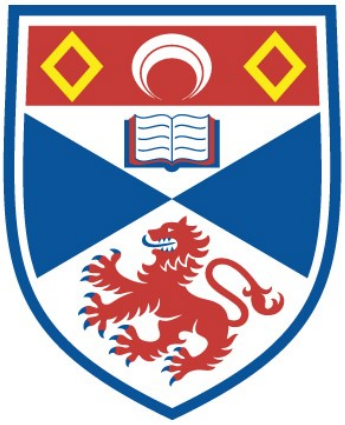
SYNTHESIS OF SOME HETEROARYLATED DIOXOPIPERAZINES

Charles Richard White

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1999

SYNTHESIS OF SOME HETEROARYLATED DIOXOPIPERAZINES

A thesis presented to the University of St. Andrews

for the degree of Doctor of Philosophy

by

Charles Richard White

December 1998

University of St. Andrews

CONTENTS

Declaration

I, Charles Richard White, hereby certify that this thesis has been composed by me, that is an accurate representation of the work undertaken by me in the University of St. Andrews since my admission as a Research Student on 1st October 1995, and that it has not been accepted in any previous application for any Higher Degree or professional qualification.

December 1998 Signed.....

I hereby certify that Charles Richard White has fulfilled the Regulations appropriate to the Degree.

December 1998 Signed.....

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Acknowledgements

I am deeply indebted to Dr. David Smith for his excellent supervision, continual encouragement and enthusiasm during my tenure of this studentship and during the writing of this thesis. His extensive knowledge and occasional threat of "the boot" have been vital in maintaining my continual interest.

I would also like to say thank you to Ciba Speciality Chemicals for their kind co-sponsorship of this work, with a special thanks going to Dr. Gary Wooden and Dr. Cécile Pasquier for their great supervision and guidance.

My many thanks must go to the following for their services during my research: Mrs. M. Smith and Dr. T. Rutherford (nmr), Mr. C. Millar (mass spectra) and Mrs. S. Williamson (microanalysis).

I must also pay special thanks to Dr. Frank Riddell who helped to interpret some of my nmr spectra and for turning a sometimes "black art" into something even I could understand.

I owe a debt of gratitude to Dr. R. A. Aitken and also Dr. R. A. Field for their enthusiastic discussions in all areas of chemistry and who I feel have helped a great deal in my training. I would also like to say thank you to Dr. Douglas Lloyd with whom I have had a great number of fascinating, informative but always informal chats with, and whom has helped keep me sane during the writing this thesis.

I would like to thank my friends in the School of Chemistry, past and present, (here come the Oscars) especially Dr. B. Royles, Dr. C. French, Dr. M. Ritchie, Dr. N. Nicolson, J. Devine, N. Wilson, T. Massil, Dr. V. Patinec, C. Morton and S. Martyr.

My final thanks is to my parents and my beautiful fiancee Joanna for staying with me and always believing.

Dedication

To my one love, Joanna

Abstract

Section 1 (Introduction) provides a short history of pigment development through selected examples. It also details some of the requirements which have to be considered during the formulation of new coloured materials. A brief outline of some synthetic routes towards arylated amino acids and substituted 2,5-dioxopiperazines is also described with the aim of including some of these ideas into the project.

Section 2 (Results and Discussion) develops some of the ideas outlined in Section 1. This Section is split into two parts, namely synthetic approaches to some arylated amino acids and some 3,6-disubstituted-2,5-dioxopiperazines. The former part covers the possible routes towards the desired amino acids and deals with the search for a suitable *N*-protecting group for glycine ethyl ester. It was shown that the propensity for the arylated amino acids either to polymerise or decarboxylate greatly hindered the removal of the various protecting groups examined.

The second part covers the search for a suitable *N*-acyl protecting group to allow the coupling of the 1,4-diprotected-2,5-dioxopiperazine with an aromatic heterocycle. Synthesis of 3,6-bis(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine was successful; however all attempts at debenzylation failed. The synthesis of 3-(1-*t*-butoxycarbonyl-benzimidazol-2-yl)-2,5-dioxopiperazine gave rise to some very interesting spectroscopic data which are discussed in this Section.

