Pyrolytic Syntheses of 6,5,5 Heterocyclic Systems as Novel Magenta Dye Couplers

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Thesis presented for the degree of
Doctor of Philosophy,
The University of Edinburgh,
March 2005

Declaration

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

The thesis describes the results of research carried out in The University of Edinburgh, Chemistry Department, under the supervision of Dr Hamish McNab since 1st October 2001, the date of my admission as a research student.

Acknowledgements

I would firstly like to thank Dr Hamish McNab for being so kind as to accept me for this particular Ph.D. project, for his unrelenting enthusiasm and generous encouragement, and his tireless support even during the hardest times of my final year.

I must thank Dr Bernard Clark at Kodak for his advice and guidance on the project, for carrying out tests on the compounds I sent to him, and for being a perfectly decent industrial supervisor during my three months at Kodak in Harrow. Thanks then go to Bernard's replacement during my final year, Dr Dave Clarke, who had already provided valuable input on the project from the start, some helpful assistance during the Kodak placement and was very kind and patient in reading through this thesis. Thanks are also due to Dr Chris Moore for his management skills, Dr Sheena Zuberi for good advice and company in the lab, and of course the powers that be at Kodak for their generous financial assistance.

I'd like to say thanks very much to some of the technical staff at the University of Edinburgh for providing assistance without which I couldn't have got very far, especially Mr John Millar for NMR, Mr Alan Taylor for mass spectrometry and Mrs Smilja Djurdjevič for quality CHN analysis.

Special thanks and mention must go to members of the McNab group with whom I have worked over the years, especially Dr Dale Cartwright for leaving me to continue his successful work, and Stuart Wharton for assisting with difficult NMR experiments. There have been some interesting characters in our group during my time, and I have to say how much I appreciated the interesting conversations, enjoyed the exciting exchanges of wit and laughed with my colleagues at the absurdity of life in general. Also, thanks to certain characters from outside the McNab group who provided some fine comedy moments with their regular visits to our office.

Finally, thanks to the most important people in my life, my family; Mum, Dad, Luke and Maya, for their love, support, understanding and encouragement, for keeping me going through the darkest times when it seemed that all was lost.

Lecture Courses Attended

Organic Research Seminars, The University of Edinburgh, School of Chemistry (3 years attendance).

Organic Colloquia, The University of Edinburgh, School of Chemistry (3 years attendance).

Royal Society of Chemistry, Perkin Division, Annual Scottish Meeting (3 years attendance).

Chemical Carcinogens, Dr Michael Paton, The University of Edinburgh, School of Chemistry (5 lectures).

Pesticides, Dr Hamish McNab, The University of Edinburgh, School of Chemistry (5 lectures).

Chemical Evolution, Dr Matt Heal, The University of Edinburgh, School of Chemistry (5 lectures).

Industrial Ecology, Prof. Peter Tasker, The University of Edinburgh, School of Chemistry (8 lectures).

Green Chemistry, Dr Neil Robertson and Prof. Andrew Harrison, The University of Edinburgh, School of Chemistry (5 lectures).

Sigma-Aldrich Contemporary Organic Synthesis, Postgraduate symposium, The University of Edinburgh, School of Chemistry (4 lectures).

Strategies for Synthesis, Postgraduate Symposium, The University of Edinburgh, School of Chemistry (5 lectures).

Contemporary Synthetic techniques, Postgraduate Symposium, The University of Edinburgh, School of Chemistry (3 lectures).

Abstract

Heterocyclic ring systems of the 6,5,5 azoloindole type have been found to have potential applications in colour photography as magenta dye couplers. The work described here has involved using flash vacuum pyrolysis (FVP) as a novel synthetic route to these tricyclic systems and structurally related tetracyclics. With new disconnections involving a key FVP stage, synthesis of complex ring systems can be reduced to as little as two or three steps, giving a significant advantage over more conventional synthetic routes. In this case FVP of substituted 2-(azolo)nitrobenzene and related heterocyclic derivatives gave the potential dye couplers, by means of a phenyl radical translocation/cyclisation reaction.

A range of pyrolysis precursors was synthesised by nucleophilic substitution reactions of an activated aromatic (or heterocyclic) compound with an appropriate azole, typically with potassium carbonate as base and dimethylformamide as solvent; however, less vigorous reaction conditions were often employed for some of the more activated species. An alternative route to phenyl radicals, utilising an allyl ester leaving group instead of the nitro group, led to an isomeric azoloindole system.

Flash vacuum pyrolysis of the precursors was carried out with a furnace temperature of 850 °C and a pressure range of 10^{-2}-10^{-1} Torr; the extreme heat caused radical cleavage of the nitro group while the low pressure permits only intramolecular reactions. In all, seven different heterocyclic ring systems were successfully synthesised (a variety of azacyclopentaindenes and indolobenzimidazoles) two of which were also produced with amino or cyano substituents Due to difficulties caused by the reactive nitrous gases which are co-products of the pyrolyses, the yields were relatively low, ranging from 20-50% on a 500 mg scale.

The potential couplers produced were reacted with a phenylenediamine developer, base and oxidising agent, giving azamethine dyes with hues ranging from reds to intense magentas. These were then analysed by liquid chromatography-mass spectrometry and UV-visible spectroscopy, the resulting data revealing a general pattern relating coupler structure to dye hue. A variety of other dye families were also produced from the couplers, including azo, methine and methylene Meldrum's acid functionalities, giving yellow hues with results at

times corresponding or contrasting to the trends observed for the magenta dyes. Other reactions of the active methylene functionality of these species were also studied and attempts were made to extend the synthetic route to provide ballasted couplers for incorporation into photographic film.

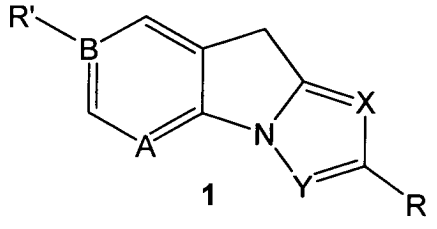
Contents

2. DISCUSSION

1. INTRODUCTION

PREAMBLE

The work carried out during this project has centred around the synthesis of 6,5,5 tricyclic systems of the type **1**, known as triazolo[1,5-*a*]indoles or cyclopenta[*a*]indenes. (A, B, X, Y = CH, N; R = H, Me; R' = H, CN, NH_2). Flash Vacuum Pyrolysis has been used as a novel synthetic route to this family of largely previously unreported compounds; in this way ordinarily complex syntheses can be reduced to two or three steps.



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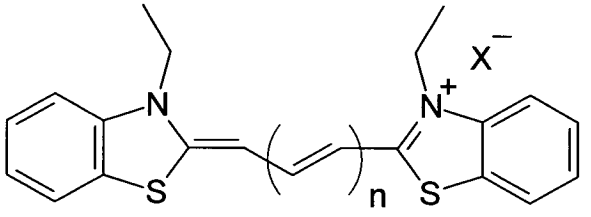
These type of compounds have significant applications in colour photography as magenta dye couplers.[1] This introductory review will initially discuss the processes behind colour photography before providing a summary of some of the typical compounds used in industry as magenta couplers. Finally this section will move on to a survey of the literature of related azole systems, featuring the two five-membered rings as shown above.

1.1 THE PHOTOGRAPHIC PROCESS

The majority of modern photographic processes are based on the use of light sensitive silver halides, usually silver bromide, which are especially suitable for short exposure times.[2,3] These are present on the film as small crystals in layers of gelatin, to form the photographic emulsion, a transparent carrier for the dye formation process. The quantity of dye produced is directly proportional to the degrees of light to which the silver halide is exposed. Often the gelatin is hardened using cross linkers to make the coated layer more resistant to possible damage from abrasions or during developing.[2,3] The silver halides are colourless or yellow, which therefore makes them sensitive towards ultraviolet and blue light only. In order to extend the sensitivity of silver

halides to all visible light, dyes known as sensitisers have been developed, which work by absorbing light and thus passing sensitivity to the silver halide. The most effective sensitisers are the cyanines, mono-acid salts in which two nitrogen containing heterocycles are linked by an odd numbered, conjugated carbon chain. A typical structure is shown below for a series **2 a-c**.



2	**a**	n = 0 yellow, blue light sensitive
	b	n = 1 magenta, green light sensitive
	c	n = 2 cyan, red light sensitive

In addition to the sensitising dyes, there is also obviously the need for actual colour forming dyes.[1,2,3] Modern colour photography makes use of the "integral tripack" system, consisting of three layers of the photographic emulsion containing silver halide and sensitisers for the three colours yellow, magenta and cyan. Each coloured layer acts as a filter, absorbing the colour to which it is sensitive, for example, the magenta layer stops green light, a third of the visible light spectrum, so leaving red and blue, which together give magenta. When the magenta and yellow layers are combined, only red light passes through, green and blue light having both been absorbed. Combining all three leaves black.

The arrangement of the three sensitised silver halide layers on a film or paper support are shown below (Figure 1).

The purpose of the yellow filter layer is to absorb any blue light which could affect the silver halide in the layers below; this layer is removed by bleaching during the developing of the film.

In the development process the exposed silver halide oxidises the colour developer reagent, to produce a species which then reacts with the colour couplers resulting in dye formation. One version of the process requires the use of three separate solutions

each containing a developer and a coupler. Firstly the exposed film is treated with a hydroquinone developer which reacts with the exposed silver halide to form silver metal. The film is then exposed to red light through the base to give a latent image where silver halide remains in the red sensitive layer in the places where red light from the original image hit the film. Processing with developer and coupler affords a cyan dye, which is present in this layer. Blue light is then used to produce yellow dye in the appropriate layer after processing with developer and a different coupler. Finally, magenta dye is formed in the middle layer, sensitive to green light, with a developer, coupler, and an agent which renders the remaining silver halide developable. Bleaching of silver to white silver bromide and removal of silver salts by thiosulfate solution completes the process.

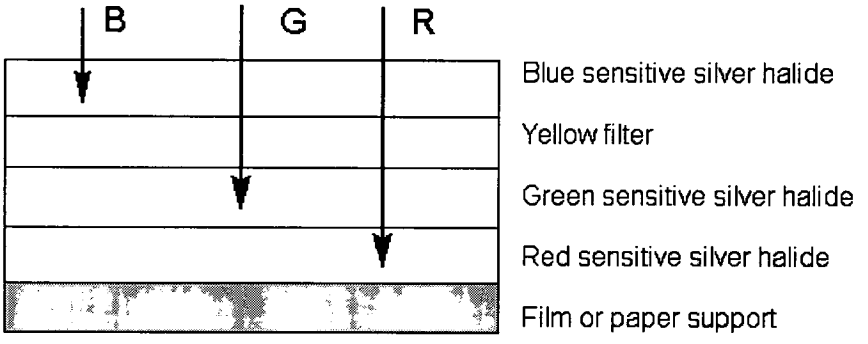
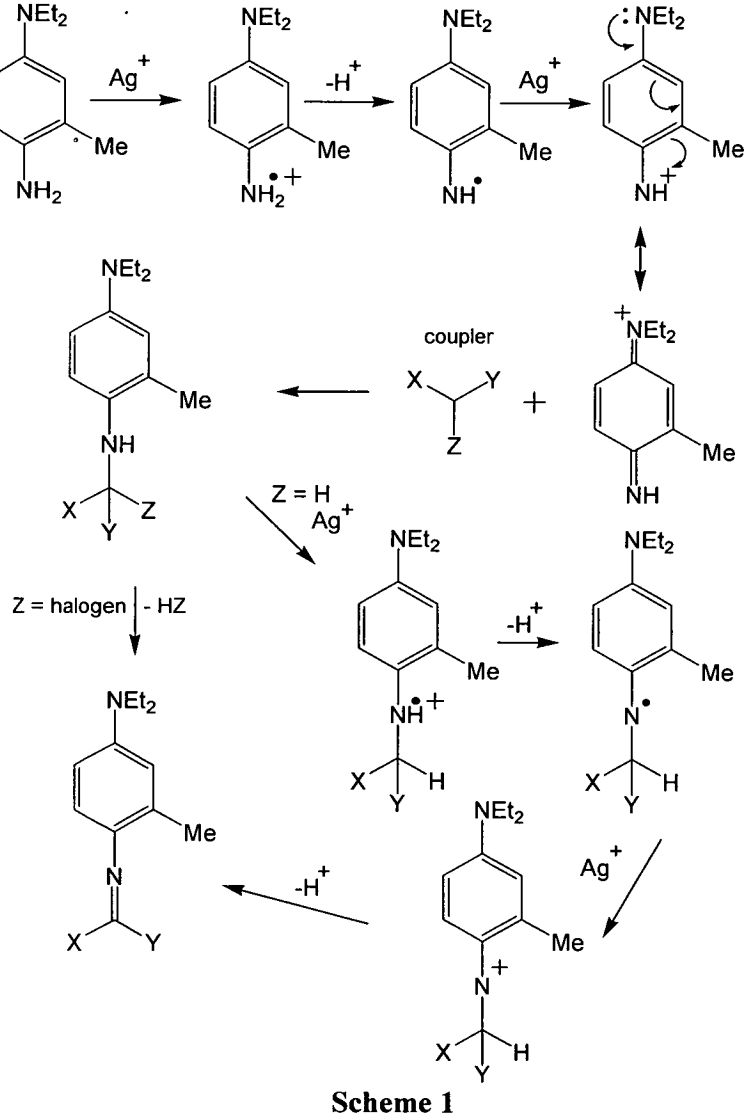


Figure 1

This process has been improved by incorporating couplers into the appropriate layers of the film so that only one developing solution is required to form the dyes in each layer. The modern method of ensuring that each coupler stays in the correct layer is to attach a long chain hydrocarbon group to the coupler molecule to serve as a ballast. The couplers are then dissolved in a suitable solvent, such as dibutyl phthalate, then incorporated into their respective silver halide emulsion layers in the film. As the unreacted couplers remain in the layers, certain properties are required for use. They must be colourless and give no discolouration under the influence of heat, light and moisture.

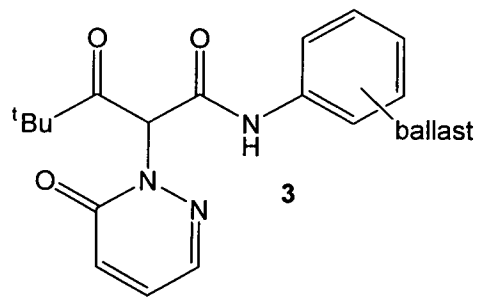
Colour developers have been in use for over 70 years and include *p*-phenylenediamines and *p*-aminophenols. Scheme 1 shows the generation of an

azamethine dye from a *p*-phenylenediamine developer, a generic coupler and exposed silver halide. The substituents on the coupler, X and Y, provide activation at the carbon atom to attack by the oxidised developer. Z is a substituent which is eliminated during the oxidative coupling reaction, and can either be a proton or a good leaving group such as a halogen. When Z is a proton, the coupling reaction requires four equivalents of silver halide to form the dye, so the coupler is termed a four-equivalent coupler. If Z is a halogen or other leaving group, known here as a coupling-off group, then only two equivalents of silver halide are needed for dye formation. This is clearly preferable as the amount of silver halide used is halved, which in turn allows thinner layers, displays increased reactivity and results in sharper images.



Scheme 1

A suitable base is also required, to deprotonate the coupler and allow the carbanion to attack the developer. An electron withdrawing coupling off group has the advantage of stabilising the intermediate anion thus aiding coupling.



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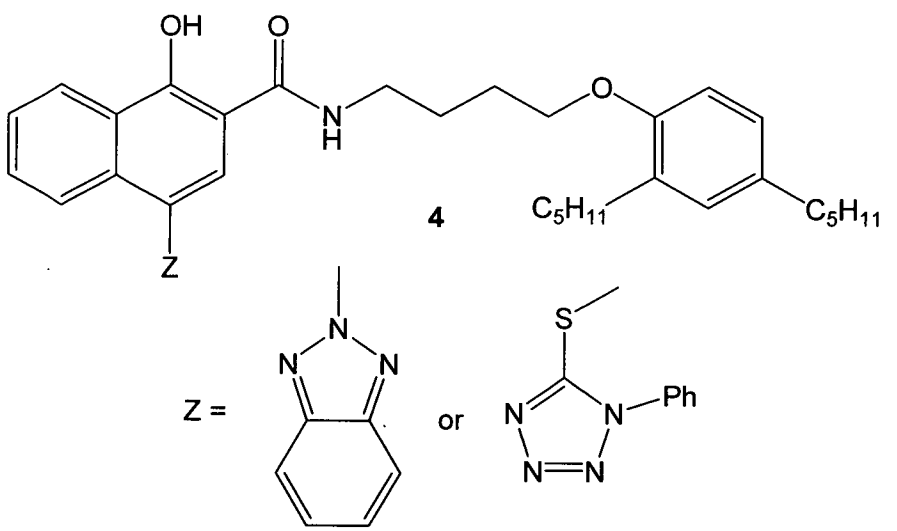
Colour couplers generally contain small aromatic systems, which must contain a reactive CHZ functionality for coupling with the developer. Yellow couplers generally include open chain methylene sections with an aromatic substituent. These are typically benzoylacetanilides or pivaloylacetanilides (**3**), the latter displaying better light stability but forming more slowly. In the system above, coupling takes place at the tri-substituted carbon between the two carbonyl groups, with the pyridazinone as the leaving group Z.



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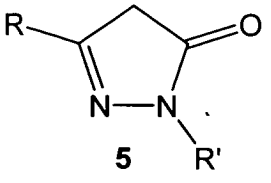
Cyan dyes are usually derived from phenols and naphthols, e.g. **4**, and, like the yellow coupler **3**, often include heterocyclic leaving groups to increase their reactivity.



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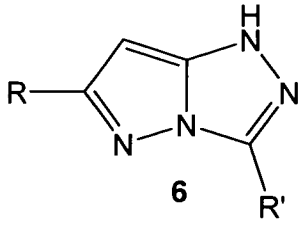

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Typical magenta dye couplers are 2-pyrazolin-5-ones of the type **5**, where R may be an alkyl or amino group and R' is a substituted aryl group, this system being a four equivalent coupler. More recently developed magenta couplers include azapentalene compounds such as the 1*H*-pyrazolo[5,1-*c*]-1,2,4-triazoles[4,5] **6**. The next part of this introduction will report in greater detail some of the various types of magenta couplers, with reference to the history of their development regarding improvements on certain deficiencies in the resultant dyes.

The remainder and major part of this introductory section is a literature review of a wide family of similar compounds, featuring the two fused five-membered rings of **1** with the four possible permutations of possible X and Y groups. In certain areas, where useful information was scarce, certain isomeric systems were investigated. Very few of the compounds found have been reported as dye couplers, but their synthesis and chemistry is of particular interest as background to the main body of work. Both the tautomer featuring the CH_2 group and the tautomer with the NH, as in **6**, are discussed, both of which are suitable for photographic coupling.

1.2 MAGENTA COUPLERS

As introduced in the previous section, magenta couplers have almost always been heterocyclic compounds, initially pyrazolones which were gradually replaced by pyrazoloazole couplers during the 1980's.[6] From about the 1960's, couplers derived from 3-aminopyrazolone were introduced into colour film and paper, giving better dye hues than the earlier couplers. Combined with the new standardised processes for developing the colour negative film, pyrazolone type magenta couplers could now be employed exclusively in photographic applications. There were two common complaints regarding the dyes derived from these couplers, the first being that they

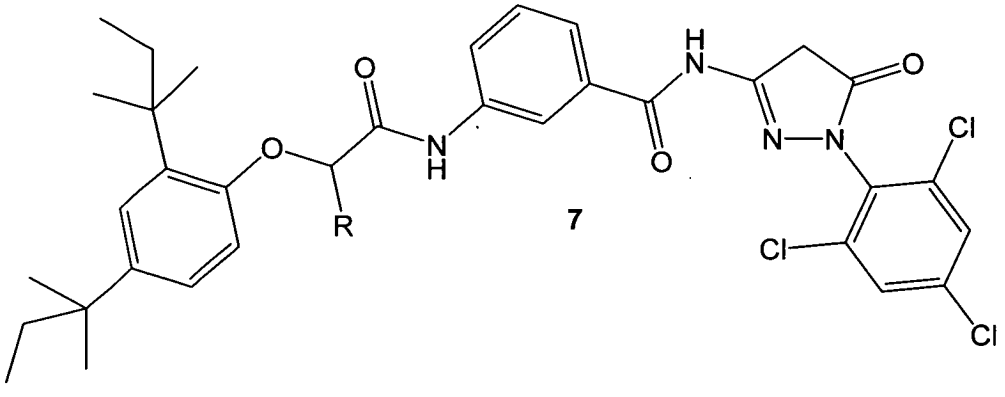
had a secondary absorption in the yellow region, obviously limiting the effectiveness of the dye hue. The way to overcome this was to incorporate yellow masking couplers into the film, which would absorb blue light and then be converted to the same magenta dyes to give a more evenly coloured result.

As pyrazoloazole couplers became available it was soon discovered that the azamethine dyes they gave were superior as the side absorption in the yellow region, although still present, had been greatly reduced. This meant there would now be no need to include masking couplers. Initially, 1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles were the main family of couplers utilised, and even as their performance was improved they have also been joined by the new 1*H*-pyrazolo[1,5-*b*][1,2,4]triazoles which are also giving impressive results (see Section 1.2.2 for structures).

1.2.1 Pyrazolone Couplers

1.2.1.1 3-Acylaminopyrazolones

3-Acylaminopyrazolones were discovered before 1950, by chemists at Eastman Kodak in America, and had a number of positive attributes which led to their introduction as couplers for colour film.[6] The dye images given by these highly reactive new couplers displayed surprisingly fine-grain structures and absorption of azamethine dyes in particular was relatively clean. In addition, the side absorption of blue light was reduced compared to earlier couplers, although yellow masking couplers, which had conveniently been invented about the same time, were still required.



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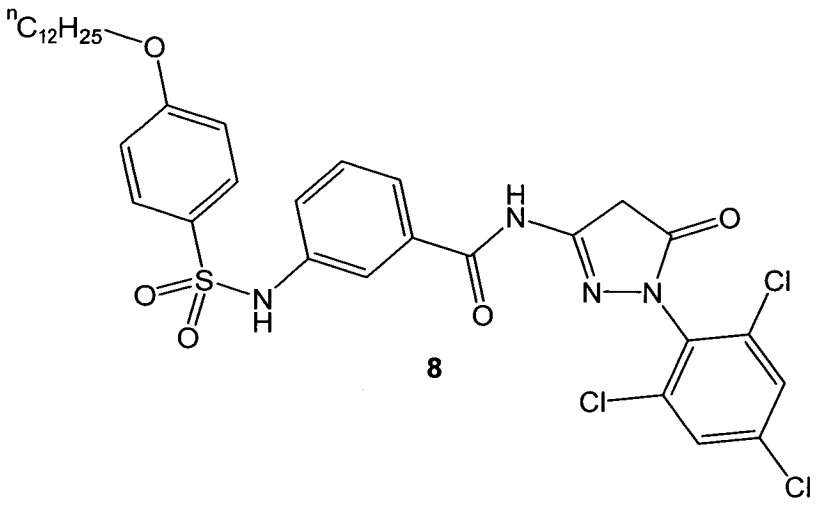

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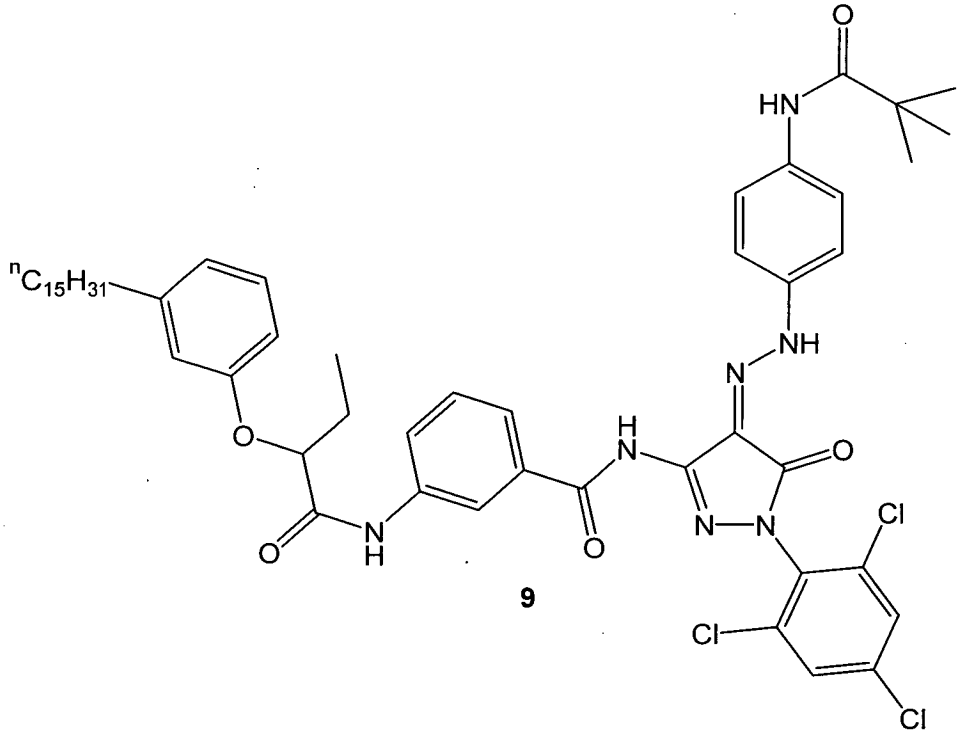
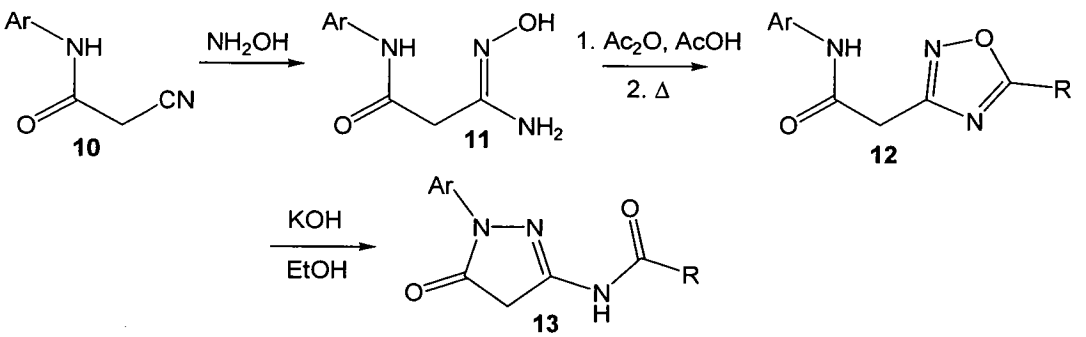
Initially it was four-equivalent versions of these couplers which were used, as in **7** (R = H, Et) and **8** shown above, the long chain substituents attached to the amide groups acting as ballasts, while the trichlorophenyl group provides an appropriate structural feature to ensure good dye hue and stability. Compound **9** is a 2-equivalent yellow azo masking coupler, the azo (or hydrazone) functionality being the leaving group which will be replaced in the development process and compensate for the minor blue light absorption of the original coupler. The main problem with four-equivalent couplers is actually their high coupling reactivity, which in particular manifested itself in sensitivity to air oxidation. This could cause staining of the latent image if the film



9

was stored for long periods, and the couplers could also react with aldehydes given off by certain types of fibre board or furniture, which resulted in loss of coupling activity so giving uneven images in the final prints. The means of overcoming this last problem was to introduce compounds known as scavengers into the photographic materials, to react with aldehydes.

Traditionally the synthesis of acylaminopyrazolones begins with the reaction of an arylhydrazine with an ester of cyanoacetic acid to give a 3-aminopyrazolone, which is then acylated by standard methods. In the 1980s new methods were introduced which dispensed with arylhydrazines and instead used a 2-cyanoacetanilide **10** (Ar = Ph, 2,4,6-$Cl_3C_6H_2$) (Scheme 2).[7] Hydroxylamine converted this to an amidoxime **11**, which could then be acetylated and cyclised in one step by addition of acetic anhydride, followed by heating, to give the 1,2,4-oxadiazole **12** (R = Me). Heating this with a base converted it to the 2-pyrazolin-5-one **13**; the R group represents the ballast, which can be introduced in an extra step by replacing the acetic anhydride with RCO_2Ac.

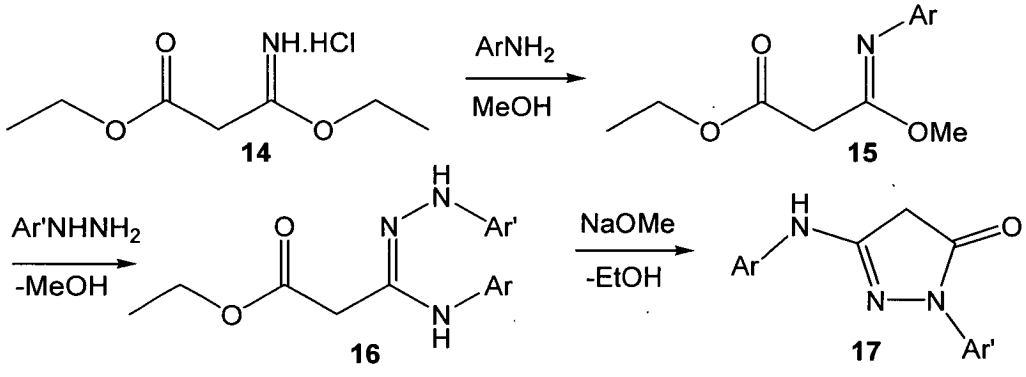


Scheme 2

The advantage of two-equivalent couplers, other than requiring half the quantity of silver halide, is that they are capable of giving higher dye yields.[6] Nitrogen-bound leaving groups are commonly used, with pyrazoles and imidazoles having been investigated in the most detail. Attaching these leaving groups to couplers such as **7** leads to a much faster photographic speed and a level of colour density considerably higher than the expected value. However, the drawbacks of the increased speed are higher levels of fog and graininess, the clouds of dye produced being excessively large in size.

1.2.1.2 3-Anilinopyrazolones

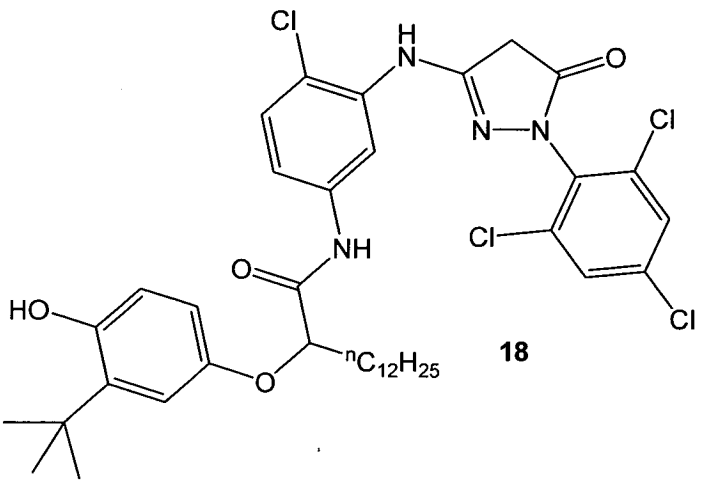
As with the synthesis of 3-acylaminopyrazolones such as that shown in Scheme 2, the starting point for 3-anilinopyrazolones is often an alkyl cyanoacetate (or the respective carbimidate) and a common step once the pyrazolone ring has been formed is to condense a substituted aniline with an ethoxy or amino substituent. The drawback with this route is the difficulty of introducing electron withdrawing groups on the aniline moiety for the purposes of improving coupling and dye hue. One useful synthesis published in 1979 (Scheme 3) overcame this by starting with ethyl 3-ethoxy-3-iminopropionate hydrochloride **14** and reacting it with a substituted aniline and methanol, with loss of ethanol to give the imidate ester **15**.[8] An arylhydrazine, as featured in many syntheses of 3-acylaminopyrazolones, is then condensed with the imidate ester **15** to produce the amidine **16**, after displacing methanol. Addition of sodium methoxide as base then effects cyclisation by deprotonation of the hydrazine adjacent to Ar', which can then attack the ester to form the pyrazolone ring of **17** after loss of ethanol (Ar = 2-Cl-5-NO_2-C_6H_3, 3-NO_2-C_6H_4; Ar' = 2,4,6-triCl-C_6H_2).



Scheme 3

A useful discovery which has considerably improved the usage of azamethine dyes of 3-anilinopyrazolones in colour paper, was that they could be efficiently stabilised to photoxidation by the inclusion of alkylphenol stabilisers which scavenge the radicals which lead to degradation.[6] The stabiliser can be an additive incorporated into the film or actually a substituent attached to the coupler itself, as shown in the ballasted coupler **18**. However, this type of protection does not protect against post-process yellowing of the coupler, and attempts at developing long term preventive measures against this problem have met with little success in this class of magenta coupler. The

most serious weak point in the performance of 3-anilinopyrazolones is stain in white areas, which is caused by slow oxidation of the coupler itself, leading to the production of dimers and other discoloured products. To diminish stain formation, unexposed coupler must itself be deactivated, for a long time this has been carried out by treatment of the finished image with a formaldehyde stabiliser solution, which is unsatisfactory for reasons of safety and ecological issues.



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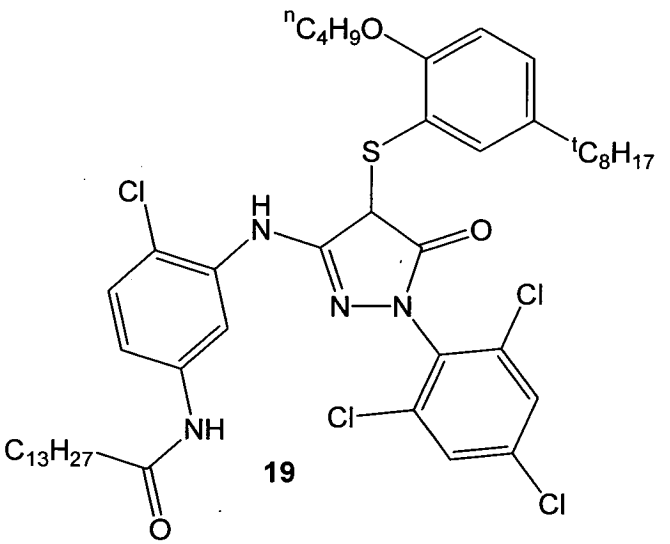
Moving onto two-equivalent 3-anilinopyrazolone couplers, arenethiol leaving groups have been recognised for a few years as a successful measure for solving the problem of yellowing. Compound **19**, with its ballasted thiophenol group, has been used in colour paper showing low yellowing, and is synthesised at low cost from reaction of the four-equivalent coupler with a sulfenyl chloride prepared from arenethiol and a chlorinating agent. The ballasted arenethiol is important as smaller compounds such



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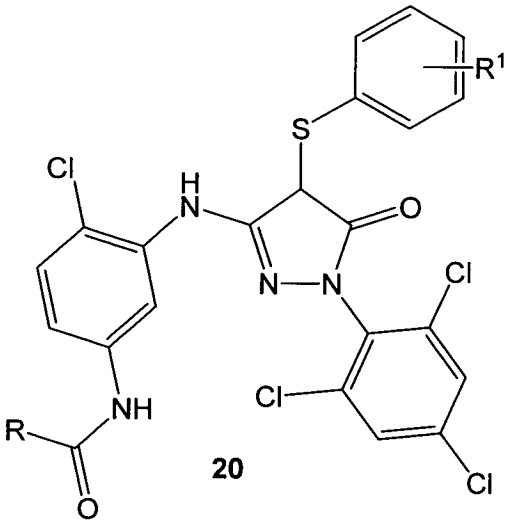
as thiophenol are volatile, interact with silver halide and give off a noxious odour noticeable even in low concentration.



20

In colour film, arenethiol-substituted equivalents such as **20** have been introduced and are still in use, where both R and R^1 act as ballasting groups. These couplers have solved common problems such as staining, dye yield and aldehyde sensitivity, although the side absorption of blue light still has to be masked. New problems encountered include higher graininess of the dye image, and the phenomenon of increase of dye density post-process. This is thought to be a form of post-process coupling and weak organic bases have been employed to reduce changes occurring within 48 h after development, generally by forming a hydrogen bond between coupler and 'density stabiliser'.

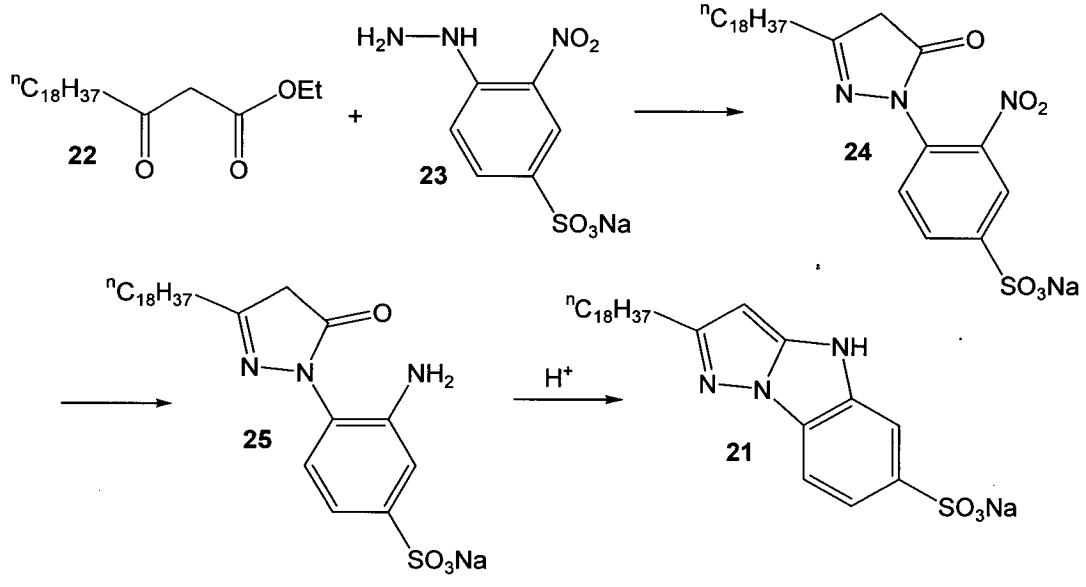
Attempts at linking other types of nucleophilic leaving groups, such as acidic nitrogen heterocyclic compounds, to anilinopyrazolones have failed for a number of reasons. Bromination of anilinopyrazolones generally leads to moderately stable dibrominated compounds, which can be reduced to the monobrominated analogue which appears to be unstable on account of its residual nucleophilic character. Monochlorinated products can be obtained cleanly with neutral chlorinating compounds such as *N*-chlorosuccinimide, but these are unstable and have poor keeping qualities. Acylation with acid chlorides or anhydrides typically leads to a mixture of products and procedures aimed at avoiding side reactions and obtaining one desired product have proved unreliable. Use of azole-substituted anilinopyrazolone couplers has been

hindered by their inherent instability, which leads to fog build-up in colour development; as well as the occasional report of synthetic difficulties.

1.2.2 Pyrazoloazole Couplers

Pyrazolo[1,5]azoles are azapentalenes with a bridgehead nitrogen atom, and display carbanion type nucleophilic character due to a high charge density in the pyrazole ring. As would be expected, they also show nucleophilic reactivity at an acidic nitrogen atom, as demonstrated by alkylation reactions at the 1-position adjacent to the methylene coupling site, but attack by soft electrophiles such as the oxidised colour developer always takes place at a methylene group.

1.2.2.1 Pyrazolo[5,1-*c*]benzimidazoles



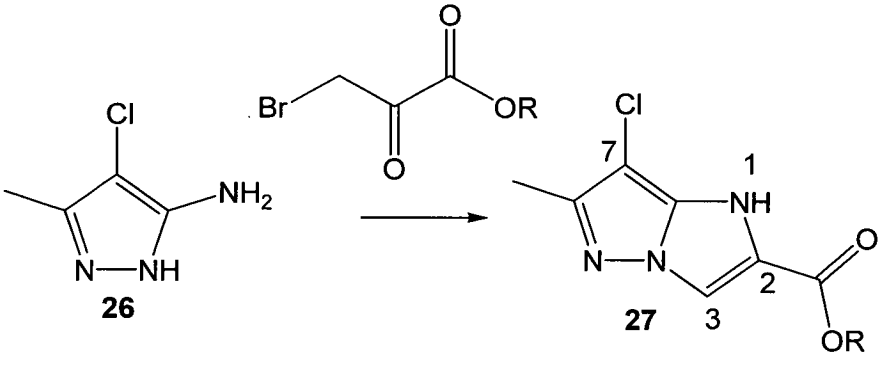
Scheme 4

The first compound of this type was a sulfonated pyrazolo[5,1-*c*]benzimidazole **21** which was used at the time in Agfa-Gevaert's colour reversal film, and was synthesised according to Scheme 4.[9] The long chain ester **22** and the aryl hydrazine **23** were used to obtain the nitrated pyrazolone **24**, which was then reduced to an amino derivative **25** and then cyclisation was carried out with acid catalysis to give the tricyclic system **21**.

Although the hue of the azamethine dye was a bluish magenta, all other positive features of azapentalene type couplers were present, such as resistance to formaldehyde damage and oxygen-induced staining, a steep UV-vis absorption curve without side absorptions and a high density dye, even as a four-equivalent coupler. Efforts to improve the hues of azamethine dyes from pyrazolobenzimidazoles led to the introduction of an alkoxy group into the pyrazole ring; as an electron donating group it leads to a lower absorption wavelength, *i.e.* a true magenta coupler.

1.2.2.2 Pyrazolo[5,1-*a*]imidazoles

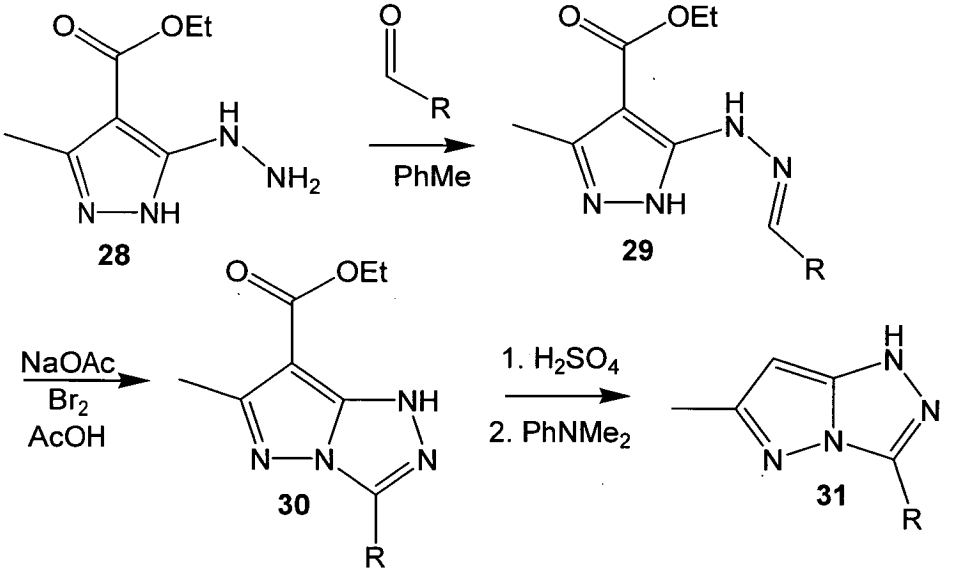
1*H*-Pyrazolo[5,1-*a*]imidazoles appear to have been reported in a number of patents as magenta couplers only in principle, and proper industrial use of these bicyclic systems has apparently not been reported. An example synthesis is shown in Scheme 5.[6] The ring system is generated by a typical Tschitschibabin condensation of an aminopyrazole **26** with an α-halogenated carbonyl compound, then the ester in the product **27** can be replaced by an amide ballast group. This should be a two-equivalent coupler with the chlorine at the predicted coupling site in the 7-position, although it is expected that the 3-carbon in the imidazole ring could also be a coupling site.



Scheme 5

1.2.2.3 Pyrazolo[5,1-*c*][1,2,4]triazoles

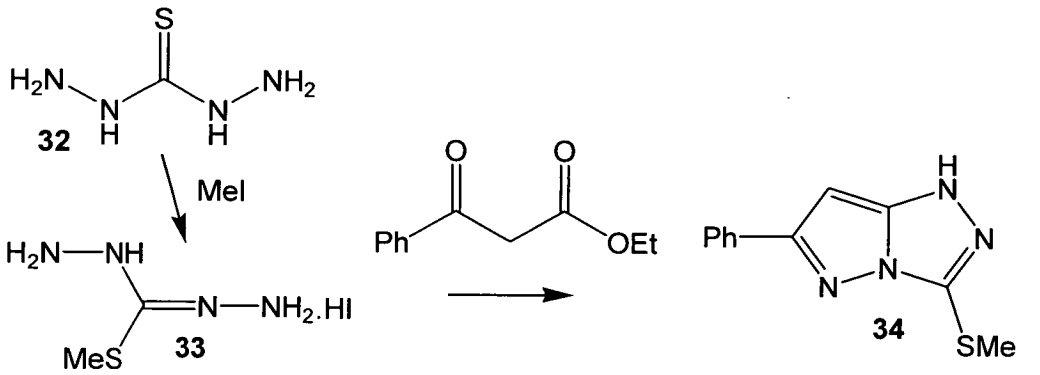
1*H*-Pyrazolo[5,1-*c*][1,2,4]triazoles were discovered by Joseph Bailey at Eastman Kodak in the mid 1960s, but it was some time before they could be applied technically. It was immediately observed that the azamethine dyes of these couplers were extremely intense in hue, so a number of various synthetic routes were investigated. The first method to be reported utilised a pyrazolyl hydrazine **28**, shown in Scheme 6.[10] The hydrazine **28** was condensed with a range of appropriate aldehydes to give a series of hydrazones **29**. These were then converted into the corresponding 1*H*-pyrazolo[5,1-*c*][1,2,4]triazole-7-carboxylates **30** by oxidative cyclisation, as a result of treatment with bromine, in acetic acid in the presence of sodium acetate. The unsubstituted couplers **31** were finally obtained in two steps; firstly heating in concentrated sulfuric acid hydrolysed the ester substituent to an acid, then heating in dimethylaniline effected decarboxylation to clear the 7-position for coupling.



Scheme 6

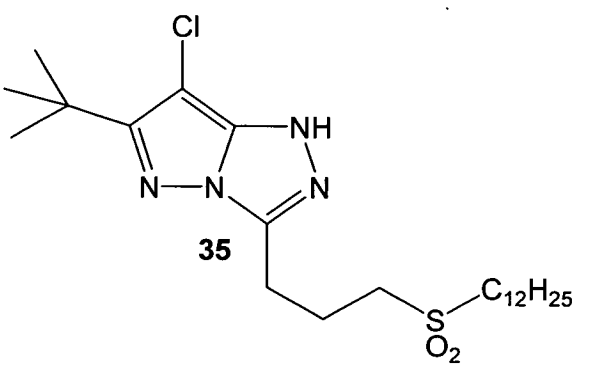
About ten years later Bailey reported a simpler synthesis, which began with thiocarbohydrazide **32** (Scheme 7), which was initially methylated with methyl iodide to give the hydroiodide **33**.[11] Heating this with ethyl benzoylacetate then gave the coupler 3-methylthio-6-phenyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole **34**, the mechanism taking place, after removal of hydrogen iodide, by attack of the newly liberated amine

on the ester carbonyl, followed by loss of the ethoxy group. The two nitrogen atoms from the terminal hydrazine group then attack both carbonyl groups to cyclise, loss of water giving the appropriate double bonds of the product **34**.



Scheme 7

A number of technical problems with 1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles were identified early on as a result of their chemistry, which would hinder their introduction into photographic film.[6] They exhibited a high tendency towards crystallisation and aggregate formation, low solubility, lower reactivity than pyrazolones and the resulting azamethine dyes had inferior light stability. The usual ballasting groups were found to be incapable of keeping the coupler dissolved within the photographic dispersion layer, so additional substituents had to be introduced to the couplers to improve solubility, in particular bearing sulfone, sulfonamide or tertiary amide groups, which in some cases also improved coupler reactivity.

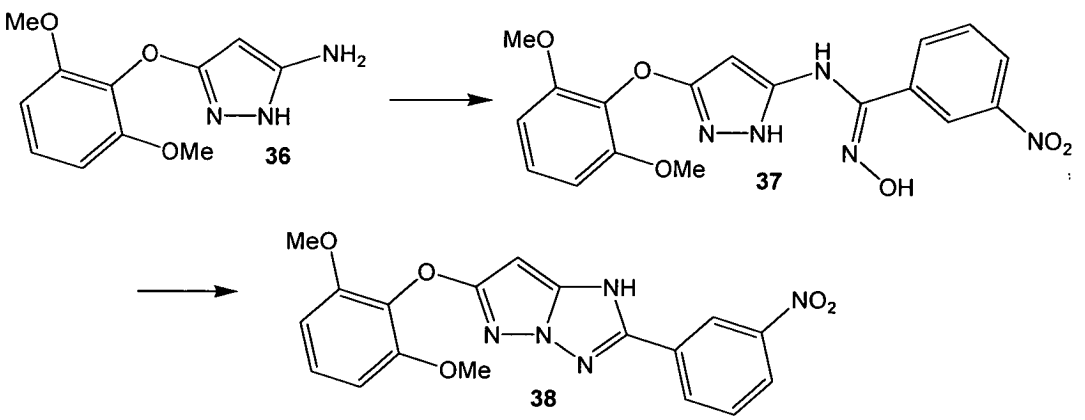


To improve the light stability of azamethine dyes formed from 1*H*-pyrazolo[5,1-*c*][1,2,4]triazole couplers, the most successful technique was to introduce a tertiary

butyl group in the 6-position of the ring system, as in the 2-equivalent ballasted coupler **35**. Since the carbon atom adjacent to the coupling position is efficiently screened, the drawback of this improvement in light stability is reduced coupling activity, although placing the tertiary butyl group in the 3-position can also improve light stability. Additionally, the introduction of a *tert*-butyl group to the 6-position has also been found to produce dyes which resist aggregation and show sharp absorption bands.

1.2.2.4 Pyrazolo[1,5-*b*][1,2,4]triazoles

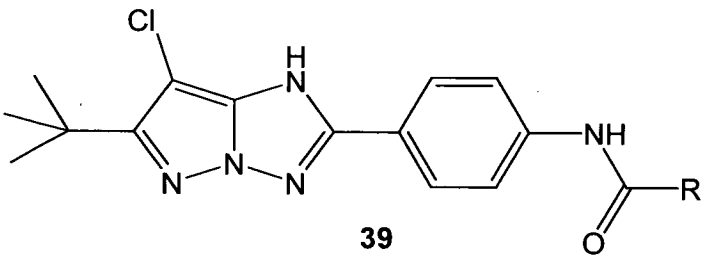
1*H*-Pyrazolo[1,5-*b*][1,2,4]triazoles were synthesised about 20 years later than the [5,1-*c*] class of couplers, discovered during the course of research for alternatives to the latter family, and were an entirely novel type of compound. As a result of this, new synthetic pathways had to be devised, usually starting with a pyrazole ring as shown in Scheme 8. This is just a small part of an 8-step procedure, where the pyrazole ring in **36** is formed from a cyanohydrin compound, and the nitrophenyl group in **37** is present for the purpose of attaching a ballast. The triazole ring in **38** is formed when **37** is treated with sulfochloride and a base, possibly by deprotonation of the future bridgehead nitrogen, which then attacks the *O*-sulfonylated amidoxime.



Scheme 8

This class of magenta coupler has been in use in colour paper for over 10 years, and as the performance has steadily improved so a new level of overall stability has been achieved. The coupler **39** was especially designed to stand up to the demands required for colour paper, and has shown high light stability even without added

stabilisers. Introducing alkoxy and aryloxy substituents to the 6-position, as in the case of Scheme 8, appears to provide couplers capable of giving dyes with higher colour intensity.



39

1.2.3 Other Classes

In principle, almost any type of azapentalene, such as imidazoimidazoles, might be able to couple with oxidised colour developer to give a dye with a colour ranging from red to blue; if the appropriate substituents can be chosen then the dye hue should be shifted to an acceptable magenta. Certain polyazapentalenes which have been considered as high strength cyan couplers were originally proposed as magenta couplers of a bluer shade, before addition of electron withdrawing substituents shifted the dye hue up to cyan.

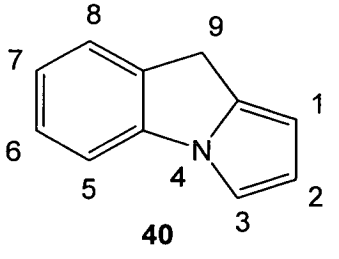
Active methylene compounds containing a nitrile group in combination with an electron-withdrawing carbonyl group have been known to couple to give red to purple dyes. However, the dyes were found to have very low extinction coefficients when analysed by UV-vis spectroscopy, the low colour intensity rendering them useless as photographic dyes. A few examples of enamine couplers have been reported since about 1990, involving cyano substituents which affect the methylene group sufficiently to permit coupling with an oxidised developer. Indazolone compounds were researched for a time, giving brilliant magenta dyes, but were withdrawn from technical use having proved susceptible to photochemical damage.

Now that a summary of the various types of magenta couplers typically used in photographic applications has been completed, the next few sections will investigate in detail the synthesis and chemistry of a wide range of compounds related to

structure **1**. This literature survey will commence with a look at bicyclic and tricyclic compounds containing pyrrole rings, before moving onto pyrazole, imidazole and triazole containing systems.

1.3 PYRROLE CONTAINING SYSTEMS

This section concerns the simplest derivative of the family **1**, featuring just the bridgehead nitrogen atom, therefore containing a fused pyrrole ring (the pyrrolizines). As there were so many examples of these, and it was already know they were of little use as couplers[4], only the compounds with a fused benzene ring, based on the parent structure **40**, 9*H*-pyrrolo[1,2-*a*]indole, have been discussed here. The numbering scheme has been included to clarify nomenclature of these systems.



40

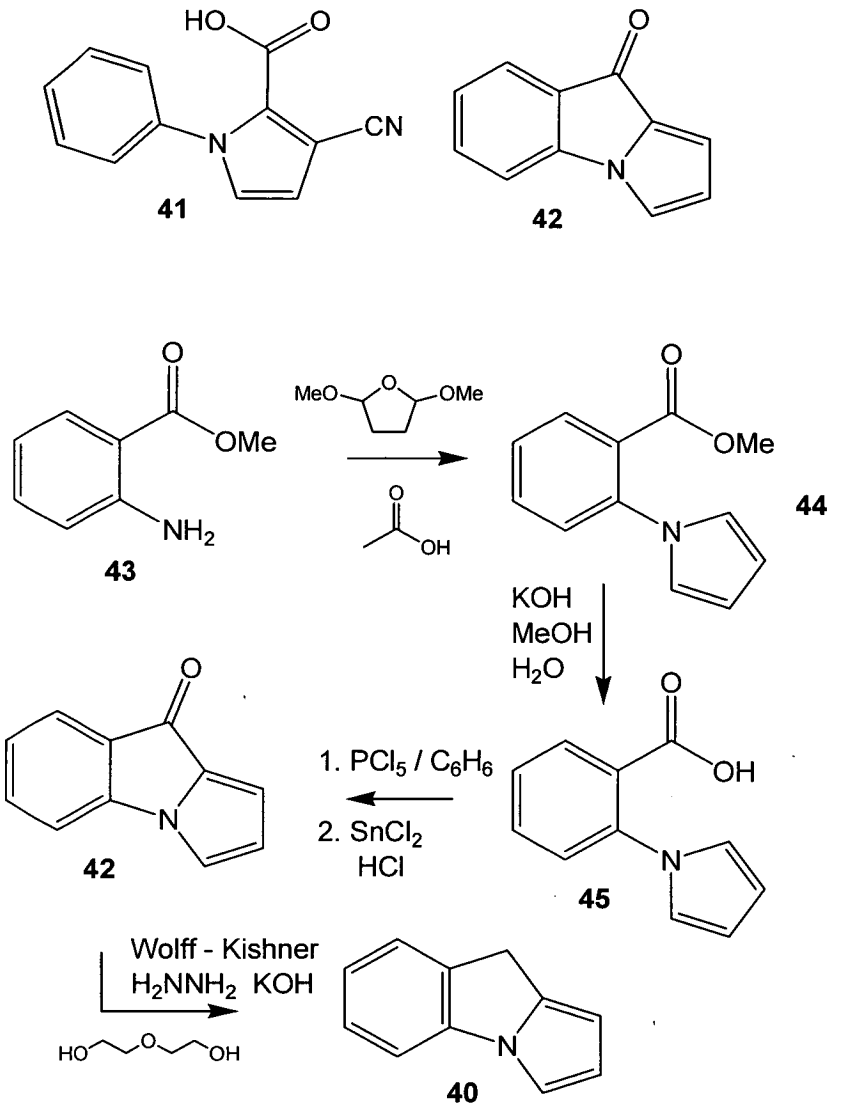
1.3.1 Synthesis of Pyrrolo[1,2-*a*]indoles

Two different classes of synthesis for these compounds have been reported. In the first class two quite different methods involve a pyrrole ring connected to a phenyl group with cyclisation forming the central ring of the product, in both cases a 9-substituted version of the parent system **40** is obtained.[12] With the second route, three loosely related syntheses form derivatives substituted in other positions leaving the central methylene site free. This time, addition of the outer five-membered ring to an indole occurs by means of a reagent containing a vinyl functionality.[13]

1.3.1.1 Closure of the Central Ring

Possibly the earliest reported instance of 9*H*-pyrrolo[1,2-*a*]indole **40** came from Germany in 1960, when Laschtuvka and Huisgen claimed to have formed it from a cyclisation of a 3-cyano-1-phenylpyrrole-2-carboxylic acid **41**.[14] This gave

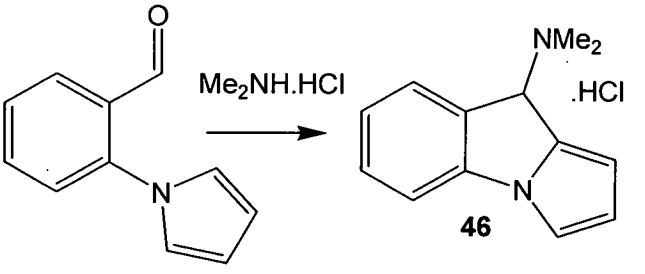
fluorazone **42** after decarboxylation of the initial product, and then the Wolff - Kishner reduction was used to remove the carbonyl group to give **40**. However, details of reagents and conditions were not fully discussed, and the starting material **41** seems unlikely, the role of the cyano group being unclear.



Scheme 9

Seven years later, Mazzola, Franck and Bernady reported a clear and concise similar synthesis of **40** as shown in Scheme 9.[12] Here they explained how methyl anthranilate **43** was used as the starting material and reacted with 2,5-dimethoxy THF to give the cyclisation precursor **45**, after hydrolysis of the ester **44**, where the reactive carboxylic

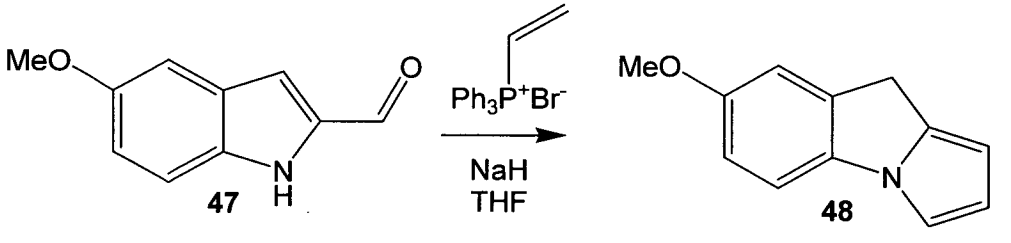
acid group is now attached to the phenyl ring. Phosphorus pentachloride was then used to substitute the hydroxy group for a good leaving group, then cyclisation was effected by addition of tin chloride and hydrochloric acid. This gave the fluorazone derivative **42**, with the advantage of no unwanted substituents by this method. Finally, **40** was obtained by the same Wolff - Kishner reduction with potassium hydroxide, hydrazine and diethylene glycol.



Scheme 10

In 1971 a variation on the previous method was reported by the team of Stephen Raines in the US, in which 2-pyrrol-1-ylbenzaldehyde was subjected to the Mannich reaction with dimethylamine hydrochloride (Scheme 10).[15] After rapid combination of starting materials in ethanol the reaction mixture was stirred at 25 °C for 3 h and the product was precipitated with addition of ether, being 9-*N*,*N*-dimethylamino-9*H*-pyrrolo[1,2-*a*]indole hydrochloride **46**.

1.3.1.2 Formation of the Outer Pyrrole Ring

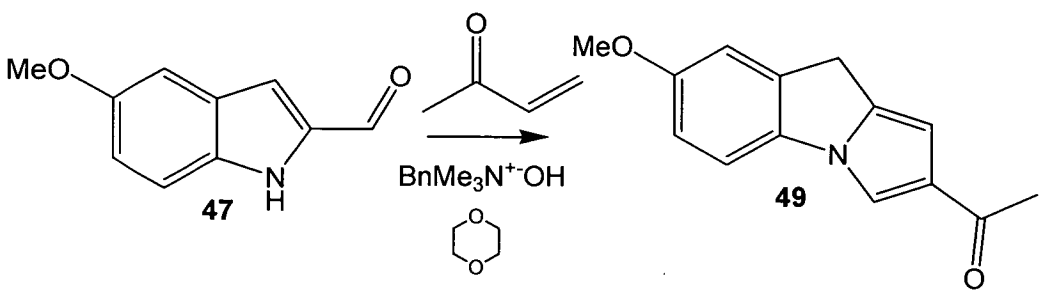


Scheme 11

In 1969 the Japanese team of Hirata, Matsui and Yamada reported quite an extensive range of work on the synthesis and chemistry of substituted pyrrolo[1,2-*a*]indoles typically starting with 5-methoxy-1*H*-indole-2-carbaldehyde **47**. In the first method

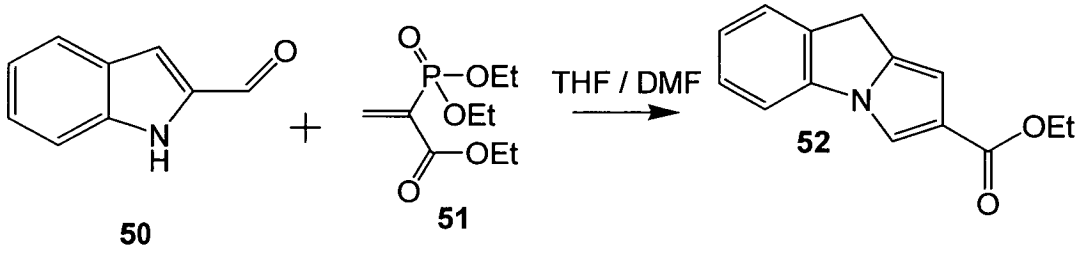
(Scheme 11), this species was reacted with vinyltriphenyl phosphonium bromide in THF in the presence of sodium hydride to give 7-methoxy-9*H*-pyrrolo[1,2-*a*]indole **48**.[16] Deprotonation of the indole heteroatom on **47** by sodium hydride allows Michael addition to the vinyl salt to give an ylide intermediate. This then reacts with the aldehyde group by way of a Wittig reaction, with loss of triphenylphosphine oxide to allow cyclisation. Having formed the outer pyrrole ring, tautomerisation then gives the structure **48** as shown.

Scheme 12 shows how a disubstituted 2-acyl analogue **49** was produced in a similar fashion by reaction of the same starting material **47** with methylvinylketone in the presence of trimethylbenzylammonium hydroxide in dioxane.[17] In this case the complex hydroxide is used to deprotonate the indole, which then leads to Michael addition to the vinyl group of the ketone reactant, followed by attack on the aldehyde to effect cyclisation.



Scheme 12

During the late seventies another group of Japanese chemists produced an ester substituted derivative of **40** while investigating the synthesis and reactions of vinylphosphonates which contain electronegative substituents.[13] A straightforward reaction of indole-2-carboxaldehyde **50** and the vinylphosphonate **51**, in THF or DMF at 70 °C, yielded the substituted pyrroloindole **52**, which exists as a mixture with its 3*H* tautomer (Scheme 13).



Scheme 13

1.3.2 Physical Properties

1.3.2.1 Infrared

No detailed studies on the infrared spectra of pyrrolo[1,2-*a*]indoles appear to have been carried out. Only stretching frequencies of certain bonds in substituent groups have been mentioned.

1.3.2.2 Ultraviolet

The ultraviolet spectrum of 9*H*-pyrrolo[1,2-*a*]indole **40** shows two absorption maxima, at 262 nm (ε 15,300) and 292 nm (2,200).[12] This shows that **40** is most likely colourless, a useful characteristic for a potential dye coupler, possibly very pale yellow if the secondary absorption tails off into the visible region. This result is not particularly surprising given that **40** is not highly conjugated, the phenyl and pyrrole rings being separate.

1.3.2.3 ^{1}H NMR

9*H*-Pyrrolo[1,2-*a*]indole **40** has been reported on a number of occasions in the past two decades, but ^{1}H NMR spectroscopic data have only recently been fully assigned by means of a proton NOESY experiment in deuteriated chloroform.[18] The methylene protons in the 9-position are represented by a singlet peak at 3.89 ppm, the first peak to be clearly assigned by the proton spectrum alone. On the outer pyrrole

ring positions 1-3 have ascending chemical shifts, 6.16, 6.44 and 7.16 ppm respectively, the proton in the 3-position clearly having the highest shift due to being adjacent to the bridgehead nitrogen atom, with its typical deshielding effects. On the phenyl ring peak assignments have been reported as follows: H 5 7.32, H 6 7.35, H 7 7.14 and H 8 7.44 ppm; the NOESY experiment shows an interaction between the methylene protons in the 9-position and the phenyl proton H 8, with further interactions revealing the shifts of the remaining protons.

The proton NMR spectrum of 7-methoxy-9*H*-pyrrolo[1,2-*a*]indole **48** (formed in Scheme 11) in $CDCl_3$ had already been fully assigned in the late 1960's, giving interesting information as to the effect of the electron donating methoxy group.[16] Firstly, as might be expected, this substituent reduces the chemical shift of the methylene protons to 3.75 ppm, which incidentally is also the shift of the protons on the methoxy group itself. On the phenyl ring all peaks are significantly lowered in shift relative to the parent system, especially the two adjacent protons, H 6 at 6.73 ppm and H 8 at 6.90 ppm. On the pyrrole ring, protons 1-3 (6.03, 6.30 and 6.93 ppm respectively) are also lowered relative to the parent compound, although to a lesser extent due to their distance from the electron donating group.

Effects of an electron withdrawing group on this system can be seen from the proton NMR spectrum of 2-acyl-7-methoxy-9*H*-pyrrolo[1,2-*a*]indole **49** (Scheme 12), where the signal for the proton in the 1-position is raised to 6.47 ppm and that in the 3-position to 7.54 ppm by the deshielding effects of the acyl group.[17]

1.3.2.4 ^{13}C NMR

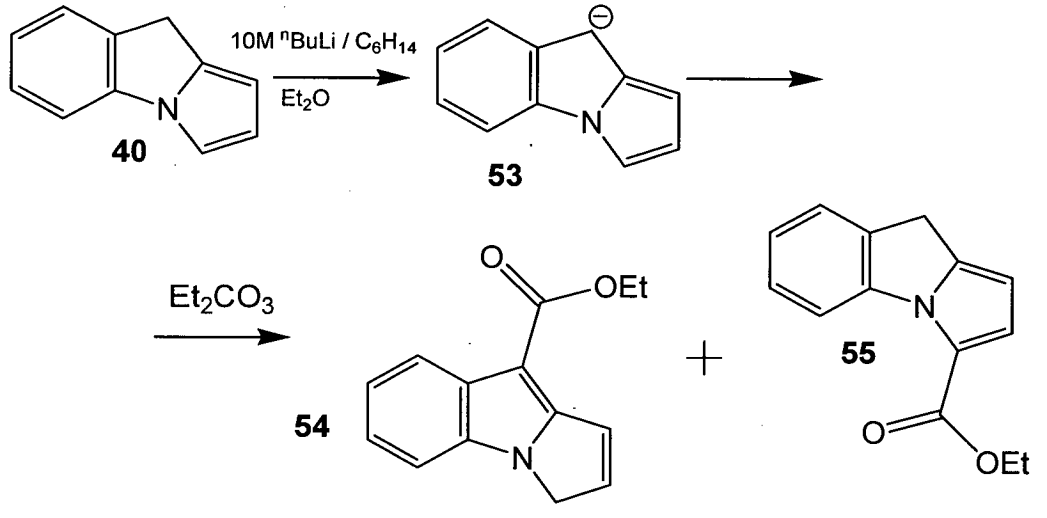
A HSQC experiment was performed on 9*H*-pyrrolo[1,2-*a*]indole **40** in order to correlate the proton peaks already assigned with those of the ^{13}C NMR spectrum.[18] The one peak which stands out from just the ^{13}C spectrum alone is the methylene carbon in the 9-position, with its typically low shift of 28.92 ppm. Then the HSQC experiment shows the phenyl carbons as follows: C 8 125.73, C 7 122.94, C 6 127.29 and C 5 109.61 ppm. The 5-carbon has a predictably lower shift due to being 2 bonds away from the nitrogen heteroatom, while the other carbons all have similar shifts being at a distance from this functionality. On the pyrrole ring the shifts are lower as would be expected; the assignments are C 1 101.57, C 2 113.01 and C 3 109.61 ppm,

the order of which is surprising, as the carbon atom 2 bonds away from the heteroatom actually has the highest shift.

1.3.3 Chemical Reactivity

The only type of reaction to be performed on the pyrrolo[1,2-*a*]indole series appears to be nucleophilic substitution with acyl species, typically at the 9-position to give 9-acyl derivatives.[19] This series of compounds is not expected to be particularly effective as couplers, as there is nothing to increase the acidity of the protons in the 9 position.

1.3.3.1 9*H*-Pyrrolo[1,2-*a*]indole 40

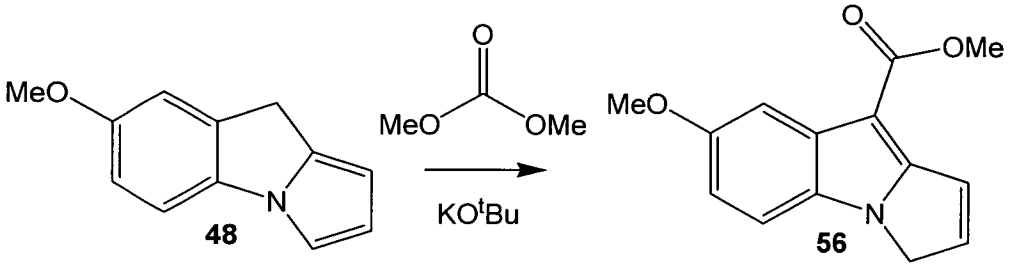


Scheme 14

This interesting reaction on **40** was performed by Franck and Bernady in the late sixties, and involved a study into reactions of a carbanion formed at the 9 position.[19] According to Scheme 14 the anion **53** was formed by the addition of a solution of butyl lithium in hexane to **40** in ether, which turned the whole solution green, indicating presence of the anion. This was then condensed *in situ* with diethyl carbonate giving 9-carbethoxy-3*H*-pyrrolo[1,2-*a*]indole **54** as the main product, where the ester group had attached to the 9 position, and tautomerisation had occurred leaving CH_2 at the 3 position. This was apparently the first example of a 3*H*-

pyrrolo[1,2-*a*]indole system. As well as unreacted starting material **40**, a minor product 3-carbethoxy-9*H*-pyrrolo[1,2-*a*]indole **55** was isolated from the crude product, a system where the carbethoxy group has substituted to the three position, and the tautomerism has returned to the 9*H* form, with addition of a proton to the 9 position. This minor product could be very useful with dye coupling compounds as the 9-substituent could be used to attach a ballast.

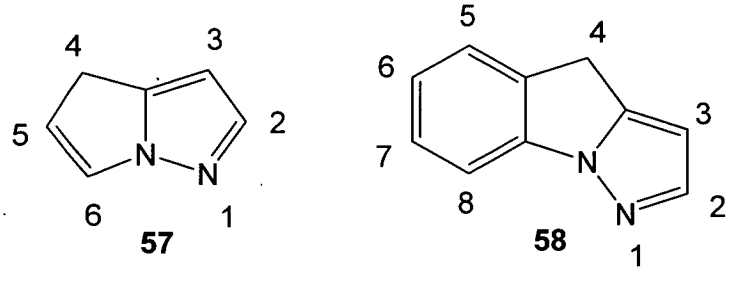
1.3.3.2 7-Methoxy-9*H*-pyrrolo[1,2-*a*]indole 48



Scheme 15

In a slightly varied reaction the methoxy derivative **48** was acylated in the 9-position as shown in Scheme 15, with potassium *tert*-butoxide used as the base to deprotonate the methylene site, which can then attack the dimethyl carbonate to give the methyl ester substituted product **56** in the 3*H* tautomeric form.[16] An aldehyde analogue was also produced in the same way using ethyl formate in place of dimethyl carbonate.

1.4 PYRAZOLE CONTAINING SYSTEMS



In this family, studying the literature revealed a single derivative of 3*H*-pyrrolo[1,2-*b*]pyrazole, a tautomer of the desired structure **57**. After that there was a large number of pyrazolo[1,5-*a*]indole derivatives, with substituents in a variety of

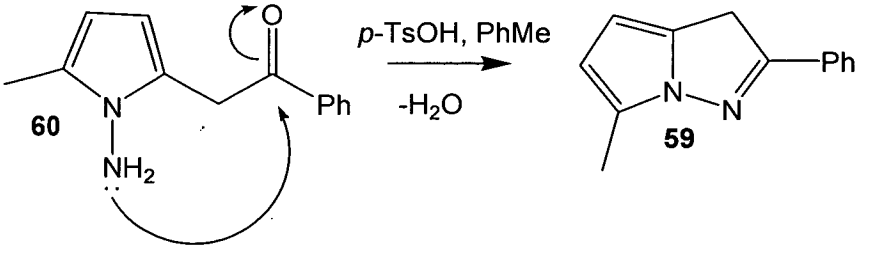
locations. No compounds were found with the benzene ring fused to the pyrazole rather than the pyrrole ring. Two general structures are shown below with the numbering scheme, the bicyclic **57** and tricyclic **58**.

1.4.1 Synthesis of Pyrrolo[1,2-b]pyrazole Containing Systems

Only one synthesis of a bicyclic 3*H*-pyrrolo[1,2-*b*]pyrazole was found, but after that there were numerous syntheses involving tricyclic pyrazolo[1,5-*a*]indole derivatives. These can be split into three main groups; cyclisation where the central, pyrrole ring is the last to be formed, cyclisation where the outer, pyrazole ring is last to be formed, and complicated two ring synthesis. As well as those there is a brief description of a synthesis where a tricyclic carbonyl system is reduced to give a mono-substituted pyrazolo[1,5-*a*]indole.

1.4.1.1 Synthesis of a 3*H*-pyrrolo[1,2-*b*]pyrazole

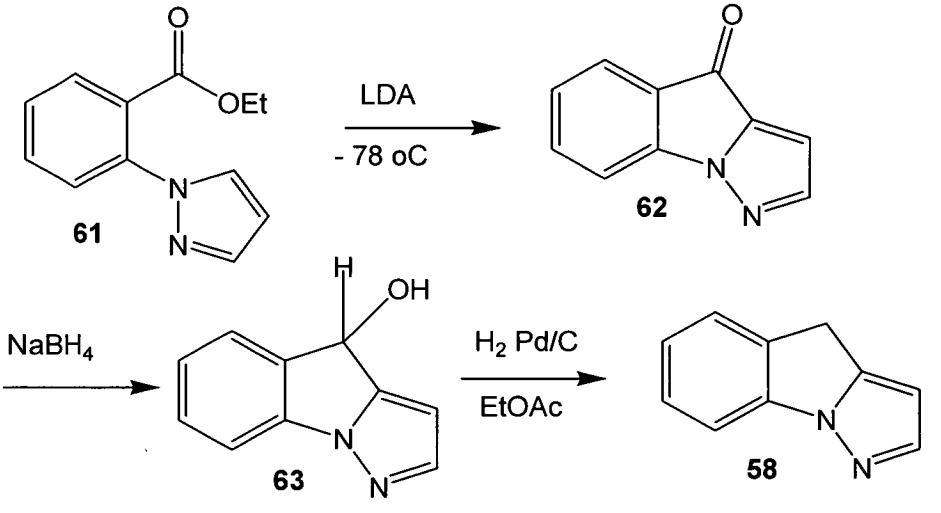
Quite recently, a Chinese team has reported a new synthetic method for the preparation of N-substituted pyrroles from derivatives of 1,6-dioxohexan-2,4-diene, and they extended this methodology to the synthesis of the novel system, 1-phenyl-6-methyl-3*H*-pyrrolo[1,2-*b*]pyrazole **59**.[20] Scheme 16 demonstrates how the amine substituent on the pyrrolyl acetophenone derivative **60** can be made to cyclise by attack at the carbonyl group, under acid catalysed conditions in toluene. After cyclisation, loss of water gives **59**.



Scheme 16

1.4.1.2 A Pyrazolo[1,5-*a*]indole Synthesis – Closure of the Pyrrole Ring

The first report of the parent compound 4*H*-pyrazolo[1,5-*a*]indole **58** was a 1992 paper by Katayama where he produced the system by closure of the central pyrrole ring, as shown in Scheme 17.[21] Reaction of the pyrazole substituted phenyl ester **61** with lithium diisopropylamine deprotonated the pyrazole at the carbon adjacent to the substituted nitrogen forming a carbanion which attacked the carbonyl to cyclise and displace the ethoxide group. This gave **62**, where the carbonyl is still intact at the 4-position. Addition of sodium borohydride reduced the carbonyl to an alcohol **63**, and then a long 4 day hydrogenolysis process using a palladium/carbon catalyst finally removed the hydroxy group to give **58**.

