where R may either be methyl (**271**) or a long saturated chain (**272**) which was required for photographic testing purposes. This long chain "ballast" group is principally required to inhibit migration of the coupler between layers in photographic film although it may also play a role in altering other photographic properties.

The acetanilides were all prepared by heating the appropriate β-keto ester with the aniline **271** or **272** in *para*-xylene under a Dean and Stark trap using an oil bath at 180°C (Scheme 83).



271 R = Me

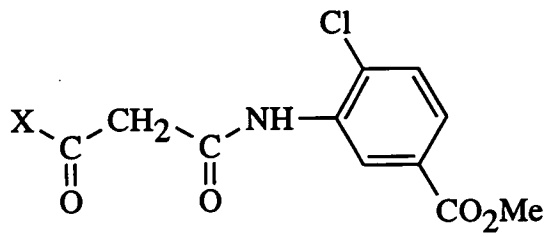
272 R = $C_{12}H_{25}$

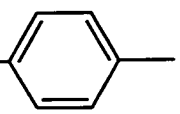
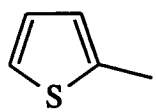
Scheme 83

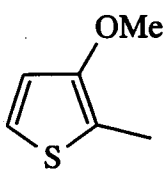
a. Methyl 4-chloro-3-[2-heteroaroylacetamido]benzoate formation

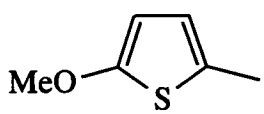
The title acetanilides were initially prepared as model compounds from the reaction of β-keto esters with methyl 3-amino-4-chlorobenzoate **271**. The generation of two standards, **273** and **274**, which are typical intermediates to compounds already in

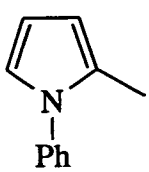
commercial use were also included. Reaction yields were found to be variable (Scheme 84, Table 22).

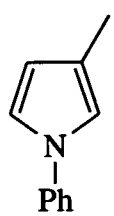


273 X = *t*Bu **274** X = MeO  **275** X = 

276 X = 

277 X = 

278 X = 

279 X = 

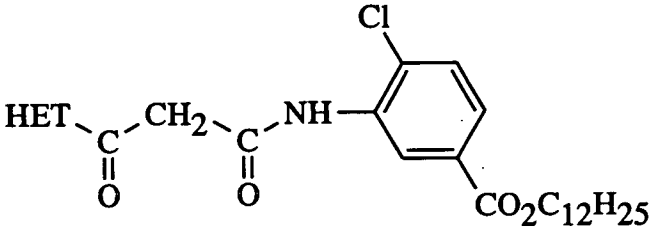
Scheme 84

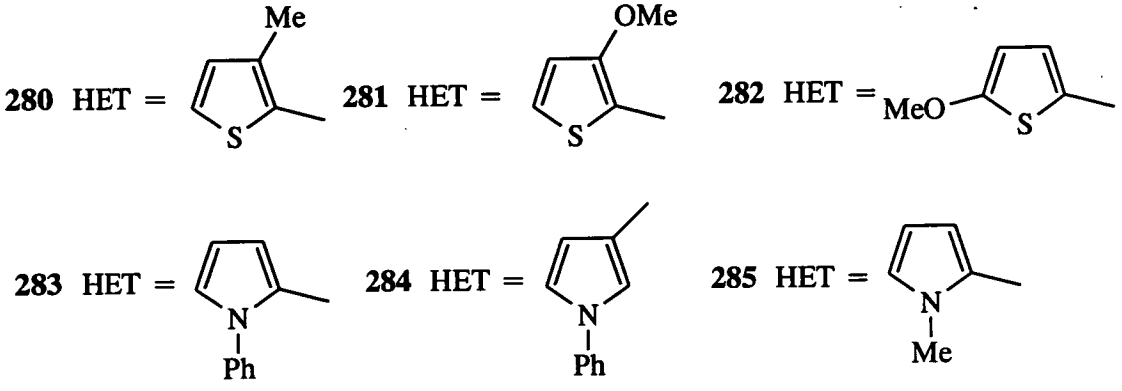
Table 22: Reaction yields for β-keto amide formation

Compound	Yield	Compound	Yield
273	17%	**277**	62%
274	79%	**278**	74%
275	17%	**279**	48%
276	63%		

b. Dodecyl 4-chloro-3-[2-heteroaroylacetamido]benzoate formation

This group of acetanilides were prepared in improved yield from the reaction of β-keto esters with dodecyl 3-amino-4-chlorobenzoate **272** (Scheme 85, Table 23).





Scheme 85

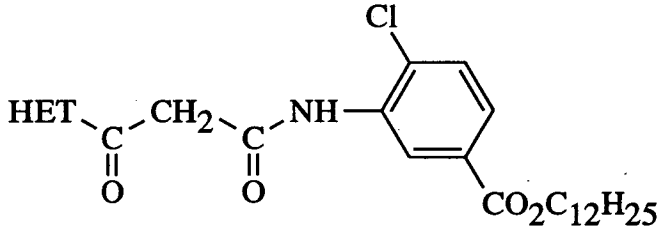
Table 23: Reaction yields for β-keto amide formation

Compound	Yield	Compound	Yield
280	99%	**283**	61%
281	65%	**284**	73%
282	52%	**285**	100%

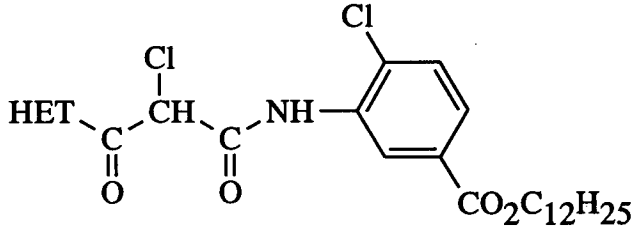
6. CHLORINATION OF β-KETO AMIDES

The β-keto amides generated thus far are four-equivalent yellow colour couplers. For photographic application, the couplers may be modified by incorporation of "coupling-off groups", suitable leaving groups which allow dye formation with two equivalents of oxidising material (see Introduction, Section A).

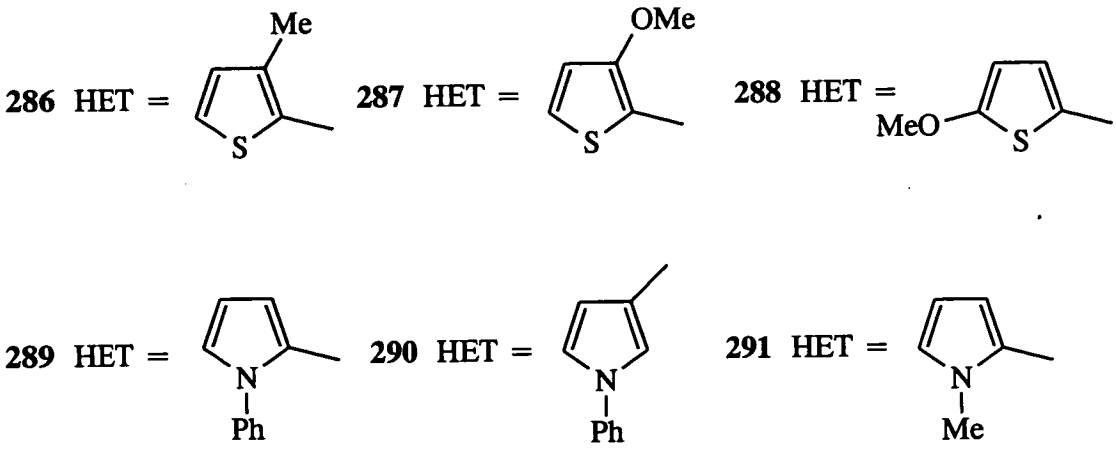
Chlorination of the β-keto amides generated in section 5b with a slight excess of sulfuryl chloride in methylene chloride generated the desired dodecyl 4-chloro-3-[2-chloro-2-heteroaroylacetamido]benzoates in good yield (Scheme 86, Table 24). These intermediates were generally carried through to the next stage of the synthesis without purification.



280 - 285



286 - 291



Scheme 86

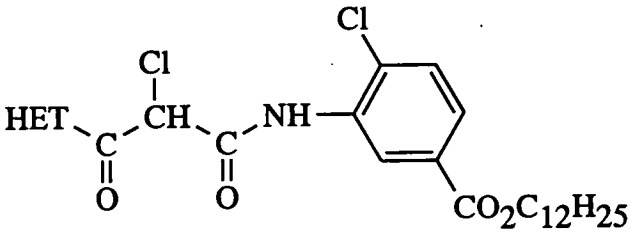
Table 24: Reaction yields for chloro-β-keto amide formation

Compound	Yield	Compound	Yield
286	100%(c)	**289**	100%(c)
287	87%	**290**	78%
288	100%(c)	**291**	65%

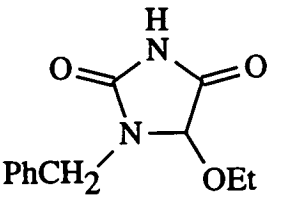
* (c) denotes crude yield

7. HYDANTOIN INCORPORATION

Although the chloro compounds **286 - 291** can function as two-equivalent couplers, it is common practice to employ heterocyclic coupling-off groups. The chloro precursors **286 - 291** prepared in the preceding section were dissolved in acetonitrile and reacted with the hydantoin-based compound **292** in the presence of tetramethylguanidine base. The use of the hydantoinyl coupling-off group serves to increase the reactivity of the coupler in film. The products of reaction were purified by column chromatography to afford the final couplers as glasses which crystallised over a period of months.

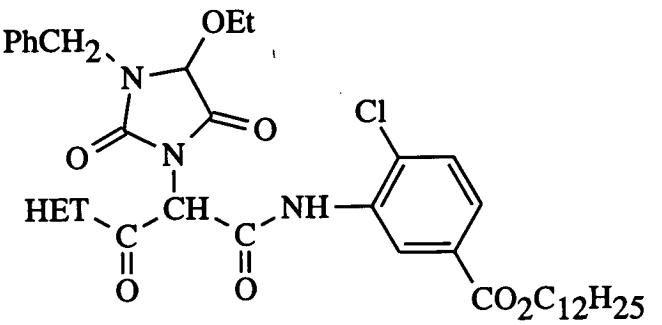


286 - 291

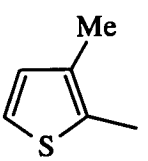


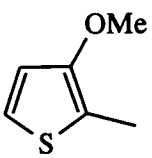
292

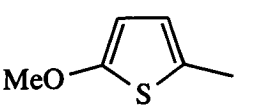
TMG MeCN

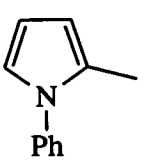


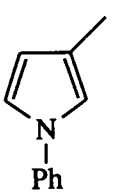
293 - 298

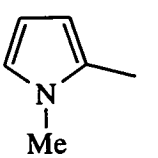
293 HET = 

294 HET = 

295 HET = 

296 HET = 

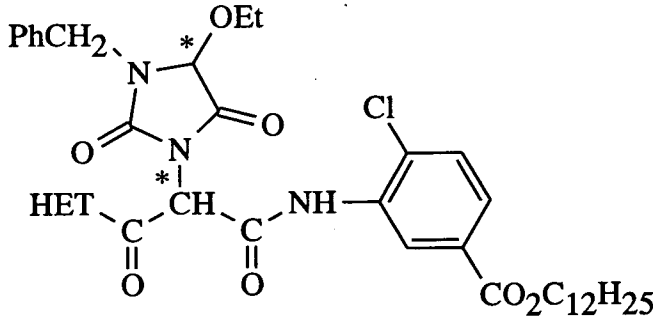
297 HET = 

298 HET = 

Scheme 87

Table 25: Reaction yields for hydantoin formation

Compound	Yield	Compound	Yield
293	35%	**296**	46%
294	46%	**297**	75%
295	55%	**298**	67%



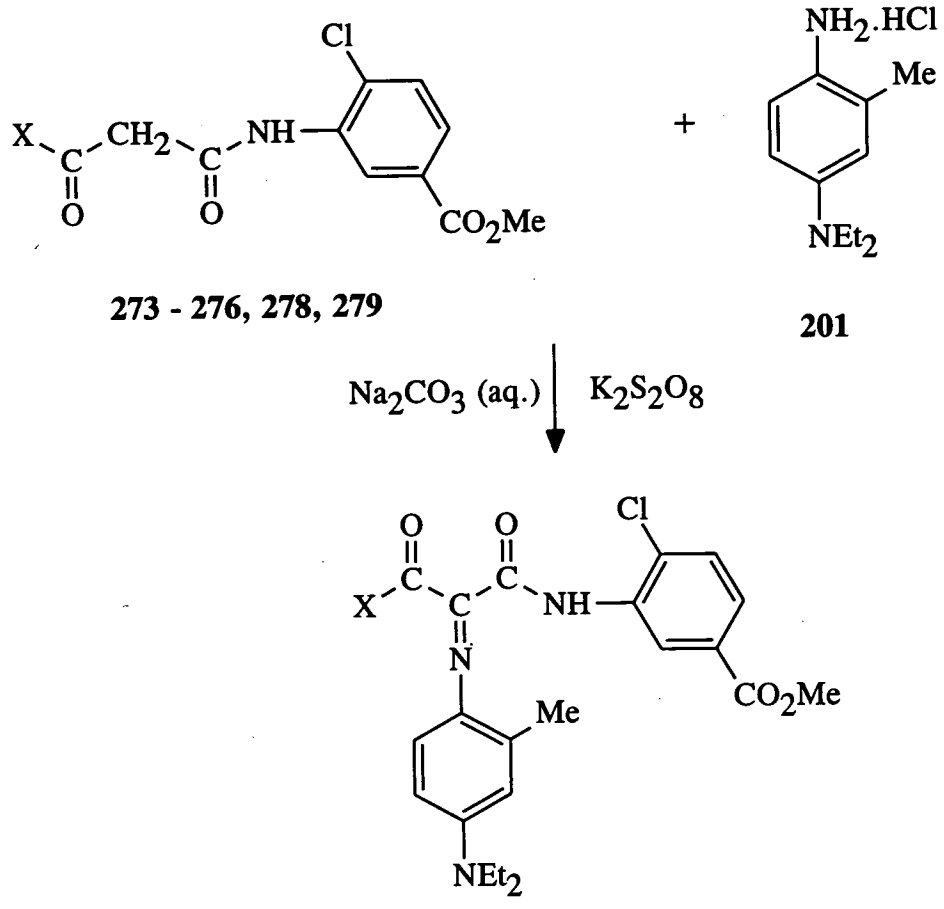
293 - 298

The final hydantoin couplers contain two chiral centres and, as such, exist as a mixture of two pairs of enantiomers, (R,R and S,S) and (R,S and S,R) in approximately equal proportions. As these were found to co-elute on column chromatography, ^{1}H and ^{13}C nmr data were obtained as the 50/50 mixture of diastereomers.

8. METHYL 4-CHLORO-3-[2-(4-DIETHYLAMINO-2-METHYLPHENYLIMINO)-2-AROYLACETAMIDO]BENZOATE FORMATION (YELLOW DYE FORMATION)

Yellow dyes were synthesized *via* the oxidative addition reaction of a β-keto amide coupler with a *p*-phenylenediamine developer, according to the method reported by Bailey[4] in 1977. Suitable four-equivalent couplers, prepared in section 5a, were reacted with 4-(*N,N*-diethylamino)-3-methylaminobenzene hydrochloride **201** in the presence of aqueous sodium carbonate. The resulting solution was oxidised with

potassium persulfate to generate the intense yellow dyes in variable yields after purification by preparative t.l.c. (Scheme 88, Table 26).



273 - 276, 278, 279

201

299 - 304

299 X = *t*Bu

300 X = MeO

301 X =

302 X =

303 X =

304 X =

Scheme 88

The visible spectra of dyes **299 - 304** were run in ethyl acetate to give a qualitative indication of the effects of substituents on the absorption maximum in solution which will act as a guide for the probable effect in film (Table 26).

Table 26: Visible spectra data for dyes **299 - 304** in ethyl acetate.

Compound	λ_{max} / nm	Yield	Compound	λ_{max} / nm	Yield
299	442	29%	**302**	432	16%
300	440	85%	**303**	436	35%
301	447.5	100%	**304**	438	35%

The thiophene-based dye **301** has an absorption maximum at 447.5 nm, significantly higher than the values obtained from the standards **299** and **300**. The presence of the methoxy substituent in **302** has the desired effect of inducing a large hypsochromic shift of 15.5 nm. This is expected on introduction of an electron donating group, as such groups increase the electronic energy gap between the ground state and the excited state. As a consequence of the destabilisation of the exited state, the energy requirement is greater resulting in a reduction of the wavelength of absorption (Figure 23).

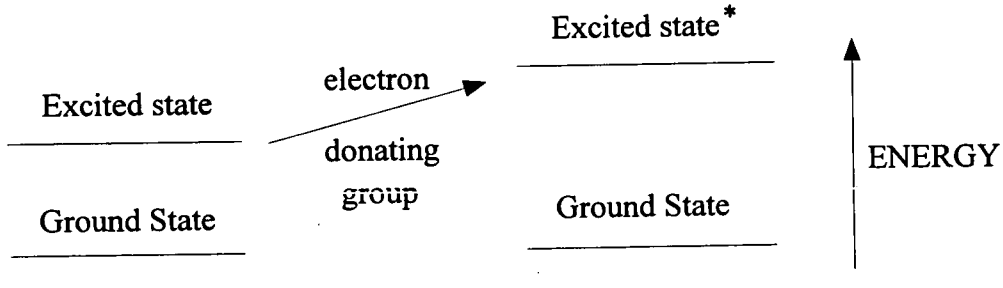


Figure 23: Representation of the effect of an electron donating substituent

The absorption maxima of the pyrrolyl derived dyes **303** and **304** are comparable to those of the standards **299** and **300** so it was not deemed necessary to explore further substituent patterns.

9. BASIC SENSITOMETRY AND PHOTOGRAPHIC EVALUATION

The final hydantoin incorporated heteroaroylacetanilide couplers **293 - 298** were submitted for genuine photographic testing. The compounds were dissolved in di-*n*-butyl phthalate, then mixed with gelatin and light sensitive silver halide. Coating of the photographic emulsion onto an acetate base material was performed in the dark. Once coated and dried, the film was cut into 35 mm strips and exposed to controlled amounts of light through the use of a "step wedge", an incremental light filter. The exposed strips were then developed to give the yellow dye product in increasing density as the amount of dye produced in the photographic emulsion layer is directly proportional to the degree of light exposure received by the silver halide (Figure 24). Measurement of dye density related to exposure to light affords a series of results pertaining to the activity of the coupler in film. These are represented in graphical form by a plot of density *vs.* log exposure, a DlogE curve, also known as a characteristic curve for a coupler. A typical DlogE curve is shown (Figure 25).

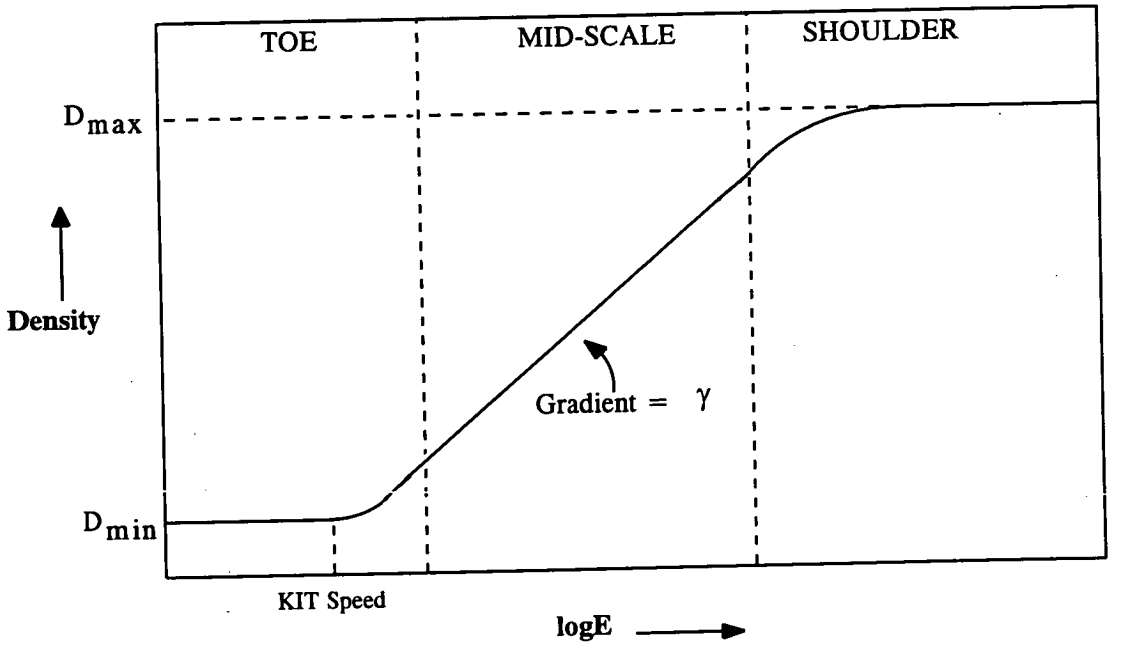
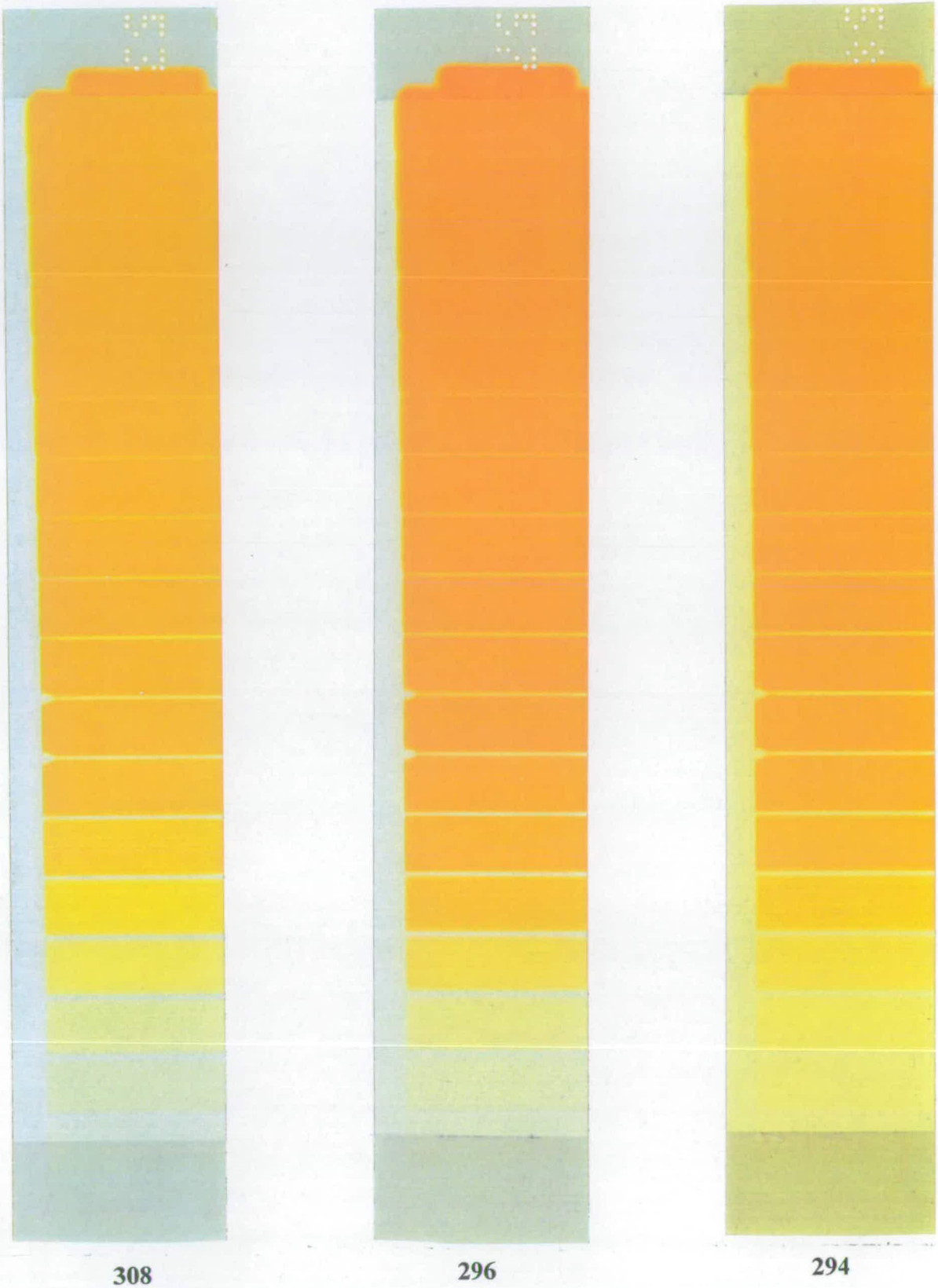


Figure 25: Curve of Density *versus* log Exposure

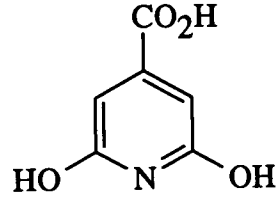
Figure 24: Photographic Coating Set



308 296 294

D_{min} is the density of dye formation at zero exposure to light, this is also known as fog. A good coupler should have a low value of D_{min} as residual dye formation is undesirable. D_{max} is the density of dye formation at maximium exposure to light and should be high in value for a good coupler. The gradient of the DlogE curve is the gamma (γ) value and is a measure of the activity of the coupler towards the oxidised developer.

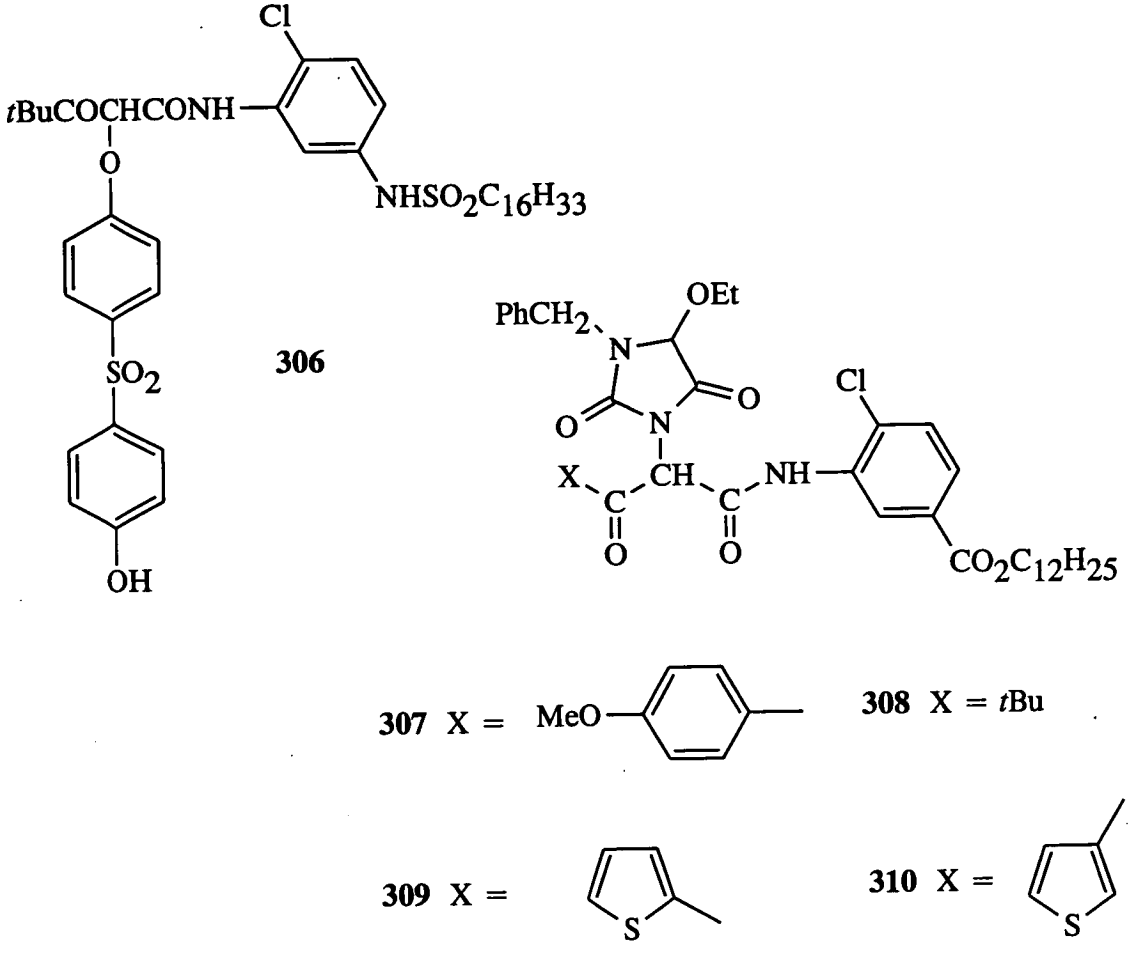
In addition to the standard dye forming process outlined above, further tests are conducted in the presence of citrazinic acid (CZA) **305**, a competing coupler which forms a water soluble dye with oxidised developer.



305

Another DlogE curve may be plotted for the chosen coupler with citrazinic acid incorporated developer, the gradient of the curve will change for the competing process. The ratio of gamma obtained for the process in which the developer contains CZA to the gamma obtained for the standard process is a measure of the coupler reactivity. Gamma ratios (γ_{CZA}/γ) above 0.5 are acceptable for couplers and obviously more reactive couplers have higher gamma ratios. The KIT speed is the "threshold" measurement of film speed, the first reaction of the coupler to oxidised developer.