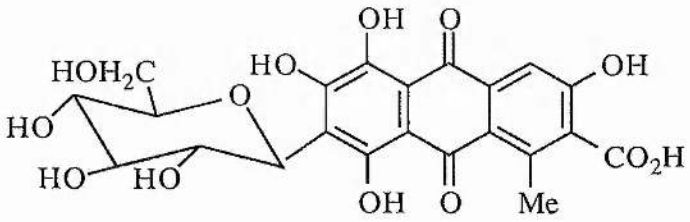
Section 3 (Experimental) details the synthetic procedures used and this is then followed by the **Bibliography**.

Introduction

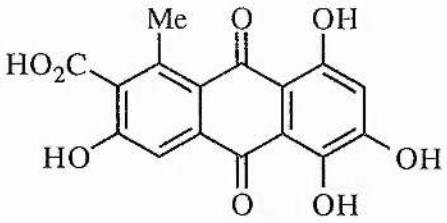
Introduction

A pigment may be defined as a coloured, black or white organic or inorganic solid which is insoluble in its application medium[1]. Pigments are distinct from dyes by their high degree of insolubility in their application medium.

Pigments from plant and animal sources have been known for many thousands of years, for example, the carmine pigments. These pigments are obtained from beetles' shells and have been used by the Aztecs, Greeks and Romans; one type in this family, Kermes carmine, is mentioned in the Old and New Testaments[2]. These polyoxygenated anthraquinone pigments can be produced by precipitating the parent acids, carminic acid (**1**) or kermesic acid (**2**) with iron free alum, to give the two pigments as red aluminium salts.



(1)



(2)

As potential applications increase for pigments then so does the demand for new and higher performing ones. The current pigments commercially available are generally very good for most applications although the demand for new ones still remains. Phthalocyanines are good examples of blue and green pigments which will perform well in some applications, anthraquinones and diketopyrrolopyrroles cover the red end of the market and diazo pigments are well established for use in orange and yellow applications.

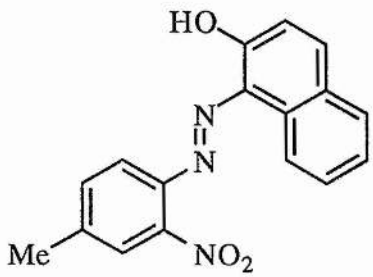
The requirements for a compound to be useful in pigment applications are manyfold. The main criteria are, however, that they are stable to heat and light, they possess good colour strength and that they are insoluble in any medium to which they may be exposed or with which they may come into contact.

It was postulated that a compound derives its colour from particular groups called the chromophores, which comprises a conjugated system of double bonds[3]. Visible light is absorbed when the energy difference between a filled and the lowest-lying unfilled energy level is sufficiently small that excitation of an electron is brought about by radiation in the visible spectrum. Auxochromes, which are electron donating or accepting groups, for example, halogens, NH_2, NO_2 *etc.*, can modify or intensify the colour to suit the requirements.

The other main requirement which must be fulfilled is that these compounds must be insoluble. This is generally achieved by the molecules having a high degree of intermolecular interactions, for example, hydrogen bonding or strong π-π interactions, or by the molecules having a high molecular weight.

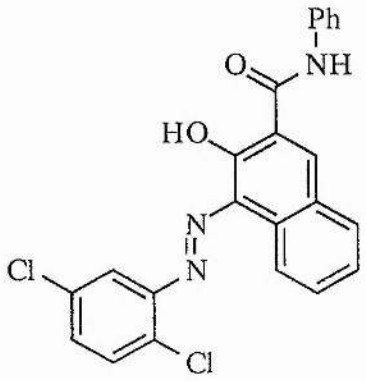
Other features to be considered when designing potential pigments are that they contain some sort of benzenoid aromatic system and that they are planar, or approximately planar. These features mean that, in the solid state where pigments produce their colour, the molecules can stack, thanks in part to the π-π–overlap, into a crystal lattice and due to the aromatic systems these compounds will not degrade when a photon of light is absorbed. This stability is important to prevent decomposition of the molecule in its excited state.

The first synthetic pigments were the azo pigments. These contain the azo, N=N, chromophore to provide the colour. An early example of such a compound is Toluidine Red (**3**), made from the coupling of β-naphthol to the diazonium salt derived from 4-methyl-2-nitroaniline.