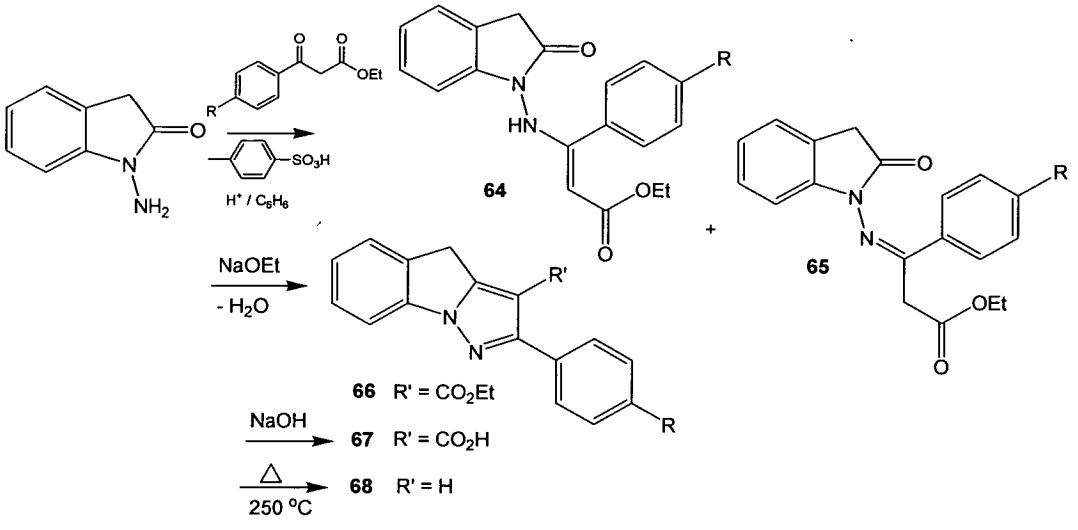


Scheme 17

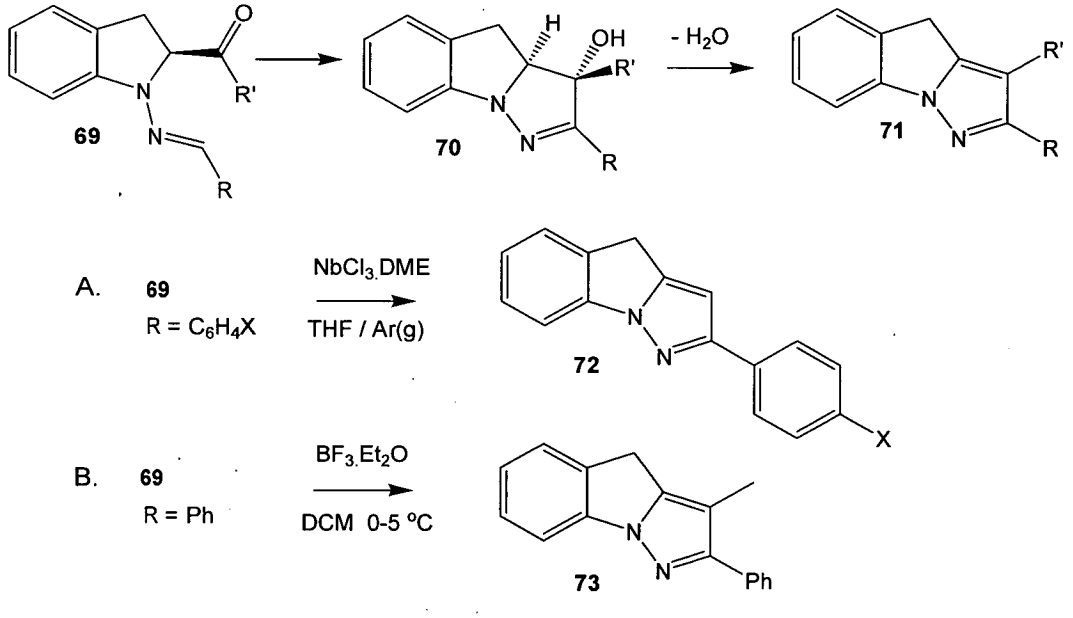
1.4.1.3 Closure of the Pyrazole Ring

The earliest synthesis of a 4*H*-pyrazolo[1,5-*a*]indole derivative involved closure of the outer pyrazole ring and was reported by Winters and his associates in 1984.[22] Scheme 18 shows how 1-amino-1,3-dihydro-indol-2-one was reacted with the ester shown and *p*-toluenesulfonic acid in benzene (R = H or OMe). Protonation of the ketone carbonyl leads to nucleophilic attack by the amino group, followed by loss of water to give an equilibrium mixture of the two tautomers **64** and **65**. Sodium ethoxide was then added to the mixture, which led both isomers to cyclise by means of deprotonation next to the ester, leading to a carbanion which attacks the indole carbonyl. Loss of water in both cases gave the 9-ester substituted pyrazoloindole **66**. Sodium hydroxide was used to hydrolyse the ester to an acid (**67**), and then this group

was removed by heating at 250 °C to give the 2-aryl substituted compound **68**. This aryl substituent could easily have a long chain attached to it, and so provide a possible ballast.



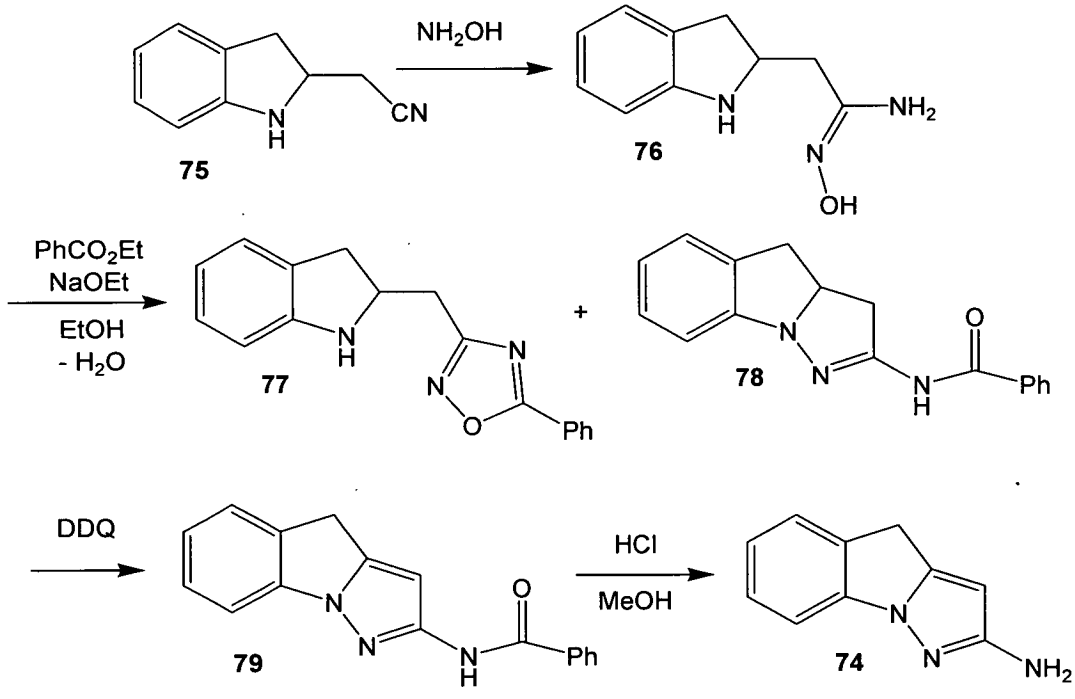
Scheme 18



Scheme 19

A pair of reactions where the pyrazole ring was the last part of the tricycle to be formed, using the same starting material, were reported according to Scheme 19.[23] The hydrazone **69** was apparently prepared *via* oxidation of the corresponding

alcohol, and in both reactions A and B it was made to cyclise to give the general intermediate **70**. Removal of water then gave the pyrazolo[1,5-*a*]indole **71**. The niobium trichloride DME method, in an argon atmosphere, appears to have worked just for the aldehyde (R' = H), giving the 2-substituted product **72** (X = H, Me, OMe, Cl, CN or NO_2). The boron trifluoride etherate method seems to have been necessary to cyclise the methyl ketones (R' = Me), and here they only appear to have synthesised the phenyl version **73**. In both cases it is likely that the reagent is acting as a Lewis acid and co-ordinating to the carbonyl oxygen to make the carbon more electrophilic. Electron density from the indole nitrogen atom delocalises to cause the imine to attack at the carbonyl, causing cyclisation, and the charge is neutralised with loss of a proton.



Scheme 20

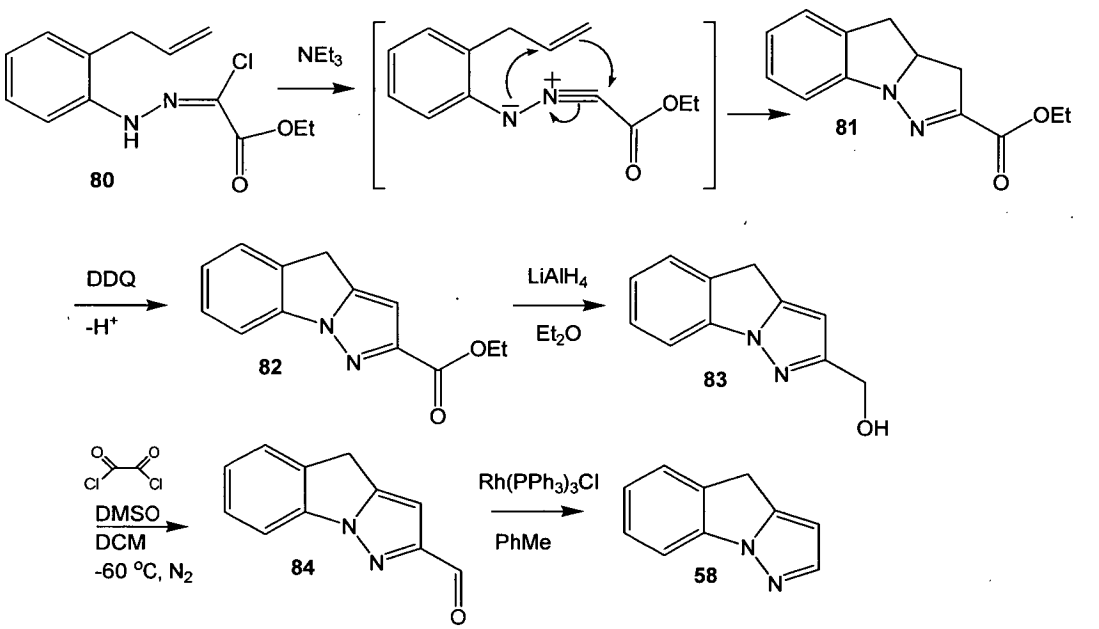
Another reaction involving final closure of the pyrazole ring is that developed by Katayama to synthesise 2-amino-4*H*-pyrazolo[1,5-*a*]indole **74**.[24] Scheme 20 details how the acetonitrile substituted dihydroindole **75** was used as the starting material and reacted with hydroxylamine to give the cyclisation precursor **76.** Addition of ethyl benzoate in the presence of sodium ethoxide and ethanol at 150 °C led primarily to 77 where sequential attack of the amine and hydroxy groups at the carbonyl of the ester

formed the oxadiazole ring with loss of water. The minor side reaction of formation of the tricycle **78** seems to involve deprotonation of the indole nitrogen allowing this to attack the oxadiazole nitrogen next to the oxygen, opening the ring and reforming the carbonyl. DDQ was then used to dehydrogenate to the pyrazoloindole **79**, which was then converted into the simpler amine derivative **74** by adding hydrochloric acid in methanol.

1.4.1.4 Closure of Two Rings

Amongst his many works in this field, Katayama also developed an interesting synthesis involving a number of steps where both the pyrazole and pyrrole rings are formed in the same cyclisation step.[21]

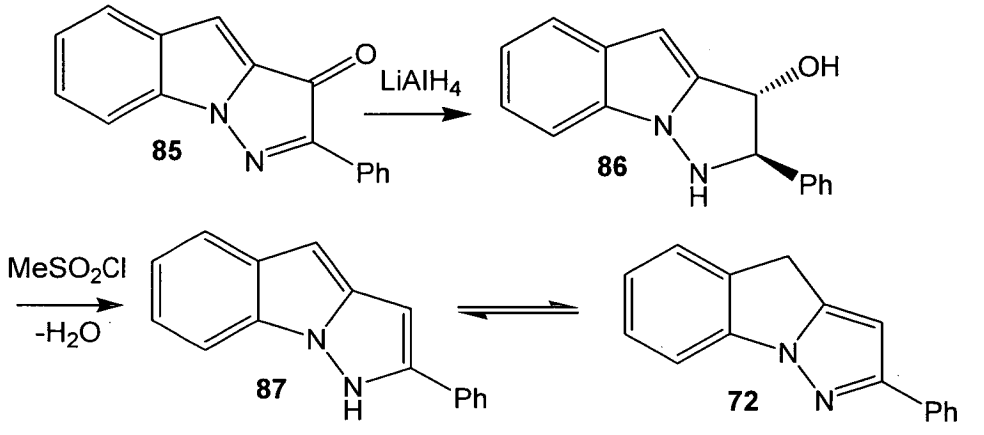
Scheme 21 shows how the complex chlorinated hydrazone **80**, which had been derived from 2-allylaniline, was used as an alternative starting material for the synthesis of **58**.[25] Addition of triethylamine deprotonates the hydrazone group, which leads to elimination of the chloride, thus creating the nitrile imine intermediate. A 1,3-dipolar cycloaddition then occurs to form the two azole rings of **81**. Subsequent steps dehydrogenate the ring system and reduce the ester **82** to an alcohol **83**, then an aldehyde **84**, before this substituent is finally removed with rhodium tris-triphenylphosphine chloride to give the parent compound 4*H*-pyrazolo[1,5-*a*]indole **58**.[21]



Scheme 21

1.4.1.5 Reduction of a Carbonyl Containing Tricyclic System

This is not the most useful synthesis as it requires the use of a tricyclic pyrazole containing system produced by an unknown reaction method, but it may be of small interest at the end of this section. Working together, Shen and Katayama took the 3*H*-pyrazolo[1,5-*a*]indole system **85**, and reacted it with lithium aluminium hydride to reduce the carbonyl to an alcohol **86**, as well as reducing the imine double bond (Scheme 22).[26] Methanesulfonyl chloride was then used to promote dehydration to give **87**, and the 4*H* tautomeric form **72** was also identified.



Scheme 22

1.4.2 Physical Properties

As there were a good number of syntheses of pyrazole compounds found in the literature mostly in papers from the last decade, these compounds have been characterised more fully than those discussed elsewhere in this report which were produced and reported earlier.

1.4.2.1 IR Spectroscopy

Fortunately, in this group of compounds, the parent system was fully characterised when Katayama synthesised it ten years ago.[21] The IR spectrum of 4*H*-pyrazolo[1,5-*a*]indole **58** was reported as having absorption maxima with wavenumbers 1622,

1542, 1472, 1397 and 755 cm^{-1}. The peak at 1622 cm^{-1} could correspond to the C=N stretch, while the C-N and N-N frequencies are probably slightly lower. The aromatic region is represented by the signal at 755 cm^{-1}, typical with an *ortho* disubstituted phenyl group.

The IR spectrum of the 2-amino substituted derivative **74** was reported a year later, as 3361, 3296, 3186, 1562, 1493, 1397, 1368 and 746 cm^{-1}.[24] The first three absorptions all correspond to the different possible N-H stretching frequencies of the NH_2 substituent. One of the peaks in the central region of the spectrum accounts for the C-N bond attaching the amino group to the imidazole ring.

1.4.2.2 UV-vis

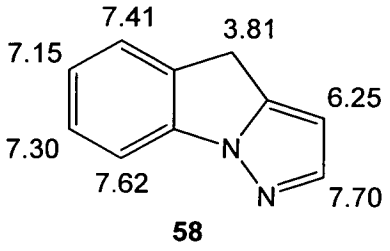
The UV-vis spectrum of 4*H*-pyrazolo[1,5-*a*]indole **58** shows three absorptions of similar intensity, at λ_{max} 254 (ε 5130), 259 (5620) and 263 nm (5250).[21] This gives very little information except that this compound would be pale yellow, so reasonable as a dye coupler.

1.4.2.3 ^{1}H NMR

The proton NMR spectrum of the bicyclic tautomer 2-phenyl-6-methyl-3*H*-pyrrolo[1,2-*b*]pyrazole **59** has been quoted as 7.83 (2H), 7.39 (2H), 7.29 (1H), 6.51 (1H), 5.61 (1H), 3.35 (2H) and 2.39 (3H).[20] The first three signals correspond to the five protons around the phenyl substituent, the signals at 6.51 ppm and at 5.61 ppm are those of the pyrrole ring. It can not be deduced from this amount of evidence whether the 4 or 5-proton would have a higher chemical shift. The only signals which can be definitely assigned are the CH_2 group at 3.35 ppm and the methyl group at 2.39 ppm, both of which are typical for these groups in this kind of aromatic environment. The fact that the peak at 3.35 ppm is a singlet shows the CH_2 group has no adjacent protons and so that this species is the 3*H* tautomer.

The tricyclic parent compound **58** has a proton spectrum with peaks at 7.70, 7.62, 7.41, 7.30, 7.15, 6.25 and 3.81 ppm, which have been fully assigned (Figure 2).[21] The first peak corresponds to the pyrazole proton in the 2-position, its chemical shift increased by being adjacent to the 1 nitrogen. The peak of next highest chemical shift is due to the 8 proton, as it is nearest to the bridgehead nitrogen. Next, 7.41 ppm, is the 5 proton, followed by the 7 proton, at 7.30 ppm. Finally on the phenyl ring is the

6 proton, 7.15 ppm, four bonds away from the nitrogen so fairly low in chemical shift. The last of the CH groups is the 3 proton at 6.25 ppm, a more usual five-membered aromatic chemical shift. Finally the CH_2 group has its peak at 3.81 ppm, which is very close to that of the pyrrole analogue **40**.

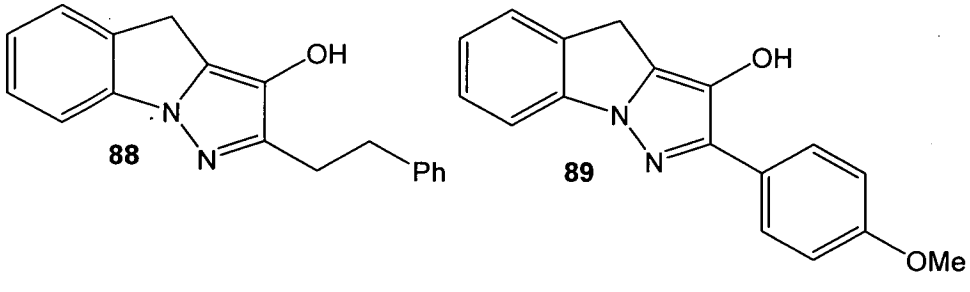


58

Figure 2: ^{1}H NMR shifts of 58

The proton spectrum for the 2-amino derivative **74** is as follows: 7.38-7.26 (3H, Ar-H), 7.04 (H 6), 5.65 (H 3), 3.90 (NH_2) and 3.74 (CH_2).[24] The proton at the 3 position is of particular interest here as its chemical shift has been greatly decreased by the electron donating amino group. Overall it appears that most of the other protons have had their shifts decreased slightly by the presence of this group.

A collection of spectra for different pyrazolo[1,5-*a*]indole derivatives with a hydroxy substituent in the 3 position were also reported, which apparently had to be carried out in deuteriated DMSO rather than chloroform.[27] Compound **89**, with a *para*-methoxyphenyl substituent in the 2 position has peaks assigned as follows: 9.23 (OH), 7.98 (H 2',6'), 7.53 (H 5,8), 7.39 (H 7), 7.18 (H 6), 6.99 (H 3',5'), 3.94 (CH_2) and 3.79 (OMe). The dashed numbers refer to the protons on the aryl substituent, and the signal for H 3' and H 5' is typically low for aromatic protons either side of an electron donating group such as the methoxy.



88 **89**

For the main part of the tricyclic ring system, the chemical shifts are not very different from those in the chloroform spectrum of the parent compound **58**, so it seems reasonable to compare the two. The CH_2 group does not appear to be affected by the hydroxy substituent very much, but it would be interesting to have a spectrum of a compound without the 2 substituent to see how the proton in this position is affected by this electron donating group.

1.4.2.4 ^{13}C NMR

4*H*-Pyrazolo[1,5-*a*]indole **58** has the following ^{13}C spectrum with all chemical shifts assigned: 144.4 (C 8a), 143.7 (C 2), 140.5 (C 3a), 133.6 (C 4a), 127.9 (C 7), 125.8 (C 5), 124.3 (C 6), 110.4 (C 8), 100.5 (C 3) and 28.0 ppm (C 4).[21] Of the three quaternary carbons, 8a and 3a are presumably higher than 4a because they are next to the bridgehead nitrogen, although not by much. Of the tertiary carbons, C 2 has predictably the highest shift being the only one adjacent to a heteroatom, and C 8 and C 3 are the lowest, being two bonds away from heteroatoms.

The amino derivative **74** has a carbon NMR spectrum where the C 2 signal is considerably higher, at 158.8 ppm, due to it now being located between two nitrogen atoms.[24] All other carbons have roughly the same shift except for C 3, which is now much lower at 89.0 ppm, the amino group being strongly electron donating. With the two compounds with the OH group, **88** and **89**, C 2 comes at 142 ppm, similar to the chloroform spectrum of the parent compound **58**, being adjacent to a carbon on the substituent.[27] C 3 is now at a much higher shift, about 130 ppm, as it is now next to the oxygen of the hydroxy substituent.

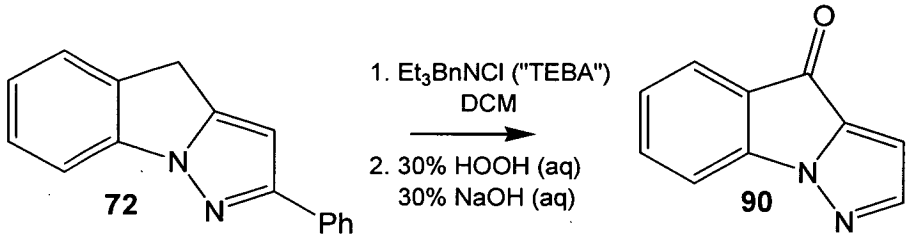
1.4.3 Chemical Reactivity

The only compound found in the literature whose chemistry had been investigated to any degree was the 2-phenyl-4*H*-pyrazolo[1,5-*a*]indole **72**, but fortunately three different reactions were reported.[26] Two of these occurred at the 4-position, obviously the most interesting place when considering these sorts of compounds for potential as dye couplers. The other reaction was a fairly standard methylation of the nitrogen in position 1, in both the parent compound **58** and the phenyl derivative **72**, another place where certain reactions would be expected to occur.

As with the pyrrole series, these compounds were not expected to make good couplers on their own, as the protons are not made sufficiently acidic by conjugation to heteroatoms.

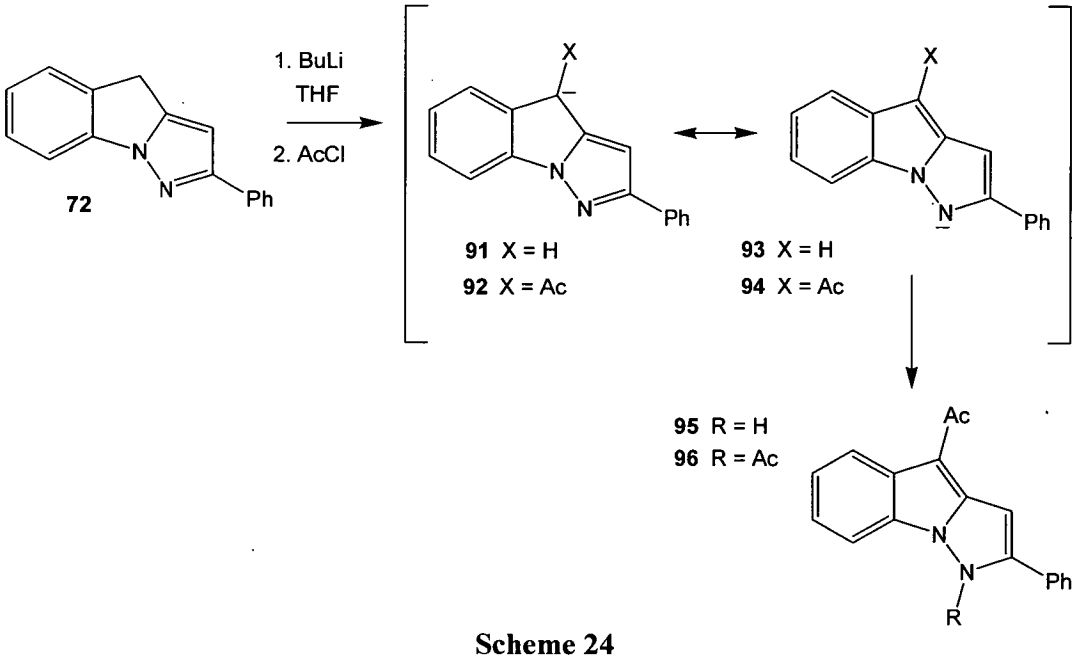
1.4.3.1 Oxidation of the CH_2 Group

According to Scheme 23 2-phenyl-4*H*-pyrazolo[1,5-*a*]indole **72** was reacted with 30% aqueous hydrogen peroxide and 30% sodium hydroxide, using the phase transfer catalyst triethylbenzylammonium chloride in DCM, to introduce a carbonyl group at the 4-position **90**.[26] This could possibly be useful if the carbonyl group could be partially reduced to give an OH, which could be methylated or replaced by a halide to give a good coupling off group, although there are probably easier ways of doing this.



Scheme 23

1.4.3.2 Acylation at the 4 Position

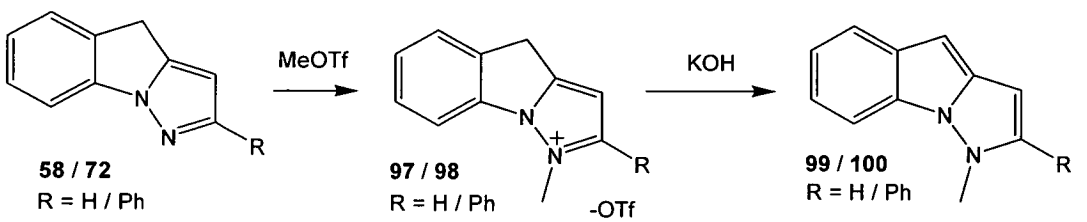


Scheme 24

Butyl lithium was added to a solution of **72** in THF at –78 °C to deprotonate at the 4-position and generate the carbanion intermediate **91** *in situ* (Scheme 24).[26] This is resonance stabilised by conjugation around the pyrazole ring to the 1 nitrogen (**93**). Acylation using acetyl chloride takes place, which initially occurs at the 4-position, and is then followed by further deprotonation to give **92** which resonance stabilises to **94**. Addition of a proton to the 1-position then gives the mono-acylated product **95** (X = H), or further acylation in the same position gives **96** (X = Ac). This might be of use for adding coupling off groups to potential dye couplers when appropriate electrophiles are used, although an acetyl is not a good leaving group and the ring system is now in the 1*H* rather than 4*H* form.

1.4.3.3 Methylation of Nitrogen 1

Addition of methyl triflate to **58**, or the phenyl substituted derivative **72**, gave the quaternary ammonium triflate salts **97** and **98** respectively, which were converted to the 1-methyl-1*H* derivatives by addition of potassium hydroxide **99/100** (Scheme 25).[26] This reaction unfortunately would not be useful for attaching ballasts to dye couplers, as there is no longer an acidic proton in the 4-position necessary for the coupling ability of the ring system.

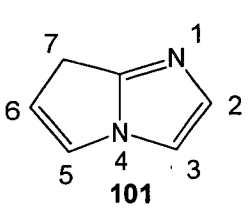


Scheme 25

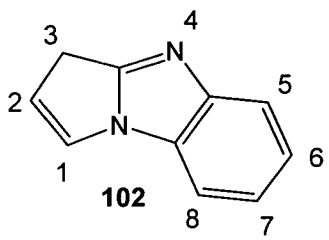
1.5 IMIDAZOLE CONTAINING SYSTEMS

Three classes of compounds containing imidazole rings were found in the literature, with a modest amount of information on derivatives of the bicyclic pyrrolo[1,2-*a*]imidazole **101** and a number of tricyclic pyrrolo[1,2-*a*]benzimidazoles (**102**). In order to increase the scope of the investigation, compounds substituted at what would be the coupling sites were also considered. The numbering schemes of the three

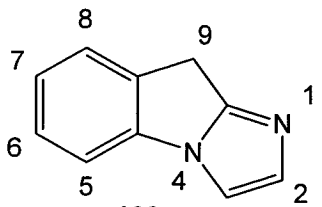
parent compounds are shown below. The only example of imidazolo[1,2-*a*]indoles (**103**) to be found, the species that would fit into the general structure **1**, and so be of most interest as potential dye couplers, features a carbonyl group in the 9-position. An unsubstituted isomeric system analogous to structure **1** was also found, with both heteroatoms in alternative positions.



101



102



103

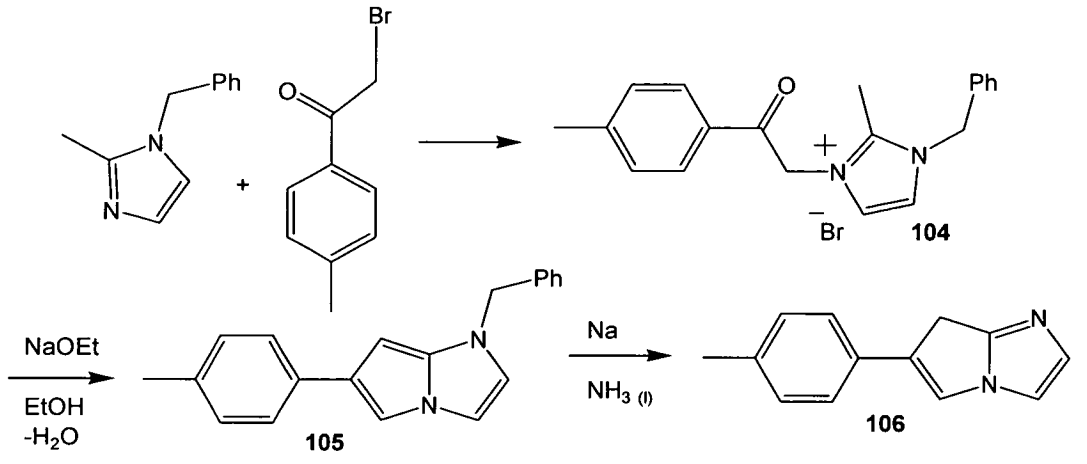
1.5.1 Synthesis of Pyrrolo[1,2-*a*]imidazole Containing Systems

Four different syntheses for various pyrrolo[1,2-*a*]imidazole derivatives were found in the literature, giving compounds ranging from one to four substituents. There were also four different synthetic approaches to pyrrolo[1,2-*a*]benzimidazoles, two of which gave species with free methylene coupling sites. These include examples of formation of the imidazole ring, the pyrrole ring as the final cyclisation step, as well as a reaction where two rings are formed. With the other two systems discovered, featuring outer imidazole rings, it was the central pyrrole ring which was formed in the cyclisation step.

1.5.1.1 Synthesis of Pyrrolo[1,2-*a*]imidazoles

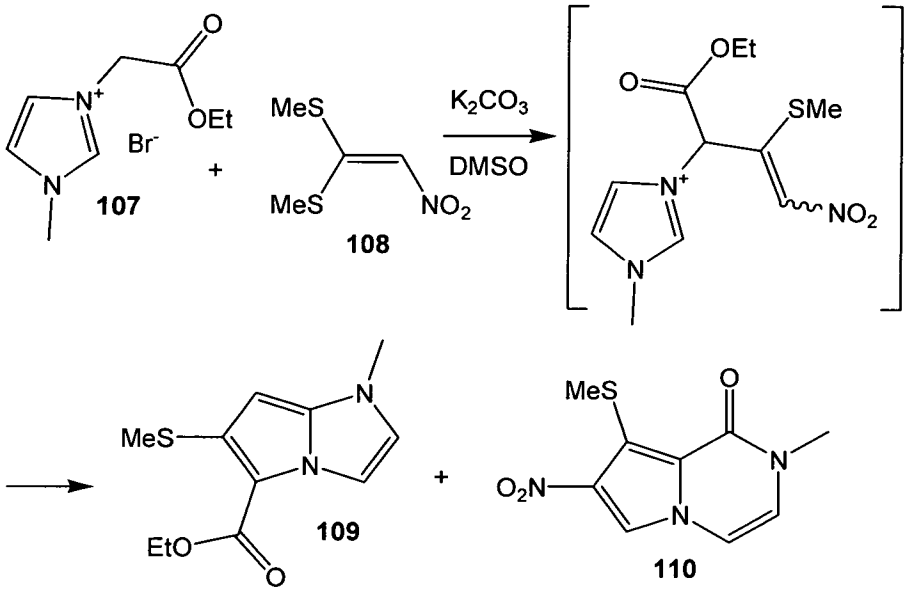
According to Scheme 26, 1-benzyl-2-methylimidazole was reacted with 4-methyl phenacyl bromide, in an unspecified manner, to give the quaternary ammonium salt **104**, where the acyl group has attached to the 3-nitrogen.[28] Addition of sodium ethoxide and ethanol then caused cyclisation to occur, forming the pyrrole ring and giving the *N*-benzyl substituted derivative 6-(4-methylphenyl)-7*H*-pyrrolo[1,2-*a*]imidazole **105** after loss of water. The mechanism for this step involves deprotonation of the imidazole methyl group, whose protons are made acidic by their proximity to the positive nitrogen. The negatively charged carbon then attacks the carbonyl to form a five-membered ring. Sodium and liquid ammonia are then used to

remove the benzyl group and give 6-(4-methylphenyl)-7*H*-pyrrolo[1,2-*a*]imidazole **106**.



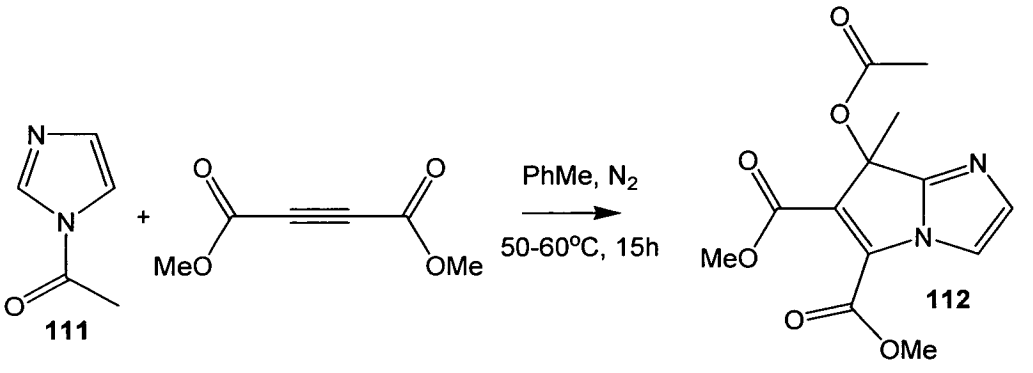
Scheme 26

A trisubstituted pyrrolo[1,2-*a*]imidazole was synthesised in 1991 by Matsuda and his team *via* a one-step reaction of the imidazolium bromide salt **107** with nitroketene dithioacetal **108** in the presence of potassium carbonate, in DMSO stirring at room temperature for 3 days (Scheme 27).[29] The base deprotonates **107** between the ester and the quaternary ammonium cation, enabling attack of **108** at the thiol end with loss of one methylthiol group, resulting in the intermediate shown. Further deprotonation in the same position then leads to electrocyclisation followed by loss of the nitro group to give the pyrrolo[1,2-*a*]imidazole product **109** in 30% yield. Also obtained in 30% yield was the pyrrolo[1,2-*a*]pyrazine by-product **110**, in which the nitro group is not lost, but the imidazole ring opens and the resulting secondary amine then attacks the carbonyl group to form the pyrazine ring with loss of the ethoxy group.



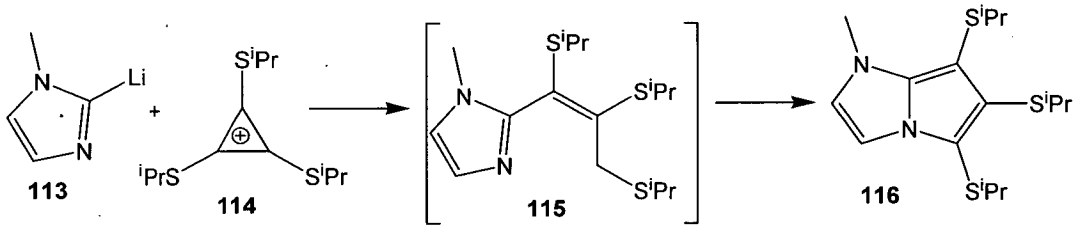
Scheme 27

A year later a German team published a loosely related synthesis resulting in a pyrrolo[1,2-*a*]imidazole disubstituted at the 7-position.[30] Scheme 28 summarises how the reaction of the acylimidazole **111** with DMAD (dimethyl acetylenedicarboxylate) in toluene under an atmosphere of nitrogen, with heating between 50 and 60 °C for 15 h, gives the heavily acyl substituted species **112**. The mechanism for this reaction commences with nucleophilic attack of the imidazole lone pair of electrons on the DMAD acetylene group, leading to a 1,2-diene imidazolium salt. The diene then attacks another acylimidazole **111** at the carbonyl group with loss of imidazole. Cyclisation then occurs between the imidazolium salt and the acyl group, followed by attack of the acyl by the resulting negatively charged oxygen on the pyrrole ring; the acyl is transferred from the imidazole to the pyrrole ring and the charge neutralised to give the final product **112**.



Scheme 28

A final synthesis of one of these compounds was reported about the same time, and is rather unusual as it involves a cyclopropenyl cation to form a pyrrole ring adjacent to the imidazole.[31] A methylimidazole is lithiated in the 2-position to give **113**, as shown in Scheme 29, allowing this position to attack tris(methylthio)cyclopropenyl cation **114** to give the intermediate **115**. The lone electron pair on the free imidazole nitrogen atom can then attack the end of the propene chain to permit cyclisation, before redistribution of electron density around the newly formed pyrrole ring provides the product **116**. With the coupling site blocked this species would clearly be of no use as a coupler, and with the three methylthio groups it looks rather too heavily substituted to have any useful applications.

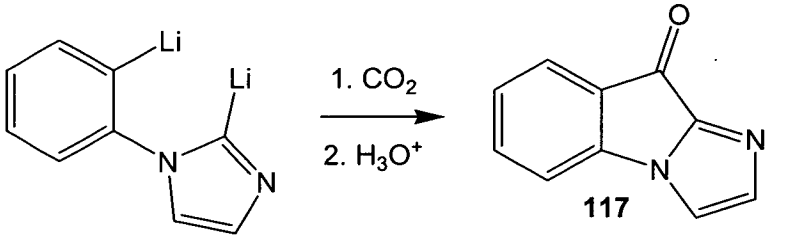


Scheme 29

1.5.1.2 An Imidazolo[1,2-*a*]indole

Very little information was provided on this lone example of the family of imidazole containing compounds which fit the structure of **1**, and this one synthesis was reported back in the 1950s.[32] 1-Phenylimidazole was lithiated with *n*-butyl lithium, and then this was reacted with carbon dioxide, followed by acidification, with the intention of producing carboxylic acids with the functional groups in positions not normally available (Scheme 30). But in this case it was found that both lithium substituted sites

attacked the same carbonyl group, resulting in cyclisation to give imidazolo[1,2-*a*]indole **117**. This could be a useful route to this family of compounds, as the carbonyl group could easily be reduced with a metal hydride, although the paper does not state if this apparently accidental result was easily reproducible.

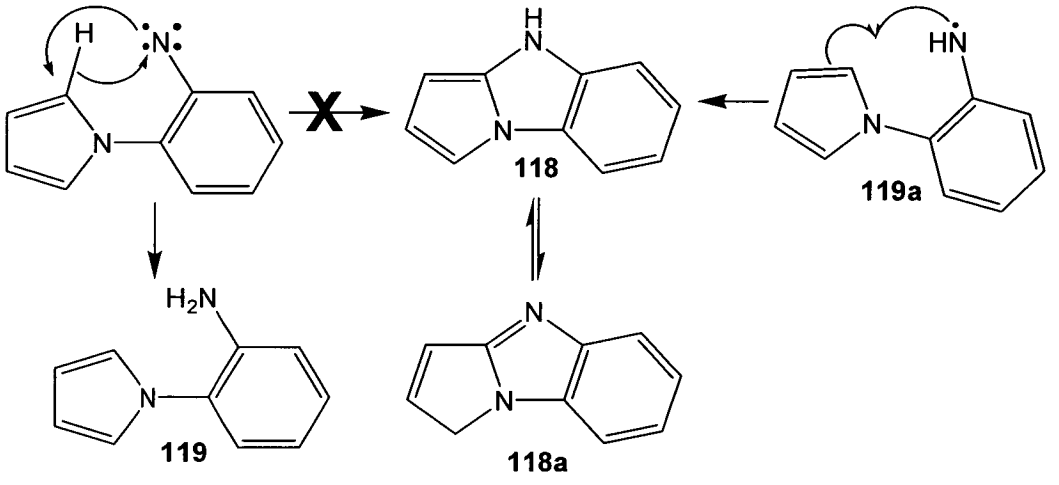


Scheme 30

1.5.1.3 A Pyrrolo[1,2-*a*]benzimidazole, Cyclisation of the Imidazole Ring

The only paper to report the synthesis of the unsubstituted parent compound **102**, in the 4*H* tautomeric form, was that of Lindley *et al.* in 1977, concerning cyclisations of various singlet and triplet nitrenes.[33] They had found carbazole could be synthesised from heating 2-substituted biphenyls, with nitro or azido groups used to generate the nitrenes. Apparently, this method was used successfully to form 4*H*-pyrrolo[1,2-*a*]benzimidazole **118** from a substituted phenylpyrrole. According to the mechanism in Scheme 31 the electrophilic nitrene inserts into the 2-CH bond of the pyrrole ring to effect cyclisation.

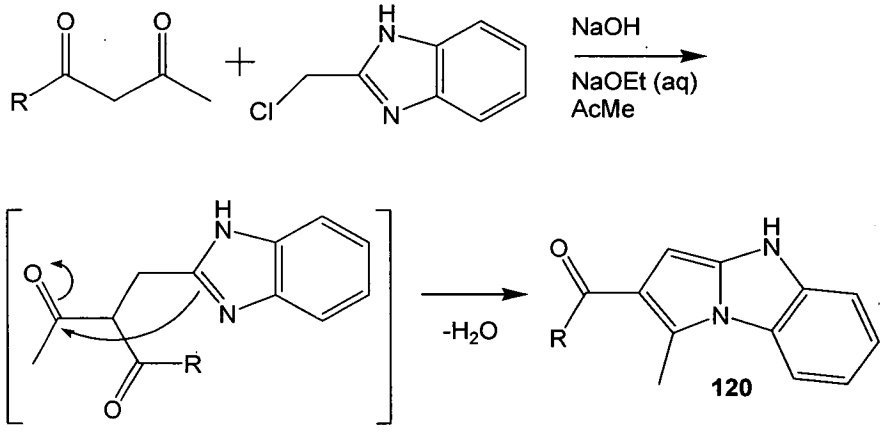
However, unpublished work suggests that the product obtained from this reaction does not have the properties expected of the cyclised system, and that it is more likely to be the amine **119**, formed by hydrogen capture from the solvent.[34] The proton NMR spectra and melting points of **118** and the pyrrolylaniline **119** are both close enough to raise doubts as to whether 4*H*-pyrrolo[1,2-*a*]benzimidazole **118** has ever actually been produced in its unsubstituted form. More recently though, an aminyl radical **119a** generated by a pyrolysis experiment has been shown to give a more stable tautomer **118a**;[18] presumably this would have no coupling ability.



Scheme 31

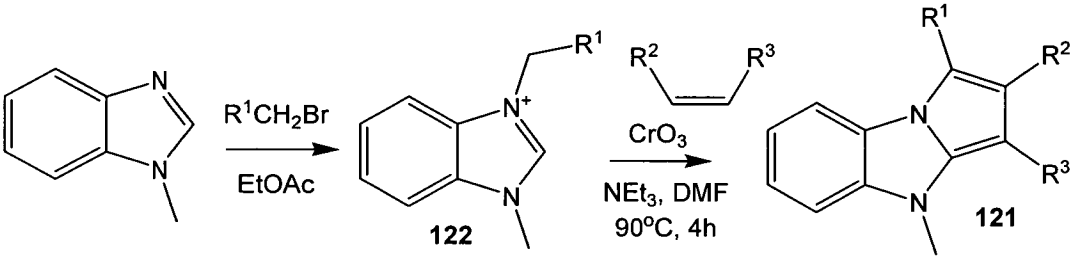
1.5.1.4 Cyclisation of the Pyrrole Ring

In 1993 Popov reported the synthesis of 2-acetyl- and 2-benzoyl-3-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazole **120** (R = Me or Ph) (Scheme 32).[35] 2-α-Chloromethylbenzimidazole was reacted with pentane-2,4-dione or 1-phenylbutane-1,3-dione in acetone using aqueous sodium hydroxide and sodium ethoxide as bases. These removed a central acidic proton from the dione which gave a carbanion, which displaced the chloride by nucleophilic substitution. Electron density from the outer double bond of the imidazole ring then attacked the methyl-substituted carbonyl group to effect cyclisation. Loss of water gave **120** (R = Me or Ph), the tautomeric form of the main family of compounds.



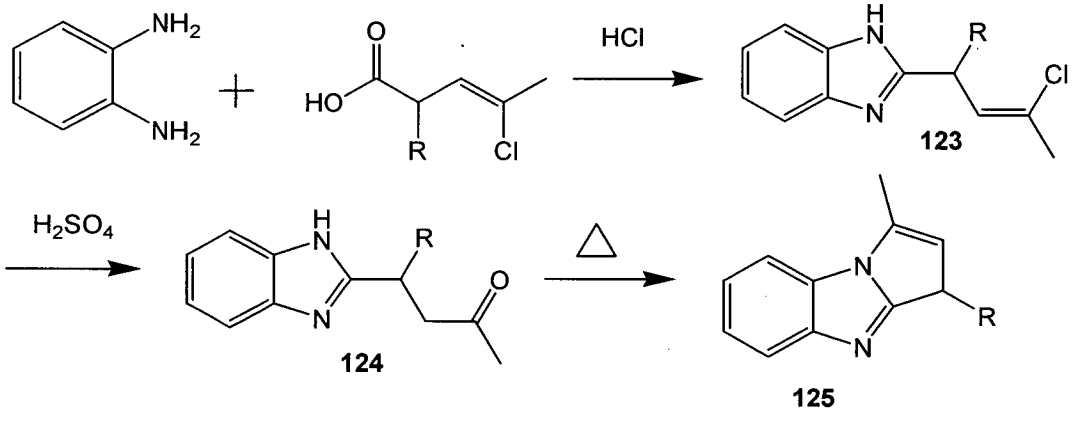
Scheme 32

In a similar synthesis to that of Matsuda when producing **109**, the Chinese team of Wang and Hu have four years ago reported the synthesis of a group of trisubstituted pyrrolo[1,2-*a*]benzimidazoles **121**.[36] Scheme 33 shows how 1-methylbenzimidazole was quaternised with a variety of carbonyl containing bromide species to give the salt **122** (R^1 = COMe, COPh or CO_2Et). This was then reacted with a range of alkenes (R^2 = H, CO_2Et; R^3 = CN, CO_2Me, CO_2Et) in the presence of chromium trioxide and triethylamine in DMF to give 18 different examples of **121** in yields ranging from 26 to 65%.



Scheme 33

1.5.1.5 Cyclisation of Both Five-membered Rings



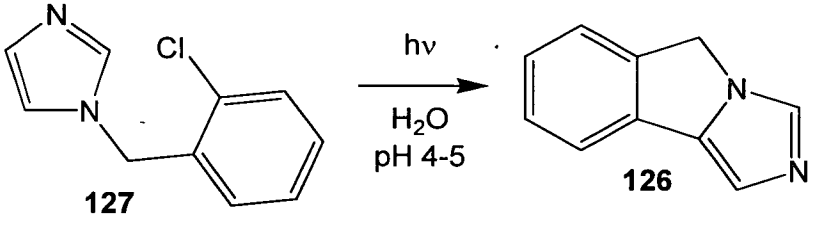
Scheme 34

A synthetic procedure starting with only the phenyl ring and involving cyclisation of both five-membered rings was reported according to Scheme 34.[37] *o*-Phenylenediamine and 4-chloropent-3-enoic acid were heated under reflux in concentrated hydrochloric acid to give 2-chlorocrotyl benzimidazole **123**. Addition of concentrated sulfuric acid hydrolysed the chloride group to **124**, and then further

heating caused cyclisation to occur to give the final product **125**. The procedure was compatible with R = H, Me, Et, Pr and Bu.

1.5.1.6 An Isomeric System

The parent compound of an isomeric system, 5*H*-imidazolo[5,1-*a*]isoindole **126**, was reported in 1995 by a Korean team doing work on intramolecular photocyclisation reactions.[38] Using a water-cooled quartz photoreactor 1-(2-chlorobenzyl)imidazole **127** was irradiated with a mercury lamp, in triple distilled water under an argon atmosphere (Scheme 35). Adjusting the pH of the reaction mixture to ~4-5 gave the product **126** in 40% yield. This system would be of no use as a coupler, having a heteroatom adjacent to what would be the coupling site, as this is in the wrong position for conjugation to the methylene anion after deprotonation.



Scheme 35

1.5.2 Physical Properties

1.5.2.1 IR Spectroscopy

The only really significant IR data found in the literature about any of this family of imidazole containing compounds was that of Popov's acetyl and benzoyl substituted benzimidazole systems **120**.[35] In this report, only the N-H stretching frequency of the benzoyl substituted system was reported, being loosely quoted as 3000 – 3200 cm^{-1}, which is typical for cyclic secondary amine N-H bonds. Presumably, the frequency of the equivalent bond on the acetyl-substituted compound would be about the same, as the substituent is quite far from the NH group and not conjugated. Other than that, only the carbonyl C=O frequencies were quoted, 1712 cm^{-1} in the acetyl group and 1678 cm^{-1} in the benzoyl. The adjacent phenyl group lowers the wavenumber as the carbonyl electron density is delocalised into the aromatic ring. Both groups possibly also display some conjugation with the adjacent pyrrole ring.

1.5.2.2 UV-vis

The only UV-vis data on the main group of imidazole containing compounds to be found in the literature tends to concern the more heavily substituted derivatives, therefore is not extremely useful. Matsuda's ethoxycarbonyl pyrrolo[1,2-*a*]imidazole **109** was analysed in ethanol solution showing just one λ_{max} of 318 nm (ε 5,400), which is possibly a higher absorption maximum than would be expected for a less substituted analogue and probably faintly pale yellow in colour.[29] The spectrum of the isopropylthiol species **116** was reported in acetonitrile solution, with three absorption maxima all in the UV region, and with significantly higher extinction coefficients; λ_{max} 307 (ε 12,900), 255 (10,000) and 212 (20,200) nm.[31]

UV-vis spectra for the isomeric system 5*H*-imidazolo[5,1-*a*]isoindole **126**, have also been reported; in methanol λ_{max} = 276 nm (ε 4,300) and in acetonitrile λ_{max} = 293 nm (no extinction coefficient reported).[38] The absorption wavelength looks fairly typical for the small number of parent compounds reported so far in this thesis, although the fact there is only one peak is not typical. Again, this is a largely colourless compound.

1.5.2.3 ^{1}H NMR

The only proton NMR data quoted for any of the pyrrolo[1,2-*a*]imidazole systems discussed earlier was for that of 6-(2-methylphenyl)-7*H*-pyrrolo[1,2-*a*]imidazole **106**.[28] The methyl group attached to the phenyl substituent has a chemical shift of 2.64 ppm, fairly standard for methyl groups on an aromatic ring, somewhat higher than aliphatic methyl protons. Next is the singlet corresponding to the CH_2 group in the 7 position, at 4.70 ppm, much higher than usual because of the interaction with the imidazole N in the 1 position. After this there is just a large multiplet from 6.7 to 7.5 ppm corresponding to the remaining protons, around the pyrroloimidazole rings and the toluyl group. These are standard values for phenyl protons, but the other shifts are quite high for the protons on the five membered rings, in the 2, 3 and 5 positions, as these are all adjacent to electronegative nitrogen heteroatoms.

Proton NMR data for the isomeric system, 5*H*-imidazolo[5,1-*a*]isoindole **126**, has also been reported and partially assigned. In a DMSO solution the methylene proton pair have a chemical shift of 5.03 ppm, considerably higher than those in the usual structures due to the proximity of an electronegative heteroatom.[38] On the imidazole

ring, the proton in the 3-position is highly shifted at 7.46 ppm, between both nitrogen atoms, while the 1-proton, next to just one nitrogen atom, is somewhat lower at 7.10 ppm. On the phenyl ring peak assignations are more subject to interpretation, having fairly typical values due to lack of substituents. The two highest shifts are unsurprisingly those of the 9-proton (7.68 ppm) and the 6-proton (7.58 ppm), both coming under the influence of the pyrrole ring.

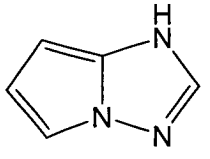
1.5.2.4 ^{13}C NMR

No ^{13}C NMR data were found in the literature.

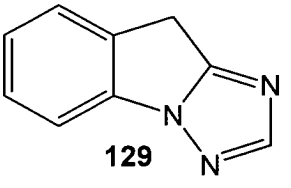
1.5.3 Chemical Reactivity

No chemical reactions of 7*H*-pyrrolo[1,2-*a*]imidazole containing systems were found in the literature. It is suspected that the CH_2 group would be very suitable for coupling with a typical developer compound, probably as the electronegative imidazole nitrogen atom in the 1 position would make the protons on the 7 position more acidic, and so more easily removed than in the pyrazole compounds.

1.6 TRIAZOLE CONTAINING SYSTEMS



128



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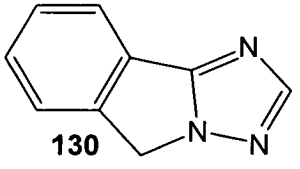


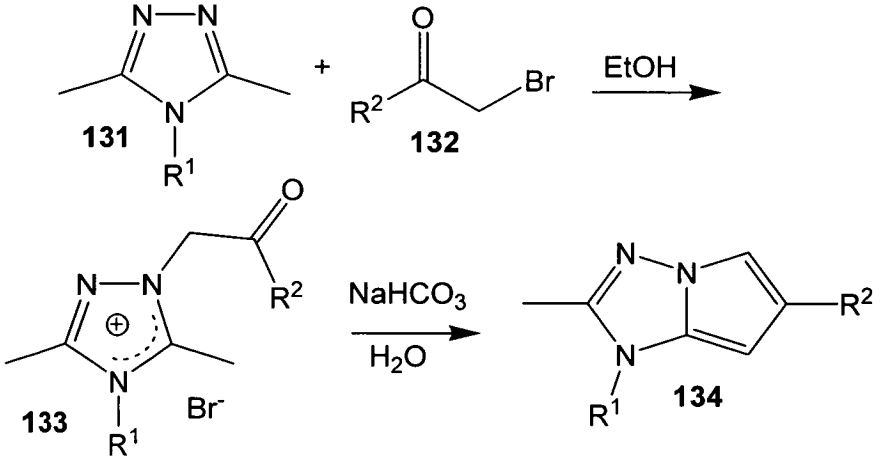
130

According to the general structure of system **1**, initially just systems containing pyrrolo[1,2-*b*][1,2,4]triazole moieties were investigated (**128** and **129**), with the adjacent nitrogen atoms of the pyrazole and the nitrogen conjugated to the CH_2 group as in the imidazoles. It is estimated that three nitrogen atoms would lead to more effective coupling reactions. As there was not a huge quantity of relevant information in the literature a variety of isomeric systems were also investigated, with papers found on a number of triazolo[5,1-*a*]isoindoles **130** and one example of a triazolo[4,3-*a*]indole.

1.6.1 Synthesis of Pyrrolo[1,2,4]triazole Containing Systems

1.6.1.1 Pyrrolo[1,2-*b*][1,2,4]triazoles

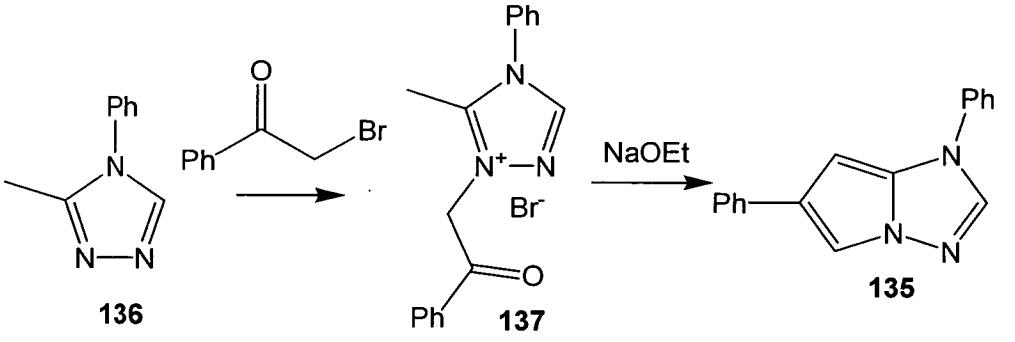
Three papers reported syntheses of this family of compounds, two employing very similar methods to reach di- and trisubstituted derivatives and the other forming a rather unusual oxime species. The first report, by H.G.O. Becker and team in 1973, concerns a range of 1,2,6-trisubstituted species, which may be unable to couple as the 1-nitrogen atom is substituted.[39] According to Scheme 36, the 1-substituted dimethyltriazole **131** (R^1 = Me, Ph) was reacted with the bromoketones **132** (R^2 = Ph, 4-BrC_6H_4, 4-ClC_6H_4), with heating in ethanol, to give the quaternary salts **133**, after the 1-nitrogen on the triazole displaces the bromide. Reaction of the salt with sodium bicarbonate then permits cyclisation, with the base deprotonating the 5-methyl group, which can then attack the carbonyl to form the pyrrole ring. Loss of water and another deprotonation to neutralise the positive charge then gives pyrrolo[1,2-*b*][1,2,4]triazoles **134**. When this second step was carried out with a stronger base, sodium hydroxide, cyclisation did not occur and a hydroxylation of the 5-position resulted.



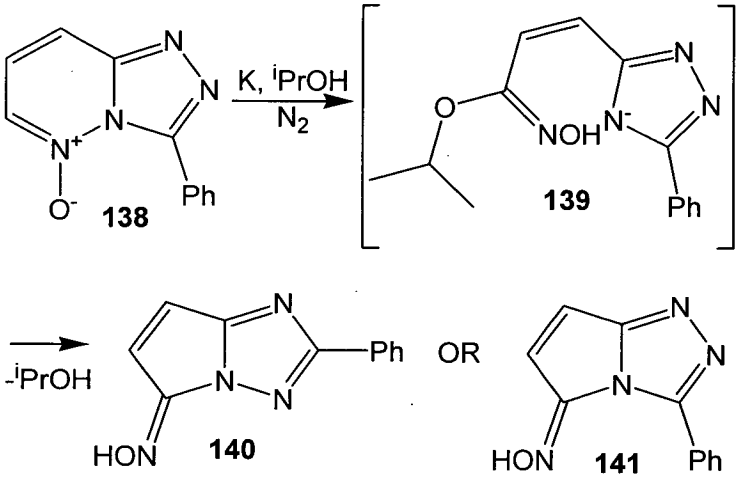
Scheme 36

A short time later, the Ukrainians, Babichev and Kovtunenko, carried out a similar synthesis to give 1,6-diphenyl-1*H*-pyrrolo[1,2-*b*][1,2,4]triazole **135** (Scheme 37).[40] This time the starting material was 3-methyl-4-phenyl-4*H*-[1,2,4]triazole **136**, reacted

with bromoacetophenone, and then the quaternary ammonium salt **137** was reacted with the mild base sodium ethanoate to give **135** in a moderate yield.



Scheme 37



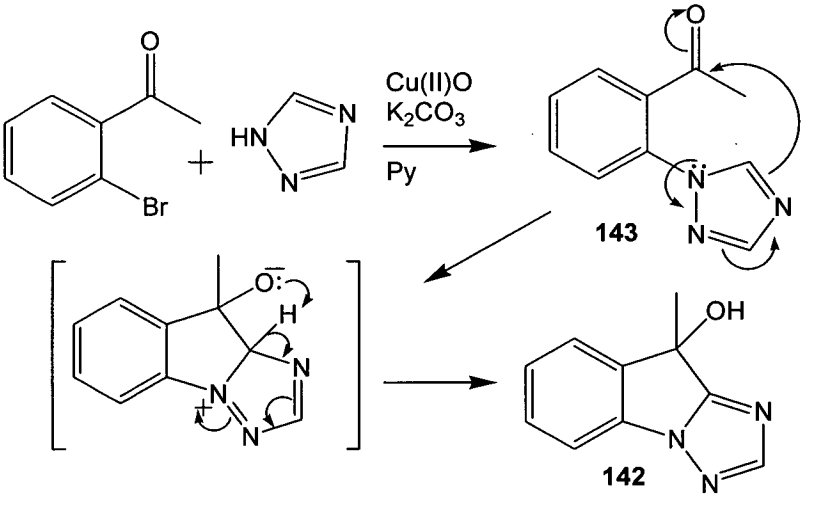
Scheme 38

A third synthesis, giving an oxime substituted species, has also been reported, although the exact isomer of the product was not established.[41] Scheme 38 shows how imidazo[1,2-*b*]pyridazine-5-oxide **138** was reacted with potassium iso-propoxide, generated *in situ* from potassium metal dissolved in isopropyl alcohol, under an atmosphere of nitrogen. The isopropylate ion attacks the pyridazine ring next to the positively charged quaternary site, neutralising the charge and opening the ring to give the intermediate **139**. This can then react in two ways as there is free rotation around the bond attached to the triazole ring, so either heteroatom can attack the oxime site to give cyclisation with loss of the isopropylate group. Spectroscopic

data recorded at the time were insufficient to determine which isomer had been obtained, either 2-phenylpyrrolo[1,2-*b*][1,2,4]triazol-5-one oxime **140** or 3-phenylpyrrolo[2,1-*c*][1,2,4]triazol-5-one oxime **141**.

1.6.1.2 The Disubstituted Triazolo[1,5-*a*]indole

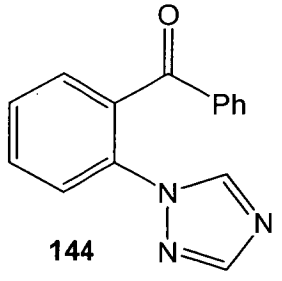
In 1968, M Khan and his team reported the first synthesis of this type of compound, the doubly substituted 9-hydroxy-9-methyl-9*H*-triazolo[1,5-*a*]indole **142**.[42] Scheme 39 shows how they reacted *o*-bromoacetophenone with 1,2,4-triazole using the Ullmann condensation with copper (II) oxide and potassium carbonate in pyridine, heated for two days. Their expected product, 1-(*o*-acetylphenyl)-1,2,4-triazole **143** was obtained in 37% yield, but then the more interesting by-product **142** was isolated by alumina chromatography in a 23% yield. The intermediate in the reaction scheme shows the mechanism they suggested, where the lone electron pair from the substituted nitrogen moves around the triazole ring anticlockwise until the double bond next to the 4 N comes out to attack the carbonyl, thus forming the pyrrole ring. The oxygen anion then abstracts the tertiary proton, returning the electron density back around the triazole ring finally to give **142**.



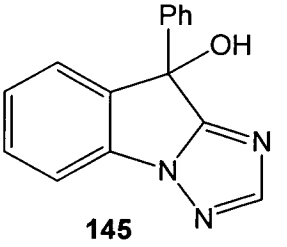
Scheme 39

At the start of the nineties the Australian team of Rosevear and Wilshire carried out a series of similar reactions with *o*-fluoroacetophenone, *o*-fluorobenzophenone and *o*-fluorobenzaldehyde.[43] *o*-Fluoroacetophenone reacted with 1,2,4 triazole and K_2CO_3, this time in DMSO without the copper oxide, to give **143** (13%) and **142** (16%). A

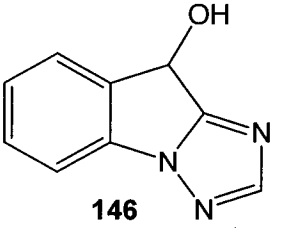
phenyl derivative of **142** was formed in the same way using *o*-fluorobenzophenone, giving the intended triazolylbenzophenone **144** in 60% yield and the tricycle 9-hydroxy-9-phenyl-9*H*-triazolo[1,5-*a*]indole **145** in 10% yield. It appears the main product was formed in much greater yield due to the carbonyl carbon being made much less electrophilic by the phenyl group, therefore less likely to cyclise. When *o*-fluorobenzaldehyde was used, with the intention of forming a derivative with just the OH group **146**, no cyclisation product was obtained, just the triazolyl benzaldehyde product in 17% yield and an unexpected benzoic acid analogue in 28% yield. A control experiment showed that the reactive benzaldehyde was cyclising, which resulted in a ketone, which was then hydrolysed to cause ring opening to give the benzoic acid.



144

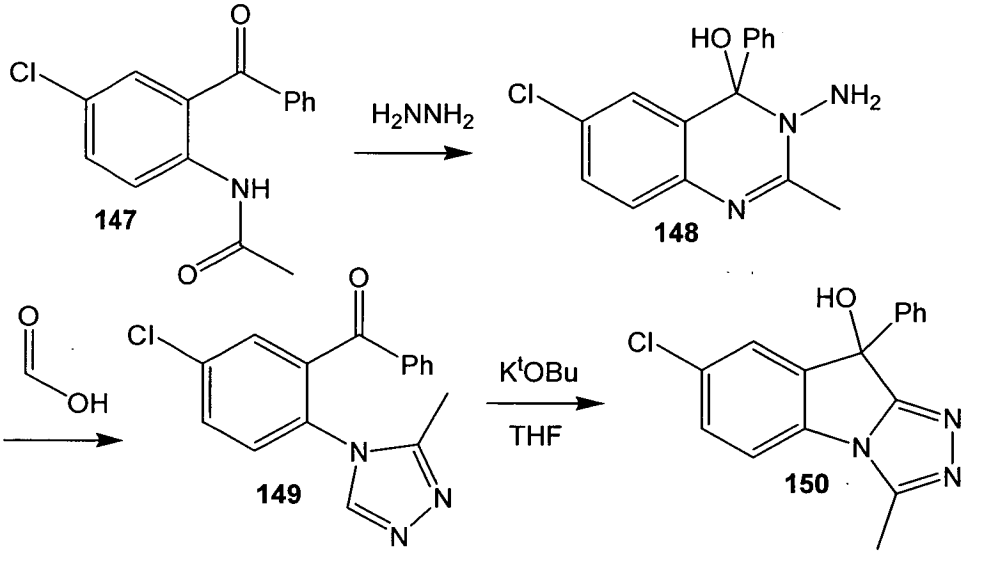


145



146

1.6.1.3 An Isomeric Triazolo[4,3-*a*[indole

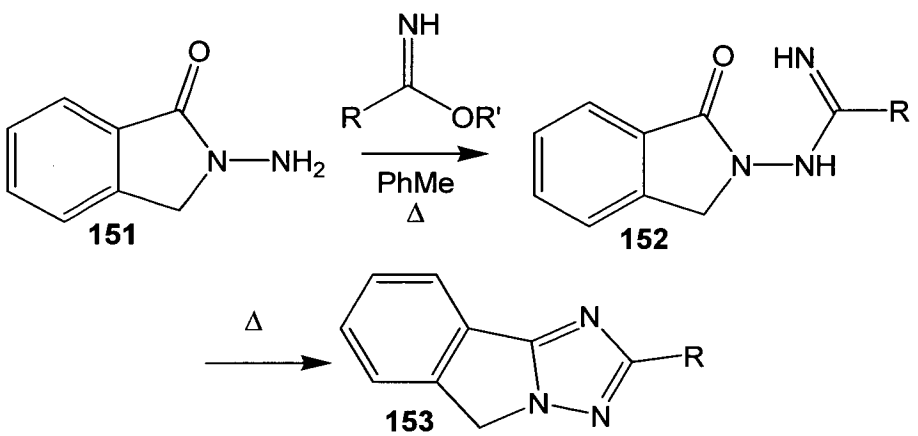


Scheme 40

A heavily substituted triazolo[4,3-*a*]indole species was reported by an American team in the mid-1970s, as demonstrated in Scheme 40.[44] Following prior research they reacted the benzophenone **147** with hydrazine to give the quinazoline **148** by a nucleophilic attack of one nitrogen atom to both carbonyl groups. This was then reacted with formic acid to give the triazole **149**, and then the original work discussed in this paper involved adding potassium *tert*-butoxide to a solution of **149** in THF and stirring at room temperature for 3 hours under an atmosphere of nitrogen. This procedure effects cyclisation by deprotonating the triazole ring which then leads to attack of the ketone to form the central pyrrole ring, resulting in 7-chloro-9-hydroxy-3-methyl-9-phenyl-9*H*-triazolo[4,3-*a*]indole **150**.

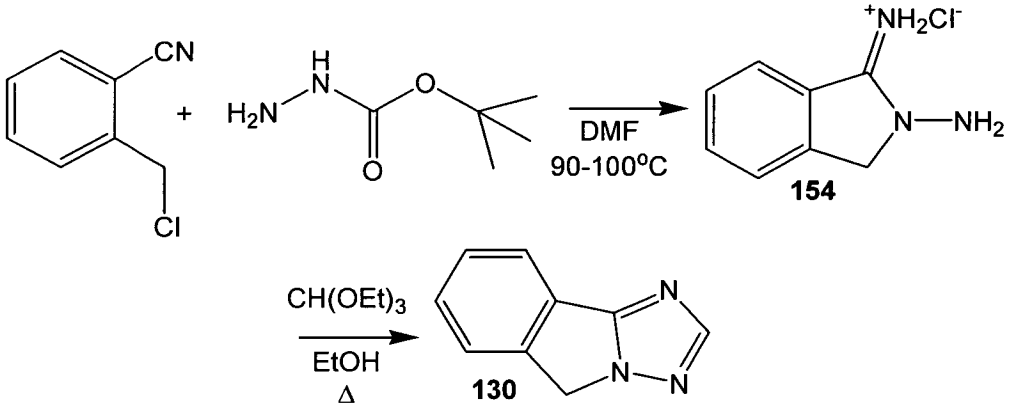
1.6.1.4 Triazolo[5,1-*a*]isoindoles

This family of compounds appears to have been more extensively researched, more likely in the industrial sector judging from the number of patents reported, and a large amount of these data have been conveniently summarised in one review published recently.[45] Scheme 41 shows how the parent system, 5*H*-1,2,4-triazolo[5,1-*a*]isoindole **130**, and 2-substituted derivatives were initially formed in the early 1970s by reaction of the aminoisoindolone **151** with a range of imidic esters in toluene with heating.[46] Further heating of the intermediate imine species **152** then leads to cyclisation, *via* attack of the imine on the carbonyl and subsequent loss of water, to give the triazolo[5,1-*a*]isoindoles **153**. Apparently 25 compounds of type **153** have been reported (R = H, alkyl, aryl), with yields ranging from 39% to 77% (R = Ph).

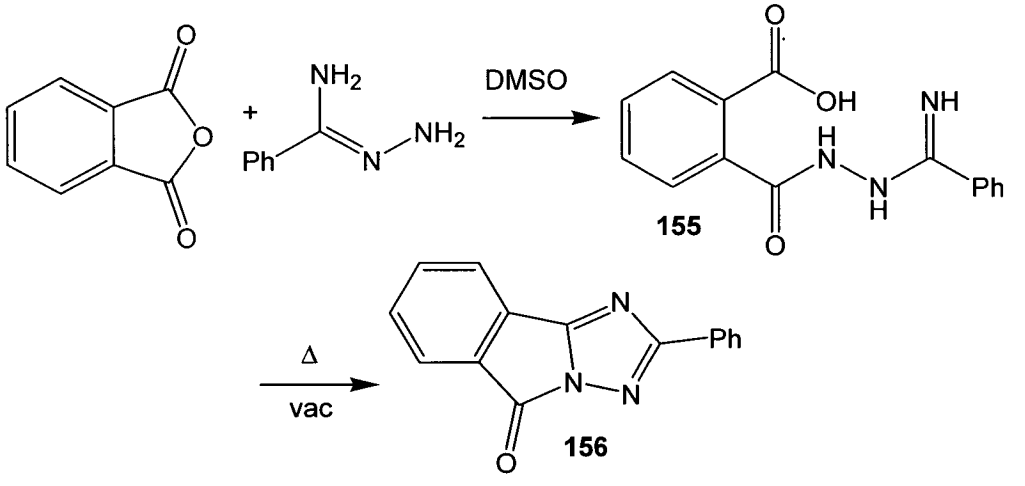


Scheme 41

An alternative method, giving just the parent compound 5*H*-1,2,4-triazolo[5,1-*a*]isoindole **130**, was reported by Babichev, starting with *o*-chloromethylbenzonitrile and reacting it with *tert*-butoxycarbonylhydrazine in DMF at 90-100 °C (Scheme 42).[47] The resulting imide salt **154** was then treated with triethyl orthoformate and heated in ethanol to give **130** in 32% yield.



Scheme 42



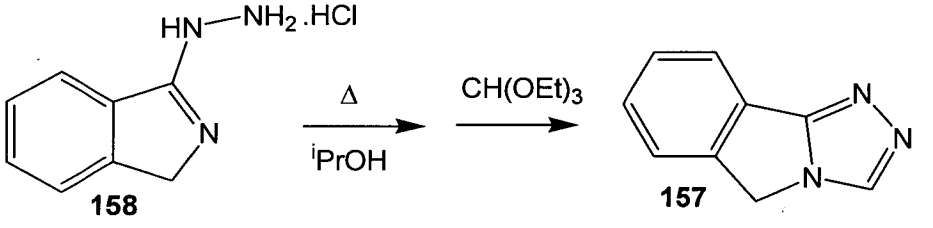
Scheme 43

A very different route to a triazolo[5,1-*a*]isoindole species was reported in which cyclisation of both five-membered rings occurs in the same step to give a carbonyl derivative.[48] As shown in Scheme 43, phthalic anhydride was reacted with benzohydrazide imide in dimethylsulfoxide to give the acylation product **155**. Heating of **155** under vacuum caused a double cyclisation to give 2-phenyl-1,2,4-

triazolo[5,1-*a*]isoindol-5-one **156**, the mechanism possibly proceeding *via* imine attack on the amide carbonyl to form the triazole ring, followed by loss of water and then triazole attack on the acid group to give the central pyrrolone ring.

1.6.1.5 Triazolo[3,4-*a*]isoindole

Babichev also published a synthesis to an isomer of the previously discussed triazolo[5,1-*a*]isoindole **130**, 5*H*-1,2,4-triazolo[3,4-*a*]isoindole **157** in which a nitrogen atom has been moved from the 3- to the 2-position.[49] Scheme 44 shows how (3*H*-isoindol-1-yl)hydrazine hydrochloride **158** was heated in isopropyl alcohol and then condensed with triethyl orthoformate to give the tricyclic product **157**. After neutralisation of the salt, the terminal amine on the hydrazine attacks the triethyl orthoformate with loss of ethanol. This is then followed by delocalisation of electron density from the central nitrogen towards the five-membered ring to allow the isoindole nitrogen atom to attack the acetal group and form the triazole ring, with loss of the second ethoxy group. Loss of the third ethoxy group then gives full aromaticity to the triazole ring to give the product **157**.



Scheme 44

1.6.2 Physical Properties

1.6.2.1 IR Spectroscopy

No IR spectroscopy data was found anywhere in the literature.

1.6.2.2 UV – vis

Becker published UV-vis results for all of his pyrrolo[1,2-*b*][1,2,4]triazoles **134**, with absorption maxima and extinction coefficients quoted for methanol solutions, plus others in ethanol or propanol.[39] Methanol solutions generally had λ_{max} values around 220 nm and extinction coefficients from 5000 to 10,000, while in the other solvents

the values were often over 270 nm (ε ~15,000). To compare two examples, **134** where R^1 and R^2 = Ph had λ_{max} = 220 nm (ε 6,500) while the product with R^1 = Ph and R^2 = 4-BrC_6H_4 had λ_{max} = 224 nm. And when R^1 = Me and R^2 = 4-BrC_6H_4, λ_{max} is again 220 nm, the methyl surprisingly having the same effect as a phenyl group. The difference here is the higher extinction coefficient, 9,100, although reasons for the higher figure are unclear.

UV-vis data for the triazolo[4,3-*a*]indole compound **150** was also reported; in isopropyl alcohol it showed four absorption maxima, 294 (ε 700), 284 (1,100), 252 (10,150) and 207 nm (46,600).[44] These are all in the typical range of compounds discussed in this introduction section, colourless to pale yellow, but it is interesting to note the large extinction coefficient for the peak at 207 nm. Presumably the four very different substituents on this compound give rise to the large number of peaks; as none of them are conjugated to the triazole ring the λ_{max} values are typically low.

1.6.2.3 ^{1}H NMR

The three types of pyrrolo[1,2-*b*][1,2,4]triazole compounds discussed in the previous section have proton NMR spectra reported, although the spectrum quoted for the oxime **140/141** in DMSO features just two multiplets and one singlet, with no integral data so assigning these peaks is not really possible.[41] Compound **134**, where R^1 = Ph and R^2 = 4-BrC_6H_4, was recorded in carbon disulfide and had a peak at 5.47 ppm for the proton in the 7-position, and a peak at 6.94 ppm for the 5-proton.[39] Evidently the aryl group lowers the shift of the 7-proton, while the 5-proton's proximity to the bridgehead nitrogen leads to a much higher chemical shift. The values for the phenyl protons and the methyl group are all fairly typically for substituents on heterocyclic systems.