Photographic evaluation of the couplers **293** - **298** (Scheme 87) was conducted in comparison with well known standards used in photographic testing **306** - **310** (Scheme 89).

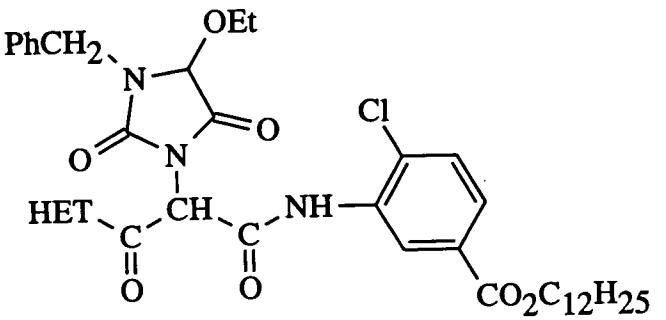


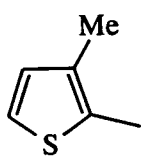
Scheme 89

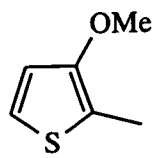
Table 27 outlines the results of photographic evaluation. The results for D_{min}, D_{max}, gamma (γ) and KIT speed are presented in two columns, the left-hand column details results in the absence of citrazinic acid **305** and the right-hand column contains results on the competing process, that is in the presence of citrazinic acid.

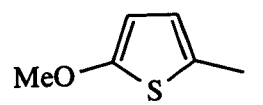
Additional information on dye hue and stability is also required in the photgraphic evaluation proces. A critical factor in determining the suitablity of a dye is the λ_{max}

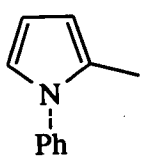
value, the wavelength at maximum density of the absorption curve. Typical absorption maxima (λ_{max}) values of standard dyes in film are *ca.* 448 - 450 nm. The half-bandwidth (HBW) is the width of the absorption curve, in nm, at half the peak height and should be in the region of 88 - 90 nm. The stability of the dye is assessed in two ways, the EDIE (Enhanced Daylight Irradiation Apparatus) fade test is a measurement of dye light stability by exposing dye strips to high levels of artificial light for extended periods. The dark/wet fade test is measurement of dye stability under controlled conditions of heat and humidity in the absence of light. After both stability tests, the loss in density of the dye is measured (Scheme 90).

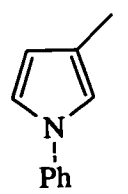


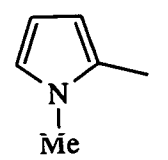
293 HET = 

294 HET = 

295 HET = 

296 HET = 

297 HET = 

298 HET = 

Scheme 90

Table 27: PHOTOGRAPHIC EVALUATION RESULTS FOR HETEROAROYLACETANILIDES **293 - 298**

Coupler	D_{min}		D_{max}		γ		KIT		γ_{CZA}/γ	λ_{max}	HBW	EDIE	FADE	DARK	WET	FADE
		CZA		CZA		CZA		CZA		(nm)	(nm)	100hrs	200hrs	1 wk	3 wks	6 wks
306	0.09	0.08	2.47	1.48	2.12	1.17	191	186	0.55	446	92.5	- 0.07	- 0.12	+ 0.09	+ 0.04	- 0.09
307	0.11	0.09	2.72	1.87	2.38	1.63	191	187	0.68	450	88.5	- 0.09	- 0.20	+ 0.02	- 0.04	- 0.10
308	0.07	0.06	1.90	1.02	1.57	0.74	166	183	0.47	448.5	88	+0.01	- 0.02	+ 0.02	+ 0.01	- 0.03
309	0.19	0.17	2.86	1.90	2.33	1.42	188	190	0.61	456	98	- 0.32	- 0.51	+ 0.01	- 0.13	- 0.28
310	0.16	0.13	2.82	1.98	2.49	1.57	192	192	0.63	453	93	- 0.17	- 0.34	- 0.02	- 0.13	- 0.23
293	0.19	0.14	2.85	2.17	2.73	1.80	181	179	0.66	456.5	95	- 0.15	- 0.30	+ 0.02	- 0.01	- 0.07
294	0.20	0.13	2.08	1.27	1.83	0.97	182	179	0.53	446	93	- 0.01	- 0.04	+ 0.02	0.00	- 0.02
295	0.21	0.18	2.76	2.12	2.72	1.78	184	183	0.65	453	96	- 0.17	- 0.33	- 0.01	- 0.13	- 0.26
296	0.09	0.08	2.42	1.56	2.10	1.31	187	183	0.62	450.5	88	- 0.04	- 0.12	0.00	- 0.07	- 0.17
297	0.09	0.08	2.41	1.63	2.17	1.37	188	185	0.63	448.5	87	- 0.44*	- 0.80*	- 0.07	- 0.28	- 0.48
298	0.08	0.07	2.25	1.37	1.95	1.18	185	181	0.61	448.5	85	- 0.01	- 0.06	0.00	- 0.05	- 0.13

* = change in curve shape

A number of features were apparent from the data, notably the good dye stability of **294**, the 3-methoxythiophene derived dye, in EDIE and dark/wet fade experiments. A loss of only 4% in density was observed after light exposure for 200h in contrast to a loss of 51% in density for the corresponding unsubstituted thiophene derived dye **309**. This stability is also observed for the dark/wet fade test, a loss of only 2% after 6 weeks in **294** compared with a 28% loss in density for **309**. The increase in stability is not conveyed to the 5-methoxythiophene derived dye **295** however which performs marginally better than **309**. Pyrrolyl dye stability was comparable to that of the standards with the exception of **297** which was very unstable in both fade tests.

The proximity of the electron donating methoxy group in **294** has a pronounced effect on the absorption maximum (λ_{max}) especially in comparison to **293** and **295**, the 3-methyl- and 5-methoxythiophene derived dyes respectively. The λ_{max} for **294** is markedly hypsochromic, that is tending to lower wavelenghths, with respect to the other thiophenes. This effect is indicative of the presence of an electron donating moiety as explained in section 7. Absorption maxima of the pyrrolyl dyes, **296 - 298**, all meet the desired requirements and lie within the range 448.5 nm - 450.5 nm.

One recurring problem with the thiophene derived dyes appears to be the rather high value for D_{min} (*ca.* 0.2) indicating residual unwanted dye formation at low exposures to light. This effect is clearly observed for **294** in figure 24 as indicated by the "fogging" at the bottom of the strip. The pyrrolyl dyes, **296 - 298**, all have low D_{min} (*ca.* 0.09), similar to the standards.

The half-bandwidth (HBW) of all thiophene-based dyes **293 - 295**, **309** and **310** is 93 - 98 nm, slightly higher than those for the standards or the pyrrole derived dyes **296 - 298**.

Gamma ratios (γ_{CZA}/γ) for all tested couplers are above 0.5 indicating good competition for developer in the presence of citrazinic acid **305**. Of the couplers

tested, **294** the 3-methoxythiophene derived dye was the least reactive with a gamma ratio of 0.53.

The work described in this section has resulted in application for two UK patents covering pyrroloylacetanilides and thenoylacetanilides.[100,101]

10. STRUCTURE DETERMINATION OF 2-ACETYL-3-METHOXYTHIOPHENE

A sample of 2-acetyl-3-methoxythiophene **259** suitable for X-ray analysis was obtained by recrystallisation from *n*-hexane. The ORTEP plot with the crystallographic numbering system is shown in Figure 26, and the structural parameters are given in Table 28.

Figure 26: ORTEP Plot of **259** with crystallographic numbering system

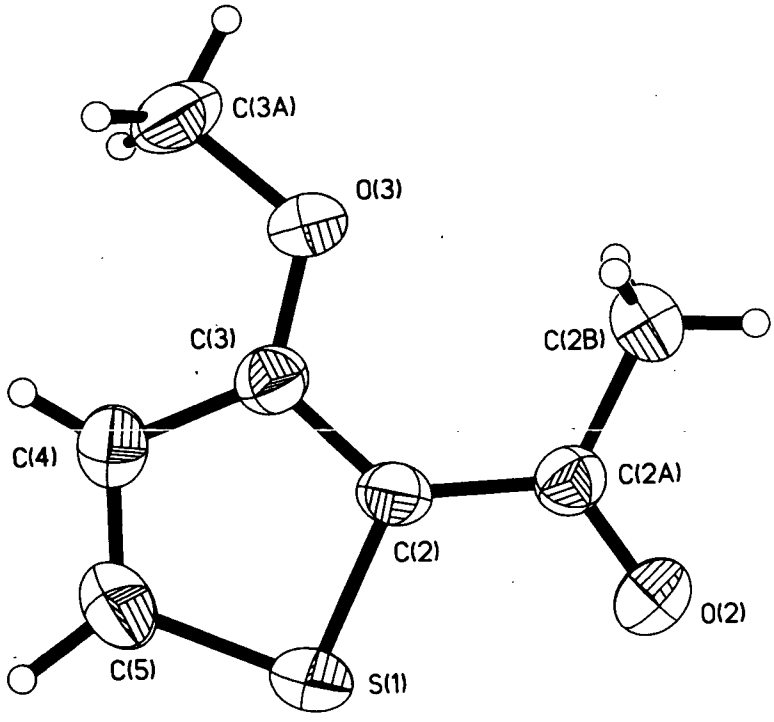
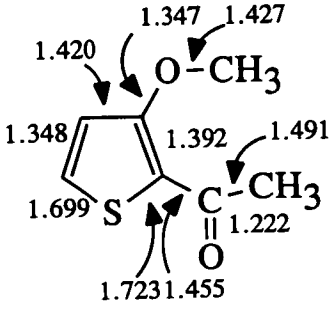


Table 27: Bond lengths (Å) and angles (°) of **259** with standard deviations

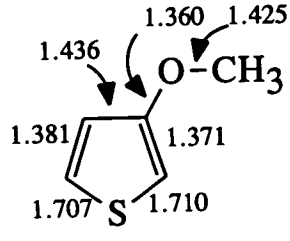
S(1)-C(2)	1.723(2)
S(1)-C(5)	1.699(2)
C(2)-C(2A)	1.455(2)
O(2)-C(2A)	1.222(2)
C(2A)-C(2B)	1.491(3)
C(2B)-H(2B)	0.90(3)
C(2B)-H(2B')	1.00(3)
C(2B)-H(2B")	0.90(3)
C(3)-O(3)	1.347(2)
C(3)-C(2)	1.392(3)
O(3)-C(3A)	1.427(2)
C(3A)-H(3A)	1.01(2)
C(3A)-H(3A')	0.92(3)
C(3A)-H(3A")	0.93(2)
C(4)-C(3)	1.420(3)
C(4)-H(4)	0.85(2)
C(5)-C(4)	1.348(3)
C(5)-H(5)	1.01(3)
C(5)-S(1)-C(2)	91.64(9)
C(3)-C(2)-C(2A)	131.6(2)
C(3)-C(2)-S(1)	110.56(13)
C(2A)-C(2)-S(1)	117.87(13)
O(2)-C(2A)-C(2)	120.2(2)
O(2)-C(2A)-C(2B)	120.9(2)
C(2)-C(2A)-C(2B)	118.9(2)
C(2A)-C(2B)-H(2B)	109(2)
C(2A)-C(2B)-H(2B')	112(2)
H(2B)-C(2B)-H(2B')	109(3)
C(2A)-C(2B)-H(2B")	114(2)
H(2B)-C(2B)-H(2B")	112(3)
H(2B')-C(2B)-H(2B")	100(3)
O(3)-C(3)-C(2)	121.2(2)
O(3)-C(3)-C(4)	126.5(2)
C(2)-C(3)-C(4)	112.3(2)
C(3)-O(3)-C(3A)	117.1(2)
O(3)-C(3A)-H(3A)	110.8(13)
O(3)-C(3A)-H(3A')	111(2)
H(3A)-C(3A)-H(3A')	107(2)
O(3)-C(3A)-H(3A")	104(2)
H(3A)-C(3A)-H(3A")	112(2)
H(3A')-C(3A)-H(3A")	112(2)
C(5)-C(4)-C(3)	112.0(2)
C(5)-C(4)-H(4)	124(2)
C(3)-C(4)-H(4)	124(2)
C(4)-C(5)-S(1)	113.5(2)
C(4)-C(5)-H(5)	127(2)
S(1)-C(5)-H(5)	120(2)

The structural parameters for 2-acetyl-3-methoxythiophene **259** may be compared with those obtained for 3-methoxythiophene[102] **311** and the analogous 2-acetyl-3-hydroxythiophene **312** as reported by Danielsen in 1969.[86]

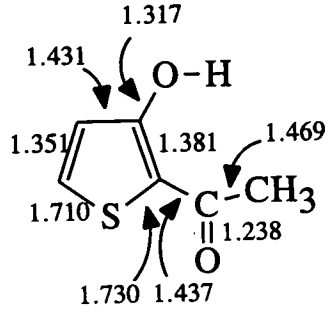
Figure 27: Bond lengths (Å) for 2-acetyl-3methoxythiophene **259**, 3-methoxythiophene **311** and 2-acetyl-3-hydroxythiophene **312**



259



311



312

Table 28: Bond lengths (Å) of **259, 311** and **312** with standard deviations

Bond	259	311	312	Bond	259	311	312
S1 - C2	1.723(2)	1.710(3)	1.730(7)	C - O	1.347(2)	1.360(3)	1.317(8)
S1 - C5	1.699(2)	1.707(3)	1.710(7)	C2 - C6	1.455(2)		1.437(8)
C2 - C3	1.392(3)	1.371(4)	1.381(8)	C6 - C7	1.491(3)		1.469(11)
C3 - C4	1.420(3)	1.426(4)	1.431(9)	C=O	1.222(2)		1.238(8)
C4 - C5	1.348(3)	1.381(4)	1.351(11)	O - Me	1.427(2)	1.425(4)	

The presence of the hydroxy or methoxy substituents in the 3-position may have an electron withdrawing inductive effect and an electron donating resonance effect. In addition, the acetyl moiety may exert electron withdrawing inductive and resonance

effects. In **259**, the S1 - C2 and C2 - C3 bond lengths are longer than those in **311**, possibly as a result of the introduction of the electron withdrawing acetyl group. The standard deviations for the structure of **312** are relatively large, making comparison ineffective, however the shorter C - O bond length may again be attributed to the electron withdrawing resonance effect of the acetyl moiety.

EXPERIMENTAL

ABBREVIATIONS

NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
p.p.m.	parts per million
IR	infra-red
UV	ultra-violet
ε	extinction coefficient
sh	shoulder
t.l.c.	thin layer chromatography
J	coupling constant
br	broad
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet (^{1}H spectra)
	quaternary (^{13}C spectra)
m	multiplet
FAB	fast atom bombardment mass spectrometry
DEI	desorption electron impact
DCI	desorption chemical ionisation
m/z	mass to charge ratio
M^+	molecular ion
DMSO	dimethylsulfoxide
DMF	dimethylformamide
THF	tetrahydrofuran

mol	moles
mmol	millimoles
M	molarity
mp	melting point
bp	boiling point
FVP	flash vacuum pyrolysis
$\mathbf{T_f}$	furnace temperature
$\mathbf{T_i}$	inlet temperature
P	pressure
$\mathbf{t_{(pyr.)}}$	time of pyrolysis
h	hours
min	minutes
p.s.i.	pounds per square inch
atm	atmospheres

A. INSTRUMENTATION AND GENERAL TECHNIQUES

1. NUCLEAR MAGENTIC RESONANCE SPECTROSCOPY

^1H NMR spectra were recorded either at 250 MHz on a Bruker AC250 (250MHz) or at 200 MHz on a Bruker WP200 (200MHz) spectrometer, unless otherwise stated. Spectra were also obtained on Bruker WP80 (80MHz) and WH360 (360MHz) instruments. Further spectra were run by the Kodak analytical service on a Jeol 400MHz instrument. Routine continuous wave spectra were obtained on a Joel PMX 60SI (60MHz) instrument. ^{13}C NMR spectra were recorded on the Bruker AC250 (63MHz) and the Bruker WP200 (50MHz) instruments, unless otherwise stated. Further ^{13}C NMR spectra were run by the Kodak analytical service on the Jeol (100MHz) instrument.

The AC250 was operated by Mr. J.R.A. Millar, the WP200 by Dr. H. McNab, Mr. J.R.A. Millar, Mr. W. Kerr and Miss H. Grant, the WP80 by Miss H. Grant and the WH360 by Dr. D. Reed.

Spectra were recorded in [^2H]chloroform, unless otherwise stated; chemical shifts (δ_H, δ_C) are quoted in parts per million, relative to tetramethylsilane, and coupling constants (J) are quoted in Hz. Standard 200 and 250 MHz ^1H spectra have an accuracy of 0.3 Hz per point and are quoted as recorded. Standard 50 and 63 MHz ^{13}C spectra have an accuracy of 0.5 Hz per point and are quoted as recorded.

2. MASS SPECTROSCOPY

Low resolution electron impact mass spectra were recorded by Miss E. Stevenson on an A.E.I. MS902 instrument. High resolution and FAB mass spectra were recorded by Mr. A. Taylor on a Kratos MS50TC instrument. Spectra quoted

were obtained by electron impact mass spectrometry unless otherwise stated. Further mass spectra were run by the Kodak analytical service.

3. ELEMENTAL ANALYSIS

Microanalyses were obtained by Mrs. L. Eades on a Perkin Elmer 240 CHN Elemental Analyser. Further analyses were carried out by the Kodak analytical service.

4. STRUCTURE DETERMINATION

X-ray crystallographic data were obtained and refined by Dr. A.J. Blake and Dr. R.O. Gould on a Stoë STADI-4 four circle diffractometer with graphite monochromator.

5. INFRA-RED SPECTROSCOPY

IR spectra were obtained as liquid films or nujol mulls on a Bio-Rad SPC 3200 FTIR instrument and are quoted in wavenumbers (cm^{-1}).

6. ULTRA-VIOLET AND VISIBLE SPECTROSCOPY

UV and visible spectra were recorded initially on a Unicam SP800A spectrometer and latterly on a Shimadzu UV-160A UV-Vis recording spectrometer. The solvent used is indicated. Wavelengths of maxima are recorded in nm.

7. CHROMATOGRAPHY

Thin-layer chromatography was carried out on pre-coated aluminium sheets (0.2 mm silica gel, Merck, grade 60) impregnated with a UV fluorescent indicator, or on pre-coated aluminium sheets (0.2 mm aluminium oxide, neutral (Type E), Merck, grade 60) impregnated with a UV fluorescent indicator.

Dry flash chromatography was carried out on silica gel [(Merck, grade 60, 230-400 mesh, 60 Å), or (Merck , t.l.c. grade 60)] by the method of Harwood.[91]

Wet flash column chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å), by the method of Still.[92]

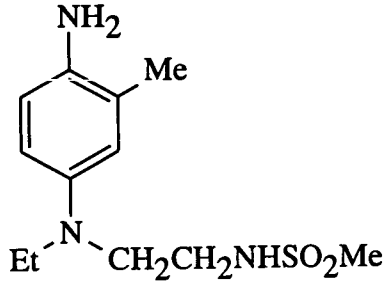
Preparative thin-layer chromatography was carried out on pre-coated glass sheets (0.2 mm silica gel, Whatman HP-KF) according to the method outlined on the Whatman Chromatography Folio Issue 1.

8. SOLVENTS

Commercially available solvents were used without further purification, except for *n*-hexane and ethyl acetate which were distilled for chromatographic purposes. Ether was generally dried by storage over sodium wire; when necessary it was dried further by distillation from sodium benzophenone ketal. All other dry solvents were obtained by storing over molecular sieve (4 Å).

9. TLC DEVELOPMENT SPRAY

The colour developer, **313**, (CD3) *ca.* 1g 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 persulfate). Active couplers showed up as coloured spots.



313

B. PYROLYSIS APPARATUS AND METHODS

The apparatus used for flash vacuum pyrolysis experiments is illustrated in Figure 28, and is based on the design of W.D. Crow, Australian National University. The system is evacuated to 10^{-2}-10^{-3} mbar by an Edwards Model ED100 high capacity oil pump and the pressure is monitored between trap and the pump. For less volatile substrates, a mercury diffusion pump was used in series with the rotary oil pump (Figure 29) to increase the vacuum to a pressure of the order of 10^{-4}-10^{-5} mbar. Experiments involve heating the substrate contained in the inlet until it is volatilised. An all glass Büchi oven is generally used for heating as it allows sublimation to be easily monitored, but for inlet temperatures approaching 200°C a metal Kugelrohr oven provides more even heating and higher temperatures. The volatilised substrate passes through a silica tube (30 x 2.5 cm). The temperature of the tube is monitored by a [platinum/(platinum 13% rhodium)] thermocouple at its centre and is maintained at the required level by Stanton Redcroft laboratory tube furnace. The estimated contact time in the hot zone is of the order of 10 milliseconds. The products are collected at the exit of the furnace in a trap cooled in liquid nitrogen. The U-shaped trap shown in Figure 28 is used for up to 1g of substrate. To prevent blockage of the trap, the large scale trap shown in Figure 30 is used for larger pyrolyses.

Small scale pyrolyses refer to 10-50 mg of substrate, and the entire pyrolysate was dissolved in deuteriated solvent ([^{2}H]chloroform unless otherwise stated) and examined by ^{1}H NMR spectroscopy without further purification of the products.

Large scale pyrolyses normally refer to pyrolyses on a scale of 0.1-1g or greater. Details of the work-up are given for each example in the following chapters.

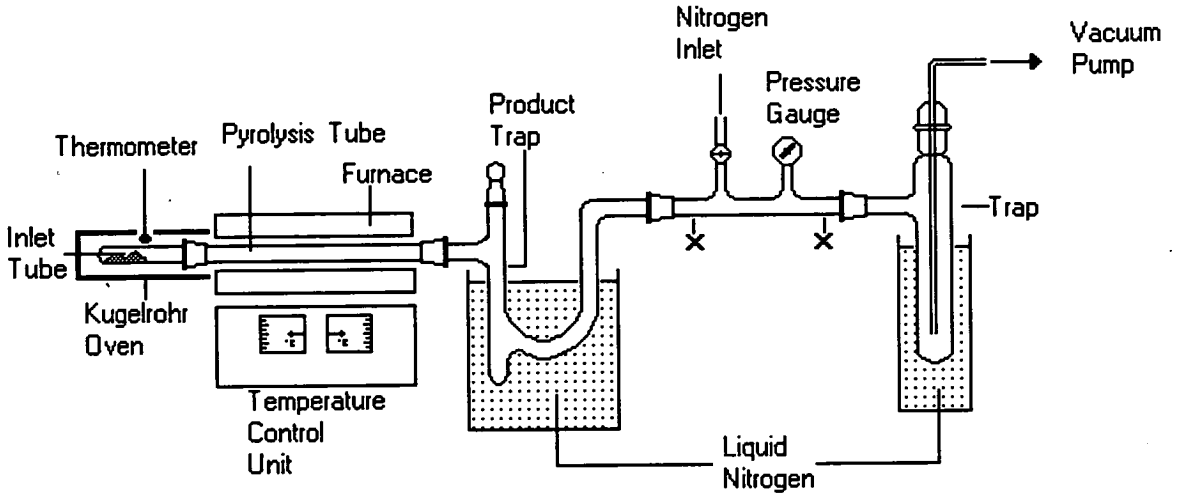


Figure 28

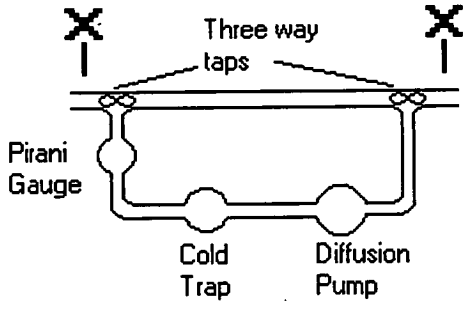


Figure 29

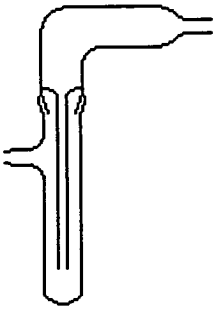


Figure 30

Pyrolysis parameters are quoted in the following order throughout this section: furnace temperature(T_f), inlet temperature(T_i), pressure(P) and the sublimation time[$t_{(pyr.)}$].

C. INVESTIGATION OF THE MECHANISM AND SCOPE OF FORMATION OF 4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLES

1-(2-Nitrophenyl)pyrazole 131a

A stirred mixture of pyrazole (5.30 g, 78 mmol), *o*-chloronitrobenzene (12.32 g, 78 mmol), anhydrous potassium carbonate (10.76 g, 78 mmol) and copper (II) oxide (0.5 g) in pyridine (15.0 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange crystalline solid. Recrystallisation from toluene afforded the title compound **131a** as orange crystals (9.52 g, 66%), mp 86-89°C (from toluene) (lit.,[47] mp 88-89°C); δ_H 7.85 (1 H, dd, ^3J 7.9, ^4J 1.5), 7.72 (1 H, s), 7.71 (1 H, s), 7.64 (1 H, dd, ^3J 7.2, ^4J 1.5), 7.58-7.45 (2 H, m) and 6.48 (1 H, t, ^3J 2.2).

1-(2-Aminophenyl)pyrazole 140

Palladium-on-charcoal (10%, 1.02 g) was carefully added to a solution of 1-(2-nitrophenyl)pyrazole **131a** (8.09 g, 43 mmol) in ethanol (430 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 4 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the title compound **140** as a brown oil (6.61 g, 97%) which did not require further purification; bp 105-106°C (0.3 Torr) [lit.,[47] bp 124°C (0.5 Torr)]; δ_H (80 MHz) 7.74-7.68 (2 H, m), 7.25-7.04 (2 H, m), 6.84 (1 H, s), 6.81-6.65 (2 H, m), 6.42 (1 H, t, ^3J 2.1) and 4.24 (2 H, br s).

1-(2-Azidophenyl)pyrazole 141

To stirred solution of 1-(2-aminophenyl)pyrazole **140** (6.61 g, 42 mmol) in concentrated hydrochloric acid solution (35%, 13 ml) and water (120 ml) at 0°C was added a solution of sodium nitrite (3.40 g, 49 mmol) in water (8.5 ml). The resulting solution was added, carefully with stirring, to a solution of sodium azide (3.21 g, 49 mmol) and sodium acetate (16.4 g) in water (80 ml) at 0°C. On addition a white foam was observed and the mixture was stirred at room temperature for a further 30 min. The mixture was extracted with ether (3 x 50 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the title compound **141** as an orange oil (7.24 g, 94%); $\nu_{max.}$ 2129 and 2097; δ_H 7.90 (1 H, dd, ^3J 2.5, ^4J 0.6), 7.69 (1 H, dd, ^3J 1.8, ^4J 0.5), 7.65-7.57 (1 H, m), 7.48-7.11 (3 H, m) and 6.42 (1 H, dd, ^3J 2.5, 1.8)

1. PYROLYSIS OF 1-(2-AZIDOPHENYL)PYRAZOLE 141 AND AN INVESTIGATION OF THE MECHANISM OF 1-(2-NITRENOPHENYL) PYRAZOLE 142 INSERTION

Pyrolysis of 1-(2-azidophenyl)pyrazole **141** was carried out by the method described in Section B, using a metal inlet for safety reasons. In order to determine the optimum temperature for 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** formation, pyrolyses of approximately 0.25 mmol were carried out at a number of furnace temperatures. A useful indication of reaction initiation was the increase in pressure associated with the evolution of nitrogen gas in the nitrene generation process. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by distillation with [$^2H_6$] acetone and the ^1H NMR spectrum run without purification of the pyrolysate. Each

pyrolysis afforded three products in varying proportions; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1**, pyrazolo[1,2-*a*]benzotriazole **132a** and quinoxaline **143**. The relative ratios of each component were determined by examination of characteristic resonance integrals in the ^{1}H NMR spectrum. Pyrolyses were carried out under the conditions indicated.

Preparative pyrolysis of 1-(2-azidophenyl)pyrazole 141 (1.56 g, 8.4 mmol), T_i 100°C, T_f 400°C, P 7.5 x 10^{-4} Torr, $t_{(pyr.)}$ 1h 30min. The products of the pyrolysis were separated by gravity elution chromatography on alumina (grade III) eluting with a mixture of *n*-hexane and ethyl acetate; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (0.27 g, 23%); mp 216-218°C (lit.,[7] 220°C); bp 110°C (0.004 Torr); δ_H (360 MHz, [$^2H_6$]acetone) 10.44 (1 H, br s), 7.76 (1 H, ddd, ^3J 7.6, ^4J 1.3, ^5J 0.6), 7.69 (1 H, d, ^3J 2.1), 7.46 (1 H, ddd, ^3J 7.6, ^4J 1.2, ^5J 0.6), 7.28 (1 H, td, ^3J 7.6, ^4J 1.3), 7.21 (1 H, td, ^3J 7.6, ^4J 1.2) and 5.77 (1 H, d, ^3J 2.1); δ_C 143.54 (q), 143.05, 135.10, 125.48 (q), 122.45 (q), 119.39, 111.11, 108.99 and 78.80; *m/z* 157 (M^+, 94%), 156(16), 149(100), 119(10), 104(10), 103(26) and 81(16); pyrazolo[1,2-*a*]benzotriazole **132a** (0.41 g, 76%); mp 100-101°C (from hexane) (lit.,[52] 102°C); δ_H (360 MHz, [$^2H_6$]acetone) 8.14 (1 H, dd, ^3J 3.2, ^4J 0.6), 7.86 (1 H, dt, ^3J 8.1, ^4J 1.1, ^5J 0.9), 7.77 (1 H, dd, ^3J 2.7, ^4J 0.6), 7.38 (1 H, ddd, ^3J 8.4, ^4J 1.2, ^5J 0.9), 7.33 (1 H, ddd, ^3J 8.4, ^4J 6.9, ^5J 1.1), 6.930 (1 H, dd, ^3J 3.2, ^4J 2.7) and 6.926 (1 H, ddd, ^3J 8.1, ^4J 6.9, ^5J 1.2); δ_C 146.53 (q), 125.14, 118.44 (q), 114.70, 111.41, 109.53, 108.30, 104.79 and 102.65; *m/z* 157 (M^+, 100%), 156(16), 103(16) and 76(10); quinoxaline **143** (0.03 g, 1%),mp 28-30°C; δ_H ([$^2H_6$]acetone) 8.93 (2 H, s), 8.10 (2 H, dd, ^3J 6.4, ^4J 3.5) and 7.86 (2 H, dd, ^3J 6.4, ^4J 3.5).