(3)

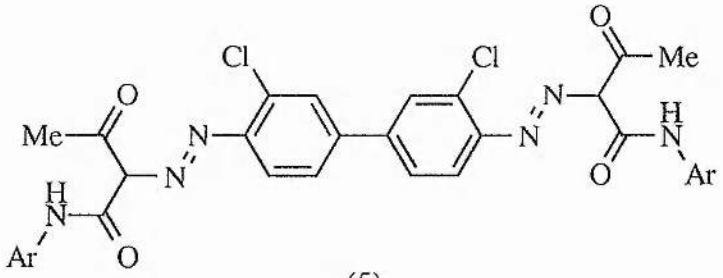
This early example was found to be of limited use as a pigment due to its relatively poor solvent and heat resistance. This problem was alleviated somewhat by modification of the two ring systems to give, after some development, another red pigment Naphthol AS Red (**4**).



(4)

It can bee seen from comparison of the two structures that there is an increase in molecular weight from Toluidine Red, m.w. 307, through to Naphthol AS Red, m.w. 436 and also the added possibility of intramolecular hydrogen bonding sites, namely the amide function. This has the overall effect of improving the performance of the pigment.

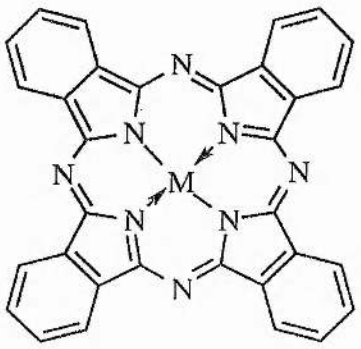
Further understanding of the limiting factors associated with azo pigments led to the development of the another class of pigments which contain two azo chromophores. Examples of these compounds are still used today, for example, the diarylide yellows and oranges (**5**).



(5)

The major disadvantage posed by the use of azo and diazo pigments is that many of the starting materials, the mono- or bis-arylamines, are either known or suspected potent carcinogens. This means that manufacturers have to take very careful precautions and in some cases apply for a licence to handle these compounds.

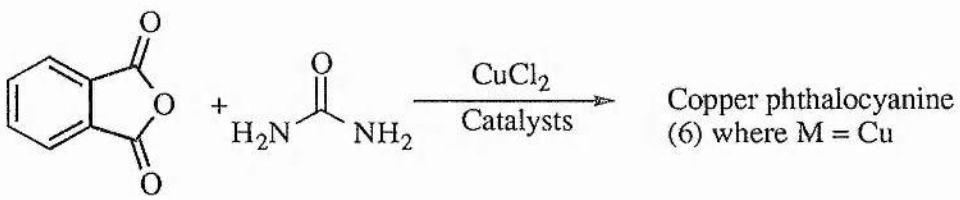
A second class of pigments in use today are the metal phthalocyanines (**6**). These molecules are believed to have been discovered by Braun and Tcherniac[4] who found traces of a blue material upon fusion of 2-cyanobenzamide, although this result has not been proven conclusively.



(6)

Iron phthalocyanine was first observed in the manufacture of phthalimide from phthalic anhydride and ammonia - the metal was thought to have originated from the reaction vessel[5]. The structure of phthalocyanine (tetrabenzotetraazaporphyrin) was deduced by Linstead and co-workers[5] when they prepared a sample by heating 2-cyanobenzamide with magnesium, followed by the removal of the metal ion from the ring with sulfuric acid.

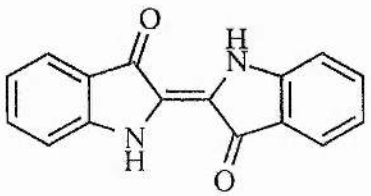
Although metal-free phthalocyanine can be used as a blue/green pigment, the most common derivative used commercially is copper phthalocyanine. Industrially this very important blue pigment is formed from the fusion of phthalic anhydride, urea, cupric chloride and catalytic amounts of boric acid and ammonium molybdate in a mixture of the isomers of trichlorobenzene[5].



Since the qualities of this blue pigment were first appreciated a great deal of work has been undertaken to exploit all the uses of this compound as well as the development of new analogues of the porphyrin ring. An understanding of the reaction mechanism led to the reporting of new starting materials and also the possibility of derivatisation of the benzenoid ring before, and after, cyclisation[6].

This work has led to the formation of some water-soluble derivatives of phthalocyanines which can be used to treat the fibres of a cloth. Subsequent work led to phthalocyanine derivatives which could have functionality introduced into the porphyrin ring which allowed the pigment to bind covalently to the fibres to produce coloured cloths.

Another example of an industrially and historically important pigment is indigo. The term indigo is properly used to refer to the family of compounds based around the parent compound indigotin (**7**).