Babichev and Kovtunenko reported a proton spectrum for their compound 1,6-diphenyl-1*H*-pyrrolo[1,2-*b*][1,2,4]triazole **135** in carbon tetrachloride, in which the 7-proton has a peak at 5.96 ppm and the 5-proton a peak at 7.18 ppm, which are probably analogous to the CS_2 results for **134**, as the only difference is the 4-bromo group.[40] The proton in the 2-position has a peak with a high shift up at 7.79 ppm, being between two nitrogen heteroatoms it is clearly highly deshielded.

Khan reported an incomplete proton NMR spectrum for 9-hydroxy-9-methyl-9*H*-triazolo[1,5-*a*]indole **142** carried out in deuteriated dimethyloxide.[42] The proton on the hydroxy group was reported at 6.33 ppm, which appears to reflect this group's proximity to the highly electron withdrawing triazole ring. The chemical shift of the methyl group is 1.68 ppm, fairly low being next to the electron donating hydroxy group. The single proton on the triazole ring, that at C 2, was reported as 8.17 ppm, which is fairly high for a proton on a five membered aromatic ring, because it is between two electronegative heteroatoms. After that there are just the four phenyl protons, which were identified together by a multiplet between 7.25 and 7.70 ppm, apparently indicating very little effect by the triazole ring.

Rosevear and Wilshire quoted an even less complete pair of spectra for their phenyl derivative **145** as well as the methyl analogue **142**, and then only the chemical shifts for the two 9-substituents.[43] As before the spectra were run in DMSO, the OH peak in **142** almost the same at 6.36 ppm, and the methyl peak at 1.67 ppm, possibly influenced by the electron donating hydroxy group. The two *ortho* protons on the phenyl ring of **145** are quoted as 8.29 ppm, which suggests that the main ring system may be quite electron withdrawing.

1.6.2.4 ^{13}C NMR

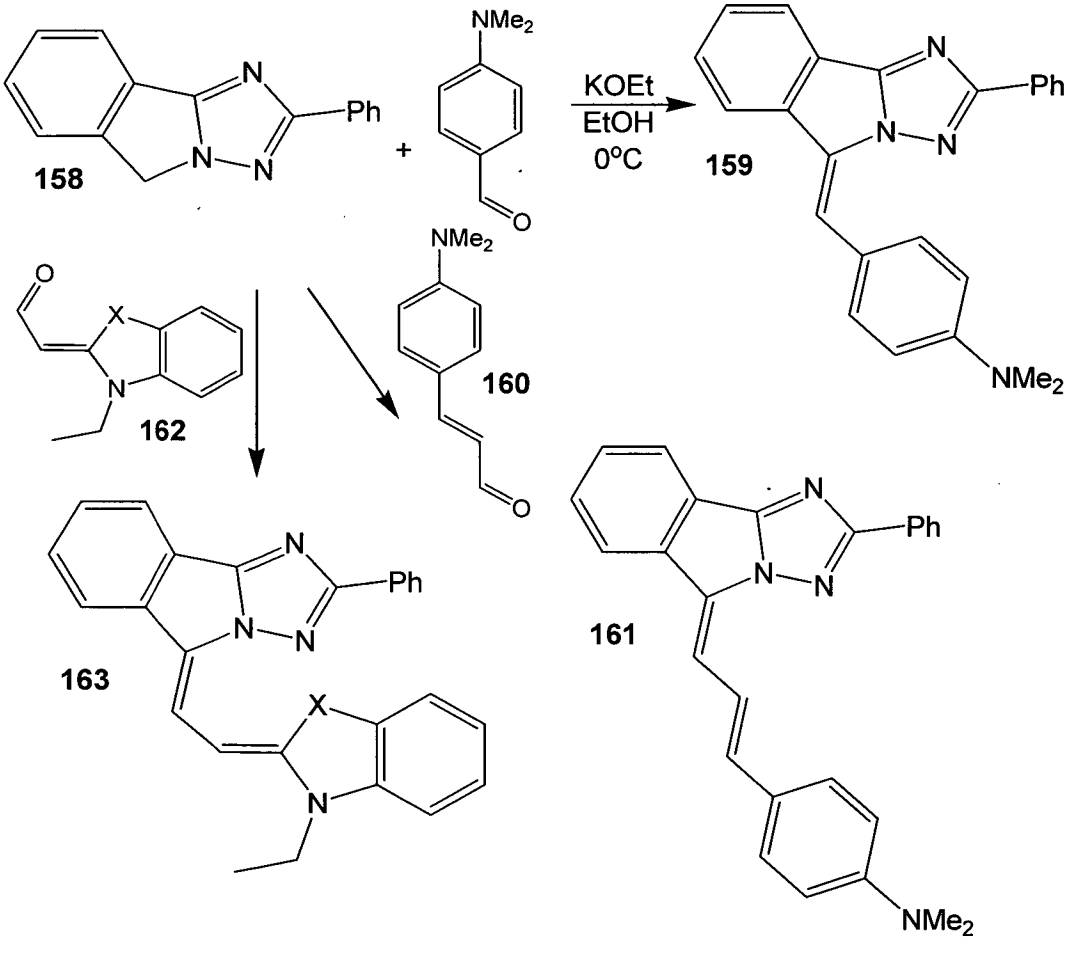
There are no relevant ^{13}C spectra in the literature.

1.6.3 Chemical Reactivity

Of the pyrrolo[1,2-*b*]triazole and triazolo[1,5-*a*]indole systems found in the literature, none appear to have had any reaction performed on them, but the family of triazolo[5,1-*a*]isoindoles **130** and the isomeric system, 5*H*-1,2,4-triazolo[3,4-*a*]isoindole **157**, have been involved in two types of reaction. Importantly, one of these is dye formation by reactions at the active methylene group, although whether these dyes were intended for photographic applications or otherwise was not stated.

1.6.3.1 Dye Formation

2-Phenyl[1,2,4]triazolo[5,1-*a*]isoindole **158** was reacted with a range of aryl aldehydes typically in the presence of potassium ethanoate, in ethanol, to give four different methine dyes (Scheme 45).[50,51] The reaction with *p*-dimethylaminobenzaldehyde, at 0 °C gave the dye **159**, the base deprotonating the reactive methylene coupling site, the resulting anion then attacks the aldehyde followed by loss of water to give the methine double bond. The same reaction with 3-(4-dimethylaminophenyl)propenal **160** gave the longer chain dye **161**, and reaction of **158** with an indole and a benzothiazole aldehyde **162** (X = CMe_2, S) with boiling gave **163**.



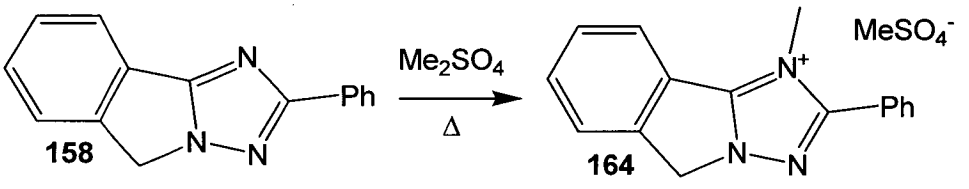
Scheme 45

UV-vis results for three of these four dyes have been published for solutions in methanol, for some reason the benzylidene dye **159** has not been analysed in this way.

The dimethylamino dye **161** had λ_{max} = 465 nm (ε 41,000), a slightly orange yellow dye, as can be inferred from the conjugation of the three carbon chain, and with a reasonably high extinction coefficient so it must be quite brightly coloured. The dimethylindole dye **163** (X = CMe_2) had λ_{max} = 484 nm (ε 56,000), evidently conjugation to the methyl substituted nitrogen heteroatom is enough to shift the dye hue into the orange region, the extinction coefficient now getting impressively high. Finally, the benzothiazole dye **163** (X = S) had λ_{max} = 510 nm (ε 69,000); adding the more electronegative sulfur heteroatom increases conjugation levels enough to give a red/magenta dye hue, and the large ε value indicates an extremely intensely coloured dye.

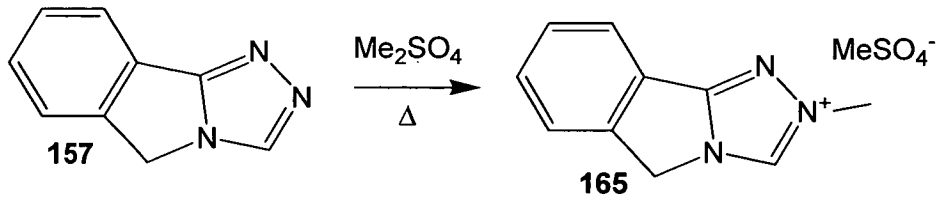
1.6.3.2 Quaternisation of Nitrogen Heteroatoms

Scheme 46 shows how alkylation of 2-phenyl[1,2,4]triazolo[5,1-*a*]isoindole **158** with dimethyl sulfate gave the quaternary ammonium salt **164**, where methylation has apparently taken place specifically at the 1-position.[50] This structure was supposedly confirmed by exchanging the methyl sulfate anion for a perchlorate, which was compared with an isomeric system.



Scheme 46

When the isomeric system 5*H*-1,2,4-triazolo[3,4-*a*]isoindole **157** was alkylated in the same way (Scheme 47), methylation this time was claimed to have occurred at the 2-position to give the salt **165**.[49] This was allegedly confirmed by quantum-chemical calculations, which, as this work was carried out in the 1970s, is not very reliable evidence. A useful way to confirm the structures of the two methyl ammonium salts **164** and **165** with contemporary instrumentation would be to perform an NOE NMR experiment, which would show which protons, if any, interact with the methyl group.



Scheme 47

2. DISCUSSION

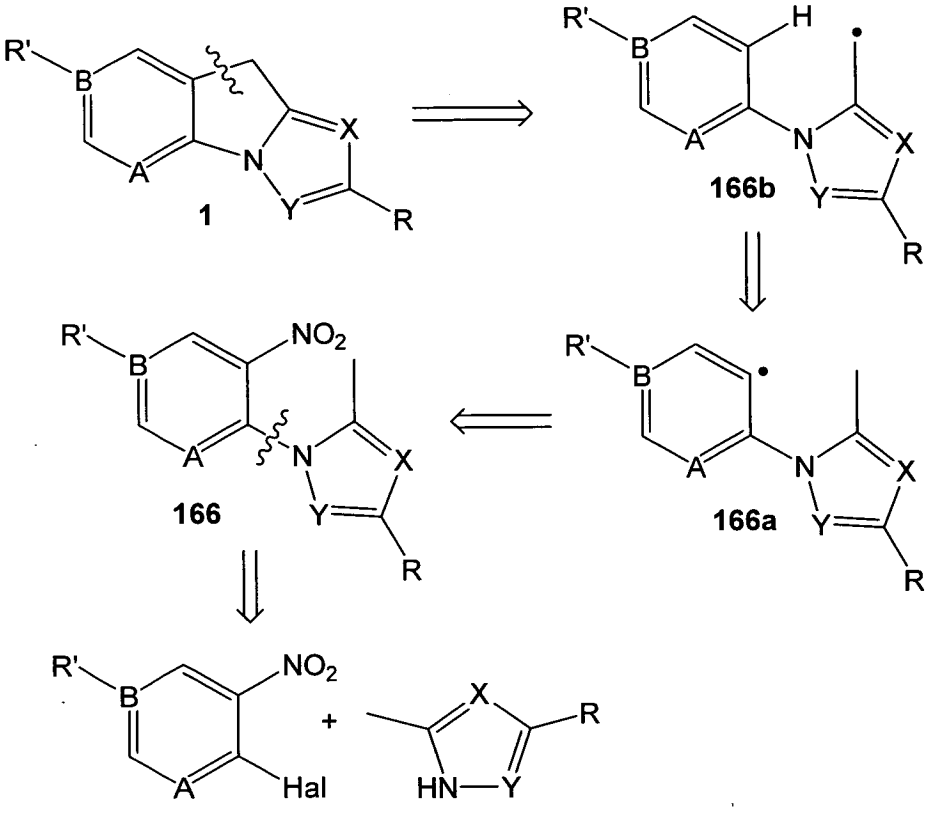
2. DISCUSSION

Overview

The work undertaken in the past three years has been to develop a new range of compounds of the type **1**, the cyclopenta[*a*]indenes, and then investigate their chemistry, including their suitability as magenta dye couplers. The numbers and positions of nitrogen heteroatoms in the tricyclic ring systems were varied in order to optimise their potential as magenta dye couplers, and to deduce how these variations affect the coupling reaction. The potential dye coupling compounds were synthesised by means of Flash Vacuum Pyrolysis (FVP) reactions on precursor compounds of the type **166** (Scheme 48), a technique which has rarely been used to make dye couplers in the past. FVP reactions can give unusual disconnection routes to complex molecules, which are not available in solution chemistry. Therefore FVP can allow the syntheses of such complex ring systems to be reduced to as little as two steps, and many desired substituents can easily be included in the precursors without affecting the cyclisation. In this case, the nitro group is eliminated by radical cleavage under the extreme conditions of the pyrolytic process, leaving a phenyl radical species **166a** which abstracts a hydrogen atom from the methyl substituent, to effect cyclisation of the central pyrrole unit. Phenyl radicals are typically generated under FVP conditions by using bromo[52] or allyl ester[53] substituents as leaving groups, but in this case the nitro group was chosen[54] as it facilitates synthesis of the precursors, by activating the halide site of the starting material to nucleophilic substitution.

The precursors were generally constructed by base catalysed nucleophilic substitution reactions attaching an azole ring to a substituted benzene or pyridine ring. All tricyclic systems successfully obtained were sent in small quantities to Kodak for testing as dye couplers. This involved reaction with a standard developer reagent, an oxidising agent and base, observation of the colour formed and then combined HPLC and UV-vis spectroscopy of the resultant dye was used to purify the product and quantitatively examine its suitability as an effective magenta dye. Following these tests, a range of experiments was carried out on the various couplers, including attempts at attaching ballasts or coupling-off groups which would enable use of these

compounds in photographic film, and other reactions designed to investigate the chemistry of these systems.



Scheme 48

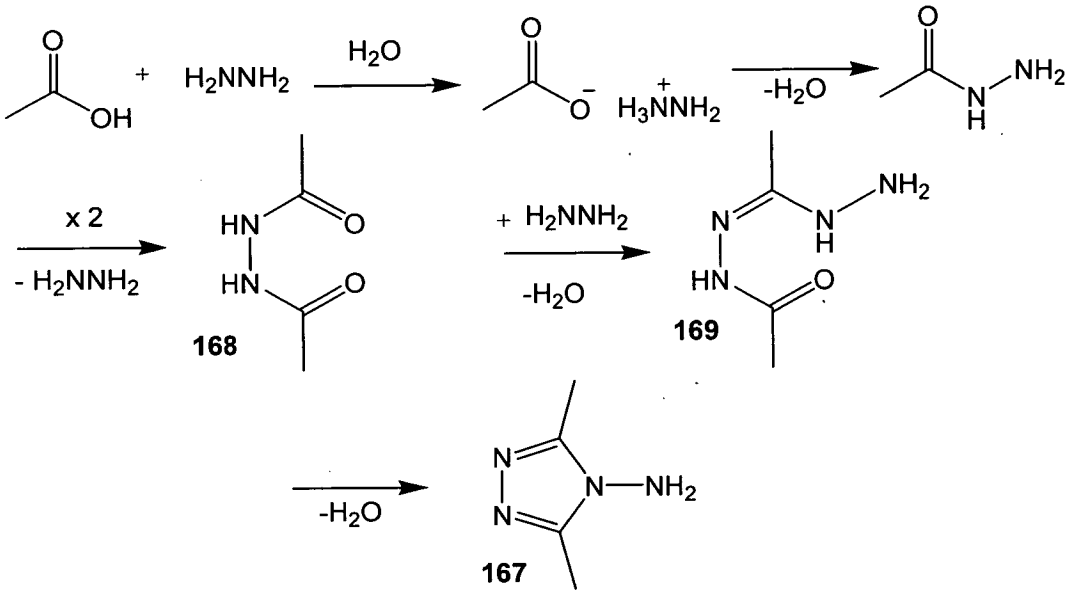
2.1 Preparation of Starting Materials

For the most part, all starting materials used to create the pyrolysis precursors were readily available from the usual chemical companies, but several of them had to be made specially, and are discussed briefly in the following section.

2.1.1 Formation of the Triazole Ring

As part of the series of compounds represented by the general structure **1**, it was clear that a range of triazole containing systems would provide some valuable results in dye formation tests, to give clues as to whether more nitrogen atoms make better couplers. Due to availability and simplicity of synthetic processes, 3,5-dimethyl-1,2,4-triazole was initially selected as a suitable starting material, the 1,2,4 configuration shown by

X and Y = N in **1**, and one methyl group being necessary for the FVP reaction. The dimethyl species was used so that the six membered ring could be attached to either of the adjacent nitrogen atoms to give the same pyrolysis precursor.

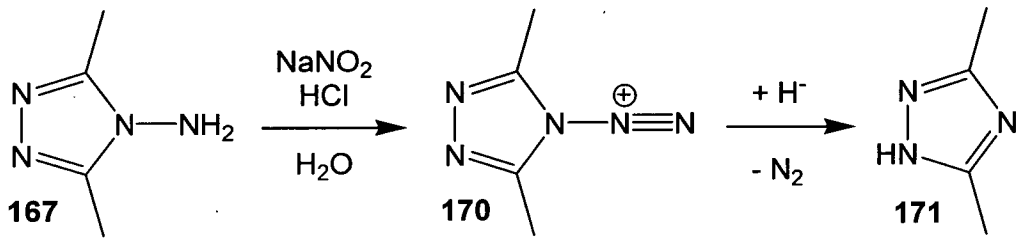


Scheme 49

The process employed took the simple reagents glacial acetic acid and hydrazine hydrate, and reacted them together in water to force them through the complex series of steps shown in Scheme 49.[55] The reagents were heated slowly over a Bunsen burner to 220 °C over 1.5 h, with the apparatus set up for distillation. Water and excess hydrazine were distilled off above 100 °C then the resultant pale brown solution was maintained at the maximum temperature for 4 h. After this time the crude product was added to isopropyl alcohol while still hot and a large quantity of white crystals precipitated. After filtration ^{1}H NMR spectroscopy confirmed these were 3,5-dimethyl-[1,2,4]triazol-4-ylamine **167**, obtained in 84% yield. It is crucial that the reaction is carried out at this temperature; much reduced yields are obtained if this reaction is attempted at lower temperatures, with intermediate species such as the hydrazide **168** or the imine containing **169** possibly produced.

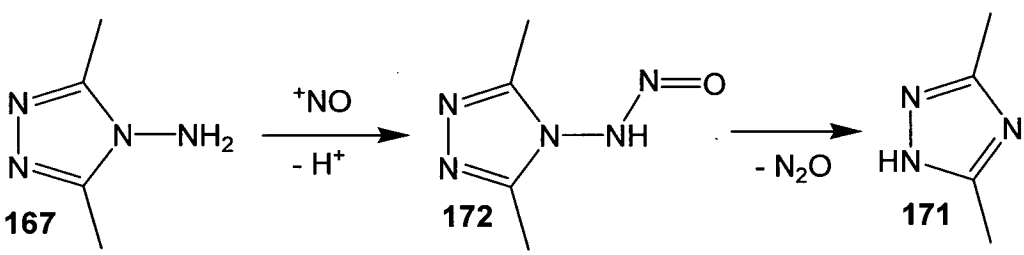
2.1.2 Removal of the Amine Substituent

The amine group on triazole **167** was removed by treatment with sodium nitrite and hydrochloric acid in aqueous solution.[56] As the literature included no details about the correct work up procedure, the reaction mixture was initially basified with sodium hydroxide, and then work up with dichloromethane failed to extract **171**, which appeared to be more soluble in water. However, evaporation of water followed by dissolving the product in DCM and removal of the sodium chloride by filtration gave an excellent 97% yield of 3,5-dimethyl-1,2,4-triazole **171**.



Scheme 50

There are two possible mechanisms for this reaction; the first one considered being a standard diazotisation to give the diazonium salt **170**. Loss of N_2 then leaves the triazole with a positively charged nitrenium ion, which may abstract a hydride ion from the water present to give the product 3,5-dimethyl-1,2,4-triazole **171**. This process is known in alcoholic solution,[57] but no examples were found in the literature of reductive cleavage of diazonium salts in aqueous solutions.

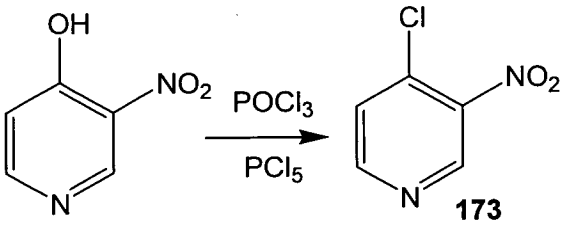


Scheme 51

Therefore, a second possible mechanism for this reaction is outlined in Scheme 51, and was judged to be more feasible than the hydride abstraction in Scheme 50.[58] The intermediate *N*-nitroso compound **172**, which previously would have led to the

diazonium salt **170**, loses N_2O to give the triazole **171**, after the hydrogen which was originally on the amino group shifts round to the ring 1-position.

2.1.3 Formation of 4-Chloro-3-nitropyridine



173

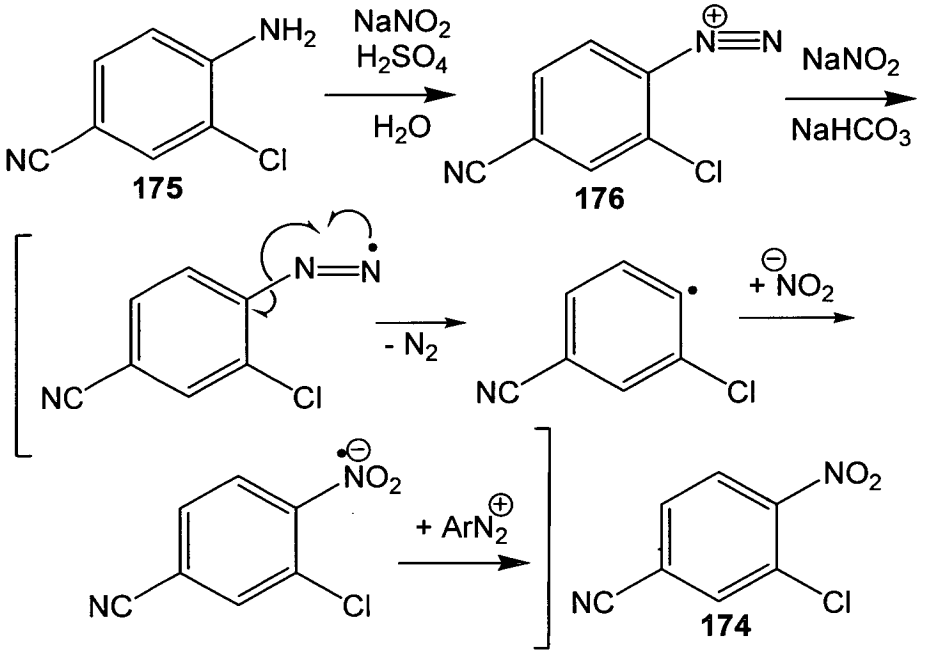
Scheme 52

Scheme 52 shows how 4-chloro-3-nitropyridine **173** was obtained by means of a simple chlorination reaction, as a route to a dye coupler **1** in which B = N.[59] 4-Hydroxy-3-nitropyridine was slowly heated in phosphoryl chloride with phosphorus pentachloride then heated under reflux for 4 h to complete the reaction, hydrogen chloride gas being evolved as the conversion progressed. Distillation of excess $POCl_3$ and DCM work up afforded an 81% yield of the product **173**. The identity of this species was confirmed by its melting point and proton NMR spectroscopy, both of which agreed closely with literature values (see Experimental section).

2.1.4 Formation of 3-Chloro-4-nitrobenzonitrile

In order to incorporate an electron withdrawing group into a coupler, 3-chloro-4-nitrobenzonitrile **174** was required for the six-membered section of the pyrolysis precursor, and was synthesised as shown in Scheme 53.[60] The starting material was 4-amino-3-chlorobenzonitrile **175**, and the amino group was converted to a nitro group by means of a diazotisation reaction adapted from a literature method used for other compounds. Treatment of **175** with dilute sulfuric acid, ice water and an aqueous solution of sodium nitrite led to formation of the intermediate diazonium salt **176**. Further reaction with a large excess of sodium nitrite and sodium bicarbonate in aqueous solution caused the nitro group to displace the diazonium group. The nitro-

compound **174** was finally obtained as a yellow precipitate, which had to be purified by column chromatography, resulting in only 18% yield.



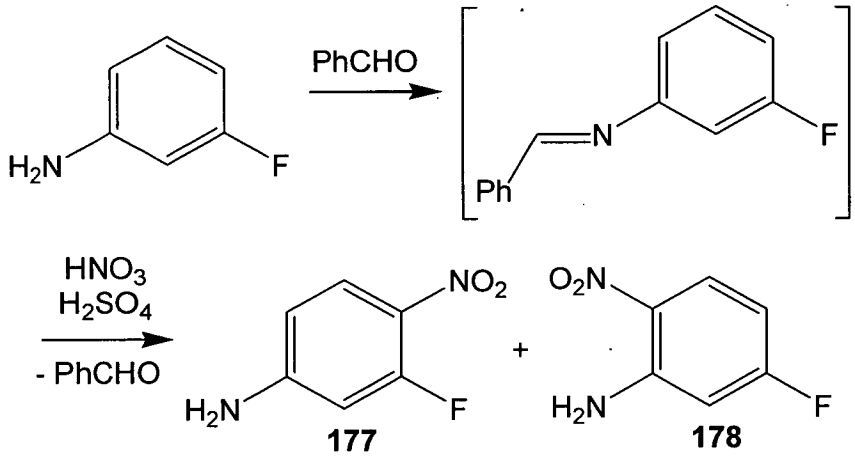
Scheme 53

The mechanism of the dediazoniation of the salt **176** is believed to take place *via* electron transfer between the diazonium group and a nitrite ion to give radicals, leading to loss of nitrogen followed by addition of another nitrite anion to the phenyl radical.[61] The melting point and proton NMR spectrum of **174** were judged to be sufficient to confirm its identity, the spectrum showing the 5-proton adjacent to the newly formed nitro group with the highest shift at 7.89 ppm, deshielded by the electron-withdrawing group where originally there was an electron-donating group.

Initially, the literature method utilised for this conversion involved hydrochloric acid, and copper oxide catalyst instead of sodium bicarbonate, but this led to displacement of the diazo salt in **176** by a chloride ion, to give a dichloro species 3,4-dichlorobenzonitrile which was mainly identified by the mass spectrum displaying the correct pattern for the chlorine isotope peaks.

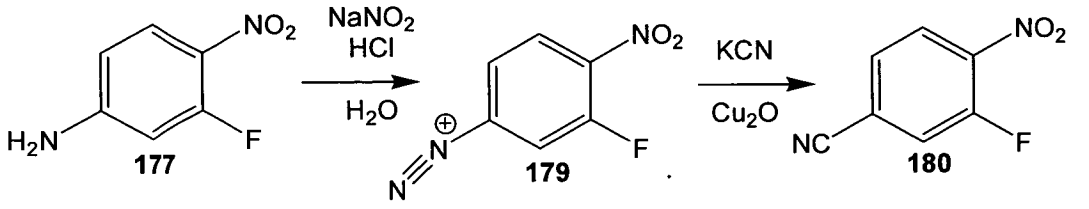
2.1.5 Formation of 3-Fluoro-4-nitrobenzonitrile

When the reaction of 3,5-dimethyl-1,2,4-triazole **171** with 3-chloro-4-nitrobenzonitrile **174** later failed (see Section 2.2.2.5), the logical solution was to replace the chloro substituent with a fluoro. This required a two-step synthesis, the first being the nitration of 3-fluoroaniline, as shown in Scheme 54.[62] The starting material was mixed with benzaldehyde and heated, to protect the amino group, and then the resulting reaction mixture was dissolved in concentrated sulfuric acid and cooled. Finally, nitration was effected by addition of concentrated nitric and sulfuric acid, followed by addition to water and purification by steam distillation. The purpose of this was to separate the unwanted isomer formed, 3-fluoro-6-nitroaniline **178**, which was removed from the reaction vessel by the steam, while the desired isomer, 3-fluoro-4-nitroaniline **177**, remained in the flask. This was then purified using Kugelrohr distillation, and the final product **177** was purified by recrystallisation to give a disappointing 18% yield.



Scheme 54

The next step was to replace the amino group of **177** with a cyano group, and this was performed according to Scheme 55, by means of a Sandmeyer reaction.[63] The diazonium salt **179** was formed in the usual way by addition of sodium nitrite to a solution of the starting material **177** dissolved in hydrochloric acid, and this was then added to an aqueous solution of potassium cyanide and copper (I) oxide. The product 3-fluoro-4-nitrobenzonitrile **180** was obtained as a brown precipitate and purified using column chromatography to give a 48% yield of orange solid product.

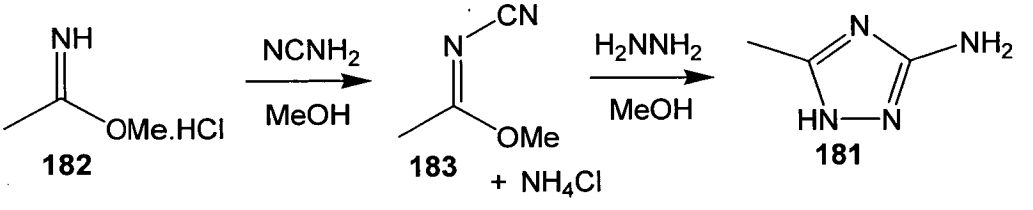


Scheme 55

The identity of the product **180** was confirmed by comparison with the literature melting point, and the proton NMR spectrum, in which the multiplet at 7.61 ppm represents the 2- and 6-protons either side of the cyano group. In the proton NMR spectrum of the starting material **177**, the peak representing these protons has a low chemical shift of 6.35 ppm, due to the electron-donating effects of the amino group, so the difference produced by replacing this with the electron-withdrawing cyano group is evident.

2.1.6 Preparation of 5-Methyl-1,2,4-triazol-3-amine

As was shown in the introduction section, many ballasts are attached to couplers by means of an amide linkage, so a common strategy is to add an acid chloride ballast to an amino-substituted coupler. One suitable place to put the amino group is the 2-position of the triazole ring, as this is usually far enough from the coupling site to have no unwanted effects. So the necessary component required for synthesising a 2-amino coupler was recognised as being 5-methyl-1,2,4-triazol-3-amine **181**, the synthesis of which is shown in Scheme 56.[64] In the first step, methyl acetimidate hydrochloride **182** was added to a solution of cyanamide in methanol, and stirred at room temperature to produce a precipitate of ammonium chloride, which was filtered off. The product, methyl-*N*-cyanoacetimidate **183** was then isolated by removal of solvent and distillation.

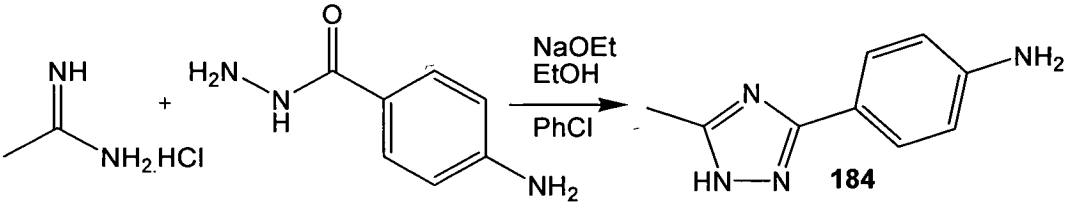


Scheme 56

For the next step, the *N*-cyanoacetimidate **183** was dissolved in methanol and treated drop-wise with hydrazine with cooling and stirred for 1 h at room temperature.[64] The final product, 5-methyl-1,2,4-triazol-3-amine **181** was obtained by trituration of the concentrate with ethyl acetate and acetonitrile, to give a 31% yield of almost colourless crystals. The melting point of the product agreed with the literature value, and confirmation of the predicted structure was obtained from the proton NMR spectrum, in which the amino group is represented by a broad singlet at 5.59 ppm and the secondary amine proton in the triazole ring corresponds to a peak at 8.34 ppm.

2.1.7 Preparation of 3-(4-Aminophenyl)-5-methyl-[1,2,4]-triazole

In order to produce an alternative amino coupler suitable for ballasting, the novel triazole compound **184** was designed as an appropriate starting material, featuring an aniline substituent. This was expected to be beneficial as the amino group should have less effect on the triazole ring when synthesising the pyrolysis precursor, and on the active methylene group of the final target coupler.



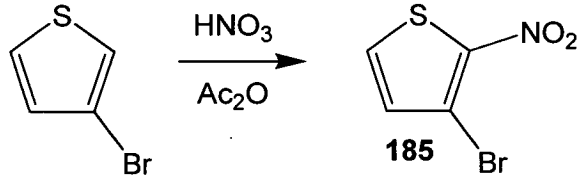
Scheme 57

According to Scheme 57, adapted from general literature routes to 3-aryltriazoles, acetamidine hydrochloride was neutralised with sodium ethoxide, and then reacted with 4-aminobenzoic hydrazide in chlorobenzene, heated under reflux for 48 h.[65] The triazole product **184** was obtained in 45% yield, and was characterised by proton and carbon NMR spectroscopy and mass spectrometry. In the proton NMR spectrum the methyl and aniline protons are seen to be part of the same molecule, but the key data in establishing the structure of **184** is in the ^{13}C spectrum. The two highest quaternary signals correspond to the two quaternary carbon atoms in the triazole ring, the chemical shifts of 158.27 and 155.85 ppm being typical of 1,2,4-triazoles, for example, 5-methyl-3-phenyl-[1,2,4]-triazole has equivalent peaks at 161.3 and 157.3 ppm.[66]

2.1.8 Towards a 5,5,5 System

According to the overview at the beginning of this thesis, the work undertaken has centred on producing a range of 6,5,5 magenta couplers which fit with the general structure **1**. The same general strategy can be applied to 5,5,5 systems, which had been rarely reported in the past due to the difficulty of their synthesis by conventional methods.[67]

In replacing the 6-membered ring, a suitable 5-membered ring was selected in the thiophene ring, and the first step towards the synthesis of such a 5,5,5 system was to nitrate 3-bromothiophene, as shown in Scheme 58.[68] 3-Bromothiophene was dissolved in acetic anhydride and added drop-wise to a stirred solution of concentrated nitric acid in acetic anhydride, with cooling. After warming to room temperature over 2 h, the reaction mixture was added to water to produce brown crystals, which were purified by recrystallisation from hexane, to give a 29% yield of 3-bromo-2-nitrothiophene **185** as beige crystals. The observed melting point agreed with the literature value, and the proton NMR spectrum showed a peak at 7.48 ppm corresponding to the 5-proton next to the sulfur heteroatom, and one at 7.06 ppm for the 4-proton adjacent to the bromo substituent.



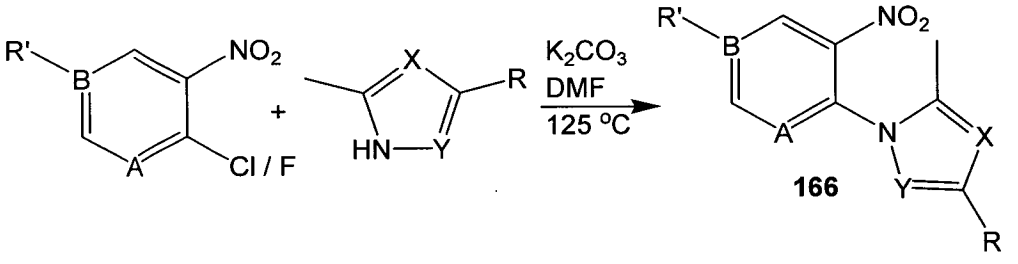
Scheme 58

Nitration takes place at the 2-position due to the activating effects of the sulfur heteroatom and bromo substituent on the nucleophilic reaction site. In the first attempt at this reaction, which employed nitric acid dissolved in acetic acid (rather than acetic anhydride), an unwanted isomer was also identified, 4-bromo-2-nitrothiophene, in which the directing effects of the sulfur atom clearly outweigh those of the bromo-substituent.

2.2 Preparation of the Pyrolysis Precursors

The general plan for making these cyclopentaindene dye coupler systems by FVP appears to be very simple, based on attachment of a six membered ring to a five membered ring by nucleophilic substitution, one with a nitro group and one with a methyl group for the cyclisation step. Joining these two sections is apparently uncomplicated, the azole ring is easily made nucleophilic by deprotonation of a secondary amine group, which can attack the benzene or pyridine ring if this has a halide substituent activated by the nitro group. Not all the combinations tried would react by the same method, and also a number of alternative routes were tried, some in order to produce isomeric systems deviating from the general structure of **1**.

2.2.1 General Substitution Methods

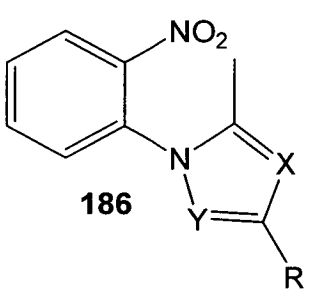


Scheme 59

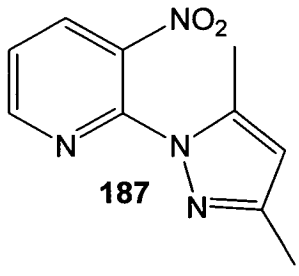
The original nucleophilic substitution reaction method chosen for adding the azole ring to the nitro-substituted aromatic ring is detailed in Scheme 59.[67] Anhydrous potassium carbonate is a good base for this type of reaction as it can deprotonate the azole species ready for nucleophilic attack at the halide (Cl or F) position of the aromatic ring, which may be further activated by electron withdrawing groups and/or heteroatoms. These extra groups were expected to have varying effects on the coupling ability of the target FVP products, and certain substituents were also selected as potential sites for attaching ballasts.

Dimethylformamide is a very suitable solvent here, as it easily dissolves the organic reagents and products, it has a high boiling point so is useful as a temperature of 125 °C was necessary for these reactions, as the azoles are relatively poor nucleophiles. Additionally, it is highly soluble in water, so can be separated from products when diethyl ether or ethyl acetate is used for extraction. Preliminary reactions[67] using azoles and nitrophenyl species required more than 24 h to go to completion, so a reaction time of 48 h was chosen as the standard. No optimisation of conditions was carried out on the successful reactions described later.

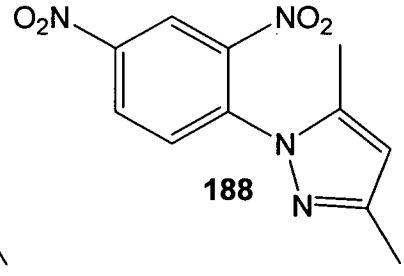
In this way, compounds **186** (R = H, X = N, Y = CH; R = Me, X = CH, Y = N; R = Me, X = Y = N), **187** and **188** have been successfully synthesised in prior research by Dale Cartwright.[67] The only variation was in time of reaction, with the first three compounds only requiring 24 hours, and were obtained in yields of 50 – 75%, though the pyrazole **187** had only a 32% yield. It is important to comment on the regiochemistry of the triazole ring, as substitution occurs preferentially at the 1- or 2-heteroatoms rather than the 4-position, due to the "alpha effect" where adjacent heteroatoms mutually enhance their nucleophilicity.[69]



186



187



188

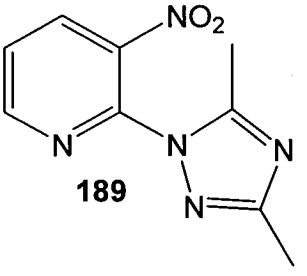
Two types of cases could be identified in which the standard conditions were unsuccessful. Where six-membered aromatic species in which the halide site was more strongly activated were used, milder reaction conditions had to be employed, typically a lower temperature and shorter heating time. Two highly reactive nitrophenyl compounds were used in certain syntheses, which also featured an electron withdrawing group *para* to the halide substituent, and these could be reacted with no added base by heating the reactants in ethanol solution for a short time.[70] In these cases, the azole species is basic enough to deprotonate itself intermolecularly. Alternatively, where the nitrohalogeno compound was made less reactive by an

additional electron donating group (or an electron withdrawing group in a non-activating position), the reactions had to be carried out in the presence of a stronger base.

2.2.2 Azolylnitropyridine Compounds

2.2.2.1 2-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine

The first compound of the series synthesised during this period of research was 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine **189**, using the previously produced 3,5-dimethyl-1,2,4-triazole **171** and 2-chloro-3-nitropyridine, heated together in DMF at 125 °C for 2 days. The product **189** was obtained in 35% yield, after recrystallisation.



189

Evidence for the formation of 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine **189** came from the mass spectrum confirming the correct molecular weight (219 Da), and proton and ^{13}C NMR spectra. In the proton NMR spectrum, it can be seen from the splitting of the aromatic peaks (three doublets of doublets) that the 4-, 5- and 6-protons on the pyridine ring are still present, therefore no rearrangement has taken place. Replacing the chloro substituent with the triazole ring has little effect on the chemical shifts of the three aromatic protons. An interesting point to note is on the triazole ring, where the methyl groups in the starting material had a chemical shift of 2.39 ppm, the 5-methyl group now has a shift of 2.67 ppm. This is due to interaction with the pyridine heteroatom, which may be affected further by non-covalent bonding between the 2-nitrogen on the triazole ring and the nitro group (Figure 3). In the phenyl equivalent **186** (R = Me, X = Y = N), the triazole methyl groups have

chemical shifts of 2.32 and 2.31 ppm, showing that the nitro group has little effect on them.[67]

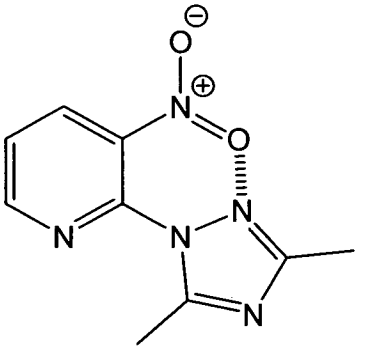
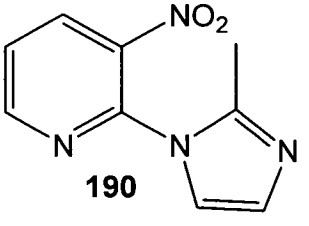


Figure 3: nitro-triazole interaction in 189

2.2.2.2 2-(2-Methylimidazol-1-yl)-3-nitropyridine

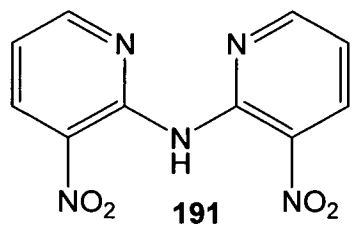
2-Chloro-3-nitropyridine and 2-methylimidazole were reacted together on a 10 mmol scale in the usual way and extracted into DCM to give the desired product 2-(2-methylimidazol-1-yl)-3-nitropyridine **190** in 34% yield. Purification by recrystallisation was not completely successful, which could explain the uncharacteristically low melting point of 60 °C. The mass spectrum of the product gave the correct molecular weight of the desired product, and the proton NMR spectrum showed the desired structure, with the pyridine and imidazole protons in the appropriate positions. The methyl group displayed a chemical shift of 2.35 ppm, indicating no interaction with the pyridine heteroatom, which appears to confirm that this observation in the triazole **189** is due to the extra heteroatom interacting with the nitro group.



190

In the initial attempt at this reaction (on the same 10 mmol scale), where the crude product was extracted with diethyl ether, only a 60 mg quantity of a red solid was obtained, which was shown by proton NMR spectroscopy not to be the desired product **190**. It was, however, a very clean product, and its identification began with

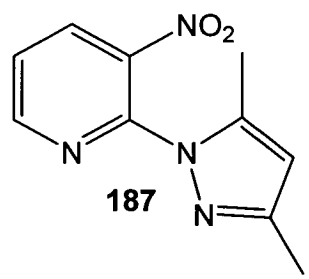
a mass spectrum giving a molecular weight of 261 Da. In the proton NMR spectrum, an NH group was identified at 11.25 ppm (1H), then the three aromatic peaks, at 8.58, 8.50 and 7.17 ppm (each 2H), suggesting a symmetrical molecule with two substituted aromatic rings. The ^{13}C NMR spectrum revealed three non-equivalent CH groups and two quaternaries, suggesting the previously reported bis-(3-nitropyridin-2-yl)-amine **191**.[71] Formation of this product suggests that a source of ammonia is required, the only obvious source of which would be hydrolytic cleavage of the imidazole caused by water contamination of the DMF. The resultant ammonia would then have been very reactive to the chloronitropyridine.



191

2.2.2.3 2-(3,5-Dimethylpyrazol-1-yl)-3-nitropyridine

In order to complete the series of pyridine (**1**: A = N) systems, 2-(3,5-dimethylpyrazol-1-yl)-3-nitropyridine **187**,[67] was re-synthesised for testing at Kodak. Comparison with the imidazole system would give helpful clues as to in which positions the heteroatoms are most beneficially placed for enhanced coupling reactivity.

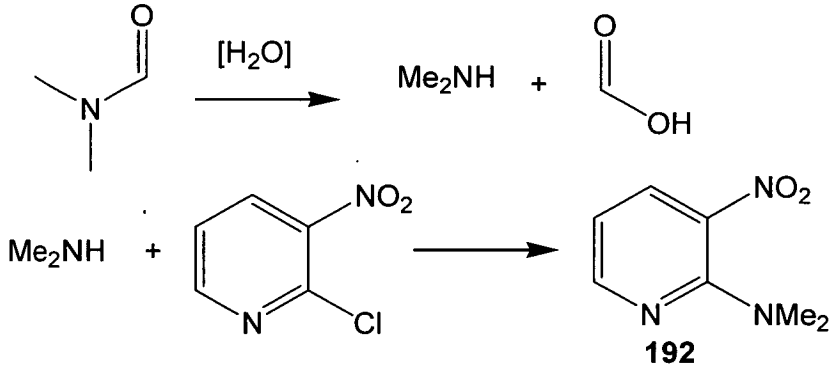


187

Compound **187** was synthesised satisfactorily by the general method, using ether extraction, and had to be separated by dry flash chromatography to give an unoptimised 12% yield. ^{1}H NMR spectroscopy and literature melting point comparison confirmed that the second component obtained from the column was the desired product. Another component was the dimethylpyrazole starting material

(23% recovery), and a third was identified as 2-dimethylamino-3-nitropyridine **192** (1% yield), principally by the proton NMR spectrum which displayed a pair of equivalent methyl groups of high shift, and no pyrazole proton.

Scheme 60 shows how **192** can be formed if DMF is contaminated with water and hydrolysed. The dimethylamine obtained then is a good nucleophile for attack of the halogenated pyridine. It is conceivable that thermal decarbonylation of DMF could be the source of dimethylamine; however, as this reaction was carried out under the typical conditions of heating at 125 °C for 2 days this seems unlikely, otherwise dimethylamino by-products would have been observed more frequently. It is interesting that in this case the DMF was hydrolysed, whereas in the previous section it was the imidazole, suggesting that pyrazoles must be more stable in the presence of water.

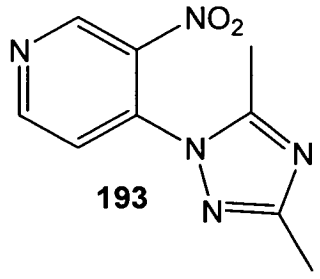


Scheme 60

2.2.2.4 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine

In an attempt to discover the best location for the heteroatom in a pyridine ring of a potential dye coupler, a new triazole-pyridine system was chosen, where the nitrogen is located at the 4-position relative to the azole-substituent **193**. The production of the starting material, 4-chloro-3-nitropyridine **173** is described in section 2.1.3. It is known that 4-chloro substituents are generally more susceptible to nucleophilic attack than 2-chloro substituents in pyridines. For example, when displacing chloro groups with methoxides, 4-chloropyridine reacted more than 30 times faster than 2-

chloropyridine, although reasons for this are unclear.[72] With these considerations taken into account, the general method for preparing the pyrolysis precursors was deemed far too vigorous and so milder reaction conditions had to be adopted.



193

The reactants 3,5-dimethyl-1,2,4-triazole **171** and 4-chloro-3-nitropyridine **173** were heated together under reflux in DMF in the presence of potassium carbonate and the progress of the reaction was monitored by TLC. The colour change to brown occurred after only 10 minutes, indicating reaction had begun to occur, and after 30 min TLC showed it had gone to completion. The product was isolated by ethyl acetate work up, and shown by proton NMR and mass spectrometry to be 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine **193**, in 55% yield. In the proton NMR spectrum, the chemical shift of the proton in the 5-position on the pyridine ring has been lowered relative to the starting material **173**, to 7.43 ppm, by replacement of the chloro group with the electron-donating triazole ring. The two methyl groups have shifts of 2.38 and 2.33 ppm, as the pyridine heteroatom is too far away in space to have any influence on the 5-methyl, which is presumably slightly deshielded by the nitro group.

In the first attempt at the synthesis of **193**, a milder variation on the general method involved the use of potassium *t*-butoxide as base and the solvent dimethyl sulfoxide.[73] The reactants were stirred together for 24 h at room temperature, and extraction into DCM gave an orange semi-solid product, which was shown by proton NMR spectroscopy to be the desired product **193**. Difficulties in removing residual DMSO, with the product being water soluble, led to this method being abandoned. It was then decided to try a weaker, organic base, diisopropylethylamine (Hunig's base), with THF as the solvent, but this reaction failed to go to completion after 24 h heating under reflux. Reacting **171** and **173** together in ethanol without base gave no identifiable product.

2.2.2.5 Proton NMR Data

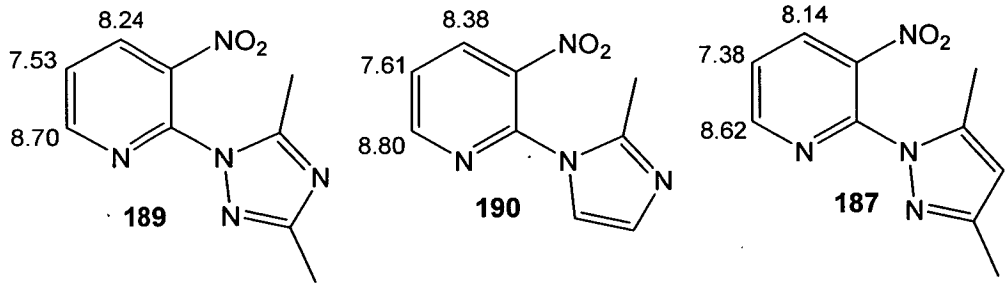


Figure 4: chemical shifts of 2-azolylpyridine compounds

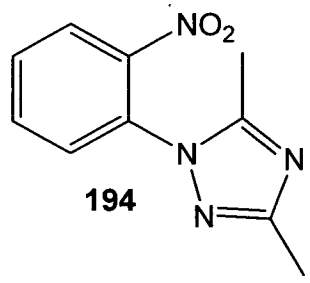
Comparison of the proton NMR spectra of the three 2-azolyl-3-nitropyridine compounds is interesting to see what effects varying the azole ring would have on the protons of the pyridine ring. Coupling frequencies confirm the positions of the three aromatic protons, with a much lower *J* value between the 5- and 6-protons (4.8 Hz) than between the 4- and 5-protons (8.1 Hz), typical of pyridine compounds.[74] The chemical shifts of compounds **187**, **189** and **190** are shown in Figure 4; in each case the pyridine heteroatom has a greater deshielding effect on the 6-proton than the electron withdrawing nitro group on the 4-proton. The imidazole containing **190** has the highest chemical shifts and the pyrazole **187** the lowest, with the 4-proton displaying a chemical shift of 8.14 ppm. A difference of ~ 0.2 ppm over the series is not large, showing that the influence of the varying azole groups is small, although the effect seems to be that the 2-heteroatom may reduce pyridine chemical shifts, while the 4-heteroatom could raise them.

2.2.3 Synthesis of Substituted Benzenes

2.2.3.1 2-(3,5-Dimethyl-1,2,4-triazol-1-yl)nitrobenzene

Reaction of 1-fluoro-2-nitrobenzene with 3,5-dimethyl-1,2,4-triazole **171** on a 0.1 mol scale gave the precursor **194** in a 49% yield, its identification confirmed by agreement of its melting point and proton NMR spectrum with the previously reported data.[67] This reaction was later repeated with the stronger base cesium carbonate in place of

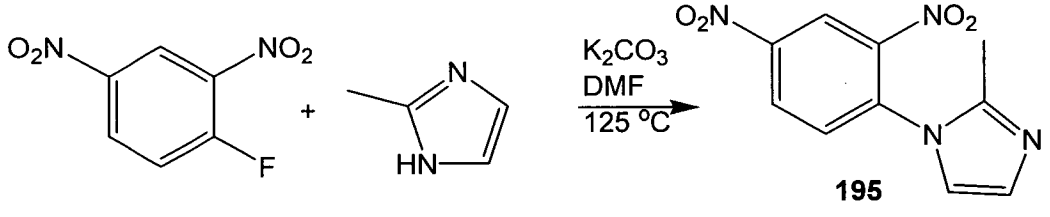
potassium carbonate; the cesium cation dissociates from the carbonate anion much more readily than potassium due to its large size, so leaving the anion more able to accept protons. However, the improvement was negligible, resulting in a 50% yield on the same scale.



194

2.2.3.2 2-Methyl-1-(2,4-dinitrophenyl)-imidazole

The first synthesis of a precursor to a 7-substituted coupler featured an extra nitro group, which would be expected to improve the coupling ability and provide a possible ballasting site. Reaction of 2-methylimidazole and 2,4-dinitrofluorobenzene proceeded in the usual manner (Scheme 61), but on this occasion only a 9% yield of the desired product, 2-methyl-1-(2,4-dinitrophenyl)-imidazole **195**, was obtained. The effect of the imidazole appears to give much poorer results than pyrazoles; this has been observed before when imidazole was reacted with methyl 2-fluorobenzoate under a variety of conditions, all giving low yields.[75] The reason for this is due to absence of the alpha effect mentioned earlier, as there is no heteroatom adjacent to the reactive amine site to increase its nucleophilicity.



195

Scheme 61

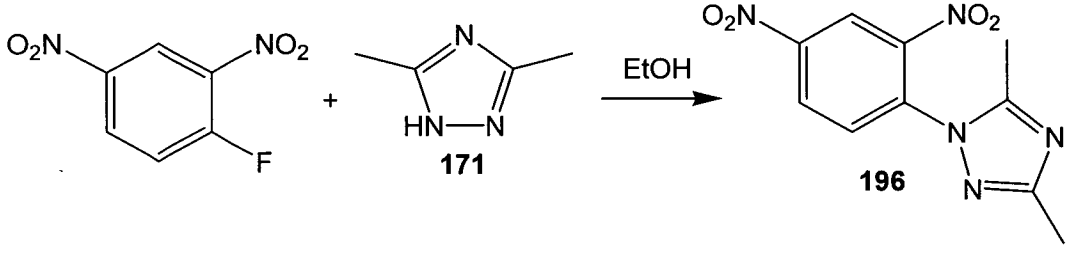
The identity of the product **195** was confirmed by its mass spectrum, giving the correct molecular weight of 248 Da, and its proton NMR spectrum. Removal of the fluoro group from the starting material is clear from the lack of fluoro coupling in the phenyl protons. The 6-proton has a chemical shift considerably lower than the other

two aromatic protons, 7.53 ppm, due to the influence of the electron donating imidazole ring.

This reaction was also attempted using the ethanol method, which resulted in unreacted starting materials crystallising out of the reaction mixture. Clearly the imidazole is not a strong enough nucleophile to react by this method. The fact the starting materials recrystallised out as they did gives a clue as to why the imidazolylpyridine compound **190** was not soluble in ether; imidazole species such as these must be considerably less soluble than the triazole or pyrazole analogues.

2.2.3.3 3,5-Dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole

When the reaction between 3,5-dimethyl-1,2,4-triazole **171** and 2,4-dinitrofluorobenzene was carried out in DMF under the usual conditions, a tiny quantity of an unidentified red solid was obtained after DCM work up. As the fluorobenzene species is highly activated by the *para* nitro group for nucleophilic substitution, it seems that the dimethyltriazole reactant **171** is actually too strong a nucleophile under these conditions. Alternatively, the product could be too reactive and decompose.



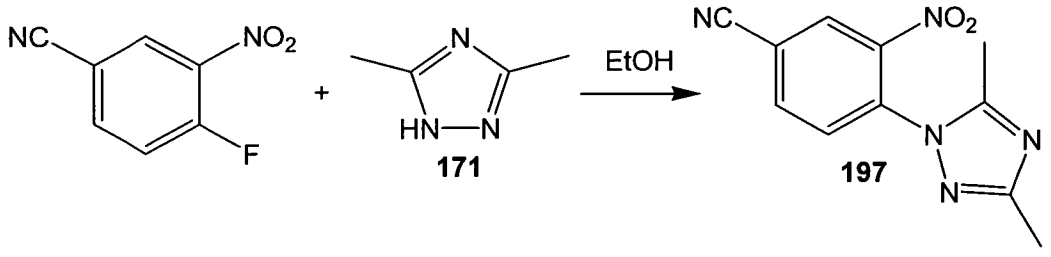
Scheme 62

However, 3,5-dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole **196** was successfully made by the literature method described in Section 2.2.1, using ethanol as solvent in the absence of added base.[70] According to Scheme 62, 3,5-dimethyl-1,2,4-triazole **171** and 2,4-dinitrofluorobenzene were heated together in ethanol under reflux for 30 min, followed by simple evaporation of ethanol to give the product **196** in 52% yield after recrystallistion from ethanol. The observed melting point agreed reasonably

closely with the literature value of 154 °C and the proton NMR spectrum was consistent with the proposed structure.

2.2.3.4 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile

The benzonitrile pyrolysis precursor **197** was the next target, and as with the dinitro compounds this was intended to give a final coupler product with an electron withdrawing group necessary to increase activity of the coupling site, and which could potentially be used to attach a ballast. The cyano substituent was chosen because it is very stable under FVP conditions.



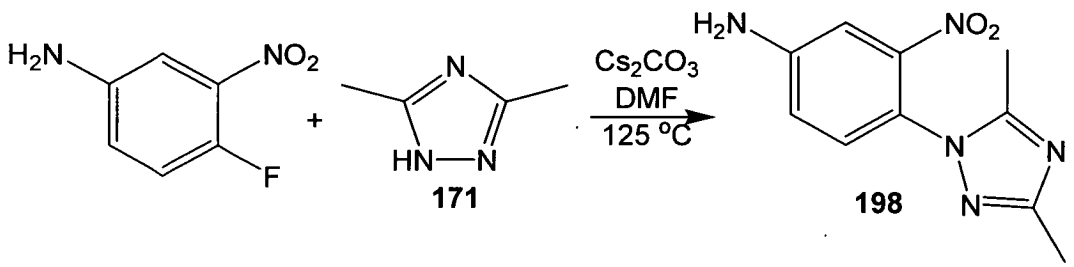
Scheme 63

The reaction of 3,5-dimethyl-1,2,4-triazole **171** with 4-fluoro-3-nitrobenzonitrile was carried out by heating the two reactants together in ethanol for five hours, which gave a crude mixture containing the product **197** (Scheme 63). Separation of this mixture using column chromatography gave 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile **197** as a pale orange solid as the third component in 50% yield. This was identified by mass spectrometry and proton NMR spectroscopy, in which the 5-proton on the benzonitrile ring shows a low shift (7.63 ppm) due to the adjacent electron donating triazole ring.

Initially, reaction of 4-fluoro-3-nitrobenzonitrile and 3,5-dimethyl-1,2,4-triazole **171** was carried out in the usual manner (potassium carbonate and DMF), but this produced an unidentified sticky semi-solid substance. Evidently, as with 2,4-dinitrofluorobenzene, the *para* cyano group activates the fluoro position too strongly for reaction by this method.

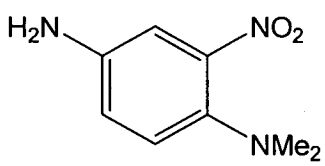
2.2.3.5 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline

4-Fluoro-3-nitroaniline was reacted with 3,5-dimethyl-1,2,4-triazole **171** to give a precursor to a fused aniline coupler, but the *para* amino group may cause the reaction site to be deactivated to nucleophilic attack. To overcome this, the stronger base cesium carbonate was used again, in place of potassium carbonate. According to Scheme 64, the reagents were heated in DMF at 125 °C for 2 days and after DCM work up and purification by column chromatography a 45% yield of **198** was obtained on a 30 mmol scale. That this reaction had worked at all in spite of the amino group in a deactivating position shows that it might not have had such a strong effect as feared, especially with the strongly activating fluoride as the leaving group, or that the cesium carbonate had a greater effect than in the synthesis of the phenyl analogue **194**.



Scheme 64

The product **198** was identified by the presence of the correct mass peak in its mass spectrum, and the proton NMR spectrum showing the integrals of the triazole and phenyl protons in accordance, and the 5-proton with a lower chemical shift than in the fluoro substituted starting material.



199

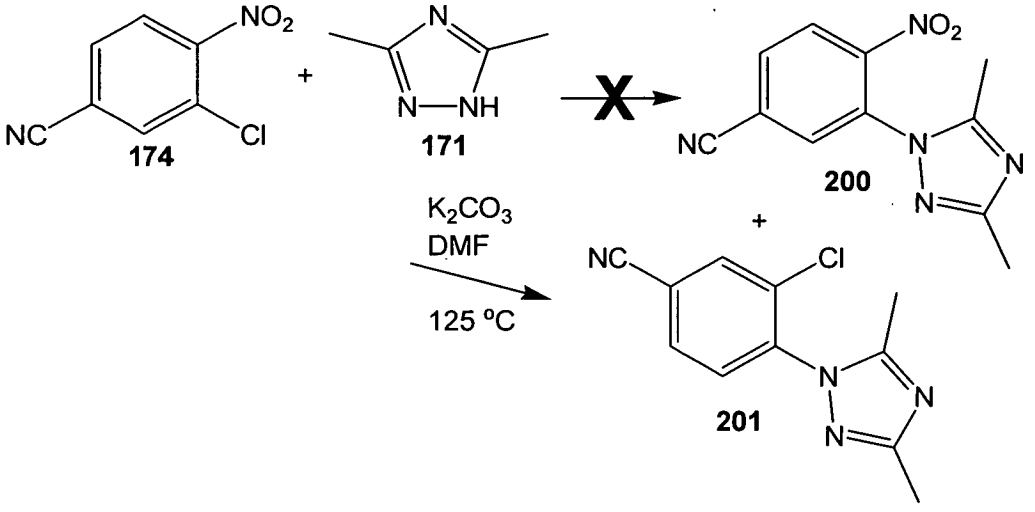
As happened in the synthesis of 2-(3,5-dimethylpyrazol-1-yl)-3-nitropyridine **187**, a red oil by-product, 4-dimethylamino-3-nitroaniline **199**, was identified as the first component retrieved from the column in 8% yield. Again, this is due to the presence of dimethylamine in the DMF, which would be expected to be a stronger nucleophile

than the triazole **171**. The proton NMR spectrum suggests the identity of **199**, as there is a single peak at 2.68 ppm corresponding to the dimethylamino group, the two equivalent methyl groups having a high shift as a result of being next to the nitrogen atom. The 5-proton on the aniline ring has a low shift because of the strongly electron donating dimethylamino group, 6.95 ppm; mass spectrometry confirms this structure conclusively. Though this compound has been described in the literature, only the UV-vis spectrum and melting point of **199** have been reported, showing this by-product was impure in oil form.[76]

2.2.3.6 Attempted Syntheses of 3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-4-nitrobenzonitrile

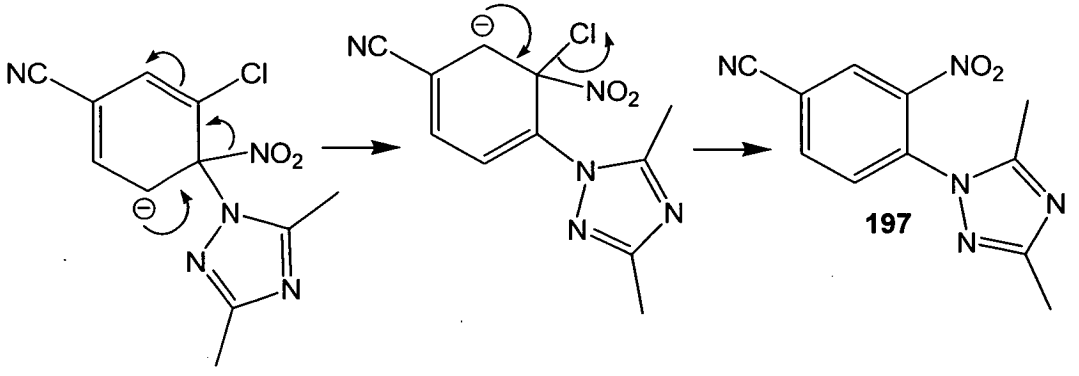
As a first example of a precursor to a 6-substituted coupler, the benzonitrile compound **200** was required, featuring a cyano group *meta* to the azole substituent. Reaction of 3-chloro-4-nitrobenzonitrile **174** with 3,5-dimethyl-1,2,4-triazole **171** was carried out in the usual manner (Scheme 65), but resulted in a mixture of products, which could not be separated by chromatography. Analysis of the mixture showed two major components in a 3:1 ratio. The major component was found to be 4-chloro-3-(3,5-dimethyl-1,2,4-triazol-1-yl)benzonitrile **201**, as shown by the mass spectrum (*m/z* 232 Da) and characteristic chlorine isotope peaks. Further evidence came from the proton NMR spectrum, in which the peak of highest chemical shift is at 7.82 ppm, which would be too low for a nitro compound. Also, the coupling frequencies of the aromatic protons disagree with the predicted structure of **200**, as the peak of highest shift, next to the nitro group, shows *meta* coupling only.

Substitution has taken place at the nitro site instead of the intended chloro site, which is activated by the *ortho* nitro group. The cyano group is *para* to the nitro, and so activates it in favour of nucleophilic attack, while only weakly activating the chloro site. The nitro substituent is a better leaving group than the chloro in aromatic nucleophilic substitution reactions where the initial addition of the nucleophile is the rate-determining step,[77] which is what completes the set of factors leading to the formation of the undesired product **201**. The solution to this problem was then to replace the chloro with a fluoro group, to activate the desired reaction site more strongly, using the starting material 3-fluoro-4-nitrobenzonitrile **180** as discussed in Section 2.1.5.



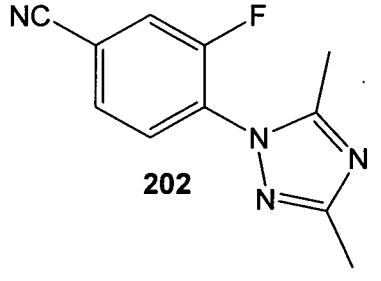
Scheme 65

The minor product obtained in the reaction was initially believed to be the desired product 3-(3,5-dimethyl-1,2,4-triazol-1-yl)-4-nitrobenzonitrile **200** as mass spectrometry showed the correct molecular weight of 243 Da, and proton NMR spectroscopy appeared to confirm the correct structure. On closer inspection, the peaks for the aromatic protons did not appear in the expected order or with the correct coupling constants. For example, the peak of highest shift, at 8.28 ppm, would be expected represent the 5-proton next to the nitro group, the strongest electron-withdrawing substituent, but this shows only *meta* splitting of 1.8 Hz, so appears more like the 2-proton between the cyano group and triazole ring. Comparing this spectrum with that of the previously synthesised isomeric structure **197**, it was immediately apparent that the minor product in this reaction was also 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile **197**. Scheme 66 shows the likely mechanism for the formation of this unexpected isomer; in the anionic intermediate, which would normally give the chloro species **201**, the nitro group must be able to migrate to the chloro position. When aromaticity is restored to the benzonitrile ring, the chloro group is lost instead of the nitro, as it is the better leaving group in this step, to result in **197**.



Scheme 66

It was hoped that replacing the chloro substituent of **174** with a fluoro group, as in 3-fluoro-4-nitrobenzonitrile **180**, might promote substitution at the required position; the stronger base cesium carbonate was once again employed as in the synthesis of the aniline **198**. Other than the stronger base, the general reaction method was followed, and after 2 days heating and DCM work-up, column chromatography gave two products. The first product obtained was suspected to be the desired product, 3-(3,5-dimethyl-1,2,4-triazol-1-yl)-4-nitrobenzonitrile **200**, but both mass and proton NMR spectra were inconclusive as there were many impurity peaks.



The second component obtained was pure, and its proton NMR spectrum showed the the fluoro substituent was still present, manifesting itself in extra fluoro splitting of the aromatic proton peaks. There are two multiplets, at 7.76 and 7.74 ppm, being so close together it is hard to be certain which is the 2-proton and which the 6-proton, the fluoro group only being mildly electron-donating. Interestingly, both methyl groups show up at 2.34 ppm, evidently the fluoro group has no effect on these even though

the 5-methyl is closer in space. Mass spectrometry showed a molecular weight of 216 Da, somewhat lower than that of the desired nitro product **200**, and this confirmed the structure of this species as 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-fluorobenzonitrile **202**, obtained in 21% yield. Clearly the nitro group is still more reactive than the fluoro, therefore the undesired product is still the main one.

2.2.3.7 Proton NMR Data

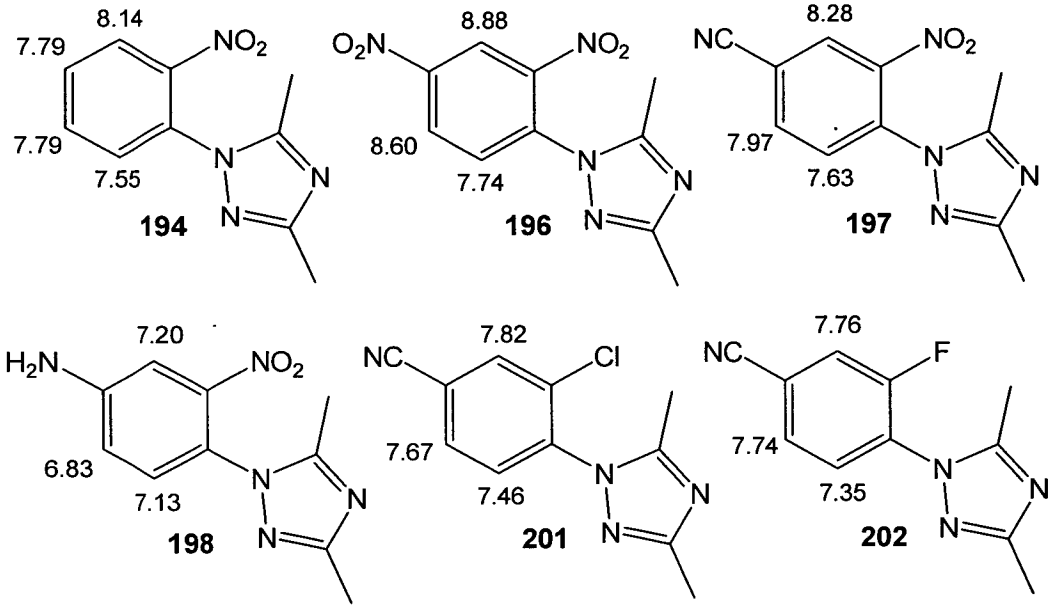


Figure 5: chemical shifts of 2-azolylbenzene compounds

When comparing the proton NMR spectra of some of these substituted nitrophenyl precursors to the parent compound **194**, it is clear to see the effects of adding various substituents *para* to the azolyl position. With the strongly electron withdrawing nitro group in **196**, the two adjacent protons are deshielded enough to raise their chemical shifts by up to 0.8 ppm; with the less strongly electron withdrawing cyano group in **197** they are raised by only 0.2 ppm. With the only example of an electron donating group, in the aniline species **198**, the effect is to reduce the shifts of the 2- and 6-protons by almost 0.9 ppm relative to the parent compound **194**. The effects of these different substituents on the methyl groups on the triazole ring is negligible, although the shifts of these groups on the aniline **198** are over 0.1 ppm lower than on the dinitrophenyl species **196**.

The unwanted products from the attempted synthesis of the isomeric benzonitrile compound **200** are interesting and can be used to show the effects of substituting the nitro group for a more weakly electron withdrawing substituent. In the chlorobenzonitrile species **201** the proton in the 2-position has a chemical shift nearly 0.5 ppm lower than in the nitro equivalent **197**; the difference in the fluoro species **202** is even greater. In comparing the two dinitrophenyl species, the imidazole **195** has aromatic protons with chemical shifts up to 0.6 ppm lower than those of the triazole **196** (8.20, 8.17 and 7.53 ppm); which is in contrast to the difference seen between the pyridine compounds **189** and **190**. This difference was not observed between the pyridine species **189** and **190**, which may have been prevented by the heteroatom next to the azole substituent.

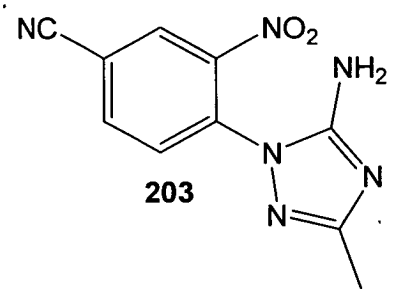
2.2.4 Substituted Triazoles

2.2.4.1 Attempted Synthesis of 4-(3-Amino-5-methyl-1,2,4-triazol-1-yl)-3-nitro-benzonitrile

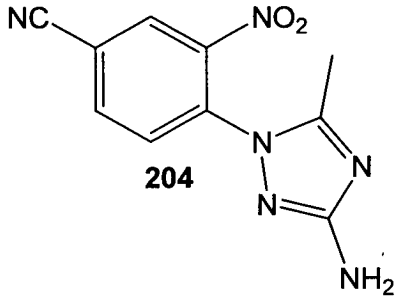
As discussed in Section 2.1.6, 5-methyl-1,2,4-triazol-3-amine **181** was synthesised in order to have an amino substituent on the triazole ring of the final 6,5,5 system, for the purpose of attaching a ballast, with potentially less effect on the coupling reaction than placing this on the phenyl ring. As a cyano substituent was already believed to be a desirable electron-withdrawing group for this type of coupler, the triazolamine **181** was reacted with 4-fluoro-3-nitrobenzonitrile by the ethanol method now adopted as the general method for this reagent. The problem with the asymmetric triazole **181**, is that reaction with the benzonitrile could conceivably take place at either the 1- or 2-nitrogen, or even the amine, so a mixture of isomers could be expected.

A reflux time of 10 h was found to be necessary, by monitoring the reaction using thin layer chromatography, and some unreacted benzonitrile had to be filtered off. The crude product obtained was found by proton NMR spectroscopy to contain both expected isomers as well as an unknown product; column chromatography only succeeded in purifying the unwanted isomer, 4-(5-amino-3-methyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile **203**. The identity of this species could not be confirmed by NMR

spectroscopy, as its spectrum is close to what would be expected for the desired isomer **204**, the chemical shifts of the methyl group and aromatic 5-proton being largely unaffected by the orientation of the triazole ring. An FVP reaction was selected as a suitable method to determine conclusively that this was the isomer **203**, being less time consuming than a NOESY NMR experiment, as it did not give a 6,5,5 tricyclic system. The yield of this unwanted isomer **203** was very low, but the fact that it was favoured over the desired isomer, 4-(3-amino-5-methyl-1,2,4-triazol-1-yl)-3-nitro-benzonitrile **204**, suggests that the electron-donating amino group activates the nitrogen in the 2-position to make this the favoured reaction site.

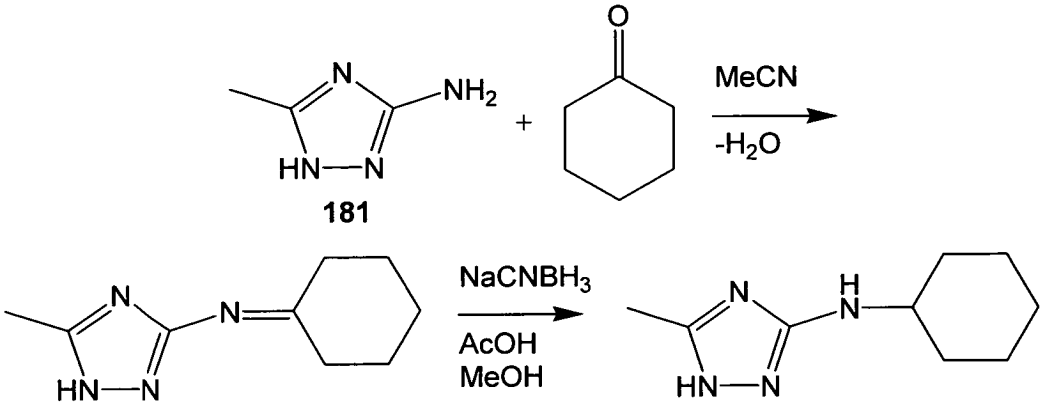


203



204

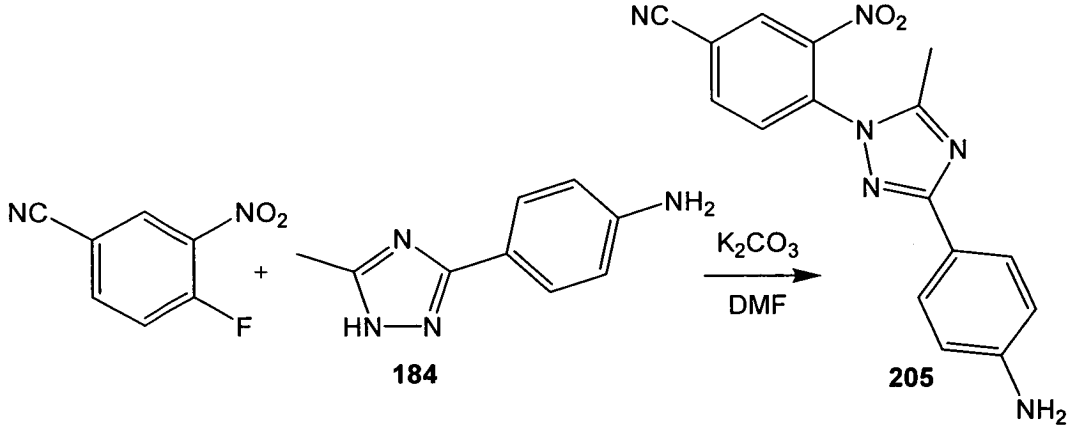
The attempted solution to the unwanted isomer problem was to a add a bulky substituent to the amino group of **181**, and a reductive amination process with cyclohexanone was selected (Scheme 67).[78] The cyclohexyl secondary amine was expected to be bulky enough to drive reaction to the 1-position of the triazole ring, and remain in the final coupler and still allow ballasting. The reagents were heated together under reflux in acetonitrile, with a Dean-Stark trap fitted to collect the water given off. The imine intermediate appeared to have been formed by NMR analysis of the crude product, and so the second step was carried out, reaction with sodium cyanoborohydride and acetic acid. Unfortunately, the crude oily product obtained could not be identified and so this experiment was discontinued.