Variable temperature pyrolyses of 1-(2-azidophenyl)pyrazole 141, 57 mg, T_f 300°C, T_i 96°C, P 0.002 Torr, $t_{(pyr.)}$ 25 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (22%); pyrazolo[1,2-*a*]benzotriazole **132a** (78%) and quinoxaline **143** (0%); 49 mg, T_f 400°C, T_i 72°C, P 0.004 Torr, $t_{(pyr.)}$ 25 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1**

(23%); pyrazolo[1,2-*a*]benzotriazole **132a** (76%) and quinoxaline **143** (1%) 78 mg, T_f 425°C, T_i 85°C, P 0.008 Torr, $t_{(pyr.)}$ 20 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (23%); pyrazolo[1,2-*a*]benzotriazole **132a** (75%) and quinoxaline **143** (2%); 44 mg, T_f 450°C, T_i 75°C, P 8 x 10^{-4} Torr, $t_{(pyr.)}$ 25 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (26%); pyrazolo[1,2-*a*]benzotriazole **132a** (61%) and quinoxaline **143** (13%); 78 mg, T_f 475°C, T_i 85°C, P 0.008 Torr, $t_{(pyr.)}$ 30 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (28%); pyrazolo[1,2-*a*]benzotriazole **132a** (51%) and quinoxaline **143** (21%); 74 mg, T_f 500°C, T_i 100°C, P 0.002 Torr, $t_{(pyr.)}$ 20 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (30%); pyrazolo[1,2-*a*]benzotriazole **132a** (30%) and quinoxaline **143** (40%); 78 mg, T_f 525°C, T_i 85°C, P 0.008 Torr, $t_{(pyr.)}$ 20 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (23%); pyrazolo[1,2-*a*]benzotriazole **132a** (17%) and quinoxaline **143** (60%); 57 mg, T_f 600°C, T_i 86°C, P 0.002 Torr, $t_{(pyr.)}$ 20 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (17%); pyrazolo[1,2-*a*]benzotriazole **132a** (0%) and quinoxaline **143** (83%); 54 mg, T_f 700°C, T_i 86°C, P 0.004 Torr, $t_{(pyr.)}$ 20 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (0%); pyrazolo[1,2-*a*]benzotriazole **132a** (0%) and quinoxaline **143** (100%).

2. PYROLYSES OF PYRAZOLO[1,2-*a*]BENZOTRIAZOLE 132a AND 4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE 1

The isolated products pyrazolo[1,2-*a*]benzotriazole **132a** and 4*H*-pyrazolo[1,5-*a*] benzimidazole **1** were pyrolysed at a number of furnace temperatures, as before, in order to investigate the reaction pathway from generation of 1-(2-nitrenophenyl)pyrazole **142**. Upon completion of each pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The products were collected by distillation of [$^2H_6$] acetone through the trap and then the ^1H NMR spectrum was run without purification of the pyrolysate.

Variable temperature pyrolyses of pyrazolo[1,2-a]benzotriazole 132a; 51 mg, T_f 400°C, T_i 110°C, P 0.008 Torr, $t_{(pyr.)}$ 45 min; pyrazolo[1,2-*a*]benzotriazole **132a** (97%) and quinoxaline **143** (3%); 54 mg, T_f 450°C, T_i 110°C, P 0.008 Torr, $t_{(pyr.)}$ 45 min; pyrazolo[1,2-*a*]benzotriazole **132a** (97%) and quinoxaline **143** (3%); 55 mg, T_f 500°C, T_i 95°C, P 0.004 Torr, $t_{(pyr.)}$ 50 min; pyrazolo[1,2-*a*]benzotriazole **132a** (93%) and quinoxaline **143** (7%); 53 mg, T_f 550°C, T_i 97°C, P 0.004 Torr, $t_{(pyr.)}$ 35 min; pyrazolo[1,2-*a*]benzotriazole **132a** (68%) and quinoxaline **143** (32%); 42 mg, T_f 600°C, T_i 93°C, P 0.004 Torr, $t_{(pyr.)}$ 30 min; pyrazolo[1,2-*a*]benzotriazole **132a** (34%) and quinoxaline **143** (66%).

Variable temperature pyrolyses of 4*H*-pyrazolo[1,5-*a*]benzimidazole 1; 42 mg, T_f 600°C, T_i 120°C, P 0.004 Torr, $t_{(pyr.)}$ 45 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (100%); 20 mg, T_f 700°C, T_i 120°C, P 0.004 Torr, $t_{(pyr.)}$ 45 min; 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (100%).

3. SYNTHESIS OF 3-CHLORO-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLE 149

4-Chloropyrazole[56] 145

To stirred solution of pyrazole (0.50 g, 7.4 mmol) in glacial acetic acid (5.0 ml) was added sodium hypochlorite solution (5% available chlorine, 7.5 ml, 7.4 mmol) resulting in a white opaque mixture which was left stirring overnight. The mixture was neutralised with dilute aqueous sodium carbonate solution, then extracted with dichloromethane (3 x 30 ml). The combined organic washings were concentrated under vacuum then washed with dilute aqueous sodium hydroxide (2M, 10 ml). The sodium hyroxide washings were then extracted with dichloromethane (2 x 20 ml), the

organic extracts were combined, dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the title compound **145** (0.47 g, 62%) as white crystals, mp 73-76°C (lit.,[56] mp 72-75°C); δ_H (60 MHz) 7.75 (2 H, s).

4-Chloro-1-(2-nitrophenyl)pyrazole 146

A stirred mixture of 4-chloropyrazole **145** (2.39 g, 23 mmol), *o*-chloronitrobenzene (3.65 g, 23 mmol), anhydrous potassium carbonate (3.2 g, 23 mmol) and copper (II) oxide (0.12 g) in pyridine (8.0 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (50 ml) and activated charcoal (1.5 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange oil. Purification by dry-flash chromatography eluting with a 1 : 9 mixture of ethyl acetate and *n*-hexane gave the *title compound* **146** as an orange solid (3.82 g, 73%), mp 63-65°C (from hexane-ethyl acetate) (Found: C, 48.45; H, 2.75; N, 18.9. $C_9H_6ClN_3O_2$ requires C, 48.3; H, 2.7; N, 18.8%); δ_H 7.84 (1 H, dd, ^3J 7.9, ^4J 1.9), 7.71 (1 H, s), 7.63 (1 H, dd, ^3J 7.2, ^4J 1.8), 7.59 (1 H, s) and 7.51 (2 H, 2 x t, ^3J 7.4); δ_C 144.31 (q), 140.66, 133.11, 132.78 (q), 128.89, 127.54, 126.08, 125.13 and 112.88 (q); *m/z* 225 (M^+, 34%), 223 (M^+, 100%), 208(18), 206(54), 193(14), 168(13), 166(34), 158(13), 150(18), 142(15), 123(11), 115(11), 114(21), 111(11), 105(21), 102(21), 91(17), 90(46) and 89(10).

4-Chloro-1-(2-aminophenyl)pyrazole 147

Palladium-on-charcoal (10%, 0.41 g) was carefully added to a solution of 4-chloro-1-(2-nitrophenyl)pyrazole **146** (3.38 g, 15 mmol) in ethanol (270 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 6 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the *title compound* **147** as a brown oil (2.90 g, 99%) which crystallised on standing and did

not require further purification; mp 71-72°C (from hexane) (Found: C, 55.15; H, 4.25; N, 21.25. $C_9H_8ClN_3.0.1H_2O$ requires C, 55.3; H, 4.2; N, 21.5%) (Found M^+, 193.0401. $C_9H_8N_3{}^{35}Cl$ requires M^+, 193.0407); δ_H 7.67 (1 H, s), 7.65 (1 H, s), 7.18-7.09 (2 H, m), 6.79-6.71 (2 H, m) and 4.76 (2 H, br s); δ_C 140.65 (q), 138.57, 128.75, 127.63, 125.60 (q), 123.86, 117.86, 117.19 and 110.94 (q); *m/z* 195 (M^+, 33%), 193 (M^+, 100%), 192(12), 158(42), 131(27), 119(15), 65(19) and 52(12).

4-Chloro-1-(2-azidophenyl)pyrazole 148

To stirred solution of 4-chloro-1-(2-aminophenyl)pyrazole **147** (1.95 g, 10 mmol) in concentrated hydrochloric acid solution (35%, 15 ml) and water (100 ml) at 0°C was added a solution of sodium nitrite (0.70 g, 10 mmol) in water (10 ml). The resulting yellow solution was added, carefully with stirring, to a solution of sodium azide (0.67 g, 10 mmol) and sodium acetate (3.30 g) in water (20 ml) at 0°C. On addition a cloudy suspension with a red oil lower layer was observed and the mixture was stirred at room temperature for 1 h. The mixture was extracted with ether (3 x 30 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 20 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **148** as an orange oil (2.07 g, 94%), bp 92-97°C (0.5 Torr), mp 36-38°C (from *n*-hexane) (Found M^+, 219.0315. $C_9H_6{}^{35}ClN_5$ requires 219.0312); $\nu_{max.}$ 3154, 2126, 1596 and 1497; δ_H 7.96 (1 H, s), 7.63 (1 H, s), 7.62 (1 H, dd, ^3J 7.8, ^4J 1.5), 7.39 (1 H, td, ^3J 7.6, ^4J 1.5) and 7.28-7.18 (2 H, m); δ_C 139.06, 132.26 (q), 130.94 (q), 129.13, 128.79, 125.88, 125.37, 119.25 and 111.19 (q); *m/z* 221 (M^+, 10%), 219 (M^+, 31%), 193(34), 192(19), 191(95), 190(27), 166(11), 165(22), 164(27), 157(18), 156(100), 130(11), 129(85) and 128(21).

b. PYROLYSIS OF 4-CHLORO-1-(2-AZIDOPHENYL)PYRAZOLE 148 AND AN INVESTIGATION OF THE MECHANISM OF 4-CHLORO-1-(2-NITRENOPHENYL)PYRAZOLE 152 INSERTION

Pyrolysis of 4-chloro-1-(2-azidophenyl)pyrazole **148** was carried out by the method described in Section B, using a metal inlet. Pyrolyses of approximately 0.25 mmol were carried out at a number of furnace temperatures as described previously. Each pyrolysis afforded three products in varying proportions which were assigned, in the ^{1}H NMR spectrum, by analogy with the unsubstituted system; 3-chloro-4*H*-pyrazolo[1,5-*a*]benzimidazole **149**, 3-chloropyrazolo[1,2-*a*]benzotriazole **150** and 2-chloroquinoxaline **151**. The relative ratios of each component were determined by examination of characteristic resonance integrals in the ^{1}H NMR spectrum. Pyrolyses were carried out under the conditions indicated.

Variable temperature pyrolysis of 4-chloro-1-(2-azidophenyl)pyrazole 148; 78 mg, T_f 400°C, T_i 95°C, P 0.004 Torr, $t_{(pyr.)}$ 25 min; 3-chloro-4*H*-pyrazolo[1,5-*a*]benzimidazole **149** (28%); 3-chloropyrazolo[1,2-*a*]benzotriazole **150** (53%) and 2-chloroquinoxaline **151** (18%); 89 mg, T_f 400°C, T_i 95°C, P 0.004 Torr, $t_{(pyr.)}$ 20 min; 3-chloro-4*H*-pyrazolo[1,5-*a*]benzimidazole **149** (33%); 3-chloropyrazolo[1,2-*a*]benzotriazole **150** (11%) and 2-chloroquinoxaline **151** (54%); 83 mg, T_f 550°C, T_i 95°C, P 0.004 Torr, $t_{(pyr.)}$ 25 min; 3-chloro-4*H*-pyrazolo[1,5-*a*]benzimidazole **149** (16%); 3-chloropyrazolo[1,2-*a*]benzotriazole **150** (0%) and 2-chloroquinoxaline **151** (84%).

4. ATTEMPTED SYNTHESIS OF 3-BROMO-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLE

4-Bromo-1-(2-azidophenyl)pyrazole 154

To a stirred solution of bromine (0.37 ml, 1.18 g, 7.4 mmol) in methanol (10 ml) was added, dropwise, a solution of 1-(2-azidophenyl)pyrazole **141** (0.85 g, 4.6 mmol) in methanol (20 ml) and the solution was left stirring for 3 h. Potassium carbonate (0.6 g) was added and the mixture was stirred for a further 15 min. Dichloromethane (50 ml) and water (50 ml) were added and the mixture shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure to yield the *title compound* **154** (1.40 g, 100%) as an orange oil; (Found M^+ 264.9789. $C_9H_6{}^{81}BrN_5$ requires 264.9787. Found M^+ 262.9815. $C_9H_6{}^{79}BrN_5$ requires 262.9807); $\nu_{max.}$ 2132 and 2101; δ_H ([$^2H_6$] acetone) 8.31 (1 H, d, ^4J 0.5), 7.74 (1 H, d, ^4J 0.5), 7.67 (1 H, dd, ^3J 7.9, ^4J 1.3), 7.65-7.39 (2 H, m) and 7.31 (1 H, td, ^3J 8.0, ^4J 1.8); δ_C ([$^2H_6$] acetone) 141.02, 132.70 (q), 131.99, 131.33 (q), 129.30, 126.09, 125.64, 120.07 and 94.17 (q); *m/z* 265 (M^+, 11%), 263 (M^+, 11%), 237(26), 235(32), 157(11), 156(100), 129(44), 104(24), 102(40) and 101(36).

b. PYROLYSIS OF 4-BROMO-1-(2-AZIDOPHENYL)PYRAZOLE 154

Pyrolysis of 4-bromo-1-(2-azidophenyl)pyrazole **154** was carried out by the method described in Section B, using a metal inlet. Pyrolyses of approximately 0.25 mmol were carried out at a number of furnace temperatures as described previously. Unlike the preceding unsubstituted and chloro-substituted azide pyrolyses, the products from the bromo-substituted azide pyrolysis were not completely soluble in [$^2H_6$] acetone,

thereby requiring the use of [$^2H_6$] DMSO. In addition, the pyrolyses did not proceed cleanly on a larger (*ca.* 4 mmol) scale; black glassy residues were observed on the inside surface of the furnace tube. 4-Bromo-1-(2-azidophenyl)pyrazole **154**, 100 mg, T_f 600°C, T_i 100°C, P 0.004 Torr, $t_{(pyr.)}$ 35 min; 2-bromoquinoxaline **155** (0.046 g, 58%) bp 96-97°C (0.2 Torr) (lit.,[87] bp 90-91°C [0.2 Torr]); δ_H 9.00 (1 H, s) and 8.20-7.92 (4 H, m).

5. SYNTHESIS OF PYRAZOLOBENZIMIDAZOLES WITH CONJUGATIVE ELECTRON DONATING SUBSTITUENTS

a. SYNTHESIS OF 7-METHOXY-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLE 162

3-Chloro-4-nitrosophenol[57] 156

Sodium nitrite (17.55 g, 254 mmol) was dissolved in cold concentrated sulfuric acid (163 ml) after vigorous reaction, and then the solution was cooled to 5°C. Ice (82 g) was added, without stirring, to the solution. A solution of *m*-chlorophenol (16.5 g, 128 mmol) in pyridine (125 ml) was then added dropwise with vigorous mechanical stirring to the solution of sodium nitrite in sulfuric acid at 5°C. The dark green mixture was stirred for a further 1 h, then water (650 ml) was added whereby an orange precipitate appeared. The mixture was left stirring overnight, then filtered and washed with water. The solid residue was dried *in vacuo* to afford the title compound **156** (13.19 g, 65%), mp 181-184°C (from toluene) (lit.,[57] mp 184°C); δ_H ([$^2H_6$] DMSO) 7.57 (1 H, d, ^3J 10.0), 6.79 (1 H, d, ^4J 1.9), 6.47 (1 H, dd, ^3J 10.0, ^4J 2.0) and 4.50 (1 H, br s); *m/z* 159 (M^+, 34%), 157 (M^+, 100), 131(14), 129(44), 127(13), 114(16), 101(19), 99(56), 88(16), 86(13), 80(11), 76(20), 75(11), 73(18), 68(14), 64(11), 63(57), 62(26), 61(15) and 60(21).

3-Chloro-4-nitrophenol[58] 157

To a solution of 3-chloro-4-nitrosophenol **156** (8.24 g, 52.3 mmol) in water (1600 ml) was added sodium hydroxide (82.3 g, 2.1 mol) and potassium ferricyanide (82.3 g, 247 mmol). On addition of the sodium hydroxide the solution was observed to change colour from orange to black. The mixture was stirred for a further 76 h, then the dark orange solution was acidified with dilute aqueous hydrochloric acid solution (2M, 300 ml) whereby a colour change to green was noted. The solution was extracted with ether (3 x 600 ml), dried ($MgSO_4$) and the solvents removed under reduced pressure to afford the title compound **157** as a brown oil which crystallised (6.21 g, 68%), mp 119-121°C (from toluene) (lit.,[58] mp 121°C); δ_H 10.13 (1 H, br s), 8.00 (1 H, d, ^3J 9.0), 7.06 (1 H, d, ^4J 2.6) and 6.97 (1 H, dd, ^3J 9.0, ^4J 2.6); *m/z* 175 (M^+, 34%), 173 (M^+, 100), 145(29), 143(95), 127(16), 117(13), 115(36), 101(24), 99(76), 75(16) and 64(12).

3-Chloro-4-nitroanisole 158

3-Chloro-4-nitrophenol **157** (2.06 g, 12 mmol) was dissolved in DMF (43 ml) and potassium carbonate (1.65 g, 12 mmol) was added. Methyl iodide (1.70 g, 0.75 ml, 12 mmol) was added dropwise to the stirred mixture and the mixture was allowed to stir at room temperature for a further 16 h. The excess of potassium carbonate was filtered through celite and the pad was washed with ether. Water (40 ml) was added to the filtrate, which was then extracted with ether (3 x 50 ml). The combined organic layers were backwashed with water (3 x 50 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the title compound **158** as orange crystals (2.08 g, 94%), mp 55-56°C (from diisopropylether) (lit.,[88] mp 56.5-57.5°C).

1-(2-Nitro-5-methoxyphenyl)pyrazole 159

A stirred mixture of pyrazole (1.63 g, 24 mmol), 3-chloro-4-nitroanisole **158** (3.00 g, 16 mmol), anhydrous potassium carbonate (2.19 g, 16 mmol) and copper (II) oxide

(0.09 g) in pyridine (4.5 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange oil. Purification by dry-flash chromatography eluting with a mixture of *n*-hexane and ethyl acetate gave the *title compound* **159** as orange crystals (2.77 g, 79%), mp 83-87°C (from toluene) (Found M^+, 219.0645. $C_{10}H_9N_3O_3$ requires 219.0644); δ_H 7.92 (1 H, d, ^3J 9.1), 7.70 (1 H, dd, ^3J 1.7, ^4J 0.5), 7.65 (1 H, dd, ^3J 2.7, ^4J 0.5), 7.01 (1 H, d, ^4J 2.6), 6.94 (1 H, dd, ^3J 9.1, ^4J 2.7), 6.46 (1 H, dd, ^3J 2.6, 1.7) and 3.89 (3 H, s); δ_C 162.86 (q), 141.75, 137.32 (q), 135.58 (q), 130.05, 127.25, 113.29, 111.92, 107.79 and 56.07; *m/z* 219 (M^+, 100%), 202(39), 189(17), 162(37), 150(27), 146(16), 130(16), 129(13), 120(17), 106(20), 104(12), 103(17), 102(18) and 92(15).

1-(2-Amino-5-methoxyphenyl)pyrazole 160

Palladium-on-charcoal (10%, 0.21 g) was carefully added to a solution of 1-(2-nitro-5-methoxyphenyl)pyrazole **159** (1.88 g, 8.6 mmol) in ethanol (115 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 6 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give a brown oil which was purified by kugelrohr distillation to afford the *title compound* **160** (1.31 g, 83%) as a yellow oil which solidified, bp 185-186°C (8 Torr); mp 51-52°C (from hexane); (Found M^+, 189.0902. $C_{10}H_{11}N_3O$ requires 189.0902) (Found: C, 59.5; H, 5.7; N, 20.9. $C_{10}H_{11}N_3O.0.66H_2O$ requires C, 59.7; H, 6.1; N, 20.9%); δ_H 7.73 (1 H, d, ^3J 1.8), 7.71 (1 H, dd, ^3J 2.4, ^4J 0.4), 6.78-6.75 (3 H, m), 6.43 (1 H, t, ^3J 2.1) and 3.75 (3 H, s); δ_C 152.25 (q), 140.48, 134.53 (q), 129.71, 127.01 (q), 118.30, 114.53, 110.04, 106.36 and 55.86; *m/z* 190(14%), 189 (M^+, 100%), 174(84), 43(19), 40(20) and 32(100).

1-(2-Azido-5-methoxyphenyl)pyrazole 161

To stirred solution of 1-(2-amino-5-methoxyphenyl)pyrazole **160** (0.50 g, 2.6 mmol) in concentrated hydrochloric acid solution (35%, 1.0 ml) and water (10 ml) at 0°C was added a solution of sodium nitrite (0.21 g, 3 mmol) in water (1 ml). The resulting solution was added, carefully with stirring, to a solution of sodium azide (0.19 g, 3 mmol) and sodium acetate (1.0 g) in water (5 ml) at 0°C. On addition the mixture became pink and opaque and was stirred at room temperature for a further 30 min. The mixture was extracted with ether (3 x 50 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **161** as a red oil (0.59 g, 99%), bp 110-115°C (0.4 Torr) (Found M^+ 215.0797. $C_{10}H_9N_5O$ requires 215.0807); $\nu_{max.}$ 2127 and 2078; δ_H 7.98 (1 H, d, ^3J 2.5), 7.71 (1 H, d, ^3J 1.9), 7.24 (1 H, d, ^4J 3.0), 7.15 (1 H, d, ^3J 8.9), 6.91 (1 H, dd, ^3J 8.9, ^4J 3.0), 6.43 (1 H, dd, ^3J 2.4, 1.8) and 3.81 (3 H, s); δ_C 157.03 (q), 140.57, 132.07 (q), 131.24, 124.25 (q), 120.21, 114.87, 110.65, 106.60 and 55.59; *m/z* 215 (M^+, 4%), 188(13), 187(63), 172(100), 160(11), 156(10), 145(12), 144(11), 80(24), 78(12), 77(21), 76(16), 67(11), 66(19), 65(11), 64(22) and 63(25).

(ii) PYROLYSIS OF 1-(2-AZIDO-5-METHOXYPHENYL)PYRAZOLE 161 AND AN INVESTIGATION OF THE MECHANISM OF 1-(2-NITRENOPHENYL)PYRAZOLE 165 INSERTION

Pyrolysis of 1-(2-azido-5-methoxyphenyl)pyrazole **161** was carried out by the method described in Section B, using a metal inlet for safety reasons. Pyrolyses of approximately 0.25 mmol were carried out at a number of furnace temperatures as described previously. Each pyrolysis afforded three products in varying proportions

which were assigned in the ^1H NMR spectrum by analogy with the unsubstituted system; 7-methoxypyrazolo[1,5-*a*]benzimidazole **162**, 7-methoxypyrazolo[1,2-*a*]benzotriazole **163** and 7-methoxyquinoxaline **164**. The relative ratios of each component were determined by examination of characteristic resonance integrals in the ^1H NMR spectrum. Pyrolyses were carried out under the conditions indicated.

Preparative pyrolysis of 1-(2-azido-5-methoxyphenyl)pyrazole 161 (0.39 g, 1.8 mmol), T_i 110°C, T_f 500°C, P 0.002 Torr, $t_{(pyr.)}$ 3h 30min. The products of the pyrolysis were dissolved in dichloromethane then removal of the solvent under reduced pressure afforded *7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole* **162** (0.31 g, 92%) as a brown solid after dry-flash column chromatography eluting with a 2:1 mixture of *n*-hexane and ethyl acetate; mp 223-225°C (from ethyl acetate); (Found M^+ 187.0751. $C_{10}H_9N_3O$ requires 187.0746); δ_H ([$^2H_6$] acetone) 10.21 (1 H, br s), 7.68 (1 H, d, ^3J 2.1), 7.36 (1 H, d, ^3J 8.8), 7.34 (1 H, d, ^4J 2.6), 6.88 (1 H, dd, ^3J 8.8, ^4J 2.6), 5.73 (1 H, d, ^3J 2.1) and 3.88 (3 H, s); δ_C ([$^2H_6$] acetone) 154.08 (q), 153.92 (q), 142.96, 129.08 (q), 125.88 (q), 111.55, 109.90, 94.00, 78.50 and 54.47; *m/z 187* (M^+, 100%), 172(53), 159(12), 144(18), 133(11), 63(11) and 52(11).

Variable temperature pyrolyses of 1-(2-azido-5-methoxyphenyl)pyrazole 161, 61 mg, T_f 400°C, T_i 105°C, P 7.5 x 10^{-4} Torr, $t_{(pyr.)}$ 25 min; 7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **162** (88%); 7-methoxypyrazolo[1,2-*a*]benzotriazole **163** (12%) and 7-methoxyquinoxaline **164** (0%); 52 mg, T_f 450°C, T_i 120°C, P 0.002 Torr, $t_{(pyr.)}$ 30 min; 7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **162** (87%); 7-methoxypyrazolo[1,2-*a*]benzotriazole **163** (9%) and 7-methoxyquinoxaline **164** (4%); 46 mg, T_f 500°C, T_i 130°C, P 0.08 Torr, $t_{(pyr.)}$ 30 min; 7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **162** (89%); 7-methoxypyrazolo[1,2-*a*]benzotriazole **163** (0%) and 7-methoxyquinoxaline **164** (11%); 53 mg, T_f 550°C, T_i 105°C, P 7.5 x 10^{-4} Torr, $t_{(pyr.)}$ 30 min; 7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **162** (87%); 7-

methoxypyrazolo[1,2-*a*]benzotriazole **163** (0%) and 7-methoxyquinoxaline **164** (13%).

b. SYNTHESIS OF 6-METHOXY-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLE 170

1-(2-Nitro-4-methoxyphenyl)pyrazole 167

A stirred mixture of pyrazole (1.63 g, 24 mmol), 4-chloro-3-nitroanisole **166** (3.00 g, 16 mmol), anhydrous potassium carbonate (2.19 g, 16 mmol) and copper (II) oxide (0.09 g) in pyridine (4.5 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange oil. Purification by dry-flash chromatography eluting with a mixture of *n*-hexane and ethyl acetate gave the *title compound* **167** as an orange solid (0.52 g, 15%), mp 105-108°C (from toluene) (Found M^+, 219.0637. $C_{10}H_9N_3O_3$ requires 219.0644) (Found: C, 54.65; H, 4.4; N, 18.95. $C_{10}H_9N_3O_3$ requires C, 54.8; H, 4.1; N, 19.2%); δ_H 7.68 (1 H, d, ^3J 1.6), 7.63 (1 H, d, ^4J 2.8), 7.45 (1 H, d, ^3J 8.8), 7.37 (1 H, d, ^3J 2.8), 7.15 (1 H, dd, ^3J 8.8, ^4J 2.9), 6.45 (1H, t, ^3J 2.1) and 3.88 (3 H, s); δ_C 159.05 (q), 145.21 (q), 141.53, 130.08, 127.95, 126.49 (q), 118.67, 109.70, 107.44 and 56.03; *m/z* 220 ($[M+1]^+$, 14%), 219 (M^+, 100%), 202(13), 162(57), 150(20), 146(31), 131(10), 130(29), 120(11), 106(11), 103(19), 102(15), 77(18) and 76(16).

1-(2-Amino-4-methoxyphenyl)pyrazole 168

Palladium-on-charcoal (10%, 0.04 g) was carefully added to a solution of 1-(2-nitro-4-methoxyphenyl)pyrazole **167** (0.34 g, 1.6 mmol) in ethanol (21 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for

4 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give a brown oil which was purified by kugelrohr distillation to afford the *title compound* **168** (0.28 g, 96%), bp 110-113°C (0.15 Torr); (Found M^+, 189.0903. $C_{10}H_{11}N_3O$ requires M^+, 189.0902); δ_H 7.69 (1 H, d, ^3J 1.6), 7.60 (1 H, d, ^3J 2.4), 7.64 (1 H, dd, ^3J 6.4, ^4J 2.7), 6.38 (1 H, t, ^3J 2.1), 6.32-6.26 (2 H, m), 4.41 (2 H br s) and 3.74 (3 H, s); δ_C 159.65 (q), 142.35 (q), 140.11, 129.95, 125.39, 120.34 (q), 105.91, 103.35, 101.62 and 55.07; *m/z* 189 (M^+, 100%), 174(24), 161(17), 147(14), 146(19), 58(27), 43(67) and 32(100).