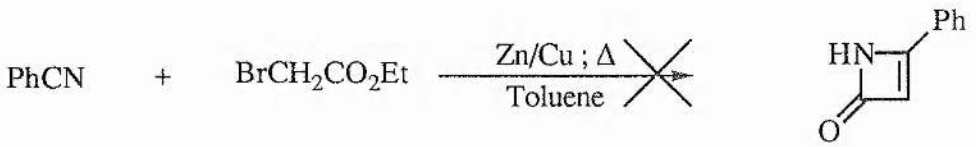


(7)

This blue pigment was reported to have been imported from India as early as 1573[7]. The interesting points worth noting from the structure of this compound are the arrangement of groups which lead to the colour produced and also the low molecular weight of the molecule.

The effect of the low molecular weight and its relatively low solubility in some solvents demonstrates the importance of intermolecular interactions between two molecules in the solid state. The colour produced also demonstrates the importance of the arrangement of groups in the molecule, and the high degree of conjugation throughout the molecule.

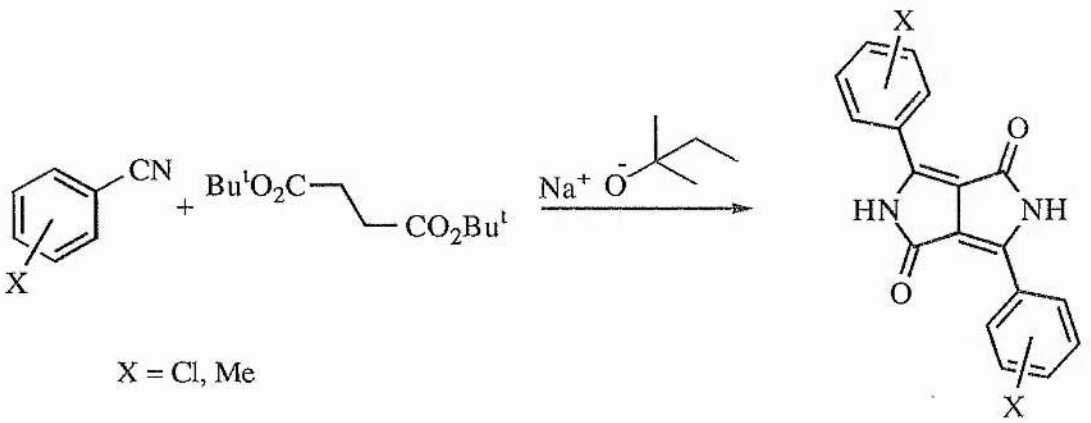
A final important class of pigments are the diketopyrrolo[3,4-*c*]pyrroles (DPPs). These were first identified in 1974 when Farnum and co-workers were attempting to use a modified Reformatskii reaction to produce 2-azetinone derivatives[8].



Upon work-up of the reaction mixture they discovered a bright red crystalline material which they managed to isolate. This red solid was later identified as diphenyldiketo-pyrrolo[3,4-*c*]pyrrole (diphenyl DPP) (**8**) and isolated in yields ranging from 5-20%.

(8)

This compound was tested by Iqbal and co-workers at Ciba-Geigy for use in pigment applications and was found to have excellent colour properties[9,10]. A great deal of work has since been done, and continues to be done, to exploit this new pigment to the full. A suitable large scale manufacturing process has been developed which uses a substituted benzonitrile and *tert*-butyl succinate, the choice of ester being important to prevent self-condensation of the anion of the succinate.

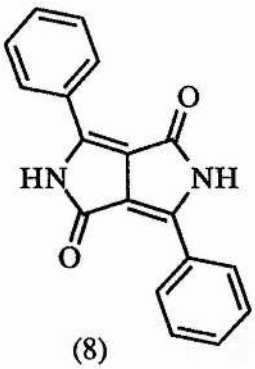


X = Cl, Me

The most interesting feature of the DPP molecule is the close proximity of the three functional groups, NH, C=O, C=C. This means that there is extensive delocalisation throughout the molecule which helps to stabilise the excited state.

An interesting physical feature of the DPP molecule is its insolubility in most organic solvents - a basic tenet for a molecule to be considered a pigment. This is again thought to arise from the high level of intermolecular interactions, both π-π overlap during stacking in the crystal lattice and also strong hydrogen bonds formed between molecules.

A comparison of indigo and diphenyl DPP reveals some interesting points of note.