Scheme 67

2.2.4.2 4-[3-(4-Aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile

Following the failure to add a cyclohexyl group to the amine **181** in the previous section, 3-(4-aminophenyl)-5-methyl-[1,2,4]-triazole **184** was synthesised (Section 2.1.7) as an alternative solution to the regioselectivity problem of the reaction with the fluoronitro-aromatics. In order to effect nucleophilic substitution at the 1-nitrogen on the triazole ring of **184**, a mild version of the general method was employed, as with the pyridine **193**. As shown in Scheme 68, the two reagents were reacted in DMF in the presence of potassium carbonate, with heating under reflux for 30 min, and after ethyl acetate work-up the crude product was separated by column chromatography to give a product of roughly 80% purity.



Scheme 68

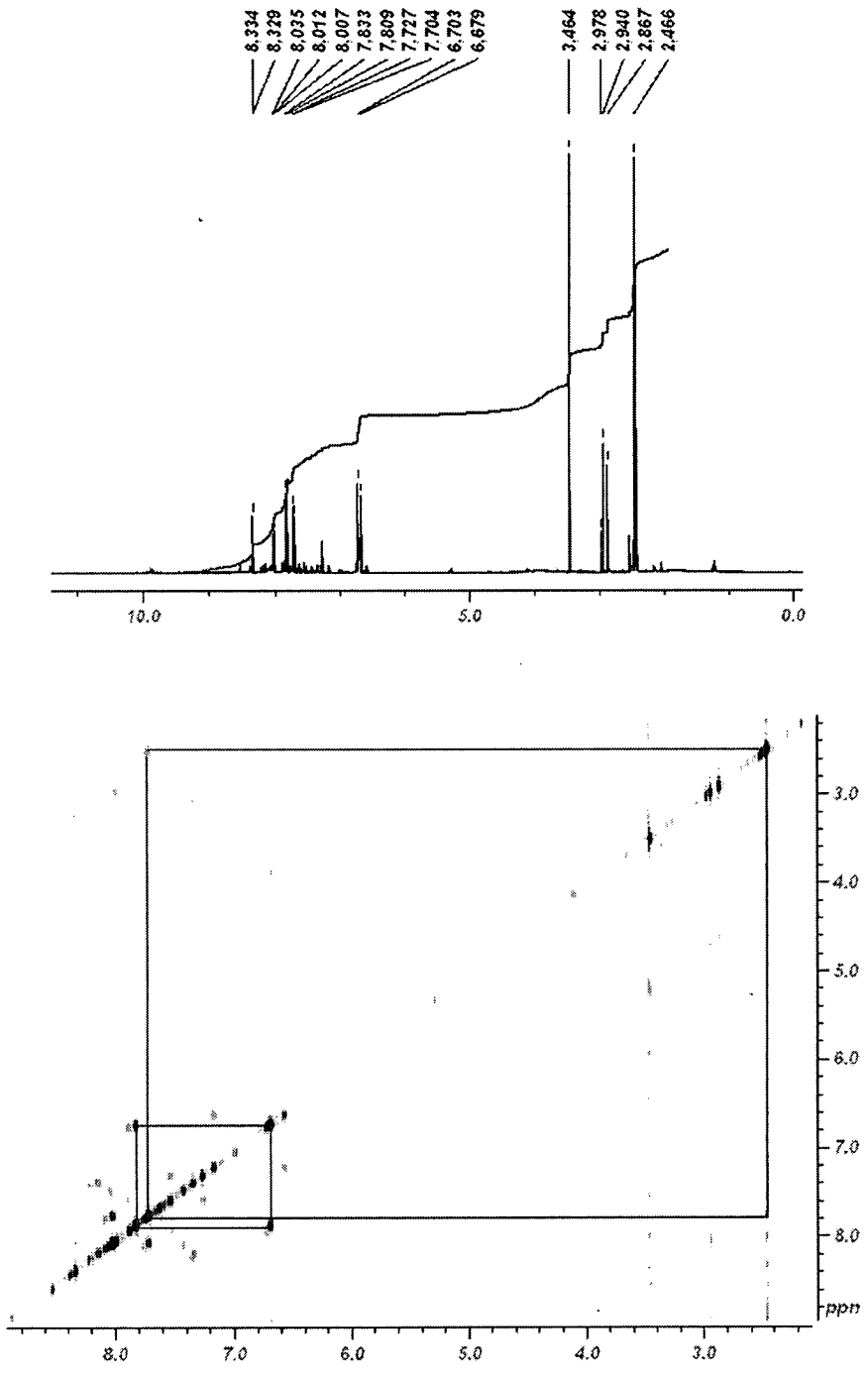
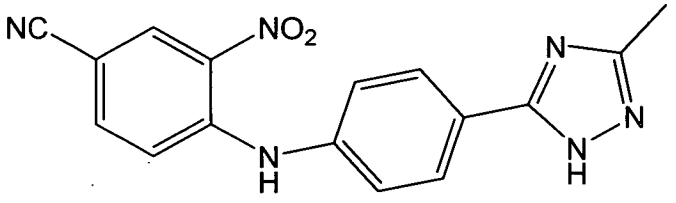


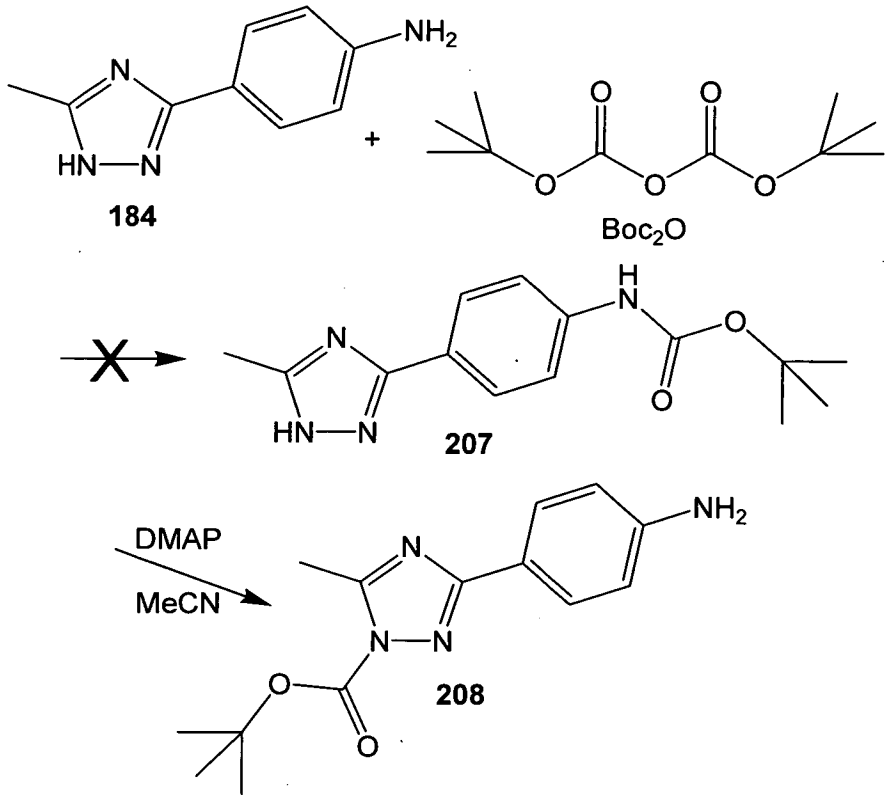
Figure 6: NOESY NMR experiment on 205

Reaction of the unsymmetrical triazole reagent **184** could take place at either the 1- or 2-nitrogen atom on the ring. But as mentioned earlier, using a bulky aryl group might be sufficient to hinder reaction at the unwanted 2-position. Proton NMR spectroscopic analysis of this product was inconclusive in itself, but the actual identity of the product was finally confirmed as the desired isomer 4-[3-(4-aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile **205** by means of a NOESY NMR experiment, shown in Figure 6, which demonstrates interaction between the protons of the methyl group and the aromatic proton in the 5-position of the benzonitrile ring. If the undesired isomer had been obtained then the expected indication might be an interaction between the two aniline protons next to the triazole ring and the benzonitrile 5-proton.



206

Initially, the synthesis of **205** was attempted using the ethanol method, as had become typical for reactions of 4-fluoro-3-nitrobenzonitrile with triazoles. The ethanol reaction took place over 4 h, and the semi-crystalline product which was obtained was found by proton NMR spectroscopy to contain only traces of the desired product **205**. The major product, obtained in 93% yield and partially purified by recrystallisation, was shown by NMR spectroscopy to be 4-[4-(5-methyl-1*H*-1,2,4-triazol-3-yl)-phenylamino]-3-nitrobenzonitrile **206**. The proton NMR spectrum of this unwanted product is characterised by a broad singlet at 9.98 ppm, which is the secondary amine proton formed by reaction of the NH_2 group and the fluoro site. Hence, the primary amino group of the aniline substituent has proved itself to be more nucleophilic than either secondary amine in the triazole ring under these conditions. Also, the methyl group is represented in the proton NMR spectrum by a peak at 2.14 ppm, a significantly lower shift than the methyl groups on pyrolysis precursors where they are close to nitro groups.



Scheme 69

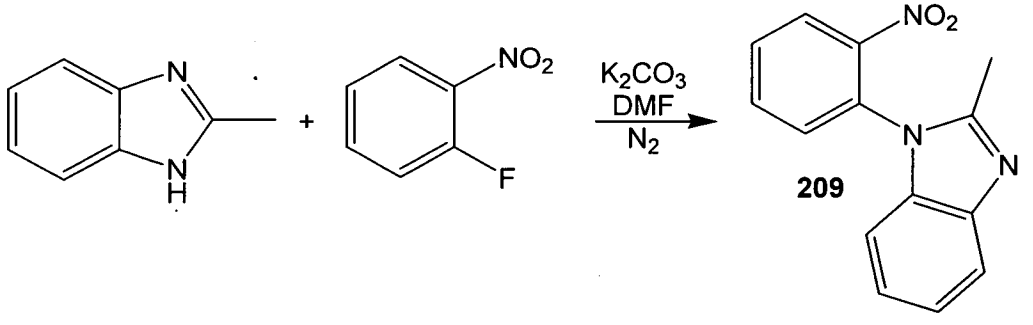
In order to increase the probability of synthesising the target coupler with an aniline group in the 2-position, the reagent 3-(4-aminophenyl)-5-methyl-[1,2,4]-triazole **184** had to be protected on the primary amino group. A Boc group (*t*-butoxycarbonyl) was chosen as a suitable protecting group, and it was expected that this would be lost during pyrolysis (by retro-ene loss of isobutene followed by decarboxylation)[79] to give the desired coupler. Reaction of the triazole **184** with di-*tert*-butyl dicarbonate (Boc_2O) and DMAP (4-dimethylaminopyridine) base was carried out overnight at room temperature in acetonitrile (Scheme 69).[80] The white crystals obtained from concentration of the reaction mixture were then found not to be the aniline protected product **207**, but an isomer where the Boc group had reacted at the triazole ring **208**. The NH_2 group was still present, as shown by a broad singlet at 5.70 ppm in the proton NMR spectrum. The regiochemistry of this product was not established, but a single isomer was obtained. This unexpected result was still very useful in that is showed that nucleophilic attack by the triazole ring was favoured in basic conditions,

so this led to the more conventional reaction of the aniline triazole **184** with 4-fluoro-3-nitrobenzonitrile described at the start of this section.

2.2.5 Benzimidazole Precursors to Tetracyclic Systems

The scope of the project was increased by work on the synthesis of a range of novel 6,5,5,6 systems, in which a benzene ring is added to the outer azole ring of **1**. These were expected to have only limited use in photographic film due to their planar structure, which leads to stacking and therefore higher crystallinity, but the effect of the extra benzene ring on coupling was an intriguing question. The routes to these systems were largely identical to those employed for most FVP precursors discussed so far, a nitrophenyl species was reacted with a methylbenzimidazole by the general method, with potassium carbonate in DMF.

2.2.5.1 2-Methyl-1-(2-nitrophenyl)benzimidazole



Scheme 70

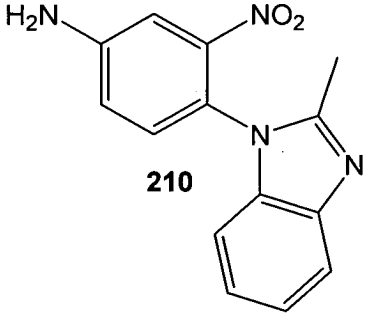
2-Methylbenzimidazole was reacted with *o*-fluoronitrobenzene in the presence of potassium carbonate, under an atmosphere of nitrogen, according to Scheme 70.[54] Work-up was carried out with DCM extraction, and residual DMF remaining after concentration of the crude product was removed by co-evaporation with toluene. The oily crude product was then triturated with ethyl acetate and light petroleum to crystallise the product, 2-methyl-1-(2-nitrophenyl)benzimidazole **209**, in a 78% yield, which is considerably higher than typical yields for 6,5,5 precursors. The increased crystallinity of the benzimidazole product naturally reduces its solubility and so leads to an easier work up. In addition to this, the nitrogen atmosphere could have some

effect on increasing yield, but it could be that benzimidazole is a stronger nucleophile than an azole, due to the electron-donating effects of the benzene ring.

Assigning the peaks from the proton NMR spectrum is not easy due to there being two benzene rings, but comparison with the related precursor **194** is worthwhile. The 3-proton on **209**, next to the nitro group has a shift of 8.17 ppm, which is only slightly higher than that of **194**. Likewise, the other clearly assignable peak, for the methyl group at 2.44 ppm, is in a similar region to both peaks for the triazole methyl groups of **194**. The difference between the benzimidazole group and the triazole group is shown by the considerably low shift of the 6-proton on the nitrophenyl ring at 6.89 ppm, the adjacent electron rich benzimidazole group is much more strongly electron-donating.

2.2.5.2 4-(2-Methylbenzimidazol-1-yl)-3-nitroaniline

In order to synthesise a ballasted version of a 6,5,5,6 coupler, an amino FVP precursor 4-(2-methylbenzimidazol-1-yl)-3-nitroaniline **210** was synthesised by the same route. 2-Methylbenzimidazole and 4-fluoro-3-nitroaniline were reacted together using the general method, under an atmosphere of nitrogen, and column chromatography gave the product **210** as the second component in a 35% yield. This was obtained in a much lower yield than for the parent compound **209** most likely because of the amino group on 4-fluoro-3-nitroaniline deactivating the fluoro site to a certain degree.



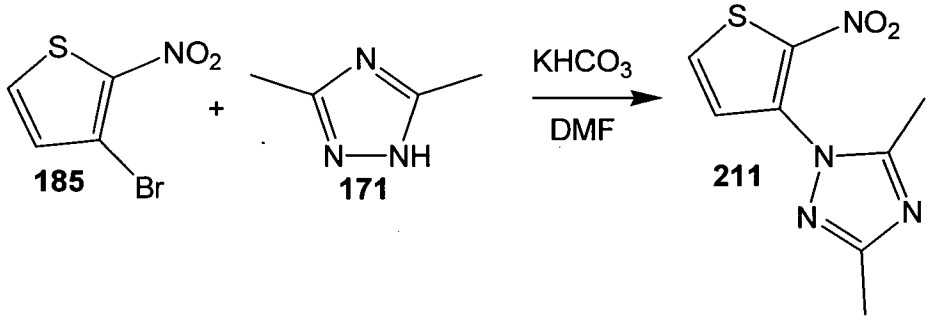
210

The product **210** was characterised by its mass spectrum (*m/z* 268 Da), and proton NMR spectroscopy, in which the benzimidazole group is clearly attached to the aniline ring judging from the matching integrals of the various peaks. The effects of the electron-donating amino group on the chemical shifts of the aromatic protons of **210** are as would be expected, lowering them significantly. The doublet of doublets at

6.92 ppm represents the proton in the 6-position, highly shielded by the amino group, but this effect is still not as great as that of the benzimidazole group on the 5-proton, with the lowest shift of the aromatic protons at 6.84 ppm.

2.2.6 The Thiophene 5,5,5 Precursor

The reaction to form this precursor was a slight variation on the general method; Scheme 71 demonstrates how 3-bromo-2-nitrothiophene **185** and 3,5-dimethyl-1,2,4-triazole **171** were reacted by an extension of the literature method, in which **185** had been reacted with a range of azoles using potassium bicarbonate as the base with heating at 110 °C.[81] With the bromo substituent on the reaction site, it would be a less effective leaving group than a fluoro or chloro group, but appears to be sufficiently activated by the nitro group.

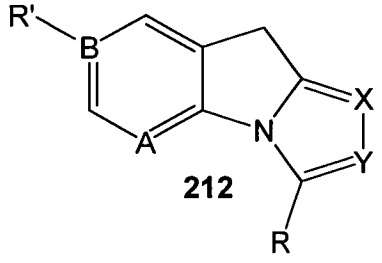


Scheme 71

These reaction conditions may not have been optimal however, as the yield of 3-(3,5-dimethyl-1,2,4-triazol-1-yl)-2-nitrothiophene **211** was only 14%. The product was characterised by its mass spectrum showing the correct mass peak, and its proton NMR spectrum. On the thiophene ring, it is interesting to observe that the two protons have slightly higher chemical shifts than in the bromo starting material **185**, the electron donating triazole ring would be expected to shield these.

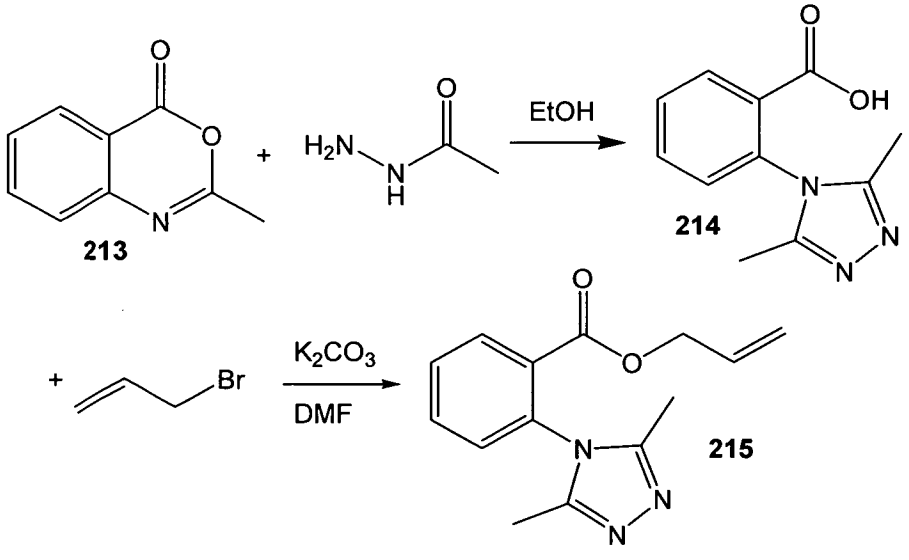
2.2.7 Precursors to Isomeric 6,5,5 Systems

So far, most compounds produced have been potential precursors to 6,5,5 tricyclic systems following the general structure of **1**. An interesting question was how would systems of the type **212** compare as couplers, where the groups R and Y have been interchanged. Since nucleophilic substitution always occurs at the 1- or 2-heteroatoms of 1,2,4-triazoles, a totally different route would have to be used. Luckily, a route to a potential triazole precursor was found in the literature and so this new direction was made possible.



212

2.2.7.1 Allyl 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate



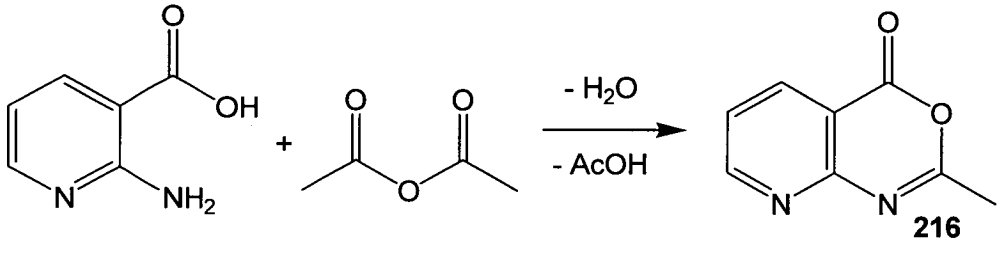
Scheme 72

Allyl esters are known precursors of phenyl radicals, as they are radically cleaved to give a stabilised allyl radical and carbon dioxide.[53] A precursor to **212** can be made from a carboxylic acid, a route to which was available in the literature and is shown in

the first step of Scheme 72.[82] 2-Methyl-4*H*-3,1-benzoxazin-4-one **213** was reacted with acetic hydrazide in ethanol, to give 2-(3,5-dimethyl-1,2,4-triazol-4)-benzoic acid **214**. The product **214** was found to be extremely insoluble in most NMR solvents, and the literature melting point was over 300 °C, but a proton NMR spectrum in deuteriated TFA, as well as mass spectrum, confirmed the product.

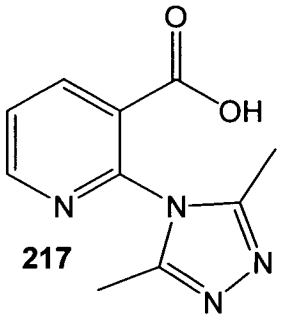
According to the second part of Scheme 72, allyl bromide was reacted with **214** in DMF in the presence of potassium carbonate, with stirring at room temperature overnight.[83] After DCM work-up the product crystallised out of a small volume of residual DMF solution, the white crystals being allyl 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate **215** in 60% yield. Mass spectrometry confirmed that the allyl ester product **215** had been successfully synthesised, and this evidence was backed up by the proton NMR spectrum. Of the aromatic protons, the proton in the 6-position, next to the electron-withdrawing ester group, has the highest shift at 8.10 ppm, while the 3-proton, next to the electron-donating triazole ring, has the lowest aromatic shift of 7.20 ppm.

2.2.7.2 Attempted Synthesis of Allyl 2-(3,5-Dimethyl-1,2,4-triazol-4-yl)-nicotinate



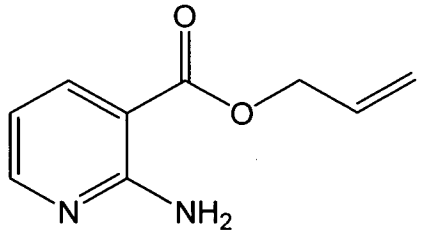
Scheme 73

In order to synthesise a pyridine equivalent of the previous compound **215**, 2-methylpyrido[2,3-*d*][1,3]oxazin-4one **216** was first made by reacting 2-aminonicotinic acid with acetic anhydride, with heating under reflux for 1 h (Scheme 73).[84] This product was confirmed by the observed melting point and the proton NMR spectrum matching those reported in the literature.



217

The next step was carried out as for the synthesis of the benzoic acid **214**, with acetic hydrazide and ethanol, and the resulting white crystalline solid was assumed to be the desired product 2-(3,5-dimethyl-1,2,4-triazol-4-yl)-nicotinic acid **217**. This was therefore allylated by the usual method (allyl bromide and potassium carbonate in DMF) to give a crystalline product, which was found to be allyl 2-aminonicotinate **218**. The proton NMR spectrum of this product showed a broad singlet at 6.71 ppm, representing the unexpected amino group, and in addition, there were no methyl peaks. The mass spectrum confirmed the structure of this unwanted product, in 95% yield. Most likely, the previous reaction of the pyrido-oxazinone **216** with acetic hydrazide had converted it back to its original starting material, 2-aminonicotinic acid; potentially nucleophilic attack by ethanol could remove the ethylene group as diethyl ether. However, repeating the reaction with a non-protic solvent, acetonitrile, only gave a similar result so the work was discontinued.



218

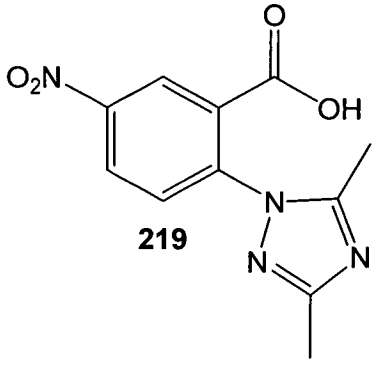
2.2.8 Allyl 2-(azolyl)benzoate Analogues

An allyl ester functionality is a favourable leaving group for a flash vacuum pyrolysis precursor, as it splits to form a stabilised allyl radical and inert carbon dioxide. This is preferable to the nitro group used in most compounds produced so far in this thesis, as this type of leaving group leads to reactive NO_x by-products, which can degrade the FVP product soon after it is formed. For this reason, a route to an allyl ester

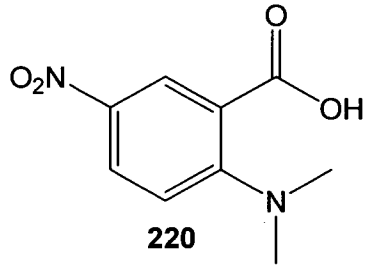
analogue of one of the previously synthesised precursors was devised, initially that of 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline **198**, as the emphasis at this point in time was to find a good route to a coupler which could be ballasted.

2.2.8.1 The Benzoic Acid Starting Material

Initially, 2-chloro-5-nitrobenzoic acid and 3,5-dimethyl-1,2,4-triazole **171** were reacted together by the general method, potassium carbonate and DMF, in order to synthesise 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoic acid **219**. The predicted problem here is that the benzoic acid might react with the potassium carbonate base, and so prevent the deprotonation of the triazole, and this did occur, resulting in none of the desired product **219**. The orange solid product obtained was found by mass spectrometry and proton NMR spectroscopy to be a mostly pure sample of 2-dimethylamino-5-nitrobenzoic acid **220** in 38% yield, presumably formed by hydrolysed DMF. Alternative reactions, which dispensed with base were attempted, in both ethanol and DMSO, but neither of these resulted in any reaction at all.



219

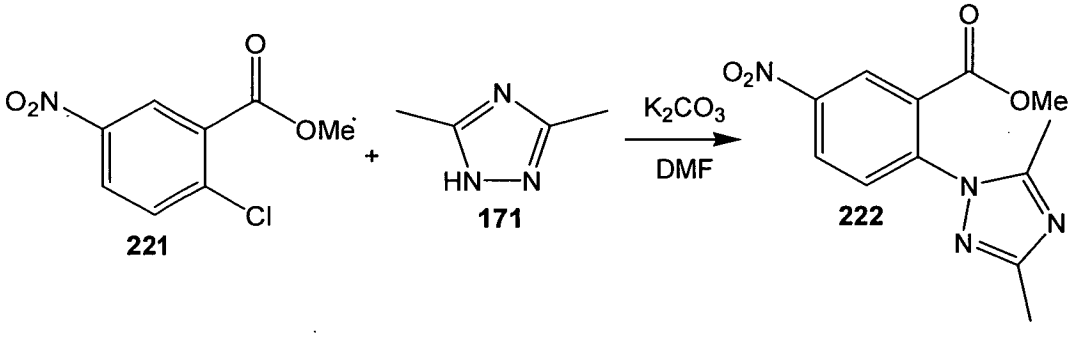


220

2.2.8.2 An Ester

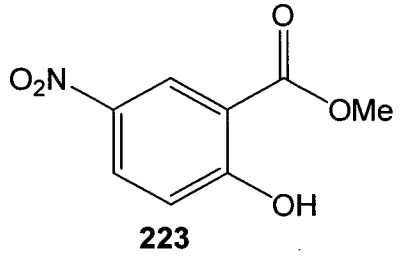
To overcome the problem of the acidic reagent it was decided to use a methyl ester, which should still be convertible to the allyl ester at a later stage by a transesterification process. Methyl 2-chloro-5-nitrobenzoate **221** and 3,5-dimethyl-1,2,4-triazole **171** were reacted together in DMF in the presence of potassium carbonate as usual, followed by extraction into ethyl acetate (Scheme 74). Mass spectrometry of a sample of the crude product identified a phenolic by-product, which would have been formed by hydrolysis of the chloro substituent, and this was removed by extraction with aqueous potassium carbonate solution after micro-scale

tests. The desired product, methyl 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoate **225**, was then obtained by column chromatography as the fourth component, which required further purification by trituration with ethyl acetate and light petroleum resulting in 14% yield.



Scheme 74

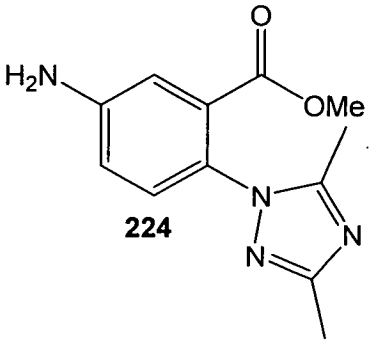
Electrospray mass spectrometry was the initial method used to identify the product as the compound **222**, giving the correct mass peak of the M+1 ion, and the proton NMR spectrum further confirmed the structure. The two peaks corresponding to the methyl groups on the triazole ring appear at 2.27 and 2.34 ppm, this higher shift showing the proximity of the 5-methyl to the ester, which would provide ring current deshielding effects. The aromatic proton in the 3-position has a chemical shift of 7.57 ppm, being situated next to the electron-donating triazole ring.



The phenolic by-product, methyl 2-hydroxy-5-nitrobenzoate **223** was isolated by acidification of the aqueous basic extracts, and then ethyl acetate extraction to give a bright orange crystalline product in 14% yield. This appears to be another result of water contaminated DMF, only instead of water causing formation of dimethylamine, the chloro site appears to be strongly activated enough by the ester and nitro groups to be directly susceptible to hydrolysis. The proton NMR spectrum displays the

characteristic phenol peak at 11.37 ppm, deshielded by hydrogen bonding to the carbonyl group, and this strongly electron donating hydroxy group affects the adjacent 3-proton by shielding it to reduce its chemical shift to 7.02 ppm. Electrospray mass spectrometry confirmed the formation of this by-product, showing the mass peak as the only negative ion.

2.2.8.3 Reduction of the Nitro Group



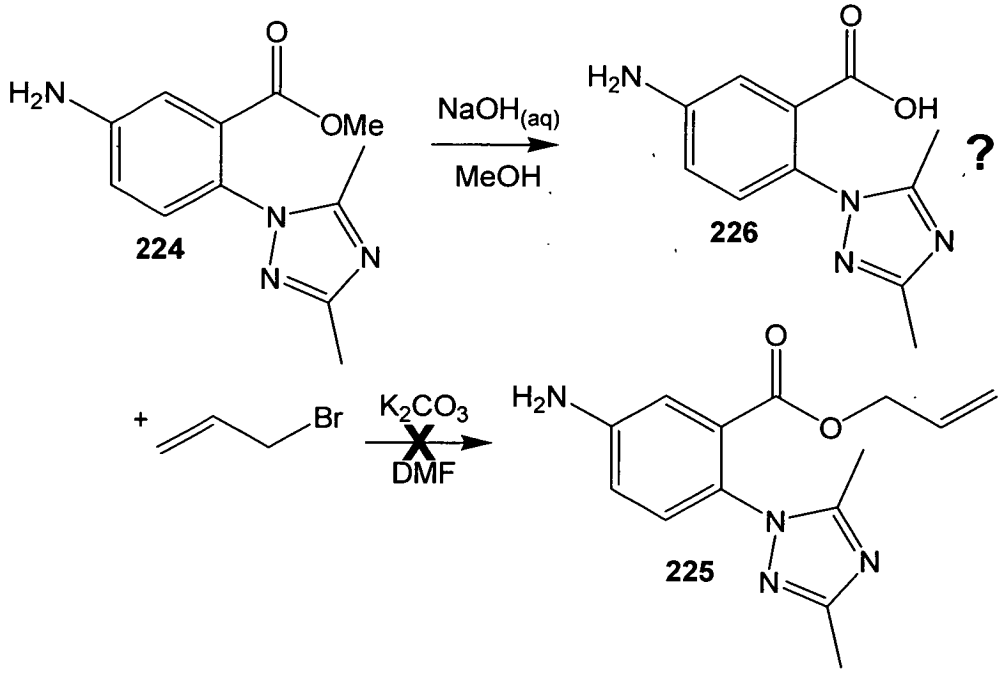
224

The nitro group in compound **222** was reduced by the standard method of hydrogenation under increased pressure with palladium/charcoal catalyst. The amino product **224** was obtained as a thick oily substance in 97% yield, confirmed by mass spectrometry. Comparing the proton NMR spectrum of this compound with that of the starting material **222** the formation of the desired product was evident by the appearance of a broad singlet at 4.02 ppm, corresponding to the amino group.

2.2.8.4 Allylation

In order to allylate **224** to give the targeted pyrolysis precursor **225**, the methyl ester would have to be hydrolysed to an acid initially, and then allylated in the usual way without purification of the intermediate.[54] According to Scheme 75, a solution of **224** in methanol was treated with aqueous sodium hydroxide, with heating under reflux for 2 h, and then the methanol was removed and replaced by DMF, and allylation of the intermediate **226** was attempted with allyl bromide and potassium carbonate in the usual manner. DCM work-up gave a small quantity of insoluble and unidentifiable grey material. Reasons for the failure were unclear, but this area of research was abandoned as yields had been consistently low (with the exception of the reduction), and so this route to an amino coupler was judged to be too long and complicated to be

worth optimising. While other pyrolysis precursors discussed earlier featured the nitro leaving group, which is not wholly satisfactory for FVP purposes, the ease of synthesis was responsible for short, acceptable routes.

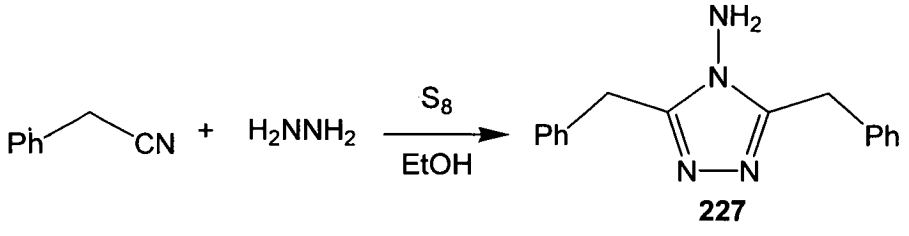


Scheme 75

2.2.9 A Triazolamine Precursor

As a result of recent work on an FVP precursor featuring a dimethylamino leaving group,[85] a new route to a version of an isomeric 6,5,5 system was devised featuring such a group.

2.2.9.1 3,5-Dibenzyl-[1,2,4]-triazol-4-amine

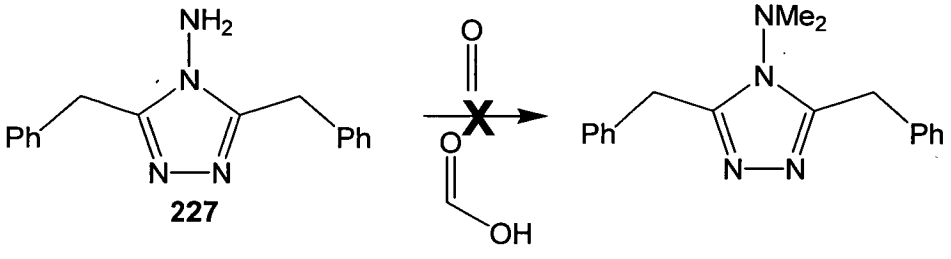


Scheme 76

A straightforward synthesis to 3,5-dibenzyl-[1,2,4]-triazol-4-amine **227** was discovered in the literature, which was predicted to be of use as a precursor to a coupler isomeric to the general structure **1**.[86] The amino group was expected to be radically cleaved during pyrolysis, and then cyclise onto one of the phenyl rings, to leave the other as a benzyl substituent. According to Scheme 76, a solution of phenylacetonitrile and hydrazine hydrate in ethanol was treated with sulfur, and then heated under reflux for 3 h under an atmosphere of nitrogen, resulting in the desired triazolamine product **227** in 65% yield. Comparison of the observed melting point and the proton NMR spectrum with the literature, and mass spectrometry giving the correct mass peak *m/z* 264 Da gave the main evidence for the successful formation of **227**.

2.2.9.2 Attempted Synthesis of (3,5-Dibenzyl-[1,2,4]-triazol-4-yl)-dimethylamine

As the original example of an amino leaving group for FVP was dimethylamine,[85] an attempt was made to methylate **227**, which was also pyrolysed as the primary amine. As shown in Scheme 77, 3,5-dibenzyl-[1,2,4]-triazol-4-amine **227** was treated with formic acid and formaldehyde, and heated at 80 °C for 24 h.[87] On this occasion however, DCM work-up gave an impure material found to be mostly unreacted starting material **227**.



Scheme 77

2.3 Flash Vacuum Pyrolysis Reactions

2.3.1 General Method

According to Scheme 48, the pyrolysis precursor compounds discussed in the previous section were subjected to flash vacuum pyrolysis to give products of the type **1**.

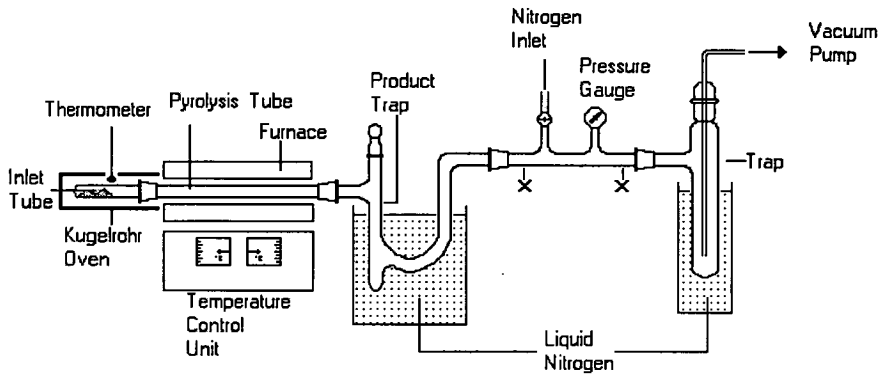
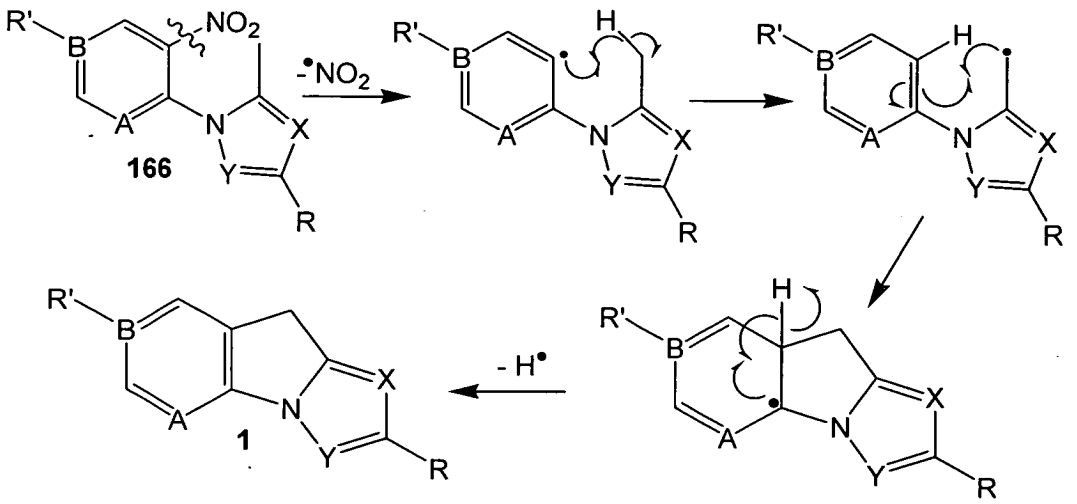


Figure 7: the FVP apparatus

Figure 7 shows the general apparatus used for flash vacuum pyrolysis, based on the design of W.D. Crow, of the Australian National University. The system is evacuated to a pressure of 10^{-2}-10^{-3} Torr, by means of a high capacity oil pump off the diagram to the right. On the small scale, samples of around 30 – 50 mg were heated in the inlet tube by a glass Buchi oven, which vaporised them into the gaseous phase, where they passed into the furnace. For formation of aryl radicals from nitro-compounds, the furnace was maintained at 850 °C, a temperature discovered earlier as optimum for this range of experiments.[67] Inside the furnace the heat is sufficient to cause bond cleavage to generate radicals, and as the pressure is so low, generally only intramolecular reactions occur. In this way, the central ring of the potential dye coupler compounds is formed in one easy step. After only milliseconds in the furnace tube, the products are collected at the entrance of the U-tube trap cooled in liquid nitrogen. The entire crude pyrolysate was then removed from the trap by dissolving in deuteriated chloroform, and then analysed by proton NMR spectroscopy. The spectra obtained generally showed the desired product as being the main species present, with only small quantities of impurities.

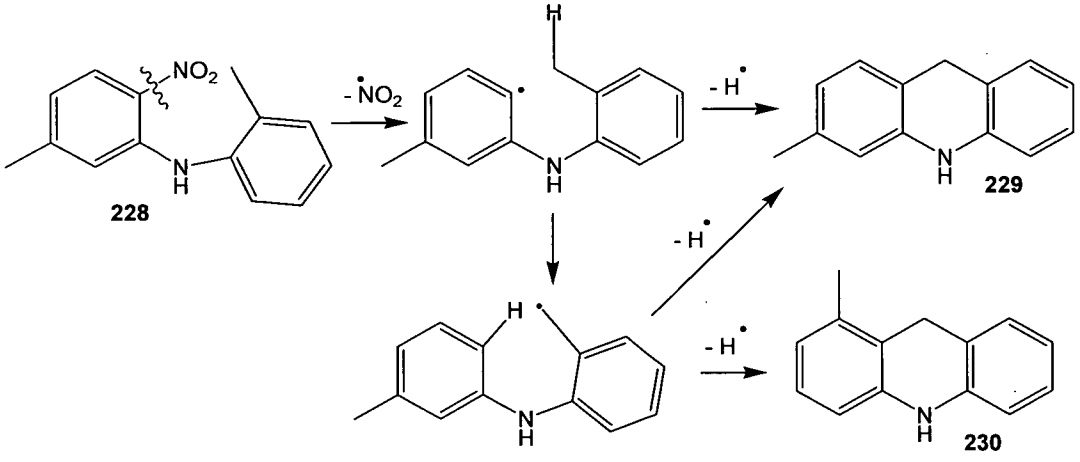


Scheme 78

The general mechanism of the cyclisation process is outlined in Scheme 78. In the first step the weak C-N bond attaching the nitro group to the six membered ring is broken by thermal homolysis caused by the high temperatures in the furnace. This leaves a phenyl or pyridyl radical species, accompanied by loss of the nitro group as a nitrogen dioxide radical. The phenyl radical then abstracts a hydrogen atom from the methyl substituent on the azole ring. The substituted methyl radical then reacts with the π-system of the six membered ring, to form a resonance-stabilised cyclohexadienyl type species, and form the central pyrrole ring. The intermediate shown is one of three resonance structures. In the final step a hydrogen atom is lost as a radical in a drive to return aromaticity to the six membered ring. This leaves the fused tricyclic pyrrole product.

Scheme 79 shows an experiment by which the second step of the mechanism, hydrogen transfer, was established for a related system.[88] A *meta*-methyl substituted diphenylamine **228**, with a nitro radical generating group in the *ortho* position, was pyrolysed. The second step could then either involve direct cyclisation straight to 3-methyl-9,10-dihydroacridine **229**, or could involve hydrogen abstraction to give a methyl radical. This new radical could then cyclise by attacking the opposing ring either *ortho-* or *para-* to the methyl substituent to give **229** or **230** respectively. with the methyl group in the 1-position. The observation of a 3:1 mixture of both products

is clear evidence that the methyl radical must be involved, **229** being favoured for steric reasons. In the range of compounds pyrolysed during this period of research, the compounds were either substituted *para* to the azole ring, giving the same product by both routes, or had a heteroatom in the other *ortho* position, thus only permitting one product.



Scheme 79

2.3.2 Large-scale FVP Reactions

In the reaction mechanism of the pyrolytic process, the first step involves loss of nitrogen dioxide, which is a reactive species. This can either decompose at the high temperatures involved, or react with itself or with other volatile species present to form a number of nitrogen oxide (NO_x) species, which might potentially react with products. There are a number of nitrous species which could be formed during these pyrolysis reactions, and observations of the U-tube confirm some of the suspected compounds. Generally, during an FVP reaction, a layer of blue or turquoise material was observed to form in the U-tube just above the level of liquid nitrogen, often before the main product started to appear. As well as this, certain pyrolyses also featured a white layer a short distance above the blue layer. After pyrolysis was complete, and the system allowed to warm to room temperature, the material in the U-tube quickly melted to a brown liquid, and evaporated soon afterwards with a noxious odour. The blue colour could be a dinitrogen trioxide, N_2O_3, which dissociates with heat to nitric oxide and nitrogen dioxide.[89] NO is also blue when solid, and when liquid, colourless as a gas, and very reactive. Nitrogen dioxide, NO_2, is also reactive

and is usually observed as a brown gas. The white layer is explained by the colourless substance dinitrogen tetroxide, N_2O_4, which dissociates when melting to NO_2.

On the small scale (~20 – 50 mg), proton NMR spectra of products have shown that the NO_x species have little effect on them, and the desired product is usually obtained in over 90% purity. On the large scale however, where samples up to half a gram are used, clearly a much larger quantity of product is formed and a lot more NO_x gases are given off. In the conventional FVP set up, large quantities of heterocyclic products are condensed in the warm area between the furnace and the U-tube, and so the NO_x gases become most problematic when they come into contact with warm products. Also, when these are collected together in the U-tube, reaction can occur when the system is warmed to room temperature.

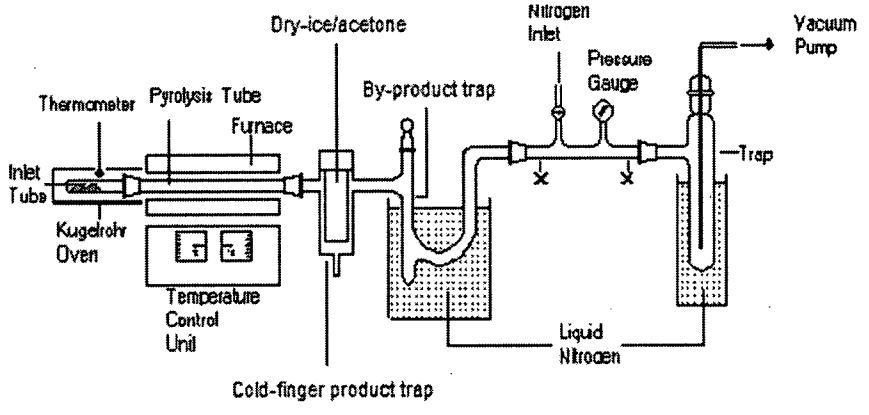


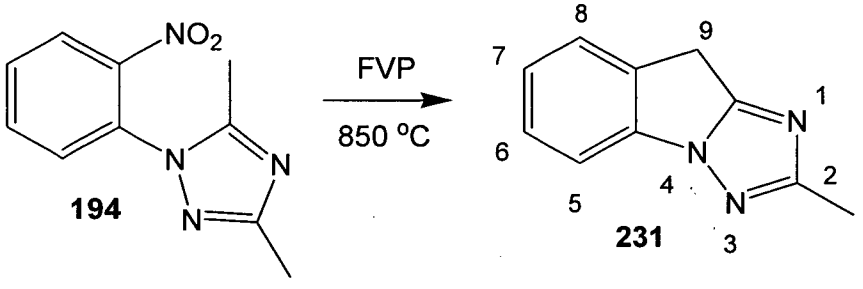
Figure 8: modified FVP apparatus

To address this problem, it was necessary to exploit the lower boiling and melting points of the NO_x by-product species. The NO_x species were still collected in the liquid nitrogen cooled U-tube, but a larger cold finger trap was added at the exit of the furnace tube to condense the organic products (Figure 8). This trap was cooled with dry ice and acetone, so being significantly warmer than the U-tube, so that the NO_x species could pass through without condensing and reacting with the product. This method was not perfect however. The cold finger trap had to be placed very close to the furnace, to create an environment where the organic products were cooled very

quickly to –80 °C rather than condensing in an intermediate warm area at the furnace exit, where the NO_x gases could react with product already collected. This led to the added problem that much of the product formed early on in the process would often decompose while waiting for the rest to come through. It is also possible that some side reactions involving NO_x by-products did occur. Crude products were removed by dissolving in dichloromethane, and were then purified by column chromatography.

2.3.3 Compounds Produced by FVP

2.3.3.1 FVP of 2-(3,5-Dimethyl-1,2,4-triazol-1-yl)nitrobenzene

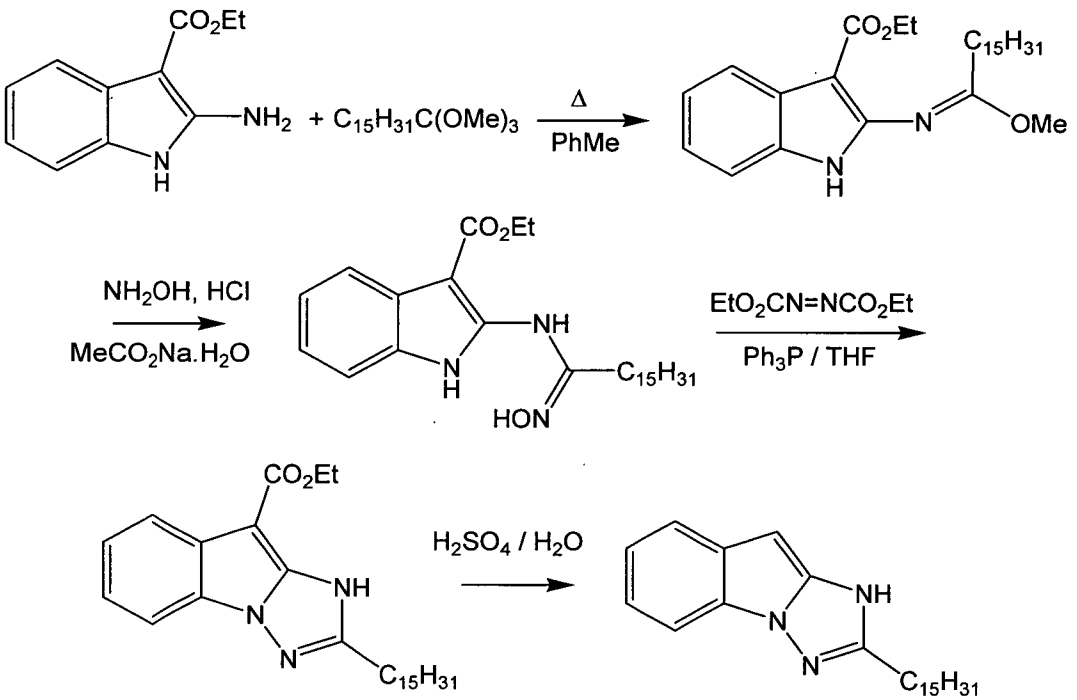


Scheme 80

The parent triazole coupler, 2-methyl-*9H*-[1,2,4]triazolo[1,5-*a*]indole **231**, had been made previously by flash vacuum pyrolysis,[67] but the scale and conditions had not been optimised. The precursor 2-(3,5-dimethyl-1,2,4-triazol-1-yl)nitrobenzene **194** was subjected to FVP under standard conditions and with column chromatography to purify the crude product (Scheme 80). Tests were carried out to increase the scale of this reaction from the small-scale, ~50 mg, up to 500 mg, using the standard U-tube trapping conditions. A sample of the crude pyrolysate was analysed by proton NMR spectroscopy, and each time was found to be of an adequate purity, with yields generally around 55%, therefore it appeared that the NO_x by-products were not reacting with this particular product.

As this compound had previously been synthesised it was characterised merely by comparison of proton NMR spectra with the literature.[67] With this and later

heterocyclic systems produced, the presence of a peak corresponding to the methylene group in the 9-position, at ~ 4.0 ppm, was good evidence that the pyrolysis was successful. In compound **231**, this signal appears at 3.85 ppm (3.83 ppm in the literature), and judging from the integrals of the spectrum, confirming that this system is present in the 9*H* tautomeric form.

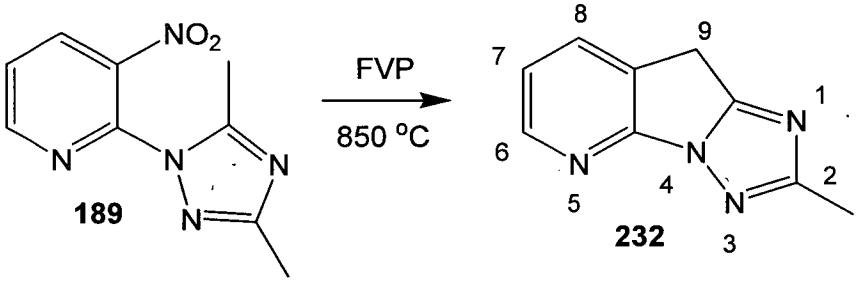


Scheme 81

A patent for a derivative of the **231** system was found in the literature, by a team of Japanese chemists who had been developing dye couplers during the 1990s.[90] Scheme 81 shows a four step synthesis starting from an aminoindole, which might have been formed in two steps starting from *o*-chloronitrobenzene and ethyl cyanoacetate,[91] to give a derivative of **231** with a long alkyl ballast in the 2-position. It is interesting to note this has been reported in the 1*H* tautomeric form, although no spectroscopic data were reported in the patent. In the key step, the triazole ring is formed by a Mitsunobu reaction using triphenylphosphine and diethyl azocarboxylate (DEAD). So the important conclusion is that synthesis of **231** using flash vacuum pyrolysis is highly advantageous over this 6-step route, and yields below 50% for the pyrolysis stage are acceptable in such a convenient synthetic route.

2.3.3.2 FVP of 2-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine

Large-scale (~330 mg) flash vacuum pyrolysis of 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine **189** gave a patch of yellow material on the cold finger, which became brown over the course of the 20 minute reaction (Scheme 82). Separation of the pyrolysate by dry flash column chromatography gave a number of minor impurities, none of which could be identified, before the desired product 2-methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene **232** eluted and was obtained as a reddish brown solid in 19% yield. The low yield suggests that there is still a problem with the trapping conditions and so more work is needed in this area. This is the first example of a family of pyridine containing 6,5,5 ring systems, which have never previously been reported, and so is an impressive result following the simple 3-step synthesis.



Scheme 82

When the reaction was repeated using the standard U-tube trap, the crude product **232** was found to be of an adequate purity when up to ~500 mg of starting material was pyrolysed, albeit less pure than the benzene analogue **231**. This did raise the question as to whether the NO_x gases produced by the leaving group might be having a much smaller effect on the nature of the product than previously imagined. The products from these later reactions were not purified but used directly for further experiments.

The proton NMR spectrum of **232** shows a singlet at 3.99 ppm, corresponding to the newly formed CH_2 group, the clearest indication that the desired 6,5,5 system has been formed successfully. The methyl group on the triazole ring is shown by a singlet at 2.62 ppm, and the three pyridine peaks were assigned by their coupling frequencies and their chemical shifts relative to the electronegative heteroatom. The full assignments of signals for **232** are shown below (Figure 9). Accurate mass

spectrometry agrees with the calculated molecular weight for this structure, and the ^{13}C NMR spectrum further confirms the identity of this compound, mainly by the presence of the CH_2 carbon at 26.95 ppm, confirmed by DEPT analysis.

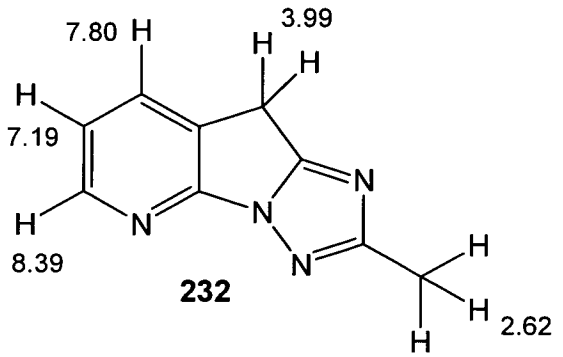
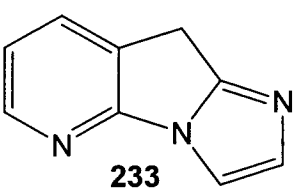


Figure 9: Chemical Shifts of 232

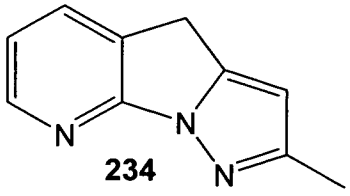
2.3.3.3 FVP of 2-(2-Methylimidazol-1-yl)-3-nitropyridine

Pyrolysis of 2-(2-methylimidazol-1-yl)-3-nitropyridine **190** proceeded in much the same way as for **189**, except that with its lower melting point, it distilled rather than subliming into the gaseous phase. The orange product was purified by dry flash chromatography to give the desired product, 9*H*-1,4,5-triaza-cyclopenta[*a*]indene **233** in a 21% yield, which still contained traces of an impurity. Again, this is the first example of a new ring system.



The product was unstable in chloroform solution and so it was characterised only by its proton NMR spectrum prepared from the small-scale pyrolysis product. This shows the characteristic CH_2 peak at 3.86 ppm, which was adequate confirmation that this new heterocyclic system had been successfully synthesised in the 9*H* tautomeric form. The three pyridine and two imidazole protons were all present as shown by their integrals, the pyridine protons coupling to each other in the expected manner while the imidazole protons appeared as apparent singlets.

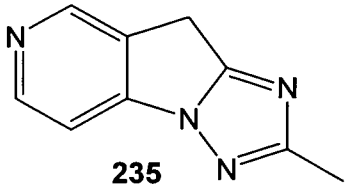
2.3.3.4 FVP of 2-(3,5-Dimethylpyrazol-1-yl)-3-nitropyridine



234

As the precursor **187** had already been pyrolysed and the product fully characterised[67] it was only pyrolysed on a small scale to produce an adequate quantity of product for the coupling tests (Section 2.4.1). The pale brown crude product collected in the trap was found by proton NMR spectroscopy to be 2-methyl-9*H*-3,4,5-triaza-cyclopenta[*a*]indene **234**, in a sufficiently pure form for testing. The characteristic singlet for the 9*H* methylene group was present at 3.76 ppm, and all peaks corresponded to the chemical shifts reported in the literature.

2.3.3.5 FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine



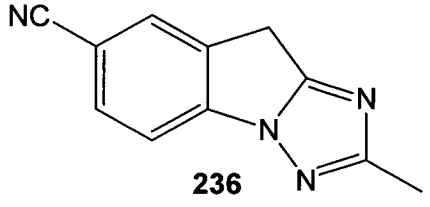
235

The small-scale pyrolysis of **193** proceeded as planned, and the crude product gave a good proton NMR spectrum of 2-methyl-9*H*-1,3,4,7-tetraaza-cyclopenta[*a*]indene **235**. A 59% yield was obtained, which was typical of the unpurified products of reactions on this scale. Another entirely novel ring system, **235** was characterised as usual by the presence of the CH_2 peak at 3.93 ppm in the proton NMR spectrum, which also showed peaks corresponding to the expected pyridine and methyl protons.

The large-scale FVP of 4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine **193** was carried out three times, and each time the product obtained decomposed before NMR analysis could be carried out.

2.3.3.6 FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile

Large-scale pyrolysis of the benzonitrile precursor **197** proceeded typically and without incident. After column chromatography of the pyrolysate, the product 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** was obtained as a reddish brown solid in 39% yield. Confirmation of this structure came from accurate mass spectrometry and proton and ^{13}C NMR spectroscopy, both showing the characteristic CH_2 group. In the proton NMR spectrum the methylene peak is present at 3.93 ppm, which is the same as in the pyridine containing system **235**, which suggests that the cyano group and pyridine heteroatom in the same position could be similarly effective for coupling purposes.



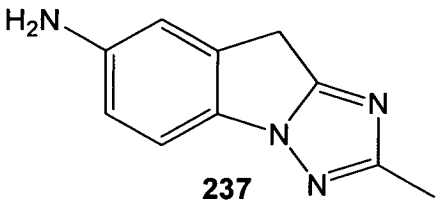
236

When this compound was later synthesised on a larger scale, pyrolysis was again attempted without the cold finger trap as had succeeded for the parent **231** and the pyridine **232**. This time however, with 100 mg of starting material **197**, the crude product was shown by proton NMR spectroscopy to consist of a complex mixture only containing a small quantity of the desired product **236**. Evidently the effects of the NO_x by-products are much greater with a cyano substituent on the ring system, and it must be this group activating the methylene site for reaction with NO_x species, which leads to degradation of the whole ring system. Looking back to the pyridine system **235**, which decomposed even with the cold finger, there appears to be some significance of having substituents or heteroatoms in the 7-position, possibly in this position they activate the coupling site more effectively by inductive effects around the ring system.

2.3.3.7 FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline

Large-scale pyrolysis of the aniline precursor **198** was carried in the usual way, and dry flash chromatography using ethyl acetate as eluent gave 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine **237** as the seventh component, there being a large

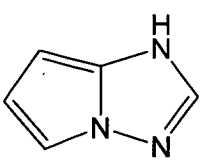
variety of impurities present. The low yield of 19% was typical, and appeared to show the inadequacies of the cold finger trapping system, as decomposition of products was visibly still occurring. The usual observations were made when characterising this new compound; the proton NMR spectrum contains the appropriate methylene peak at 3.71 ppm and the ^{13}C NMR spectrum shows the carbon from this group at 27.60 ppm, confirming the usual 9*H* tautomeric form. Mass spectrometry confirmed these observations with the correct molecular ion peak, *m/z* 186 Da.



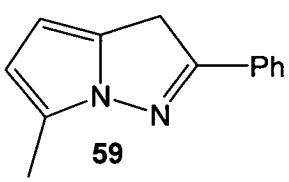
237

When this pyrolysis was repeated without the cold finger trap, a similar result as that of the pyrolysis of the benzonitrile **197** was observed, with decomposition of the crude product occurring for as little as 100 mg of precursor. In this case, the nucleophilic substituent would itself react with NO_x by-products to cause decomposition of the products.

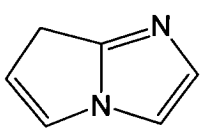
2.3.3.8 Proton NMR Data of 6,5,5 Systems



128



59



101

So far, the main observation from the proton NMR spectra of the heterocyclic systems produced is that they all appear exclusively in the 9*H* tautomeric form. In the literature survey in the introduction section bicyclic pyrrolo[1,2-*b*][1,2,4]triazole systems of the type **128** were observed almost exclusively in the 1*H* tautomeric form, usually with a substituent on the 1-nitrogen, which would prevent the 7*H* tautomeric form and their use as couplers (Section 1.6.1). In Section 1.4.1, a 3*H*-pyrrolo[1,2-*b*]pyrazole system **59** was also reported in the same form, but in Section 1.5.1, there were two substituted derivatives of the system pyrrolo[1,2-*a*]imidazole **101** shown with the same tautomerisation (7*H*) as seen in the 6,5,5 systems (proton NMR

spectroscopic data provides the evidence). The logical reason for the tricyclic systems of the type **1** appearing in their 9*H* tautomeric forms might be that bicyclic structures in the 1*H* form are 10π aromatic systems, with cyclic delocalisation of electron density. Addition of a fused benzene ring can prevent this as it acts as an independent 6π system with much greater resonance energy, and so the fused bond will not delocalise into the 10π bicyclic system. With the 6,5,5 systems in the 9*H* tautomeric form, the azole ring itself acts as another separate 6π system, with high resonance energy, thus making this form the more stable.

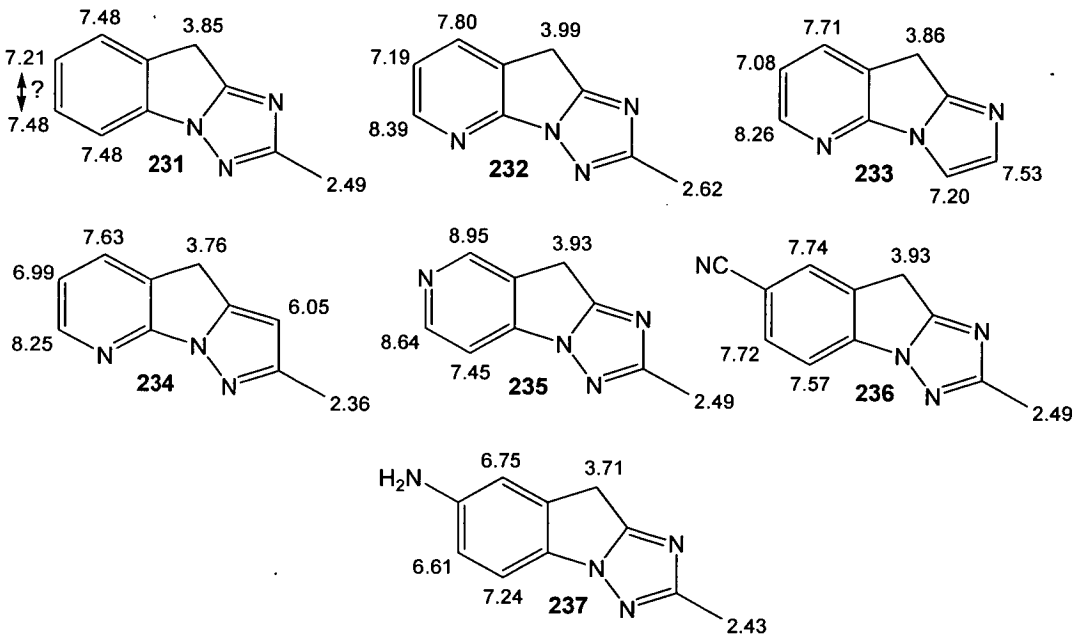


Figure 10: chemical shifts of 6,5,5 systems

The chemical shifts of the methylene protons in the 9-position are interesting when compared to one another (Figure 10), and may provide clues to the suitability of each compound as a photographic dye coupler. The simplest derivative of the family **1** was already described in Section 1.3.2.3, 9*H*-pyrrolo[1,2-*a*]indole **40**, which has protons in the 9-position with a chemical shift of 3.89 ppm, which is a useful starting point for comparison with the systems produced here. The parent triazole-benzene system **231** has a methylene shift of 3.85 ppm, which is surprisingly lower, as the additional heteroatoms might be expected to have an inductive electron withdrawing effect on the methylene site. The pyridine analogue **232** has methylene protons with a chemical shift of 3.99 ppm, the additional heteroatom in **232** having more of the expected

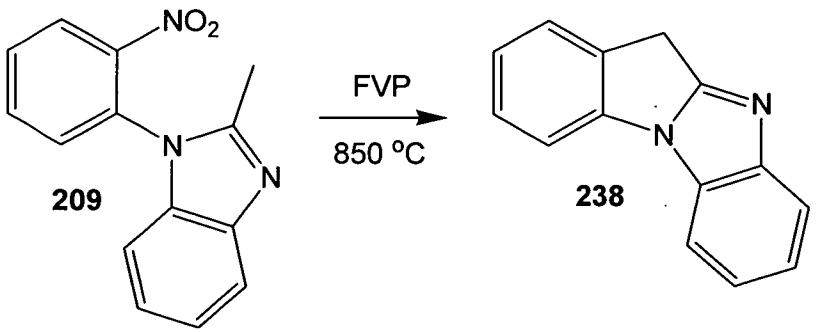
effect. The isomeric triazole-pyridine system **235** has a slightly lower chemical shift of 3.93 ppm, which is unexpected as the pyridine heteroatom is at the same distance from the methylene group in terms of bonds. A more interesting comparison comes from the other fused pyridine systems; the imidazole **233** has a methylene signal at 3.86 ppm, while the pyrazole system **234** has methylene protons with a much lower shift, at 3.76 ppm, which shows the large effect of adding heteroatoms to the azole ring, more so in the 1- than the 3-position. It is surprising though, that the methylene peaks in **233** and **234** are at lower shifts than in **40**. The effects of these differing azole rings on the pyridine protons is interesting relative to the precursors, as the triazole system **232** now displays the highest shifts, in keeping with the pattern observed for the methylene protons and with differences of the same order.

In examining the effects of different substituents on these ring systems, the cyano electron withdrawing group attached to the phenyl ring in **236** deshields the methylene group and raises its chemical shift relative to the parent compound **231**. As was seen with the precursors, the cyano group raises the chemical shifts of the two *ortho* protons by ~0.25 ppm, and the 5-proton by a lower amount. In considering the one example of a compound containing an electron donating group, the aniline species **237** displayed a chemical shift of 3.71 ppm, the lowest value observed so far. The amino group evidently affects the methylene protons in the opposite manner to high numbers of heteroatoms, and in this case seems to outweigh those effects as seen when comparing the pyrazole **234** to the triazole **232**. The effects of the amino group on the aromatic protons are also significant, lowering their chemical shifts relative to the parent **231** by up to ~0.8 ppm.

2.3.3.9 FVP of 2-Methyl-1-(2-nitrophenyl)benzimidazole

2-Methyl-1-(2-nitrophenyl)benzimidazole **209** had already been pyrolysed[54] to give the parent 6,5,5,6 system indolo[1,2-*a*]benzimidazole **238** (Scheme 83), which was synthesised here mainly to investigate its chemistry and suitability as a coupler relative to the 6,5,5 systems. As with the tricyclic parent precursor **194**, the tetracyclic precursor **209** was found to be unaffected by the NO_x gases produced during pyrolysis, so the cold finger trap was not required when producing moderate amounts of the tetracycle **238** needed for further experiments. It was already known

that this family of FVP products are unstable in silica columns, leading to decomposition by chromatography,[54] and so reasonable purification was effected by dissolving the crude product in DCM and filtering off the insoluble impurities. The yield of **238** obtained this way was roughly calculated as 87%, which relative to crude yields of the 6,5,5 systems around 50-60%, is rather impressive and shows these systems may well be significantly more stable to the reactive NO_x gases formed during pyrolysis.



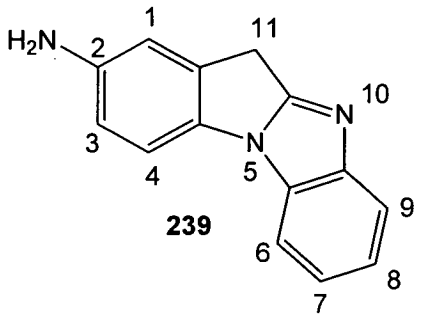
Scheme 83

Melting point and the proton NMR spectrum of the tetracycle **238** were used to confirm its identity. The latter roughly matched the literature spectrum with six of the aromatic protons showing a multiplet at 7.24 ppm and the other two giving a multiplet at 7.67 ppm, but more importantly the methylene peak was present at 4.02 ppm, showing the same tautomerisation as the 6,5,5 systems. This CH_2 group has a chemical shift a little higher than that of the parent tricyclic compound **231**, and this could indicate that this kind of tetracyclic system might have the same potential for coupling with oxidised developer and base. Comparison must be made to the imidazole containing system **233**, which has a chemical shift of 3.86 ppm, so the extra fused phenyl ring in **238** must be having a large effect on the methylene group, possibly by increasing the electron withdrawing nature of the nearby imidazole heteroatom.

2.3.3.10 FVP of 4-(2-Methylbenzimidazol-1-yl)-3-nitroaniline

4-(2-Methylbenzimidazol-1-yl)-3-nitroaniline **210** was pyrolysed using the cold finger trap as it was expected the amino substituent would react with the NO_x gases generated to cause decomposition, as seen in FVP of the tricyclic aniline **198**. Apart

from removal of impurities insoluble in DCM the crude pyrolysate could not be purified due to the incompatibility of these tetracycles with column chromatography, but was deemed after proton NMR spectroscopy to be adequately pure for the subsequent ballasting reaction which was to be carried out. The crude product 2-aminoindolo[1,2-*a*]benzimidazole **239**, was a dark brown semi-solid obtained in ~79% yield.



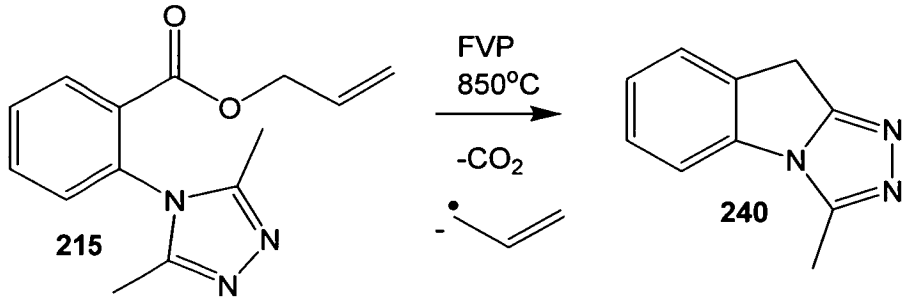
239

Characterisation of this product came solely from the proton NMR spectrum, as the unpurified material was used directly for a later experiment. On this spectrum the methylene protons in the 11-position are represented by a peak at 3.95 ppm, confirming successful cyclisation. This is again a high chemical shift relative to the 6,5,5 systems, and appears to be affected less by the electron-donating amino group than the equivalent methylene group in the tricyclic equivalent **237**. Two of the aromatic protons show very low chemical shifts, so are presumably those *ortho* to the amino group; at 6.66 ppm is an *ortho* doublet corresponding to the 3-proton, and at 6.80 ppm a singlet for the 1-proton, slightly deshielded by the methylene group.

2.3.3.11 FVP of Allyl 2-(3,5-Dimethyl-[1,2,4]-triazol-4-yl)benzoate

As it contains an allyl ester leaving group rather than the typical nitro group, the pyrolysis of allyl 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate **215** could be carried out without the use of the cold finger trap, as shown in Scheme 84. After a number of large-scale reactions the average yield of 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** obtained after column purification was 35%. Observations during the pyrolysis process were obviously different from the reactions with nitro leaving groups, with some white material collected in the U-tube which evaporated on warming to room temperature. The crude pyrolysate was a dull brown colour, which darkened upon

contact with the air, and the product **240** obtained after the column appeared almost black in colour.

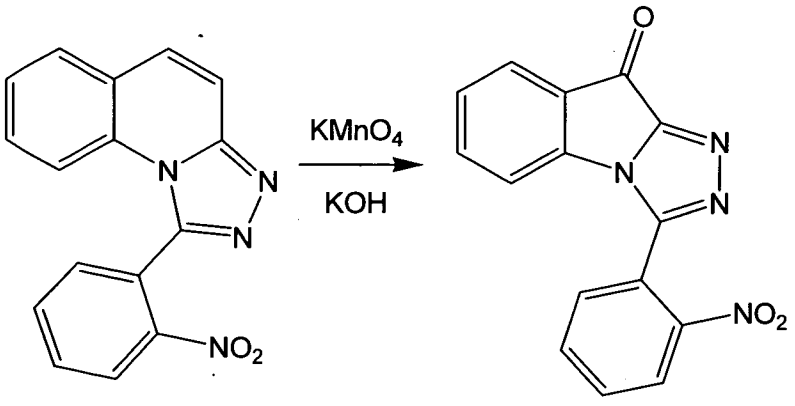


Scheme 84

Mass spectrometry of **240** confirmed the correct molecular weight, and the ^{13}C NMR spectrum showed the characteristic methylene group formed in the cyclisation as a CH_2 carbon with a chemical shift of 26.38 ppm. In the proton NMR spectrum, the methylene coupling site protons are represented by a singlet with a chemical shift of 3.89 ppm, so the 9*H* tautomeric structure is once again observed for this isomeric system. This CH_2 shift is slightly lower than all the other triazole couplers except the aniline **237**, so this isomeric configuration of the triazole ring appears to affect the coupling protons in a similar way to an electron donating substituent. The peak corresponding to the methyl group is slightly higher than **231**, at 2.68 ppm, which suggests that the bridgehead nitrogen atom must have some deshielding effect greater than the other heteroatoms. On the aromatic ring, the protons generally have lower shifts than on the parent **231**, so the weakly electron-donating methyl substituent may have some effect even as far away as the triazole ring.

A derivative of **240** has been patented by the same Japanese team which reported the parent system **231**, again obtained by a synthetic route featuring numerous steps.[92] Scheme 85 shows the key step, in which the pyrrole ring is formed, where a pyridine ring is oxidised by potassium permanganate and potassium hydroxide to give a pyrrolone ring, which is later reduced by sodium borohydride. Formation of the starting material is not described in the patent, but could potentially have been carried

out in two steps starting with quinoline.[93] Again, it is clear that FVP provides a far simpler route to this ring system.



Scheme 85

2.3.4 Limitations of the General Method

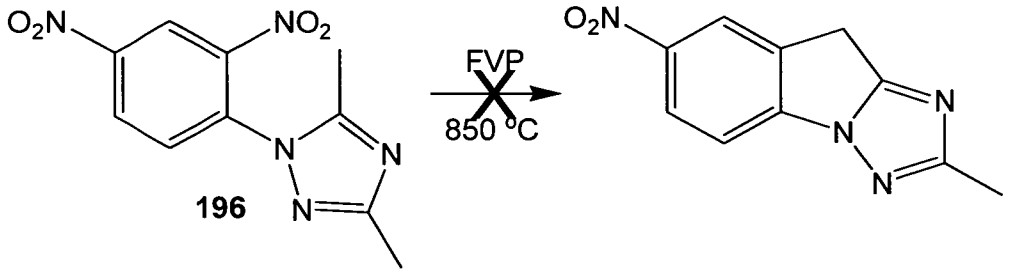
So far it has been seen that the general FVP mechanism discussed in Section 2.3.1 has a reasonably wide range of applications, with a number of substituents and two different leaving groups being employed successfully. However, for certain precursors, problems arose preventing successful formation of the desired pyrolysis products. Examples were observed of volatility problems, issues caused by additional leaving groups and failures resulting from varying the chemistry of the precursors by too significant a degree.