1-(2-Azido-4-methoxyphenyl)pyrazole 169

To stirred solution of 1-(2-amino-4-methoxyphenyl)pyrazole **168** (0.28 g, 1.5 mmol) in concentrated hydrochloric acid solution (35%, 0.7 ml) and water (10 ml) at 0°C was added a solution of sodium nitrite (0.11 g, 1.6 mmol) in water (0.5 ml). The resulting orange solution was added, carefully with stirring, to a solution of sodium azide (0.10 g, 1.6 mmol) and sodium acetate (0.5 g) in water (3 ml) at 0°C. On addition the mixture became pink and opaque and was stirred at room temperature for a further 30 min. The mixture was extracted with ether (3 x 50 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **169** as a dark red oil (0.20 g, 63%); bp 103-105°C (0.4 Torr) (Found M^+ 215.0798. $C_{10}H_9N_5O$ requires 215.0807); $\nu_{max.}$ 2116; δ_H (80 MHz) 7.76 (1 H, dd, ^3J 2.4, ^4J 0.6), 7.69 (1 H, dd, ^3J 1.9, ^4J 0.6), 7.47 (1 H, m), 6.74 (2 H, m), 6.42 (1 H, dd, ^3J 2.4, 1.9) and 3.85 (3 H, s); δ_C 159.67 (q), 140.31, 134.64 (q), 131.28, 127.89, 125.25 (q), 110.43, 106.23, 104.70 and 55.56; *m/z* 215 (M^+, 77%), 188(14), 187(100), 172(44), 160(30), 156(11), 145(22), 144(25), 133(14), 117(20), 106(11), 80(11), 77(16), 76(13), 63(13), 52(22), 51(11), 43(12) and 39(15).

(ii) PYROLYSIS OF 1-(2-AZIDO-4-METHOXYPHENYL)PYRAZOLE 169

Pyrolysis of 1-(2-azido-4-methoxyphenyl)pyrazole **169** was carried out by the method described in Section B, using a metal inlet for safety reasons. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by distillation with [$^2H_6$] acetone and the ^1H NMR spectrum run without purification of the pyrolysate. The pyrolysis afforded three products in varying proportions which were assigned in the ^1H NMR spectrum by analogy with the unsubstituted and 7-methoxy systems; 6-methoxypyrazolo[1,5-*a*]benzimidazole **170**, 6-methoxypyrazolo[1,2-*a*]benzotriazole **171** and 7-methoxyquinoxaline **164**. The relative ratios of each component were determined by examination of characteristic resonance integrals in the ^1H NMR spectrum. Pyrolysis was carried out under the conditions indicated.

Pyrolysis of 1-(2-azido-4-methoxyphenyl)pyrazole 169 (0.059 g, 0.27 mmol), T_i 110°C, T_f 500°C, P 0.002 Torr, $t_{(pyr.)}$ 50 min; 6-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **170** (31%); 6-methoxypyrazolo[1,2-*a*]benzotriazole **171** (22%) and 7-methoxyquinoxaline **164** (47%).

C. ATTEMPTED SYNTHESIS OF 7-*N*-SUBSTITUTED AMINO-4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLES

3-Fluoro-4-nitroaniline[59]

3-Fluoroaniline (10.0 g, 0.09 mol) and benzaldehyde (10.0 g, 0.094 mol) were heated at 100°C for 40 min and then the mixture was dissolved in concentrated sulfuric acid (40 ml). The mixture was cooled to 5°C then a mixture of concentrated nitric acid (d 1.42, 6.0 ml) and concentrated sulfuric acid (d 1.83, 20.0 ml) was added dropwise

over 1 h. Water (100 ml) was added and the oily mixture was heated under reflux for a further 2 h. The mixture was neutralised with dilute aqueous potassium hydroxide solution (2 M) and the aqueous layer was extracted with dichloromethane (3 x 200 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give an orange crystalline solid. Purification by wet flash chromatography on alumina (grade III) eluting with a mixture of *n*-hexane and ethyl acetate afforded the title compound **173** (6.34 g, 45%) as a red crystalline solid, mp 153-155°C (from ethanol) (lit.,[59] mp 153°C); δ_H 7.89 (1 H, m), 6.97 (2 H, br s), 6.46-6.36 (2 H, m); *m/z* 156 (M^+, 67%), 140(16), 126(100), 110(59), 109(24), 98(31), 94(11), 91(18), 90(18), 83(100), 63(40), 57(40), 52(22) and 40(34). 3-Fluoro-6-nitroaniline **174** was also isolated as yellow feathery needles (5.64 g, 40%), mp 93-95°C (from water) (lit.,[59] mp 97°C); δ_H 8.03 (1 H, dd, ^3J 9.6, ^4J 7.6), 7.58 (2 H, br s), 6.73 (1 H, dd, ^3J 11.4, ^4J 2.8) and 6.43 (1 H, ddd, ^3J 9.6, 7.6, ^4J 2.8); *m/z* 156 (M^+, 88%), 126(33), 110(57), 109(12), 98(45), 90(16), 83(100), 82(21), 63(30), 57(37), 52(17) and 40(61).

1-(2-Nitro-5-aminophenyl)pyrazole 177

A stirred mixture of pyrazole (2.18 g, 32 mmol), 3-fluoro-4-nitroaniline **173** (5.00 g, 32 mmol), anhydrous potassium carbonate (4.12 g) and copper (II) oxide (0.22 g) in pyridine (11.0 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange oil. Purification by dry-flash chromatography eluting with a 1 : 1 mixture of *n*-hexane and ethyl acetate gave the *title compound* **177** as an orange oil (2.99 g, 46%), bp 150-153°C (0.3 Torr) (Found M^+, 204.0635. $C_9H_8N_4O_2$ requires 204.0647); δ_H 7.85 (1 H, d, ^3J 8.9), 7.68 (1 H, d, ^3J 1.5), 7.58 (1 H, d, ^3J 2.2), 6.63 (1 H, d, ^4J 2.5), 6.55 (1 H, dd, ^3J 8.9, ^4J 2.5), 6.43 (1 H, dd, ^3J 2.4, 1.9) and 4.75 (2 H, br s); δ_C 151.62 (q),

141.41, 136.39 (q), 134.37 (q), 130.52, 128.20, 112.66, 111.96 and 107.42; *m/z* 205 ($[M+1]^+$, 20%), 204 (M^+, 100%), 187(36), 174(25), 148(15), 147(66), 135(12), 132(16), 131(61), 120(11), 119(21), 111(18), 109(14), 105(48), 97(26), 92(28), 91(26), 83(24), 73(34), 57(48), 55(32) and 52(31).

1-(2-Nitro-5-*N*-acetylaminophenyl)pyrazole 178

A solution of 1-(2-nitro-5-aminophenyl)pyrazole **177** (0.74 g, 3.6 mmol) in acetic anhydride (17.5 ml, 18.9 g, 185 mmol) was heated under reflux monitoring the reaction by t.l.c. After 5 h, toluene (50 ml) was added and the solvents were removed under reduced pressure to leave brown residue. Purification by dry-flash chromatography eluting with a 1 : 1 mixture of *n*-hexane and ethyl acetate gave the *title compound* **178** (0.60 g, 67%), mp 159-162°C (from ethyl acetate); (Found: C, 53.7; H, 4.25; N, 22.9. $C_{11}H_{10}N_4O_3$ requires C, 53.65; H, 4.05; N, 22.75%); δ_H 10.65 (1 H, br s), 8.18 (1 H, d, ^4J 2.5), 8.03 (1 H, d, ^3J 8.9), 7.98 (1 H, d, ^3J 2.2), 7.74 (1 H, d, ^3J 1.7), 7.70 (1 H, dd, ^3J 8.9, ^4J 2.2), 6.55 (1 H, t, ^3J 2.1) and 2.12 (3 H, s); δ_C 169.95 (q), 143.86 (q), 142.01, 138.48 (q), 134.07 (q), 130.90, 126.80, 117.64, 115.49, 108.16 and 24.34; *m/z* 246 (M^+, 39%), 229(18), 204(62), 187(11), 174(15), 147(24), 131(21), 43(100) and 32(88). The diacetylated product 1-(2-nitro-5-*N,N*-diacetylaminophenyl)pyrazole **179** (0.24 g, 23%) was also obtained, mp 180-182°C (from toluene) (Found M^+, 288.0843. $C_{13}H_{12}N_4O_4$ requires 288.0859); δ_H 7.91 (1 H, d, ^3J 8.5), 7.44 (1 H, d, ^4J 2.1), 7.69 (2 H, m), 7.28 (1 H, dd, ^3J 8.5, ^4J 2.2), 6.47 (1 H, dd, ^3J 2.5, 1.9) and 2.30 (6 H, s); δ_C 171.79 (q), 143.52 (q), 143.11 (q), 142.61, 134.32 (q), 129.60, 128.39, 126.44, 126.24, 108.67 and 26.71, *m/z* 288 (M^+, 6%), 246(76), 231(100), 185(11) and 43(80).

An alternative preparation of 1-(2-nitro-5-*N*-acetylaminophenyl)pyrazole **178** was carried out latterly. A solution of 1-(2-nitro-5-aminophenyl)pyrazole **177** (2.1 g, 10.3 mmol) in dry THF (100 ml) was stirred with acetyl chloride (0.89 g, 0.81 ml, 11.3 mmol, 1.1 eq.) and pyridine (0.81 g, 0.83 ml, 10.3 mmol) at room temperature

monitoring the reaction by t.l.c.. After 1 h, saturated aqueous ammonium chloride solution (70 ml) was added, then the THF layer was separated. The aqueous layer was extracted with ether (3 x 75 ml), the combined ether extracts and THF layer were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the *title compound* **178** (2.33 g, 92%) as an orange crystalline solid which was purified by recrystallisation from ethyl acetate.

1-(2-Amino-5-*N*-acetylaminophenyl)pyrazole 180

Palladium-on-charcoal (5%, 0.21 g) was carefully added to a solution of 1-(2-nitro-5-*N*-acetylphenyl)pyrazole **178** (0.20 g, 0.8 mmol) in ethanol (20 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 6 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the *title compound* **180** (0.18 g, 100%) as a brown oil which crystallised and did not require further purification, mp 137-138°C (from toluene); (Found M^+, 216.1026. $C_{11}H_{12}N_4O$ requires 216.1011); δ_H 8.24 (1 H, br s), 7.68 (1 H, d, ^3J 1.6), 7.60 (1 H, d, ^4J 2.3), 7.40 (1 H, d, ^3J 2.3), 7.02 (1 H, dd, ^3J 8.5, ^4J 2.3), 6.62 (1 H, d, ^3J 8.5), 6.37 (1 H, t, ^3J 2.0), 4.49 (2 H, br s) and 2.03 (3 H, s); δ_C 168.70 (q), 140.36, 137.55 (q), 129.92, 128.81 (q), 125.74 (q), 121.16, 117.10, 117.05, 106.38 and 23.79; *m/z* 216 (M^+, 100%), 174(56), 173(36), 147(15), 146(24) and 43(15).

1-(2-Azido-5-*N*-acetylaminophenyl)pyrazole 181

To stirred solution of 1-(2-amino-5-*N*-acetylphenyl)pyrazole **180** (0.65 g, 3.0 mmol) in concentrated hydrochloric acid solution (35%, 1.0 ml) and water (3 ml) at 0°C was added a solution of sodium nitrite (0.25 g, 3.6 mmol) in water (1 ml). The resulting solution was added, carefully with stirring, to a solution of sodium azide (0.24 g, 3.6 mmol) and sodium acetate (1.9 g) in water (6 ml) at 0°C. On addition a white foam precipitate appeared and the mixture was stirred at room temperature for a further 30 min. The mixture was extracted with ether (3 x 50 ml), the organic extracts were

washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **181** as a fawn powder (0.67 g, 92%); (Found M^+ 242.0921. $C_{11}H_{10}N_6O$ requires 242.0916); $\nu_{max.}$ 2121; δ_H 8.34 (1 H, br s), 7.93 (1 H, d, ^4J 2.5), 7.76 (1 H, dd, ^3J 8.7, ^4J 2.5), 7.71 (1 H, d, ^3J 1.7), 7.65 (1 H, d, ^3J 2.4), 7.14 (1 H, d, ^3J 8.8), 6.46 (1 H, t, ^3J 2.3, 2.0) and 2.04 (3 H, s); δ_C 168.65 (q), 140.72, 135.67 (q), 131.62, 131.15 (q), 127.79 (q), 120.17, 119.76, 117.52, 106.82 and 24.09; *m/z* 242 (M^+, 1%), 214(13), 172(14), 171(12), 145(11) and 43(31).

(ii) PYROLYSIS OF 1-(2-AZIDO-5-*N*-ACETYLAMINOPHENYL) PYRAZOLE 181

Pyrolysis of 1-(2-azido-5-*N*-acetylaminophenyl)pyrazole **181** was carried out by the method described in Section B, using a metal inlet for safety reasons. Decomposition of the substrate in the inlet was observed at standard vacuum, however this was reduced to some extent with the use of the mercury diffusion pump. Upon completion of the pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by distillation with [$^2H_6$] acetone and the ^1H NMR spectrum run without purification of the pyrolysate. The pyrolyses afforded a mixture of products from which ^1H NMR assignments were not possible. The characteristic resonance of H-3 at δ_H 5.73 in the desired 7-*N*-acetylamino-4*H*-pyrazolo[1,5-*a*]benzimidazole **182** was obvious however, contrary to expectations, the integral was negligible. Pyrolyses were carried out under the conditions indicated.

Pyrolyses of 1-(2-azido-5-*N*-acetylaminophenyl)pyrazole 181; 64 mg, T_f 400°C, T_i 100°C, P 0.004 Torr, $t_{(pyr.)}$ 45 min; 82 mg, T_f 500°C, T_i 90°C, 3 x 10^{-4} Torr (mercury diffusion pump), $t_{(pyr.)}$ 4 h 30 min.

(iii) 1-(2-Amino-5-*N*-ethylaminophenyl)pyrazole 183

To a mixture of lithium aluminium hydride (1.0 M solution in THF, 4.8 ml, 4.8 mmol) was added a solution of 1-(2-amino-5-*N*-acetylaminephenyl)pyrazole **180** (0.32 g, 1.46 mmol) in dry THF (30 ml) at such a rate as to produce gentle reflux. On addition, the mixture went yellow in colour and was heated under reflux for 2 h monitoring the reaction by t.l.c. Wet ether (40 ml) was added followed by careful addition of water (30 ml), then a saturated aqueous solution of potassium sodium tartrate (40 ml) was added and the mixture was shaken well. The organic and aqueous layers were filtered through celite, the ether layer was separated and the aqueous layer was added to a saturated solution of brine (20 ml). The aqueous layer was extracted with dichloromethane (3 x 40 ml). The combined organic extracts and ether layer were dried ($MgSO_4$) and the solvents were removed under reduced pressure to afford the *title compound* **183** (0.21 g, 72%) as a dark crystalline solid, mp 79-80°C (from cyclohexane) (Found M^+, 202.1220. $C_{11}H_{14}N_4$ requires 202.1219); δ_H 7.70 (1 H, d, ^3J 1.6), 7.67 (1 H, d, ^4J 2.7), 6.69 (1 H, dd, ^3J 6.8, ^4J 2.4), 6.51 (1 H, d, ^3J 2.4), 6.49 (1 H, d, ^3J 6.8), 6.39 (1 H, t, ^3J 2.2), 3.71 (2 H, br s), 3.07 (2 H, q, ^3J 7.1) and 1.20 (3 H, t, ^3J 7.1); δ_C 141.30 (q), 140.18, 132.02 (q), 129.67, 127.53 (q), 118.75, 114.031, 109.06, 106.03, 39.25 and 14.72; *m/z* 203 ($[M+1]^+$, 14%), 202 (M^+, 100%), 187(71), 174(18), 173(32) and 146(13).

Attempted formation of 1-(2-azido-5-*N*-ethylaminophenyl)pyrazole

To stirred solution of 1-(2-amino-5-*N*-ethylphenyl)pyrazole **183** (0.22 g, 1.1 mmol) in concentrated hydrochloric acid solution (35%, 0.4 ml) and water (1 ml) at 0°C was added a solution of sodium nitrite (0.25 g, 3.6 mmol) in water (1 ml). The resulting solution was added, carefully with stirring, to a solution of sodium azide (0.09 g, 1.3 mmol) and sodium acetate (0.6 g) in water (3 ml) at 0°C. On addition a brown oil separated and the mixture was stirred at room temperature for a further 30 min. The

mixture was extracted with ether (3 x 30 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 5 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield a brown oil. The product was purified by dry-flash chromatography eluting with a mixture of *n*-hexane and ethyl acetate to give the unknown dimer **184**; $\nu_{max.}$ 3362, 2973, 2117 and 1615; δ_H 8.07 (1 H, d, ^4J 2.6), 7.92 (1 H, d, ^4J 2.4), 7.87 (1 H, d, ^4J 2.6), 7.72 (1 H, d, ^3J 1.8), 7.67 (1 H, d, ^3J 1.7), 7.59 (1 H, dd, ^3J 8.7, ^4J 2.6), 7.33 (1 H, d, ^3J 8.8), 7.03 (1 H, d, ^3J 8.7), 6.85 (1 H, d, ^4J 2.7), 6.59 (1 H, dd, ^3J 8.7, ^4J 2.7), 6.47 (1 H, t, ^3J 2.1), 6.41 (1 H, t, ^3J 2.2), 4.04 (2 H, q, ^3J 7.2), 3.13 (2 H, q, ^3J 7.1) and 1.25-1.11 (6 H, 2 x t, ^3J 7.1); δ_C 146.24 (q), 140.99, 140.25, 138.56 (q), 132.26 (q), 132.02 (q), 131.32, 131.20, 130.44 (q), 120.36, 120.24, 118.67, 116.37, 112.78, 109.40, 107.08, 106.27, 38.70, 38.34, 14.46 and 11.49 (1 quaternary missing); *m/z* 371 (13%), 227(14), 213(17), 203(14), 202(30), 201(36), 200(60), 199(50), 187(32), 186(32), 185(38), 184(72), 183(25), 173(58), 172(40), 171(37), 159(29), 158(41), 157(30), 156(70), 145(22), 144(20), 131(55), 130(23), 129(18), 119(12), 103(37) and 79(100).

(iv) Attempted *N*-methylations of 3-fluoro-4-nitroaniline 173

1. 3-Fluoro-4-nitroaniline **173** (0.44 g, 2.8 mmol) was dissolved in DMF (13 ml) and potassium carbonate (0.7 g, 5.1 mmol) was added. Methyl iodide (1.1 g, 7.7 mmol) was added dropwise to the stirred mixture which was then left stirring at room temperature. After 64 h, the solution had changed colour from dark brown to pale red. Water (12 ml) was added and the solution was extracted with ether (3 x 15 ml). The combined organic extracts were backwashed with water (4 x 25 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to leave an orange oil which was not the desired compound **176**. Purification by dry-flash chromatography eluting with a mixture of *n*-hexane and ethyl acetate afforded N, N-

dimethyl-N'-*(3-fluoro-4-nitrophenyl)-formamidine* **175** as orange crystals (0.17 g, 29%) mp 135-137°C; δ_H ([$^2H_6$] DMSO) 8.09 (1 H, s), 8.00 (1 H, t, ^3J 9.1), 7.01 (1 H, dd, ^3J 14.6, ^4J 2.3), 6.88 (1 H, ddd, ^3J 9.0, ^4J 2.3, ^5J 0.7), 3.10 (3 H, s) and 2.98 (3 H, s); *m/z* 212 ([M+1]$^+$, 35%, 211 (M$^+$, 100%), 210(30), 196(34), 183(10), 169(16), 164(19), 150(15), 124(10), 123(11), 121(15), 94(20), 83(13) and 44(53).

The above procedure was repeated with an authentic sample of 4-nitroaniline (0.2 g, 1.5 mmol). After purification by dry-flash chromatography eluting with a 3 : 2 mixture of *n*-hexane and ethyl acetate, the expected *N,N*-dimethyl-*N'*-4-nitrophenylformamidine was obtained as a yellow crystalline solid (0.052 g, 19%); δ_H 8.10-8.04 (2 H, m), 7.58 (1 H, s), 6.97-6.91 (2 H, m), 3.06 (3 H, s) and 3.03 (3 H, s); δ_C 158.28 (q), 153.77, 142.31 (q), 125.00, 120.82, 40.35 and 34.46 (in agreement with published data).[89]

2. 3-Fluoro-4-nitroaniline **173** (1.0 g, 6.4 mmol) was dissolved in methanol (4 ml) and methyl sulfate (2.93 g, 2.2 ml, 23 mmol) and the mixture was heated in an evacuated sealed tube at 170°C for 6 h. Work-up as outlined in the literature[59] failed to afford the title compound **176**, yielding only a black tar.

6. SYNTHESIS OF 2-*t*-Bu-4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE 191

3-*t*-Bu-pyrazole[60] 185

To slurry of dry powdered sodium methoxide (46.67 g, 0.86 mol) in dry toluene (270 ml) was added, with rapid stirring, a mixture of pinacolone (90.0 g, 0.90 mol) and ethyl formate (74.0 g, 1.0 mol). On addition, an exothermic, but well contained reaction ensued. The reaction was stirred for a further 10 min then low boiling materials were removed under reduced pressure. Ice water (300 ml) was added and the resulting two-phase system was stirred, during which time the colour of the reaction mixture passed into the aqueous phase. The aqueous phase was separated and added to a solution of hydrazine monohydrochloride (59.94 g, 0.86 mol) in water (250 ml). On addition a white emulsion was observed from which an oil separated. The system was extracted with dichloromethane (3 x 300 ml), dried ($MgSO_4$) and the solvents removed under reduced pressure to yield the title compound **185** (76.28 g, 68%) as a yellow oil; bp 80-85°C (0.5 Torr) (lit.,[60] bp 76-80°C [0.3 Torr]); δ_H (60 MHz) 7.56 (1 H, d, ^3J 2.5), 6.15 (1 H, d, ^3J 2.5) and 1.36 (9 H, s).

3-*t*-Bu-1-(2-nitrophenyl)pyrazole 187

A stirred mixture of 3-*t*-Bu-pyrazole **185** (1.0 g, 8 mmol), *o*-chloronitrobenzene (1.26 g, 8 mmol), anhydrous potassium carbonate (1.12 g, 8 mmol) and copper (II) oxide (0.04 g) in pyridine (2.0 ml) was heated under reflux for 72 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give a brown oil. Purification by dry-flash chromatography eluting with a mixture of *n*-hexane and ethyl acetate gave the *title compound* **187** as an orange crystalline solid (0.77 g, 39%), mp 60-62°C (from cyclohexane-hexane), bp 87°C (0.02 Torr) (Found: C, 63.5; H, 6.35; N,

16.95. $C_{13}H_{15}N_3O_2$ requires C, 63.65; H, 6.1; N, 17.15%); δ_H (80 MHz) 7.76 (1 H, ddd, ^3J 7.4, ^4J 1.5, ^5J 1.0), 7.59 (1 H, d, ^3J 2.5), 7.65-7.54 (2 H, m), 7.49-7.28 (1 H, m), 6.33 (1 H, d, ^3J 2.5) and 1.31 (9 H, s); δ_C 164.82 (q), 144.35 (q), 133.42 (q), 132.58, 129.43, 127.33, 125.19, 124.80. 104.83, 32.23 (q) and 30.14; *m/z* 245 (M^+, 18%), 231(14), 230(100), 184(13) and 32(14).

3-*t*-Bu-1-(2-aminophenyl)pyrazole 189

Palladium-on-charcoal (10%, 0.03 g) was carefully added to a solution of 3-*t*-Bu-1-(2-nitrophenyl)pyrazole **187** (0.27 g, 1.1 mmol) in ethanol (15 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 4 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the *title compound* **189** as a brown oil (0.23 g, 99%) which did not require further purification; bp 104-107°C (0.5 Torr); (Found M^+, 215.1425. $C_{13}H_{17}N_3$ requires 215.1419); δ_H 7.59 (1 H, d, ^3J 2.4), 7.15 (1 H, ddd, ^3J 7.6, ^4J 1.5, ^5J 0.5), 7.07 (1 H, ddd, ^3J 7.6, ^4J 1.5, ^5J 0.5), 6.80 (1 H, ddd, ^3J 7.6, ^4J 1.4, ^5J 0.5), 6.73 (1 H, ddd, ^3J 7.6, ^4J 1.4, ^5J 0.5), 6.26 (1 H, d, ^3J 2.4) and 1.36 (9 H, s); δ_C 162.94 (q), 140.65 (q), 129.68, 127.72, 126.51 (q), 123.33, 117.84, 117.22, 102.58, 32.09 (q) and 30.37; *m/z* 215 (M^+, 60%), 200(48), 158(14), 133(27), 132(14), 131(20), 119(42), 100(17), 93(10), 92(37), 86(16), 82(100), 80(10), 77(14), 68(12), 66(10), 65(52), 58(12), 57(27), 53(11), 52(14), 43(21), 42(19), 41(36) and 39(22).

3-*t*-Bu-1-(2-azidophenyl)pyrazole 190

To stirred solution of 3-*t*-Bu-1-(2-aminophenyl)pyrazole **189** (0.19 g, 0.9 mmol) in concentrated hydrochloric acid solution (35%, 0.5 ml) and water (10 ml) at 0°C was added a solution of sodium nitrite (0.073 g, 1.05 mmol) in water (1 ml). The resulting yellow solution was added, carefully with stirring, to a solution of sodium azide (0.07 g, 1.07 mmol) and sodium acetate (0.34 g) in water (2 ml) at 0°C. On addition the mixture became yellow and opaque and was stirred at room temperature

for a further 30 min. The mixture was extracted with ether (3 x 20 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **190** as an fawn oil (0.22 g, 100%); (Found M^+, 241.1330. $C_{13}H_{15}N_5$ requires 241.1327); $\nu_{max.}$ 2128 and 2096; δ_H 7.83 (1 H, d, ^3J 2.5), 7.77-7.63 (1 H, m), 7.33-7.17 (3 H, m), 6.30 (1 H, d, ^3J 2.5) and 1.37 (9 H, s); δ_C 163.17 (q), 132.31 (q), 132.03(q), 131.51, 127.82, 126.41, 125.37, 119.43, 103.34, 32.10 (q) and 30.37; *m/z* 241 (M^+, 10%), 214(11), 213(44), 199(14), 198(100), 184(11), 183(12), 157(31), 155(18), 154(21), 131(19), 78(15), 77(19), 67(13), 57(64), 52(21), 51(15), 43(13), 41(45) and 39(23).

b. PYROLYSIS OF 3-*t*-Bu-1-(2-AZIDOPHENYL)PYRAZOLE 190

Pyrolysis of 3-*t*-Bu-1-(2-azidophenyl)pyrazole **190** was carried out by the method described in Section B, using a metal inlet. Products were removed from the trap by distillation with acetone and the ^1H NMR spectrum run without purification of the pyrolysate. According to the furnace temperature, each pyrolysis afforded a mixture of products in varying proportions including 2-*t*-Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191**, 2-*t*-Bu-pyrazolo[1,2-*a*]benzotriazole **192** and quinoxaline **143**. The relative ratios of each component were determined by characteristic resonance integrals in the ^1H NMR spectrum. Pyrolyses were carried out under the conditions indicated.

Preparative pyrolysis of 3-*t*-Bu-1-(2-azidophenyl)pyrazole 190 (0.62 g, 2.6 mmol), T_i 50°C, T_f 500°C, P 0.004 Torr, $t_{(pyr.)}$ 50 min. The products of the pyrolysis were separated by dry-flash chromatography eluting with a 85:15 mixture of *n*-hexane and ethyl acetate; 2-*t*-Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191** (0.47 g, 84%); mp 257-259°C (from toluene) (Found M^+, 213.1272. $C_{13}H_{15}N_3$ requires

213.1266); δ_H (250 MHz, [$^2H_6$] DMSO) 11.26 (1 H, br s), 7.67 (1 H, dd, ^3J 7.7, ^4J 1.5), 7.37 (1 H, dd, ^3J 7.7, ^4J 1.5), 7.21 (1 H, td, ^3J 7.6, ^4J 1.4), 7.13 (1 H, td, ^3J 7.6, ^4J 1.4), 5.69 (1 H, s) and 1.33 (9 H, s); δ_C ([$^2H_6$] DMSO) 166.63 (q), 144.39 (q), 135.13 (q), 125.75 (q), 122.66, 119.89, 111.70, 109.35, 76.24, 32.96 (q) and 30.74; *m/z* 213 (M^+, 84%), 198(100), 183(24), 171(42), 157(30), 131(24), 103(12), 57(13) and 41(12).

Variable temperature pyrolyses of 3-*t*-Bu-1-(2-azidophenyl)pyrazole 190, 38 mg, T_f 400°C, T_i 60°C, P 8 x 10^{-4} Torr, $t_{(pyr.)}$ 30 min; Complicated mixture including 2-*t*-Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191** and quinoxaline **143**; 20 mg, T_f 500°C, T_i 60°C, P 0.002 Torr, $t_{(pyr.)}$ 30 min; 2-*t*-Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191** (34%), 2-*t*-Bu-pyrazolo[1,2-*a*]benzotriazole **192** (9%) and quinoxaline **143** (57%); 23 mg, T_f 600°C, T_i 60°C, P 0.002 Torr, $t_{(pyr.)}$ 35 min; 2-*t*-Bu-4*H*-pyrazolo[1,5-*a*]benzimidazole **191** (29%) and quinoxaline **143** (71%).