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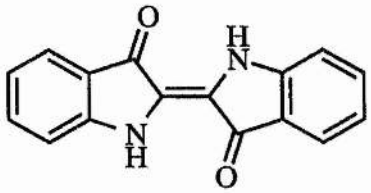


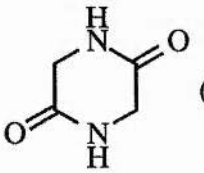
(7)

It can be seen from their structures that diphenyl DPP (**8**) and indigo (**7**) are quite similar, in that they both contain the same groups all held closely together, they both have sites for hydrogen bond formation, and they both contain benzene rings.

Their physical properties are, however, quite different; diphenyl DPP is red, while indigo is blue; diphenyl DPP is insoluble in most organic solvents, while indigo is relatively more soluble in a range of solvents; and finally diphenyl DPP has excellent all-round pigment characteristics whereas indigo simply has good ones.

These differences in their physical behaviour must therefore be due to the arrangement of the functionalities in each molecule and so it is believed that by altering the type, arrangement and number of these functional groups into novel heterocyclic molecules then potentially new pigments may be developed.

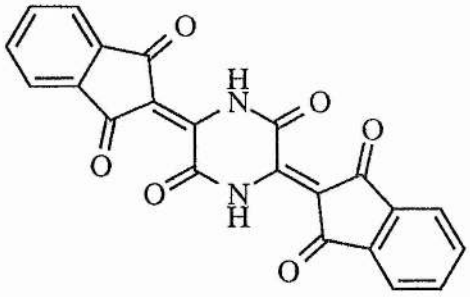
2,5-Dioxopiperazine (piperazine-2,5-dione, 2,5-diketopiperazine, DKP) (**9**) contains both the NH and C=O groups as well as two methylene groups which, being α- to a carbonyl group, makes them potentially acidic.



(9)

Reported attempts to utilise derivatives of DKPs for use in colour applications has, to date, been limited, although the synthesis of some compounds containing the dioxopiperazine unit for possible use in this field have been described.

Katritzky and co-workers[11] reported a brief study in this area synthesising the two compounds (**10**) and (**11**) shown below.



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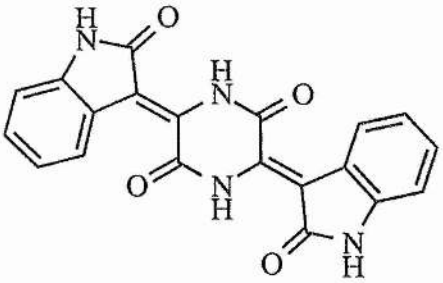
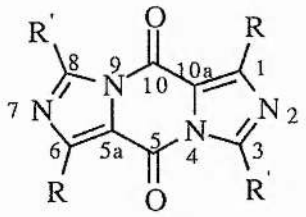


(11)

These compounds were coloured, brown and purple respectively, although they were later shown to be of little use in pigment applications[12].

A second investigation in this area by Griffiths and Sekihachi[13] used a different approach to obtain some bis-heteroannelated dioxopiperazines (**12**) and (**13**), again with a view to their potential use in colour applications.



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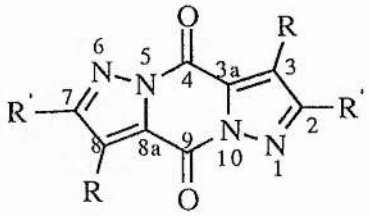


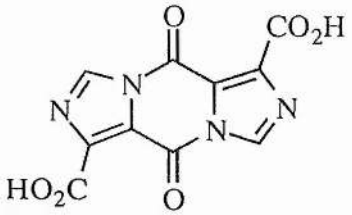
(13)

The group synthesised many derivatives of the above heterocycles, namely substituted diimidazopiperazinediones (**12**) and dipyrazolopiperazinediones (**13**), and found that many were in fact colourless. However by the introduction of electron donating substituents, especially arylamino groups, into the 1- and 6- or 3- and 8- positions of the diimidazopiperazinediones, coloured materials could be obtained.

In the case of the dipyrazolopiperazinedione family of compounds, introduction of electron donating groups into the 3- and 8- positions gave rise to some coloured materials which had a lower colour strength then the similarly substituted diimidazopiperazinediones.