2.3.4.1 FVP of 3,5-Dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole

The dinitro compounds contained two potential radical leaving groups, but it was hoped that the group *ortho* to the azole substituent might be lost preferentially. This is because the *ortho* nitro group is not planar relative to the benzene ring, due to spatial constraints brought about by the nearby azole ring. This has been shown by the publication of a crystal structure for a related 2,4-dinitrophenylazole compound, where the *para* nitro group is planar with the phenyl ring, whereas the *ortho* nitro is seen to be twisted.[94] Its orbitals therefore interact less efficiently with the π-system of

the benzene ring, and so the C-N bond may be weaker than for the planar *para* nitro group. If successful, the remaining nitro group could be used, after pyrolysis, to attach a ballast to the potential dye coupler, or could possibly increase reactivity of the CH_2 in the same way as a heteroatom in the ring.

Small-scale FVP of 3,5-dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole **196** resulted in a thick black tar. When analysed by proton NMR spectroscopy, no distinguishable products were observed. A large-scale pyrolysis was also performed, but very little of the orange/brown semi-solid product obtained was soluble in DCM, suggesting most was decomposed. This was found to be inseparable by chromatography, and proton NMR spectroscopy gave a poor spectrum with only a large number of indeterminable peaks in the aliphatic region.



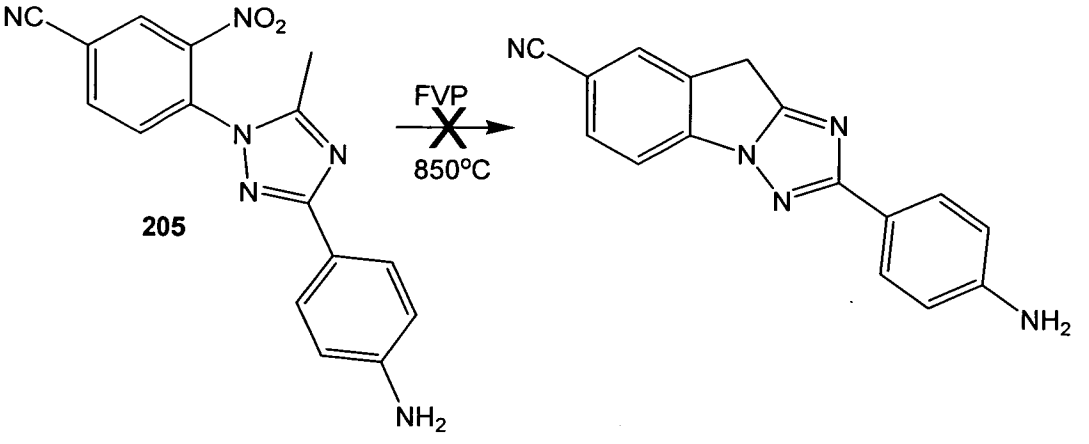
Scheme 86

Here it was concluded that dinitro compounds cannot be pyrolysed in this way. Presumably, both nitro groups may be lost as radicals, leading to formation of unusual polymers, thus explaining the tar like nature of the product. Small-scale FVP of 2-methyl-1-(2,4-dinitrophenyl)-imidazole **195** also resulted in the same type of indeterminable product. Thereafter, all research into pyrolysis of 2,4-dinitro compounds was abandoned.

2.3.4.2 FVP of 4-[3-(4-Aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile

The aniline containing benzonitrile precursor **205** was expected to pyrolyse successfully in the same way as the methyl substituted system **197**, assuming the aniline substituent would have no effect on the cyclisation reaction (Scheme 87). During three different small-scale pyrolysis reactions of the precursor **205**, varying

the inlet temperature from the melting point of 160 °C up to 200 °C, each time the sample in the inlet tube decomposed to a dark brown oil and only a tiny quantity of crude product was obtained in the U-tube. Proton NMR spectra of the pyrolysate showed a mix of many decomposition products, with a possible methylene peak around 4 ppm to indicate the desired product, but the suspected peak was so small and the yield so low that it was judged to be impractical to attempt purification. Evidently, the precursor **205** has a low volatility for FVP under standard conditions.

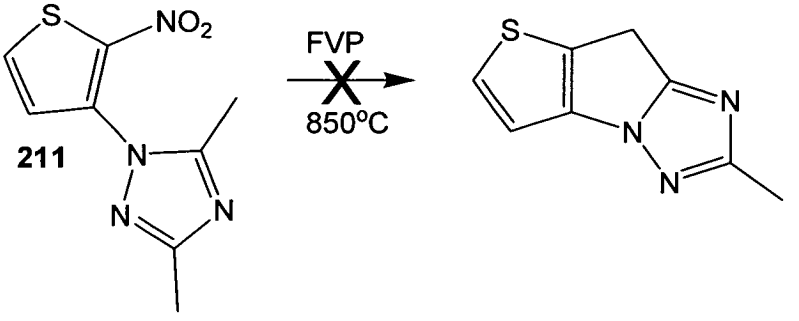


Scheme 87

2.3.4.3 FVP of 3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-2-nitrothiophene

Pyrolysis of the 5,5,5 thiophene precursor **211** required an inlet temperature of 200 °C, at which point the sample appeared to sublime into the furnace with only a small amount of decomposed material remaining in the inlet tube. However, the brownish yellow semi-solid product obtained in the U-tube was found to be poorly soluble in deuteriated chloroform, and proton NMR spectroscopy of this solution showed a mixture of aromatic products, but no clear methylene peak therefore it was unlikely that a potential coupler species had been obtained. The material obtained did have a sulfurous odour, which implied that decomposition of the thiophene ring could have taken place, although other thiophene materials have successfully been pyrolysed in the past.[67] Possibly the radical generated by loss of the nitro group is in a position where it favours interaction within the thiophene ring, rather than the methyl group on

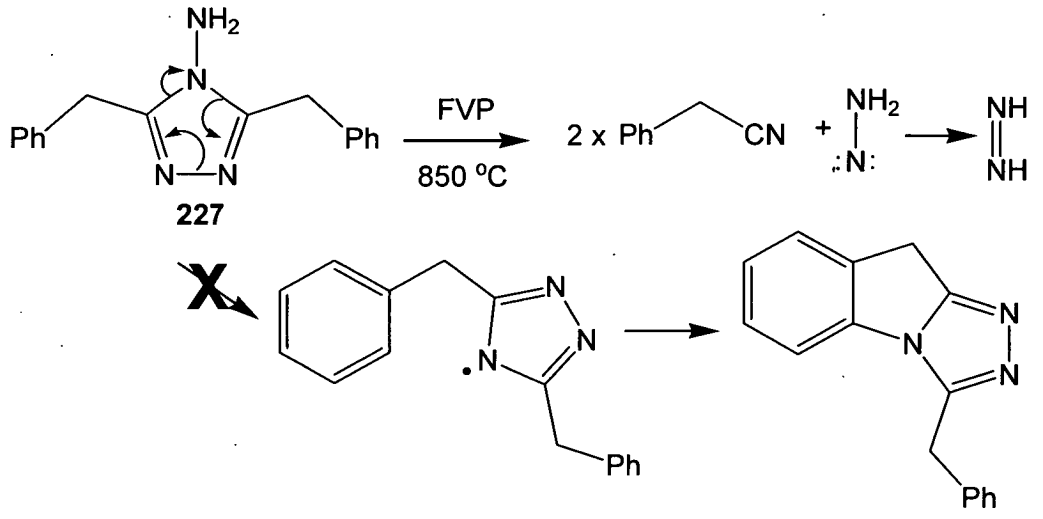
the triazole ring, which could lead to ring-opening. More work is therefore needed to understand the effect of the fused 5-membered ring in these reactions.



Scheme 88

2.3.4.4 FVP of 3,5-Dibenzyl-[1,2,4]-triazol-4-ylamine

Pyrolysis of 3,5-dibenzyl-[1,2,4]-triazol-4-ylamine **227** was expected to cause radical cleavage of the amino group to allow cyclisation to one of the phenyl groups, resulting in a benzyl substituted derivative of the isomeric system **240**. The FVP proceeded in the typical manner and a pale brown solid product was obtained in the U-tube, the dry ice/acetone cold finger trap being unnecessary as the relatively unreactive ammonia was expected to be given off in this case. Proton NMR spectroscopy of the crude pyrolysate then confirmed a rather unexpected result, showing no pyrrole methylene peak and thus indicating that cyclisation had not taken place. What had been obtained was fairly clean and easily identifiable, containing only a multiplet at 7.27 ppm for a phenyl group and a singlet at 3.68 ppm for an aliphatic CH_2 group; comparison with the literature showed this product to be phenylacetonitrile (Scheme 89). Presumably the primary amino group is not a good leaving group under pyrolysis conditions, and previous work had been more successful when using a dimethylamino group,[85] which was why methylation was later attempted (Section 2.2.9.2). A possible mechanism for decomposition of the triazole ring is shown in Scheme 89, leading to two phenylacetonitrile molecules and one diimide which could decompose to hydrogen and nitrogen as it is highly unstable.[95]



Scheme 89

2.4 Dyes

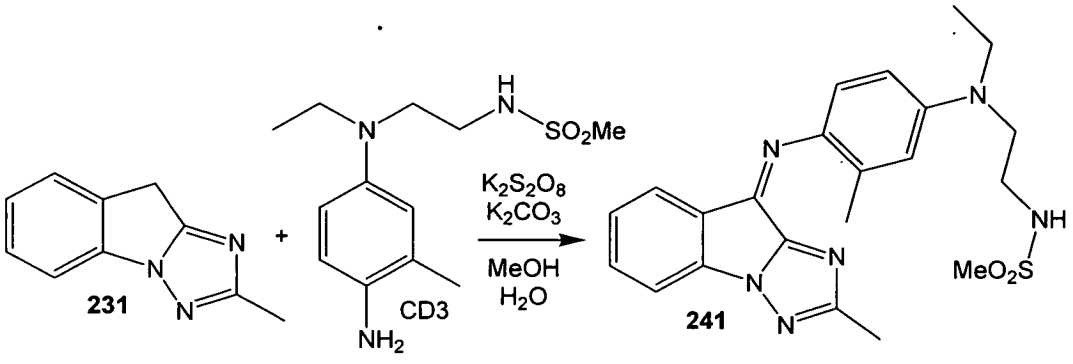
2.4.1 Coupling Tests

The first, and most important dyes to be produced from the potential couplers produced by FVP were azamethine dyes made from reaction with oxidised *p*-phenylenediamine developer, as would happen in the photographic process (see Section 1.1). The speed of the coupling reaction and the resultant dye hue would indicate how useful each compound would be as a magenta dye coupler.

2.4.1.1 The Testing Process

The various systems successfully produced by FVP were sent to Kodak for preliminary testing as potential couplers (tests carried out by Dr. Bernard Clark). Only quantities of around 20 milligrams are needed and high purity is not essential at this stage. The first step of the process is to carry out the dye coupling procedure to see if the reaction occurs. This involves simply mixing the potential coupler with a small amount of a mixture containing a standard developer, such as a substituted *p*-phenylenediamine like that shown in the standard coupling reaction in Scheme 1. For all of these systems, the Kodak sulfonamide developer CD3 was used. The mixture

must also contain the base, potassium carbonate, to deprotonate the coupler, and an oxidising agent, potassium persulfate, which takes the place of the silver halide, which would be present in the photographic process (Scheme 90). A quick colour change is expected of a good coupler, and the particular dye hue of the product is carefully noted. In this case, a bright magenta is desired.



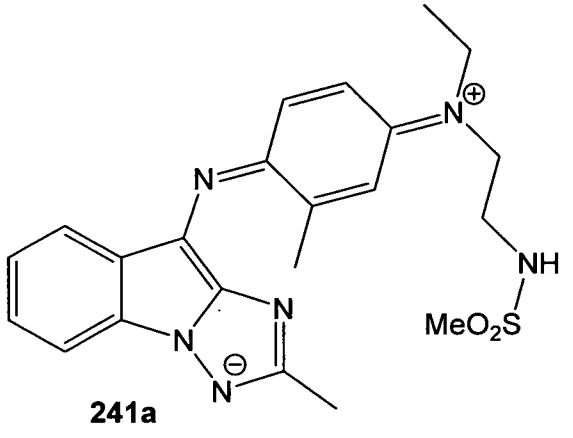
Scheme 90

The dyes are extracted from the aqueous reaction mixture with ethyl acetate, and then concentrated and dissolved in methanol for analysis. The crude mixture was analysed by PDA-LC-MS; the components were separated by HPLC and subsequently analysed by mass spectrometry and UV-vis spectroscopy. A good magenta dye is expected to have a maximum absorption at 550 nm, and the peak is ideally symmetrical and quite narrow, with a half bandwidth less than 100 nm, so that it does not absorb in the adjacent yellow or cyan regions. To date, the problem with most magenta dyes is that they have a small secondary absorption, which creates a "tail" in the yellow sensitive region making the dye slightly red. The reactive methylene protons must be acidic for successful coupling, and this is improved by incorporation of electron withdrawing groups onto coupler systems, to assist deprotonation thereby enabling attack on the electrophilic oxidised developer.

2.4.1.2 Results

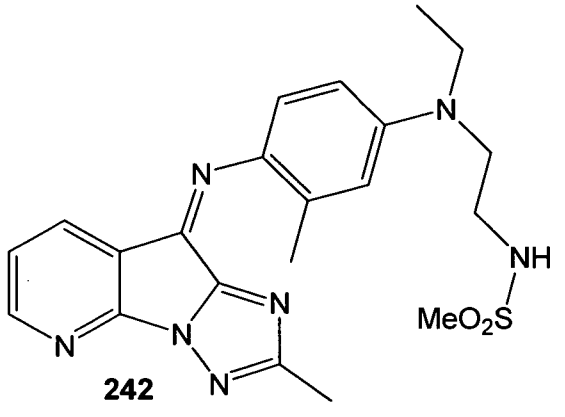
The parent 6,5,5 triazole system, 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231**, coupled successfully to give a reddish magenta dye, confirmed as the correct species **241** (Scheme 90) by mass spectrometry. The dye was found to be hypsochromic (absorbs at too short a wavelength) with a λ_{max} of 512 nm, but with a narrow half

bandwidth ($w_{1/2}$) of 100 nm. The curve of the UV-vis spectrum was not only sharper than many more conventional azamethine dyes,[6] but there was no sign of any secondary absorption in the yellow region. The resonance structure of this dye is shown in Figure 11, demonstrating how conjugation can run from the tertiary amino group of the developer through to the 3-position heteroatom of the triazole ring, which gives the magenta colour of this type of dye.



241a

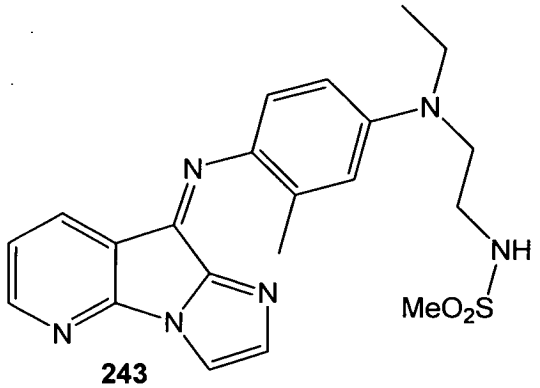
Figure 11: Resonance Structure of 241



242

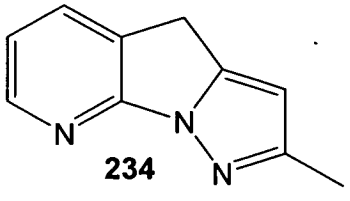
The pyridine-triazole system 2-methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene **232** was found to couple more quickly than **231** to give a fine magenta dye **242**. Again the absorption curve on the UV-vis spectrum was symmetrical and completely in the magenta region, which was very promising. The λ_{max} is 524 nm, which is closer to the desired absorption wavelength, but still slightly hypsochromic. This dye also had a half bandwidth of 100 nm. This result confirms the theory that a pyridine rather

than a phenyl ring is better for coupling, and begins to suggest that more successful dyes in this series require more electron withdrawing nitrogen atoms.



243

The imidazole containing analogue, 9*H*-1,4,5-triaza-cyclopenta[*a*]indene **233** coupled more slowly, as might have been expected if it is assumed that the methylene protons of the coupling site are made more acidic by electron withdrawing groups or extra heteroatoms. The dye hue of the product **243** was redder than the previous two dyes, λ_{max} 510 nm; again $w_{1/2}$ of 100 nm was found for this symmetrical absorption curve. Evidently, the extra nitrogen heteroatom in the azole ring both increases coupling reactivity and improves the resulting dye hue, the methyl group being unlikely to have any significant effect upon absorption behaviour. Conjugation of the electron density from the deprotonated methylene site to the heteroatom in the 1-position of the azole ring may be required for coupling, the 3-nitrogen in the triazole ring therefore allows further conjugation and so improves dye hue.

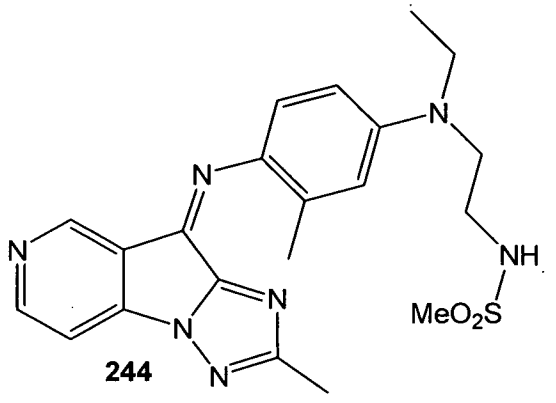


234

The pyrazole species, 2-methyl-9*H*-3,4,5-triaza-cyclopenta[*a*]indene **234** could not be made to couple at all, which confirms the predictions about the advantage of having a nitrogen atom in the 1-position, adjacent to the reactive site and providing an electronegative heteroatom for conjugation. But having seen the performance of the triazole over the imidazole, it was somewhat surprising that the nitrogen atom in the

3-position would be insufficient to allow coupling. Possibly, this system **234** could couple if the right coupling off group was used, to stabilise the anionic intermediate.

After these results it was decided that the triazole was the best option for the outer five membered ring, so studies on imidazoles and pyrazoles were discontinued.

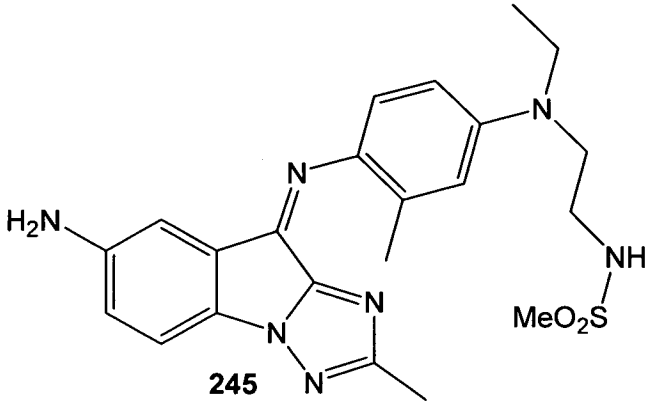


244

The second pyridine system, 2-methyl-9*H*-1,3,4,7-tetraaza-cyclopenta[*a*]indene **235,** coupled very quickly and cleanly to give a beautiful magenta dye. The λ_{max} of **244** of 534 nm is getting very close to the ideal absorption. The absorption curve was very symmetrical, and narrower than for the earlier systems with a half bandwidth of only 80 nm. This appears to demonstrate that having the pyridine heteroatom in the 6-position results in better performance than when it is in the 4-position, which is unexpected as both heteroatoms are at the same distance from the coupling site. Neither position is conjugated to the developer section, so the heteroatoms must be improving coupling and dye hue by inductive electron withdrawing effects, therefore reasons why the 6-position should be favourable are unclear at this stage.

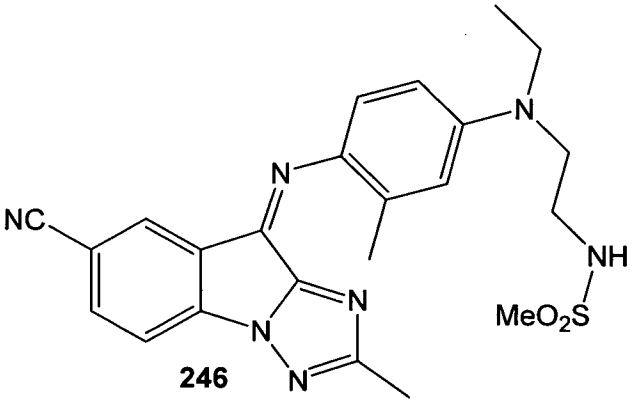
The amino-substituted compound 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine **237** was expected to be a poor coupler with an electron donating group in the important 7-position, but it did couple successfully, the amino group not reducing acidity of the methylene protons sufficiently to prevent coupling. The coupling was slow, and the resultant dye **245** very red in hue, with a hypsochromic λ_{max} of 506 nm, and the typical $w_{1/2}$ of 100 nm. So the effect of the amino group appears to be more significant on the dye hue, reducing conjugation into the fused benzene ring of the dye molecule from the electron-donating tertiary amine group on the CD3 section.

This result was not believed to be a problem for this system as a potential coupler, as ballasting the amino group *via* reaction with a typical acid chloride ballast would give a less electron donating amide group, and so lead to a bathochromic shift in dye hue.



245

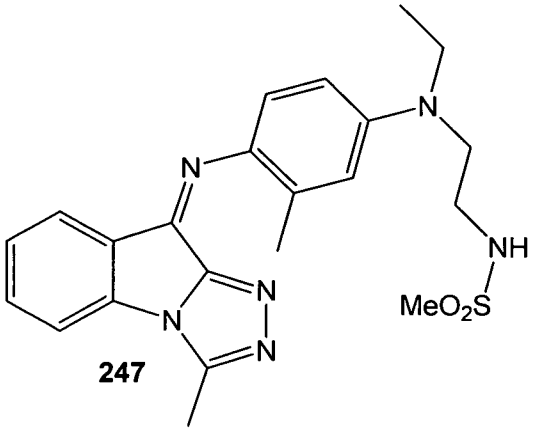
The cyano derivative, 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** interestingly gave almost an identical result as the pyridine **235**. The λ_{max} value of **246** is again 534 nm, and the dye hue was a near perfect bright magenta. Also, the curve was very sharp, with a half bandwidth of 80 nm. This result demonstrates that the effects of a cyano substituent can be equated with those of a pyridine nitrogen atom, which has very positive implications for future research. The benzonitrile species **236** was much easier to synthesise than the pyridine **235**, and the presence of the cyano functional group allows the possibility of ballasting more easily than a heteroatom. This dye **246** was synthesised again later on a preparative scale in order to carry out full characterisation (Section 2.4.3.2).



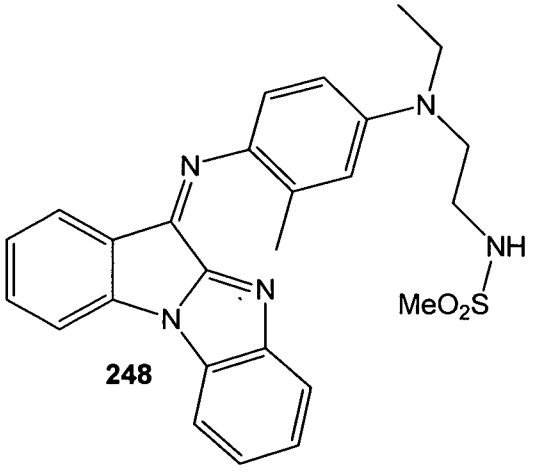
246

The only tricyclic system isomeric to structure **1**, 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240**, would be expected to provide information on which positions in the triazole ring were advantageous to place the heteroatoms. Coupling was extremely

slow, and the resultant dye **247** was very red, and hypsochromic λ_{max} 502 nm ($w_{1/2}$ 100 nm). As was shown in the resonance structure of **241** in Figure 10, and the comparison of the imidazole **243** with the triazole **242**, the heteroatom in the 3-position improves coupling and dye hue by conjugation through the developer section of the dye molecule. It is interesting to discover here with the isomeric triazole **240** that having a nitrogen atom in the 2-position actually hinders coupling to a certain extent. In comparing the four pyridine systems, it is now surprising that placing a heteroatom in a non-conjugated position of the fused aromatic ring improves coupling. Following the observation regarding the triazole ring, the work on couplers of this isomeric structure was discontinued and systems containing the structure of **1** were judged to be more useful.



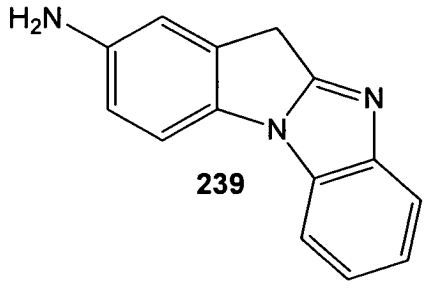
247



248

The parent tetracyclic system indolo[1,2-*a*]benzimidazole **238** coupled fairly quickly to give a reddish magenta dye **248** with λ_{max} of 508 nm and a narrow, symmetrical curve with $w_{1/2}$ 100 nm. This is very close to the result of the pyridine-imidazole dye

243, which suggests that the extra phenyl ring is having very little effect on coupling, as it contains no heteroatoms for improving conjugation. It is interesting to note here, that the first example of a 6,5,5,6 tetracyclic system has coupled with only two heteroatoms, while most tricyclic systems appear to require at least three, and bicyclic systems used commercially generally have at least four.



239

The aniline derivative, 2-aminoindolo[1,2-*a*]benzimidazole **239** failed to couple at all; it is likely that the electron-donating amino group reduces the acidity of the methylene protons to such an extent that they could not be removed by the coupling reaction. This therefore implies that it was the important 3-position heteroatom in the triazole ring of the tricyclic amino system **237** which counteracted the effects of the amino group enough to permit coupling.

Dye	λ_{max} / nm	$w_{1/2}$ / nm
241	512	100
242	524	100
243	510	100
244	534	80
245	506	100
246	534	80
247	502	100
248	508	100

Table 1: UV-vis results for azamethine dyes in methanol solution

The UV-vis results from the various azamethine dyes are summarised in Table 1. In general it appears that a higher number of nitrogen heteroatoms improves coupling ability. Firstly, the nitrogen atom in the 1-position is clearly required to make the protons in the 9-position acidic enough for the coupling reaction. The extra 3-nitrogen in the triazole ring improves this by conjugating the reactive site to a further heteroatom, but in the isomeric triazole system, where the 2-nitrogen is not conjugated, coupling is hindered. A heteroatom in the six membered ring has been proved to make a better coupler, and placing this in the 6-, rather than 4-, position improves coupling further. An electron-withdrawing nitrile group attached to the ring improves coupling and works in exactly the same way as heteroatom in the same position, while an electron-donating group has the expected opposite effect.

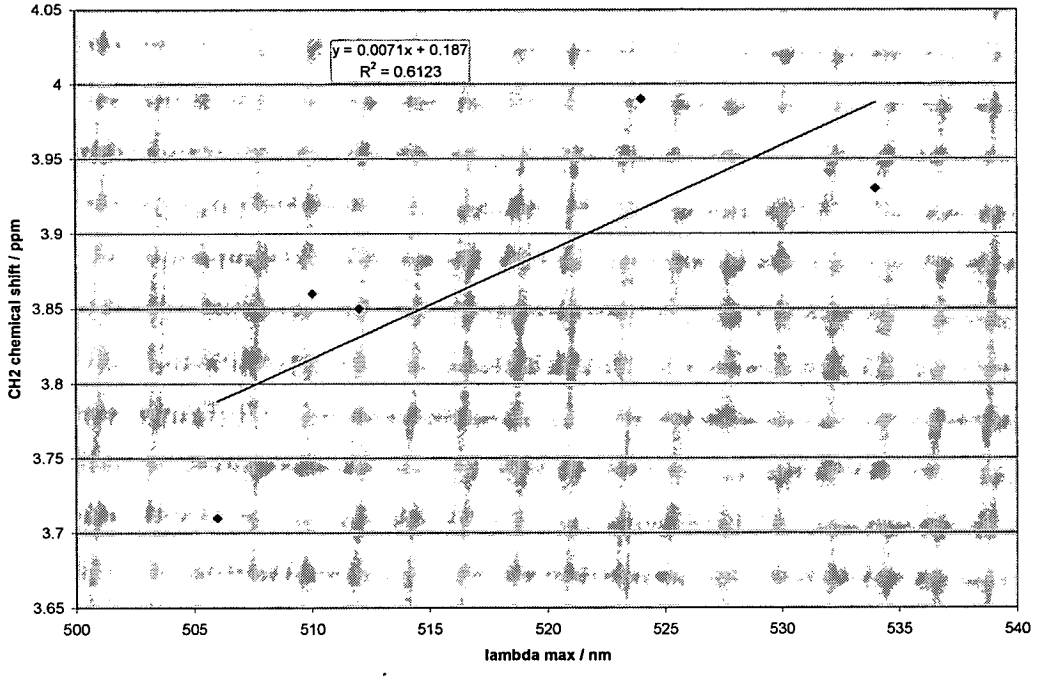


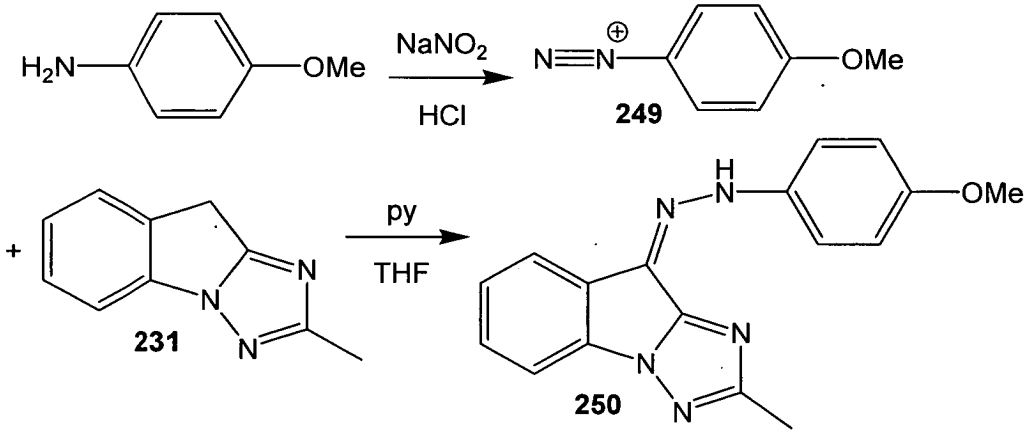
Figure 12: λ_{max} against coupler CH_2 chemical shift

As has been speculated earlier, it could be possible that coupler performance could be related to the acidity of the methylene coupling site, which in turn may be related to the proton NMR chemical shifts of these positions. Proton acidity should relate to coupling rate due to deprotonation by the base, but rates were not measured and so absorption maxima were plotted against methylene chemical shifts (Figure 12). The

line is a poor fit, but there does appear to be a loose correlation, where the better couplers clearly have higher chemical shifts, their coupling protons being deshielded by electron withdrawing groups or extra heteroatoms. It is interesting to note that the cyano coupler **236** and the pyridine **235** have the same coupling site chemical shift (3.93 ppm) and give azamethine dyes **246** and **244** with the same λ_{max} values. It is surprising that the poorer coupler **232** has a higher shift than the two most effective couplers; if this was lower then a non-linear relationship between the two values becomes more visible.

2.4.2 Azo Dyes

Yellow azo dyes have been mentioned in the introduction section for their use as masking couplers; they absorb blue light as well as the secondary absorption of conventional magenta couplers, and are then converted to the same magenta couplers during the development process. The azo functionality is effectively a leaving group, and the end result is that the magenta dye formed by the masking couplers compensates for the extra yellow absorption.



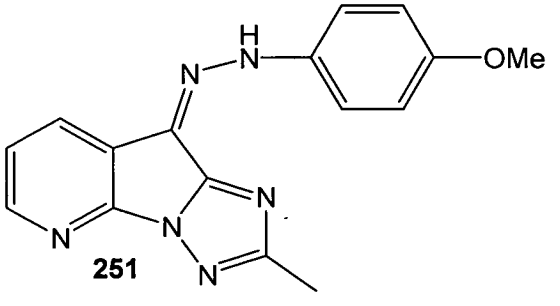
Scheme 91

A range of these dyes was produced on the micro-scale, using a stock of diazonium salt formed from reaction of an acidic solution of *p*-anisidine with sodium nitrite. As shown in Scheme 91, the various couplers were then dissolved in THF with pyridine for base, and treated with the diazonium salt **249**, which typically gave a colour

change to yellow or orange. The dye was then extracted into ethyl acetate and purified by preparative TLC to give sufficient quantities for characterisation by mass spectrometry and evaluation of the dye hue by UV-vis spectroscopy in ethyl acetate solution. The parent coupler **231** and cyano derivative **236**, which should give fairly representative results having produced widely differing azamethine dyes, were analysed in methanol solution as standard for LC-MS at the Kodak laboratories. The way in which absorption maxima vary with solvent used is known as solvatochromism, and usually a more polar solvent will lead to a bathochromic shift in dye hue.[96] The azo dyes are yellow and not magenta, as conjugation cannot extend beyond the hydrazone functionality into the phenyl ring.

2.4.2.1 Results

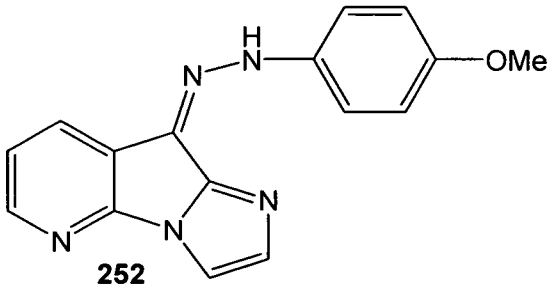
The parent triazole compound 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** coupled quite quickly to give a yellow dye **250**, which was found to have λ_{max} of 418 nm and $w_{1/2}$ of 80 nm. This is interesting to compare with the analogous azamethine dye **241**, as the curve is sharper, and the absorption maximum somewhat closer to the ideal yellow (λ_{max} 450 nm), than the λ_{max} of **241** is to the ideal magenta absorption of 550 nm. However, this difference is not very meaningful, as varying the substituent on the phenyl azo group could easily alter dye hue. When the dye **250** was analysed in methanol solution, a slightly higher λ_{max} of 420 nm was obtained, with half bandwidth 100 nm, a predictable solvatochromic effect for the more polar solvent.



251

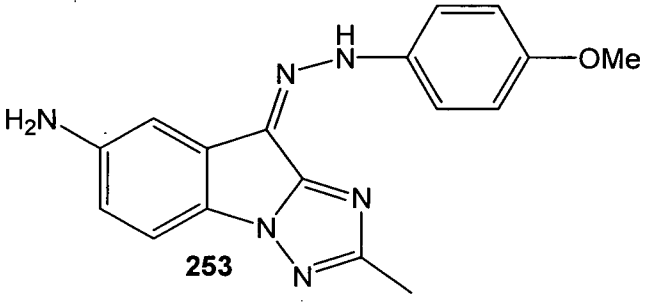
The pyridine-triazole coupler 2-methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene **232** coupled quickly to give a bright yellow dye **251**, and UV-vis spectroscopy of the ethyl acetate solution gave a curve with λ_{max} 421 nm and $w_{1/2}$ 90 nm. As expected, this dye is bathochromic relative to the benzene equivalent **250**, but the difference is not as great as with the azamethine dyes. The azo dye **251** differs from **250** in that its

absorption maximum is roughly 100 nm less than its azamethine equivalent **242**, the additional heteroatom having a smaller effect on dye hue.



252

The imidazole coupler 9*H*-1,4,5-triaza-cyclopenta[*a*]indene **233** coupled more slowly to give a duller yellow dye **252**, with λ_{max} 414 nm and $w_{1/2}$ 90 nm for ethyl acetate solution. Again this dye has a slightly sharper curve than its azamethine equivalent **243**, and like the benzene azo dye **250** it is a better yellow than the azamethine analogue is magenta.

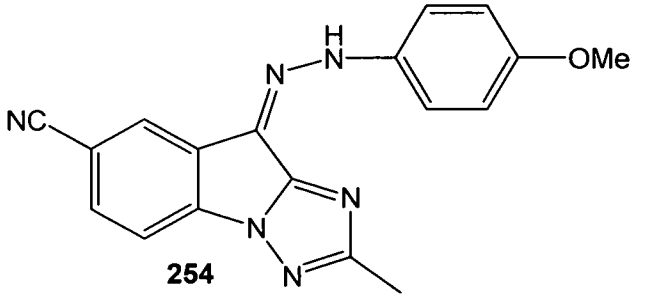


253

The fused aniline coupler 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine **237** coupled quite slowly to give a moderately yellow dye **253**, the UV-vis spectrum for which showed a λ_{max} of 411 nm and $w_{1/2}$ of 90 nm. The pattern which appears to be emerging here is that the less successful couplers produce azo dyes which are less hypsochromic than their azamethine equivalents, which really means that including electron donating groups or having fewer heteroatoms in the coupler produces less of an effect on reducing absorption maxima in an azo dye.

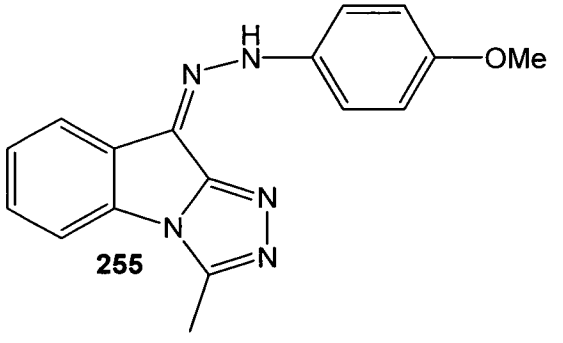
The benzonitrile system 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** coupled very quickly to give an intense yellow dye **254**, with λ_{max} 432 nm and $w_{1/2}$ 80 nm. The result is as expected given this was the best coupler from the azamethine dye results, and like the pyridine dye **251**, the absorption maximum is roughly 100 nm lower than that of its azamethine analogue. This dye **254**, being the best of its class,

was also analysed in methanol and gave a slightly higher λ_{max} 434 nm and $w_{1/2}$ 80 nm, the λ_{max} value exactly 100 nm lower than that of the azamethine analogue **246** in the same solvent.



254

The isomeric system 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** coupled very slowly to give a faintly yellow dye **255**, which had an expectedly low λ_{max} of 409 nm and a typical $w_{1/2}$ of 90 nm. As befitting the pattern emerging, this most hypsochromic of couplers gives an azo dye closer to the ideal yellow than its azamethine analogue is to the ideal magenta. Finally, the tetracycle indolo[1,2-*a*]benzimidazole **238** was reacted in the usual way and a yellow dye was observed, but when TLC separation was carried out, the dye appeared to have decomposed. This result must be related to the general inability of this class of tetracyclic coupler to be separated by column chromatography.



255

Dye	λ_{max} / nm	$w_{1/2}$ / nm
250	418	80
251	421	90
252	414	90
253	411	90
254	432	80
255	409	90

Table 2: UV-vis results for azo dyes in ethyl acetate solution

The results of all the azo dyes formed are summarised in Table 2. Dye hue clearly follows the same rules as for the magenta azamethine dyes in methanol, incorporation of more heteroatoms into the ring system or addition of an electron withdrawing group leading to bathochromic shifts. Half bandwidth is slightly different this time, as the sharper curves occurred for the more bathochromic azamethine dyes, whereas this time the parent dye **250**, with the third highest absorption maximum, has a sharper curve than all except the cyano **254**. As well as the azo dyes appearing in the same order as their azamethine analogues, they all display absorption maxima values roughly 100 nm lower than the magenta dyes. The correlation of these values and certain variations can be seen in the graph in Figure 13, and the line of best fit is quite accurate. The two most bathochromic azo dyes (**251** and **254**) have absorption maxima just over 100 nm below their azamethine analogues, while the rest are less than 100 nm below. The difference between λ_{max} values is smallest for the isomeric system dyes **247** and **255**, and the difference grows as λ_{max} increases, until the parent dyes **241** and **250** show a significantly lower difference therefore deviating noticeably from the trend. So this shows that the extra heteroatoms and electron withdrawing groups leading to more effective couplers have similar effects in azamethine and azo dyes, while with the less effective couplers, the differences are smaller for the azo dyes.

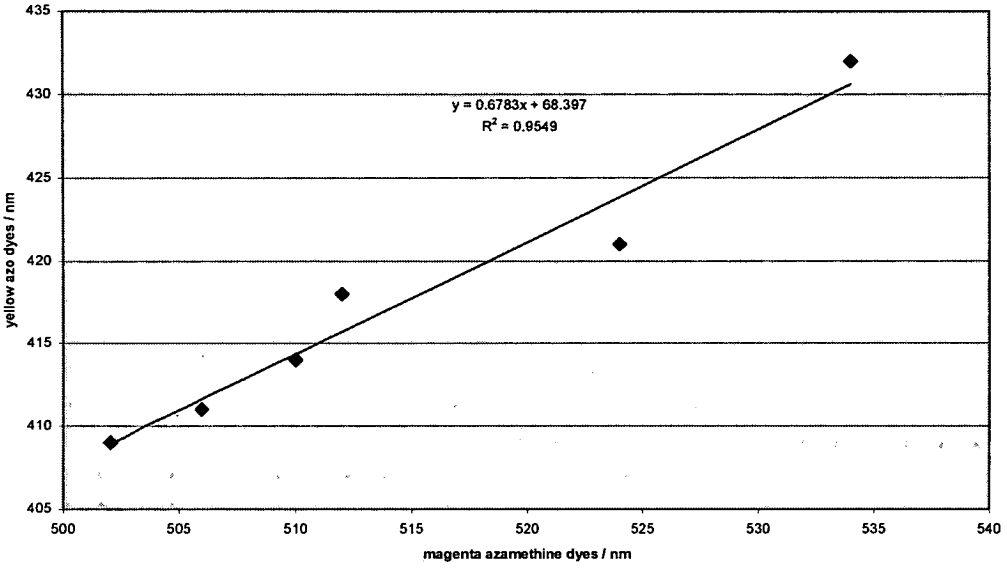


Figure 13: absorption maxima of azo dyes against azamethine dyes

2.4.2.2 Preparative Scale Synthesis

The parent azo dye **250** was resynthesised on a preparative scale for the purpose of carrying out a conversion to the azamethine dye **241**, as would occur with masking couplers in the photographic development process. Separation of the crude dye product was carried out by small-scale column chromatography using a pre-packed Flashtube^{TM} column, and the pure dye **250** was obtained in a 36% yield. Full characterisation was carried out, including UV-vis analysis of a solution of known concentration, so that the extinction coefficient could be calculated. The value obtained, ε 23,000 $dm^3mol^{-1}cm^{-1}$, is approaching the required standard of dye strength, as values of ε over 30,000 $dm^3mol^{-1}cm^{-1}$ are usually desirable for photographic applications. These solutions were made by dissolving 1 mg of material in 50 cm^3 of solvent, so on a 4 figure balance there is a minimum 10% error, which could lead to errors in extinction coefficient around 3000 $dm^3mol^{-1}cm^{-1}$, which must be taken into account when considering values of ε reported later.

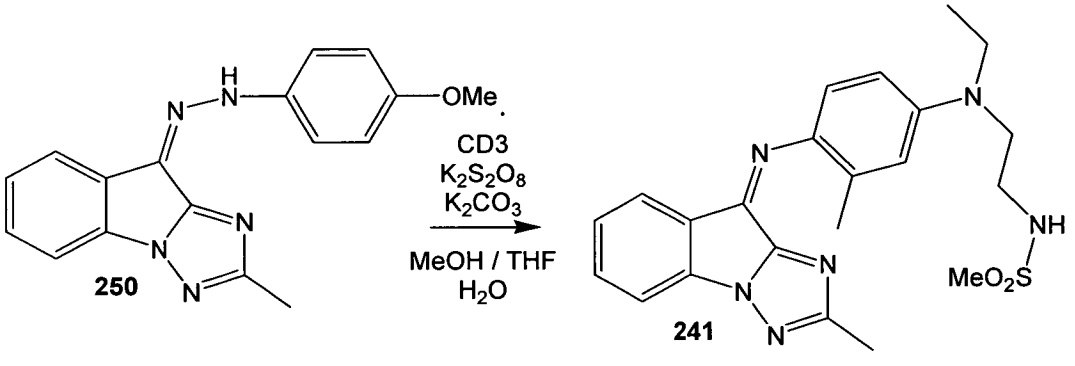
The proton NMR spectrum for this dye does not show the secondary amino proton from the azo functionality, but the integrals of the coupler ring system and the methoxyphenyl group match accordingly. The *ortho* doublet at 6.86 ppm corresponds

to the pair of protons adjacent to the strongly electron-donating methoxy group, which itself is represented by a singlet at 3.76 ppm. The highest shift peak, at 7.77 ppm, corresponds to the 8-proton on the coupler, which is deshielded by the nearby azo functionality.

2.4.3 Azamethine Dyes – Preparative Scale

Formation of azamethine dyes was also carried out on a preparative scale for characterisation purposes. In addition to making these dyes from the appropriate couplers, they could also be made in the same way from their azo dye analogues, as in the photographic development of masking couplers. Two dyes were chosen here; the parent dye **241** for an example of the conversion of an azo dye, and the cyano dye **246** to be synthesised directly from its coupler, as it had given the best UV-vis result.

2.4.3.1 Azo to Azamethine Conversion



Scheme 92

As the azo dye of the parent coupler **250** had been synthesised on a preparative scale (Section 2.4.2.2) it was then converted to the azamethine dye **241**, in order to characterise this species fully, and demonstrate the development of a masking coupler. The azo dye **250** was found to be considerably less soluble than the original coupler **231**, and it had to be dissolved in a mixture of THF and methanol, before being treated with aqueous solutions of Kodak CD3 developer, potassium persulfate and potassium carbonate (Scheme 92). The reaction mixture was stirred for several minutes and the colour change from yellow to magenta occurred at a much slower rate than is commonly observed in commercial development of azo masking couplers.[97]

Following ethyl acetate extraction, TLC analysis showed that the reaction had not gone to completion as a yellow spot was observed on the eluted plate in addition to the expected magenta one. The two components were separated easily by Flashtube column, and the unreacted azo dye **250** was reacted again, this time with stirring for 2 h, to give a total yield of the azamethine dye **241** of 68%.

A UV-vis spectrum of **241** was run in ethyl acetate, and a significant solvent variation was observed relative to the original methanol test, in that λ_{max} was now 496 nm where previously it had been 512 nm. The other difference was that the curve was narrower, with half bandwidth of just 80 nm, which was common for the azo dyes in ethyl acetate (see Section 2.4.2). These data were obtained using a solution of known concentration and so the extinction coefficient ε was calculated as 27,000 $dm^3mol^{-1}cm^{-1}$, which is higher than the azo dye **250**, and much closer to the kind of high intensity required for photographic dyes in commercial use.

Solvent	λ_{max} / nm	E_T / kcalmol^{-1}
Methanol	505	55.4
Acetonitrile	497	45.6
Ethyl acetate	496	38.1
Chloroform	495	39.1
Toluene	492	33.9

Table 3: solvatochromism effects on absorption maxima of dye 241

In order to demonstrate further examples of solvent difference, UV-vis spectra were run of **241** in a variety of solvents. The results are shown in Table 3, listed in order of polarity with available E_T values for comparison, these being transition energies (in kcalmol^{-1}) calculated from the charge transfer peaks of an ionic organic complex.[98] The result for methanol solution was surprising in that it showed λ_{max} 505 nm, which was 7 nm lower than the value obtained at the Kodak laboratories, but still the highest absorption maximum as expected for the most polar solvent tested. Acetonitrile and chloroform have λ_{max} values 1 nm either side of the ethyl acetate result, but their E_T values are 6.5 kcalmol^{-1} apart, therefore the solvatochromism effect appears to not be

proportional relative to methanol. Toluene was the least polar solvent tried and its lambda max and E_T values are proportionally low as would be expected. The only anomaly is that ethyl acetate has a λ_{max} value 1 nm higher than chloroform but its E_T value is exactly 1 kcalmol^{-1} lower, although this is not significant. These figures were plotted in a graph (Figure 14) and the trend line fits surprisingly well with little deviation; evidently there is a definite linear relationship between solvent polarity and absorption maxima.

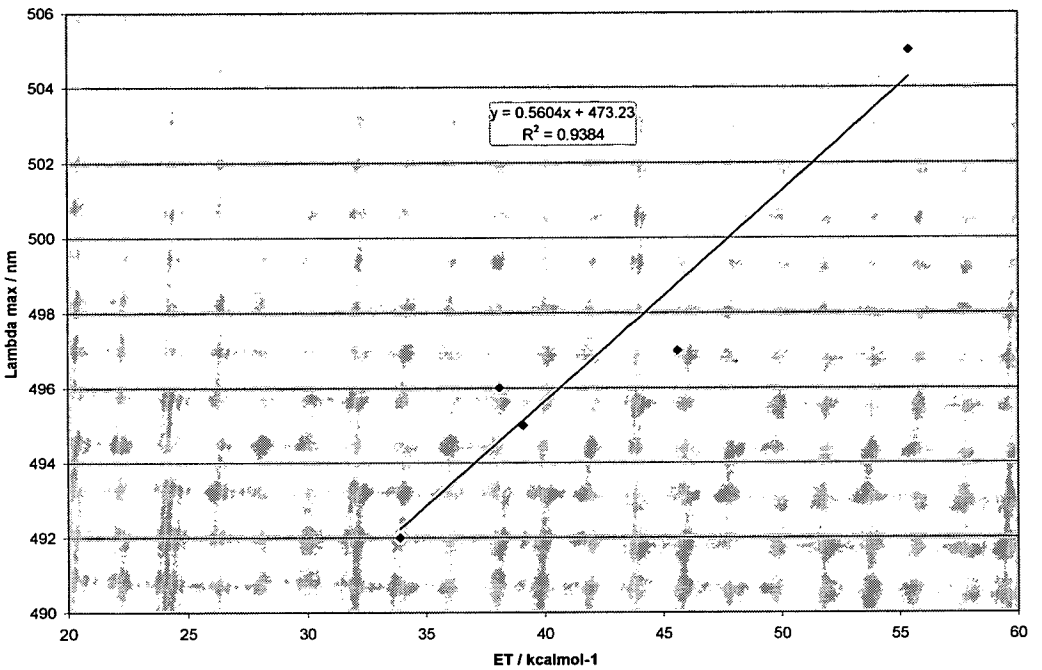
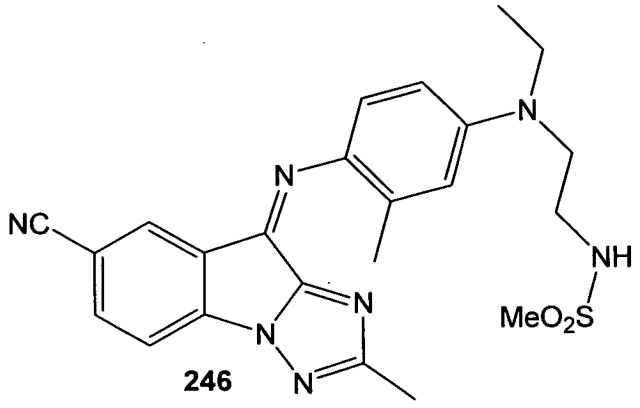


Figure 14: λ_{max} against solvent polarity E_T

The proton NMR spectrum for the azamethine dye **241** is complex and difficult to assign, but the predicted structure was indicated by the presence of all protons, with matching integrals to show that the coupler and developer were attached. There are seven aromatic peaks corresponding to the coupler and phenylenediamine protons, three CH_2 groups, four methyl peaks and a broad triplet at 4.63 ppm characteristic of the sulfonamide proton. Mass spectrometry confirmed the structure with a very weak mass peak *m/z* 439 Da, but more intense breakdown peaks showing loss of the sulfonamide and ethyl groups.

2.4.3.2 The Benzonitrile Derivative



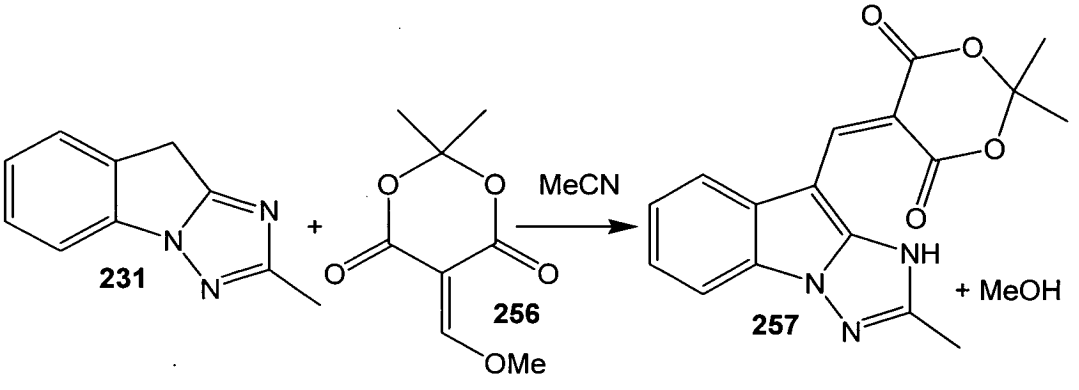
246

The benzonitrile coupler **236** was reacted with CD3, potassium persulfate and potassium carbonate in the usual development process, with overnight stirring at room temperature to ensure complete reaction, even though the strong magenta colour was observed immediately. Ethyl acetate workup and separation by Flashtube column chromatography then gave the azamethine dye **246** in a disappointing 14% yield; possibly the extended reaction time may have led to decomposition or excess self coupling of the developer, which is itself a coupler giving a purple colour. UV-vis spectroscopy of the dye **246** in ethyl acetate gave a λ_{max} value of 522 nm, (12 nm lower than the Kodak methanol result), with a half bandwidth of only 70 nm. The extinction coefficient, ε 23,000 $dm^3mol^{-1}cm^{-1}$, was lower than the parent dye **241**. In methanol solution the absorption maximum was found to be 527 nm, again 7 nm lower than the result obtained at Kodak. In addition, the curve was slightly broader than the Kodak result, with $w_{1/2}$ 90 nm.

Mass spectrometry of **246** gave the correct mass peak *m/z* 463 Da, and the proton NMR spectrum further confirmed the structure with all expected signals present and the integrals of each section matching up. This spectrum is similar to that of **241**, the interesting difference being that the phenyl proton on the CD3 section next to the azamethine group is now highly shifted at 8.48 ppm (8.17 ppm on **241**), which could indicate it is quite close to the cyano group. On the benzonitrile ring of the coupler, the 8-proton, between the nitrile group and the azamethine functionality, is deshielded to a shift of 8.07 ppm.

Following the results obtained for the azamethine and azo dyes produced from the full range of couplers synthesised, it was decided to save time by selecting four couplers to test for further dye families. In order to achieve a representative set of UV-vis data, couplers were chosen spanning the full range of coupling abilities, and three different ring systems were investigated, plus the substituted cyano coupler **236**, which had given the best dyes results so far. Rather than name each coupler in full the following names have been used; 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** is referred to as the "parent" 6,5,5 coupler, 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** is the "benzonitrile derivative", 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** is the "isomeric system", and indolo[1,2-*a*]benzimidazole **238** is the "tetracyclic system".

2.4.4 Meldrum's Acid Dyes



Scheme 93

Methoxymethylene Meldrum's acid **256** was selected as a reagent to form another class of yellow dyes, this having been found to be a useful electrophile for activated substrates such as pyrroles and indoles.[99] Scheme 93 shows the general synthesis where each coupler is reacted with methoxymethylene Meldrum's acid **256** by stirring in acetonitrile at room temperature for 3 days, the long reaction time necessary as there is no base to deprotonate the reactive methylene site on the coupler. Usually, the dye was obtained as a strongly coloured dark yellow precipitate, and if it stayed in solution then the brown reaction mixture had a definite yellow tinge.

There are four possible tautomers for the product, the first structure for the parent dye **257** shown above in Scheme 93 and the other three are depicted below in Figure 15. Structures **257a** and **b** can easily be eliminated as they are not conjugated so would not appear yellow, and no extra aliphatic protons would be observed in the proton NMR spectra. The enol structure **257c** would give a similar proton NMR spectrum to that of the **257**, as the hydrogen bonded OH or NH moieties would have similar chemical shifts, and both should be conjugated in a similar way required to give a yellow dye. However, the enol structure is probably unfavourable, as similar compounds have undergone ring opening to ketenes with loss of acetone in a reverse Diels-Alder reaction, which can occur in a matter of minutes at room temperature.[100] The secondary amine **257** is therefore the most likely structure, and the interesting point for dye studies is that the conjugation this time runs from an electron rich site in the coupler through to electron withdrawing groups in the Meldrum's acid moiety.

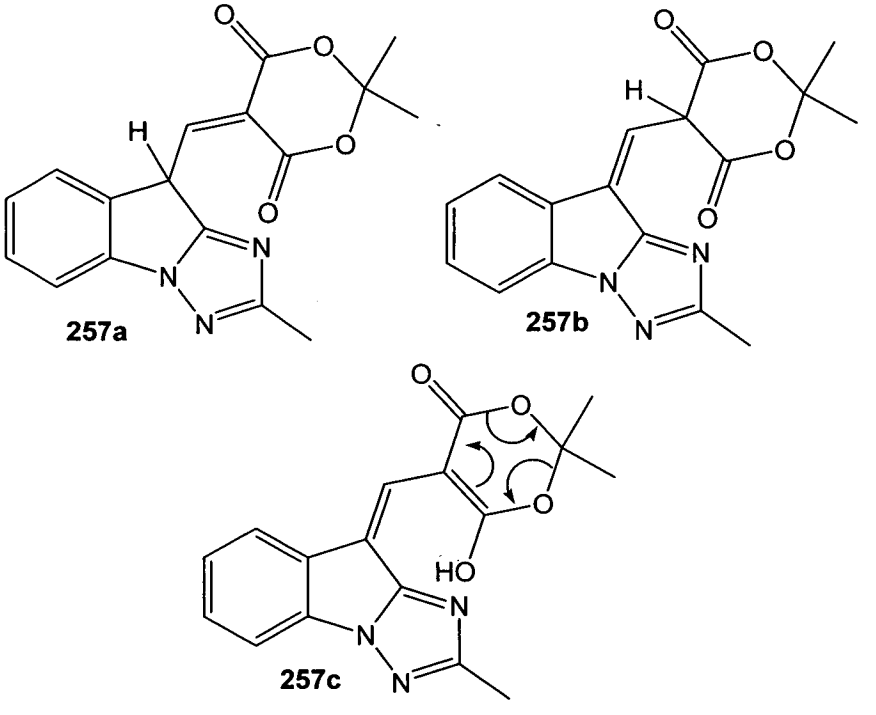


Figure 15: tautomeric structures of Meldrum's dye 257

2.4.4.1 The Parent 6,5,5 Coupler

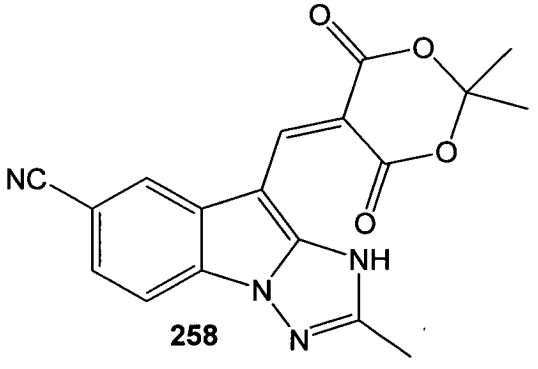
The reaction of the parent tricyclic coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** with methoxymethylene Meldrum's acid **256** gave the Meldrum's acid dye **257** in 17% yield after Flashtube column. UV-vis spectroscopy of this dye in ethyl acetate gave a λ_{max} of 428 nm, which is significantly bathochromic relative to the azo analogue **250**. The most striking thing about this absorption curve was its sharpness, with an extremely narrow $w_{1/2}$ of 40 nm, which indicates an extremely intense yellow colour. The extinction coefficient was calculated as 47,000 $dm^3mol^{-1}cm^{-1}$, which was expected as the colour was extremely intense and the solution had to be run in a much higher dilution than usual. For comparison a methanol solution of unknown concentration was analysed, and surprisingly gave a lower absorption maximum, λ_{max} of 421 nm, the opposite observation from the solvent difference found for azo and azamethine dyes. This is an example of negative solvatochromism, where the first excited state is less polar than the ground state, which is most likely polarised by the carbonyl groups.[96] The usual difference in half bandwidth between ethyl acetate and methanol was observed, with a slightly less sharp curve with $w_{1/2}$ 50 nm.

The proton NMR spectrum for the dye **257** appears to confirm the 1*H* tautomer as evident from the broad singlet up at 11.99 ppm for the triazole NH, the possible enol tautomer **257c** having already been discounted for stability reasons. This high shift is an indication that the amine proton is highly deshielded by hydrogen bonding to the Meldrum's acid carbonyl, which has been demonstrated earlier in X-ray crystal structures of similar compounds.[101] Another interesting point is the methine proton represented by a singlet at 8.54 ppm, a signal which is characteristic of these dyes. On the tricyclic coupler system, the phenyl proton in the 8-position is only increased slightly by the nearby methine functionality, with shift 7.83 ppm, and the triazole methyl peak is slightly lowered in shift by the NH group, at 2.59 ppm. Mass spectrometry gave further evidence for the desired product, with the correct *m/z* 325 Da at 10% intensity, and a breakdown peak typical of Meldrum's derivatives,[102] with loss of acetone and carbon dioxide (223 Da at 66% intensity).

2.4.4.2 The Benzonitrile Derivative

The reaction of the cyano derivative 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** gave a bright orange precipitate which was filtered off and shown by

proton NMR spectroscopy to be the desired dye product **258** in 29% yield. The UV-vis spectrum for this compound in ethyl acetate solution had a λ_{max} of 427 nm, which was slightly lower than the dye of the parent coupler **257** (428 nm), contrary to the usual trend of electron-withdrawing groups leading to bathochromic shifts in dye hue. The difference with these Meldrum's acid dyes from those seen previously is that the coupler is in the 1*H* tautomeric form, and so conjugation from the carbonyl groups can only extend to the 1-nitrogen of the triazole ring, and not into the phenyl ring. Therefore, the nitrile group here has little effect relative to the unsubstituted parent dye **257**. The curve was slightly sharper, $w_{1/2}$ of 35 nm, but more striking was the extinction coefficient of 64,000 $dm^3mol^{-1}cm^{-1}$, which is much higher than anything observed before. As it has already been noted that the cyano group cannot have a great effect on the Meldrum's acid dye hue, it is most likely that this result is due to a weighing error as discussed in Section 2.4.2.2. In methanol solution the opposite solvent difference from usual was again observed with a λ_{max} of 424 nm.



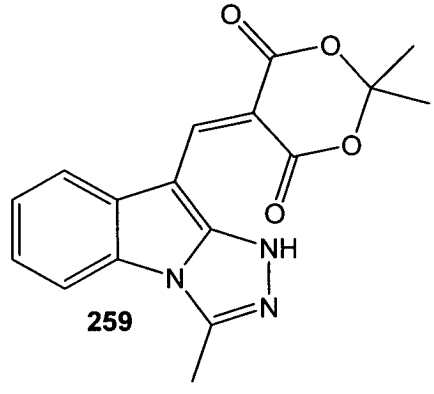
258

Mass spectrometry of **258** gave the correct mass peak for the predicted structure (*m/z* 350 Da), and in the proton NMR spectrum the NH peak is present at 11.92 ppm, confirming the 1*H* tautomer favoured by the parent dye **257**. The methine proton is shown by a peak at 8.55 ppm, which is almost the same shift as on the parent dye **257**. The effect of the dye forming group on the 8-proton, adjacent to the nitrile group, is to increase the shift from 7.74 ppm on the original coupler **236** to 8.17 ppm here, which is a much greater difference than with the parent system.

2.4.4.3 The Isomeric System

When the isomeric coupler 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** was reacted with methoxymethylene Meldrum's acid **256**, a yellow precipitate was formed, which

was found to be the desired dye product **259** in a 56% yield. The UV-vis curve for this dye is typically narrow with $w_{1/2}$ 40 nm, but another unexpected result was obtained for absorption maximum, a λ_{max} of 428 nm, exactly the same as the parent system **257**. This could be explained again by the tautomeric structure, as conjugation goes in the opposite direction from the other dyes, starting at the NH in the 1-position, so varying the rest of the triazole ring has little effect on dye hue. The extinction coefficient was slightly lower than that of the parent system **257**, at 40,000 $dm^3mol^{-1}cm^{-1}$, which continues the high values shown by this class of dyes.



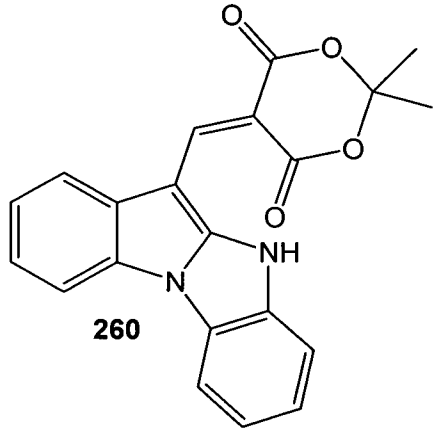
259

The structure of **259** was confirmed by its proton NMR spectrum, in which the NH group is shown by a broad singlet of typical shift, at 11.94 ppm, and a singlet corresponding to the methine proton, with a shift of 8.49 ppm. Mass spectrometry confirmed the correct product with a mass peak *m/z* 325 Da, and a characteristic breakdown peak at 223 Da of 100% intensity.

2.4.4.4 The Tetracyclic System

The final Meldrum's acid dye to be synthesised was from the tetracyclic system indolo[1,2-*a*]benzimidazole **238**, which resulted in a yellow brown precipitate, which was shown to be the dye **260** in a 34% yield. This dye produced perhaps the most surprising UV-vis spectra, with the ethyl acetate solution displaying an absorption maximum of 445 nm, which is nearly a "perfect" yellow. This is the complete opposite relative to the other Meldrum's acid dyes compared to the trends observed for other dye classes, the azamethine analogue **248** in methanol having shown a λ_{max} of 508 nm. This can only be explained by the effect of the extra phenyl ring on the

conjugated NH group, donating electron density to the ammonium cation in the excited state to stabilise it and give a bathochromic shift. This was all round a very impressive yellow dye, with the typically sharp curve of $w_{1/2}$ 35 nm, and the expected high extinction coefficient of 46,000 $dm^3mol^{-1}cm^{-1}$. The methanol solution displayed the usual differences, with a slightly lower λ_{max} value of 442 nm, and a slightly broader curve with $w_{1/2}$ 45 nm.



260

Mass spectrometry of **260** showed the desired mass peak *m/z* 360 Da with an intensity of only 2%, but with a breakdown peak of *m/z* 302 (21%), showing loss of acetone. The proton NMR spectrum showed the appropriate NH peak for the 10*H* tautomer at 11.77 ppm and the methine proton was present at 8.61 ppm, confirming the expected structure.

2.4.4.5 Summary of Spectroscopic Data

Dye	λ_{max} / nm	ε / $dm^3mol^{-1}cm^{-1}$	$w_{1/2}$ / nm
257	428	47,000	40
258	427	64,000	35
259	428	40,000	40
260	445	46,000	35

Table 4: UV-vis data for Meldrum's acid dyes in ethyl acetate solution

The UV-vis results obtained for the four Meldrum's acid dyes are summarised in Table 4. It is interesting to note how close the absorption maxima of the tricyclic

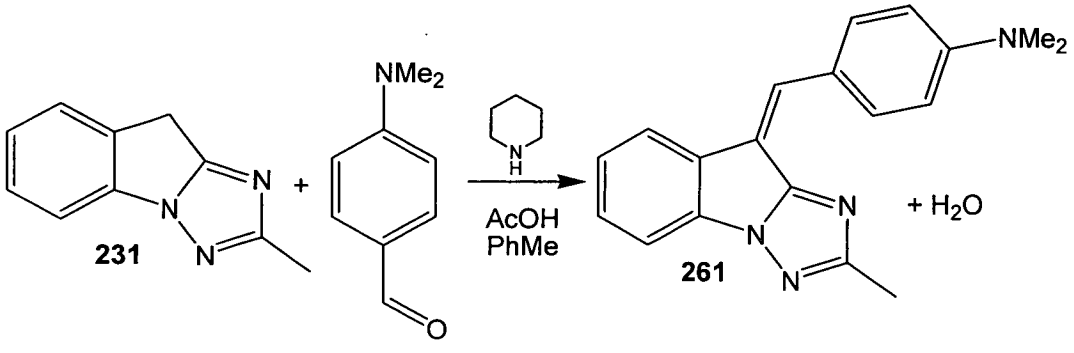
dyes are, which must be explained by the conjugation running from the coupler to the dye forming group, so the usual effects of heteroatom position or electron withdrawing groups on the coupler are not occurring here. As mentioned in the previous subsection, the tetracyclic dye **260** has the electron donating fused benzene ring next to the amino site, which is itself the donor group for conjugation to the Meldrum's acid carbonyls and is thus stabilised. The half bandwidth values and extinction coefficients are all in the same range as structural effects are negligible; the great difference for **258** being more likely a result of inaccuracies in weighing the sample.

Ethyl acetate solutions of the derivatives **257** – **260** faded to colourless after less than a week. Evidently, these dyes are not very stable to light (or the solvent), and so may be unsuitable for many practical applications.

The parent dye **257** has a methine peak with a chemical shift of 8.54 ppm, and the cyano derivative **258** 8.55 ppm, showing that the electron withdrawing substituent has little effect at this distance. The shift of the methine peak in the isomeric dye **259** is a little lower at 8.49 ppm, which suggests the configuration of the azole ring could have some effect on this position, although this is unlikely as the NH peak is in the same region for all three of these compounds. The proton NMR spectrum of **260** is interesting as the methine proton has a slightly higher shift than usual, at 8.61 ppm, which might relate to the increased conjugation brought about by the extra benzene ring. This also has the effect of giving the NH group a lower shift, 11.77 ppm, which is deshielded by the electron donating effects of this aromatic ring. In comparing these dyes to the original couplers, the proton in the 8-position (1-position in the tetracyclic system) nearest the coupling site is significantly deshielded by the addition of the highly electron withdrawing methylene Meldrum's acid functionality. The cyano and isomeric dyes **258** and **259** show an increase of 0.4 ppm relative to the shifts of the original couplers, and the tetracyclic dye **260** an increase of 0.6 ppm, but the parent dye **257** sees a rise of less than 0.1 ppm, which is hard to explain.

2.4.5 Methine Dyes

Yellow methine dyes with an aminophenyl substituent have certain applications in colour photography, the dye hue resulting from conjugation from the amino group through to the coupler system. The general synthetic method adopted is shown in Scheme 94, where each coupler was reacted with *p*-dimethylaminobenzaldehyde in toluene solution, using acetic acid and piperidine catalysts.[103] Stirring at room temperature overnight usually gave a brightly coloured precipitate of the methine dye, formed by attack of the deprotonated coupling site on the aldehyde, followed by loss of water to give the methine functionality (Knoevenagel reaction). As these compounds are closer in structure to the azo and azamethine dyes than the Meldrum's acid dyes, more conventional results were expected.



Scheme 94

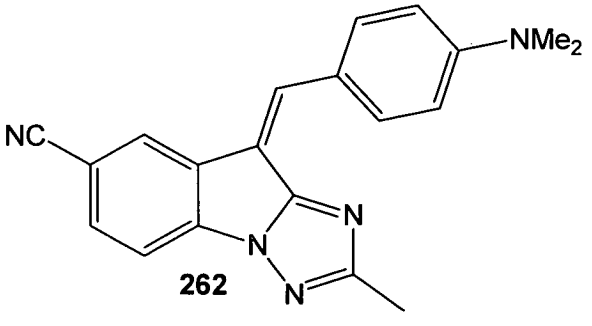
2.4.5.1 The Parent 6,5,5 Coupler

Reaction of the parent tricyclic coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** and *p*-dimethylaminobenzaldehyde gave no precipitate, so the toluene was evaporated off and the pure yellow dye **261** obtained by trituration in a 37% yield. UV-vis spectroscopy of an ethyl acetate solution gave a curve of similar width as the azamethine dyes, with $w_{1/2}$ 100 nm. The surprising result here was that the absorption maximum and extinction coefficient almost exactly matched those of the Meldrum's acid dye **257**, with a λ_{max} of 428 nm and ε 45,000 $dm^3mol^{-1}cm^{-1}$, so this is a very strong dye, with a good yellow hue. The spectrum obtained from a methanol solution of **261** showed the expected solvent variation, albeit to a greater extent than for the azo or azamethine dyes, with λ_{max} of 443 nm, an almost "perfect" yellow.

In the proton NMR spectrum of **261**, the characteristic chemical shift is that of the methine proton at 7.62 ppm, and the two aromatic proton pairs and dimethylamino singlet at 3.22 ppm are clearly visible. On the coupler benzene ring, the proton in the 8-position is only slightly deshielded by the methine group, its chemical shift being raised a small amount to 7.85 ppm. The ^{13}C NMR spectrum shows the methine carbon at 134.55 ppm and the dimethylamino carbon pair at 40.46 ppm, as well as two phenyl CH pairs. The mass spectrum finally confirmed the structure of **261**, with the expected *m/z* 302 Da at 100% intensity.

2.4.5.2 The Benzonitrile Derivative

The reaction of the cyano coupler 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** with *p*-dimethylaminobenzaldehyde gave a red orange precipitate, which was found to be the desired methine dye **262** in 38% yield. The UV-vis spectrum for the ethyl acetate solution of **262** was very surprising, with a hugely bathochromic shift of λ_{max} 460 nm, higher than the "perfect" yellow wavelength and approaching the orange region of the spectrum. As conjugation runs from the dimethylamino group to the coupler phenyl ring, the cyano group must have a strong effect on this even though it is not directly conjugated itself. The absorption curve is considerably sharper than that of the parent methine dye **261**, with half bandwidth of 70 nm. The other unexpected result was that the extinction coefficient 33,000 $dm^3mol^{-1}cm^{-1}$ was much lower than that of the parent. In methanol the dye was even more bathochromic, with a definite orange colour, λ_{max} 470 nm and $w_{1/2}$ 70 nm, so the cyano group is clearly having a large effect on conjugation in this compound.



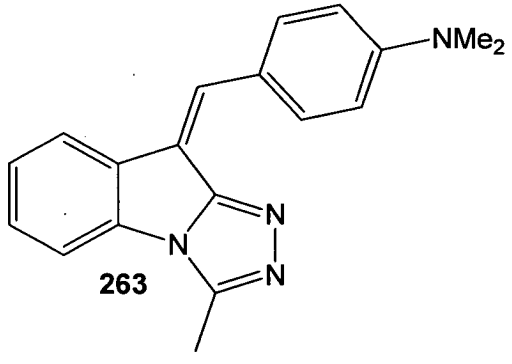
262

The structure of **262** was initially confirmed by its proton NMR spectrum; the characteristic methine proton peak is present with a chemical shift of 7.88 ppm, and the dimethylamino protons at 3.05 ppm. The mass spectrum displays the correct mass

peak *m/z* 327 Da at only 1% intensity (the cyano group could potentially contribute to breakdown under electron impact conditions), and subsequent breakdown peaks are also of low intensity, but do show loss of the dimethylaminophenyl and methine groups. The ^{13}C NMR spectrum shows the methine CH group at 136.61 ppm and the dimethylamino signal at 39.93 ppm.

2.4.5.3 The Isomeric System

Reaction of the isomeric coupler 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** with *p*-dimethylaminobenzaldehyde gave no precipitate, which indicates higher solubility of the unsubstituted dyes. Removal of toluene and trituration with ethyl acetate gave the desired dye **263** in 37% yield. When the UV-vis spectrum was obtained for the ethyl acetate solution of **263**, the absorption maximum was 423 nm, which is a little lower than that for the parent **261** and so in keeping with the trend observed for the azo dyes. The interesting difference, however, was that this curve was much sharper, with a half bandwidth of only 75 nm. The extinction coefficient was 38,000 $dm^3mol^{-1}cm^{-1}$, which is closer to the result for the cyano dye **262**.



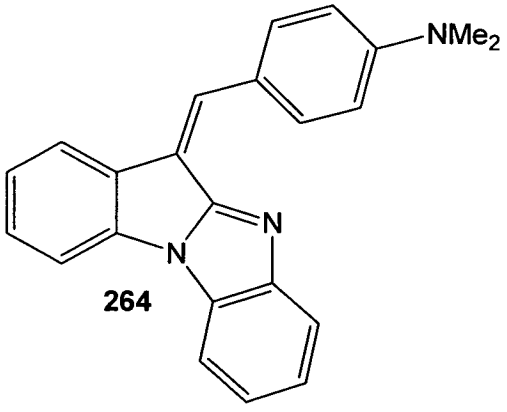
263

Again, the constitution of this product was initially confirmed by its proton NMR spectrum, in which the methine proton appears at 7.61 ppm and the dimethylamino group at 3.26 ppm. Further characterisation of **263** came from the mass spectrum, which displayed the correct mass peak *m/z* 302 with 100% intensity, and the ^{13}C NMR spectrum showing the methine carbon with a chemical shift of 132.45 ppm.

2.4.5.4 The Tetracyclic System

Finally, the tetracyclic coupler indolo[1,2-*a*]benzimidazole **238** was reacted with *p*-dimethylaminobenzaldehyde and a thick orange precipitate was formed, found to be

the desired dye product **264** in 30% yield. Another surprising UV-vis result followed, with the ethyl acetate solution showing an unexpectedly high λ_{max} of 441 nm, which is probably a result of the conjugation being extended into the extra phenyl ring. The curve had a typical half bandwidth of 90 nm, and the extinction coefficient was lower than the other methine dyes, at 31,000 $dm^3mol^{-1}cm^{-1}$. In methanol, the expected solvent difference meant that this was the most "perfect" yellow dye yet, with a λ_{max} of 447 nm.



264

The structure of **264** was indicated by its proton NMR spectrum, the methine proton has a shift of 7.45 ppm, and the dimethylamino group 3.00 ppm. The mass spectrum shows the correct mass peak *m/z* 337 Da at an intensity of 10%, with all the breakdown peaks coming at much lower mass numbers.