7. SYNTHESIS OF 2-*t*-Bu-7-METHOXY-4*H*-PYRAZOLO[1,5-*a*] BENZIMIDAZOLE 196

3-*t*-Bu-1-(2-nitro-5-methoxyphenyl)pyrazole 193

A stirred mixture of 3-*t*-Bu-pyrazole **185** (1.0 g, 8 mmol), 3-chloro-4-nitroanisole **158** (1.5 g, 8 mmol), anhydrous potassium carbonate (1.12 g, 8 mmol) and copper (II) oxide (0.04 g) in pyridine (2.0 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an orange oil. Purification by dry-flash chromatography eluting with a mixture of *n*-hexane and

ethyl acetate gave the *title compound* **193** (0.73 g, 33%), mp 72-74°C (from *n*-hexane) (Found: C, 61.2; H, 6.0; N, 15.1. $C_{14}H_{17}N_3O_3$ requires C, 61.1; H, 6.2; N, 15.3); δ_H 7.85 (1 H, d, ^3J 9.1), 7.54 (1 H, d, ^3J 2.5), 7.02 (1 H, d, ^4J 2.7), 6.89 (1 H, dd, ^3J 9.1, ^4J 2.7), 6.32 (1 H, d, ^3J 2.6), 3.89 (3 H, s) and 1.31 (9 H, s); δ_C 164.62 (q), 162.79 (q), 137.46 (q), 135.88 (q), 130.03, 127.23, 112.51, 111.37, 104.67, 56.02, 32.22 (q) and 30.20; *m/z* 275 (M^+, 20%), 261(16), 260(100), 214(14) and 32(78).

3-*t*-Bu-1-(2-amino-5-methoxyphenyl)pyrazole 194

Palladium-on-charcoal (10%, 0.05 g) was carefully added to a solution of 3-*t*-Bu-1-(2-nitro-5-methoxyphenyl)pyrazole **193** (0.5 g, 1.8 mmol) in ethanol (25 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 4 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give a brown oil which was purified by kugelrohr distillation to afford the *title compound* **194** (0.43 g, 97%), bp 121-123°C (0.75 Torr); (Found M^+ 245.1518. $C_{14}H_{19}N_3O$ requires 245.1524) (Found: C, 68.1; H, 8.15; N, 16.85. $C_{14}H_{19}N_3O.0.1H_2O$ requires C, 68.05; H, 7.8; N, 17.0%); δ_H 7.59 (1 H, d, ^3J 2.4), 6.77-6.72 (3 H, m), 6.27 (1 H, t, ^3J 2.4), 4.42 (2 H, br s), 3.73 (3 H, s) and 1.36 (9 H, s); δ_C 162.94 (q), 151.99 (q), 134.24 (q), 129.60, 126.97 (q), 118.22, 113.63, 109.29, 102.67, 55.64, 32.02 (q) and 30.28; *m/z* 246($[M+1]^+$, 17%), 245 (M^+, 100%), 230(46), 188(10), 82(12) and 57(13).

3-*t*-Bu-1-(2-azido-5-methoxyphenyl)pyrazole 195

To stirred solution of 3-*t*-Bu-1-(2-amino-5-methoxyphenyl)pyrazole **194** (0.22 g, 0.9 mmol) in concentrated hydrochloric acid solution (35%, 0.4 ml) and water (30 ml) at 0°C was added a solution of sodium nitrite (0.08 g, 1.2 mmol) in water (0.5 ml). The resulting suspension was added, carefully with stirring, to a solution of sodium azide (0.07 g, 1.15 mmol) and sodium acetate (0.4 g) in water (2 ml) at 0°C. On addition the mixture became pink and opaque and was stirred at room temperature for a

further 30 min. The mixture was extracted with ether (3 x 25 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 5 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **195** as an red oil (0.2 g, 84%); (Found M^+ 271.1430. $C_{14}H_{17}N_5O$ requires 271.1433); $\nu_{max.}$ 2120 and 2075; δ_H 7.89 (1 H, d, ^3J 2.2), 7.28 (1 H, d, ^4J 2.9), 7.11 (1 H, d, ^3J 8.9), 6.85 (1 H, dd, ^3J 8.9, ^4J 3.0), 6.30 (1 H, d, ^3J 2.4), 3.81 (3 H, s) and 1.37 (9 H, s); δ_C 163.05 (q), 157.03 (q), 132.50 (q), 131.43, 124.01 (q), 120.22, 113.80, 110.93, 103.34, 55.48, 32.02 (q) and 30.27; *m/z* 271 (M^+, 10%), 245(18), 244(17), 243(93), 229(16), 228(100), 213(17), 188(13), 187(65), 186(10), 172(74), 170(14), 161(15), 84(14), 80(17), 77(11), 68(12), 57(76), 52(14), 42(22), 41(52), 40(18) and 39(17).

b. PYROLYSIS OF 3-*t*-Bu-1-(2-AZIDO-5-METHOXYPHENYL) PYRAZOLE 195

Pyrolysis of 3-*t*-Bu-1-(2-azido-5-methoxyphenyl)pyrazole **195** was carried out by the method described in Section B, using a metal inlet. Products were removed from the trap by distillation with [$^2H_6$] acetone and the ^1H NMR spectrum run without purification of the pyrolysate. Pyrolyses were carried out under the conditions indicated.

Pyrolysis of 3-*t*-Bu-1-(2-azido-5-methoxyphenyl)pyrazole **195** (0.057 g, 0.23 mmol) T_i 100°C, T_f 500°C, P 0.004 Torr, $t_{(pyr.)}$ 50 min. The products of the pyrolysis were separated by preparative t.l.c. eluting with a 2:1 mixture of *n*-hexane-ethyl acetate; *2-t-Bu-7-methoxy-4H-pyrazolo[1,5-a]benzimidazole* **196** (0.03 g, 59%) (Found M^+, 243.1368. $C_{14}H_{17}N_3O$ requires 243.1372), mp 185-190°C (dec.) ; δ_H (400 MHz, [$^2H_6$] acetone) 10.08 (1 H, br s), 7.42-7.38 (2 H, m), 6.93(1 H, dd, ^3J 8.8, ^4J 2.8), 5.74 (1 H, s), 4.00 (3 H, s) and 1.48 (9 H, s); δ_C ([$^2H_6$] DMSO) 166.63 (q), 144.39

(q), 135.13 (q), 125.75 (q), 122.66, 119.89, 111.70, 109.35, 76.24, 32.97 (q) and 30.74; *m/z* 243 (M^+, 100%), 228(94), 213(22), 201(23), 187(17), 172(19) and 165(15).

8. SYNTHESIS OF 4*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLE 1 *via* THE CYCLISATION REACTION OF 1-(2-AMINYLPHENYL)PYRAZOLE RADICALS

1-(2-*N*-Benzyliminophenyl)pyrazole 198

A solution of 1-(2-aminophenyl)pyrazole **140** (2.04 g, 13 mmol) and re-distilled benzaldehyde (1.3 g, 13 mmol) in ethanol (20 ml) was kept for *ca.* 48 h in the presence of 4 Å molecular seives. Removal of the solvent under reduced pressure gave the crude *imine* **198** as an oil, which was freed from unchanged amine by bulb-to-bulb distillation at 120-123°C (0.02 Torr) (2.56 g, 80%) (Found M^+, 247.1120. $C_{16}H_{13}N_3$ requires 247.1109); δ_H 8.47 (1 H, s), 8.1-7.1 (11 H, m) and 6.40 (1 H, t, ^3J 2.1); δ_C 161.08, 143.45 (q), 140.21, 135.82 (q), 133.89 (q), 132.12, 131.67, 128.93, 128.77, 127.52, 126.61, 124.30, 119.34 and 106.28; *m/z* 247 (M^+, 31%), 219(15), 170(70), 145(11), 144(100), 143(13), 118(11), 117(19), 90(19), 89(18) and 77(26).

1-(2-Benzylaminophenyl)pyrazole 199

Sodium borohydride (0.72 g, 19 mmol) was added to a solution of 1-(2-*N*-benzyliminophenyl)pyrazole **198** (1.12 g, 4.5 mmol) in methanol (20 ml) and the resulting solution was heated under reflux for a further 15 min. The reaction mixture was added to water (30 ml) and then extracted with dichloromethane (2 x 30 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to yield the *title compound* **199** (0.76 g, 67%) as an oil which crystallised, mp 76-77°C (from *n*-hexane) (Found: C, 77.05; H, 6.1; N 17.0. $C_{16}H_{15}N_3$ requires

C, 77.1; H, 6.0; N, 16.85%); δ_H 7.78-7.74 (2 H, m), 7.40-7.15 (7 H, m), 6.79-6.71 (2 H, m), 6.47 (1 H, t, ^3J 2.1), 6.10-5.75 (1 H, br s) and 4.43 (2 H, s); δ_C 141.84 (q), 140.25, 138.75 (q), 129.85, 128.46, 128.25, 126.68, 125.93 (q), 123.69, 116.09, 112.17, 106.05 and 47.13 (1 peak missing); *m/z* 249 (M^+, 100%), 248(19), 195(18), 180(29), 172(28), 170(14), 145(34), 144(17), 131(20), 130(15), 106(17), 104(13), 92(10), 91(83), 89(12), 78(15) and 77(37).

Pyrolysis of 1-(2-benzylaminophenyl)pyrazole 199 (0.41 g, 1.6 mmol), T_i 100°C, T_f 750°C, P 0.004 Torr, $t_{(pyr.)}$ 1h 30min. The products of the pyrolysis were separated by gravity elution chromatography on alumina (grade III) eluting with a mixture of *n*-hexane and ethyl acetate, 4*H*-pyrazolo[1,5-*a*]benzimidazole **1** (0.05 g, 20%), mp 216-218°C (lit.,[7] 220°C) and bibenzyl (0.14 g, 48%), δ_H (60 MHz, [$^2H_6$] acetone) 6.68-7.12 (10 H, m) and 2.65 (4 H, s).

9. SYNTHESIS OF 3-(4-DIETHYLAMINO-2-METHYLPHENYLIMINO) -3*H*-PYRAZOLO[1,5-*a*]BENZIMIDAZOLES (MAGENTA AZAMETHINE DYES)

N,N-Diethyl-2-methyl-1,4-phenylene diamine monohydrochloride **201** (0.06 g, 0.28 mmol) was added to a stirred solution of the appropriate pyrazolobenzimidazole (0.25 mmol), dissolved in a mixture of methanol (3 ml) and dilute aqueous sodium carbonate solution (5% w/v, 5 ml). Potassium persulfate (0.15 g, 0.55 mmol) was added to the mixture resulting in an intense colour change to purple. Stirring was continued for 1 h then the mixture was extracted with ethyl acetate (3 x 40 ml). The organic solutions were combined, dried ($MgSO_4$) and the solvents were removed *in vacuo* to afford the product as a dark purple solid.

The following magenta dyes were prepared in this way. The pyrazolobenzimidazole compound used is indicated in brackets in each case.

3-(4-Diethylamino-2-methylphenylimino)-3*H*-pyrazolo[1,5-*a*]benzimidazole 202 (4*H*-pyrazolo[1,5-*a*]benzimidazole **1**) (100%), (Found M^+, 331.1795. $C_{20}H_{21}N_5$ requires 331.1797); $\lambda_{max.}$/EtOAc (ε) 556 (22661), $\lambda_{max.}$/methanol 578, $\lambda_{max.}$/cyclohexane 529 and 554; δ_H 9.45 (1 H, d, ^3J 9.4), 7.86 (1 H, dt, ^3J 8.1, ^4J 1.0, ^5J 1.0), 7.80 (1 H, s), 7.68 (1 H, d, ^3J 7.6), 7.37 (1 H, dd, ^3J 7.3, ^4J 1.2), 7.32-7.22 (1 H, m), 6.79 (1 H, d, ^3J 5.5), 6.61 (1 H, d, ^4J 2.9), 3.48 (4 H, q, ^3J 7.1), 2.55 (3 H, s) and 1.26 (6 H, t, ^3J 7.1); δ_C 153.87, 151.39 (q), 146.81 (q), 146.06 (q), 142.95 (q), 136.58 (q), 135.26 (q), 128.40 (q), 126.73, 124.40, 122.47, 121.45, 112.46, 109.72, 109.22, 44.73, 19.43 and 12.68; *m/z* 333 ($[M+2]^+$, 21%), 332 ($[M+1]^+$, 25%), 331 (M^+, 99%), 318(10), 317(13), 316(58), 290(21), 289(90), 261(19), 260(37), 259(15), 233(25), 232(25), 231(11), 198(34), 189(15), 178(49) and 173(11).

3-(4-Diethylamino-2-methylphenylimino)-7-methoxy-3*H*-pyrazolo[1,5-*a*] benzimidazole 203 (7-methoxy-4*H*-pyrazolo[1,5-*a*]benzimidazole **162**) (87%), (Found M^+, 361.1902. $C_{21}H_{23}N_5O$ requires 361.1882); $\lambda_{max.}$/EtOAc 566; δ_H 9.35 (1 H, d, ^3J 9.3), 7.76 (1 H, s), 7.70 (1 H, d, ^3J 8.9), 7.11 (1 H, d, ^4J 2.4), 6.88 (1 H, dd, ^3J 9.0, ^4J 2.4), 6.74 (1 H, m), 6.79 (1 H, dd, ^3J 9.4, ^4J 2.9), 6.59 (1 H, d, ^4J 2.9), 3.88 (3 H, s), 3.47 (4 H, q, ^3J 7.1), 2.53 (3 H, s) and 1.24 (6 H, t, ^3J 7.1); δ_C 158.18 (q), 154.21, 151.08 (q), 145.51 (q), 142.65 (q), 141.39 (q), 136.62 (q), 135.83 (q), 129.16 (q), 126.32, 122.27, 112.88, 112.56, 109.65, 92.05, 55.64, 44.76, 19.45 and 12.76; *m/z* 361 (M^+, 55%), 346(27), 319(25), 223(11), 198(19), 160(42), 149(100), 97(17), 71(23) and 57(37).

D. ATTEMPTED FORMATION OF 4*H*-PYRROLO[1,5-*a*] BENZIMIDAZOLE 206

1-(2-Azidophenyl)pyrrole 205

To a stirred solution of 1-(2-aminophenyl)pyrrole **204** (0.16 g, 1.0 mmol) in concentrated hydrochloric acid solution (35%, 1.0 ml) and water (8.0 ml) at 0°C was added a solution of sodium nitrite (0.12 g, 1.7 mmol) in water (1 ml). The resulting orange solution was added, carefully with stirring, to a solution of sodium azide (0.11 g, 1.7 mmol) and sodium acetate (0.55 g) in water (5 ml) at 0°C. On addition an orange suspension was observed and the mixture was stirred for a further 30 min after which time a foam had developed. The mixture was extracted with dichloromethane (3 x 20 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 5 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to give an orange crystalline solid which was not the *title compound* **206**, but was pyrrolo[2,1-*c*] [1,2,4]benzotriazine **208** (see discussion) (0.13 g, 77%), mp 241-243°C (from ethyl acetate) (lit.,[62] mp 243-244°C); $\nu_{max.}$ 1733; *m/z* 170 ($[M+1]^+$, 13%), 169 (M^+, 100%), 149(12), 140(30), 114(29) and 39(10).

E. ATTEMPTED SYNTHESIS OF 4*H*-IMIDAZO[1,5-*a*] BENZIMIDAZOLE 213

1. SYNTHESIS OF 9*H*-IMIDAZO[1,2-*a*]BENZIMIDAZOLE

1-(2-Nitrophenyl)imidazole[47] 210

A stirred mixture of imidazole (1.09 g, 16 mmol), *o*-fluoronitrobenzene (2.26 g, 1.69 ml, 16 mmol), anhydrous potassium carbonate (2.24 g, 16 mmol) and copper (II) oxide (0.08 g) in pyridine (4.0 ml) was heated under reflux for 16 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark brown residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give the title compound **210** as orange crystals (2.80 g, 92%), mp 96-98°C (from cyclohexane-chloroform) (lit.,[47] mp 96-98°C); δ_H 7.92 (1 H, dd, ^3J 8.0, ^4J 1.6), 7.67 (1 H, td, ^3J 7.7, ^4J 1.6), 7.58-7.52 (2 H, m), 7.40 (1 H, dd, ^3J 7.8, ^4J 1.5), 7.11 (1 H, br s) and 7.00 (1 H, t, ^3J 1.2).

1-(2-Aminophenyl)imidazole 211

Palladium-on-charcoal (10%, 0.27 g) was carefully added to a solution of 1-(2-nitrophenyl)imidazole **210** (2.00 g, 10.6 mmol) in ethanol (150 ml) and the mixture was hydrogenated at medium pressure (3 atm, 45 p.s.i.) and ambient temperature for 4 h. The mixture was filtered through a celite pad and washed thoroughly with ethanol. The solvents were removed under reduced pressure to give the *title compound* **211** as a brown solid (1.67 g, 99%) which did not require further purification; mp 103-106°C (from cyclohexane-toluene) (Found: C, 67.9, H, 5.85; N, 26.2. $C_9H_9N_3$ requires C, 67.9; H, 5.65; N, 26.4%); δ_H 7.59 (1 H, s), 7.25-7.16 (2 H, m), 7.09-7.05 (2 H, m), 6.82-6.73 (2 H, m) and 4.24 (2 H, br s); δ_C 141.81 (q), 137.44, 129.68, 129.59, 126.91, 123.01 (q), 119.92, 118.25 and 116.17; *m/z* 159 (M^+,

51%), 133(12), 132(100), 131(98), 119(34), 104(21), 92(10), 78(12), 77(15), 65(28), 52(19), 51(14), 41(11) and 39(16).

1-(2-Azidophenyl)imidazole 212

To stirred solution of 1-(2-aminophenyl)imidazole **211** (1.03 g, 6.5 mmol) in concentrated hydrochloric acid solution (35%, 3 ml) and water (10 ml) at 0°C was added a solution of sodium nitrite (0.50 g, 7.2 mmol) in water (3 ml). The resulting solution was added, carefully with stirring, to a solution of sodium azide (0.47 g, 7.2 mmol) and sodium acetate (2.5 g) in water (15 ml) at 0°C. On addition a light brown precipitate appeared, however the mixture was stirred at room temperature for a further 30 min. The mixture was extracted with ether (3 x 50 ml), the organic extracts were washed with dilute aqueous sodium hydroxide solution (2M, 10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure at a temperature of less than 40°C to yield the *title compound* **212** as an brown oil (1.17 g, 98%), (Found M^+, 185.0704. $C_9H_7N_5$ requires 185.0701); $\nu_{max.}$ 2130 and 2097; δ_H 7.64 (1 H, t, ^4J 1.1), 7.38 (1 H, ddd, ^3J 8.1 ,7.0, ^4J1.9), 7.25-7.13 (3 H, m) and 7.11-7.09 (3 H, m); δ_C 137.25, 134.05 (q), 129.02, 128.11 (q), 126.34, 125.18, 120.02 and 119.27; *m/z* 185 (M^+, 74%), 158(12), 157(100), 156(18), 131(17), 130(65), 129(18), 104(26), 103(94), 102(11), 90(33), 84(16), 77(35), 76(45), 65(12), 64(18), 63(12), 53(21), 52(26), 51(22), 50(21), 39(15) and 32(41).

b. PYROLYSIS OF 1-(2-AZIDOPHENYL)IMIDAZOLE 212

Pyrolysis of 1-(2-azidophenyl)imidazole **212** was carried out by the method described in Section B, using a metal inlet for safety reasons. Decomposition of the substrate in the inlet was observed at standard vacuum, however this was reduced to some extent with the use of the mercury diffusion pump. The pyrolysis was repeated three times in order to obtain enough material for ^1H NMR analysis. Upon completion of

each pyrolysis the trap was allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by distillation with acetone and the combined products were purified by dry-flash chromatography eluting with a 1:20 mixture of methanol and ethyl acetate. The pyrolysis afforded only one product, the other possible nitrene insertion product, 9*H*-imidazo[1,2-*a*]benzimidazole **214**. Pyrolyses were carried out under the conditions indicated.

Preparative pyrolysis of 1-(2-azidophenyl)imidazole 212 (0.28 g, 1.2 mmol), T_i room temperature, T_f 500°C, P 2 x 10^{-4} Torr (mercury diffusion pump), $t_{(pyr.)}$ 7 h. 9*H*-imidazo[1,2-*a*]benzimidazole **214** (24 mg, 12%), mp 188°C (dec.); δ_H ([$^2H_6$] acetone) 7.72 (1 H, d, ^3J 6.7), 7.58 (1 H, d, ^3J 1.8), 7.48 (1 H, d, ^3J 6.0), 7.26 (1 H, td, ^3J 7.7, ^4J 1.4), 7.14 (1 H, td, ^3J 7.7, ^4J 1.3) and 7.10 (1 H, d, ^3J 1.8); δ_C 149.56(q), 137.89 (q), 126.68, 124.73(q), 123.36, 119.56, 113.55, 110.89 and 105.74; *m/z* 157 (M^+, 33%), 88(12), 86(62), 84(100), 49(13), 47(20), 40(12) and 32(100).

2. ATTEMPTED SYNTHESIS OF 9*H*-IMIDAZO[1,2-*a*]INDOLE 221 *via* 1-(2-CARBENOPHENYL)IMIDAZOLE

1-(2-Cyanophenyl)imidazole 222

A stirred mixture of imidazole (2.03 g, 30 mmol), 2-chlorobenzonitrile (4.11 g, 30 mmol), anhydrous potassium carbonate (4.2 g, 30 mmol) and copper (II) oxide (0.15 g) in pyridine (6.0 ml) was heated under reflux for 48 h under nitrogen. Dichloromethane (100 ml) and activated charcoal (2.0 g) were added to the resulting dark blue residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give an beige solid. Gravity chromatography eluting with a 1:20 mixture of ethanol and dichloromethane afforded unreacted starting material, 2-chlorobenzonitrile (2.43 g, 59%) mp 43-45°C (lit.,[97a]

mp 42-43°C) and the title compound **222** (1.05 g, 21%) as fawn crystals, mp 146-147°C (from toluene) (lit.,[97b] mp 147-148°C).

Attempted synthesis of 1-(2-tetrazol-5-ylphenyl)imidazole 223

A mixture of 1-(2-cyanophenyl)imidazole **222** (0.34 g, 2.0 mmol), sodium azide (0.14 g, 2.2 mmol), ammonium chloride (0.12 g, 2.2 mmol) in DMF (3.0 ml) was stirred at 100°C monitoring the reaction by t.l.c.. After 48 h, the reaction mixture was worked-up as in the literature[68] to afford only unreacted starting material.

Synthesis of 5-phenyltetrazole 224

A mixture of benzonitrile (0.20 g, 2.0 mmol), sodium azide (0.14 g, 2.2 mmol), ammonium chloride (0.12 g, 2.2 mmol) in DMF (3.0 ml) was stirred at 100°C monitoring the reaction by t.l.c.. After 4 h, the solvent was removed under reduced pressure then water (3 ml) was added to the residue causing precipitation. The mixture was acidified to pH 0 with concentrated hydrochloric acid solution, then the product was filtered off and washed with ice water to leave the tetrazole **224** (0.12 g, 42%), mp 212-215°C (dec.) (from water) (lit.,[68] mp 213-215°C (dec.)) as a white solid.

b. Routes to 2-(imidazol-1-yl)benzaldehyde 225

(i) Reduced activity hydrides[69]

To a stirred suspension of lithium aluminium hydride (0.09 g, 2.3 mmol) in dry ether (5 ml) was added anhydrous ethyl acetate (0.34 ml, 0.3 g, 3.46 mmol) over a period of 15 min at 0°C under nitrogen. After stirring for a further 15 min, 1-(2-cyanophenyl)imidazole **222** (0.39 g, 2.3 mmol) was added with ether (5 ml). The mixture was stirred for 1 h at 0°C and then decomposed with dilute aqueous sulfuric

acid solution(2 M, 3 ml). Work-up as in the literature[69] failed to yield any indication of an aldehyde.

(ii) The McFayden-Stevens[70] route

Ethyl 2-(1*H*-imidazol-1-yl)benzoate 226

A stirred mixture of imidazole (6.8 g, 0.1 mol), *o*-fluoroethylbenzoate (16.8 g, 0.1 mol), anhydrous potassium carbonate (13.9 g, 0.1 mol) and copper (II) oxide (0.5 g) in pyridine (20 ml) was heated under reflux for 48 h under nitrogen. Dichloromethane (200 ml) and activated charcoal (4.0 g) were added to the resulting grey residue and the mixture was heated under reflux for 30 min. The mixture was filtered through a celite pad then washed thoroughly with fresh dichloromethane. The solvents were removed under reduced pressure to give the product **226** (6.61 g, 31%) as an orange oil which crystallised on standing, mp 45-47°C (from cyclohexane) (lit.,[98] mp 46-47°C), δ_H 7.88 (1 H, dd, ^3J 7.7, ^4J 1.6), 7.41-7.58 (3 H, m), 7.27 (1 H, dd, ^3J 7.6, ^4J 1.5), 7.09 (1 H, t, ^3J 1.0), 7.00 (1 H, t, ^3J 1.3), 4.08 (2 H, q, ^3J 7.1) and 1.06 (3H, t, ^3J 7.1).

2-(1*H*-imidazol-1-yl)phenylhydrazide 227

A stirred mixture of ethyl 2-(1*H*-imidazol-1-yl)benzoate **226** (1.27 g, 5.9 mmol) and hydrazine hydrate (10 ml) was heated at 100°C monitoring the reaction by t.l.c.. After 5 h, water (20 ml) was added and the mixture was extracted with dichloromethane (3 x 30 ml), then dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the title compound **227** (0.87 g, 73%) as a yellow crystalline solid, mp 140-142°C (from ethanol) (lit.,[99] mp 141-143°C), *m/z* 202 (M^+, 91%), 201(10), 171(68), 144(100), 116(38), 89(23) and 32(41).

2-(1*H*-imidazol-1-yl)phenylhydrazide 228

Tosylation of the hydrazide **227** in dry pyridine was attempted by the standard method of treatment with an equimolar amount of *p*-toluenesulfonyl chloride. No extractable products were obtained.

F. SYNTHESIS OF 5*H*-PYRROLO[1,2-*a*]IMIDAZOLE 240 AND 5*H*-PYRROLO[1,2-*c*]IMIDAZOLE 245

1. PREPARATION OF METHYL 3-(IMIDAZOLYL)PROPENOATES

Preparation of imidazole-2-carbaldehyde 235

Imidazole-2-carbaldehyde **235** was prepared by the Organic Synthesis[72] method, mp 200-202°C (lit.,[72] mp 206-207°C) and ^{1}H NMR spectrum (60 MHz) [$^2H_6$] DMSO were identical with an authentic sample. Latterly, commercially available imidazole-2-carbaldehyde was used.

Methyl (*E/Z*)-3-(imidazol-2-yl)propenoate 234

To a stirred solution of imidazole-2-carbaldehyde **235** (5.0 g, 52 mmol) in dry pyridine (100 ml) was added methyl (triphenylphosphoranylidene)acetate **236** (17.44 g, 52 mmol) and the mixture was heated under reflux for 1 h. After thorough removal of the solvents, coevaporating with toluene, the residue was taken up as much as possible in dichloromethane. Filtration gave a solid which was washed with a little fresh dichloromethane and identified as methyl (*E*)-3-(imidazol-2-yl)propenoate **234** (*E*) (3.15 g, 40%), mp 209-211°C (from water) (lit.,[65] mp 210-212°C); δ_H ([$^2H_6$] DMSO) 12.72 (1 H, br s), 7.40 (1 H, d, ^3J 16.0), 7.24 (2 H, br s), 6.56 (1 H, d, ^3J 16.0) and 3.71 (3 H, s).

After the combined filtrate and washings had been evaporated to dryness, the residue was taken up in ether (100 ml), stirred for 30 min and then the triphenylphosphine oxide remaining was removed by filtration. The ether was removed from the filtrate and the residue was subjected to vacuum sublimation (*ca.* 100°C, 0.4 Torr) to yield methyl (*Z*)-3-(imidazol-2-yl)propenoate **234** (*Z*) (1.55 g, 20%) after further recrystallisation from cyclohexane, mp 61.5-62.5°C (from cyclohexane) (lit.,[65] mp 63.5-64.5°C); δ_H 9.76 (1 H, br s), 7.31-7.15 (2 H, m), 7.04 (1 H, d, ^3J 12.8), 5.91 (1 H, d, ^3J 12.8) and 3.78 (3 H, s).