2.4.5.5 Summary of Spectroscopic Data

Ethyl acetate solutions of the four methine dyes **261** - **264** were set aside, and after several months they were still bright yellow. This shows these dyes are much more light and solvent stable than the Meldrum's analogues.

Dye	λ_{max} / nm	ε / $dm^3mol^{-1}cm^{-1}$	$w_{1/2}$ / nm
261	428	45,000	100
262	460	33,000	70
263	423	38,000	75
264	441	31,000	90

Table 5: UV-vis data for methine dyes in ethyl acetate solution

Coupler	Azamethines	Azos	Methines
"Parent" 231	512	418	428
"Cyano" 236	534	432	460
"Isomeric" 240	502	409	423
"Tetracycle" 238	508	-	441

Table 6: λ_{max} of azamethine, azo and methine dyes / nm

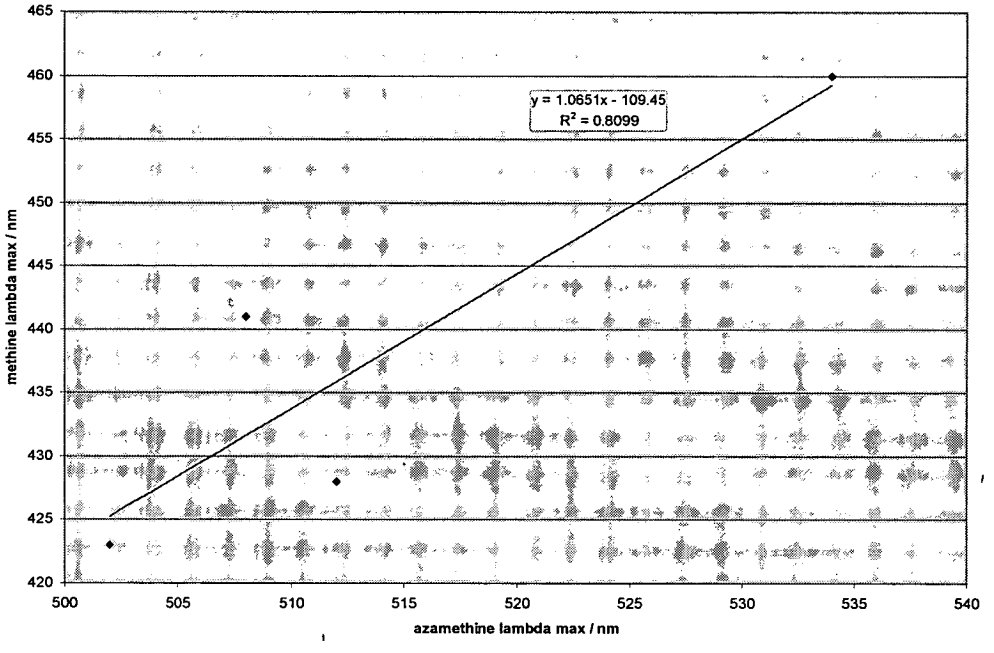


Figure 16: absorption maxima of methine dyes against azamethines

The UV-vis data obtained for these compounds **261 - 264** is summarised in Table 5, and their absorption maxima are listed next to those of the corresponding azamethine and azo dyes in Table 6, and the azamethine and methine λ_{max} values plotted against each other in Figure 16. Here the absorption maximum for the tetracyclic species **264** deviates from the trend observed for the azo and azamethine dyes with a significant bathochromic shift, while the parent methine dye **261** has as almost as significant hypsochromic shift. In all, these methine dyes are bathochromic relative to their azo analogues, and are closer to the ideal yellow absorption maximum of 450 nm

than their azamethine analogues are to the ideal magenta λ_{max} of 550nm, but the graph does show a definite relationship with the azamethine dyes.

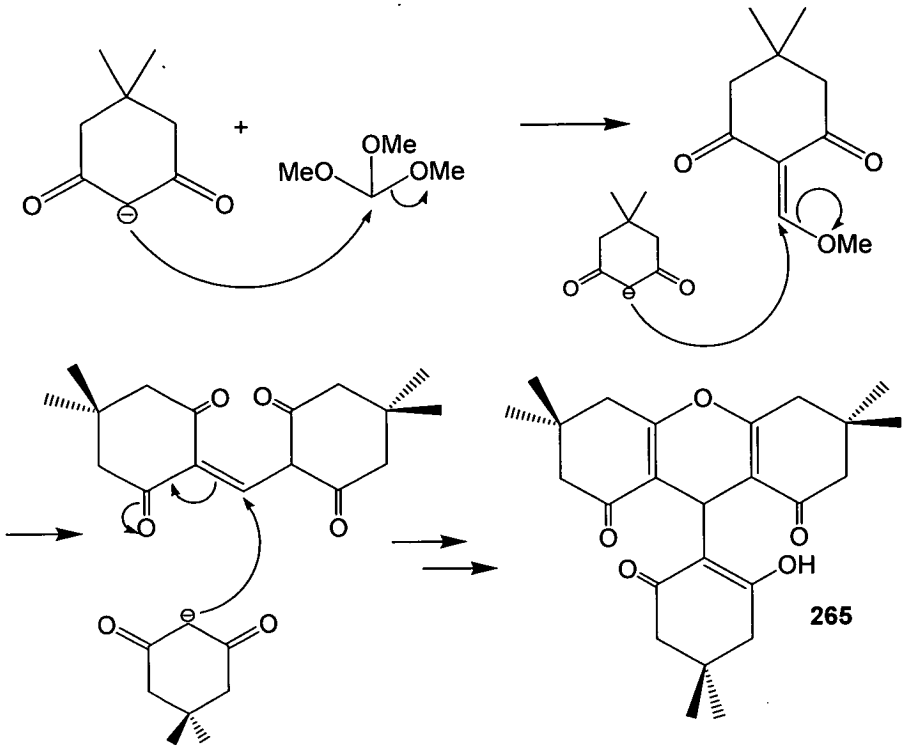
In the proton NMR spectra of the methine dyes, the parent dye **261** has a methine proton with a chemical shift of 7.62 ppm, while in the cyano dye **262**, this is value is raised to 7.88 ppm, which is a surprisingly high deshielding effect from the nitrile group at this distance. The isomeric dye **263** has a methine shift of 7.61 ppm, indicating that configuration of the azole ring has little influence on this position, but the tetracyclic species **264** shows this proton at a much lower shift, 7.45 ppm, possibly as a result of the electron donating effects of the extra benzene ring. The proton in the 8-position on the coupler ring system is typically raised in shift relative to the unsubstituted coupler by the deshielding effects of the methine functionality, although in the cyano species **262** it is actually lowered relative to the benzonitrile coupler **236**. On the dimethylaminophenyl group, the pair of protons adjacent to the methine group appears to follow the opposite trend from the methine proton. The parent **261** and tetracycle **264** have chemical shifts of just over 8.60 ppm, while on the cyano **262** pair this position is lowered to 8.41 ppm, and raised on the isomeric system **263** to 8.74 ppm.

2.4.6 Other Dyes

2.4.6.1 *N,N*-Dimethylbarbituric Acid Dye

As the Meldrum's acid dyes described in Section 2.4.4 had produced interesting results with trends in sharp contrast to the other classes of dyes, an attempt was made to produce an analogue of just the parent dye **257** using dimedone, that is Meldrum's acid with CH_2 groups instead of the ester oxygen atoms. This would then show the effect of the electronegative oxygen atoms in the ring on dye hue, and increased stability was expected having removed the ester linkages. The synthesis of methoxymethylene dimedone was attempted according to Scheme 95,[104] by heating dimedone in trimethyl orthoformate under reflux for 2 h, which resulted in a white precipitate found to be the trimeric xanthene **265** in 90% yield, with no trace of the desired product. The proton NMR spectrum showed an OH peak at 9.84 ppm and a single aliphatic proton with a shift of 4.30 ppm, then two CH_2 groups and two pairs,

and three pairs of methyl groups. A pair of reports on the accidental synthesis of **265** were found where various trialkyl orthoformates had been used;[105] the observed melting point of the product agreed with the literature value[106] and mass spectrometry showed the correct mass peak *m/z* 412 Da.

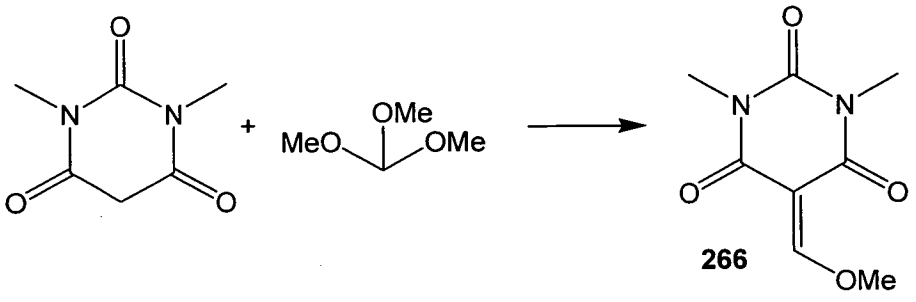


Scheme 95

The trimeric product is formed when a second and then third dimedone molecules attack the methoxymethylene intermediate, the final dimedone ring is attached in the enol form and an ether linkage formed between the other two. The major difference between dimedone and Meldrum's acid is the ester oxygens in the ring, which make the ring more electron rich and so the methoxymethylene species is less reactive to nucleophilic attack.

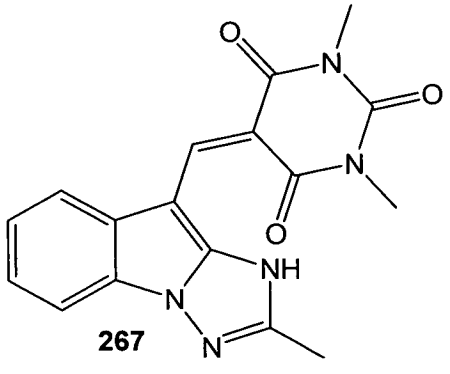
A suitable Meldrum's acid analogue was chosen in *N,N*-dimethylbarbituric acid, which was heated under reflux in trimethyl orthoformate for 30 min, which gave the product **266** as a yellow precipitate on cooling in 70% yield (Scheme 96).[104] There was a significant hydroxymethylene impurity, which could not be separated. Mass spectrometry showed the correct mass peak for **266** (*m/z* 198 Da), and the proton

NMR spectrum shows the methylene proton with a shift of 8.81 ppm, the methoxy group at 4.45 ppm, and the two methyl groups on the barbituric acid ring slightly separated at 3.49 and 3.47 ppm. With the heteroatoms in the barbituric acid ring, the methoxymethylene product **266** is insufficiently electrophilic for further reaction to a trimeric species.



Scheme 96

Reaction of methoxymethylene-*N*,*N*-dimethylbarbituric acid **266** and the parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** was carried out in the same way as for the Meldrum's acid dyes, with stirring in acetonitrile at room temperature for 3 days. The yellow precipitate obtained was found by proton NMR spectroscopy to be the desired barbituric acid dye **266** in 45% yield, although the hydroxymethylene impurity was still present, presumably unreacted as the hydroxy is not a good enough leaving group for this type of reaction. Separation by Flashtube column was attempted, but this just gave enough of the dye **267** for characterisation.



Analysis by UV-vis spectroscopy of an ethyl acetate solution showed this to be a near "perfect" yellow dye with a λ_{max} of 446 nm, which is very bathochromic relative to the Meldrum's acid analogue **257**. This result may be to do with the extra carbonyl

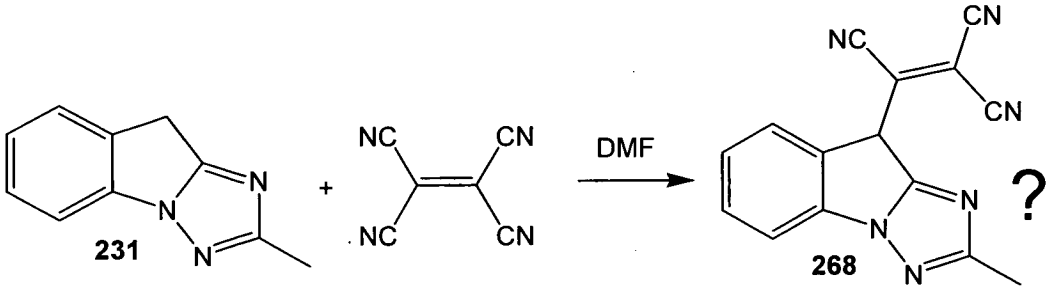
group of the barbituric acid ring and the nitrogen heteroatoms encouraging greater conjugation from the coupler triazole ring by inductive electron withdrawing effects. The half bandwidth was in the same extremely sharp region as the Meldrum's acid dyes, $w_{1/2}$ 40 nm, but the extinction coefficient was apparently closer to the methine dyes, at 34,000 $dm^3mol^{-1}cm^{-1}$. The barbituric acid dye **267** is the prototype of a whole new range of products, which should be more useful as the amide groups are more hydrolytically stable than the esters in the Meldrum's acid dyes. The solution used for the UV-vis data did lose its yellow colour after a number of weeks exposed to light, so confirming the improved light stability which might have been expected.

Mass spectrometry confirmed the identity of the product **267** with the correct mass peak *m/z* 337 present at 100% intensity, and the proton NMR spectrum showed the methine proton as a singlet with a shift of 8.59 ppm. On the barbituric acid group, the two methyl groups are non-equivalent, with shifts of 3.33 and 3.25 ppm, as hydrogen bonding between one carbonyl group and the triazole secondary amine occurs. When comparing the proton NMR spectrum of the barbituric acid dye **267** with its Meldrum's acid analogue **257**, the various protons which exist on both compounds all have similar chemical shifts, as the differing section on each acid ring is too far away to affect the coupler ring system.

2.4.6.2 Tetracyanoethylene

Tetracyanoethylene is known to react with arylamines to give tricyanovinyl derivatives, which have occasionally been used as the dyes in photographic applications, the three electron-withdrawing groups potentially having a strong enough effect to give an appropriate colour. Scheme 97 shows how the parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** was reacted with tetracyanoethylene, the method being to heat the two species together under reflux in DMF for 4 h.[107] Removal of the solvent and trituration then gave a brown solid crude product which was purified further by column to give orange crystals which appeared to be the intended product **268** in 27% yield. Confirmation of the identity of this product was difficult by proton NMR, appearing as the coupler **231** without its methylene protons and with the proton in the 8-position having an increased shift, at 8.17 ppm. The ^{13}C NMR spectrum showed none of the characteristic shifts of nitrile

groups, and mass spectrometry by both electron impact and fast atom bombardment techniques gave many peaks but none with the correct mass of the desired product **268**. CHN analysis was also attempted, but the results did not suggest structure **268**.



Scheme 97

In contrast to the dyes which were obtained successfully, this product was rather dull in colour, and UV-vis spectroscopy of an ethyl acetate solution of known concentration gave an unsymmetrical curve with a very low absorption maximum of 324 nm, well over 100 nm below the yellow region. In addition to this, the extinction coefficient was calculated as only 10,000 $dm^3mol^{-1}cm^{-1}$. The nature of this material evidently requires further investigation.

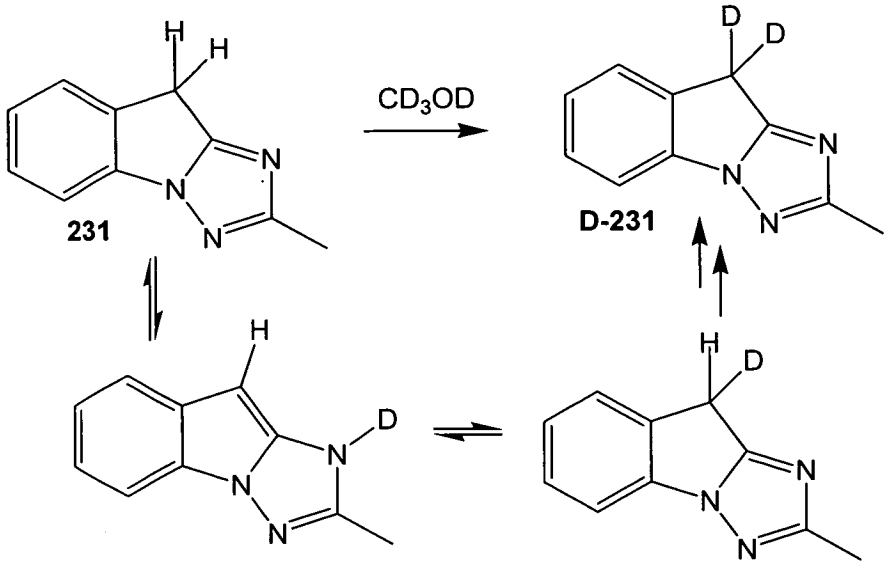
2.5 Other Chemistry of Couplers

As well as the range of dyes produced in the previous section, the chemistry of some of the couplers was further investigated by various reactions; most of which were intended to add coupling-off groups or ballasts, as would be required in photographic film, but others gave valuable information to support the results of the dye tests.

2.5.1 Deuterium Exchange

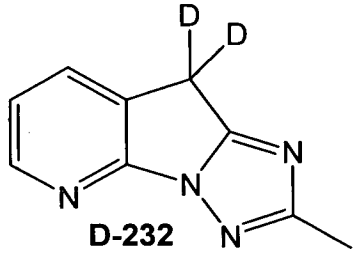
A deuterium exchange reaction was selected as a simple way of comparing the reactivity of the coupling sites of various couplers, and results were expected to correspond with those found for formation of the azamethine dyes. Four different couplers were selected from across the range of the azamethine dye results, and a small quantity of each (~20 mg) was dissolved in deuteriated methanol. According to

Scheme 98, the deuterium atoms from the methanol would exchange with the acidic protons in the 9-position of the coupler by means of a tautomerisation mechanism. By regular analysis of the solution by proton NMR spectroscopy, the rate at which the methylene peak diminished would be the indication of the rate of deuteriation.



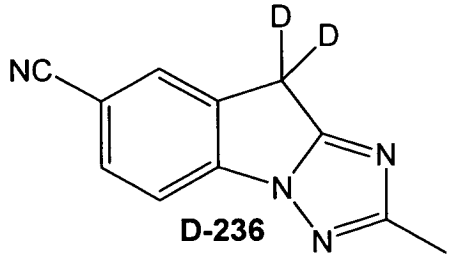
Scheme 98

The parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** showed only half complete deuteriation after 3 days, so the reaction rate was increased by addition of Hünig's base (diisopropylethylamine), which caused an immediate colour change of the *d*-methanol solution from orange to brown. Proton NMR spectroscopy then revealed that the base had deprotonated the coupling site to allow complete deuteriation within minutes.



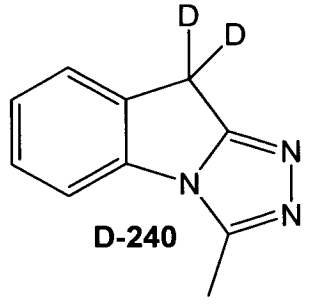
The pyridine-triazole species 2-methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene **232** showed complete deuteriation after just 1 h. As this compound coupled only slightly more quickly with the oxidised CD3 developer than **231** did, it was unexpected that

the deuterium exchange would happen at such a fast rate and without added base. A possible explanation would be that the pyridine heteroatom is basic enough to be able to deprotonate the methylene site and so aid deuteriation.



D-236

The benzonitrile coupler 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** was found to exchange the acidic protons for deuterium isotopes in under 15 min. This extremely quick deuterium exchange corresponds impressively with the fast coupling rate of this compound, the electron-withdrawing cyano group activating the acidic protons in the 9-position to a sufficient degree that base is not required.

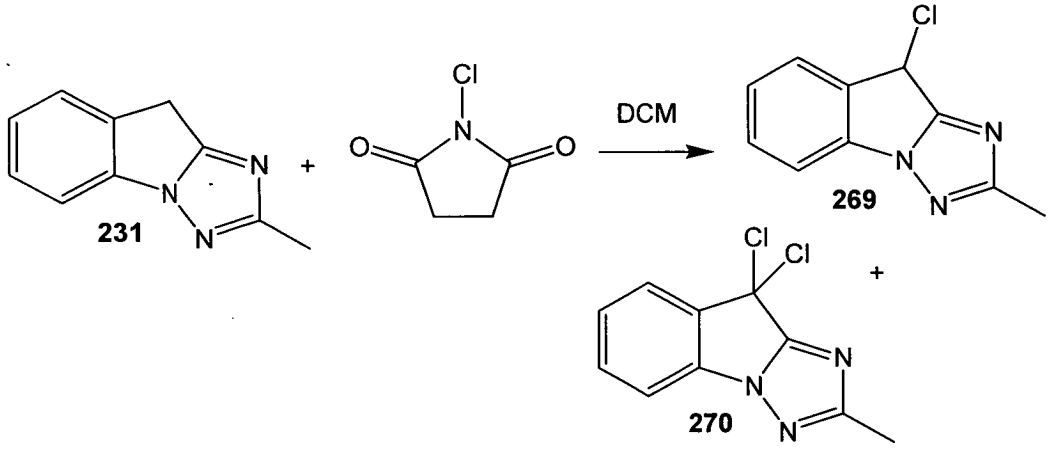


D-240

The isomeric system, 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** showed no deuteriation at all after 24 h of analysis, so Hünig's base was added and deuteriation was finally observed after a few minutes. So overall, the variation in deuteriation rate appears to correspond with the coupling rates of these four couplers, though the relationship appears to be exponential rather than linear. The reactivity of the deprotonated methylene coupling site to an oxidised developer in the photographic process clearly relates to the ability of the 1*H* tautomer to abstract a deuterium atom from the solvent as it reverts to the 9*H* tautomer.

2.5.2 Adding a Coupling-off Group

As was described in the introduction section, a coupler with two protons in the coupling site is known as a 4-equivalent coupler, and requires four equivalents of silver halide for the dye forming reaction to occur. Replacing one of these protons with a leaving group such as a halide doubles efficiency as only two equivalents of silver halide are required, the reaction often proceeding more quickly as an electronegative coupling-off group can stabilise the anion on the intermediate. A chloro group is commonly used in photographic couplers, and the initial attempt at chlorination of the parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** was made using sulfuryl chloride in DCM, with stirring at room temperature for 1 h,[108] but these conditions were found to be too vigorous, with an inseparable mixture of crude products being obtained.



Scheme 99

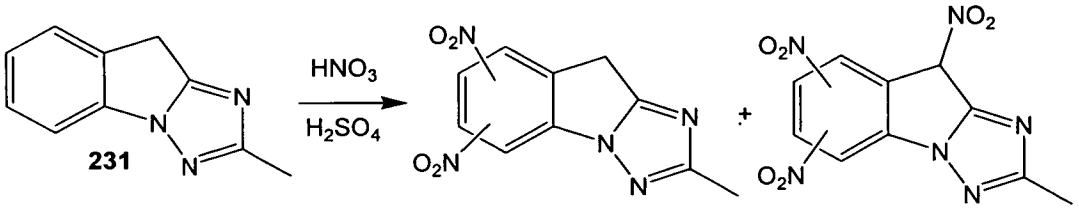
In a milder reaction, the coupler **231** was reacted with a slight excess of *N*-chlorosuccinimide, with room temperature stirring in DCM for 3 h, as shown in Scheme 99.[109] TLC of the reaction mixture showed that two products had been formed, the desired monochloro species **269**, but, as often happens with this reaction, the dichloro species **270** was also obtained as confirmed by LC-MS. A useful practical technique, which was employed to monitor reactions such as these, was to spray the TLC plate with a solution of CD3 developer and a solution of base and oxidiser. This would develop the coupler to a coloured spot of its respective dye, and other species would remain colourless, so the various species present in a reaction

mixture could be easily distinguished. In this case, the desired monochloro product **269** coupled quickly to a reddish magenta colour, while the dichloro species **270** gave a dull red spot.

Reduction of dichloro-compounds such as **270** to the monochloro derivatives such as **269** is commonly carried out by stirring the reaction mixture with an aqueous solution of tin (II) chloride for 30 min. This time was possibly too long as the result was complete reduction to the original coupler **231**, so the whole reaction was repeated, and this time an equilibrium mixture of the two products **269** and **270** appeared to have been reached. Flashtube column chromatography was then used to separate the two products; the desired monochloro species **269** was obtained in only 13% yield, while the unwanted dichloro product **270** was present in 21% yield. Electrospray mass spectrometry indicated the identity of these two species, which were further characterised by their proton NMR spectra, the monochloro **269** showing a methylene proton at 5.67 ppm not present in the dichloro **270**. As there was such a small quantity of product obtained, there was no chance to compare how this would couple relative to the original 4-equivalent coupler **231**. So the only example of a coupling-off group in action in the series synthesised here was the conversion of the azo dye **250** to the azamethine **241** described in Section 2.4.3.1.

2.5.3 Nitration

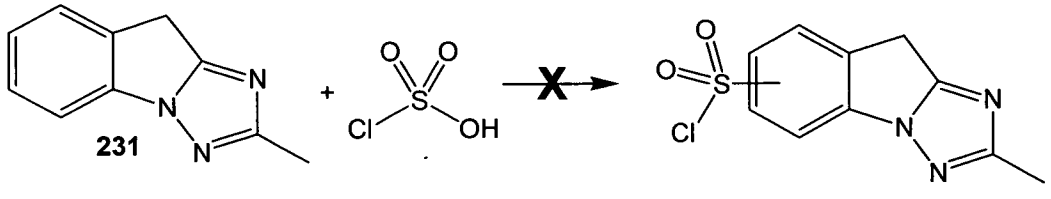
Because the flash vacuum pyrolysis of the dinitro precursors had failed, an alternative was to attempt nitration of the parent coupler **231**, which would be expected to take place on the benzene ring. The nitro group could be reduced to an amino functionality for attaching a ballast, which would give the amino coupler **237**, or an isomer which might be a better coupler. A conventional nitration reaction was carried out on the parent coupler **231**, as shown in Scheme 100, using nitric acid and sulfuric acid. These conditions were found to be far too vigorous however, as electrospray mass spectrometry showed that a mixture of di- and trinitro isomers had been produced. With the trinitro product, it is quite likely that one of the nitro groups may have attached to the 9-position, which could potentially be a useful leaving group if such a species had been isolable.



Scheme 100

In a milder reaction, the sulfuric acid was replaced by glacial acetic acid, and this time the mixture of crude products appeared to contain a dinitro product when analysed by electrospray mass spectrometry, as well as a small quantity of the desired mononitro species, but mostly unreacted starting material **231**. When column purification of the crude mixture was attempted, this was the only compound which could be retrieved. While this reaction had not achieved a satisfactory result, the useful information to be obtained is that couplers such as **231** are highly susceptible to electrophilic attack.

2.5.4 Chlorosulfonation

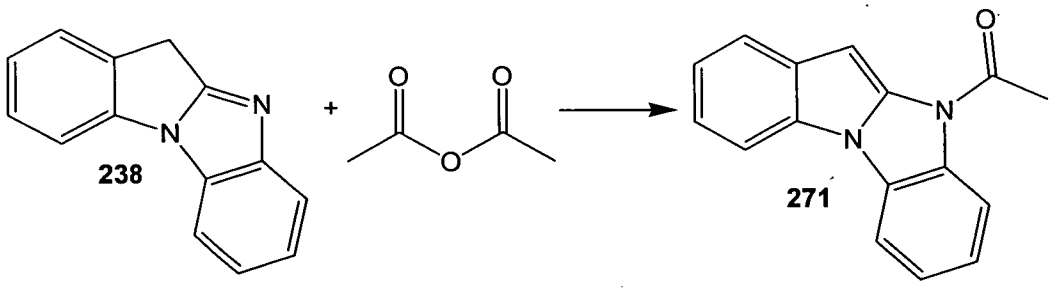


Scheme 101

Chlorosulfonation was selected as another possible route to a ballasted coupler, the chlorosulfonyl group could then be attached to a nucleophilic ballast, and being electron-withdrawing was expected to improve coupling. The parent coupler **231** was reacted according to Scheme 101, by stirring overnight at room temperature in chlorosulfonic acid.[110] A very small quantity of brown precipitate was formed on work up, which could not be characterised by proton NMR spectroscopy.

2.5.5 Acylation

So far, all reactions carried out on the couplers took place at the coupling site or on the phenyl ring, so a useful variation was to try to add a substituent onto the azole ring. Acylation was selected as a straightforward example, although it would prevent coupling due to loss of the important acidic proton. This reaction had previously been carried out on the tetracyclic coupler indolo[1,2-*a*]benzimidazole **238**,[111] and was carried out again here to confirm characterisation of the product **271**. According to Scheme 102, heating **238** in acetic anhydride for ~10 min gave a crude product, which was separated by Flashtube column, to give a 19% yield of the desired product 1-acetylindolo[1,2-*a*]benzimidazole **271**, which remained slightly impure. The problem with the tetracyclic systems decomposing during column chromatography appears to not be so severe with the substituent in the 1-position. Proton NMR spectroscopy of **271** shows successful addition of the acyl group by the presence of the methyl peak at 2.64 ppm, and an interesting feature is the appearance of two broad singlets, at 8.37 and 6.06 ppm, which represent the protons in the 9- and 11-positions respectively, demonstrating restricted rotation of the acyl group, which affects the two adjacent protons differently according to its position.



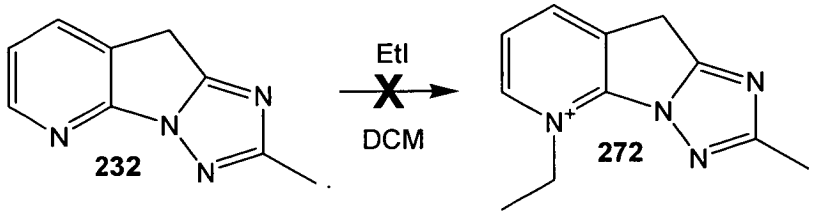
Scheme 102

A small quantity of the parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** was reacted in acetic anhydride under the same conditions as for the synthesis of **271**. After removal of the solvent, proton NMR spectroscopy showed there was mostly unreacted starting material, so the reaction was repeated with heating under reflux for 1 h. This resulted in a mixture of products, which could not be identified, presumably with a high degree of decomposition. The reaction conditions were clearly too

vigorous, potentially resulting in multiple acylations in various locations, or even breaking of the ring system. It would appear that the heteroatom in the 1-position, where substitution was expected to occur, is not sufficiently nucleophilic to attack the acyl carbonyl. The fact that this reaction failed where that of the tetracyclic parent compound **238** worked shows that the nitrogen atom of the 1-position of the tetracyclic ring system is a much stronger nucleophile, most likely because it receives additional electron density from the extra benzene ring.

2.5.6 Quaternisation of the Pyridine Heteroatom

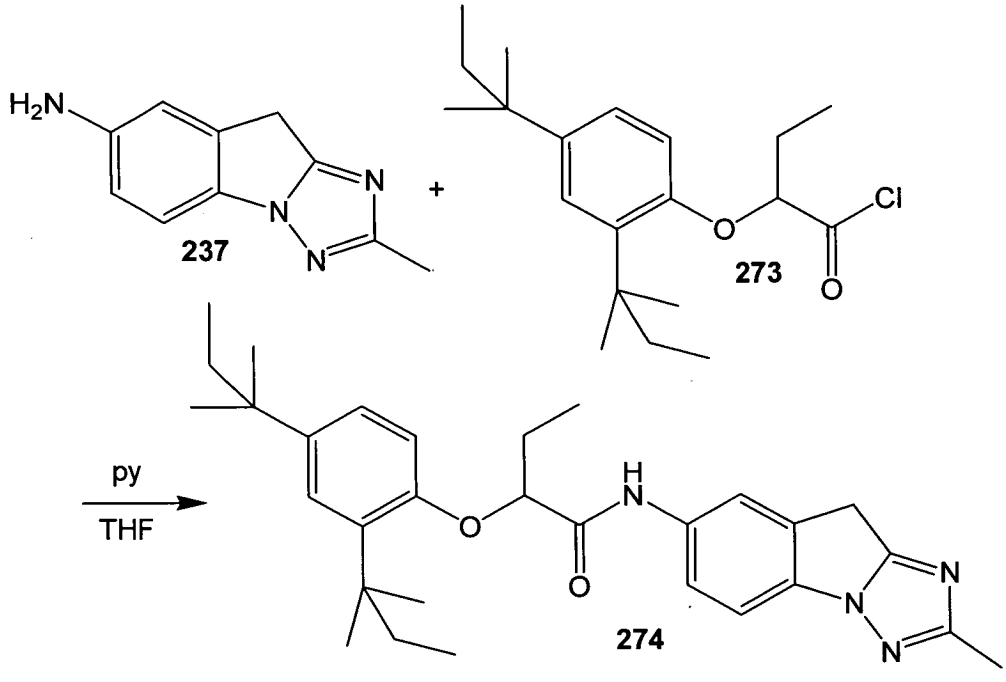
A possible method for attaching a ballast to the pyridine ring of the coupler **232** involved quaternisation of the heteroatom. Generating a quaternary ammonium salt could potentially be problematic, as the charge could lead to solubility problems in photographic media, although the large size of the ballast would reduce this effect. Initially, **232** was reacted with ethyl iodide by stirring in DCM at room temperature overnight, as shown in Scheme 103.[112] Analysis by electrospray mass spectrometry showed that no reaction had occurred, so the reaction was repeated in acetonitrile with heating under reflux for ~2 h. After the solvent was removed, LC-mass spectrometry showed a mixture containing unreacted starting material **232**, a mono-ethylated product, which could have been **272**, but mostly various diethyl isomers. It is uncertain if the pyridine heteroatom would be the preferred location for quaternisation, and ethyl iodide is not the best reagent for these purposes, but this was a promising start. Further progress could be made investigating alternative reaction conditions.



Scheme 103

2.5.7 Ballasting Reactions

Amino substituted systems, while being relatively poor couplers due to the electron-donating nature of the substituent, provide one of the easiest methods of attaching a ballast. The primary amino group will generally react with an acid chloride species, in preference to the ring heteroatoms. For this experiment the Kodak acid chloride ballast **273** was selected, featuring a dimethylpropyl substituted phenoxy group, which provides the necessary bulk required to keep the coupler in the appropriate layer of the photographic film dispersion. A solution of this ballast in THF was added drop-wise to a solution of the amino coupler **237** in THF, in the presence of pyridine as base (Scheme 104).[7] The reaction mixture was stirred at room temperature overnight, giving the ballasted coupler **274** as a thick orange oil in a 25% yield after column chromatography.



Scheme 104

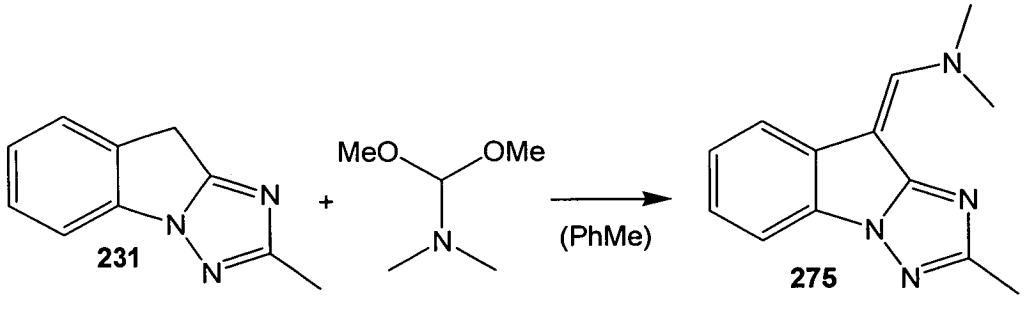
The identity of this large molecule was initially confirmed by electrospray mass spectrometry, showing the correct mass peak *m/z* 488 Da at 100% intensity. The proton NMR spectrum enabled further characterisation of **274**, and although difficult to interpret fully most groups of interest could be identified. The main peak of note regarding the amide ballast is the NH peak, with a high chemical shift of 7.96 ppm.

On the aromatic ring, the 6- and 8-protons either side of the ballast have been raised relative to the coupler **237**, with chemical shifts of 6.99 and 7.18 ppm respectively, and the 5-proton is also slightly deshielded at 7.37 ppm.

A total of nearly 1 g of **274** was taken for a coating test at the Kodak laboratories, in which it was spread over a film in a simulation of the photographic film. It was then exposed to light of varying shades and developed. Unfortunately, the ballasted system **274** did not couple at all in these conditions, the problem is likely to be that poorer couplers such as this amide would perform even worse as the oxidised developer must penetrate through the gelatine emulsion to allow dye formation. In addition to this, the conditions of the photographic process are less basic than the coupling tests performed earlier, so less of the coupler is ionised. The tetracyclic amino species **239** was ballasted in the same way, but no product was obtained by column chromatography.

2.5.8 Dimethylamino Methine Species

The final set of reactions performed on some of the coupler systems was to add a dimethylamino methine group to the coupling site, a reaction very much like the dye forming reactions, which would give compounds with interesting structural features which should vary between the different couplers. As shown in Scheme 105, the general reaction scheme was to dissolve each coupler in toluene, then add DMF dimethylacetal and heat the reaction mixture under reflux for 1 h to produce a precipitate.[113] As the conjugation pathway from the amino group into the heterocyclic ring system is relatively small, these compounds were expected to be colourless.



Scheme 105

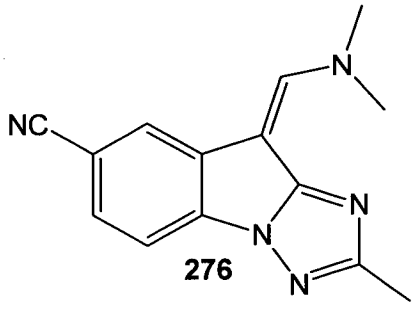
2.5.8.1 The Parent 6,5,5 Coupler

When the parent coupler 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** was reacted by the general method, the reaction could not be made to go to completion, even after several hours of heating. DMF dimethylacetal was therefore used as the solvent, then the mixture was heated under reflux for the usual 1 h. The third component obtained after Flashtube column chromatography was a brown semi-crystalline solid, found to be the desired product **275** in 26% yield.

The mass spectrum of **275** showed the correct mass peak *m/z* 226 at 50% intensity, and the proton NMR spectrum shows the proton on the methine group with a chemical shift of 7.21 ppm, with integrals corresponding to the protons on the coupler ring system. The most interesting signal on this spectrum is that corresponding to the dimethylamino group, being a broad singlet at 3.52 ppm. The fact that this is not a sharp peak shows that a certain degree of restricted rotation is occurring; the C-N bond tending towards double bond character.

2.5.8.2 The Benzonitrile Derivative

When the cyano coupler 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** was reacted with DMF dimethylacetal in toluene, it had to be heated for 3 h to drive the reaction to completion. After a cooling a brown precipitate was formed, and this was found to be the desired methine product **276** in 34% yield.



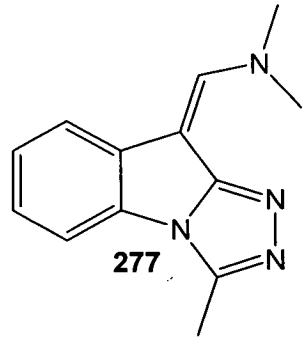
276

Mass spectrometry was used to confirm the identity of **276**, showing the correct mass peak *m/z* 251 at 40% intensity. On the proton NMR spectrum, the characteristic methine peak is present with a chemical shift of 7.30 ppm. This time, the two amino methyl peaks are separated, appearing at 3.85 and 3.32 ppm. The effect of the cyano group is clearly to increase the double bond character of the C-N bond, its electron-

withdrawing nature contributing to the conjugation through the system (although it is unable to conjugate directly itself). This phenomenon potentially relates to the cyano coupler's excellent performance in dye testing; both the reactivity of the methylene protons in the 9-position and the double bond character in these amino methine species relate to the electron withdrawing nature of coupler **236**.

2.5.8.3 The Isomeric System

The reaction of the isomeric coupler 3-methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** was carried out in neat DMF dimethylacetal as with the parent coupler **231**, and after 1 h reflux this time a brown precipitate was obtained. After filtration and drying this was shown by proton NMR spectroscopy to be the desired product **277** in 34% yield. The mass spectrum showed the mass peak of the desired structure, *m/z* 226 at 80% intensity, and the proton NMR spectrum displayed the important methine proton peak at 7.47 ppm. The dimethylamino group is represented here by a broad singlet at 3.83 ppm, which is somewhat narrower than for the parent compound **275**. This shows that there is less double bond character in this structure, which agrees with the previous observations, as this is a less successful coupler with a relatively unreactive methylene site.

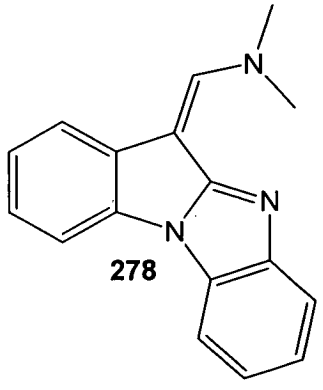


277

2.5.8.4 The Tetracyclic System

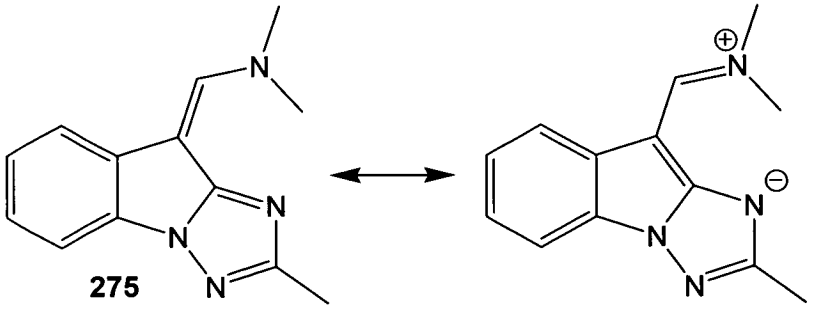
The tetracyclic coupler indolo[1,2-*a*]benzimidazole **238** was found to react with DMF acetal in toluene, with heating under reflux, which contradicted the supposition that the poorer couplers would need a more highly concentrated reaction mixture. No precipitate was obtained so the solvents were removed, and the crude material purified using a Flashtube column, to give the desired product **278** as the third component, in 56% yield.

The constitution of the dimethylamino methine product **278** was confirmed by mass spectrometry, with a mass peak *m/z* 261 Da, and in the proton NMR spectrum the methine proton peak has a shift of 7.22 ppm, almost the same shift as in the parent compound **275**. The dimethylamino group is represented by two broad singlets, which was initially surprising, as the starting material **238** is a less successful coupler than the tricyclic system **231**, so it would be expected that **278** would have less double bond character than **275**. However, there are other factors contributing to this variation, such as the frequency difference between the two signals, which is particularly wide in this case (see below).



278

2.5.8.5 Variable Temperature NMR Experiments



275

Figure 17: resonance structure of 275

The rate of rotation of the C-N bond in the dimethylamino methine compounds is temperature dependent and typical coalescence phenomena were observed. At low temperatures, two N-Me peaks occurred and at high temperatures, one peak was observed due to rapid rotation on the NMR time scale. Figure 17 shows the resonance structure for the parent compound **275**. On the proton NMR spectrum, this point is

identified by an almost complete absence of any signal for the groups in question, often an extremely low and broad signal is shown. Determining the coalescence temperature for each compound can give valuable information, as this can be used, together with the frequency difference between the two peaks at low temperatures, to calculate the free energy for rotation ($\Delta G^{\ddagger}$ /kJmol^{-1}) using the following equation.

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

T_c is the coalescence temperature in Kelvin and $\Delta\nu$ is the difference in Hz between the two methyl peaks at low temperatures.

The variable temperature NMR experiments were carried out on a 360 MHz instrument, and the samples were heated or cooled to find the coalescence temperature. As the distance between the two peaks at lower temperatures is frequency dependent, so using the 360 MHz instrument rather than 200 or 250 MHz had the effect of raising the coalescence temperatures. So, for example, where the parent compound **275** showed a broad singlet at 200 MHz, it now showed two low intensity broad peaks on the 360 MHz instrument, and had to be heated to find the coalescence temperature. The experiments were carried out in deuteriated acetone solution, except for the cyano **276** which required higher temperatures and so was run in DMSO. Three proton NMR spectra of the parent compound **275** are shown below; in Figure 18, the spectrum at 21 °C shows broad singlets at 3.9 and 3.4 ppm, Figure 19 shows coalescence at 33 °C and Figure 20, at 40 °C, shows one peak at 3.6 ppm. The results from the experiments for the four dimethylamino methine compounds are shown in Table 7.

Compound	**Coalescence temperature / °C**	**Peak separation / Hz**	**Activation energy / kJmol^{-1}**
275	33	184.5	59.6
276	71	177.6	67.5
277	10	195.4	54.8
278	23	253.1	56.8

Table 7: the variable temperature NMR experiment

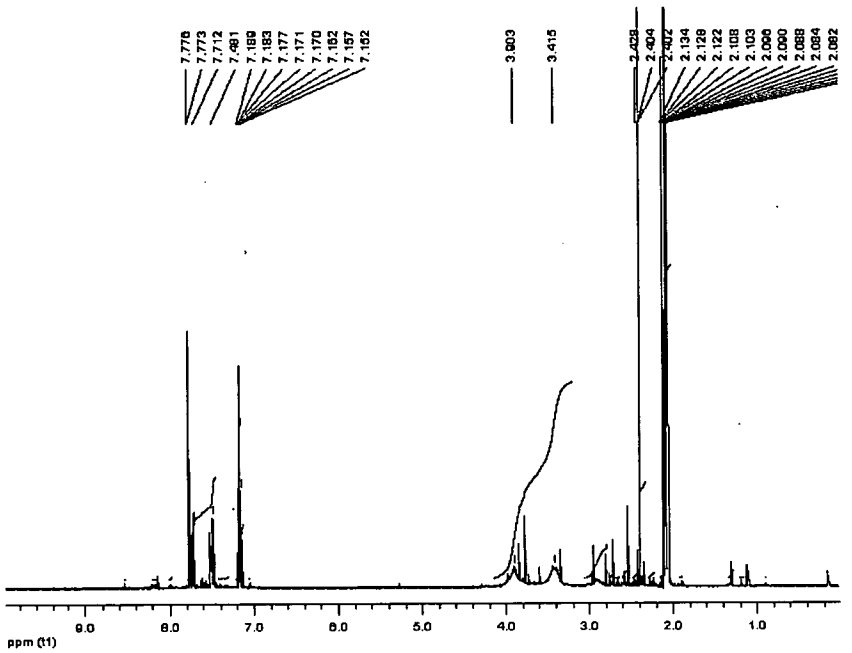


Figure 18: proton NMR spectrum of 275 at 21 °C

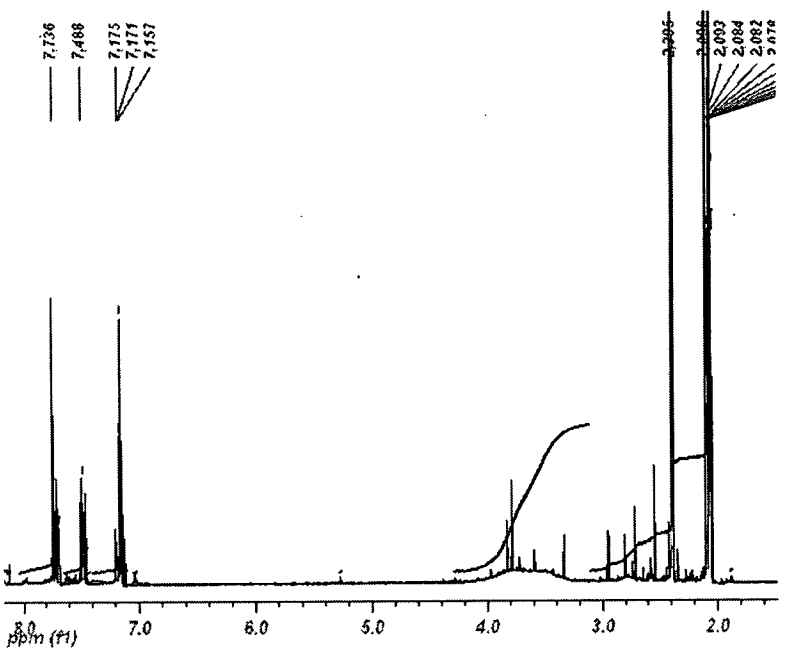


Figure 19: proton NMR spectrum of 275 at 33 °C

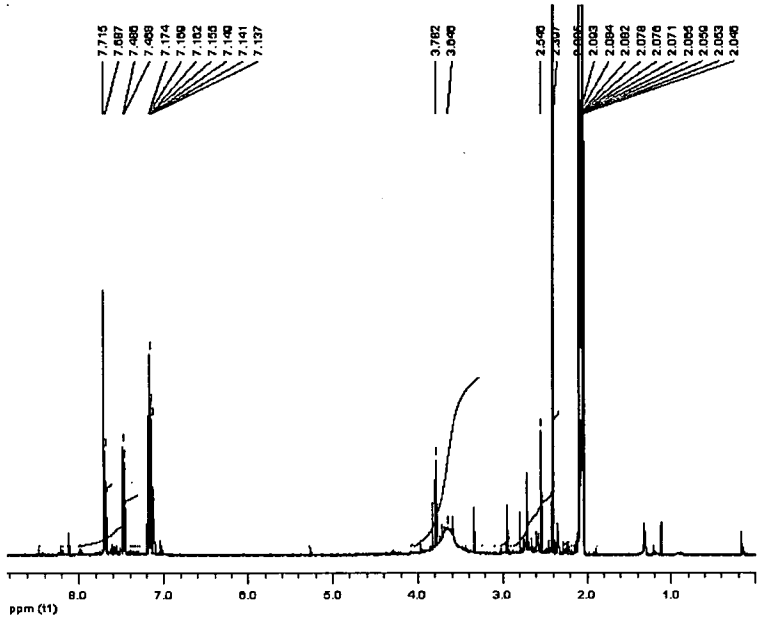
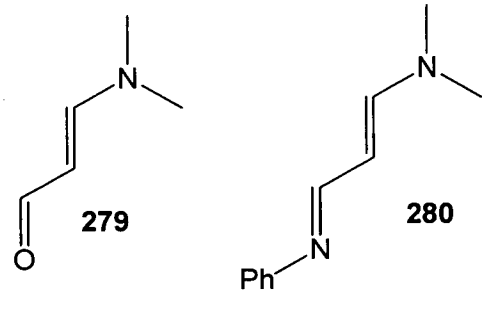


Figure 20: proton NMR spectrum of 275 at 40 °C

These results are useful for showing the electron withdrawing character of each coupler pulling on the aminomethine functionality. For comparison, the $\Delta G^{\ddagger}$ value of DMF is 88 $kJmol^{-1}$, which shows that an oxygen atom is considerably more strongly electron withdrawing than any of the coupler systems. When an extra ethylene section is added, as in the enone **279**, the activation energy is 64 $kJmol^{-1}$, and replacing the carbonyl by a phenyl imine moiety as in **280** lowers $\Delta G^{\ddagger}$ to 51 $kJmol^{-1}$.[114] These two structures are therefore much more closely comparable to the heterocyclic coupler systems, particularly **280**, which is much the same conjugated system as in the couplers.



Because both dye hue and restricted rotation depend on the electron withdrawing nature of the coupler, it was believed that the activation energy calculated from the results could correlate with the absorption maxima results obtained for the various dyes produced in Section 2.4. Table 8 shows activation energy against the λ_{max} values of the azamethine, azo, methine and Meldrum's acid dyes in nm, and graphs have been plotted for each dye family in Figures 21 - 24.

Coupler	Activation energy / $kJmol^{-1}$	Azamethine λ_{max} / nm	Azo λ_{max} / nm	Methine λ_{max} / nm	Meldrum's λ_{max} / nm
Parent **231**	59.6	512	418	428	428
Cyano **236**	67.5	534	432	460	427
Isomer **240**	54.8	502	409	423	428
Tetra **238**	56.8	508	-	441	445

Table 8: activation energies against dye absorption maxima

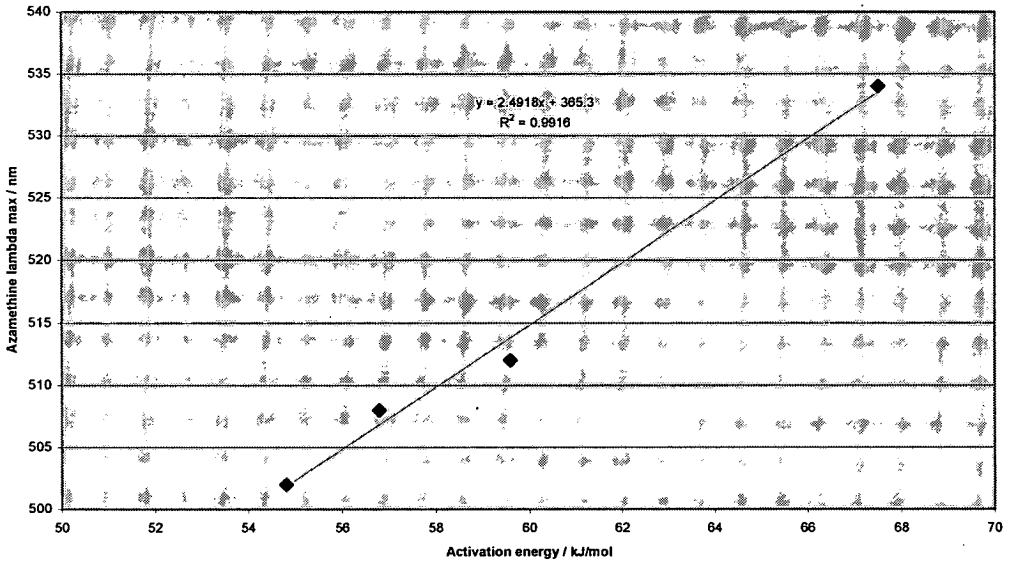


Figure 21: azamethine dye absorption maxima against activation energy

The results for the azamethine dyes appear to fit quite conclusively with the predictions, all values on the graph in Figure 21 being very close to the trend line.

The cyano compound **276**, having given a dye with the most bathochromic hue, was found to have by far the highest coalescence temperature and so the highest activation energy. The other three compounds have activation energies closer together, as are their absorption maxima for their azamethine dyes, and they appear in the order expected. So for the most important family of dyes, the magenta azamethines produced by the photographic process, calculating the activation energy for rotation of their methine analogues is a useful tool for demonstrating coupling ability and subsequent dye hue.

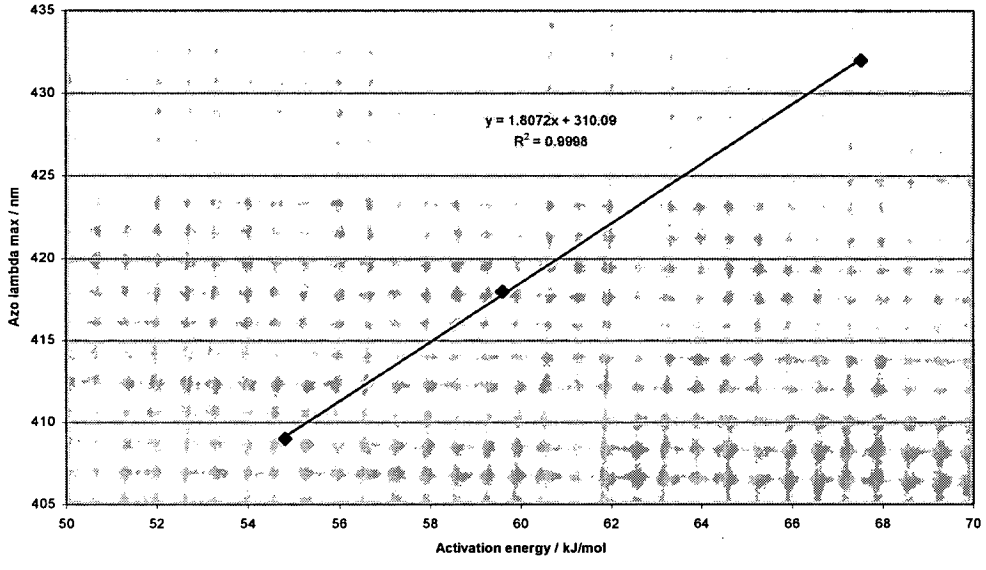


Figure 22: azo dye absorption maxima against activation energy

There was no azo dye produced from the tetracyclic coupler **238**, but the three absorption maxima for ethyl acetate solution plotted correlate to the activation energy figures even more closely than the azamethine analogues, with no points deviating from the trend line (Figure 22).

The absorption maxima of the methine dyes had deviated slightly from the previously observed trends, particularly the parent dye **261** and the tetracyclic **264**. Therefore, the correlation with the activation energies of the aminomethine compounds is very poor (Figure 23).

Finally, the Meldrum's acid λ_{max} values should not be expected to correlate to activation energy for free rotation, as conjugation in these dyes runs from the coupler to the Meldrum's acid section, therefore the electron withdrawing power of the coupler has no effect on dye hue. With three of the dyes produced having almost identical absorption maxima, it was clear that no correlation would be seen, and the graph in Figure 24 shows no trend.

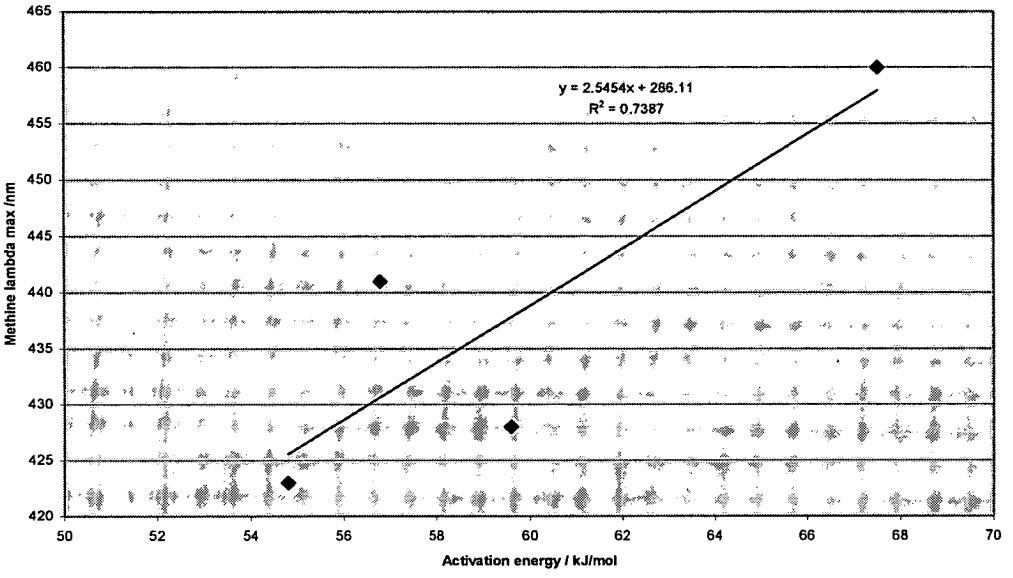


Figure 23: methine dye absorption maxima against activation energy

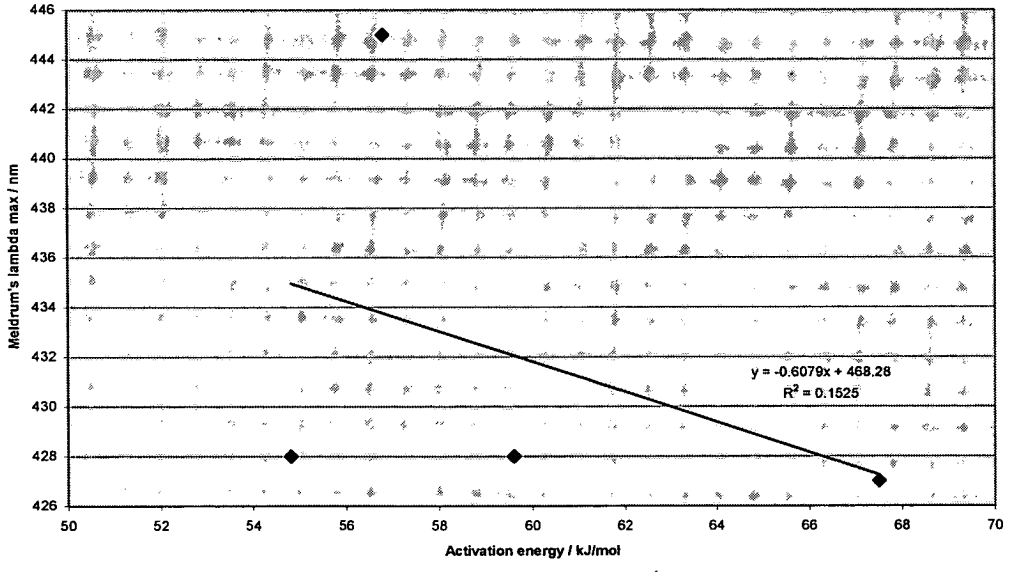


Figure 24: Meldrum's acid dye absorption maxima against activation energy

Conclusions

- Seven different heterocyclic ring systems, based on or related to the general structure **1**, have been produced by Flash Vacuum Pyrolysis in as little as two steps.
- In azamethine dye coupling tests more nitrogen heteroatoms improve coupling and dye hue.
- The nitrogen atom in the 1-position is required to make coupling protons sufficiently acidic, conjugating to reactive site.
- The extra nitrogen in the triazole ring (3-position) improves this by extending conjugation to a further heteroatom.
- In the isomeric system, with the third heteroatom in the 2-position, coupling is hindered significantly.
- A heteroatom in the six-membered ring improves coupling, better in the 6- than 4-position.
- A nitrile substituent serves the same purpose as the pyridine heteroatom.
- The tetracyclic system appears to produce an azamethine dye roughly analogous with tricyclic imidazole.
- Azamethine absorption maxima show some correlation to coupler methylene proton chemical shifts.
- Solvent variations reveal bathochromic shift with more polar solvents (positive solvatochromism).
- Coupling reactions with diazonium salts give yellow azo dyes, with absorption maxima which correlate with those of the magenta azamethine dyes.
- Reactions with methoxymethylene Meldrum's acid gave yellow dyes with extremely sharp curves, but reversed trend in dye hues and solvent variations as conjugation runs in the opposite direction.
- The couplers reacted with *p*-dimethylaminobenzaldehyde to produce yellow methine dyes, which show much greater effect of electron withdrawing group on dye hue.
- An amine substituent provides the easiest way so far to attach a ballast.
- There were interesting results concerning the chemistry of the couplers; notably that they appear to be highly susceptible to electrophilic attack.

- Activation energies of restricted rotation of the dimethylamino methine compounds were found to correlate to azo and azamethine absorption maxima.

3. EXPERIMENTAL

Abbreviations

NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
ppm	parts per million
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
td	triplet of doublets
dt	doublet of triplets
q	quartet (^{1}H-NMR spectra)
quat	quaternary (^{13}C-NMR spectra)
m	multiplet
J	coupling constant
m/z	mass to charge ratio
M^+	molecular ion mass
FVP	flash vacuum pyrolysis
T_f	furnace temperature (°C)
T_i	inlet temperature (°C)
P	pressure (Torr)
t	time of pyrolysis
mol	moles
mp	melting point (°C)
bp	boiling point (°C)
h	hours
min	minutes
M	molarity (mol dm^{-3})
LC-MS	liquid chromatography-mass spectrometry
UV-vis	ultra violet-visible light spectroscopy
λ_{max}	wavelength of maximum absorption
ε	extinction coefficient
$\lambda_{1/2}$	half band width

DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Boc	*t*-butoxycarbonyl
NOESY	Nuclear Overhauser Enhancement Spectroscopy

3.1 Instrumentation and general techniques

3.1.1 Nuclear Magnetic Resonance Spectroscopy

Unless otherwise stated, ^{1}H NMR spectra were recorded on Bruker DPX360 (360 MHz), Bruker ARX250 (250 MHz) and Varian Gemini 200 (200 MHz) spectrometers. ^{13}C NMR spectra were recorded on the Bruker ARX250 (63 MHz) instrument. At the Kodak laboratories spectra were recorded on the Jeol 400 MHz instrument.

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

3.1.2 Mass Spectrometry

Low resolution mass spectra were obtained under electron impact conditions using a Kratos Profile instrument while high resolution spectra were recorded on a Kratos MS50 TC instrument. At the Kodak laboratories, positive and negative electrospray mass spectra were recorded on a Micromass Platform LC mass spectrometer, following HPLC purification on the attached Hewlett Packard HP 1100 Series instrument, with 1100 series diode array detector. Only the spectrum which showed the appropriate mass ions is reported here.

3.1.3 Elemental Analysis

Microanalyses were carried out on a Perkin Elmer 440 CHN Elemental Analyser.

3.1.4 Ultra-Violet and Visible Spectroscopy

Most UV-vis spectra were carried out on a Perkin Elmer 900 Lambda spectrometer instrument and at the Kodak laboratories on a Hewlett Packard HP 8453 series uv/vis spectrometer, linked to the mass spectrometer. The solvent used is indicated and wavelengths of maxima (λ_{max}) are recorded in nm.

3.1.5 Melting Points

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

3.1.6 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.

Dry-flash chromatography was generally carried out using Fluka silica gel H. The crude materials were usually preabsorbed onto silica gel and loaded onto the column, which was then eluted under a vacuum provided by water pump or diaphragm pump. On a small scale (<200 mg) Flashtubes (Trikonex) were utilised, which are polyethylene tubes filled with silica (8 g) and a fluorescence indicator. A solution of the crude material in the appropriate eluent (1-2 cm^3) was added to the top of the column followed by further washings of eluent, and the column allowed to develop under gravity. Finally, the Flashtube was cut into sections and the different components extracted from the silica.

3.1.7 Solvents

Commercially available solvents were generally used without further purification although some were dried over molecular sieves or kept under an atmosphere of nitrogen.

3.1.8 Flash Vacuum Pyrolysis (FVP)

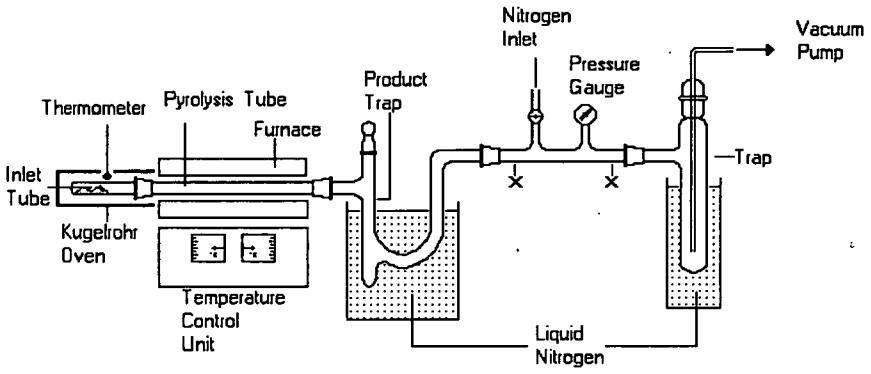


Figure 25: FVP apparatus

Figure 25 shows the general apparatus used for flash vacuum pyrolysis, based on the design of W.D. Crow, of the Australian National University. The system is evacuated to a pressure of 10^{-2}-10^{-3} Torr, by means of an Edwards Model ED100 high capacity oil pump off the diagram to the right. On the small scale, samples of around 30 – 50 mg are heated in the inlet tube by a glass Büchi oven, which sublimes them into the gaseous phase, where they pass into a silica tube (30 × 2.5 cm), heated by a Carbolite electronically controlled tube furnace. After only milliseconds in the furnace tube, the products are collected at the entrance of the U-tube trap cooled in liquid nitrogen. The entire crude pyrolysate is then removed from the trap by dissolving in deuteriated chloroform, and then analysed by ^{1}H NMR spectroscopy.

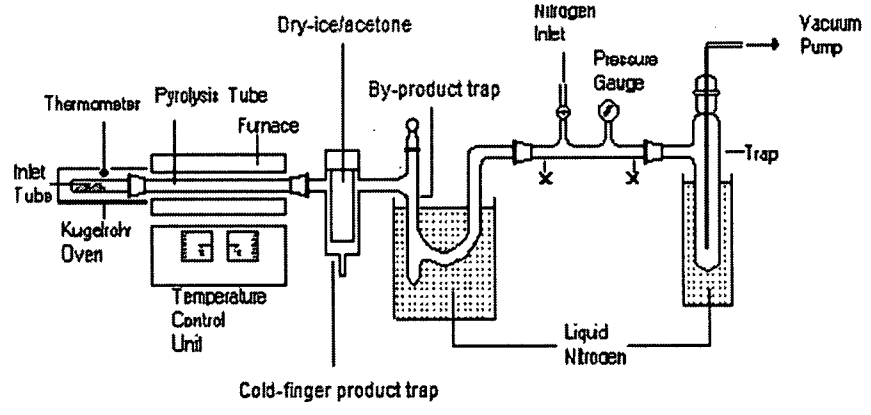


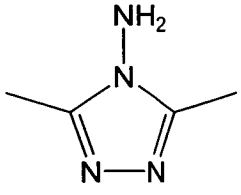
Figure 26: modified FVP apparatus

On the larger scale (>100 mg), a special addition is often necessary due to reactive leaving groups which can decompose the products collecting in the warm space at the entrance to the U-tube. Figure 26 shows how a cold finger trap, cooled with dry ice and acetone, is added at the exit of the furnace tube to catch the FVP products, while the reactive by-products pass through to the U-tube. Crude products are removed by dissolving in dichloromethane, and are then purified by column chromatography. Nitrous gases trapped in the U-tube are allowed to evaporate while warming to room temperature in a fume cupboard.

3.2 Preparation of Specific Starting Materials

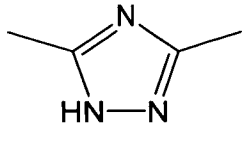
Non generic reactions used to prepare starting materials for the pyrolysis precursors are described below.

3,5-Dimethyl-[1,2,4]-triazol-4-amine 167



Glacial acetic acid (60 g, 1 mol) and hydrazine hydrate (85%, 85 g, 1.5 mol) were mixed cautiously with cooling in an ice bath.[55] The reaction mixture was then heated slowly using a Bunsen burner and gauze, with the apparatus set up for distillation. Distillation of water began at 100 °C and excess hydrazine hydrate at a higher temperature. The temperature was raised to 220 °C over 1.5 h, and then maintained at this level for 4 h. The reaction mixture was allowed to cool, and while still above 100 °C it was added to isopropyl alcohol (150 cm^3) resulting in precipitation of white crystals. These were filtered off, and the filtrate concentrated to give further product plus an oily impurity which was removed by dissolving in acetone. The product was found to be 3,5-dimethyl-[1,2,4]-triazol-4-amine **167** (47.18 g, 84%), mp 198-200 °C [lit.,[55] 197 °C]; δ_H 5.78 (2H, s) and 2.25 (6H, s).

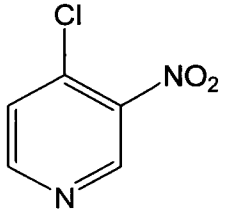
3,5-Dimethyl-1,2,4-triazole 171



To a solution of 3,5-dimethyl-[1,2,4]-triazol-4-amine **167** (46.65 g, 0.42 mol) in hydrochloric acid (6M, 69.5 cm^3) was added a solution of sodium nitrite (32.88 g, 0.48 mol) in water

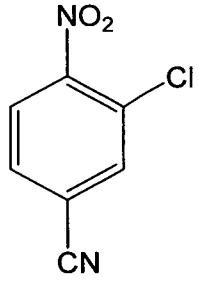
(520 cm^3), drop-wise over a period of 100 min.[56] The reaction vessel was placed in an ice bath to keep the temperature below 30 °C. After addition of the reactants was complete, the flask was shaken until evolution of nitrogen ceased. The water was then evaporated under reduced pressure to leave a white crystalline mixture of product and sodium chloride. Dichloromethane (500 cm^3) was added to dissolve the product, aided with gentle heating, then the sodium chloride was filtered off through celite. The DCM was then removed *in vacuo* to leave the white crystalline product 3,5-dimethyl-1,2,4-triazole **171** (39.13 g, 97%), mp 139-141 °C [lit.,[56] 142 °C]; δ_H 2.39 (6H, s).

4-Chloro-3-nitropyridine 173



To 4-hydroxy-3-nitropyridine (5 g, 0.036 mol) was added phosphoryl chloride (12 cm^3, 0.135 mol) with stirring.[59] Then, phosphorus pentachloride (5.88 g, 0.028 mol) was added at 30 °C and the reaction mixture was heated slowly on an oil bath to 80 °C over 1.3 h, then to 108 °C over a further 1.5 h. Finally, it was heated under reflux for 2.5 h until hydrogen chloride evolution ceased. Excess phosphoryl chloride was distilled off under vacuum, then the crude product was added to ice (20 cm^3) and extracted into DCM (3 × 20 cm^3). The combined organic layers were then washed with water (3 × 10 cm^3), dried over $MgSO_4$ and then concentrated *in vacuo* to give 4-chloro-3-nitropyridine **173** (4.6 g, 81%), mp 37-40 °C [lit.,[114] 45 °C]; δ_H 9.07 (1H, s), 8.62 (1H, d, ^3J 8.1) and 7.53 (1H, d, ^3J 8.1).

3-Chloro-4-nitrobenzonitrile 174



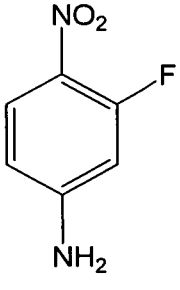
A solution of 4-amino-3-chlorobenzonitrile (5 g, 0.033 mol) in a mixture of sulfuric acid (10 M, 12 cm^3) and water (30 cm^3) was added, with vigorous stirring, to ice water (25 cm^3) causing precipitation of the organic solid.[60] Crushed ice (10 g) was added, and then a solution of sodium nitrite (4 g, 0.058 mol) in water (7 cm^3) was added quickly with continued stirring, causing the solid to dissolve. After 5 min, the resulting diazonium salt solution was added, portion-wise through a wide necked glass tube below the surface, to a stirred solution of sodium nitrite (50 g, 0.725 mol) and sodium hydrogen carbonate (22.5 g, 0.268 mol) in water

(500 cm^3), containing a small quantity of silicone "Anti-foam", at 60 °C. This was stirred for 30 min and then left to settle overnight.

The resulting yellow precipitate was filtered off, washed with HCl (2 M) and water then purified by column chromatography (methanol and toluene as eluent) to give as the first component 3-chloro-4-nitrobenzonitrile **174** as a crystalline orange solid (1.10 g, 18%), mp 84-86 °C [lit.,[115] 85-87 °C]; δ_H 7.89 (1H, d, ^3J 8.6), 7.81 (1H, d, ^3J 1.7) and 7.66 (1H, dd, ^3J 8.6 and 1.7).

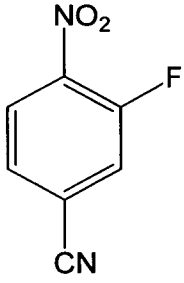
In the original method attempted a solution of sodium nitrite (3.65 g, 0.053 mol) in water (18 cm^3) was added to a suspension of 4-amino-3-chlorobenzonitrile (5 g, 0.033 mol) in dilute hydrochloric acid (5 M, 26 cm^3) at 0 – 5 °C, and the reaction mixture was stirred for 10 min.[116] The mixture was then added to a suspension of sodium nitrite (16.20 g, 0.234 mol) and copper (I) oxide ($Cu^{(I)}_2O$) (1.71 g, 0.012 mol) in water (72 cm^3) and stirred at 0 °C for 30 min, then at room temperature for a further 30 min. The reaction mixture was then extracted with DCM (7 × 50 cm^3) and then the combined organic layers were washed with brine (3 × 30 cm^3) and dried over $MgSO_4$. The crude product was separated by column chromatography (chloroform as eluent) and resulted in none of the desired product, but gave as the first component 3,4-dichlorobenzonitrile as an impure orange solid (3.96 g, 70%) mp 62-70 °C [lit.,[117] 71-72 °C]; δ_H 7.90 (1H, d, ^3J 8.4), 7.82 (1H, d, ^3J 2.0) and 7.66 (1H, dd, ^3J 8.4 and 2.0); *m/z* 171 (M^+ 89%), 137 (100), 100 (63), 75 (73) and 50 (93).

3-Fluoro-4-nitroaniline 177



3-Fluoroaniline (4.8 g, 0.043 mol) and benzaldehyde (5.0 g, 0.047 mol) were mixed together, giving a brown emulsion, and then heated under reflux for 30 min, with stirring.[62] The resulting orange/brown solution was then dissolved in concentrated sulfuric acid (20 cm^3) and then cooled below 5 °C. To this was then added concentrated nitric acid (3 cm^3, *d* 1.5) and concentrated sulfuric acid (10 cm^3) over a period of 90 min. The reaction mixture was then added to water (50 cm^3) and purified by steam distillation, Kugelrohr distillation and finally by recrystallisation to give 3-fluoro-4-nitroaniline **177** as an orange crystalline solid (1.23 g, 18%) mp 156-158 °C [lit.,[62] 153 °C]; δ_H 7.92 (1H, t, ^3J 8.7), 6.35 (2H, m) and 4.23 (2H, bs).

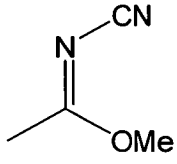
3-Fluoro-4-nitrobenzonitrile 180



To a solution of 3-fluoro-4-nitroaniline **177** (1.0 g, 6.37 mmol) in dilute hydrochloric acid (3 M, 15 cm^3) at 0 °C was added drop-wise sodium nitrite (0.55 g, 8 mmol) dissolved in water (7 cm^3), and the resulting reaction mixture was stirred for 30 min.[63] The mixture was then filtered to remove a small quantity of insoluble material and the filtrate was then added slowly to a solution of potassium cyanide (3.9 g, 0.06 mol) and copper (I) oxide (0.4 g, 2.8 mmol) in water (20 cm^3) at 0 °C. This was then stirred for 30 min, warmed to 30 °C, and then allowed to cool slowly overnight. The resulting brown precipitate was filtered off and dried under high vacuum for 2 h. The product was then purified by column chromatography (DCM and hexane as eluent) giving as the second and third fractions 3-fluoro-4-nitrobenzonitrile **180** as a bright orange solid (0.51 g, 48%) mp 71-75 °C [lit.,[63] 72-74 °C]; δ_H 8.09 (1H, t, ^3J 8.1) and 7.61 (2H, m).

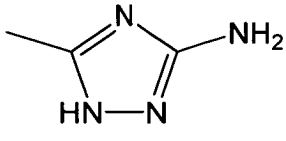
The first component which eluted from the column was an orange oil found to be 4-chloro-2-fluoronitrobenzene (0.12 g, 11%); δ_H 7.95 (1H, t, ^3J 8.4) and 7.24 (2H, m); *m/z* 175 (M^+ 100%), 145 (92), 129 (90), 117 (73) and 93 (50).

Methyl-*N*-cyanoacetimidate 183



Methyl acetimidate hydrochloride (21 g, 0.192 mol) was added to a solution of cyanamide (8.05 g, 0.192 mol) in methanol (35 cm^3) and stirred at room temperature for 3 h.[64] The resultant precipitate of ammonium chloride was filtered off, then the methanol was removed *in vacuo* to leave the crude product as a colourless liquid. This was then purified by Kugelrohr distillation to give methyl-*N*-cyanoacetimidate **183** (12.8 g, 68%) bp 55-60 °C, 2.5 mm Hg [lit.,[64] 98 °C, 25 mm Hg]; δ_H 3.82 (3H, s) and 2.38 (3H, s).

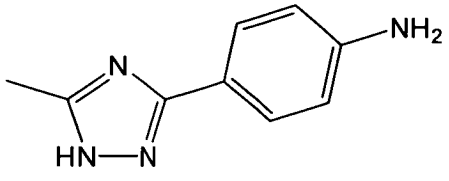
5-Methyl-1,2,4-triazol-3-amine 181



A solution of methyl-*N*-cyanoacetimidate **183** (12 g, 0.122 mol) in methanol (30 cm^3) was treated drop-wise with 98% hydrazine (3.98 g, 0.122 mol) with stirring and cooling in an ice bath.[64] After effervescence and a colour change to pink

were observed the reaction mixture was allowed to warm slowly to room temperature. After ~1 h the methanol was evaporated off along with an unidentified purple liquid to leave the crude product as a pink oil. This was purified by trituration from ethyl acetate and acetonitrile and recrystallisation from acetonitrile to give 5-methyl-1,2,4-triazol-3-amine **181** as almost colourless crystals (3.71 g, 31%) mp 144-146 °C [lit.,[64] 147 °C]; δ_H (d_6-DMSO) 8.34 (1H, s), 5.59 (2H, bs) and 2.12 (3H, s); **^{13}C?**.

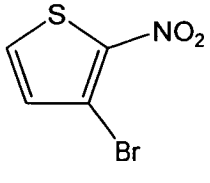
3-(4-Aminophenyl)-5-methyl-[1,2,4]-triazole 184



A solution of sodium ethoxide, made *in situ* from sodium (2.99 g, 0.13 mol) dissolved in ethanol (125 cm^3), was added to a solution of acetamidine hydrochloride (9.27 g, 0.098 mol) in ethanol (150 cm^3) and stirred at room temperature for 45 min.[65] The resulting sodium chloride precipitate was filtered off through celite and the ethanol removed under vacuum to leave the acetamidine intermediate as a thick oil.

4-Aminobenzoic hydrazide (9.88 g, 0.065 mol) and chlorobenzene (250 cm^3) were added and the mixture heated under reflux for 48 h. After this time a semi-crystalline solid product was observed so the solvent was decanted off, and water added giving a beige suspension. This settled overnight to beige crystals, which were filtered off, washed with water and dried under high vacuum to give the product *3-(4-aminophenyl)-5-methyl-[1,2,4]-triazole* **184** (5.05 g, 45%), mp 174-178 °C (from methanol) (Found: M$^+$ 174.0907. $C_9H_{10}N_4$ requires *M* 174.0906); δ_H (d_6-DMSO) 7.75 (2H, dd, ^3J 8.5 and 1.8), 6.74 (2H, dd, ^3J 8.6 and 1.8), 5.55 (2H, bs) and 2.44 (3H, s); δ_C 158.27 (quat), 155.85 (quat), 149.73 (quat), 126.89 (2 × CH), 116.98 (quat), 113.50 (2 × CH) and 12.48 (CH_3); *m/z* 174 (M$^+$ 42%), 119 (25), 81 (29), and 69 (100).

3-Bromo-2-nitrothiophene 185



A solution of 3-bromothiophene (5 g, 0.03 mol) in acetic anhydride (10 cm^3) was added drop-wise to a stirred solution of concentrated nitric acid (1.5 cm^3, *d* 1.52) in acetic anhydride (10 cm^3) with cooling in cold water (~5 °C).[68] The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture

was then cooled using dry ice, and the flask scraped to produce some crystals, which were filtered off. The filtrate was added to water to give orange crystals, which were filtered and then dried with heating, giving a dark brown semi-crystalline product. Dissolving the product in hot hexane and decanting this solution off the insoluble impurities recrystallised the product as beige crystals, found to be 3-bromo-2-nitrothiophene **185** (1.86 g, 29%), mp 79-81 °C [lit.,[68] 81-83 °C]; δ_H (400 MHz) 7.48 (1H, d, ^3J 5.7) and 7.06 (1H, d, ^3J 5.7).

Initially, a stronger version of this reaction was performed, with the nitric acid dissolved in acetic acid (20 cm^3). After the 2 h stirring the reaction mixture was added to ice water (30 cm^3) and then extracted into ethyl acetate (5 × 30 cm^3), then the combined organic extracts washed with water (3 × 20 cm^3) and dried over $MgSO_4$ overnight.

TLC showed the presence of two isomers of the product, and column chromatography (ethyl acetate and light petroleum as eluent) was only partially successful, with most of the material unseparated. The second component of peach coloured crystals was found to be a pure sample of the desired isomer 3-bromo-2-nitrothiophene **185** (0.86 g, 13%). Trituration of the first component using light petroleum gave more of the desired product (0.33 g, total yield 19%). The other component, not purified, was found to be 4-bromo-2-nitrothiophene; δ_H (400 MHz) 7.79 (1H, d, ^3J 1.8) and 7.06 (1H, d, ^3J 1.8).

3.3 Preparation of 2-(azolyl)nitrobenzenes and analogous species

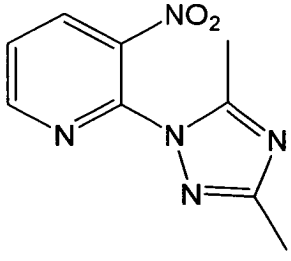
3.3.1 General Methods

The pyrolysis precursors of the type **166** were prepared by the reaction between the stated aromatic nitro compound (0.01 mol) and the appropriate heterocycle (0.01 mol) in DMF (15 cm^3) with anhydrous potassium carbonate (1.38 g, 0.01 mol) at 125 °C, with stirring, for 48 h.[67] Where quantities differ all reactants are stated. The reaction mixture was then poured into water (100 cm^3) and then extracted with ether (6 × 30 cm^3) (unless otherwise stated). The combined organic layers were washed with water (3 × 15 cm^3) and dried ($MgSO_4$) then concentrated *in vacuo* to give the products. The

following products were made by this method and alternative preparations are described where appropriate. Where stronger six-membered aromatic species were used milder reaction conditions had to be employed, and where less reactive species were used they had to be reacted in the presence of a stronger base. With certain highly activated aromatic species, featuring an electron-withdrawing group *para* to the halide position, ethanol was used as the solvent and the azole acted as its own base.

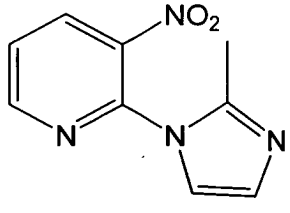
3.3.2 Azolylnitropyridine Compounds

2-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine 189



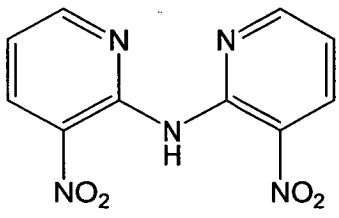
Reaction of 2-chloro-3-nitropyridine (16.33 g, 0.103 mol) with 3,5-dimethyl-1,2,4-triazole **171** (10.0 g, 0.103 mol), in the presence of anhydrous potassium carbonate (14.23 g, 0.103 mol), gave *2-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine* **189** as an orange solid, (10.96 g, 49%), mp 150-152 °C (from isopropyl alcohol) (Found: C, 49.4; H, 4.2; N, 31.9. $C_9H_9N_5O_2$ requires C, 49.3; H, 4.1; N, 32.0%); δ_H 8.70 (1H, dd, ^3J 4.8 and 1.6), 8.24 (1H, dd, ^3J 8.1 and 1.6), 7.53 (1H, dd, ^3J 8.1 and 4.8), 2.67 (3H, s) and 2.34 (3H, s); δ_C 161.18 (quat), 154.28 (quat), 151.00 (CH), 142.28 (quat), 140.58 (quat), 133.96 (CH), 123.63 (CH), 13.62 (CH_3) and 13.46 (CH_3); *m/z* 219 (M^+ 21%), 178 (29), 107 (62), 91 (47), 64 (59), 52 (44), 43 (100) and 31 (43).

2-(2-Methylimidazol-1-yl)-3-nitropyridine 190



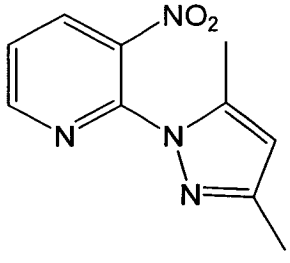
Reaction of 2-chloro-3-nitropyridine (1.59 g, 0.01 mol) with 2-methylimidazole (0.81 g, 0.01 mol), followed by extraction into DCM and purification by removal of impurities by Kugelrohr distillation gave *2-(2-methylimidazol-1-yl)-3-nitropyridine* **190** as an orange solid, (0.69 g, 34%), mp 58-63 °C (Found: M^+ 204.0644. $C_9H_8N_4O_2$ requires *M* 204.0647); δ_H 8.80 (1H, dd, ^3J 4.8 and 1.7), 8.38 (1H, dd, ^3J 8.1 and 1.7), 7.61 (1H, dd, ^3J 8.1 and 4.8), 7.04 (1H, d, ^3J 1.6), 6.97 (1H, d, ^3J 1.6) and 2.35 (3H, s); δ_C 153.53 (CH), 145.21 (quat), 143.02 (quat), 142.23 (quat), 134.23 (CH), 128.80 (CH), 124.24 (CH), 119.07 (CH) and

13.51 (CH_3); *m/z* 204 (M^+ 35%), 186 (100), 159 (72), 118 (67), 78 (69), 65 (32), 43 (52) and 29 (36).



When the reaction mixture was extracted into diethyl ether rather than DCM, bis-(3-nitropyridin-2-yl)-amine **191** was obtained as a red solid, (0.06 g, 5%), mp 176-178 °C [lit.,[71] 180 °C] (Found: M^+ 261.0497. $C_{10}H_7N_5O_4$ requires *M* 261.0498); δ_H 11.25 (1H, s), 8.58 (2H, dd, ^3J 4.6 and 1.7), 8.50 (2H, dd, ^3J 8.3 and 1.7) and 7.17 (2H, dd, ^3J 8.3 and 4.6); δ_C 153.82 (2 × CH), 146.59 (2 × quat), 135.27 (2 × CH), 134.23 (2 × quat) and 118.91 (2 × CH); *m/z* 261 (M^+ 62%), 215 (100), 169 (96), 143 (47), 118 (60), 93 (44), 78 (52) and 51 (60).

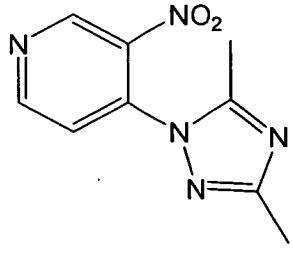
2-(3,5-Dimethylpyrazol-1-yl)-3-nitropyridine 187



Reaction of 2-chloro-3-nitropyridine (1.59 g, 0.01 mol) with 3,5-dimethylpyrazole (0.96 g, 0.01 mol) by the standard method gave after ether work up and separation by dry flash chromatography (silica, ethyl acetate and hexane as eluent) 2-(3,5-dimethylpyrazol-1-yl)-3-nitropyridine **187** as the second component (250 mg, 12%), mp 108-110 °C [lit.,[67] 110-112 °C]; δ_H 8.56 (1H, dd, ^3J 4.7 and 1.8), 8.08 (1H, dd, ^3J 8.2 and 1.8), 7.32 (1H, dd, ^3J 8.2 and 4.7), 5.97 (1H, s), 2.43 (3H, s) and 2.14 (3H, s).[67]

The first component was an orange semi-solid identified as 2-dimethylamino-3-nitropyridine **192** (20 mg, 1%), δ_H 8.22 (1H, d, ^3J 4.2), 8.04 (1H, d, ^3J 8.0), 6.58 (1H, dd, ^3J 8.0 and 4.2) and 2.95 (6H, s). The third component was a mixture, and the fourth component was the starting material 3,5-dimethylpyrazole (220 mg, 23%), δ_H 5.86 (1H, s) and 2.38 (6H, s).

4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine 193



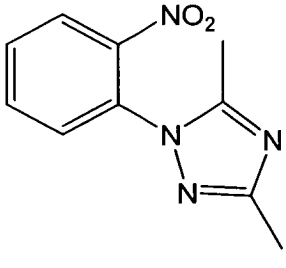
A solution of 4-chloro-3-nitropyridine **173** (0.32 g, 2 mmol), 3,5-dimethyl-1,2,4-triazole **171** (0.19 g, 2 mmol) and anhydrous potassium carbonate (0.28 g, 2 mmol) were heated under reflux in DMF (10 cm^3) for 30 min. The reaction mixture was then added to water (60 cm^3),

extracted into ethyl acetate (5 × 20 cm^3), the combined organic layers were washed with water (3 × 10 cm^3) and then dried over $MgSO_4$. After concentration *in vacuo* *4-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine* **193** was obtained as an orange solid, (0.24 g, 55%), mp 141-143 °C (from isopropyl alcohol) (Found: C, 49.8; H, 4.1; N, 31.3. $C_9H_9N_5O_2$ requires C, 49.3; H, 4.1; N, 32.0%); δ_H 9.21 (1H, s), 8.92 (1H, d, ^3J 5.2), 7.43 (1H, d, ^3J 5.2), 2.38 (3H, s) and 2.33 (3H, s); δ_C 182.58 (quat), 162.49 (quat), 154.87 (CH), 153.96 (quat), 147.03 (CH), 138.49 (quat), 121.88 (CH), 13.85 (CH_3) and 12.63 (CH_3); *m/z* 219 (M^+ 52%), 185 (32), 78 (30), 64 (59), 43 (100) and 30 (57).

A number of reaction conditions were tried unsuccessfully before arriving at the one above. The only reasonable one was to stir the reactants in DMSO with potassium *tert*-butoxide as base, overnight at room temperature.[73] This gave the product **193**, but DMSO could not be removed without losing the apparently water soluble product. When the two reactants were heated under reflux together in ethanol, with no base, overnight, an unidentifiable orange solid was obtained. When this method was repeated with sodium acetate as base, an unidentifiable yellow product was formed. Finally, overnight reflux of the reactants in THF with Hunig's base (diisopropylethylamine) gave no reaction.

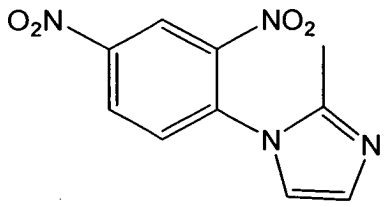
3.3.2 Synthesis of Substituted Benzenes

2-(3,5-Dimethyl-1,2,4-triazol-1-yl)nitrobenzene 194



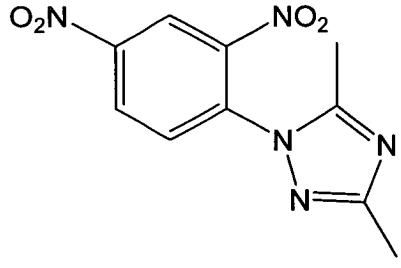
Reaction of 1-fluoro-2-nitrobenzene (14.53 g, 0.103 mol) with 3,5-dimethyl-1,2,4-triazole **171** (10.0 g, 0.103 mol), in the presence of anhydrous potassium carbonate (14.23 g, 0.103 mol), gave 2-(3,5-dimethyl-1,2,4-triazol-1-yl)nitrobenzene **194** as a bright yellow solid, (10.94 g, 49%), mp 85-87 °C [lit.,[67] 90 °C]; δ_H 8.14 (1H, dd, ^3J 7.8 and 1.6), 7.79 (2H, m), 7.55 (1H, dd, ^3J 7.8 and 1.6), 2.43 (3H, s) and 2.41 (3H, s).[67]

2-Methyl-1-(2,4-dinitrophenyl)-imidazole 195



Reaction of 2,4-dinitrofluorobenzene (1.85 g, 0.01 mol) with 2-methylimidazole (0.81 g, 0.01 mol) gave *2-methyl-1-(2,4-dinitrophenyl)-imidazole* **195** as a pale yellow solid (0.23 g, 9%), mp 102-104 °C (from cyclohexane) (Found: C, 48.8; H, 3.6; N, 22.1. $C_{10}H_8N_4O_4$ requires C, 48.4; H, 3.2; N, 22.6%); δ_H 8.20 (1H, d, ^3J 2.6), 8.17 (1H, dd, ^3J 8.0 and 2.6), 7.53 (1H, t, ^3J 8.0), 7.10 (1H, d, ^3J 1.5), 7.00 (1H, t, ^3J 1.5) and 2.34 (3H, s); δ_C 158.47 (quat), 154.38 (quat), 148.44 (quat), 145.76 (quat), 129.47 (CH), 121.00 (CH), 120.63 (CH), 113.86 (CH), 113.45 (CH) and 13.83 (CH_3); *m/z* 248 (M^+ 2%), 221 (100), 194 (56), 175 (73), 148 (58), 134 (70), 107 (71) and 94 (64).

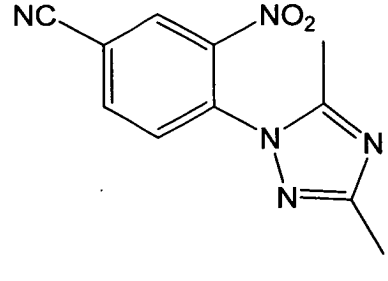
3,5-Dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole 196



A solution of 2,4-dinitrofluorobenzene (0.46 g, 2.5 mmol) and 3,5-dimethyl-1,2,4-triazole **171** (0.24 g, 2.5 mmol) in ethanol (10 cm^3) were heated under reflux for 30 min with stirring.[70] The ethanol was removed *in vacuo* to give 3,5-dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole **196** (0.34 g, 52%), mp 148-150 °C [lit.,[70] 154 °C]; δ_H 8.88 (1H, dd, ^3J 2.5 and 0.4), 8.60 (1H, dd, ^3J 8.7 and 2.5), 7.74 (1H, dd, ^3J 8.7 and 0.4), 2.41 (3H, s) and 2.37 (3H, s).

Reaction of 2,4-dinitrofluorobenzene (1.85 g, 0.01 mol) and 3,5-dimethyl-1,2,4-triazole (0.97 g, 0.01 mol) by the general method gave an unidentified red solid from DCM extraction (0.04 g).

4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile 197



A solution of 4-fluoro-3-nitrobenzonitrile (1.66 g, 0.01 mol) in ethanol (20 cm^3) and 3,5-dimethyl-1,2,4-triazole **171** (0.97 g, 0.01 mol) in ethanol (20 cm^3) were mixed and heated under reflux together, with stirring, for 5 h.[70] After removal of the solvent, separation of the crude product by dry flash chromatography (silica, ethyl acetate and hexane as eluent) gave *4-(3,5-Dimethyl-*

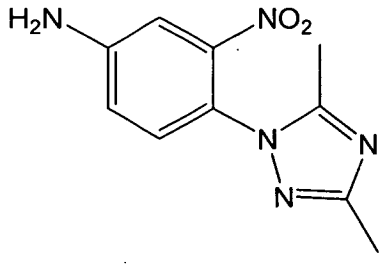
1,2,4-triazol-1-yl)-3-nitrobenzonitrile **197** as a pale orange solid, as the third component, (1.22 g, 50%), mp 132-134 °C (from isopropyl alcohol) (Found: C, 54.6; H, 3.8; N, 28.6. $C_{11}H_9N_5O_2$ requires C, 54.3; H, 3.7; N, 28.8%); δ_H 8.28 (1H, d, ^3J 1.8), 7.97 (1H, dd, ^3J 8.2 and 1.8), 7.63 (1H, d, ^3J 8.2), 2.35 (3H, s) and 2.32 (3H, s); δ_C 162.33 (quat), 154.06 (quat), 145.59 (quat), 136.93 (CH), 134.26 (quat), 130.05 (CH), 129.37 (CH), 115.63 (quat), 114.69 (quat), 13.83 (CH_3) and 12.49 (CH_3); *m/z* 243 (M^+ 45%), 202 (39), 161 (22), 103 (39), 64 (39), 43 (100) and 30 (78).

The first component from the column was the starting material 4-fluoro-3-nitrobenzonitrile (270 mg, 16% recovery), δ_H 8.38 (1H, m), 7.90 (1H, m) and 7.42 (1H, m). The second component was a mixture and the fourth a mixture of product **197** and starting material **171** (1.32 g).

On a large scale, after reaction of 4-fluoro-3-nitrobenzonitrile (6.64 g, 0.04 mol) in ethanol (80 cm^3) and 3,5-dimethyl-1,2,4-triazole **171** (3.88 g, 0.04 mol) in ethanol (80 cm^3), column separation was found to be unnecessary. Washing with ethyl acetate initially dissolved the product while removing insoluble impurities, then after removing the solvent repeated triturations of the soluble crude product afforded the desired product *4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile* **197** (4.11 g, 42%).

Before this method was attempted, the usual K_2CO_3 and DMF conditions (general method) gave an unidentifiable orange solid. An alternative work-up, involving removal of DMF *in vacuo*, followed by dissolving the crude product in DCM resulted in formation of an unidentifiable sticky yellow solid.

4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline 198

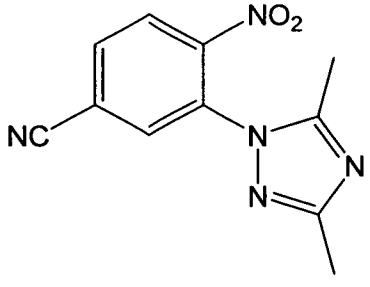


Reaction of 4-fluoro-3-nitroaniline (5 g, 0.032 mol) with 3,5-dimethyl-1,2,4-triazole **171** (3.11 g, 0.032 mol) in the presence of caesium carbonate (10.44 g, 0.032 mol) gave after DCM work up and separation by dry flash chromatography (silica, ethyl acetate as eluent) gave *4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline* **198** as a yellow/orange solid, as the fourth component, (3.34 g, 45%), mp 198-200 °C (from methanol) (Found: C, 51.4; H, 4.8; N, 29.7. $C_{10}H_{11}N_5O_2$ requires C, 51.5; H, 4.8; N, 30.1%); δ_H 7.20 (1H, d, ^3J 2.5), 7.13 (1H, d, ^3J 8.5), 6.83 (1H, dd, ^3J

8.5 and 2.5), 2.29 (3H, s) and 2.25 (3H, s); δ_C 160.25 (quat), 148.45 (quat), 130.47 (CH), 119.26 (quat), 118.31 (CH), 110.14 (CH), 13.67 (CH_3) and 11.99 (CH_3); *m/z* 233 (M^+ 100%), 192 (36), 151 (82), 91 (62), 79 (67), 66 (71) and 43 (95).

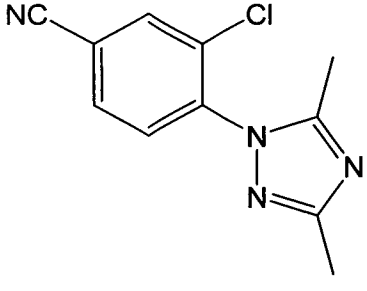
The first component was a dark red oil identified as 4-dimethylamino-3-nitroaniline **199** (0.46 g, 8%), δ_H 7.02 (1H, d, ^3J 2.9), 6.95 (1H, d, ^3J 8.8), 6.75 (1H, dd, ^3J 8.8 and 2.8), 3.68 (2H, bs) and 2.68 (6H, s); *m/z* 181 (M^+ 91%), 156 (78), 134 (57), 120 (100), 110 (69), 83 (80) and 65 (41).

Attempted synthesis of 3-(3,5-dimethyl-1,2,4-triazol-1-yl)-4-nitrobenzonitrile 200



Reaction of 3-chloro-4-nitrobenzonitrile **174** (1.10 g, 6 mmol) with 3,5-dimethyl-1,2,4-triazole **171** (0.58 g, 6 mmol) in the presence of potassium carbonate (0.83 g, 6 mmol) gave after ethyl acetate work up *4-chloro-3-(3,5-dimethyl-1,2,4-triazol-1-yl)benzonitrile* **201** as the main product, unpurified (0.23 g, ~3:1); δ_H 7.82 (1H, d, ^3J 1.8), 7.67 (1H, dd, ^3J 8.2 and 1.8), 7.46 (1H, d, ^3J 8.2), 2.36 (3H, s) and 2.28 (3H, s); *m/z* 232 (M^+ 46%), 191 (74), 150 (100), 115 (34), 84 (34), 64 (13) and 49 (24).

The minor product could not be isolated by column chromatography and was initially believed to be *3-(3,5-dimethyl-1,2,4-triazol-1-yl)-4-nitrobenzonitrile* **200** as desired;

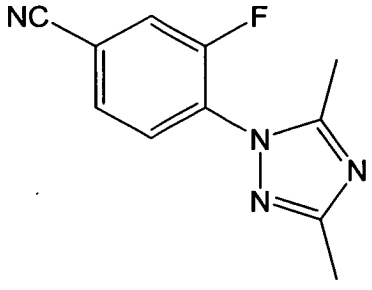


however, closer inspection of the spectroscopic data revealed it to be *4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile* **197**; δ_H 8.28 (1H, d, ^3J 1.8), 7.98 (1H, dd, ^3J 8.2 and 1.8), 7.63 (1H, d, ^3J 8.2), 2.37 (3H, s) and 2.32 (3H, s); δ_C 162.33 (quat), 154.06 (quat), 145.59 (quat), 136.93 (CH), 134.26 (quat), 130.05 (CH), 129.37 (CH), 115.63 (quat), 114.69 (quat), 13.83 (CH_3) and 12.49 (CH_3); *m/z* 243 (M^+ 19%), 202 (28), 137 (100), 102 (85), 73 (51), 43 (85) and 30 (31).

Reaction of 3-fluoro-4-nitrobenzonitrile **180** (0.3 g, 1.8 mmol) with 3,5-dimethyl-1,2,4-triazole **171** (0.18 g, 1.8 mmol) in the presence of cesium carbonate (0.59 g, 1.8 mmol) gave after DCM extraction and column chromatography (ethyl acetate and

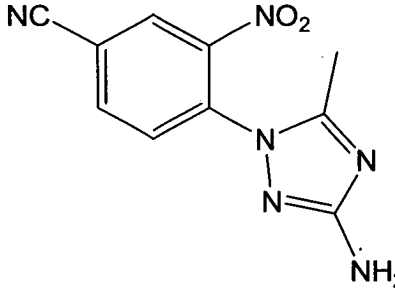
hexane as eluent) an impure sample of material which could not be confirmed as the desired product **200**, as the mass spectrum was inconclusive.

3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-4-fluorobenzonitrile **202** was obtained as the second component (80 mg, 21%); δ_H 7.76 (1H, m), 7.74 (1H, m), 7.35 (1H, t; ^3J 9.1) and 2.34 (6H, s); δ_C 161.63 (quat), 156.19 (quat), 154.18 (quat), 134.80 (quat), 134.65 (CH), 132.65 (CH), 118.21 (CH), 116.41 (quat), 109.74 (quat), 13.62 (CH_3) and 12.09 (CH_3); *m/z* 216 (M^+ 48%), 175 (72), 134 (100) and 107 (29).

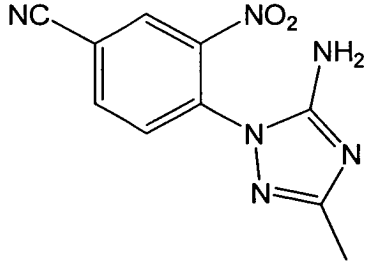


3.3.3 Substituted Triazoles

Attempted synthesis 4-(3-amino-5-methyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile 204



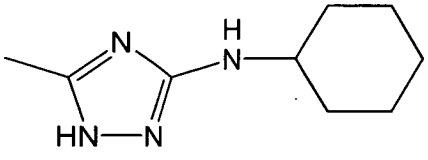
A suspension of 3-amino-5-methyl-1,2,4-triazole **181** (2 g, 0.02 mol) in ethanol (40 cm^3) and a suspension of 4-fluoro-3-nitrobenzonitrile (3.39 g, 0.02 mol) in ethanol (40 cm^3) were heated under reflux for 10 h. Unreacted benzonitrile precipitate was filtered off, the solvent removed and then the crude product purified by column chromatography (methanol and DCM as eluent) to give as the fourth component a product which precipitated out of the eluent as yellow crystals. This was found to be the unwanted isomer, confirmed later by a failed pyrolysis experiment, *4-(5-amino-3-methyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile* **203** (0.11 g, 6%), mp 230-240 °C (decomp) (from DCM) Found: M^+ 244.0707. $C_{10}H_8N_6O_2$ requires *M* 244.0709; δ_H (DMSO) 8.73 (1H, d, ^3J 1.7), 8.35 (1H, dd, ^3J 8.3 and 1.7), 7.97 (1H, d, ^3J 8.3), 6.77 (2H, bs) and 2.14 (3H, s); δ_C (DMSO) 159.35 (quat), 155.65 (2



× quat), 144.12 (quat), 137.33 (CH), 132.99 (quat), 129.24 (CH), 128.40 (CH) and 13.59 (CH_3); *m/z* 244 (M^+ 52%), 161 (7), 98 (100), 84 (33), 57 (54), 43 (94) and 30 (56).

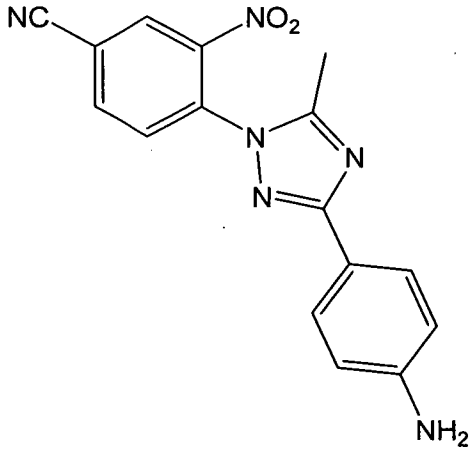
The desired isomer *4-(3-amino-5-methyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile* **204** did appear to be present in the crude product, shown by the appropriate signals in the proton NMR spectrum, but this could not be isolated or properly characterised from the mixture.

Attempted preparation of cyclohexyl-(5-methyl-1H-[1,2,4]triazol-3)-amine 181a



3-Amino-5-methyl-1,2,4-triazole **181** (1 g, 0.01 mol) and cyclohexanone (1 g, 0.01 mol) were heated together under reflux in acetonitrile (100 cm^3), with a Dean-Stark trap fitted to collect the water given off, overnight.[78] The proton NMR spectrum of the crude intermediate in DMSO appeared to confirm full conversion of starting materials as the primary amine group was no longer present. Therefore the intermediate was dissolved in methanol (100 cm^3), and sodium borohydride (0.72 g, 0.011 mol) and acetic acid (0.67 g, 0.011 mol) were added. The mixture was then stirred at room temperature overnight. The resulting mixture was added to water (300 cm^3) and extracted with DCM (5 × 50 cm^3), then the combined organic layers were washed with water (3 × 25 cm^3) and dried over $MgSO_4$ for ~4 h. After removing the solvents the crude material obtained did not contain the desired product **181a** or any identifiable species. Concentrating the aqueous layers gave an off-white oil, which also could not be identified.

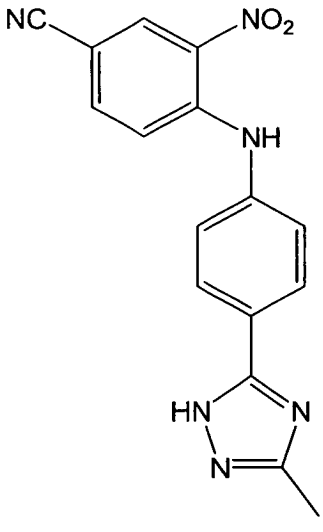
4-[3-(4-Aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile 205



3-(4-Aminophenyl)-5-methyl-[1,2,4]-triazole **184** (0.5 g, 2.87 mmol), 4-fluoro-3-nitrobenzonitrile (0.48 g, 2.87 mmol) and anhydrous potassium carbonate (0.39 g, 2.87 mmol) in DMF (15 cm^3) were heated under reflux, with stirring, for 30 min. After this time the reaction mixture was poured into water (50 cm^3) and extracted with ethyl

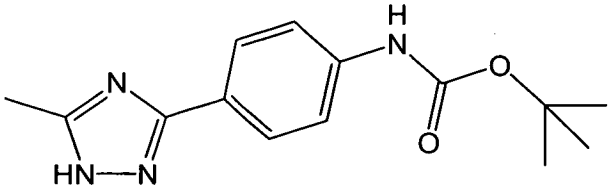
acetate (5 × 20 cm^3); the combined organic layers were washed with water (3 × 10 cm^3) and then dried over $MgSO_4$ overnight. Removing all the solvents under high vacuum left a thick orange gum which was then purified by column chromatography (methanol and DCM as eluent) the third component still being an orange gum, a small quantity of which was crystallised by trituration from toluene.

The main product was found to be a ~80% pure sample of *4-[3-(4-aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile* **205**, (the correct isomer being determined by a NOESY NMR experiment which showed the methyl protons interacting with benzonitrile proton in the 5-position), (0.65 g, 71%), mp 164-166 °C (Found: M^+ 320.1029. $C_{16}H_{12}N_6O_2$ requires *M* 320.1022); δ_H 8.21 (1H, d, ^3J 1.8), 7.88 (1H, dd, ^3J 8.2 and 1.8), 7.74 (2H, d, ^3J 8.6), 7.63 (1H, d, ^3J 8.2), 6.57 (2H, d, ^3J 8.6), 3.83 (2H, bs) and 2.34 (3H, s); δ_C 163.40 (quat), 153.99 (quat), 148.05 (quat), 136.67 (CH), 134.27 (quat), 129.77 (CH), 129.13 (CH), 127.81 (2 × CH), 119.68 (quat), 115.06 (quat), 114.65 (2 × CH), 114.17 (quat), and 12.40 (CH_3); *m/z* 320 (M^+ 41%), 118 (43), 91 (100), 69 (18) and 43 (13).

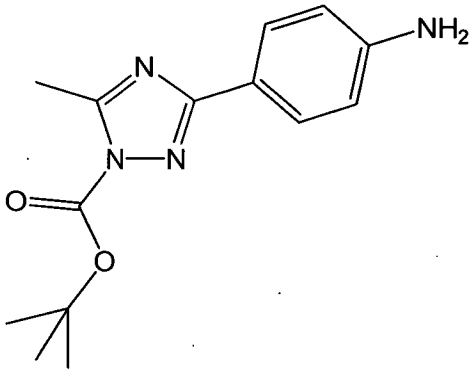


In the initial attempt at the synthesis of **205**, 3-(4-aminophenyl)-5-methyl-[1,2,4]-triazole **184** (0.5 g, 2.87 mmol) and 4-fluoro-3-nitrobenzonitrile (0.48 g, 2.87 mmol) were heated together in ethanol (6 cm^3), under reflux for 4 h. The resulting sticky, semi-crystalline precipitate was filtered off and dried under high vacuum and found by proton NMR to be an impure mixture containing possible traces of the desired product **205**, but mostly being *4-[4-(5-Methyl-1H-1,2,4-triazol-3-yl)-phenylamino]-3-nitrobenzonitrile* **206** (0.85 g, 93%), which was partially purified by recrystallisation from methanol; δ_H (DMSO) 9.98 (1H, bs), 8.66 (1H, d, ^3J 1.9), 8.09 (2H, d, ^3J 8.4), 7.86 (1H, dd, ^3J 9.0 and 1.9), 7.49 (2H, d, ^3J 8.4), 7.28 (1H, d, ^3J 9.0), and 2.14 (3H, s).

Attempted synthesis of *tert*-butyl [4-(5-methyl-1*H*-[1,2,4]triazol-3-yl) - phenyl]carbamate 207

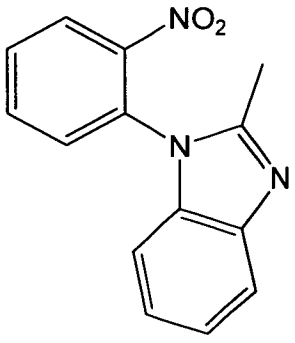


An attempt was made to add a Boc protecting group to 3-(4-aminophenyl)-5-methyl-[1,2,4]-triazole **184** (0.5 g, 2.87 mmol) by its reaction with di-*tert*-butyl dicarbonate (1.25 g, 5.74 mmol) and 4-dimethylaminopyridine (DMAP) (88 mg, 0.718 mmol), stirring in acetonitrile (50 cm^3) at room temperature overnight.[80] Concentration of the reaction mixture to a small volume promoted crystallisation of the product, which was filtered off and washed with acetonitrile. The white crystals obtained were then found to not to be the desired product **207**, but tert-*butyl 3-(4-aminophenyl)-5-methyl-[1,2,4]triazole-1-carboxylate* **208** (343 mg, 44%), mp 150-152 °C (from methanol) (Found: C, 61.4; H, 6.6; N, 20.4. $C_{14}H_{18}N_4O_2$ requires C, 61.3; H, 6.6; N, 20.4%); δ_H (d_6-DMSO) 7.85 (2H, d, ^3J 7.8), 6.77 (2H, d, ^3J 7.8), 5.70 (2H, bs), 2.80 (3H, s) and 1.76 (9H, s); δ_C (d_6-DMSO) 160.25 (quat), 156.95 (quat), 150.40 (quat), 146.50 (quat), 127.36 (2 × CH), 116.46 (quat), 113.26 (2 × CH), 85.36 (quat), 27.20 (3 × CH_3) and 15.40 (CH_3); *m/z* 274 (M^+ 19%), 230 (69), 215 (62), 174 (100), 133 (81), 118 (75), 104 (67) and 56 (62).



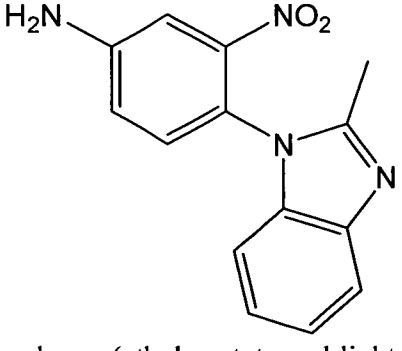
3.3.4 Benzimidazole precursors to tetracyclic systems

2-Methyl-1-(2-nitrophenyl)benzimidazole 209



2-Methylbenzimidazole (5 g, 0.038 mol), *o*-fluoronitrobenzene (5.34 g, 0.038 mol) and anhydrous potassium carbonate (5.32 g, 0.039 mol) in DMF (120 cm^3) were heated at 125 °C, with stirring, for 8 h under an atmosphere of nitrogen.[54] The reaction mixture was added to water (300 cm^3), extracted with DCM (5 × 50 cm^3), washed with water (3 × 25 cm^3) and dried over $MgSO_4$. The DCM was removed under reduced pressure, then the residual DMF removed by co-evaporation with toluene, leaving a thick, oily crude product. Trituration with ethyl acetate and light petroleum gave pale orange coloured crystals found to be 2-methyl-1-(2-nitrophenyl)benzimidazole **209** (7.47 g, 78%), mp 108-110 °C [lit.,[54] 110-111 °C]; δ_H 8.17 (1H, dd, ^3J 8.2 and 1.6), 7.83 (1H, td, ^3J 7.8 and 2.0), 7.72 (2H, m), 7.49 (1H, dd, ^3J 7.4 and 1.5), 7.22 (2H, m), 6.89 (1H, dd, ^3J 8.6 and 0.8) and 2.44 (3H, s).

4-(2-Methylbenzimidazol-1-yl)-3-nitroaniline 210

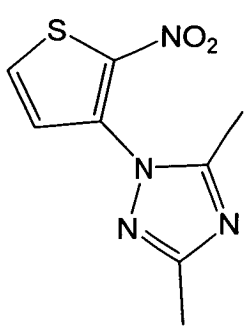


A mixture of 2-methylbenzimidazole (5 g, 0.038 mol), 4-fluoro-3-nitroaniline (5.93 g, 0.038 mol) and anhydrous potassium carbonate (5.32 g, 0.039 mol) in DMF (120 cm^3) was heated overnight at 125 °C, with stirring, under an atmosphere of nitrogen. The crude product was obtained by DCM work up as in the previous section, and purified by dry flash column (ethyl acetate and light petroleum as eluent) to give as the second component *4-(2-methylbenzimidazol-1-yl)-3-nitroaniline* **210** (3.52 g, 35%), mp 180-182 °C (from toluene) (Found: C, 62.8; H, 4.8; N, 20.4. $C_{14}H_{12}N_4O_2$ requires C, 62.7; H, 4.5; N, 20.7%); δ_H 7.65 (1H, d, ^3J 7.7), 7.30 (1H, d, ^3J 2.7), 7.14 (3H, m), 6.92 (1H, dd, ^3J 8.5 and 2.7), 6.84 (1H, d, ^3J 7.3), 4.28 (2H, bs) and 2.36 (3H, s); δ_C 201.68 (quat), 198.34 (quat), 153.58 (quat), 148.29 (2 × quat), 144.28 (quat), 131.72 (CH), 122.68

(CH), 122.36 (CH), 119.00 (2 × CH), 110.44 (CH), 109.10 (CH) and 13.89 (CH_3); *m/z* 268 (M^+ 37%), 196 (16), 87 (31), 73 (100) and 44 (77).

3.3.5 Nitrothiophene precursor to a 5,5,5 system

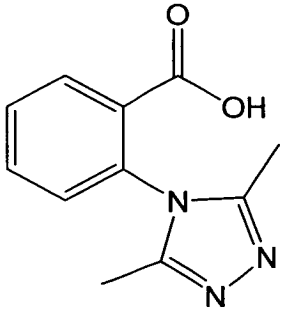
3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-2-nitrothiophene



A suspension of 3-bromo-2-nitrothiophene **185** (1.5 g, 7.2 mmol), 3,5-dimethyl-1,2,4-triazole **171** (0.7 g, 7.2 mmol) and potassium bicarbonate (0.72 g, 7.2 mmol) in DMF (20 cm^3) was stirred at 110 °C for 20 h.[81] The reaction mixture was added to water (200 cm^3) and extracted into ethyl acetate (5 × 40 cm^3), washed with water (3 × 20 cm^3) and then dried over $MgSO_4$. The solvents were removed *in vacuo*, and the resulting brown oil triturated with ethyl acetate and light petroleum to give yellow crystals confirmed as *3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-2-nitrothiophene* **211** (0.22 g, 14%), mp 168-170 °C (from ethanol) (Found: C, 42.2; H, 3.5; N, 24.0. $C_8H_8N_4O_2S$ requires C, 42.9; H, 3.6; N, 25.0%); δ_H 7.65 (1H, d, ^3J 5.7), 7.18 (1H, d, ^3J 5.7), 2.43 (3H, s) and 2.37 (3H, s); δ_C 162.04 (quat), 154.68 (quat), 129.56 (CH), 127.35 (CH), 13.66 (CH_3) and 12.30 (CH_3); *m/z* 224 (M^+ 31%), 183 (17), 113 (25), 96 (37), 70 (32), 57 (39) and 43 (100).

3.3.6 Precursors to isomeric 6,5,5 systems

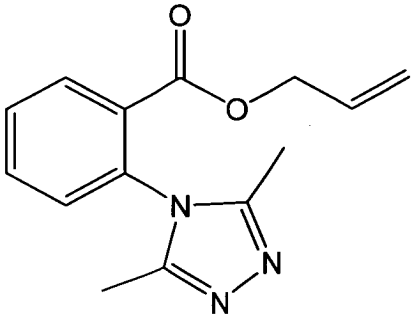
2-(3,5-Dimethyl-1,2,4-triazol-4-yl)-benzoic acid 214



2-Methyl-4*H*-3,1-benzoxazin-4-one **213** (13 g, 0.081 mol) and acetic hydrazide (5.98 g, 0.081 mol) were heated together in ethanol (150 cm^3) under reflux for 4 h.[82] After this time some white precipitate had formed and the mixture was left overnight to complete the crystallisation. The crystals were filtered off, washed with ethanol and dried on the sinter. The product was found to be 2-(3,5-dimethyl-1,2,4-triazol-4)-

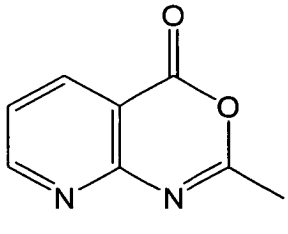
benzoic acid **214** (6.03 g, 34%); δ_H (d-TFA) 11.71 (1H, s), 9.01 (1H, dd, ^3J 6.5 and 2.0), 8.45 (2H, m), 8.10 (1H, t, ^3J 1.2) and 2.93 (6H, s); *m/z* 217 (M^+ 45%), 175 (100), 146 (66), 137 (42), 119 (76), 92 (76) and 43 (23).

Allyl 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate 215



2-(3,5-Dimethyl-1,2,4-triazol-4-yl)-benzoic acid **214** (6 g, 0.028 mol), allyl bromide (3.37 g, 0.028 mol) and anhydrous potassium carbonate (3.82 g, 0.028 mol) were stirred together in DMF (60 cm^3) at room temperature overnight.[83] The reaction mixture was added to water (500 cm^3), extracted into DCM (5 × 100 cm^3) and then the combined organic layers washed with water (3 × 50 cm^3) and dried over $MgSO_4$. The ethanol and some excess DMF were removed under reduced pressure then the resulting concentrated DMF solution left for several days, after which time the product crystallised suddenly on opening the mixture to the atmosphere. The sharp, white crystals were filtered off, washed with ether and then dried under high vacuum, this being the product *allyl 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate* **215** (4.33 g, 60%), mp 128-130 °C (from toluene) (Found: C, 65.4; H, 5.9; N, 16.3. $C_{14}H_{15}N_3O_2$ requires C, 65.4; H, 5.9; N, 16.3%); δ_H 8.10 (1H, dd, ^3J 7.5 and 1.6), 7.62 (2H, m), 7.20 (1H, dd, ^3J 7.7 and 1.4), 5.66 (1H, m), 5.19 (2H, td, ^3J 9.3 and 1.3), 4.54 (2H, dt, ^3J 6.2 and 1.3) and 2.08 (6H, s); δ_C 165.52 (quat), 151.29 (2 × quat), 133.68 (CH), 133.45 (quat), 132.21 (CH), 130.80 (CH) 130.20 (CH), 129.00 (CH), 128.87 (quat), 119.91 (CH_2), 66.50 (CH_2) and 10.84 (2 × CH_3); *m/z* 257 (M^+ 9%), 239 (18), 212 (100), 186 (39), 172 (58), 131 (48), 90 (55) and 41 (87).

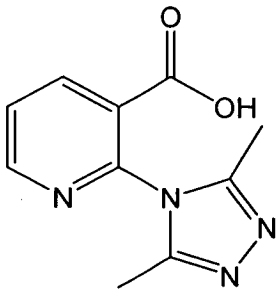
2-Methylpyrido[2,3-*d*][1,3]oxazin-4-one 216



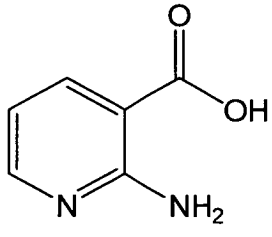
A suspension of 2-aminonicotinic acid (4.69 g, 0.034 mol) in acetic anhydride (25 cm^3) was heated under reflux with stirring for 1 h.[84] The solvent was removed under high vacuum and the crude product was recrystallised from toluene giving dull orange crystals of 2-methylpyrido[2,3-*d*][1,3]oxazin-4one **216** (4.85 g, 88%), mp 174-178 °C [lit.,[84] 175-178 °C]; δ_H 9.05

(1H, dd, ^3J 4.9 and 2.0), 8.59 (1H, dd, ^3J 7.8 and 2.0), 7.55 (1H, dd, ^3J 7.8 and 4.9) and 2.63 (3H, s).

Attempted synthesis of 2-(3,5-dimethyl-1,2,4-triazol-4-yl)-nicotinic acid 217

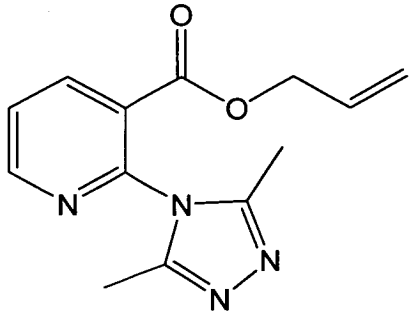


2-Methylpyrido[2,3-*d*][1,3]oxazin-4-one (4.35 g, 0.027 mol) and acetic hydrazide (1.99 g, 0.027 mol) were heated together in ethanol (50 cm^3) under reflux for 4 h, with stirring. The solvent was removed to give a sticky crude product, which was then triturated with diethyl ether to give a white crystalline solid; mass spectrometry appeared to confirm the presence of *2-(3,5-dimethyl-1,2,4-triazol-4-yl)-nicotinic acid* **217**. NMR results, however, were inconclusive, as there appeared to be a methyl group present although the integral did not properly correspond with those of the aromatic protons. Allylation of this species showed the product to contain an amino group instead of a triazole which lead to confirmation of the product as the original starting material from the previous reaction, 2-aminonicotinic acid; *m/z* 138 (M^+ 100 %), 112 (62), 93 (84), 74 (42) and 43 (81).



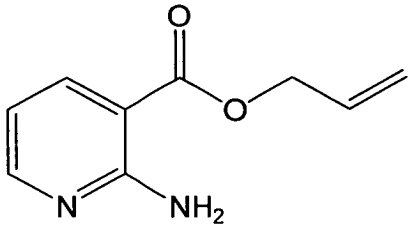
Repeating the reaction in a non-protic solvent, 2-methylpyrido[2,3-*d*][1,3]oxazin-4-one (2.45 g, 0.015 mol) and acetic hydrazide (1.12 g, 0.015 mol) in acetonitrile (25 cm^3) gave a similar result.

Allyl 2-aminonicotinate 215



This product was formed when trying to allylate what was thought to be 2-(3,5-dimethyl-1,2,4-triazol-4-yl)-nicotinic acid **217**. 2-Aminonicotinic acid (0.5 g, 3.62 mmol), allyl bromide (0.28 g, 2.3 mmol) and anhydrous potassium carbonate (0.32 g, 2.3 mmol) were stirred together in DMF (7 cm^3) at room temperature overnight. The reaction mixture was added to water (70 cm^3), extracted with DCM (5 × 20 cm^3) and then the combined organic layers washed with water (3 × 10 cm^3) and dried over $MgSO_4$.

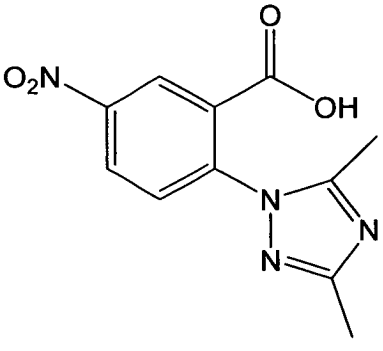
Removal of the solvents under high vacuum and purifying by Kugelrohr sublimation gave a yellow oil which crystallised and was found to be *allyl-2-aminonicotinate* **218** (0.68 g, 95%), (Found: M^+ 178.1902. $C_9H_{10}N_2O_2$ requires *M* 178.1900); δ_H 8.40 (1H, dd, ^3J 4.8 and 1.9), 8.38 (1H, dd, ^3J 7.8 and 1.9), 6.82 (1H, dd, ^3J 7.8 and 4.8), 6.71 (2H, bs), 6.21 (1H, m), 5.55 (2H, td, ^3J 9.1 and 1.2) and 4.99 (2H, dt, ^3J 5.6 and 1.2);



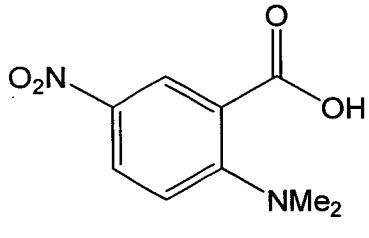
δ_C 166.96 (quat), 159.84 (quat), 154.00 (CH), 140.55 (CH) 132.41 (CH), 118.80 (CH_2), 113.05 (CH), 106.55 (quat) and 65.77 (CH_2); *m/z* 178 (M^+ 100%), 145 (21), 121 (99), 94 (93), 78 (70), 63 (75) and 39 (50).

3.3.7 Allyl 2-(azolyl)benzoate analogues

Attempted synthesis of 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoic acid 219

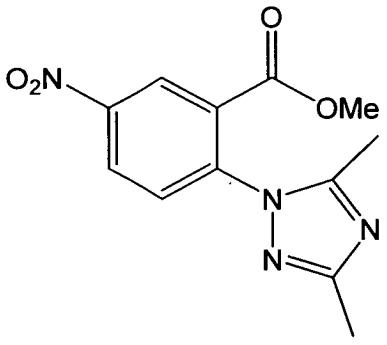


2-Chloro-5-nitrobenzoic acid (1 g, 5 mmol), 3,5-dimethyl-1,2,4-triazole **171** (0.49 g, 5 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) were heated together in DMF (10 cm^3), under reflux, overnight.[67] The reaction mixture was added to dilute HCl (2M, 50 cm^3), extracted with ethyl acetate (5 × 25 cm^3), washed with water (3 × 10 cm^3) and dried over $MgSO_4$. The solvents were removed *in vacuo* to leave an orange solid. This was found to be mostly 2-dimethylamino-5-nitrobenzoic acid **220** (0.4 g, 38%), mp 160-162 °C [lit.,[121] 164 °C]; δ_H (400 MHz) 7.72 (1H, d, ^3J 2.9), 7.28 (1H, dd, ^3J 9.3 and 2.9), 6.07 (1H, d, ^3J 9.3) and 2.22 (6H, s); (electrospray) ES-: 209 (M^+ 58%), 182 (100) and 179 (74).



Alternative attempts at the synthesis of **219** involved dispensing with the base and using ethanol and DMSO as solvents, but neither of these reactions proceeded at all.

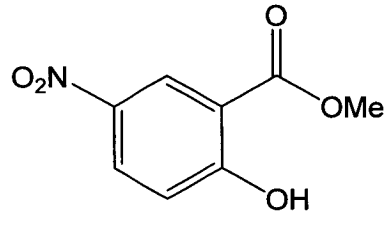
Methyl 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoate 222



Methyl 2-chloro-5-nitrobenzoate **221** (5 g, 0.023 mol) and 3,5-dimethyl-1,2,4-triazole **171** (2.25 g, 0.023 mol) were stirred in DMF (50 cm^3) with potassium carbonate (3.2 g, 0.023 mol) at 125 °C overnight. The reaction mixture was added to water (300 cm^3), extracted with ethyl acetate (6 × 50 cm^3), washed with water (5 × 25 cm^3) and dried over $MgSO_4$. This solution was then extracted with aqueous potassium carbonate solution (5 × 25 cm^3) to remove a phenolic by-product, which had been identified by mass spectroscopy of a sample of crude material, and dried again over $MgSO_4$.

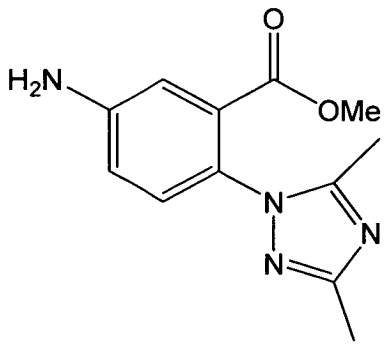
After removal of DCM the crude product was purified by column chromatography (ethyl acetate and light petroleum as eluent), and the fourth component obtained was found to be an impure sample of the desired product **222**. Trituration with ethyl acetate and light petroleum finally gave dull brown crystals found to be *methyl 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoate* **222** (0.89 g, 14%), δ_H (400 MHz) 8.79 (1H, d, ^3J 2.5), 8.44 (1H, dd, ^3J 8.8 and 2.5), 7.57 (1H, d, ^3J 8.8), 3.75 (3H, s), 2.34 (3H, s) and 2.27 (3H, s); δ_C (400 MHz) 163.60 (quat), 161.21 (quat), 154.01 (quat), 147.83 (quat), 141.53 (quat), 129.81 (quat), 129.61 (CH), 127.49 (CH), 126.73 (CH), 53.31 (CH_3), 13.78 (CH_3) and 12.47 (CH_3); *m/z* (electrospray) ES+: 277 (M^+ 100%).

The aqueous basic extracts were acidified with dilute HCl and then the phenol by-product extracted with ethyl acetate (3 × 50 cm^3), washed with water (3 × 25 cm^3) and dried over $MgSO_4$. Removing the solvent left the bright orange crystalline product



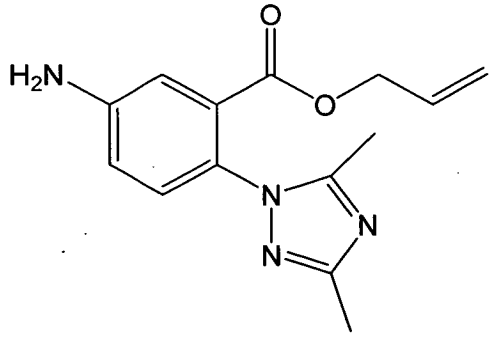
methyl 2-hydroxy-5-nitrobenzoate **223** 0.89 g, 14%), mp 110-112 °C [lit.,[118] 115-116 °C]; δ_H (400 MHz) 11.37 (1H, s), 8.72 (1H, d, ^3J 2.9), 8.26 (1H, dd, ^3J 9.3 and 2.9), 7.02 (1H, d, ^3J 9.3) and 3.97 (3H, s); *m/z* (electrospray) ES-: 196 (M^+ 100).

Methyl 5-amino-2-(3,5-dimethyl-1,2,4-triazol-1-yl)-benzoate 224



A suspension of methyl 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-5-nitrobenzoate **222** (0.8 g, 2.9 mmol) and 10% palladium/charcoal catalyst (0.1 g) in a 1:1 mixture of methanol and THF (100 cm^3) was subjected to hydrogenation at 270 mm water pressure, at room temperature, overnight. The catalyst was filtered off through Kieselguhr and the solvent removed to leave an oily product which was found to be *methyl 5-amino-2-(3,5-dimethyl-1,2,4-triazol-1-yl)-benzoate* **224** (0.69 g, 97%), δ_H (400 MHz) 7.26 (1H, d, ^3J 2.8), 7.11 (1H, d, ^3J 8.4), 6.83 (1H, dd, ^3J 8.4 and 2.8), 4.02 (2H, bs), 3.65 (3H, s), 2.36 (3H, s) and 2.22 (3H, s); δ_C (400 MHz) 166.68 (quat), 159.94 (quat), 153.58 (quat), 147.61 (quat), 129.71 (CH), 129.22 (quat), 126.67 (quat), 118.04 (CH), 116.74 (CH), 52.38 (CH_3), 13.73 (CH_3) and 12.09 (CH_3); *m/z* (electrospray) ES+: 247 (M^+ 100%).

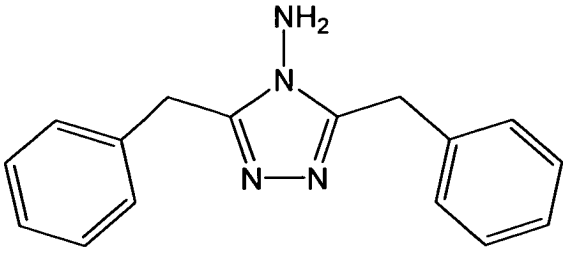
Attempted preparation of allyl 5-amino-2-(3,5-dimethyl-[1,2,4]-triazol-1-yl)-benzoate 225



Methyl 5-amino-2-(3,5-dimethyl-1,2,4-triazol-1-yl)-benzoate **224** (0.69 g, 2.8 mmol) was dissolved in methanol (40 cm^3) and aqueous sodium hydroxide (1M, 10 cm^3) added.[54] The reaction mixture was then heated under reflux for 2 h. The solvents were then removed and the resulting crude intermediate dissolved in DMF (30 cm^3) and then allyl bromide (0.34 g, 2.8 mmol) and anhydrous potassium carbonate (0.39 g, 2.8 mmol) were added. The resultant mixture was then stirred at room temperature overnight. After this time the reaction mixture was added to water (100 cm^3), extracted with DCM (5 × 50 cm^3), washed with water (3 × 25 cm^3) and dried over $MgSO_4$. Removing the solvent then left a small quantity of grey material which could not be identified. The desired allyl product **225** could not be found.

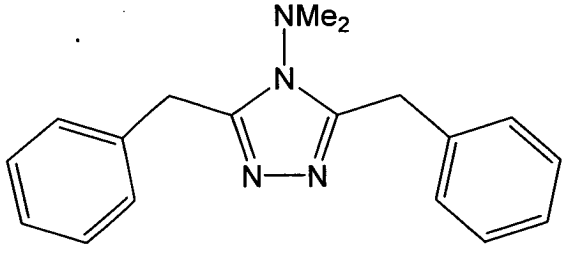
3.3.8 A triazolamine precursor

3,5-Dibenzyl-[1,2,4]-triazol-4-amine 227



Flowers of sulfur (3 g, 0.094 mol) were added slowly to a solution of phenylacetonitrile (5.85 g, 0.05 mol) in hydrazine hydrate (50 cm^3) and ethanol (75 cm^3) at 0 °C.[86] After effervescence had subsided the reaction mixture was heated under reflux in an atmosphere of nitrogen for 3 h. Concentration of the reaction mixture gave a solid yellow crude product which was recrystallised from water and methanol to give a highly crystalline white product 3,5-dibenzyl-[1,2,4]-triazol-4-ylamine **227** (4.26 g, 65%), mp 158-160 °C [lit.,[86] 161-163 °C]; δ_H 7.21 (10H, m), 4.13 (2H, s) and 4.06 (4H, s); δ_C 153.93 (2 × quat), 135.34 (2 × quat), 128.77 (4 × CH), 128.42 (4 × CH), 127.00 (2 × CH) and 30.75 (2 × CH_2); *m/z* 264 (M^+ 52%), 248 (17), 131 (30), 117 (35), 103 (24), 91 (100) and 65 (19).

Attempted preparation of (3,5-dibenzyl-[1,2,4]-triazol-4-yl)-dimethylamine



3,5-Dibenzyl-[1,2,4]-triazol-4-ylamine **227** (1 g, 3.79 mmol) was cooled in an ice bath and to this was slowly added 88% formic acid (0.55 g, 0.014 mol) followed by 36% formaldehyde (0.77 g, 9.24 mmol) plus extra water (5 cm^3) (cf. ref. 87).[87] The reaction mixture was then heated at 80 °C for 24 h. It was then added to 6M HCl (10 cm^3), extracted into ether (3 × 5 cm^3), washed with water (3 × 3 cm^3) and dried over $MgSO_4$ overnight. Removing the ether left a tiny spread of oil unidentifiable by proton NMR spectroscopy.

The aqueous layers from the original extraction were basified with sodium hydroxide (2M, 30 cm^3) and then the product extracted into DCM (3 × 20 cm^3), washed with water (3 × 10 cm^3) and dried over $MgSO_4$. Removal of the solvents then gave a semi-

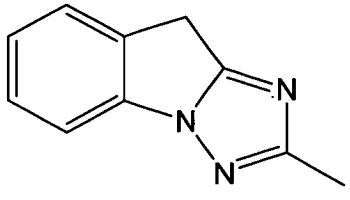
crystalline solid which was found by proton NMR to be mostly unreacted starting material.

3.4 Flash vacuum pyrolysis experiments

Conditions for the pyrolyses were established in small scale (<50 mg) experiments in which the product(s) were dissolved in deuteriated chloroform and analysed immediately by ^{1}H NMR spectroscopy. When carrying out large-scale (~500 mg) pyrolysis of compounds with nitro leaving groups the crude products were collected in a cold finger trap containing dry ice and acetone, placed directly after the furnace, while the reactive nitrous by-products passed through and were collected in the usual U-tube suspended in liquid nitrogen. Later tests showed this set up was only necessary for heavily substituted precursors such as the anilines and benzonitriles. All large-scale products were dissolved in DCM and purified by column chromatography; in each case only the desired product was isolated and no significant by-products were identified.

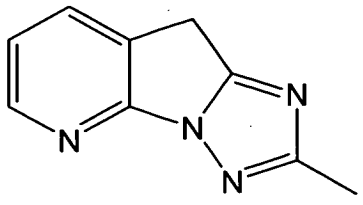
The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), pressure range (P) and pyrolysis time (t)] and, where appropriate, approximate yields are given.

FVP of 2-(3,5-Dimethyl-1,2,4-triazol-1-yl)nitrobenzene 194 (5.63 g, 0.0258 mol)

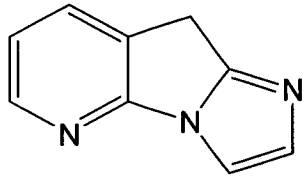


(10 × ~500 mg, T_f 850 °C, T_i 140 °C, P 0.02 - 0.18 Torr, t 25 min). The crude pyrolysate was separated by dry flash chromatography (silica, ethyl acetate and light petroleum as eluent), the fifth component being 2-methyl-*9H*-[1,2,4]triazolo[1,5-*a*]indole **231** obtained as an orange/red semi-solid (2.41 g, 55%), δ_H 7.48 (3H, m), 7.21 (1H, dd, ^3J 7.6 and 1.7), 3.85 (2H, s) and 2.49 (3H, s).[67]

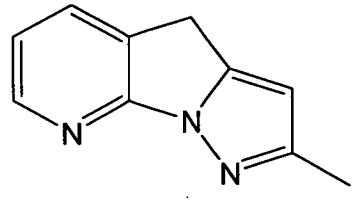
FVP of 2-(3,5-dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine 189 (335 mg, T_f 850 °C, T_i 150 °C, P 0.02 - 0.18 Torr, t 20 min). The crude pyrolysate was separated by dry flash chromatography (silica, ethyl acetate and hexane as eluent), the sixth component being *2-methyl-9H-1,3,4,5-tetraaza-cyclopenta[a]indene* **232** obtained as a reddish brown solid (50 mg, 19%), mp 153-155 °C (Found: M^+ 172.0751. $C_9H_8N_4$ requires M 172.0749); δ_H 8.39 (1H, dd, ^3J 5.2 and 1.5), 7.80 (1H, dd, ^3J 7.5 and 1.5), 7.19 (1H, dd, ^3J 7.5 and 5.2), 3.99 (2H, s) and 2.62 (3H, s); δ_C 167.40 (quat), 161.78 (quat), 151.68 (quat), 148.28 (CH), 134.89 (CH), 126.62 (quat), 121.02 (CH), 26.95 (CH_2), and 15.31 (CH_3); *m/z* 172 (M^+ 100%), 130 (12), 104 (43), 69 (28) and 43 (26).



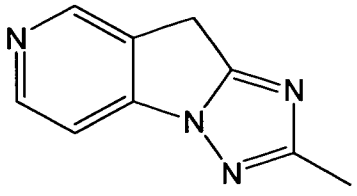
FVP of 2-(2-Methylimidazol-1-yl)-3-nitropyridine 190 (380 mg, T_f 850 °C, T_i 140 °C, P 0.09 - 0.16 Torr, t 25 min). The crude pyrolysate was separated by dry flash chromatography (silica, ethyl acetate and hexane, then methanol and toluene as eluents), the fourth component being *9H-1,4,5-triaza-cyclopenta[a]indene* **233** obtained as a sticky reddish brown solid (60 mg, 21%), which could not be purified completely; δ_H 8.26 (1H, d, ^3J 4.7), 7.71 (1H, d, ^3J 7.4), 7.53 (1H, s), 7.20 (1H, s), 7.08 (1H, dd, ^3J 7.4 and 4.7) and 3.86 (2H, s); the sample apparently decomposed before the ^{13}C NMR and mass spectra could be recorded.



FVP of 2-(3,5-Dimethylpyrazol-1-yl)-3-nitropyridine 187 (38 mg, T_f 850 °C, T_i 150 °C, P 0.05 - 0.13 Torr, t 10 min). The crude pyrolysate was dissolved in deuteriated chloroform and found by ^1H NMR spectroscopy to be 2-methyl-9*H*-3,4,5-triaza-cyclopenta[*a*]indene **234** (20 mg, 67%); δ_H 8.25 (1H, d, ^3J 5.1), 7.63 (1H, d, ^3J 7.6), 6.99 (1H, dd, ^3J 7.6 and 5.1), 6.05 (1H, s), 3.76 (2H, s) and 2.36 (3H, s).[67]

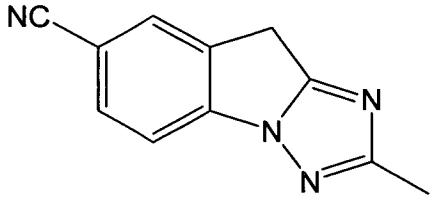


FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitropyridine 193 The original small-scale pyrolysis of **193** (43 mg, T_f 850 °C, T_i 150 °C, P 0.17 - 0.20 Torr, t 10 min), with the pyrolysate dissolved in deuteriated chloroform gave mostly *2-methyl-9H-1,3,4,7-tetraaza-cyclopenta[a]indene* **235** (20 mg, 59%); δ_H 8.95 (1H, m), 8.64 (1H, m), 7.45 (1H, m), 3.93 (2H, s) and 2.49 (3H, s).

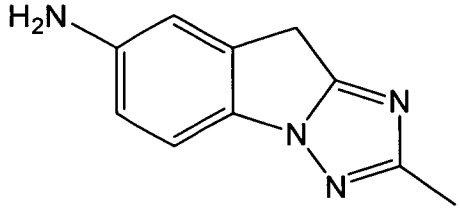


Scale up of this reaction resulted in decomposition of the pyrolysis product even with the precaution of the cold finger trap, therefore this species could not be fully characterised.

FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitrobenzonitrile 197 (287 mg, T_f 850 °C, T_i 150 °C, P 0.03 - 0.19 Torr, t 30 min). The crude pyrolysate was separated by dry flash chromatography (silica, methanol and toluene as eluent), the second component being *2-methyl-9H-[1,2,4]-triazolo[1,5-a]indole-7-carbonitrile* **236** obtained as a reddish brown solid (90 mg, 39%), mp 130-150 °C (decomp) (Found: M^+ 196.0752. $C_{11}H_8N_4$ requires M 196.0749); δ_H 7.74 (1H, m), 7.72 (1H, m), 7.57 (1H, m), 3.93 (2H, s) and 2.49 (3H, s); δ_C 167.17 (quat), 161.66 (quat), 141.21 (quat), 133.89 (CH), 133.20 (quat), 129.94 (CH), 118.44 (quat), 111.66 (CH), 109.06 (quat), 27.75 (CH_2), and 14.92 (CH_3); *m/z* 196 (M^+ 100%), 167 (22), 128 (41) and 64 (16).

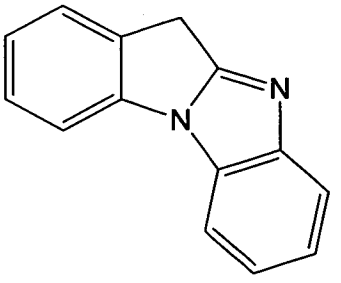


FVP of 4-(3,5-Dimethyl-1,2,4-triazol-1-yl)-3-nitroaniline 198 (5.29 g, 0.0227 mol) (10 × ~500 mg, T_f 850 °C, T_i 200 °C, P 0.01 - 0.20 Torr, t 30 min). The crude pyrolysate was separated by dry flash chromatography (silica, ethyl acetate as eluent), the seventh component being *2-methyl-9H-[1,2,4]-triazolo[1,5-a]indol-7-ylamine* **237** obtained as a reddish brown solid (0.86 g, 19%), mp 190-194 °C (decomp); δ_H 7.24 (1H, d, ^3J 8.5), 6.75 (1H, d, ^3J 1.4), 6.61 (1H, dd, ^3J 8.5 and 1.4), 3.71 (2H, s) and 2.43 (3H, s); δ_C 164.41 (quat), 159.01 (quat), 144.38

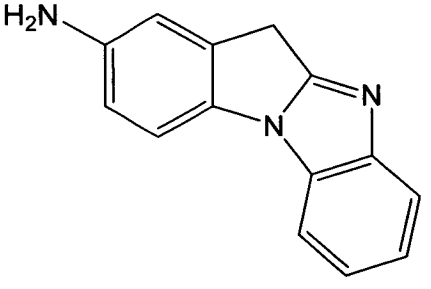


(quat), 133.42 (quat), 130.46 (quat), 113.84 (CH), 113.24 (CH), 111.25 (CH), 27.60 (CH_2), and 14.50 (CH_3); *m/z* 186 (M^+ 63%), 145 (25), 138 (19), 91 (100) and 31 (81). This material was all used for a ballasting reaction at the Kodak laboratories before an accurate mass mass spectrum was taken.

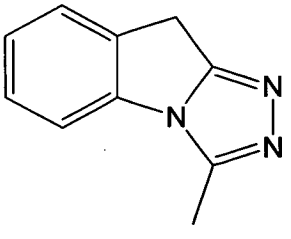
FVP of 2-Methyl-1-(2-nitrophenyl)benzimidazole 209 (2.51 g, 9.92 mmol) (5 × ~500 mg, T_f 850 °C, T_i 150 °C, *P* 0.02 - 0.16 Torr, *t* 35 min). This class of tetracycle was known to decompose during dry flash chromatography,[54] so was partially purified by dissolving in DCM and filtering off the insoluble impurities to give the product indolo[1,2-*a*]benzimidazole **238** obtained as an dark brown, semi-crystalline solid (1.78 g, 87%), mp 160-162 °C [lit.,[54] 162-163 °C]; δ_H 7.67 (2H, m), 7.24 (6H, m) and 4.02 (2H, s).



FVP of 4-(2-Methylbenzimidazol-1-yl)-3-nitroaniline 210 (2.2 g, 8.21 mmol) (4 × ~500 mg, T_f 850 °C, T_i 200 °C, *P* 0.02 - 0.15 Torr, *t* 50 min). The crude product could not be purified by column or recrystallisation but was found to be mostly *2-aminoindolo[1,2-a]benzimidazole* **239** obtained as an dark brown, semi-solid (1.43 g, 79%); δ_H 7.74 (1H, d, ^3J 8.4), 7.64 (1H, d, ^3J 9.8), 7.23 (3H, m), 6.80 (1H, s), 6.66 (1H, d, ^3J 8.4), and 3.95 (2H, s). As this product was not purified, but used straight for the next reaction, characterisation was not possible.

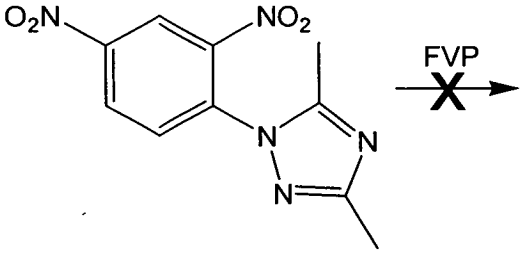


FVP of Allyl-2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)benzoate 215 (4.22 g, 0.016 mol) (8 × ~500 mg, T_f 850 °C, T_i 150 °C, *P* 0.02 - 0.25 Torr, *t* 45 min). The crude pyrolysate was separated by dry flash chromatography (silica, methanol and toluene as eluent), the fourth component being *3-methyl-9H-[1,2,4]triazolo[4,3-a]indole* **240** obtained as a dark brown solid (970 mg, 35%), mp 100-120 °C (decomp) (Found: M^+ 171.0799. $C_{10}H_9N_3$ requires *M* 171.0797); δ_H

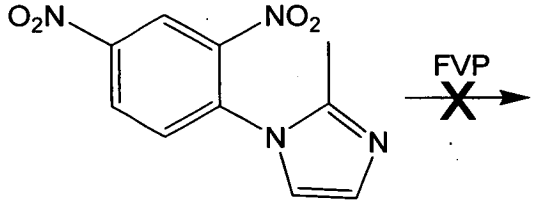


7.42 (1H, d, ^3J 7.5), 7.34 (2H, d, ^3J 2.7), 7.21 (1H, m), 3.89 (2H, s) and 2.68 (3H, s); δ_C 159.71 (quat), 144.93 (quat), 136.20 (quat), 134.27 (quat), 128.13 (CH), 126.90 (CH), 125.66 (CH), 111.52 (CH), 26.38 (CH_2), and 11.39 (CH_3); *m/z* 171 (M^+ 100%), 132 (91), 103 (92), 91 (43), 77 (54), 69 (73), 51 (68) and 42 (67).

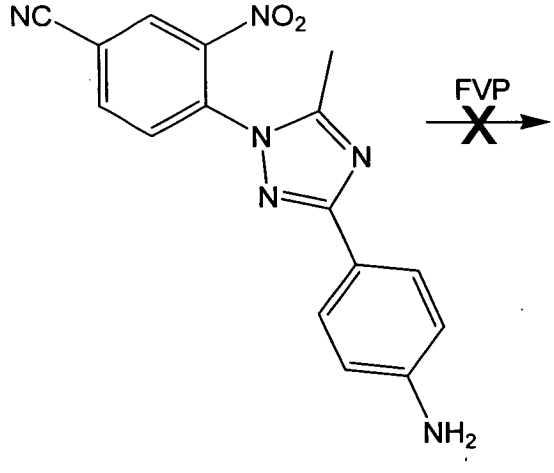
FVP of 3,5-Dimethyl-1-(2,4-dinitrophenyl)-1,2,4-triazole 196 (263 mg, T_f 850 °C, T_i 160 °C, P 0.02 - 0.25 Torr, t 40 min). The crude pyrolysate was a thick black tar, which, when analysed by ^{1}H NMR spectroscopy, was found to contain no useful products.