Methyl 3-(imidazol-4-yl)propenoate[65] 242

Methyl 3-(imidazol-4-yl)propenoate **242** was obtained esterification of the commercially available propenoic acid (urocanic acid). Urocanic acid (8.2 g, 59 mmol) was added to methanolic hydrogen chloride solution (23% w/v, 62 ml) and the suspension was heated under reflux for 3.5 h. The solution was set aside overnight and the white crystalline solid which appeared was collected by filtration. Concentration of the filtrate gave further methyl 3-(imidazol-4-yl)propenoate hydrochloride (10.01 g, 89%), mp 230-232°C (lit.,[75] mp 233-234°C); δ_H ([$^2H_6$] DMSO) 9.27 (1 H, d, ^4J 0.9), 8.07 (1 H, d, ^4J 0.8), 7.57 (1 H, d, ^3J 16.2), 6.90 (1 H, d, ^3J 16.2) and 3.72 (3 H, s). The hydrochloride salt was dissolved in water (70 ml). Treatment of this solution with potassium hydroxide (3.20 g) in water (12 ml) caused precipitation of the free base which was collected by filtration and dried *in vacuo*. The filtrate was extracted continuously with dichloromethane over 12 h, the extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give another crop of product. Methyl 3-(imidazol-4-yl)propenoate **241** (7.35 g, 82% from acid), mp 93-95°C (from ethyl acetate) (lit.,[95] mp 94-96°C); δ_H 11.23 (1 H, br s), 7.70 (1 H, s), 7.60 (1 H, d, ^3J 15.8), 7.28 (1 H, s), 6.45 (1 H, d, ^3J 15.8) and 3.75 (3 H, s).

2. PYROLYSIS OF METHYL 3-(IMIDAZOLYL)PROPENOATES

Pyrolysis of the methyl 3-(imidazolyl)propenoates was carried out by the method described in Section B. Upon completion of the pyrolysis the methanol generated in the reaction was removed by allowing the product trap to warm up partially while the system was still under vacuum. The trap was then allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by dissolving in dry ether. Pyrolysis of methyl 3-(imidazol-4-yl)propenoate **241** gave a bright orange coloured material which was only partially soluble in dry ether. As the desired pyrrolo[1,2-*c*]imidazol-5-one **243** was known to be soluble in ether, it is assumed that the product polymerises with time. The substrate and pyrolysis parameters are quoted.

Pyrrolo[1,2-*a*]imidazol-5-one 233 [methyl (*Z*)-3-(imidazol-2-yl)propenoate **234** (*Z*) (0.15 g, 0.99 mmol), T_f 800°C, T_i 40-70°C, P 0.002 Torr, $t_{(pyr.)}$ 35 min], (0.09 g, 76%), bp 72-74°C (0.1 Torr)[lit.,[90] bp 90°C (0.1 Torr)]; δ_H 7.19 (1 H, dd, ^3J 6.2, J 0.5), 7.00 (1 H, dd, ^3J 1.7, J 0.5), 6.92 (1 H, dd, ^3J 1.7, J 0.8) and 5.98 (1 H, dd, ^3J 6.1 and J 0.8) (in agreement with published data[90]): **Pyrrolo[1,2-*c*]imidazol-5-one 243** [methyl (*E*)-3-(imidazol-4-yl)propenoate **241** (0.1 g, 0.66 mmol), T_f 850°C, T_i 150-160°C, P 0.002 Torr, $t_{(pyr.)}$ 35 min], (0.055 g, 69%), δ_H (60 MHz) 7.84 (1 H, s), 7.42 (1 H, d), 6.90 (1 H, s) and 5.98 (1 H, d) (in agreement with published data[90]).

3. PREPARATION OF 3-IMIDAZOLYL-2-PROPEN-1-OLS (ALLYLIC ALCOHOLS)

Ring opening reductions were carried out using a 1.0M solution of lithium aluminium hydride in THF, under anhydrous conditions at all times. The apparatus

was flame or oven dried before use and allowed to cool to room temperature under dry nitrogen, reactions were performed under dry nitrogen, and additions were made by injections *via* septa.

To a stirred solution of lithium aluminium hydride (1.0 M solution in THF, 6.6 ml, 6.6 mmol) was added a solution of the appropriate pyrroloimidazol-5-one (6.6 mmol) in dry ether (150 ml) at such a rate as to produce gentle relux. On addition, the mixture was observed to lose all colour and the system was heated under reflux for a further 1 h, then cooled to 0°C. Wet ether (40 ml) was added followed by dropwise addition of water (20 ml). A saturated aqueous solution of potassium sodium tartrate (30 ml) was added, the mixture was shaken vigorously and then filtered through a celite pad. The ether layer was separated, and the aqueous layer was taken to pH 7 with the addition of dilute aqueous hydrochloric acid solution (10%). A saturated solution of brine (50 ml) was added and the aqueous layer was extracted continuously with methylene chloride over 72 h. The combined ether layer and organic extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to afford the crude *alcohol* as a yellow oil, which was subjected to bulb to bulb (Kugelrohr) distillation.

The following allylic alcohols were prepared in this way. The pyrroloimidazolone compound used is indicated in brackets.

3-Imidazol-2-yl-2-propen-1-ol 237 (pyrrolo[1,2-*a*]imidazol-5-one **233**) (59%), bp 110-112°C (0.4 Torr) (Found: C, 58.4; H, 6.6; N, 22.5. $C_6H_8N_2O$ requires C, 58.05; H, 6.45; N, 22.6%) (Found M^+, 124.0635. $C_6H_8N_2O$ requires 124.0637); δ_H 8.81 (2 H, br s), 7.02 (2 H, s), 6.39 (1 H, dt, ^3J 12.1, ^4J 1.2), 6.01 (1 H, dt, ^3J, 12.1, 5.7) and 4.35 (2 H, dd, ^3J 5.7, ^4J 1.2); δ_C 144.71 (q), 132.15, 122.58, 122.41, 119.87 and 58.64; *m/z* 124 (M^+, 28%), 95(100), 81(29), 79(23), 69(63), 68(42), 52(30), 41(25) and 40(27). A volatile impurity of 2-vinylimidazole **238** was observed, bp 58-62°C

(0.4 Torr), δ_H 7.05 (2 H, s), 6.64 (1 H, dd, ^3J 17.8, 11.3), 5.93 (1 H, dd, ^2J 0.7, ^3J 17.8) and 5.31 (1 H, dd, ^2J 1.4, ^3J 11.3) (in agreement with published data).[73]

3-Imidazol-4-yl-2-propen-1-ol 244 (pyrrolo[1,2-*c*]imidazol-5-one **243**) (50%), bp 88-90°C (0.1 Torr); *m/z* (FAB) Found 125.0714. $C_6H_9N_2O$ requires 125.0715; δ_H 8.76 (2 H, br s), 7.53 (1 H, s), 6.94 (1 H, s), 6.41 (1 H, d, ^3J 12.0), 5.79 (1 H, dt, ^3J, 12.0, 5.8) and 4.32 (2 H, dd, ^3J 5.8, ^4J 1.2); δ_C 135.86 (q), 135.25, 127.00, 122.17, 118.31 and 58.69; *m/z* 124 (M^+, 36%), 96(13), 95(100), 81(22), 80(10), 68(31), 41(13), 39(13) and 32(12).

4. PYROLYSIS OF 3-IMIDAZOLYL-2-PROPEN-1-OLS

Pyrolysis of the 3-imidazolyl-2-propen-1-ols was carried out by the method described in Section B. Upon completion of the pyrolysis the water generated in the reaction was removed by allowing the product trap to warm up partially while the system was still under vacuum. The trap was then allowed to warm to room temperature under an atmosphere of nitrogen. The product was removed from the trap by distillation with [^{2}H] chloroform and the ^{1}H NMR spectrum was run without further purification of the products. The following pyrroloimidazoles were prepared in this way. The substrate and pyrolysis parameters are quoted.

5*H*-Pyrrolo[1,2-*a*]imidazole **240** [3-Imidazol-2-yl-2-propen-1-ol **237** (0.25 g, 2.0 mmol), T_f 650°C, T_i 120°C, P 0.01 Torr, $t_{(pyr.)}$ 4 h]) (0.14 g, 66%), bp 52-55°C (0.4 Torr) [lit.,[74] bp 85°C (0.55 Torr)]; δ_H (360 MHz) 7.14 (1 H, m), 7.11 (1 H, m), 6.71 (1 H, dtd, ^3J 6.1, ^4J 1.9, ^5J 0.4), 6.64 (1 H, dtd, ^3J 6.1, ^4J 1.7, ^6J 0.4) and 4.39 (2 H, td, ^3J and ^4J 1.9, ^4J 0.7); δ_C (50 MHz) 157.06 (q), 134.52, 132.66, 122.18, 116.02 and 50.35, *m/z* 106 (M^+, 100%), 84(17), 79(56), 52(45), 51(54) and 32(39).

5*H*-Pyrrolo[1,2-*c*]imidazole **245** [3-Imidazol-4-yl-2-propen-1-ol **244** (0.12 g, 1.0 mmol), T_f 650°C, T_i 120-130°C, P 0.005 Torr, $t_{(pyr.)}$ 1h 30min]) (0.073 g, 71%), bp 72-76°C (0.4 Torr) [lit.,[74] bp 65°C (0.25 Torr)], δ_H 7.66 (1 H, s), 6.82 (1 H, s), 6.60 (1 H, dtd, ^3J 6.0, ^4J 2.2, ^5J 0.5), 6.28 (1 H, dt, ^3J 6.1, ^4J 2.2) and 4.50 (2 H, td, ^3J and ^4J 2.2), δ_C (50 MHz) 141.10 (q), 132.38, 129.22, 121.27, 116.74 and 49.92; *m/z* 106 (M^+, 100%), 84(14), 79(43), 52(55), 51(17), 39(11) and 32(34).

G. SYNTHESIS AND PHOTOGRAPHIC EVALUATION OF NOVEL HETEROAROYLACETANILIDES

1. *C*-ACETYLATION REACTIONS OF THIOPHENES AND PYRROLES

Acetylation reactions were carried out under anhydrous conditions at all times. The apparatus was flame or oven dried before use and allowed to cool to room temperature under dry nitrogen. Reactions were performed under nitrogen and additions were made by injections *via* septa where appropriate. For reactions involving additions of tin (IV) chloride on a small scale (up to 50 mmol, *ca.* 5 ml), the use of an oven dried syringe which was purged with nitrogen three times before use was required. For large scale additions of tin (IV) chloride (175 mmol, *ca.* 20 ml) a double-ended needle technique was employed whereby the air sensitive Lewis acid was forced through to a sealed, dried measuring cylinder with a flow of nitrogen. Once the required volume of tin (IV) choride was collected in the measuring cylinder the position of the needles was changed to allow subsequent addition into the reaction flask.

2-Acetyl-3-methoxythiophene 259

To a stirred solution of 3-methoxythiophene (5.0 g, 44 mmol) and freshly distilled acetyl chloride (3.44 g, 3.12 ml, 44 mmol) in dry toluene (75 ml) was added, dropwise, a solution of tin (IV) chloride (11.4 g, 5.12 ml, 44 mmol) in dry toluene (15 ml). On addition the solution was observed to change colour from green to dark brown accompanied by the formation of a dark precipitate. After 1 h, the reaction mixture was acidified with dilute aqueous hydrochloric acid (10%, 15 ml) and the aqueous phase was extracted with ether (3 x 80 ml). The combined organic phase and ether extracts were washed with dilute aqueous sodium hydroxide solution (2M,

20 ml) and water (20 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give a black crystalline solid. Successive reccrystallisation from *n*-hexane afforded the *title compound* **259** as colourless needles (5.49 g, 80%), mp 68-70 °C (from *n*-hexane) (Found: C, 53.70; H, 5.10. $C_7H_8O_2S$ requires C, 53.85; H, 5.15%); δ_H 7.48 (1 H, d, ^3J 5.5), 6.84 (1 H, d, ^3J 5.5), 3.95 (3 H, s) and 2.49 (3 H, s); δ_C 190.61 (q), 160.40 (q), 132.48, 122.48 (q), 115.86, 58.58 and 29.05; *m/z* 156 (M^+, 64%), 142 (11), 141 (100), 126 (26), 45 (12), 43 (34) and 32 (34).

2-Acetyl-5-methoxythiophene 260

To a stirred solution of 2-methoxythiophene (25.0 g, 22.0 ml, 219 mmol) and freshly distilled acetyl chloride (17.2 g, 25.0 ml, 219 mmol) in dry toluene (750 ml) was added, dropwise, a solution of tin (IV) chloride (57.0 g, 25.0 ml, 219 mmol) in dry toluene (80 ml). On addition the solution was observed to develop a blood red colour. After 3 h, the reaction mixture was acidified with dilute aqueous hydrochloric acid solution (10%, 100 ml) and the aqueous phase was extracted with ether (3 x 400 ml). The combined organic phase and ether extracts were washed with dilute aqueous sodium hydroxide solution (2M, 50 ml) and water (50 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give a red oil. Gravity chromatography eluting with a 1:4 mixture of ethyl acetate and petroleum ether (bp 60-80°C) afforded the title compound **260** (10.21 g, 30%), bp 72-75°C (0.2 Torr) [lit.,[93] 60°C (0.001 Torr)]; mp 33-34°C (lit.,[93] 34-35°C) (from *n*-hexane); δ_H 7.30 (1 H, d, ^3J 4.3), 6.10 (1 H, d, ^3J 4.3), 3.80 (3 H, s) and 2.30 (3 H, s); δ_C 189.40 (q), 174.02 (q), 132.64, 130.29 (q), 105.40, 59.87 and 24.77; *m/z* 156 (M^+, 61%), 141(100), 98(20), 70(13), 69(10), 43(49) and 32(28).

b. ACETYLATION OF *N*-PHENYLPYRROLE

2-Acetyl-*N*-phenylpyrrole 261

The literature[83] method for the preparation of the title compound stated that the reaction proceeded with selective acetylation in the pyrrole 2-position. In contrast to that reported, however, both 2- and 3-acetylated *N*-phenylpyrroles were isolated after repeating the experimental procedure. Thus to a stirred solution of *N*-phenylpyrrole (49.76 g, 0.35 mol) in acetic anhydride (39.27 g, 36.6 ml, 0.385 mol) was added magnesium perchlorate (8.59 g, 0.038 mol) and the mixture was heated at 120°C for 30 min, then stirred at room temperature for a further 16 h. The mixture was added to water (500 ml) and neutralised with dilute aqueous sodium carbonate solution until carbon dioxide evolution ceased. The dark viscous product was extracted with ether (3 x 600 ml), dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give a red oil. Gravity chromatography eluting with a 1:20 mixture of ethyl acetate and petroleum ether (bp 60-80°C) afforded unreacted starting material, *N*-phenylpyrrole (4.90 g, 10%) mp 58-59°C (lit.,[83] mp 58-60°C), 2-acetyl-*N*-phenylpyrrole **261** (24.81 g, 39%), mp 55-57°C (lit.,[83] mp 57-58°C); bp 72-75°C (0.05 Torr) (lit.,[83] bp 147-150°C [12 Torr]); δ_H (360 MHz) 7.43-7.37 (3 H, m), 7.28-7.25 (2 H, m), 7.10 (1 H, dd, ^3J 4.0, ^4J 1.7), 6.95 (1 H, dd, ^3J 2.6, ^4J 1.7), 6.30 (1 H, dd, ^3J 4.0, 2.6) and 2.42 (3 H, s); δ_C 186.85 (q), 140.66 (q), 131.37 (q), 130.87, 128.35, 127.40, 125.86, 120.20, 108.95 and 26.98; *m/z* 185 (M^+, 67%), 171(13), 170(100), 115(28), 77(14), 63(13), 44(13) and 40(31); and 3-acetyl-*N*-phenylpyrrole **262** (21.27 g, 33%), bp 72-75°C (0.05 Torr); δ_H (360 MHz) 7.63 (1 H, dd, ^4J 2.2, 1.7), 7.46-7.28 (5 H, m), 7.00 (1 H, dd, ^3J 3.0, ^4J 2.2) and 6.74 (1 H, dd, ^3J 3.0, ^4J 1.7), δ_C 193.18 (q), 139.40 (q), 129.49, 127.36 (q), 126.74, 123.78, 120.93, 120.69, 110.39 and 26.89; *m/z* 185 (M^+, 88%), 171(26), 170(100), 115(35), 85(15), 77(38), 51(30), 43(12), 39(18) and 32(11).

c. ATTEMPTED SELECTIVE ACETYLATIONS OF *N*-PHENYLPYRROLE

The acetylation of *N*-phenylpyrrole was carried out as for the methoxythiophenes. Thus to a stirred solution of *N*-phenylpyrrole (0.24 g, 1.7 mmol) and freshly distilled acetyl chloride (0.13 g, 0.12 ml, 1.7 mmol) in dry toluene (6 ml) was added, dropwise, a solution of tin (IV) chloride (0.44 g, 0.2 ml, 1.7 mmol) in dry toluene (1 ml). After 1h, the reaction mixture was acidified with dilute aqueous hydrochloric acid solution (10%, 1 ml) and the aqueous phase was extracted with ether (3 x 20 ml). The organic phase and ether extracts were washed with dilute aqueous sodium hydroxide solution (2M, 5 ml) and water (5 ml), then dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give a mixture of starting material, 2- and 3-acetylated products in the ratio of 1.7 : 2 : 1 respectively.

This procedure was repeated at -40 °C using a $CaCl_2.6H_2O$ / ice bath and also at room temperature using acetic anhydride however both methods afforded a mixture of products as before.

Acetyl chloride (1.13 g, 14.3 mmol) and *N*-phenylpyrrole (0.41 g, 2.8 mmol) were dissolved in toluene (20 ml) and the mixture was heated under reflux for 264 h. The solvent was evaporated under reduced pressure to give a brown crystalline solid which, on purification by dry-flash chromatography eluting with a mixture of ethyl acetate and *n*-hexane, was found to comprise unreacted starting material (0.15 g, 37%), 2-acetyl-*N*-phenylpyrrole **261** (0.042 g, 8%) and 3-acetyl-*N*-phenylpyrrole **262** (0.05 g, 9%). Repeating the above procedure with acetyl bromide (1.76 g, 1.06 ml, 14.3 mmol) and heating under reflux for 100 h still gave a mixture of products.

2. ETHYL HETEROAROYLACETATE FORMATION (β-KETO ESTERS)

Sodium hydride (6.0 g of an 80% dispersion in mineral oil, 200 mmol) was washed twice with toluene to remove the oil, then suspended in diethyl carbonate (14.6 g, 15.0 ml, 123 mmol) and the stirred mixture was heated to 70°C. The appropriate acetyl derivative (40 mmol) dissolved in diethyl carbonate (9.75 g, 10.0 ml, 83 mmol) was added at such a rate as to maintain reflux. During the addition, the mixture solidified and was heated to 100°C for 1 h, then allowed to cool. Glacial acetic acid (8 ml) was added followed by ethyl acetate (300 ml) and water (100 ml). The mixture was shaken thoroughly then it was allowed to settle before the organic layer was separated off. The aqueous layer was extracted once more with ethyl acetate (100 ml) and the organic solutions were combined, dried ($MgSO_4$) and the solvents were removed under reduced pressure to afford the product.

The following β-ketoester derivatives were prepared in this way. The acetyl compound used is indicated in brackets in each case.

Ethyl 3-methoxythen-2-oylacetate 265 (2-acetyl-3-methoxythiophene **259**) (99%), bp 154-156°C (0.15 Torr) (Found M^+, 228.0455. $C_{10}H_{12}O_4S$ requires M^+, 228.0456); δ_H 7.53 (1 H, d, ^3J 5.5), 6.82 (1 H, d, ^3J 5.5), 4.15 (2 H, q, ^3J 7.1), 3.92 (3 H, s), 3.84 (2 H, s) and 1.21 (3 H, t, ^3J 7.1); δ_C 184.63 (q), 167.72 (q), 160.80 (q), 133.89, 121.43 (q), 115.68, 60.68, 58.59, 47.63 and 13.95; *m/z* 228 (M^+, 9%), 141(100), 126(18), 45(13), 43(30), 39(11) and 32(17).

Ethyl 5-methoxythen-2-oylacetate 266 (2-acetyl-5-methoxythiophene **260**) (91%) bp 141-144°C (0.3 Torr) (Found M^+, 228.0457. $C_{10}H_{12}O_4S$ requires M^+, 228.0456); δ_H 7.47 (1 H, d, ^3J 4.4), 6.25 (1 H, d, ^3J 4.4), 4.18 (2 H, q, ^3J 7.1), 3.95 (3 H, s), 3.79 (2 H, s) and 1.24 (3 H, t, ^3J 7.1); δ_C 183.68 (q), 175.42 (q), 167.13 (q), 133.94, 129.19 (q), 106.19, 61.21, 60.35, 44.94 and 13.89; *m/z* 228 (M^+, 42%), 182(8), 156(6), 141(100), 126(10), 98(20), 70(15), 43(10) and 29(23).

Ethyl 3-methylthen-2-oylacetate 269 (2-acetyl-3-methylthiophene **263**) (100%), bp 134-135°C (0.2 Torr) (Found M^+, 212.0510. $C_{10}H_{12}O_3S$ requires M^+, 212.0507); δ_H (400 MHz) 7.45 (1 H, d, ^3J 4.9), 6.95 (1 H, d, ^3J 4.9), 4.20 (2 H, q, ^3J 7.3), 3.86 (2 H, s), 2.55 (3 H, s) and 1.27 (3 H, t, ^3J 7.3); δ_C (100 MHz) 185.33 (q), 166.86 (q), 146.33 (q), 134.40 (q), 132.69, 130.49, 61.07, 47.99, 16.49 and 13.76; *m/z* 212 (M^+, 15%), 125(100), 97(23), 69(17), 53(19), 45(43), 31(56), 29(32) and 27(18).

Ethyl *N*-phenylpyrrol-2-oylacetate 267 (2-acetyl-*N*-phenylpyrrole **261**) (98%), bp 134-141°C (0.05 Torr) (Found M^+, 257.1033. $C_{15}H_{15}NO_3$ requires M^+, 257.1052); δ_H (80 MHz) 7.44-7.18 (5 H, m), 7.10 (1 H, dd, ^3J 4.1, ^4J 1.7), 6.98 (1 H, dd, ^3J 2.7, ^4J 1.7), 6.30 (1 H, dd, ^3J 4.1, 2.7), 4.16 (2 H, q, ^3J 7.1), 3.78 (2 H, s) and 1.24 (3 H, t, ^3J 7.1); δ_C (50 MHz) 180.83 (q), 167.56 (q), 140.12 (q), 131.84, 130.21 (q), 128.41, 127.51, 125.69, 120.98, 109.45, 61.00, 46.21 and 13.84; *m/z* 257 (M^+, 37%), 171(13), 170(100), 115(14), 43(21) and 32(15).

Ethyl *N*-phenylpyrrol-3-oylacetate 268 (3-acetyl-*N*-phenylpyrrole **262**) (96%), bp 119-123°C (0.04 Torr) (Found M^+, 257.1059. $C_{15}H_{15}NO_3$ requires M^+, 257.1052); δ_H 7.70 (1 H, t, ^4J 2.0), 7.49-7.25 (5 H, m), 7.02 (1 H, dd, ^3J 3.1, ^4J 2.2), 6.75 (1 H, dd, ^3J 3.1, ^4J 1.8), 4.18 (2 H, q, ^3J 7.1), 3.79 (2 H, s) and 1.24 (3 H, t, ^3J 7.1); δ_C 187.00 (q), 167.66 (q), 139.34 (q), 129.65, 127.09, 126.25 (q), 124.59, 121.43, 120.94, 110.72, 61.15, 46.87 and 13.93; *m/z* 257 (M^+, 25%), 171(14), 170(100), 115(13) and 37(10).

Ethyl *N*-methylpyrrol-2-oylacetate 270 (2-acetyl-*N*-methylpyrrole **264**) (99%), bp 123-125°C (0.05 Torr) (Found M^+, 195.0913. $C_{10}H_{13}NO_3$ requires M^+, 195.0895); δ_H (400 MHz) 6.95 (1 H, dd, ^3J 4.3, ^4J 1.8), 6.84 (1 H, dd, ^3J 2.4, ^4J 1.8), 6.14 (1 H, dd, ^3J 4.3, 2.4), 4.20 (2 H, q, ^3J 7.3), 3.94 (3 H, s), 3.79 (2 H, s) and 1.27 (3 H, t, ^3J 7.3); δ_C (100 MHz) 182.18 (q), 167.87 (q), 131.94 , 129.79 (q), 120.40, 108.37, 61.19, 46.29, 37.56 and 14.02; *m/z* 195 (M^+, 22%), 149(11), 108(100), 80(10), 53(14) and 39(12).

3. METHYL 4-CHLORO-3-[2-HETEROAROYLACETAMIDO] BENZOATE FORMATION (β-KETO AMIDES)

A stirred solution of the appropriate β-ketoester (2 mmol) and methyl 3-amino-4-chlorobenzoate **271** (0.37 g, 2 mmol) in *p*-xylene (8.0 ml) was heated under a Dean and Stark head for 5 h in an oil bath at 180°C. The solution was allowed to cool to room temperature, petroleum-ether (bp 60-80°C) (10 ml) was added and the mixture allowed to stir overnight during which time a precipitate formed. The mixture was filtered, washed with petroleum-ether (bp 60-80°C) and dried to afford the product. The following β-ketoamide derivatives were prepared in this way. The β-ketoester compound used is indicated in brackets in each case.

Methyl 4-chloro-3-[2-then-2-oylacetamido]benzoate 275 (ethyl then-2-oylacetate **253**) (17%) mp 138-140°C (from toluene), (Found: C, 53.7, H, 4.0; N, 4.4. $C_{15}H_{12}ClNO_4S$ requires C, 53.35; H, 3.55; N, 4.15%) (Found M^+, 338.9997. $C_{15}H_{12}{}^{37}ClNO_4S$ requires M^+, 339.0146; Found M^+, 337.0163. $C_{15}H_{12}{}^{35}ClNO_4S$ requires M^+, 337.0176); δ_H 9.98 (1 H, br s), 8.95 (1 H, d, ^4J 1.8), 7.85 (1 H, d, ^3J 3.6), 7.76 (1 H, d, ^3J 4.8), 7.70 (1 H, dd, ^3J 8.4, ^4J 1.8), 7.42 (1 H, d, ^3J 8.4), 7.17 (1 H, t, ^3J 4.3), 4.12 (2 H, s) and 3.87 (3 H, s); δ_C 188.24 (q), 165.96 (q), 163.55 (q), 142.74 (q), 136.19, 134.53 (q), 133.98, 129.42 (q), 129.11, 128.62, 128.19 (q), 125.84, 122.71, 52.22 and 45.55; *m/z* 337 (M^+, 9%), 302(25), 187(22), 185(69), 181(14), 169(13), 154(31), 152(12), 131(19), 126(47), 119(16), 111(100), 69(72), 43(15), 39(23) and 32(41).

Methyl 4-chloro-3-[2-(3-methoxythen-2-oyl)acetamido]benzoate 276 (ethyl 3-methoxythen-2-oylacetate **265**) (63%), mp 170-172°C (from toluene) (Found: C, 52.50, H, 3.80; N, 3.65. $C_{16}H_{14}ClNO_5S$ requires C, 52.25; H, 3.80; N, 3.80%); δ_H 10.33 (1 H, br s), 9.00 (1 H, d, ^4J 2.0), 7.71 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.66 (1 H, d, ^3J 5.5), 7.44 (1 H, d, ^3J 8.4), 6.88 (1 H, d, ^3J 5.5), 4.17 (2 H, s), 4.04 (3 H, s) and 3.87

(3 H, s); δ_C 187.97 (q), 166.11 (q), 164.93 (q), 161.82 (q), 135.24, 134.90 (q), 129.37 (q), 128.90, 128.16 (q), 125.39, 122.83, 121.27 (q), 115.82, 58.91, 52.02 and 46.24; *m/z* 369 (M^+, 2%), 367 (M^+, 5%), 338(12), 187(11), 185(32), 180(20), 156(23), 154(23), 141(100) and 126(15).

Methyl 4-chloro-3-[2-(5-methoxythen-2-oyl)acetamido]benzoate 277 (ethyl 5-methoxythen-2-oylacetate **266**) (62%); mp 172-174°C (from toluene), (Found: C, 52.4, H, 4.35; N, 3.55. $C_{16}H_{14}ClNO_5S$ requires C, 52.25; H, 3.8; N, 3.8%) (Found M^+, 369.0127. $C_{16}H_{14}{}^{37}ClNO_5S$ requires M^+, 369.0252; Found M^+, 367.0294. $C_{16}H_{14}{}^{35}ClNO_5S$ requires M^+, 367.0281); δ_H ([$^2H_6$]DMSO) 10.08 (1 H, br s), 8.47 (1 H, d, ^4J 1.9), 7.89 (1 H, d, ^3J 4.3), 7.73 (1 H, dd, ^3J 8.4, ^4J 1.9), 7.65 (1 H, d, ^3J 8.4), 6.53 (1 H, d, ^3J 4.3), 4.15 (2 H, s), 3.98 (3 H, s) and 3.86 (3 H, s); δ_C ([$^2H_6$]DMSO) 186.29 (q), 174.63 (q), 165.93 (q), 165.37 (q), 143.07 (q), 135.84, 135.15 (q), 130.15, 129.23 (q), 128.88 (q), 128.41, 125.33, 106.84, 60.90, 52.54 and 45.97; *m/z* 369 (M^+, 5%), 367 (M^+, 13%), 185(20), 182(12), 156(100), 154(14), 141(78), 98(10) and 32(34).