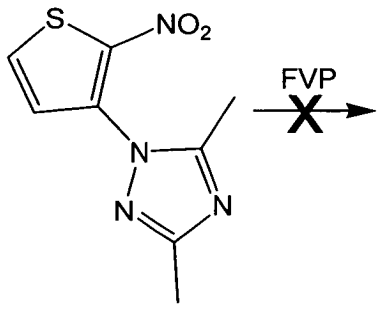
FVP of 2-Methyl-1-(2,4-dinitrophenyl)-imidazole 195 (50 mg, T_f 850 °C, T_i 150 °C, P 0.02 - 0.07 Torr, t 10 min). The crude pyrolysate was found by ^{1}H NMR spectroscopy to contain no clearly defined products, and, after the previous FVP, this reaction was not scaled up.



FVP of 4-[3-(4-Aminophenyl)-5-methyl-1,2,4-triazol-1-yl]-3-nitrobenzonitrile 205 (50 mg, T_f 850 °C, T_i 160 °C, P 0.03 - 0.05 Torr, t 25 min). The majority of the sample decomposed in the inlet tube to an involatile dark brown substance; the crude pyrolysate obtained was in very low yield and its ^{1}H NMR spectrum showed an impure product which could not be confirmed as the desired species.

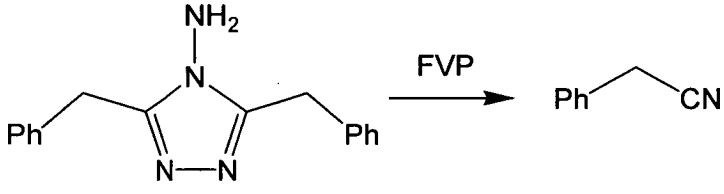


FVP of 3-(3,5-Dimethyl-1,2,4-triazol-1-yl)-2-nitrothiophene 211 (20 mg, T_f 850 °C, T_i 200 °C, P 0.02 - 0.09 Torr, t 10 min).



Approximately half the crude pyrolysate was successfully dissolved in $CDCl_3$ and proton NMR of this showed a wide mixture of various products; the desired tricyclic system appeared to be absent as there was no clear methylene peak. The remaining material was dissolved in d_6-acetone, and the NMR spectrum of this orange solution showed only solvent peaks.

FVP of 3,5-Dibenzyl-[1,2,4]-triazol-4-ylamine 227 (45 mg, T_f 850 °C, T_i 200 °C, P 0.03 - 0.04 Torr, t 40 min).



The crude pyrolysate was dissolved in deuteriated chloroform and ^{1}H NMR spectroscopy showed that cyclisation had not occurred, but that the precursor had broken up to its original starting material phenylacetonitrile (20 mg, 50 %); δ_H 7.27 (5H, m) and 3.68 (2H, s).

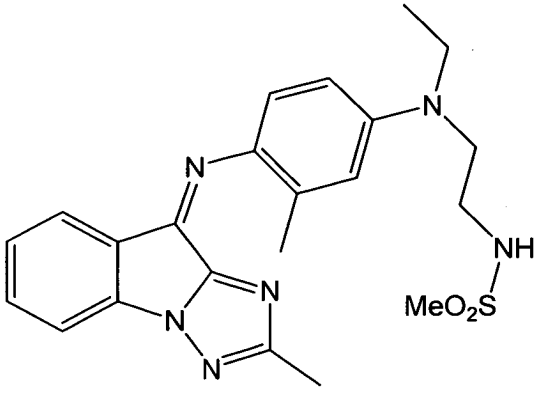
3.5 Dyes

3.5.1 Azamethine dyes – microscale

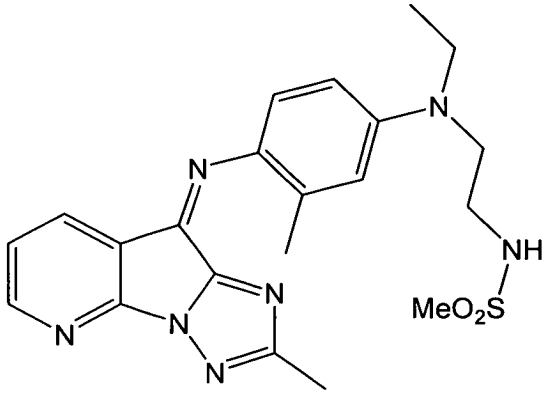
Couplers formed by FVP reactions in the previous section were initially tested at Kodak by converting to azamethine dyes. The crude products from the small-scale pyrolyses (~20 mg) were dissolved in methanol (~ 1 cm^3) and to these solutions were added a few drops each of aqueous solutions of Kodak CD3 developer (4-amino-3-methyl-*N*-ethyl-*N*-*b*-(methanesulfonamido)ethylaniline sesquisulfate), potassium persulfate (oxidiser) and potassium carbonate (base). The dyes were generally formed quickly with visible colour change and then were extracted with ethyl acetate. After removal of solvent the crude dyes were then purified and analysed by liquid chromatography-mass spectrometry, and UV-vis spectroscopy (in methanol) on the HP 8453 series uv/vis spectrometer. These compounds were produced on too small a

scale to obtain any NMR data and the purified material was not retrieved from the LC-MS instrument so no melting points were recorded.

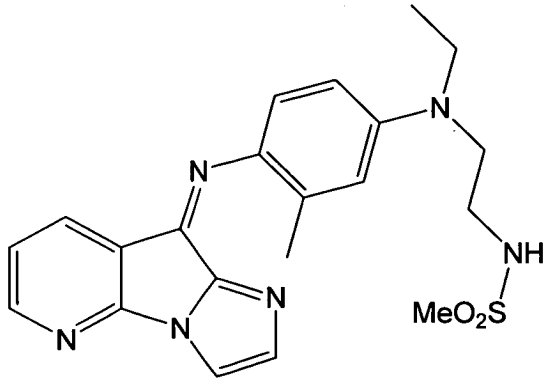
2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231 coupled quite quickly to give a reddish magenta dye **241**; λ_{max} 512 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 439 (M^+ 100%).



2-Methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene 232 coupled quickly to give a magenta dye **242**; λ_{max} 524 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 440 (M^+ 100%).

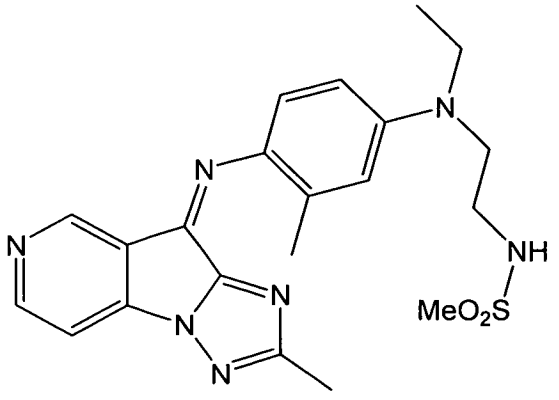


9*H*-1,4,5-Triaza-cyclopenta[*a*]indene 233 coupled more slowly to give a redder coloured dye **243**; λ_{max} 506 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 425 (M^+ 100%) and 318 (32).

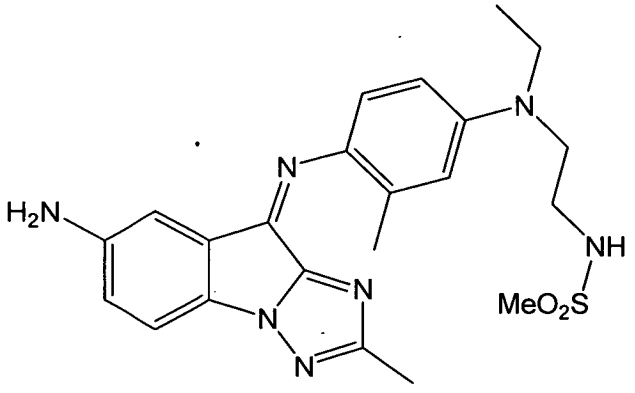


2-Methyl-9*H*-3,4,5-triaza-cyclopenta[*a*]indene 234 failed to couple at all.

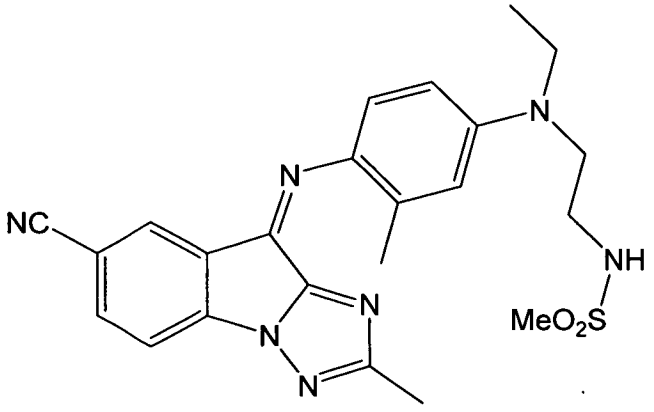
2-Methyl-9*H*-1,3,4,7-tetraaza-cyclopenta[*a*]indene 235 coupled very quickly to give a fine magenta dye **244**; λ_{max} 534 nm ($\lambda_{1/2}$ 80 nm); *m/z* (electrospray) ES+: 440 (M^+ 100%).



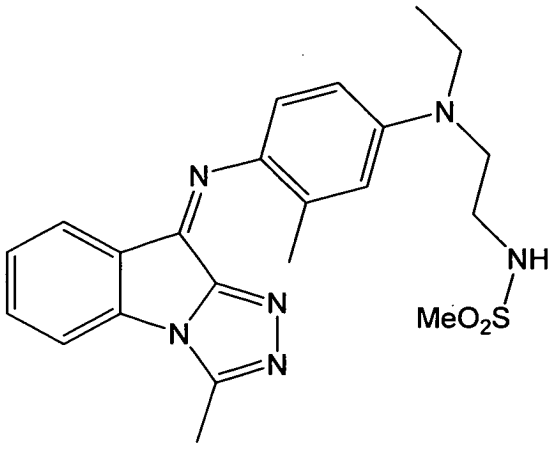
2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine 237 coupled quite slowly to give a reddish magenta dye **245**; λ_{max} 506 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 454 (M^+ 100%), 219 (12) and 141 (15).



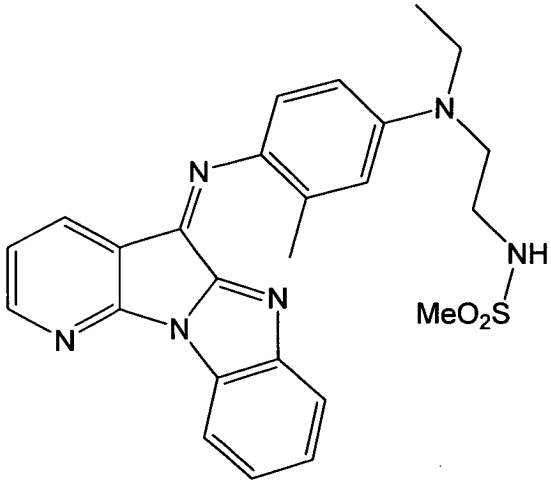
2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236 coupled very quickly to give an intense magenta dye **246**; λ_{max} 534 nm ($\lambda_{1/2}$ 80 nm); *m/z* (electrospray) ES+: 464 (M^+ 100%) and 141 (66).



3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole 240 coupled very slowly to give a red dye **247**; λ_{max} 500 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 439 (M^+ 100%), 119 (15) and 91 (20).



Indolo[1,2-*a*]benzimidazole 238 coupled quite quickly to give a reddish magenta dye **248**; λ_{max} 508 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 474 (M^+ 36%), 318 (47), 141 (100) and 100 (52).



2-Aminoindolo[1,2-*a*]benzimidazole 239 failed to couple at all.

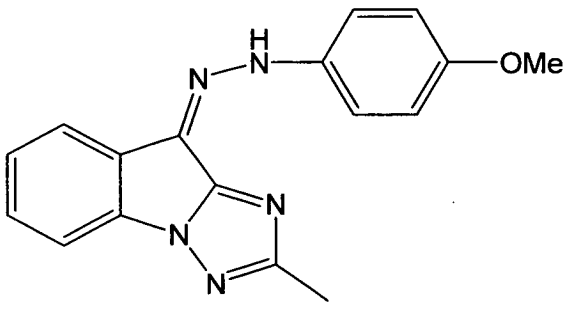
3.5.2 Azo dyes

These were also generally performed on the micro-scale, the required diazonium salt was formed as follows: a suspension of *p*-anisidine (3.2 g, 0.026 mol) in 5M HCl (20 cm^3) was cooled to ~-5 °C in an ice/acetone bath.[119] To this was added drop-wise a solution of sodium nitrite (1.9 g, 0.027 mol) in water (3 cm^3). This was then stirred at -5-0 °C for 30 min.

Micro-scale samples of each coupler (typically leftovers from small-scale FVP reactions) were dissolved in THF (~2 cm^3) along with a few drops of pyridine. To each coupler solution was then added a small volume of the diazonium salt solution

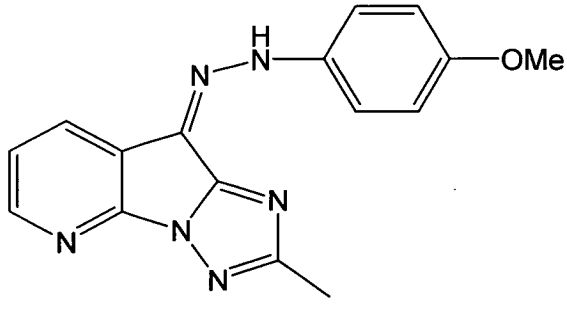
249, the reaction mixture shaken for a few seconds and then acidified with dilute HCl. The dye was then extracted into ethyl acetate and generally purified by preparative TLC (ethyl acetate and light petroleum as eluent). Dyes scraped off the TLC plates were then analysed by electron impact mass spectrometry and UV-vis spectroscopy in ethyl acetate solution.

2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231 coupled quite quickly to give a yellow dye *9-(4-methoxyphenyl)hydrazone-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **250**; λ_{max} 418 nm ($\lambda_{1/2}$ 80 nm); (Found: M^+ 305.1270. $C_{17}H_{15}N_5O$ requires *M* 305.1277); *m/z* 305 (M^+ 27%), 185 (26), 169 (36), 144 (18), 123 (43), 105 (31), 101 (38), 85 (67) and 57 (100).

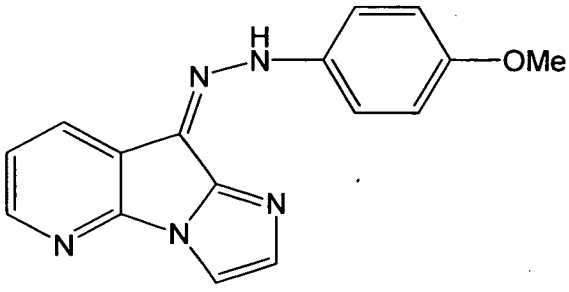


This dye was also prepared at Kodak with similar observations. The crude product was purified by column (ethyl acetate and light petroleum as eluent) and the UV-vis data obtained in methanol solution; λ_{max} 420 nm ($\lambda_{1/2}$ 100 nm); *m/z* (electrospray) ES+: 306 (M^+ 100%), 242 (12) and 141 (7).

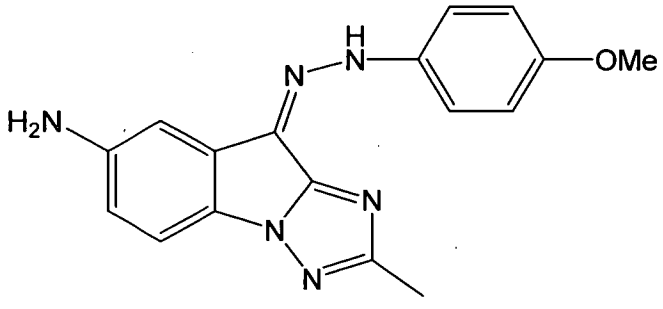
2-Methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene 232 coupled quickly to give a bright yellow dye *9-(4-methoxyphenyl)hydrazone-2-methyl-9H-1,3,4,5-tetraaza-cyclopenta[a]indene* **251**; λ_{max} 421 nm ($\lambda_{1/2}$ 90 nm); (Found: M^+ 306.1227. $C_{16}H_{14}N_6O$ requires *M* 306.1229); *m/z* 306 (M^+ 4%), 185 (100), 170 (23), 142 (40), 115 (21), 108 (19), 69 (20) and 43 (47).



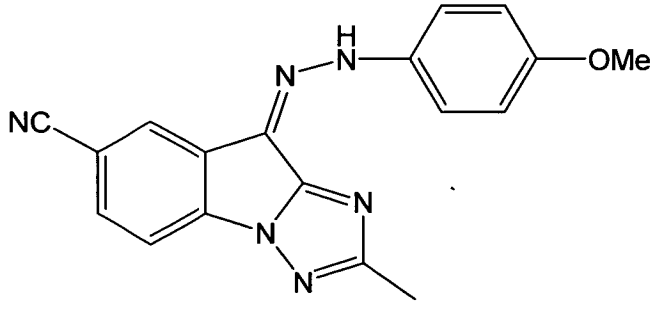
9*H*-1,4,5-Triaza-cyclopenta[*a*]indene 233 coupled more slowly to give a duller yellow dye *9-(4-methoxyphenyl)hydrazone-9H-1,4,5-triaza-cyclopenta[a]indene* **252**; λ_{max} 414 nm ($\lambda_{1/2}$ 90 nm); (Found: M^+ 291.1121. $C_{16}H_{13}N_5O$ requires *M* 291.1120); *m/z* 291 (M^+ 22%), 276 (14), 185 (11), 169 (18), 149 (22), 135 (31), 83 (29), 69 (48), 57 (66) and 43 (100).



2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine 237 coupled quite slowly to give a moderately yellow dye *9-(4-methoxyphenyl)hydrazone-2-methyl-9H-[1,2,4]-triazolo[1,5-a]indol-7-ylamine* **253**; λ_{max} 411 nm ($\lambda_{1/2}$ 90 nm); *m/z* 320 (M^+ 16%), 185 (100), 170 (37), 151 (47), 142 (45), 123 (56), 115 (30), 108 (58), 101 (59), 85 (76), 69 (61) and 55 (74). There was insufficient material remaining for an accurate mass result.



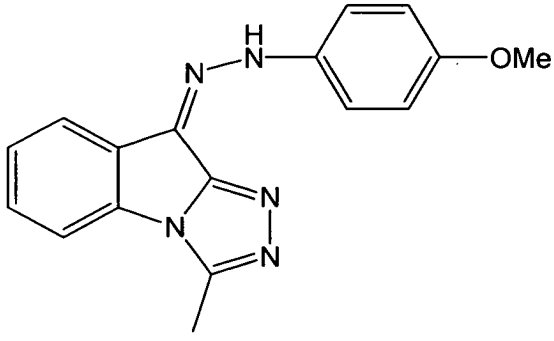
2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236 coupled very quickly to give an intense yellow dye *9-(4-methoxyphenyl)hydrazone-2-methyl-9H-[1,2,4]-triazolo[1,5-a]indol-7-carbonitrile* **254**; λ_{max} 432 nm ($\lambda_{1/2}$ 80 nm); (Found: M^+ 330.1225. $C_{18}H_{14}N_6O$ requires *M* 330.1229); *m/z* 330 (M^+ 13%), 185 (100), 170 (24), 151 (25), 142 (38), 108 (30), 69 (31), 57 (36) and 43 (84).



This dye was also prepared at Kodak and similar results observed. The crude product was purified by column (ethyl acetate and light petroleum as eluent) and the UV-vis

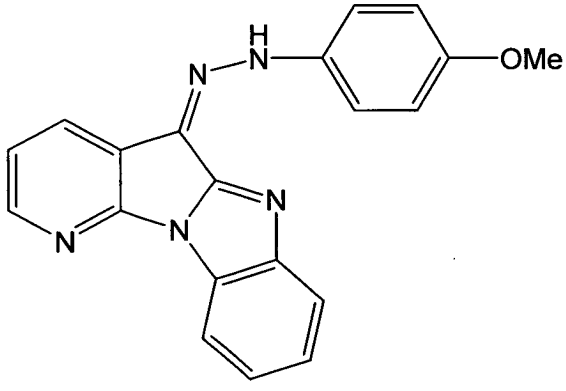
spectrum run in methanol had λ_{max} 434 nm ($\lambda_{1/2}$ 80 nm); *m/z* (electrospray) ES+: 331 (M^+ 75%) and 242 (100).

3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole 240 coupled very slowly to give a faintly

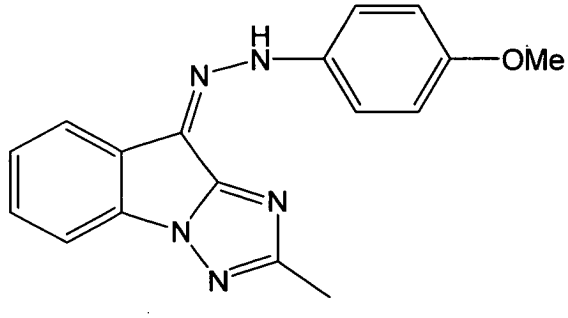


yellow dye *9-(4-methoxyphenyl)hydrazone-3-methyl-9H-[1,2,4]triazolo[4,3-a]indole* **255**; λ_{max} 409 nm ($\lambda_{1/2}$ 90 nm); (Found: M^+ 305.1279. $C_{17}H_{15}N_5O$ requires *M* 305.1277); *m/z* 305 (M^+ 47%), 290 (22), 185 (57), 144 (100), 122 (32), 116 (41), 69 (29), 57 (42) and 43 (59).

Indolo[1,2-*a*]benzimidazole 238 appeared to couple to a yellow dye, but when separated no dye was obtained, which may be a result of the tetracyclic systems' tendency to decompose during column chromatography.



Preparative scale synthesis of 9-(4-methoxyphenyl)hydrazone-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole 250

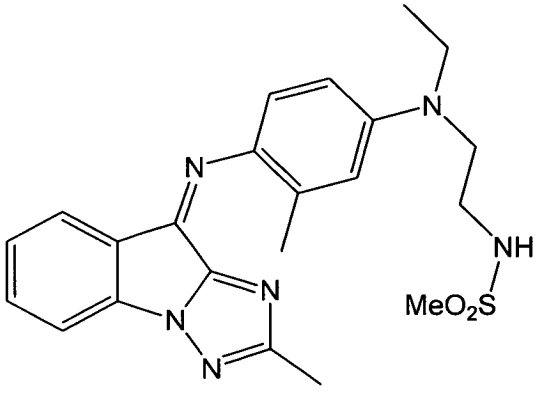


A portion of the *p*-methoxyphenyl diazonium salt **249** described earlier (2 cm^3, 2.17 mmol) was added to a solution of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (0.17 g, 1 mmol) in THF (40 cm^3) with pyridine (0.1 g, 1.27 mmol). This was then stirred for ~10 min and a colour change observed. The reaction mixture was then acidified with dilute HCl (15 cm^3), extracted with ethyl acetate (4 × 10 cm^3) and

the combined organic layers washed with water (3 × 5 cm^3) and then dried over $MgSO_4$. The crude product was then purified by column chromatography (ethyl acetate and light petroleum as eluent) to give the pure dye *9-(4-methoxyphenyl)hydrazone-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **250** (0.11 g, 36%), mp 116-120 °C; λ_{max} 418 nm (ε 23,000) ($\lambda_{1/2}$ 80 nm); δ_H 7.77 (1H, d, ^3J 7.7), 7.43 (1H, d, ^3J 7.7), 7.28 (4H, m), 6.86 (2H, d, ^3J 9.0), 3.76 (3H, s) and 2.54 (3H, s); δ_C 165.71 (quat), 136.93 (quat), 127.87 (CH), 125.34 (CH), 121.01 (CH), 115.33 (2 × CH), 114.67 (2 × CH), 110.66 (CH), 55.52 (CH_3), and 14.39 (CH_3).

3.5.3 Azamethine dyes – small-scale

Azo to azamethine conversion

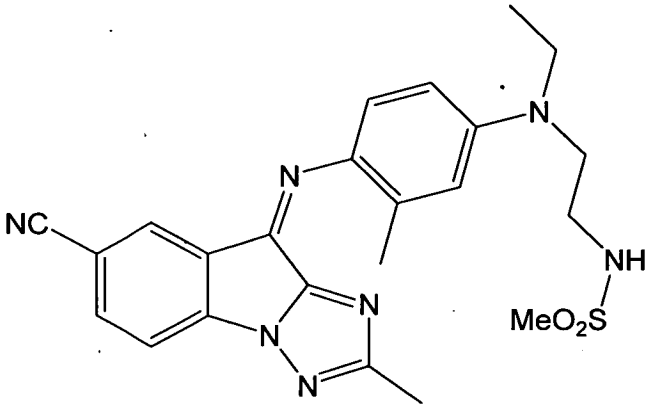


To a solution of the azo dye of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **250** (0.05 g, 0.16 mmol) in methanol (10 cm^3) and THF (13 cm^3) was added separate aqueous solutions (2 cm^3) of Kodak CD3 developer (54 mg, 0.2 mmol), potassium carbonate (28 mg, 0.2 mmol) and potassium persulfate (108 mg, 0.4 mmol). The reaction mixture was stirred for several minutes as the colour change from yellow to magenta was observed. The reaction mixture was extracted with ethyl acetate (4 × 10 cm^3) and the combined organic layers washed with water (3 × 10 cm^3) and dried over $MgSO_4$.

TLC showed the reaction had not reached completion, but the two dyes were separated by column (ethyl acetate and light petroleum), giving the azamethine dye **241** (32 mg) and the unreacted azo dye **250** (20 mg). This was then reacted again in the same way, this time with stirring for 1-2 h to ensure complete conversion. Ethyl acetate work up then gave the azamethine dye **241** (17 mg, total yield 68%); λ_{max} (ethyl acetate) 496 nm (ε 27,000) ($\lambda_{1/2}$ 80 nm); δ_H 8.17 (1H, d, ^3J 8.7), 7.85 (1H, d, ^3J 7.4), 7.42 (2H, d, ^3J 4.0), 7.23 (1H, m), 6.63 (1H, d, ^3J 2.7), 6.59 (1H, s), 4.63 (1H, bt, ^3J 6.4), 3.68 (2H, t, ^3J 6.4), 3.53 (2H, q, ^3J 7.0), 3.33 (2H, q, ^3J 6.3), 2.90 (3H, s), 2.49

(3H, s) 2.45 (3H, s) and 1.18 (3H, t, ^3J 7.0); *m/z* 439 (M^+ 4%), 330 (31), 305 (27), 277 (27), 239 (60), 211 (71), 187 (50), 144 (47), 99 (48), 85 (60), 71 (81) and 43 (100). UV-vis results in various solvents: λ_{max} (methanol) 505 nm ($\lambda_{1/2}$ 100 nm), λ_{max} (chloroform) 495 nm ($\lambda_{1/2}$ 90 nm), λ_{max} (acetonitrile) 497 nm ($\lambda_{1/2}$ 90 nm), λ_{max} (toluene) 492 nm ($\lambda_{1/2}$ 80 nm).

2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236

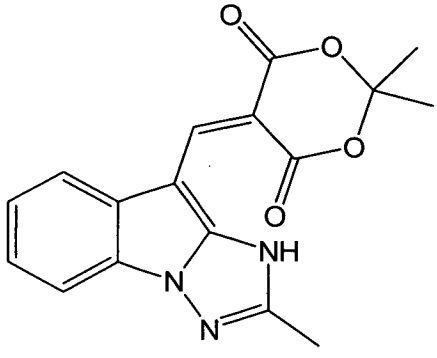


To a solution of 2-methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** (60 mg, 0.31 mmol) in methanol (5 cm^3) was added separate solutions (water, 3 cm^3) of Kodak CD3 developer (95 mg, 0.35 mmol), potassium carbonate (48 mg, 0.35 mmol) and potassium persulfate (189 mg, 0.7 mmol). The reaction mixture was then stirred overnight at room temperature to ensure complete dye formation. It was then added to water (20 cm^3) and extracted with ethyl acetate (5 × 10 cm^3). The combined organic layers washed with water (3 × 5 cm^3) and dried over $MgSO_4$ for ~2 h. The crude product was purified by column chromatography (ethyl acetate as eluent) the third component being the dye **246** obtained as a dark magenta semi-solid (20 mg, 14%); λ_{max} (ethyl acetate) 522 nm (ε 23,000) ($\lambda_{1/2}$ 70 nm); λ_{max} (methanol) 527 nm ($\lambda_{1/2}$ 90 nm); (Found: M^+ 463.1791. $C_{23}H_{25}N_7O_2S$ requires *M* 463.1791); δ_H 8.48 (1H, d, ^3J 9.0), 8.07 (1H, d, ^3J 1.5), 7.65 (1H, dd, ^3J 8.0 and 1.5), 7.46 (1H, d, ^3J 9.0), 6.66 (1H, d, ^3J 3.2), 6.61 (1H, s), 4.67 (1H, bt, ^3J 6.5), 3.57 (2H, t, ^3J 6.5), 3.47 (2H, q, ^3J 7.1), 3.34 (2H, q, ^3J 6.5), 2.92 (3H, s), 2.52 (3H, s) 2.50 (3H, s) and 1.18 (3H, m); *m/z* 463 (M^+ 12%), 388 (18), 355 (67), 325 (21), 242 (51), 209 (100), 168 (60), 116 (86), 64 (65) and 42 (63).

3.5.4 Meldrum's acid dyes

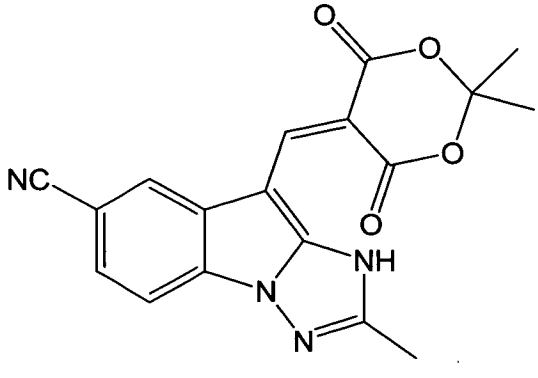
Generally each coupler (~1 mmol) and methoxymethylene Meldrum's acid **256** (~1 mmol) were stirred in acetonitrile (2.5 cm^3) at room temperature for up to 3 days.[99] Usually a precipitate was obtained, filtered and dried under vacuum to give the pure dye product.

2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231



2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (190 mg, 1.11 mmol) and methoxymethylene Meldrum's acid **256** (207 mg, 1.11 mmol) gave no precipitate so the solvent was removed and the crude product purified by Flashtube column (ethyl acetate and DCM as eluent) to give as the second component dye **257** as a bright yellow solid (60 mg, 17%), mp 168-170 °C; λ_{max} (ethyl acetate) 428 nm (ε 47,000) ($\lambda_{1/2}$ 40 nm); λ_{max} (methanol) 421 nm ($\lambda_{1/2}$ 50 nm); (Found: M^+ 325.1061. $C_{17}H_{15}N_3O_4$ requires *M* 325.1063); δ_H 11.99 (1H, bs), 8.54 (1H, s), 7.83 (1H, dd, ^3J 7.2 and 1.2), 7.61 (1H, dd, ^3J 7.2 and 1.2), 7.30 (2H, m), 2.59 (3H, s) and 1.69 (6H, s); δ_C 165.46 (quat), 152.55 (quat), 146.41 (quat), 140.38 (CH), 132.04 (quat), 128.88 (quat), 125.50 (CH), 124.10 (CH), 119.11 (CH), 110.61 (CH), 103.19 (2 × quat), 93.95 (quat), 92.10 (quat), 26.73 (2 × CH_3) and 12.42 (CH_3); *m/z* 325 (M^+ 10%), 223 (66), 183 (43), 154 (60), 127 (53), 103 (33), 75 (36), 63 (37) and 43 (100).

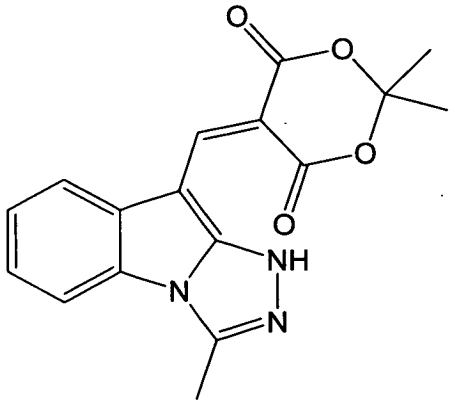
2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236



2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** (200 mg, 1.02 mmol) and methoxymethylene Meldrum's acid **256** (207 mg, 1.02 mmol) gave an orange precipitate found to be the desired dye **258** (105 mg, 29%), mp 180-190 °C (decomp); λ_{max} (ethyl acetate) 427 nm (ε 64,000) ($\lambda_{1/2}$ 35 nm); λ_{max} (methanol) 424 nm ($\lambda_{1/2}$ 40 nm); (Found: M^+ 350.1015. $C_{18}H_{14}N_4O_4$

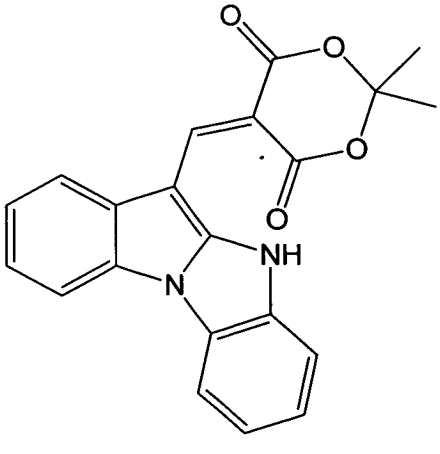
requires *M* 350.1018); δ_H 11.92 (1H, bs), 8.55 (1H, s), 8.17 (1H, s), 7.75 (1H, d, ^3J 8.3), 7.55 (1H, dd, ^3J 8.3 and 1.2), 2.63 (3H, s) and 1.72 (6H, s); *m/z* 350 (M^+ 4%), 277 (9), 248 (15), 225 (20), 197 (78), 169 (20), 118 (100), 89 (71), 63 (73) and 43 (72). The dye **258** proved to be too poorly soluble in both $CDCl_3$ and deuteriated DMSO to obtain an adequate ^{13}C NMR spectrum.

3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole 240



3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** (200 mg, 1.17 mmol) and methoxymethylene Meldrum's acid **256** (218 mg, 1.17 mmol) gave a yellow precipitate found to be the desired dye product **259** (213 mg, 56%), mp 215-225 °C (decomp); λ_{max} (ethyl acetate) 428 nm (ε 40,000) ($\lambda_{1/2}$ 40 nm); (Found: M^+ 325.1062. $C_{17}H_{15}N_3O_4$ requires *M* 325.1063); δ_H 11.94 (1H, bs), 8.49 (1H, s), 7.8 (1H, d, ^3J 7.9), 7.51 (1H, d, ^3J 7.9), 7.35 (1H, t, ^3J 7.4), 7.24 (1H, d, ^3J 7.4), 2.79 (3H, s) and 1.70 (6H, s); δ_C 165.48 (quat), 150.79 (quat), 141.94 (quat), 139.96 (CH), 135.60 (quat), 127.13 (quat), 126.34 (CH), 123.81 (CH), 119.45 (CH), 111.56 (CH), 103.10 (2 × quat), 93.63 (quat), 92.43 (quat), 26.75 (2 × CH_3) and 11.63 (CH_3); *m/z* 325 (M^+ 21%), 267 (11), 223 (100), 182 (21), 154 (83), 127 (67), 103 (33), 75 (27), 63 (18) and 43 (24).

Indolo[1,2-*a*]benzimidazole 238



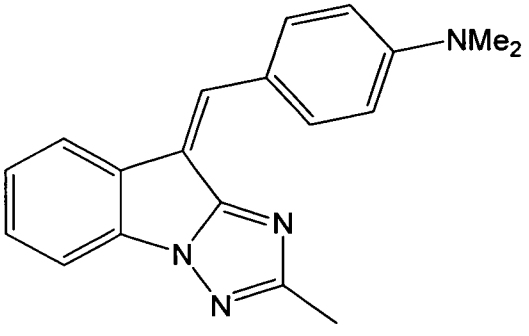
Indolo[1,2-*a*]benzimidazole **238** (200 mg, 0.97 mmol) and methoxymethylene Meldrum's acid **256** (181 mg, 0.97 mmol) gave a yellow brown precipitate found to be the desired dye 2,2-dimethyl-5-(10*H*-indolo[1,2-*a*]benzimidazol-11-yl-methylene)-1,3-dioxan-4,6-dione **260** (120 mg, 34%); λ_{max} (ethyl acetate) 445 nm (ε 46,000) ($\lambda_{1/2}$ 35 nm); λ_{max} (methanol) 442 nm ($\lambda_{1/2}$ 45 nm); δ_H 11.77 (1H, bs), 8.61 (1H, s), 7.84 (2H, d, ^3J 3.9), 7.69 (1H, dd, ^3J 5.2 and 3.1), 7.54 (1H, d, ^3J 3.9), 7.41 (2H, d, ^3J

3.9), 7.32 (2H, dd, ^3J 5.2 and 3.1) and 1.70 (6H, s); *m/z* 360 (M^+ 2%), 302 (21), 258 (100), 229 (86), 205 (60), 176 (28), 140 (39), 115 (73), 102 (56), 76 (59), 63 (60) and 44 (79).

3.5.5 Methine dyes

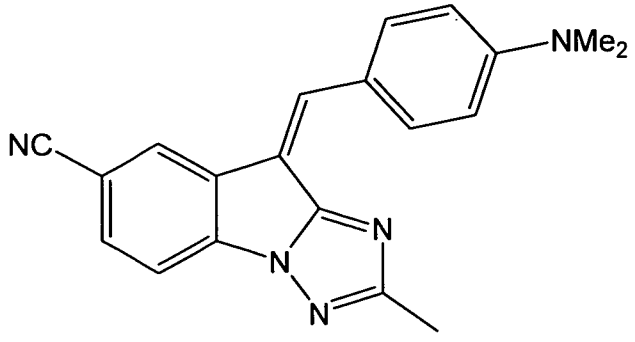
Typically, these dyes were formed by treating a suspension of the coupler (~1 mmol) and *p*-dimethylaminobenzaldehyde (~1 mmol) in toluene (2 cm^3) with acetic acid (1 drop) and piperidine (1 drop).[103] The reaction mixture was stirred at room temperature overnight and usually a precipitate formed which was filtered and dried to give the pure dye.

2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231



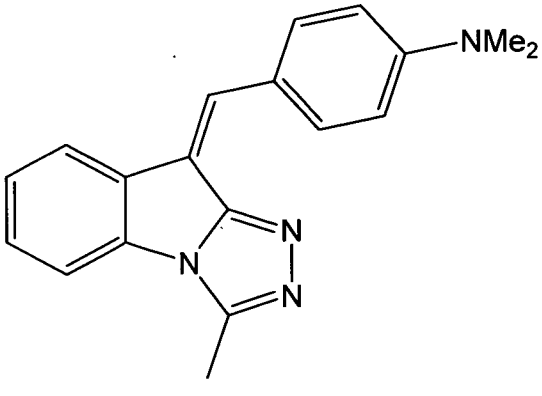
2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (230 mg, 1.35 mmol) and *p*-dimethylaminobenzaldehyde (200 mg, 1.35 mmol) gave no precipitate so the solvent was removed and the crude product was purified by trituration with hexane to give yellow crystals of the desired product dye *9-(4-dimethylaminophenyl)methylene-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **261** (120 mg, 37%), mp 168-170 °C (decomp); λ_{max} (ethyl acetate) 428 nm (ε 45,000) ($\lambda_{1/2}$ 100 nm); λ_{max} (methanol) 443 nm ($\lambda_{1/2}$ 100 nm); (Found: M^+ 302.1535. $C_{19}H_{18}N_4$ requires *M* 302.1532); δ_H 8.61 (2H, d, ^3J 9.0), 7.85 (1H, dd, ^3J 7.6 and 1.3), 7.64 (1H, dd, ^3J 7.6 and 1.3), 7.62 (1H, s), 7.44 (1H, td, ^3J 7.6 and 1.2), 7.39 (1H, td, ^3J 7.6 and 1.2), 6.95 (2H, d, ^3J 9.0), 3.22 (6H, s) and 2.76 (3H, s); δ_C 165.40 (quat), 152.18 (quat), 140.01 (quat), 134.55 (CH), 134.23 (2 × CH), 132.23 (quat), 127.42 (CH), 124.81 (CH), 123.19 (2 × quat), 120.28 (CH), 113.29 (quat), 112.11 (2 × CH), 110.60 (CH), 40.46 (2 × CH_3) and 15.47 (CH_3); *m/z* 302 (M^+ 100%), 260 (9), 200 (37), 170 (23), 148 (56), 87 (82) and 43 (86).

2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236



2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** (200 mg, 1.02 mmol) and *p*-dimethylaminobenzaldehyde (150 mg, 1.02 mmol) gave a red orange precipitate found to be the desired dye *9-(4-dimethylaminophenyl)methylene-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole-7-carbonitrile* **262** (127 mg, 38%), mp 260-270 °C (decomp); λ_{max} (ethyl acetate) 460 nm (ε 33,000) ($\lambda_{1/2}$ 70 nm); λ_{max} (methanol) 470 nm ($\lambda_{1/2}$ 70 nm); (Found: M^+ 327.1481. $C_{20}H_{17}N_5$ requires *M* 327.1484); δ_H 8.41 (2H, d, ^3J 9.0), 7.88 (1H, s), 7.52 (1H, d, ^3J 2.8), 7.18 (1H, dd, ^3J 8.3 and 2.8), 7.11 (1H, d, ^3J 8.3), 6.72 (2H, d, ^3J 9.0), 3.05 (6H, s) and 2.55 (3H, s); δ_C 166.47 (quat), 158.18 (quat), 152.51 (quat), 136.61 (CH), 135.63 (quat), 134.62 (2 × CH), 132.24 (quat), 130.67 (CH), 123.45 (CH), 121.95 (2 × quat), 111.59 (2 × CH), 110.57 (CH), 109.84 (quat), 107.39 (quat), 39.93 (2 × CH_3) and 14.99 (CH_3); *m/z* 327 (M^+ 1%), 209 (3), 196 (5), 148 (12), 128 (3), 91 (100), 6 (39) and 45 (45).

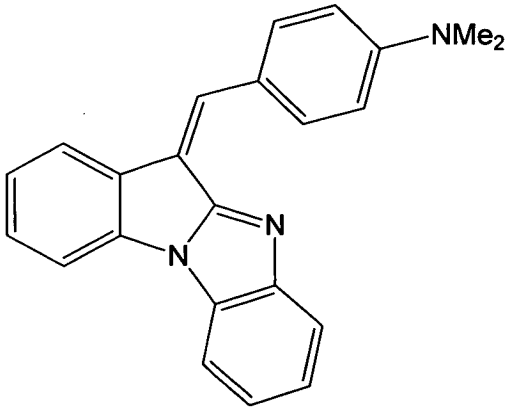
3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole 240



3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** (200 mg, 1.17 mmol) and *p*-dimethylaminobenzaldehyde (174 mg, 1.17 mmol) gave no precipitate, so the toluene was removed and the crude product triturated from ethyl acetate, to give the desired dye product *9-(4-dimethylaminophenyl)methylene-3-methyl-9H-[1,2,4]triazolo[4,3-a]indole* **263** as a yellow orange solid (131 mg, 37%), mp 247-249 °C; λ_{max} (ethyl acetate) 423 nm (ε 38,000) ($\lambda_{1/2}$ 75 nm); (Found: M^+ 302.1534. $C_{19}H_{18}N_4$ requires *M* 302.1532); δ_H 8.74 (2H, d, ^3J 8.6), 7.93 (1H, d, ^3J 7.8), 7.61 (1H, s), 7.50 (3H, m), 7.01 (2H, d, ^3J 8.6), 3.26 (6H, s) and 2.98 (3H, s); δ_C

157.97 (quat), 151.41 (quat), 144.13 (quat), 134.95 (quat), 133.48 (2 × CH), 132.45 (CH), 126.66 (CH), 125.00 (CH), 122.59 (2 × quat), 120.53 (CH), 111.68 (quat), 111.56 (2 × CH), 111.16 (CH), 39.92 (2 × CH_3) and 11.65 (CH_3); *m/z* 302 (M^+ 100%), 260 (34), 218 (9), 151 (11) and 130 (10).

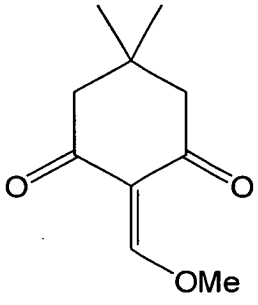
Indolo[1,2-*a*]benzimidazole 238



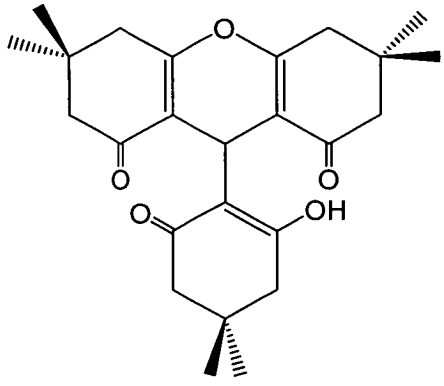
Indolo[1,2-*a*]benzimidazole **238** (206 mg, 1 mmol) and *p*-dimethylaminobenzaldehyde (149 mg, 1 mmol) gave a thick orange precipitate found to be the desired product dye *9-(4-dimethylaminophenyl)methylene-9H -indolo[1,2-a]benzimidazole* **264** (100 mg, 30%), mp 200-210 °C (decomp); λ_{max} (ethyl acetate) 441 nm (ε 31,000) ($\lambda_{1/2}$ 90 nm); λ_{max} (methanol) 447 nm ($\lambda_{1/2}$ 90 nm); (Found: M^+ 337.1577. $C_{23}H_{19}N_3$ requires *M* 337.1579); δ_H 8.62 (2H, d, ^3J 9.0), 8.01 (1H, dd, ^3J 7.0 and 2.0), 7.81 (2H, d, ^3J 7.8), 7.47 (1H, d, ^3J 7.6), 7.45 (1H, s), 7.26 (2H, m), 7.11 (1H, dd, ^3J 7.6 and 2.0), 6.76 (2H, d, ^3J 9.0) and 3.00 (6H, s); δ_C 133.69 (2 × CH), 133.24 (CH), 126.93 (CH), 123.26 (CH), 122.85 (quat), 121.56 (CH), 119.50 (CH), 118.03 (CH), 111.68 (quat), 111.55 (2 × CH), 110.64 (CH), 110.58 (CH) and 39.98 (2 × CH_3); *m/z* 337 (M^+ 10%), 84 (98), 56 (59), 43 (100) and 29 (64). The dye **264** was insufficiently soluble in $CDCl_3$ and DMSO for a full ^{13}C NMR spectrum, so an incomplete one has been reported here.

3.5.6 Other dyes

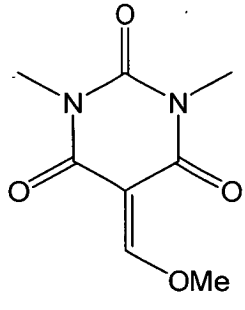
Attempted synthesis of methoxymethylene dimedone



5,5-Dimethyl-1,3-cyclohexanedione (dimedone) (14.0 g, 0.1 mol) in trimethylorthoformate (70 cm^3) was heated under reflux for 2 h.[104] A white precipitate formed on cooling and the reaction mixture was left overnight to increase the yield; this was then filtered and dried under vacuum. Methoxymethylene dimedone was not obtained but a trimeric xanthene species **265** (12.38 g, 90%), mp 218-220 °C [lit.,[106] 222 °C]; δ_H 9.84 (1H, s), 4.30 (1H, s), 2.40 (4H, s), 2.31 (2H, s), 2.24 (4H, s), 1.98 (2H, s), 1.08 (6H, s), 0.98 (6H, s) and 0.94 (6H, s); δ_C 198.61 (2 × quat), 197.07 (quat), 171.78 (quat), 165.56 (2 × quat), 115.13 (quat), 112.78 (2 × quat), 51.09 (CH_2), 50.19 (2 × CH_2), 42.86 (CH_2), 40.56 (2 × CH_2), 29.24 (CH_3), 27.79 (CH_3) and 26.80 (CH_3); *m/z* 412 (M^+ 66%), 328 (100), 273 (93), 244 (71), 217 (47), 161 (50), 83 (78), 55 (75) and 41 (61).



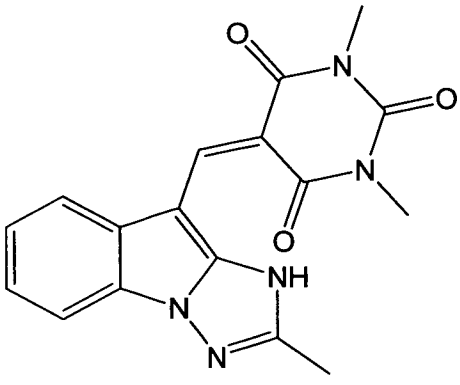
***N,N*-Dimethylbarbituric acid dye**



N,N-Dimethylbarbituric acid (1.56 g, 0.01 mol) was heated under reflux in trimethylorthoformate (10 cm^3) for 30 min.[104] A yellow precipitate formed on cooling and was filtered off and dried under vacuum. This product was found to be methoxymethylene-*N,N*-dimethylbarbituric acid **266** with a significant and inseparable impurity (~20%) of hydroxymethylene-*N,N*-dimethylbarbituric acid (1.36 g, 70%); δ_H 8.81 (1H, s), 4.45 (3H, s), 3.49 (3H, s) and 3.47 (3H, s); [δ_H (hydroxy) 9.42 (1H, s) and 3.62 (6H, s)]; δ_C 175.15 (CH), 163.09 (quat), 154.43 (quat), 101.55 (quat), 101.16 (quat), 66.23 (CH_3), 28.57 (CH_3) and 27.97 (CH_3); [δ_C (hydroxy) 160.27 (CH), 152.25

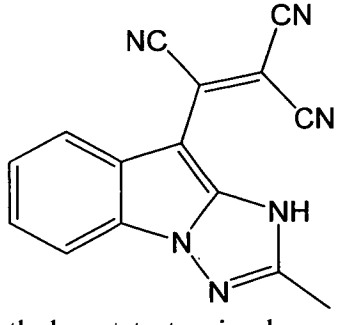
(quat), 150.37 (quat), 109.95 (quat), 107.86 (quat) and 29.82 (2 × CH_3)]; *m/z* 198 (methoxy M^+ 9%), 184 (hydroxy M^+ 80), 156 (99), 99 (100), 82 (57), 71 (84), 58 (68) and 42 (71).

2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (195 mg, 1.14 mmol) was dissolved in



acetonitrile (3 cm^3) and crude 5-methoxymethylene-*N*,*N*-dimethylbarbituric acid **266** (210 mg, 1.14 mmol) was added; the resulting reaction mixture was stirred at room temperature for 3 days.[99] The yellow precipitate formed was filtered off and dried, and found by proton NMR spectroscopy still to contain the unreacted hydroxy species, but was mostly the desired dye **267** (176 mg, 45%). Purification by Flashtube column (methanol and toluene as eluent) gave only 29 mg of **267** as the second component, the only identifiable product retrieved; λ_{max} (ethyl acetate) 446 nm (ε 34,000) ($\lambda_{1/2}$ 40 nm); (Found: M^+ 337.1176. $C_{17}H_{15}N_5O_3$ requires *M* 337.1175); δ_H 8.59 (1H, s), 7.84 (1H, d, ^3J 8.0), 7.60 (1H, d, ^3J 7.4), 7.24 (2H, m), 3.33 (3H, s), 3.25 (3H, s) and 2.64 (3H, s); *m/z* 337 (M^+ 100%), 322 (21), 250 (17), 235 (23), 223 (13), 154 (15), 127 (14) and 69 (15). The dye **267** appeared to be too poorly soluble in both $CDCl_3$ and *d*-DMSO to obtain a ^{13}C NMR spectrum.

Attempted synthesis of 9-tricyanovinyl-2-methyl-1*H*-[1,2,4]triazolo[1,5-*a*]indole



Tetracyanoethylene (173 mg, 1.35 mmol) was added to a solution of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (231 mg, 1.35 mmol) in DMF (2 cm^3), stirring at ~25-40 °C.[107] The reaction mixture was then heated under reflux for 3-4 h. The solvent was removed under high vacuum and the crude product was triturated with ethyl acetate to give brown crystals. These were then purified further by Flashtube column (ethyl acetate as eluent) to give a pure product of orange solid believed to be *9-tricyanovinyl-2-methyl-1H-[1,2,4]triazolo[1,5-a]indole* **268** (99 mg, 27%), mp 185-187 °C; λ_{max} (ethyl acetate) 324 nm (ε 10,000) ($\lambda_{1/2}$ 80 nm); δ_H 8.17 (1H, d, ^3J 7.8),

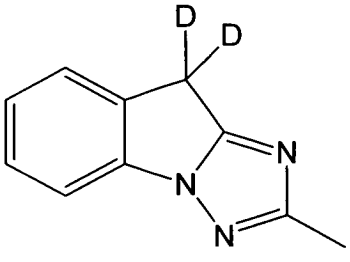
7.55 (1H, t, ^3J 7.8), 7.37 (1H, d, ^3J 7.8), 7.26 (1H, t, ^3J 7.8) and 2.50 (3H, s); δ_C 168.96 (2 × quat), 153.93 (quat), 144.87 (quat), 137.66 (quat), 136.13 (CH), 127.53 (CH), 127.33 (CH), 125.32 (2 × quat), 111.80 (CH), 111.48 (quat), 110.52 (quat) and 14.75 (CH_3); mass spectrometry by both electron impact and fast atom bombardment showed no sign of the correct mass peak and the CHN result was far out from the calculated figures.

3.6 Other Chemistry of Couplers

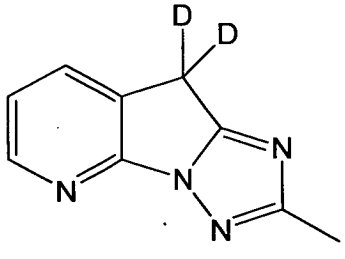
3.6.1 Deuterium exchange

The coupler was dissolved in deuteriated methanol and analysed by proton NMR spectroscopy at regular intervals looking for loss of the methylene peak.

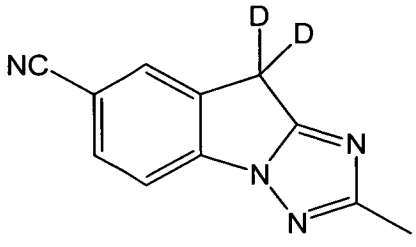
2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231 (8 mg, 0.058 mmol) showed only partial deuteriation after 3 days, so diisopropylethylamine (Hünig's base) (5 cm^3) was added, which almost immediately gave the deuteriated species *2-methyl-9[$^2H_2$]-[1,2,4]triazolo[1,5-a]indole* **D-231**; δ_H (d_4-methanol) 7.58 (3H, m), 7.39 (1H, m) and 2.52 (3H, s).



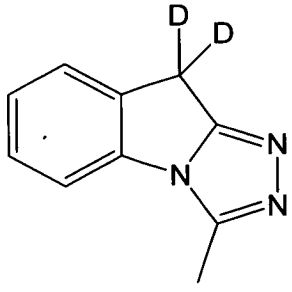
2-Methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene 232 (8 mg, 0.047 mmol) showed complete deuteriation after 1 h, *2-methyl-9-[$^2H_2$]-1,3,4,5-tetraaza-cyclopenta[a]indene* **D-232**; δ_H (d_4-methanol) 8.41 (1H, m), 8.15 (1H, m), 7.40 (1H, m) and 2.58 (3H, s).



2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile 236 (8 mg, 0.041 mmol) was deuteriated in under 15 min, to give *2-methyl-9-[$^2H_2$]-[1,2,4]-triazolo[1,5-a]indole-7-carbonitrile* **D-236**; δ_H (d_4-methanol) 7.88 (1H, s), 7.77 (1H, d, ^3J 8.2), 7.60 (1H, d, ^3J 8.2) and 2.40 (3H, s).

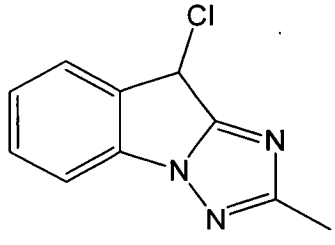


3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole 240 (10 mg, 0.058 mmol) showed no deuteriation after 24 h, so diisopropylethylamine (Hünig's base) (5 cm^3) was added. Within minutes the deuteriated species *3-methyl-9-[$^2H_2$]-[1,2,4]triazolo[4,3-a]indole* **D-240** was observed; δ_H (d_4-methanol) 7.70 (2H, m), 7.51 (2H, m) and 2.84 (3H, s).



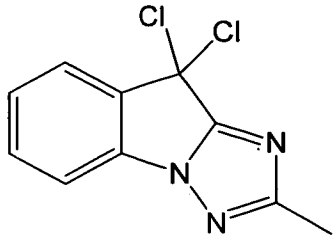
3.6.2 Coupling-off group

9-Chloro-2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 269



N-Chlorosuccinimide (0.11 g, 0.78 mmol) was added portion-wise to a solution of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (0.1 g, 0.59 mmol) in DCM (8 cm^3) and stirred at room temperature for 3 h.[109] TLC appeared to show the reaction mixture contained the 9,9-dichloro species so it was stirred together with an aqueous solution of tin (II) chloride (30 cm^3, 0.5 g, 2.6 mmol) for 30 min to reduce back to the desired monochloro product. This had the effect of reducing much of the material back to the original coupler, so then another 1 equivalent of *N*-chlorosuccinimide was added and the mixture stirred for 1 h. The reaction mixture appeared to have reached an equilibrium so was then worked up by washing with dilute HCl (1M, 10 cm^3) and drying over $MgSO_4$. The crude product was purified by column (ethyl acetate and light petroleum as eluent) to give as the second component *9-chloro-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **269** as a pink crystalline solid (15

mg, 13%); δ_H (400 MHz) 7.56 (1H, dd, ^3J 7.6 and 0.7), 7.44 (2H, m), 7.26 (1H, td, ^3J 7.6 and 1.5), 5.67 (1H, s) and 2.48 (3H, s); *m/z* (electrospray) ES+: 218 (100%), 206 (M^+ 56) and 172 (17).

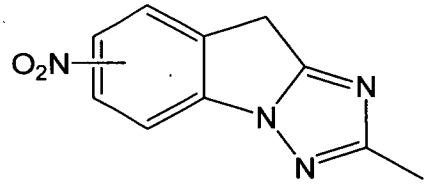


The first component from the column was *9,9-dichloro-2-methyl-9H-[1,2,4]triazolo[1,5-a]indole* **270** as a pale orange solid (30 mg, 21%); δ_H (400 MHz) 7.74 (1H, d, ^3J 7.5), 7.42 (2H, m), 7.31 (1H, td, ^3J 7.5 and 1.2) and 2.50 (3H, s); *m/z* (electrospray) ES+: 330 (100%), 281 (85), 240 (M^+ 39) and 218 (74).

Another attempt at chlorinating **231** on the same scale involved stirring with sulfuryl chloride (80 mg, 0.59 mmol) in DCM (5 cm^3) at room temperature for 1 h,[108] but the conditions were found to be too vigorous and an inseparable mixture of many crude resulted.

3.6.3 Nitration

Attempted nitration of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231

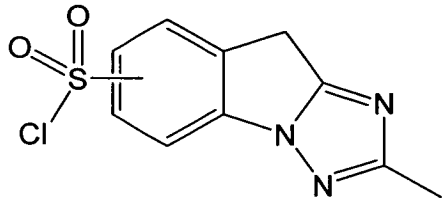


2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (0.1 g, 0.59 mmol) was dissolved in glacial acetic acid (2.5 cm^3) and added drop-wise, with stirring, to a solution of concentrated nitric acid (0.05 cm^3, g 1.52) in acetic acid (3 cm^3) with cooling in cold water.[68] This was allowed to warm up to warm temperature and stirred for 2 h. The reaction mixture was added to ice water (10 cm^3) and then left overnight to allow precipitation. As there was only a small quantity of precipitate the reaction mixture was extracted with ethyl acetate (4 × 10 cm^3), washed with water (5 × 5 cm^3) and dried over $MgSO_4$. The crude product was separated by column chromatography (ethyl acetate as eluent) and the third component was a mixture which did appear to contain one nitro product, although in insufficient quantity (20 mg) to establish which isomer. The major product in this mixture was a dinitro product; *m/z* (electrospray) ES-: 260 (M^+ 100%), 215 (37), 179 (38) and 95 (52). The second and largest component from the column (40 mg) was found to be unreacted coupler.

Initially a more conventional nitration reaction was carried out with the reagents dissolved in concentrated sulfuric acid but this was found to be too vigorous because a mixture of di- and trinitro isomers were produced; *m/z* (electrospray) ES-: 305 (M^+ 100%) and 260 (48).

3.6.4 Chlorosulfonation

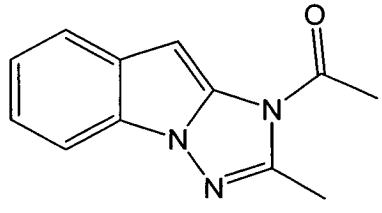
Attempted chlorosulfonation of 2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole 231



2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (100 mg, 0.59 mmol) was added portion-wise to chlorosulfonic acid (5 cm^3, 0.076 mol) cooled on an ice bath.[110] The reaction mixture was stirred at room temperature overnight then the reaction mixture was cautiously added to water and a brown precipitate was formed. This was filtered off giving only 20 mg of material which could not be characterised by NMR spectroscopy, although there were some weak peaks which corresponded with those of the original coupler **231** but without the methylene peak. This suggests chlorosulfonation could have taken place at the coupling site instead of on the benzene ring.

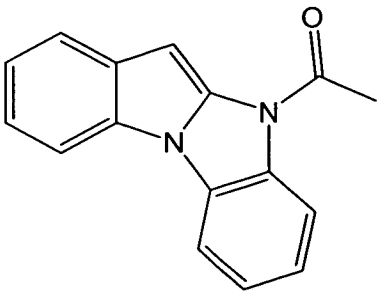
3.6.5 Acylation

Attempted Preparation of 1-Acetyl-2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole



2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (50 mg, 0.3 mmol) was dissolved in acetic anhydride (3 cm^3) and heated for 5-10 min.[111] The solvent was then removed under high vacuum and then proton NMR of the crude product showed it to be mostly unreacted. Repeating the reaction under reflux for 1 h then resulted in a highly decomposed and indecipherable product, as there was a multitude of peaks in the proton NMR spectrum.

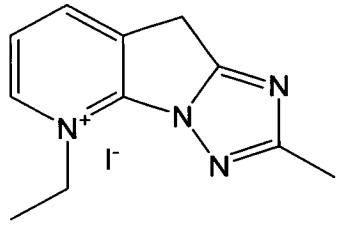
1-Acetylindolo[1,2-*a*]benzimidazole 271



Indolo[1,2-*a*]benzimidazole **238** (100 mg, 0.48 mmol) was dissolved in acetic anhydride (3 cm^3) and heated for ~10 min. The solvent was removed under high vacuum and the crude product purified by column chromatography, which was not entirely successful as the yield was low and the product still impure; 1-acetylindolo[1,2-*a*]benzimidazole **271** (22 mg, 19%); δ_H 8.37 (1H, bs), 7.74 (1H, m), 7.61 (2H, m), 7.27 (2H, m), 7.22 (3H, m), 6.06 (1H, bs) and 2.64 (3H, s).

3.6.6 Quaternisation of the pyridine heteroatom

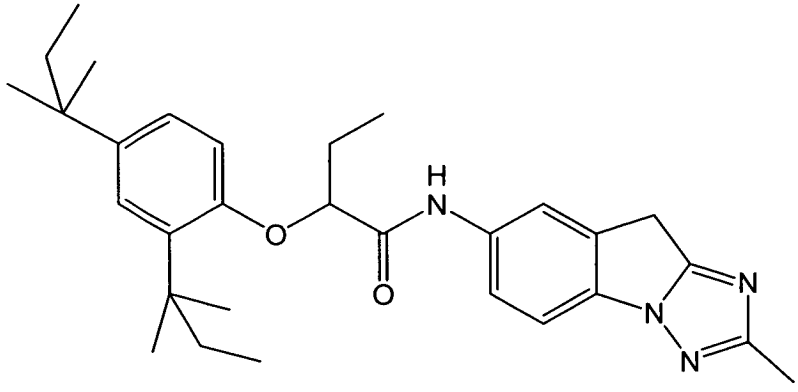
Attempted preparation of 5-ethyl-2-methyl-9*H*-1,3,4,5-triaza-5-azonia - cyclopenta[*a*]indene iodide 272



2-Methyl-9*H*-1,3,4,5-tetraaza-cyclopenta[*a*]indene **232** (100 mg, 0.58 mmol) was dissolved in DCM (10 cm^3), ethyl iodide (91 mg, 0.58 mmol) was added and the reaction mixture stirred overnight.[112] Analysis by LC-MS showed no reaction had occurred so the reaction was repeated in acetonitrile (10 cm^3) with heating under reflux for ~2 h. The solvent was removed and mass spectrometry appeared to show the crude product was a mixture of diethylated species, some of the desired product **272** and unreacted coupler **232**; *m/z* (electrospray) ES+: 229 (64%), 201 (M^+ 68), 175 (100) and 162 (46), ES-: 127 (18) and 119 (100).

3.6.7 Ballasting reactions

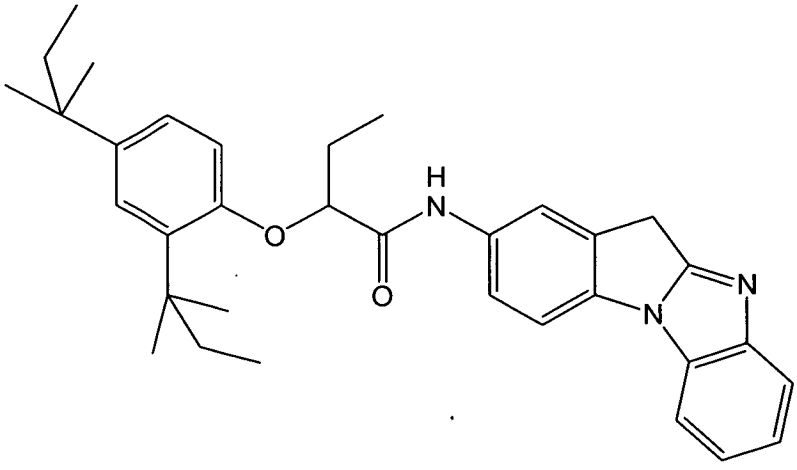
2-[2,4-Bis-(1,1-dimethylpropyl)-phenoxy]-*N*-(2-methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indol-7-yl) butyramide 274



2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indol-7-ylamine **237** (0.75 g, 4 mmol) was dissolved in THF (10 cm^3) with pyridine (4 cm^3), and to this was added drop-wise the acid chloride ballast **273** (2-[2,4-Bis-(1,1-dimethylpropyl)-phenoxy]-butyryl chloride) (1.36 g, 4 mmol) dissolved in THF (6 cm^3).[7] The reaction mixture was then stirred at room temperature overnight. After this time the mixture was added to ice water (100 cm^3) and acidified with concentrated HCl. It was then extracted with ethyl acetate (5 × 20 cm^3) and the combined organic layers washed with water (3 × 10 cm^3) and dried over $MgSO_4$. The crude product was purified by dry flash chromatography (ethyl acetate and light petroleum as eluent) giving as the third component *2-[2,4-Bis-(1,1-dimethylpropyl)-phenoxy]-N-(2-methyl-9H-[1,2,4]triazolo[1,5-a]indol-7-yl) butyramide* **274** as an orange oil (0.49 g, 25%); δ_H (400 MHz) 7.96 (1H, bs), 7.85 (1H, d, ^3J 2.2), 7.37 (1H, d, ^3J 8.5), 7.19 (1H, dd, ^3J 8.5 and 2.2), 7.18 (1H, d, ^3J 2.4), 6.99 (1H, dd, ^3J 8.5 and 2.4), 6.61 (1H, d, ^3J 8.5), 4.63 (2H, t, ^3J 5.5), 3.81 (2H, s), 2.44 (3H, s), 2.05 (2H, q, ^3J 5.5), 1.90 (2H, q, ^3J 4.4), 1.51 (2H, q, ^3J 7.6), 1.42 (3H, s), 1.39 (3H, s), 1.17 (6H, s), 1.08 (3H, t, ^3J 7.3), 0.67 (3H, t, ^3J 7.6) and 0.57 (3H, t, ^3J 7.6); δ_C (400 MHz) 170.31 (2 × quat), 165.50 (quat), 160.37 (quat), 152.96 (quat), 142.24 (quat), 134.87 (quat), 134.77 (quat), 134.68 (quat), 133.05 (quat), 126.59 (CH), 124.56 (CH), 119.58 (CH), 118.54 (CH), 111.16 (CH), 110.90 (CH), 79.54 (CH), 60.32 (quat), 38.71 (CH_3), 37.40 (CH_2), 36.92 (CH_3), 33.68 (CH_2), 28.39 (CH_3), 28.20 (CH_3), 27.87 (CH_2), 26.53 (CH_2), 14.66 (CH_3), 9.77 (CH_3), 9.65 (CH_3) and 9.04 (CH_3); *m/z* (electrospray) ES+:

489 (M^+ 100%), 141 (78) and 100 (61). No accurate mass result was obtained at the Kodak laboratories and all product was used in the coating test.

Attempted Preparation of 2-[2,4-Bis-(1,1-dimethylpropyl)-phenoxy]-*N*-(indolo[1,2-*a*]benzimidazol-2-yl) butyramide

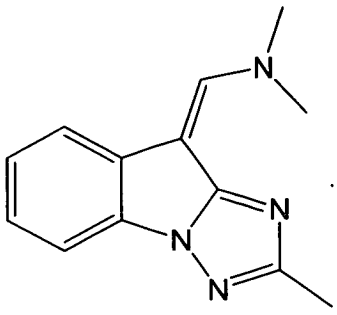


An unpurified sample of 4-(2-methylbenzimidazol-1-yl)-3-nitroaniline **239** (1.2 g, ~4.5 mmol) was dissolved in THF (15 cm^3) with pyridine (4 cm^3) and to this was added the acid chloride ballast **273** (1.53 g, 4.5 mmol) in THF (8 cm^3). The reaction mixture was then stirred at room temperature overnight, then added to ice water (100 cm^3) and acidified with concentrated HCl. This was then extracted with ethyl acetate (5 × 25 cm^3) and the combined organic layers washed with water (3 × 15 cm^3) and dried over $MgSO_4$ overnight. After removal of the solvent the crude product was mistakenly put through a column, which evidently decomposed the desired product, as many more components came out than were shown by TLC of the crude mixture, none of these being the one intended.

3.6.8 Dimethylamine methine species

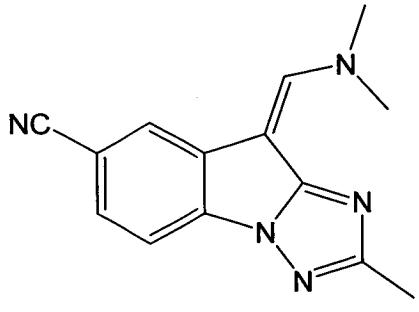
Typically the coupler (~1 mmol) was dissolved in toluene (5 cm^3) and *N,N*-dimethylformamide dimethylacetal (~1 mmol) was added, then the reaction mixture heated under reflux for 1 h.[113] Either a precipitate was formed, in which case it was filtered off and dried; or the solvent was removed and the pure product obtained by column chromatography.

_N_-(2-Methyl-9_H_-[1,2,4]triazolo[1,5-_a_]indol-9-ylmethylene)dimethylamine 275



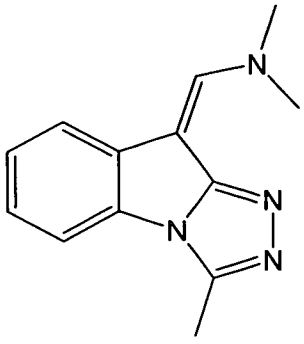
2-Methyl-9*H*-[1,2,4]triazolo[1,5-*a*]indole **231** (227 mg, 1.33 mmol) in neat *N,N*-dimethylformamide dimethylacetal (5 cm^3), heated under reflux for 1 h provided a crude product which was purified by Flashtube column (methanol and DCM as eluent) to give as the third component *N-(2-methyl-9H-[1,2,4]triazolo[1,5-a]indol-9-ylmethylene)dimethylamine* **275** as a brown semi-crystalline solid (78 mg, 26%), mp 125-130 °C; (Found: M^+ 226.1217. $C_{13}H_{14}N_4$ requires *M* 226.1219); δ_H 7.50 (1H, dd, ^3J 6.7 and 2.2), 7.40 (1H, dd, ^3J 6.7 and 2.2), 7.21 (1H, s), 7.12 (2H, m), 3.52 (6H, bs) and 2.47 (3H, s); δ_C 163.69 (quat), 142.72 (CH), 132.16 (quat), 130.25 (quat), 122.98 (CH), 122.85 (CH), 116.40 (CH), 109.92 (CH), 88.09 (quat) and 14.91 (CH_3); *m/z* 226 (M^+ 50%), 211 (34), 197 (56), 184 (69), 160 (26), 143 (24), 91 (42), 73 (81) and 42 (100).

9-[1-Dimethylaminomethylidene]-2-methyl-9_H_-[1,2,4]-triazolo[1,5-_a_]indole-7-carbonitrile 276



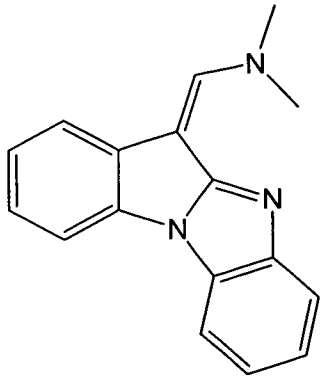
2-Methyl-9*H*-[1,2,4]-triazolo[1,5-*a*]indole-7-carbonitrile **236** (150 mg, 0.77 mmol) and *N,N*-dimethylformamide dimethylacetal (323 mg, 2.72 mmol) in toluene (4 cm^3) was heated under reflux for 3 h. After cooling a brown precipitate formed found to be *9-[1-dimethylaminomethylidene]-2-methyl-9H-[1,2,4]-triazolo[1,5-a]indole-7-carbonitrile* **276** (65 mg, 34%), mp 260-270 °C (decomp); (Found: M^+ 251.1171. $C_{14}H_{13}N_5$ requires *M* 251.1171); δ_H 7.70 (1H, s), 7.55 (1H, d, ^3J 8.3), 7.40 (1H, d, ^3J 8.3), 7.30 (1H, s), 3.85 (3H, bs), 3.32 (3H, bs) and 2.47 (3H, s); δ_C 164.89 (quat), 144.12 (CH), 133.17 (quat), 132.25 (quat), 126.59 (CH), 120.52 (CH), 119.13 (quat), 110.40 (CH), 105.49 (quat), 87.05 (quat) and 14.96 (CH_3); *m/z* 251 (M^+ 40%), 236 (33), 222 (46), 209 (43), 167 (17), 140 (17), 91 (100) and 42 (36).

***N*-(3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indol-9-ylmethylene)dimethylamine 277**



3-Methyl-9*H*-[1,2,4]triazolo[4,3-*a*]indole **240** (200 mg, 1.17 mmol) in neat *N,N*-dimethylformamide dimethylacetal (5 cm^3), heated under reflux for 1 h, gave a brown precipitate found to be *N-(3-methyl-9H-[1,2,4]triazolo[4,3-a]indol-9-ylmethylene)dimethylamine* **277** (89 mg, 34%), mp 164-166 °C; (Found: M^+ 226.1221. $C_{13}H_{14}N_4$ requires *M* 226.1219); δ_H 7.65 (1H, td, ^3J 7.2 and 1.5), 7.47 (1H, s), 7.40 (1H, td, ^3J 7.2 and 1.5), 3.83 (6H, bs) and 3.03 (3H, s); δ_C 157.64 (quat), 142.22 (quat), 141.68 (CH), 135.78 (quat), 129.15 (quat), 124.00 (CH), 122.38 (CH), 116.74 (CH), 110.97 (CH), 87.39 (quat) and 11.70 (CH_3); *m/z* 226 (M^+ 80%), 211 (44), 197 (100), 184 (87), 170 (30), 142 (22), 115 (25), 73 (77) and 44 (59).

***N*-(Indolo[1,2-*a*]benzimidazol-11-ylmethylene)dimethylamine 278**



Indolo[1,2-*a*]benzimidazole **238** (100 mg, 0.48 mmol) and *N,N*-dimethylformamide dimethylacetal (202 mg, 1.7 mmol)) in toluene (5 cm^3) was heated under reflux for 1 h. No precipitate was obtained so the solvent was removed and the crude product purified by Flashtube column (ethyl acetate as eluent), the third component being *N*-(indolo[1,2-*a*]benzimidazol-11-ylmethylene)dimethylamine **278** as a brown semi-solid (70 mg, 56%), (Found: M^+ 261.1262. $C_{17}H_{15}N_3$ requires *M* 261.1266); δ_H 7.68 (2H, td, ^3J 6.5 and 2.6), 7.52 (1H, td, ^3J 7.0 and 1.1), 7.37 (1H, td, ^3J 7.0 and 1.1), 7.22 (1H, s), 7.14 (4H, m) and 3.56 (6H, bs); δ_C 148.24 (quat), 143.01 (CH), 133.70 (quat), 132.24 (quat), 128.82 (quat), 122.75 (CH), 122.33 (CH), 121.95 (CH), 120.64 (CH), 118.68 (CH), 116.05 (CH), 110.06 (CH), 109.97 (CH) and 90.20 (quat); *m/z* 261 (M^+ 41%), 246 (26), 238 (56), 219 (100), 208 (67), 102 (22), 77 (40), 43 (99) and 29 (72).

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