Methyl 4-chloro-3-[2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate 278 (ethyl *N*-phenylpyrrol-2-oylacetate **267**) (74%); mp 154-156°C (from toluene), (Found: C, 63.95, H, 4.55; N, 6.9. $C_{21}H_{17}ClN_2O_4$ requires C, 63.55; H, 4.3; N, 7.05%) (Found M^+, 398.0721. $C_{21}H_{17}{}^{37}ClN_2O_4$ requires M^+, 398.0847; Found M^+, 396.0865. $C_{21}H_{17}{}^{35}ClN_2O_4$ requires M^+, 396.0877); δ_H 9.59 (1 H, br s), 8.90 (1 H, d, ^4J 2.0), 7.69 (1 H, dd, ^3J 8.3, ^4J 2.0), 7.46-7.25 (7 H, m), 7.06 (1 H, dd, ^3J 2.6, ^4J 1.7), 6.36 (1 H, dd, ^3J 4.1, ^4J 2.6), 3.96 (2 H, s) and 3.88 (3 H, s); δ_C 183.60 (q), 165.97 (q), 164.35 (q), 140.20 (q), 134.56 (q), 133.30, 130.31 (q), 129.35 (q), 129.02, 128.63, 128.43 (q), 127.92, 125.86, 125.76, 123.02, 122.48, 110.10, 52.17 and 46.26; *m/z* 398 (M^+, 8%), 396 (M^+, 13%), 187(13), 185(87), 184(18), 183(10), 170(100), 154(26), 126(11), 115(28), 106(11), 94(17), 91(10) and 32(104).

Methyl 4-chloro-3-[2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate 279 (ethyl *N*-phenylpyrrol-3-oylacetate **268**) (48%); mp 167-169°C (from toluene), (Found: C, 63.95, H, 4.65; N, 6.85. $C_{21}H_{17}ClN_2O_4$ requires C, 63.55; H, 4.3; N, 7.05%) (Found M^+, 398.0722. $C_{21}H_{17}{}^{37}ClN_2O_4$ requires M^+, 398.0847; Found M^+, 396.0875. $C_{21}H_{17}{}^{35}ClN_2O_4$ requires M^+, 396.0877); δ_H 10.33 (1 H, br s), 9.00 (1 H, d, ^4J 2.0), 7.80 (1 H, t, ^4J 1.9), 7.70 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.50-7.30 (6 H, m), 7.07 (1 H, dd, ^3J 3.0, ^4J 2.2), 6.84 (1 H, dd, ^3J 3.0, ^4J 1.7), 3.99 (2 H, s) and 3.88 (3 H, s); δ_C 190.63 (q), 166.06 (q), 164.62 (q), 139.20 (q), 134.85 (q), 129.79, 129.39 (q), 129.09, 128.13 (q), 127.45, 126.20 (q), 125.59, 125.30, 122.63, 122.14, 121.07, 110.76, 52.19 and 46.64; *m/z* 396 (M^+, 5%), 211(24), 187(28), 185(89), 182(16), 180(48), 171(13), 170(100), 156(33), 154(89), 128(15), 127(11), 126(46), 124(14), 115(15), 99(12), 90(38), 77(15), 63(19), 51(14), 39(11) and 32(65).

Methyl 4-chloro-3-[2-(4-methoxybenzoyl)acetamido]benzoate 274 (ethyl 4-methoxybenzoylacetate) (79%), mp 174-175°C (from toluene) (Found: C, 59.85; H, 4.60; N, 3.85. $C_{18}H_{16}ClNO_5$ requires C, 59.75; H, 4.45; N, 3.85%); δ_H 10.14 (1 H, br s), 9.00 (1 H, d, ^4J 2.0), 8.02 (2 H, d, ^3J 8.9), 7.73 (1 H, d, ^3J 8.3, ^4J 2.0), 7.46 (1 H, d, ^3J 8.4), 6.97 (1 H, d, ^3J 8.9), 4.13 (2 H, s), 3.90 (3 H, s) and 3.89 (3 H, s); δ_C 194.27 (q), 166.03 (q), 164.55 (q), 164.30 (q), 134.76 (q), 130.99, 129.55 (q), 129.11, 128.84 (q), 128.18 (q), 125.76, 122.81, 114.10, 55.51, 52.19 and 44.77; *m/z* 361 (M^+, 6%), 187(15), 185(41),154(19), 150(31), 135(100), 126(11), 92(16), 90(11), 77(27), 64(12), 63(12) and 32(83).

Methyl 4-chloro-3-[2-(2,2-dimethylpropanoyl)acetamido]benzoate 273

The alternative solvent *n*-heptane was used in this case due to the heat sensitivity of the required β-ketoester. A stirred solution of the β-ketoester ethyl 2,2-dimethylpropanoylacetate (2.00 g, 12.7 mmol) and methyl 3-amino-4-chlorobenzoate **271** (2.35 g, 12.7 mmol) in *n*-heptane (25 ml) was heated under a Dean and Stark head for 16 h in an oil bath at 100°C. The solution was allowed to cool to room

temperature, petroleum-ether (bp 60-80°C) (10 ml) was added and the mixture allowed to stir overnight during which time a precipitate formed. The mixture was filtered, washed with petroleum-ether (bp 60-80°C) and dried to afford a white crystalline solid. Successive recrystallisation with *n*-hexane gave the *title compound* **273** (0.68 g, 17%), mp 128-130°C (from cyclohexane) (Found M^+, 313.0895. $C_{15}H_{18}{}^{37}ClNO_4$ requires M^+, 313.0895; Found M^+, 311.0937. $C_{15}H_{18}{}^{35}ClNO_4$ requires M^+, 311.0924); δ_H 9.88 (1 H, br s), 8.97 (1 H, d, ^4J 2.0), 7.73 (1 H, d, ^3J 8.5, ^4J 2.0), 7.45 (1 H, d, ^3J 8.5), 3.90 (3 H, s), 3.71 (2 H, s) and 1.22 (9 H, s); δ_C 212.39 (q), 165.99 (q), 164.09 (q), 134.59 (q), 129.43 (q), 129.08, 128.04 (q), 125.72, 122.61, 52.21, 45.18 (q), 43.59 and 25.68; *m/z* 313 (M^+, 8%), 311(M^+, 24), 276(45), 227(19), 222(12), 192(22), 187(34), 186(12), 185(95), 154(17), 58(14), 57(100), 41(29) and 32(17).

4. DODECYL 4-CHLORO-3-[2-HETEROAROYLACETAMIDO] BENZOATE FORMATION (β-KETO AMIDES)

A stirred solution of the appropriate β-ketoester (35 mmol) and dodecyl 3-amino-4-chlorobenzoate **272** (11.89 g, 35 mmol) in *p*-xylene (300 ml) was heated under a Dean-Stark head for 6 h in an oil bath at 185°C. The solution was allowed to cool to room temperature, petroleum-ether (bp 60-80°C) (200 ml) was added and the mixture was allowed to stir overnight. The solvents were removed under reduced pressure and the residue was trituratred with petroleum-ether (bp 60-80°C) to afford a solid. The solid was filtered, washed with petroleum-ether (bp 60-80°C) and dried to yield the product.

The following β-ketoamide derivatives were prepared in this way. The β-ketoester compound used is indicated in brackets in each case.

Dodecyl 4-chloro-3-[2-(3-methoxythen-2-oyl)acetamido]benzoate 281 (ethyl 3-methoxythen-2-oylacetate **265**) (65%), mp 108-110°C (from acetonitrile) (Found: C, 61.85; H, 7.0; N, 2.65. $C_{27}H_{36}ClNO_5S$ requires C, 62.1; H, 6.95; N, 2.7%); δ_H (400 MHz) 10.35 (1 H, br s), 9.03 (1 H, d, ^4J 1.8), 7.72 (1 H, dd, ^3J 8.5, ^4J 1.8), 7.66 (1 H, d, ^3J 5.5), 7.44 (1 H, d, ^3J 8.5), 6.89 (1 H, d, ^3J 5.5), 4.30 (2 H, t, ^3J 6.7), 4.18 (2 H, s), 4.04 (3 H, s), 1.75 (2 H, t, ^3J 7.3), 1.53-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.7); δ_C (100 MHz) 188.04, 165.73, 164.99, 161.87, 135.46, 134.96, 129.84, 129.06, 128.11, 125.59, 122.95, 121.33, 116.05, 65.38, 59.12, 46.43, 31.84, 29.56, 29.51, 29.43, 29.27, 29.19, 28.56, 25.86, 22.61 and 14.05 (1 peak missing, quaternaries not defined); *m/z* 522 (MH^+, 4%), 486 (5%), 341(11), 339(25), 199(10), 197(26), 173(14), 171(47), 156(49), 141(100), 126(23), 83(12), 70(16), 69(27), 57(19), 55(42), 45(12) and 43(48).

Dodecyl 4-chloro-3-[2-(5-methoxythen-2-oyl)acetamido]benzoate 282 (ethyl 5-methoxythen-2-oylacetate **266**) (52%), mp 113-114°C (from acetonitrile) (Found: C, 62.0; H, 7.2; N, 2.6. $C_{27}H_{36}ClNO_5S$ requires C, 62.15; H, 6.9; N, 2.7%); δ_H (400 MHz) 9.22 (1 H, br s), 8.97 (1 H, d, ^4J 1.8), 7.76 (1 H, dd, ^3J 8.5, ^4J 1.8), 7.73 (1 H, d, ^3J 5.6), 7.47 (1 H, d, ^3J 8.5), 6.91 (1 H, d, ^3J 5.6), 6.00 (1 H, s), 4.30 (2 H, t, ^3J 6.7), 4.06 (3 H, s), 1.75 (2 H, m), 1.31-1.25 (18 H, m) and 0.88 (3 H, t, ^3J 7.0); δ_C (100 MHz) 182.37, 165.48, 162.92, 162.12, 136.88, 134.03, 130.24, 129.14, 128.20, 126.34, 122.42, 119.72, 116.15, 65.52, 59.44, 57.48, 31.87, 29.59, 29.58, 29.53, 29.45, 29.29, 29.21, 28.61, 25.87, 22.64 and 14.06 (quaternaries not defined); *m/z* 521 (M^+, 3%), 486(3), 341(8), 339(18), 199(9), 197(21), 173(17), 171(52), 156(100), 141(100), 126(23), 98(19), 83(12), 70(20), 69(31), 57(17), 55(37), 43(58), 41(37) and 29(22).

Dodecyl 4-chloro-3-[2-(3-methylthen-2-oyl)acetamido]benzoate 280 (ethyl 3-methylthen-2-oylacetate **269**) (99%), mp 95.5-96.5°C (from petroleum-ether bp 60-80°C) (Found: C, 64.3; H, 7.25; N, 2.75. $C_{27}H_{36}ClNO_4S$ requires C, 64.05; H, 7.15;

N, 2.75%); δ_H (400 MHz) 10.37 (1 H, br s), 9.00 (1 H, d, ^4J 1.8), 7.73 (1 H, dd, ^3J 8.5, ^4J 1.8), 7.54 (1 H, d, ^3J 4.9), 7.45 (1 H, d, ^3J 8.5), 7.00 (1 H, d, ^3J 4.9), 4.30 (2 H, t, ^3J 7.0), 4.06 (2 H, s), 2.63 (3 H, s), 1.76 (2 H, m), 1.42-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.7); δ_C (100 MHz) 188.72, 165.63, 163.87, 147.84, 134.69, 134.48, 133.28, 131.90, 129.89, 129.08, 128.13, 125.76, 122.88, 65.39, 47.70, 31.84, 29.56, 29.51, 29.43, 29.28, 29.19, 28.55, 25.85, 22.61, 17.27 and 14.06 (1 peak missing, quaternaries not defined); *m/z* 505 (M^+, 8%), 341(10), 339(30), 173(15), 171(50), 154(20), 140(27), 125(100), 97(13), 90(7), 69(19), 55(22), 43(26), 41(22) and 28(51).

Dodecyl 4-chloro-3-[2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate 283 (ethyl *N*-phenylpyrrol-2-oylacetate **267**) (61%), mp 76-77°C (from methanol) (Found: C, 69.5; H, 7.3; N, 4.9. $C_{32}H_{39}ClN_2O_4$ requires C, 69.75; H, 7.15; N, 5.1%); δ_H (400 MHz) 9.57 (1 H, br s), 8.89 (1 H, d, ^4J 2.0), 7.70 (1 H, dd, ^3J 8.3, ^4J 2.0), 7.45-7.25 (7 H, m), 7.06 (1 H, dd, ^3J 2.6, ^4J 1.7), 6.37 (1 H, dd, ^3J 4.2, ^4J 2.6), 4.28 (2 H, t, ^3J 6.7), 3.96 (2 H, s), 1.74 (2 H, m), 1.33-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.5); δ_C (100 MHz) 183.78 (q), 165.68 (q), 164.45 (q), 140.32 (q), 134.64 (q), 133.44, 130.44, 129.88, 129.09, 128.77, 128.53, 128.05, 125.99, 125.88, 123.26, 122.60, 110.23, 65.45, 46.33, 31.88, 29.62, 29.55, 29.47, 29.32, 29.23, 28.60, 25.87, 22.66 and 14.10 (1 peak missing, some quaternaries not defined); *m/z* 552 (M^+, 5%), 550 (M^+, 10%), 515(11), 341(10), 339(23), 185(55), 171(100), 170(97), 154(38), 143(21), 115(38), 90(22), 77(20), 69(15), 55(23), 44(27), 43(56), 42(52), 39(28) and 28(62).

Dodecyl 4-chloro-3-[2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate 284 (ethyl *N*-phenylpyrrol-3-oylacetate **268**) (73%), mp 82-83°C (from methanol) (Found: C, 69.7; H, 7.1; N, 4.9. $C_{32}H_{39}ClN_2O_4$ requires C, 69.75; H, 7.15; N, 5.1%); δ_H (400 MHz) 10.35 (1 H, br s), 9.02 (1 H, d, ^4J 2.0), 7.79 (1 H, d, ^4J 1.9), 7.70 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.48-7.25 (6 H, m), 7.06 (1 H, dd, ^3J 3.1, ^4J 2.1), 6.83 (1 H, dd, ^3J 3.1, ^4J 1.7), 4.27 (2 H, t, ^3J 6.8), 3.99 (2 H, s), 1.73 (2 H, m), 1.38-1.23 (18 H, m) and 0.85 (3 H,

t, ^3J 6.5); δ_C (100 MHz) 190.78 (q), 165.77 (q), 164.68 (q), 139.33 (q), 134.95 (q), 129.92, 129.16, 129.08 (q), 128.18 (q), 127.58, 126.35 (q), 125.68, 125.41, 122.83, 122.28, 121.23, 110.89, 65.45, 45.79, 31.89, 29.62, 29.56, 29.48, 29.32, 29.24, 28.61, 25.91, 22.66 and 14.10 (1 peak missing); *m/z* 552 (M^+, 20%), 550 (M^+, 12%), 517(2), 515(13), 341(10), 339(30), 185(53), 171(100), 170(80), 154(30), 121(14), 115(15), 90(19), 77(12), 69(13), 55(19), 44(18), 43(49), 41(53), 39(28) and 28(25).

Dodecyl 4-chloro-3-[2-(*N*-methylpyrrol-2-oyl)acetamido]benzoate 285 (ethyl *N*-methylpyrrol-2-oylacetate **270**) (99%), mp 92-93°C (from methanol) (Found: C, 66.3; H, 7.6; N, 5.7. $C_{27}H_{37}ClN_2O_4$ requires C, 66.3; H, 7.65; N, 5.75%); δ_H (400 MHz) 9.97 (1 H, br s), 9.01 (1 H, d, ^4J 2.0), 7.71 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.43 (1 H, d, ^3J 8.4), 7.11 (1 H, dd, ^3J 4.4, ^4J 1.6), 6.91 (1 H, t, ^3J 2.0, ^4J 1.6), 6.18 (1 H, dd, ^3J 4.0, ^4J 2.4), 4.27 (2 H, t, ^3J 6.8), 3.98 (3 H, s), 3.96 (2 H, s), 1.73 (2 H, m), 1.43-1.23 (18 H, m) and 0.89 (3 H, m); δ_C (100 MHz) 184.81 (q), 165.64 (q), 164.68 (q), 134.83, 133.21, 129.88, 129.75, 129.01, 127.97, 125.57, 122.75, 121.60, 108.96, 65.37, 45.69, 37.90, 31.81, 29.54, 29.48, 29.42, 29.26, 29.16, 28.53, 25.91, 25.83, 22.60 and 14.04 (quaternaries not defined); *m/z* 490 (M^+, 20%), 488 (M^+, 47%), 453(44), 339(10), 171(15), 123(92) and 108(100).

5. DODECYL 4-CHLORO-3-[2-CHLOROHETEROAROYL ACETAMIDO]BENZOATE FORMATION (CHLORO-β-KETO AMIDES)

A solution of sulfuryl chloride (4.2 g, 31 mmol) in dichloromethane (20.0 ml) was added over 20 minutes to a stirred solution of the appropriate β-ketoamide (31 mmol) in dichloromethane (75.0 ml) at room temperature. The mixture was stirred for a further 2 h then the volatiles were removed under reduced pressure. Trituration with

acetonitrile gave a solid which was filtered off, washed with acetonitrile and dried to yield the product.

The following chloro-β-ketoamide derivatives were prepared in this way. The starting β-ketoamide used is indicated in brackets in each case.

Dodecyl 4-chloro-3-[2-chloro-2-(3-methoxythen-2-oyl)acetamido]benzoate 287 (dodecyl 4-chloro-3-[2-(3-methoxythen-2-oyl)acetamido]benzoate **281**) (87%), mp 100-102°C (from acetonitrile) (Found: C, 58.2; H, 6.5; N, 2.4. $C_{27}H_{35}Cl_2NO_5S$ requires C, 58.3; H, 6.3; N, 2.5%); δ_H (400 MHz) 9.22 (1 H, br s), 8.95 (1 H, d, ^4J 2.0), 7.74 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.70 (1 H, d, ^3J 5.5), 7.44 (1 H, d, ^3J 8.4), 6.88 (1 H, d, ^3J 5.5), 5.99 (1 H, s), 4.27 (2 H, t, ^3J 6.8), 4.03 (3 H, s), 1.72 (2 H, t, ^3J 7.3), 1.36-1.22 (18 H, m) and 0.85 (3 H, t, ^3J 6.7); δ_C (100 MHz) 165.32 (q), 162.80 (q), 161.99 (q), 136.88, 133.81 (q), 129.98 (q), 129.00, 128.00 (q), 126.18, 122.19, 119.39 (q), 116.03, 65.37, 59.31, 57.30, 31.71, 29.44, 29.38, 29.30, 29.16, 29.06, 28.42, 25.70, 22.50 and 13.95 (2 peaks missing); *m/z* NH_3DCI 575 (MNH_4^+, 11%), 573 (MNH_4^+, 14%), 556 (MH^+, 11), 524(15), 522(31), 340(11), 210(10), 208(28), 193(33), 191(100), 157(24) and 141(26).

Dodecyl 4-chloro-3-[2-chloro-2-(5-methoxythen-2-oyl)acetamido]benzoate 288 (dodecyl 4-chloro-3-[2-(5-methoxythen-2-oyl)acetamido]benzoate **282**) (100%), mp 93-95°C (from methanol) (Found: C, 58.15; H, 6.25; N, 2.5. $C_{27}H_{35}Cl_2NO_5S$ requires C, 58.3; H, 6.3; N, 2.5%); δ_H 9.16 (1 H, br s), 8.89 (1 H, d, ^4J 2.0), 7.77-7.72 (2 H, m), 7.44 (1 H, d, ^3J 8.3), 6.34 (1 H, d, ^3J 4.6), 5.58 (1 H, s), 4.27 (1 H, t, ^3J 6.8), 3.99 (3 H, s), 1.76-1.69 (2 H, m), 1.40-1.23 (18 H, m) and 0.85 (3 H, t, ^3J 6.6); δ_C 181.05 (q), 177.80 (q), 165.29 (q), 162.29 (q), 136.47, 133.64 (q), 130.04 (q), 129.07, 128.27 (q), 126.39, 122.25, 107.42, 65.42, 60.73, 56.87, 31.75, 29.47, 29.41, 29.34, 29.18, 29.09, 28.47, 25.74, 22.53 and 13.96 (2 peaks missing); *m/z* NH_3DCI 575 (MNH_4^+, 14%), 573 (MNH_4^+, 12%), 556 (MH^+, 14), 524(19), 522(44), 340(23), 208(28), 193(45), 191(100), 157(23) and 141(41).

Dodecyl 4-chloro-3-[2-chloro-2-(3-methylthen-2-oyl)acetamido]benzoate 286

(dodecyl 4-chloro-3-[2-(3-methylthen-2-oyl)acetamido]benzoate **280**) (99%)

mp 55-57°C (from *n*-hexane) (Found M^+, 539.1684. $C_{27}H_{35}{}^{35}Cl_2NO_4S$ requires 539.1664); δ_H 9.15 (1 H, br s), 8.94 (1 H, d, ^4J 2.0), 7.75 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.60 (1 H, d, ^3J 5.0), 7.45 (1 H, d, ^3J 8.4), 7.01 (1 H, d, ^3J 5.0), 5.51 (1 H, s), 4.27 (2 H, t, ^3J 6.8), 2.60 (3 H, s), 1.72 (2 H, t, ^3J 7.3), 1.39-1.23 (18 H, m) and 0.85 (3 H, t, ^3J 6.7); δ_C 165.25 (q), 162.01 (q), 150.00 (q), 133.55 (q), 133.21, 132.96, 132.79 (q), 131.79 (q), 130.08 (q), 129.04, 128.13 (q), 126.43, 122.14, 65.41, 59.32, 31.73, 31.41, 29.46, 29.40, 29.32, 29.18, 29.08, 28.45, 25.73, 22.51, 17.14 and 13.95; *m/z* NH_3DCI 575 (MNH_4^+, 11%), 573 (MNH_4^+, 14%), 556 (MH^+, 11), 524(15), 522(31), 340(11), 210(10), 208(28), 193(33), 191(100), 157(24) and 141(26).

Dodecyl 4-chloro-3-[2-chloro-2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate 289

(dodecyl 4-chloro-3-[2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate **283**) (100%); mp 67-69°C (from acetonitrile) (Found: C, 65.75; H, 6.45; N, 4.9. $C_{32}H_{38}Cl_2N_2O_4$ requires C, 65.65; H, 6.55; N, 4.8%); δ_H (400 MHz) 9.00 (1 H, br s), 8.92 (1 H, d, ^4J 1.8), 7.74 (1 H, dd, ^3J 8.6, ^4J 1.8), 7.50-7.38 (5 H, m), 7.32-7.25 (2 H, m), 7.13 (1 H, s), 6.43 (1 H, dd, ^3J 4.2, ^4J 2.6), 5.62 (1 H, s), 4.29 (2 H, t, ^3J 6.7), 1.74 (2 H, m), 1.39-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.7); δ_C (100 MHz) 178.13, 165.43, 162.70, 139.87, 134.35, 133.73, 130.12, 129.12, 128.93, 128.82, 128.36, 128.32, 128.21, 126.44, 125.93, 125.89, 123.47, 122.35, 110.70, 65.53, 58.44, 31.86, 29.59, 29.52, 29.46, 29.30, 29.20, 28.59, 25.86, 22.64 and 14.08 (1 extra peak, quaternaries not defined); *m/z* NH_3DCI 604 (MNH_4^+, 32%), 602 (MNH_4^+, 45%), 585 (MH^+, 49), 553(22), 551(64), 359(8), 357(19), 340(32), 254(22), 222(37), 220(100), 186(40), 184(88), 170(71) and 144(42).

Dodecyl 4-chloro-3-[2-chloro-2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate 290

(dodecyl 4-chloro-3-[2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate **284**) (78%), mp 63.5-65.5°C (from acetonitrile) (Found: C, 65.7; H, 6.35; N, 4.85. $C_{32}H_{38}Cl_2N_2O_4$

requires C, 65.65; H, 6.55; N, 4.8%); δ_H (400 MHz) 9.17 (1 H, br s), 8.93 (1 H, d, ^4J 1.8), 7.91 (1 H, s), 7.75 (1 H, dd, ^3J 8.6, ^4J 1.8), 7.48-7.34 (6 H, m), 7.08 (1 H, t, ^4J 2.4), 6.90 (1 H, dd, ^3J 3.0, ^4J 1.8), 5.54 (1 H, s), 4.28 (2 H, t, ^3J 6.7), 1.72 (2 H, m), 1.40-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.7); δ_C (100 MHz) 184.36, 165.35, 162.83, 139.09, 133.81, 130.07, 129.79, 129.10, 128.33, 127.57, 126.46, 126.35, 123.70, 122.35, 121.17, 111.49, 65.35, 58.93, 31.80, 29.52, 29.46, 29.39, 29.24, 29.14, 28.51, 25.79, 22.58 and 14.02 (2 peaks missing, quaternaries not defined); *m/z* 584 (M^+, trace), 550(trace), 515(trace), 339(15), 341(8), 221(11), 219(29), 171(40), 170(100), 197(31), 154(14), 115(13), 55(25), 29(27) and 28(52); *m/z* NH_3DCI 604 (MNH_4^+, 14%), 602 (MNH_4^+, 20%), 587 (MH^+, 51), 585 (MH^+, 72), 553(18), 551(42), 341(12), 340(22), 222(12), 221(21), 220(40), 219(52), 187(6), 186(25) and 170(100).

Dodecyl 4-chloro-3-[2-chloro-2-(*N*-methylpyrrol-2-oyl)acetamido]benzoate 291 (dodecyl 4-chloro-3-[2-(*N*-methylpyrrol-2-oyl)acetamido]benzoate **285**) (65%), mp 79-82°C (from acetonitrile) (Found: C, 61.8; H, 7.15; N, 5.3. $C_{27}H_{36}Cl_2N_2O_4$ requires C, 61.95; H, 6.95; N, 5.35%); δ_H (400 MHz) 9.15 (1 H, br s), 8.95 (1 H, d, ^4J 1.8), 7.76 (1 H, dd, ^3J 8.5, ^4J 1.8), 7.45 (1 H, d, ^3J 8.5), 7.21 (1 H, dd, ^3J 4.3, ^4J 1.2), 6.98 (1 H, s), 6.24 (1 H, dd, ^3J 4.3, 2.4), 5.56 (1 H, s), 4.29 (2 H, t, ^3J 7.0), 3.97 (3 H, s), 1.75 (2 H, m), 1.42-1.25 (18 H, m) and 0.87 (3 H, t, ^3J 6.7); δ_C (100 MHz) 179.30, 165.45, 162.94, 134.41, 134.04, 130.35, 129.17, 128.27, 128.14, 126.41, 122.72, 122.40, 109.69, 65.55, 58.21, 37.83, 31.89, 29.60, 29.54, 29.47, 29.31, 29.23, 28.67, 25.91, 22.65 and 14.04 (1 peak missing, quaternaries not defined); *m/z* 522 (M^+, trace), 488(trace), 453(trace), 390(trace), 373(trace), 339(trace), 301(trace), 273(trace), 238(trace), 191(trace), 171(6%), 159(28), 157(84), 123(12), 108(100), 80(7), 81(6), 43(17), 32(18) and 28(74); *m/z* NH_3DCI 542(MNH_4^+, 27%), 540(MNH_4^+, 32%), 525(MH^+, 24), 491(32), 489(100), 453(10), 357(10), 340(12), 157(19), 124(20), 116(21), 108(34) and 82(13).

6. DODECYL 4-CHLORO-3-[2-(1-BENZYL-5-ETHOXY-2,4-DIOXOIMIDAZOLIDIN-3-YL)-2-AROYLACETAMIDO] BENZOATE FORMATION (HYDANTOINYL-β-KETO AMIDES)

1,1,3,3-Tetramethylguanidine (39 mmol) was added over 5 minutes to a stirred suspension of the appropriate chloro-β-ketoamide (19 mmol) and the hydantoin **292** (4.7 g, 20 mmol) in acetonitrile (90.0 ml). The mixture was stirred at room temperature for 20 h then it was added to water (500 ml) containing concentrated hydrochloric acid (30 ml). The mixture was extracted with ethyl acetate (250 ml), then the extract was back-washed with saturated brine (100 ml) before it was dried ($MgSO_4$). The solvents were removed under reduced pressure to leave a viscous liquid. Purification by column chromatography on 63-200 mesh silica gel eluting with a mixture of ethyl acetate and petroleum-ether (bp 60-80°C) gave the product as a glass. The products contain two chiral centres and, as such, exist as an inseparable mixture of two pairs of enantiomers, (R,R and S,S) and (R,S and S,R) in approximately equal proportions. ^{1}H and ^{13}C nmr data in the following section is presented as the 50/50 mixture of diasteriomers. As the products were glasses there were problems in obtaining correct microanalyses - in these cases accurate mass was required, however several of the compounds did not exhibit a molecular ion peak. In one instance, an accurate mass measurement of a characteristic breakdown peak is presented.

The following hydantoinyl-β-ketoamide derivatives were prepared in this way. The starting chloro-β-ketoamide used is indicated in brackets in each case.

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(3-methoxythen-2-oyl)acetamido]benzoate 294 (dodecyl 4-chloro-3-[2-chloro-2-(3-methoxythen-2-oyl)acetamido]benzoate **287**) (46%); (Found: C, 61.6; H, 6.05; N,

6.25. $C_{39}H_{48}ClN_3O_8S$ requires C, 62.1; H, 6.4; N, 5.6%); δ_H (400 MHz) 8.90 (2 H, 2 x s), 8.74 (1 H, br s), 8.69 (1 H, br s), 7.74-7.68 (4 H, m), 7.41-7.27 (12 H, m), 6.82 (2 H, 2 x d, ^3J 5.5), 6.08 (2 H, 2 x s), 4.89-4.83 (4 H, m), 4.28 (4 H, 2 x t, ^3J 6.7), 4.23-4.15 (2 H, 2 x s), 3.89 (6 H, 2 x s), 3.67-3.43 (4 H, m), 1.74 (4 H, 2 x t, ^3J 7.0), 1.38-1.13 (42 H, m) and 0.87 (6 H, 2 x t, ^3J 6.7); δ_C (100 MHz) 181.92, 181.70, 169.65, 168.81, 168.60, 165.51, 162.30, 162.20, 161.78, 161.56, 154.77, 154.38, 136.34, 136.29, 135.24, 135.18, 135.15, 134.25, 134.19, 130.11, 129.02, 128.82, 128.46, 128.42, 128.17, 128.11, 128.07, 128.03, 126.24, 126.18, 123.30, 119.92, 119.89, 115.76, 115.66, 83.57, 82.86, 82.76, 65.47, 62.32, 62.13, 61.61, 61.55, 61.27, 60.34, 59.16, 59.09, 44.18, 43.62, 31.82, 29.55, 29.50, 29.42, 29.26, 29.18, 28.56, 25.79, 22.60, 14.83, 14.10 and 14.05; (quaternaries not defined); *m/z* NH_3DCI 773 (MNH_4^+, 5%), 771 (MNH_4^+, 11%), 756 (MH^+, 20), 754 (MH^+, 32), 524(4), 522(8), 390(12), 389(51), 388(79), 360(35), 340(52), 339(37), 253(14), 252(100), 235(26), 197(17), 141(80), 115(48) and 91(22).

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(5-methoxythen-2-oyl)acetamido]benzoate 295 (dodecyl 4-chloro-3-[2-chloro-2-(5-methoxythen-2-oyl)acetamido]benzoate **288**) (55%); (Found: C, 59.5; H, 6.15; N, 5.3. $C_{39}H_{48}ClN_3O_8S.1.7H_2O$ requires C, 59.7; H, 6.55; N, 5.35%); δ_H (400 MHz) 10.36 (1 H, br s), 10.32 (1 H, br s), 8.90 (2 H, 2 x d, ^4J 1.8), 7.76-7.73 (2 H, m), 7.69 (2 H, 2 x d, ^3J 4.3), 7.44 (2 H, 2 x d, ^3J 8.6), 7.37-7.27 (10 H, m), 6.26 (2 H, 2 x d, ^3J 4.3), 5.93 (2 H, 2 x s), 5.06-4.87 (4 H, m), 4.30 (4 H, 2 x t, ^3J 7.0), 4.26-4.14 (2 H, 2 x s), 3.97 (6 H, 2 x s), 3.69-3.48 (4 H, m), 1.75 (4 H, 2 x t, ^3J 7.0), 1.41-1.16 (42 H, m) and 0.88 (6 H, 2 x t, ^3J 6.7); δ_C (100 MHz) 182.97, 182.87, 177.41, 177.32, 171.72, 169.69, 166.18, 162.97, 162.83, 155.13, 154.89, 136.16, 136.11, 135.54, 135.20, 135.16, 130.55, 129.87, 129.56, 129.52, 129.47, 129.44, 129.09, 128.84, 128.80, 128.72, 126.92, 126.59, 124.04, 123.92, 107.83, 83.37, 77.86, 66.07, 62.97,

62.64, 61.39, 60.97, 59.21, 44.89, 44.82, 44.28, 32.48, 30.21, 30.17, 30.09, 30.00, 29.93, 29.85, 29.23, 26.49, 23.27, 21.61, 15.52, 15.50, 14.77 and 14.69 (quaternaries not defined); *m/z* 755 (M^+, 13%), 753 (M^+, 21), 710(14), 708(32), 618(10), 616(21), 521(13), 338(40), 197(29), 171(21), 141(100), 91(61), 69(17), 55(24) and 43(28); *m/z* NH_3DCI 771 (MNH_4^+, 3%), 756 (MH^+, 6), 754 (MH^+, 11), 522(4), 389(22), 340(32), 252(100), 235(25), 206(13), 189(10), 141(28), 115(16) and 91(13).

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(3-methylthen-2-oyl)acetamido]benzoate 293 (dodecyl 4-chloro-3-[2-chloro-2-(3-methylthen-2-oyl)acetamido]benzoate **286**) (35%); (Found: C, 62.4; H, 6.5; N, 5.3. $C_{39}H_{48}ClN_3O_7S.0.7H_2O$ requires C, 62.4; H, 6.6; N, 5.6%) (Found: [M-$C_{20}H_{28}ClNO_3$]$^+$, 372.1149. [$C_{19}H_{20}N_2O_4S$]$^+$ requires 372.1144); δ_H (400 MHz) 9.97 (1 H, br s), 9.86 (1 H, br s), 8.95 (1 H, d, ^4J 2.0), 8.94 (1 H, d, ^4J 2.0), 7.73 (2 H, dd, ^3J 8.3, ^4J 2.0), 7.45-7.42 (4 H, m), 7.33-7.27 (8 H, m), 7.19-7.17 (2 H, m), 6.95 (2 H, 2 x d, ^3J 4.9), 5.83 (2 H, 2 x s), 5.07-4.89 (4 H, m), 4.29 (4 H, 2 x t, ^3J 7.0), 4.25-4.17 (2 H, m), 3.66-3.39 (4 H, m), 2.59 (6 H, 2 x s), 1.75 (4 H, 2 x t, ^3J 7.0), 1.40-1.12 (42 H, m) and 0.87 (6 H, 2 x t, ^3J 6.7); δ_C (100 MHz) 185.39, 184.90, 168.77, 168.64, 165.44, 161.70, 161.59, 154.10, 153.97, 149.99, 149.85, 134.87, 134.83, 134.43, 132.41, 132.26, 131.38, 131.14, 130.43, 130.39, 129.88, 129.04, 128.84, 128.74, 128.69, 128.62, 128.55, 128.38, 128.33, 128.30, 128.18, 128.11, 128.03, 127.94, 126.05, 123.06, 123.03, 82.76, 82.60, 65.34, 62.33, 61.58, 60.22, 60.19, 59.80, 44.10, 43.91, 31.74, 29.47, 29.43, 29.39, 29.35, 29.19, 29.10, 28.49, 25.82, 25.74, 22.52, 20.84, 17.17, 17.07, 14.85, 14.81, 14.74, 14.02 and 13.97 (quaternaries not defined); *m/z* 737 (M^+, 5%), 692(24), 372(11), 326(9), 197(31), 180(14), 125(100), 97(12), 91(41), 69(12), 55(15), 43(18) and 28(32); *m/z* NH_3DCI 757 (MNH_4^+, 27%), 755 (MNH_4^+, 49%), 740 (MH^+, 23), 738(50), 390(23), 372(62), 344(36), 340(50), 339(31), 253(14), 252(100), 235(21), 197(13), 171(15), 164(11), 125(60) and 91(16).

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate 296 (dodecyl 4-chloro-3-[2-chloro-2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate **289**) (46%); (Found: C, 66.85; H, 6.35; N, 6.95. $C_{44}H_{51}ClN_4O_7.0.5H_2O$ requires C, 66.7; H, 6.55; N, 7.05%); δ_H (400 MHz) 9.90 (1 H, br s), 9.85 (1 H, br s), 8.89 (2 H, 2 x d, ^4J 1.8), 7.72 (2 H, 2 x dd, ^3J 8.6, ^4J 1.8), 7.45-7.20 (24 H, m), 7.12-7.02 (2 H, m), 6.31-6.28 (2 H, m), 5.90 (2 H, 2 x s), 5.08-4.92 (4 H, m), 4.29 (4 H, 2 x t, ^3J 6.7), 4.23 (2 H, 2 x s), 3.66-3.32 (4 H, m), 1.75 (4 H, 2 x t, ^3J 7.3), 1.40-1.09 (42 H, m) and 0.88 (6 H, 2 x t, ^3J 7.0); δ_C (100 MHz) 181.66, 181.07, 169.33, 169.09, 165.88, 162.48, 162.35, 154.78, 140.04, 135.25. 134.83, 132.94, 132.69, 130.20, 129.41, 129.38, 129.33, 129.22, 129.20, 128.97, 128.65, 128.46, 128.44, 128.36, 128.09, 128.02, 126.48, 125.45, 125.40, 123.67, 123.62, 121.24, 120.85, 110.49, 83.19, 83.03, 65.73, 62.48, 61.74, 60.64, 58.97, 58.57, 44.52, 44.44, 32.16, 29.90, 29.85, 29.76, 29.60, 29.52, 28.89, 26.20, 26.15, 22.94, 15.20, 15.11, 14.45 and 14.39 (quaternaries not defined); *m/z* 783 (MH^+, self protonation, 4%), 737(5), 615(11), 613(28), 569(10), 567(18), 341(3), 339(6), 171(19), 170(32), 144(17), 143(100), 116(22), 115(52), 91(31), 77(19), 51(26) and 28(52); *m/z* NH_3DCI 802 (MNH_4^+, 4%), 800 (MNH_4^+, 6%), 783 (MH^+, 14), 737(3), 340(10), 252(21), 145(12) and 144(100).

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate 297 (dodecyl 4-chloro-3-[2-chloro-2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate **290**) (75%); (Found: C, 67.8; H, 6.5; N, 6.25. $C_{44}H_{51}ClN_4O_7$ requires C, 67.45; H, 6.55; N, 7.15%); δ_H (400 MHz) 10.56 (1 H, br s), 10.46 (1 H, br s), 8.94 (2 H, s), 7.85 (2 H, 2 x t, ^4J 1.8), 7.73 (2 H, 2 x dd, ^3J 8.6, ^4J 1.8), 7.48-7.28 (22 H, m), 7.03 (2 H, m), 6.83 (2 H, 2 x dd, ^3J 3.0, ^4J 1.8), 5.88 (2 H, 2 x s), 5.07-4.89 (4 H, m), 4.29 (4 H, 2 x t, ^3J 6.7), 4.26-4.17 (2 H, m), 3.71-3.49 (4 H, m), 1.75 (4 H, 2 x t, ^3J 7.0), 1.41-1.11 (42 H, m) and 0.87 (6 H, 2 x t, ^3J 6.7); δ_C (100 MHz) 186.45, 186.40, 169.29, 169.22, 165.76, 162.90, 162.78,

154.79, 154.66, 139.29, 139.25, 135.15, 135.08, 134.88, 134.81, 130.11, 130.03, 130.00, 129.93, 129.37, 129.12, 129.04, 128.98, 128.92, 128.89, 128.52, 128.29, 128.23, 127.66, 127.63, 126.31, 125.60, 125.33, 123.62, 123.57, 123.49, 123.39, 121.91, 121.85, 121.28, 121.19, 121.16, 111.44, 111.30, 83.02, 82.98, 65.58, 62.74, 61.98, 59.56, 59.21, 44.45, 44.34, 32.01, 29.74, 29.70, 29.62, 29.46, 29.38, 29.34, 28.76, 28.68, 26.06, 25.93, 22.80, 15.05, 14.97 and 14.24 (quaternaries not defined); *m/z* 785 (MH^+, self protonation, 4%), 783 (MH^+, 9), 737(21), 645(8), 616(10), 417(14), 339(12), 173(13), 171(50), 154(14), 143(19), 115(13), 91(26), 55(16), 43(18) and 28(37); *m/z* NH_3DCI 801 (MNH_4^+, 5%), 783 (MH^+, 22), 418(32), 357(42), 341(43), 340(100), 340(100), 339(62), 252(52), 171(32), 170(60), 144(57), 143(18) and 108(11).

Dodecyl 4-chloro-3-[2-(1-benzyl-5-ethoxy-2,4-dioxoimidazolidin-3-yl)-2-(*N*-methylpyrrol-2-oyl)acetamido]benzoate 298 (dodecyl 4-chloro-3-[2-chloro-2-(*N*-methylpyrrol-2-oyl)acetamido]benzoate **291**) (67%); (Found: C, 64.3; H, 6.75; N, 7.65. $C_{39}H_{49}ClN_4O_7.0.3H_2O$ requires C, 64.45; H, 6.85; N, 7.7%) (Found: M^+ 720.3294. $C_{39}H_{49}ClN_4O_7$ requires 720.3290); δ_H (400 MHz) 9.96 (1 H, br s), 9.95 (1 H, br s), 8.94 (2 H, 2 x d, ^4J 1.8), 7.74 (2 H, 2 x d, ^3J 8.5), 7.44 (2 H, 2 x d, ^3J 8.0), 7.37-7.22 (12 H, m), 7.03 (2 H, 2 x d, ^3J 3.1), 6.92 (2 H, 2 x s), 6.14 (2 H, 2 x d, ^3J 4.3), 5.94 (2 H, 2 x s), 5.03-4.88 (4 H, m), 4.31-4.28 (4 H, 2 x t, ^3J 7.0), 4.25-4.20 (2 H, m), 3.95 (6 H, 2 x s), 3.63-3.35 (4 H, m), 1.76 (2 H, 2 x t, ^3J 7.0), 1.40-1.10 (42 H, m) and 0.88 (6 H, 2 x t, ^3J 6.7); δ_C (100 MHz) 181.13, 180.75, 169.20, 169.06, 165.88, 162.98, 162.85, 154.81, 154.66, 135.23, 134.92, 134.88, 133.45, 133.20, 130.29, 129.45, 129.20, 129.17, 128.76, 128.70, 128.58, 128.45, 128.38, 128.09, 128.03, 126.46, 123.53, 123.41, 120.79, 120.50, 109.48, 109.46, 83.03, 82.91, 65.75, 62.34, 61.90, 59.25, 59.11, 44.49, 44.45, 37.92, 37.87, 32.16, 29.89, 29.85, 29.76, 29.60, 29.52, 28.91, 26.15, 22.94, 15.17, 15.09, 14.45 and 14.39 (quaternaries not defined); *m/z* 721 (M^+, trace), 381(11%), 355(26), 339(32), 197(34), 171(58),

108(100), 91(48), 69(13), 55(19), 43(24) and 29(16); *m/z* NH_3DCI 738 (MNH_4^+, 11%), 722 (MH^+, 22), 721 (MH^+, 56), 692(4), 675(4), 489(15), 355(49), 340(18), 252(100), 235(18), 108(19) and 82(50).

7. METHYL 4-CHLORO-3-[2-(4-DIETHYLAMINO-2-METHYLPHENYLIMINO)-2-AROYLACETAMIDO] BENZOATES (YELLOW DYE FORMATION)

N,N-Diethyl-2-methyl-1,4-phenylene diamine monohydrochloride **201** (0.25 g, 1.2 mmol) was added to a stirred solution of the appropriate β-ketoamide (1.0 mmol), dissolved in a mixture of THF (20 ml) and dilute aqueous sodium carbonate solution (5% w/v, 20 ml). Potassium persulfate (0.6 g, 2.2 mmol) was added to the mixture resulting in a darkening of the solution. Stirring was continued for 1 h then water (50 ml) and ethyl acetate (50 ml) were added, the mixture was shaken thoroughly and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 40 ml) and the organic solutions were combined, dried ($MgSO_4$) and the solvents were removed *in vacuo* to afford the product. The products were purified by preparative t.l.c. eluting with a mixture of *n*-hexane and ethyl acetate.

The following yellow dyes were prepared in this way. The β-ketoamide compound used is indicated in brackets in each case.

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino)-2-(3-methoxythen-2-oyl)acetamido]benzoate 302 (Methyl 4-chloro-3-[2-(3-methoxythen-2-oyl)acetamido]benzoate **276**) (16%), (Found M^+, 541.1441. $C_{27}H_{28}ClN_3O_5S$ requires 541.1438); $\lambda_{max.}$/EtOAc 432; δ_H 10.22 (1 H, br s), 9.20 (1 H, d, ^4J 2.0), 7.72 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.63 (1 H, d, ^3J 5.5), 7.47 (1 H, d, ^3J 8.4), 7.02 (1 H, d, ^3J 9.0), 6.76 (1 H, d, ^3J 5.5), 6.50 (1 H, d, ^4J 3.3), 6.29 (1 H, dd, ^3J 8.9, ^4J 2.8), 3.86 (3 H, s), 3.79 (3 H, s), 3.32 (4 H, q, ^3J 7.1), 2.49 (3 H, s) and 1.13 (6 H, t, ^3J 7.1); δ_C

187.01 (q), 166.09 (q), 162.75 (q), 161.38 (q), 149.36 (q), 148.14 (q), 138.31 (q), 135.70, 134.67 (q), 130.95 (q), 129.72 (q), 129.01, 127.28 (q), 125.15, 122.56, 121.43 (q), 121.11, 115.91, 112.56, 109.12, 58.95, 52.16, 44.24, 19.33 and 12.49; *m/z* 543 (M^+, 11%), 541 (M^+, 29%), 263(27), 261(19), 189(100), 167(22), 166(35), 165(35), 141(70), 77(14) and 32(100).

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino)-2-(then-2-oyl) acetamido]benzoate 301 (Methyl 4-chloro-3-[2-(then-2-oyl)acetamido]benzoate **275**) (100%), (Found M^+, 541.1441. $C_{27}H_{28}ClN_3O_5S$ requires 541.1438); $\lambda_{max.}$/EtOAc 447.5; *m/z* 513 (M^+, 17%), 512 (15), 511(M^+, 36), 189(100), 111(85) and 32(96).

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino)-2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate 303 (Methyl 4-chloro-3-[2-(*N*-phenylpyrrol-2-oyl)acetamido]benzoate **278**) (35%), (Found M^+, 570.2022. $C_{32}H_{31}ClN_4O_4$ requires 570.2034); $\lambda_{max.}$/EtOAc 436; *m/z* NH_3 DCI 571 (MH^+, trace), 348(40), 320(10), 285(11), 251(16), 249(100), 205(54), 189(80) and 179(80).

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino)-2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate 304 (Methyl 4-chloro-3-[2-(*N*-phenylpyrrol-3-oyl)acetamido]benzoate **279**) (35%), (Found M^+, 570.2033. $C_{32}H_{31}ClN_4O_4$ requires 570.2034); $\lambda_{max.}$/EtOAc 438; δ_H 10.32 (1 H, br s), 9.27 (1 H, d, ^4J 2.0), 7.74 (1 H, dd, ^3J 8.4, ^4J 2.0), 7.57 (1 H, s), 7.48 (1H, d, ^3J 8.4), 7.46-7.40 (2 H, m), 7.36-7.30 (3 H, m), 7.16 (1 H, d, ^3J 9.0), 7.02 (1 H, s), 6.76 (1 H, s), 6.52 (1 H, d, ^4J 3.3), 6.30 (1 H, dd, ^3J 8.9, ^4J 2.8), 3.85 (3 H, s), 3.30 (4 H, q, ^3J 7.1), 2.57 (3 H, s) and 1.10 (6 H, t, ^3J 7.1); *m/z* 572 (M^+, trace), 570 (M^+, trace), 347(13), 249(15), 236(10), 221(20), 211(42), 182(33), 180(100), 170(100, 154(45), 124(47) and 100(50).

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino)-2-(4-methoxybenzoyl)acetamido]benzoate 300 (Methyl 4-chloro-3-[2-(4-methoxybenzoyl)acetamido]benzoate **274**) (85%), (Found M^+, 535.1872.

$C_{29}H_{30}ClN_3O_5$ requires 535.1874); $\lambda_{max.}$/EtOAc 440; δ_H 10.31 (1 H, br s), 9.20 (1 H, d, ^4J 2.0), 7.84 (1 H, d, ^3J 8.7), 7.71 (1 H, d, ^3J 8.3), 7.46 (1 H, d, ^3J 8.4), 6.94-6.87 (4 H, m), 6.48 (1 H, s), 6.20 (1 H, d, ^3J 9.0), 3.82 (3 H, s), 3.80 (3 H, s), 3.28 (4 H, q, ^3J 7.0), 2.55 (3 H, s) and 1.13 (6 H, t, ^3J 6.9); δ_C 187.10 (q), 165.98 (q), 164.44 (q), 161.56 (q), 148.56 (q), 148.05 (q), 139.52 (q), 134.45 (q), 131.11, 130.24 (q), 129.63 (q), 128.97, 127.69 (q), 127.13 (q), 125.18, 123.26, 120.93, 114.27, 112.48, 109.09, 55.35, 52.07, 44.18, 19.55 and 12.41; *m/z* 537 (M^+, 16%), 535(28), 190(13), 189(100), 145(12), 135(97) and 32(44).

Methyl 4-chloro-3-[2-(4-diethylamino-2-methylphenylimino) -2-(2,2-dimethylpropanoyl)acetamido]benzoate 299 (Methyl 4-chloro-3-[2-(2,2-dimethylpropanoyl)acetamido]benzoate **273**) (29%), (Found M^+, 485.2080. $C_{26}H_{32}ClN_3O_4$ requires 485.2081); $\lambda_{max.}$/EtOAc 442; *m/z* 485 (M^+, 13%), 189(100), 57(44), 41(14) and 32(46).

8. ALTERNATIVE ROUTES TO ALKYL THEN-2-OYLACETATES

a. ATTEMPTED FORMATION OF METHYL THEN-2-OYLACETATE

Preparation of thiophenecarboxylic acid anhydride 247

A stirred solution of 2-thiophenecarboxylic acid (3.12 g, 24 mmol) and acetic anhydride (3.0 ml, 6.48 g, 63 mmol) in toluene (9.0 ml) was heated under reflux for 6 h. The solvents were removed under reduced pressure and the product was purified by kugelrohr distillation. Further purification by recrystallisation from a mixture of hexane and ethyl acetate gave the title compound **247** (1.51 g, 52%) mp 57-59°C (lit.[94] mp 62°C); bp 220°C (15 Torr) [lit.[94] bp 218-220°C (15 Torr)]; *m/z* 238 (M^+, 18%), 112(11), 111(100) and 39(43).

To a stirred suspension of the sodium salt of Meldrum's acid[77] (0.35 g, 2 mmol) in dry DMF (4 ml) at 0°C was added a solution of the 2-thiophenecarboxylic anhydride **247** (0.49 g, 2 mmol) in dry DMF (2 ml) under nitrogen. The mixture was left stirring overnight whereby a colour change from colourless to pale yellow was observed. The work-up was followed from the literature[77] however the dark red oil product obtained was not the title compound **249**.

b. PREPARATION OF ETHYL THEN-2-OYLACETATES

(i) Synthesis of 3-Methoxythiophene-2-carboxylic acid 254

The metallation reactions were carried out using a 1.6M solution of *n*-butyllithium in hexane, under anhydrous conditions at all times. The apparatus was flame or oven dried before use and allowed to cool to room temperature under dry nitrogen, reactions were performed under dry nitrogen, and additions were made by injections *via* septa.

To a stirred solution of 3-methoxythiophene (5.00 g, 4.35 ml, 43.9 mmol) in freshly distilled THF (100 ml) was added *n*-butyllithium (1.1 equiv., 30.13 ml, 48.3 mmol) and the subsequent opaque orange mixture was allowed to stir at room temperature for 15 min. The reaction mixture was poured into a slurry of dry ice in THF (200 ml) whereby a colour change to pale pink was observed. The mixture was allowed to warm up for 15 min to *ca.* -10°C then water (40 ml) and dilute aqueous hydrochloric acid solution (5%, 40 ml) were added to afford a white precipitate after vigorous reaction. The aqueous solution was extracted with ether (3 x 100 ml), then washed with water (50 ml), dried ($MgSO_4$) and the solvents removed *in vacuo* to give the title compound **254** (78%), mp 175-177°C (from ethanol) (lit.[95] mp 178.5-179.5°C); δ_H ([$^2H_6$]DMSO) 7.75 (1 H, d, ^3J 5.5), 7.08 (1 H, d, ^3J 5.5) and 3.87 (3 H, s) with an

impurity of 3-methoxythiophene-5-carboxylic acid **255** (12%); δ_H 7.33 (1 H, d, ^4J 1.9), 6.95 (1 H, d, ^4J 1.9) and 3.76 (3 H, s).

(ii) Sythesis of Acid Chlorides

3-Methoxythen-2-oyl chloride 256

A solution of 3-methoxythiophene-2-carboxylic acid (1.10 g, 7 mmol) in thionyl chloride (2.4 ml, 3.9 g, 33 mmol) was heated under reflux for 30 min until the evolution of gas ceased. The solvents were removed under reduced pressure to afford the *title compound* **256** (100%, crude) which was used without further purification; *m/z* 178 (M^+, 3%), 176(M^+, 11%), 141(100), 126(30), 98(13), 81(14), 72(29), 70(30), 69(36), 58(11), 56(13), 53(35), 48(41) and 44(21).

Thiophene-2-oyl chloride 252

A solution of thiophene-2-carboxylic acid (3.13 g, 24 mmol) in thionyl chloride (8.3 ml, 13.6 g, 114 mmol) was heated under reflux for 1 h until the evoluion of gas ceased. The solvents were removed under reduced pressure to afford the title compound **252** (3.25 g, 91%) bp 90-92°C (10 mmHg) [lit.,[96] 206-208°C]; *m/z* 148 (M^+, 10%), 146 (M^+, 22%), 135(15), 120(46), 111(100), 83(12), 39(36), 36(12) and 32(29).

(iii) Synthesis of Ethyl then-2-oylacetates [78]

To a stirred solution of potassium ethyl malonate[79] (1.87 g, 11 mmol) in dry acetonitrile (17 ml) at 10-15°C was added triethylamine (1.55 ml, 11 mmol) followed by magnesium chloride (1.29 g, 13.5 mmol) and stirring was continued at room temperature for 3 h under nitrogen. The resulting white slurry was cooled to 0°C and the appropriate thiophene carboxylic acid chloride (5.7 mmol) dissolved in acetonitrile (3 ml) was added dropwise over 10 min, followed by the addition of

more triethylamine (0.1 ml, 0.7 mmol). The yellow coloured mixture was then allowed to stir at room temperature overnight. The solvents were removed *in vacuo*, then toluene (20 ml) was added to the residue and the resulting mixture was reconcentrated under reduced pressure. More toluene (20 ml) was added and the mixture was stirred and cooled to 10°C. Aqueous hydrochloric acid solution (13%, 10 ml) was added at such a rate as to ensure the temperature did not rise above 25°C. The aqueous layer was separated and the toluene layer was washed with dilute aqueous hydrochloric acid solution (13%, 2 x 5 ml), followed by water (2 x 5 ml), then dried ($MgSO_4$) and the solvents were removed under reduced pressure to afford the product.

The following β-ketoester derivatives were prepared in this way. The acid chloride used is indicated in brackets in each case.

Ethyl 3-methoxythen-2-oylacetate 257 (3-methoxythen-2-oyl chloride **256**) 85% (Found M^+, 228.0455. $C_{10}H_{12}O_4S$ requires M^+, 228.0456); *m/z* 228 (M^+, 12%), 141(85), 127(10), 58(13), 45(16), 43(100), 39(14) and 32(40).

Ethyl then-2-oylacetate 253 (thiophene-2-oyl chloride **252**) 74% (Found M^+, 198.0350. $C_9H_{10}O_3S$ requires M^+, 198.0351); *m/z* 198 (M^+, 6%), 111(100) and 39(11).

The β-keto esters are present as a mixture of keto/enol tautomeric forms, however full charaterisation of the keto form is presented from independent synthesis outlined in Section G.2.

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PUBLICATIONS

The following publications are abstracts for UK Patent Applications;

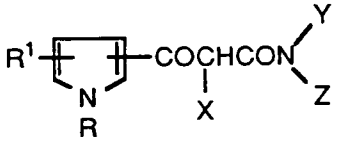
1. Novel image-dye-forming couplers (pyrroloylacetanilides)
   UK patent application no. 9513114.0

2. Novel image-dye-forming couplers (thenoylacetanilides)
   UK patent application no. 9513108.2

ABSTRACT

NOVEL IMAGE-DYE-FORMING COUPLERS AND PHOTOGRAPHIC ELEMENTS CONTAINING THEM

The present invention comprehends the use of novel pyrroloylacetamides as image-dye-forming couplers, specifically yellow dye-forming couplers, for use with silver halide based photographic systems. In one aspect the invention provides a coupler of formula (I):-



(I)

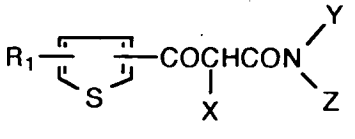
wherein X is H or a coupling-off group, R and R_1 are independently selected from H and coupler-modifying functional groups; Y and Z are the same or different and are H or independently selected from alkyl, aryl or heteroaryl, each of which is unsubstituted or substituted with one or more coupler modifying functional groups; or Y and Z taken together with the nitrogen atom form a 5-10 membered heterocyclic ring which may contain one or more further heteroatoms selected from N, O and S, said heterocyclic ring being unsubstituted or substituted with one or more coupler modifying functional groups.

Preferred compounds are those wherein Y is H and Z is a phenyl group, which may be mono- or di- substituted.

ABSTRACT

DYE-FORMING COUPLER AND PHOTOGRAPHIC ELEMENTS CONTAINING THEM

The present invention comprehends the use of thenoylacetamide materials as image-dye-forming couplers, specifically yellow dye-forming couplers, for use with silver halide based photographic systems. In one aspect, the invention provides a coupler of formula (I):-

(I) 

wherein X is H or a coupling-off group, R_1 is H or is a coupler-modifying functional group; Y and Z are the same or different and are H or independently selected from alkyl, aryl or heteroaryl, each of which is unsubstituted or substituted with one or more coupler-modifying functional groups; or Y and Z taken together with the nitrogen atom form a 5-10 membered heterocyclic ring which may contain one or more further heteroatoms selected from N, O and S, said heterocyclic ring being unsubstituted or substituted with one or more coupler-modifying functional groups.

Preferred couplers are those where Y is H and Z is a phenyl group, which may be mono- or di-substituted.