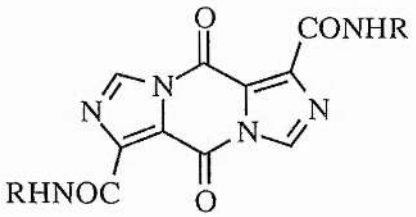
Interestingly it had been reported previously[14] that some substituted diimidazopiperazinediones are unstable to varying degrees. For example, the 1,6-

dicarboxylic acid (**14**) is known to be hydrolysed very readily upon storage to an imidazole dicarboxylic acid , even when refrigerated.



(14)

The corresponding diamides (**15**) are more stable than the diacid, although they will undergo aminolysis under mild conditions to give a range of diamido- imidazoles.



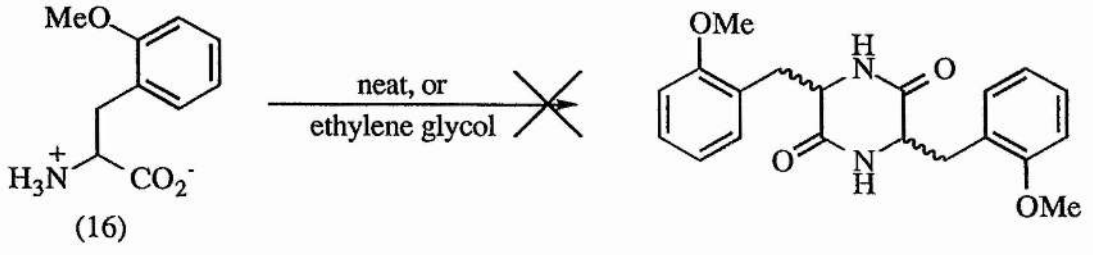
R = $(CH_3)_2CHCH_2$ or CH_2Ph

(15)

Chemistry of Dioxopiperazines

Dioxopiperazines are generally formed from the dimerisation of α-amino acids or, more usually, their esters.

The use of the acids themselves in this process is, however, not always successful. For example Danthi and Hill[15] have shown that simply heating, either dry or in ethylene glycol, a C-2 benzylated amino acid (**16**), did not result in any dioxopiperazine being formed. This result is contrary to a previous result, where Cain and Porter showed it to be possible to induce cyclodimerisation of an amino acid (**17**) by simply heating in ethylene glycol[16].



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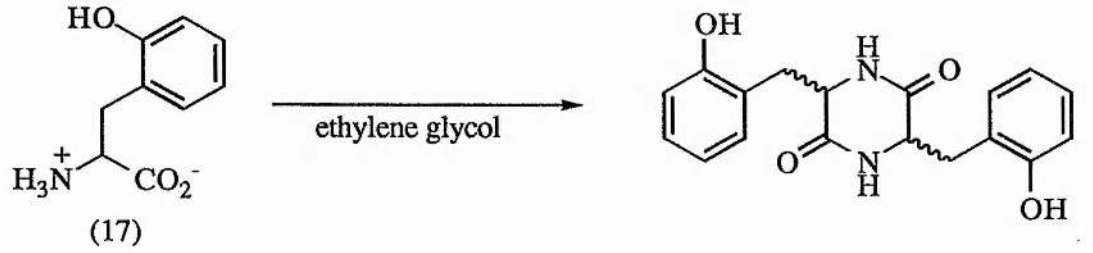
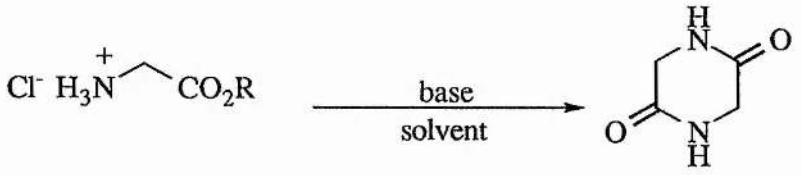


(17)

The formation of a dioxopiperazine is in general far simpler when the starting materials are amino acid esters. A good example is the formation of 2,5-dioxopiperazine itself. Liberation of the free amine group of glycine ethyl ester hydrochloride with a suitable base[17,18] gives the free amino acid ester, which, in solution, spontaneously cyclises to give dioxopiperazine.



(9)

R = Me, base = NH_3 and solvent = $CHCl_3$
R = Et, base = Et_3N and solvent = H_2O

Dipeptides will also cyclise to give dioxopiperazines and the stereochemistry and rates of cyclisation has been investigated[19]. For cyclisation of a dipeptide to occur the amide bond of the dipeptide must be in a *cis*- orientation, thereby allowing the two reaction centres, the amine and the ester, to come into close proximity.

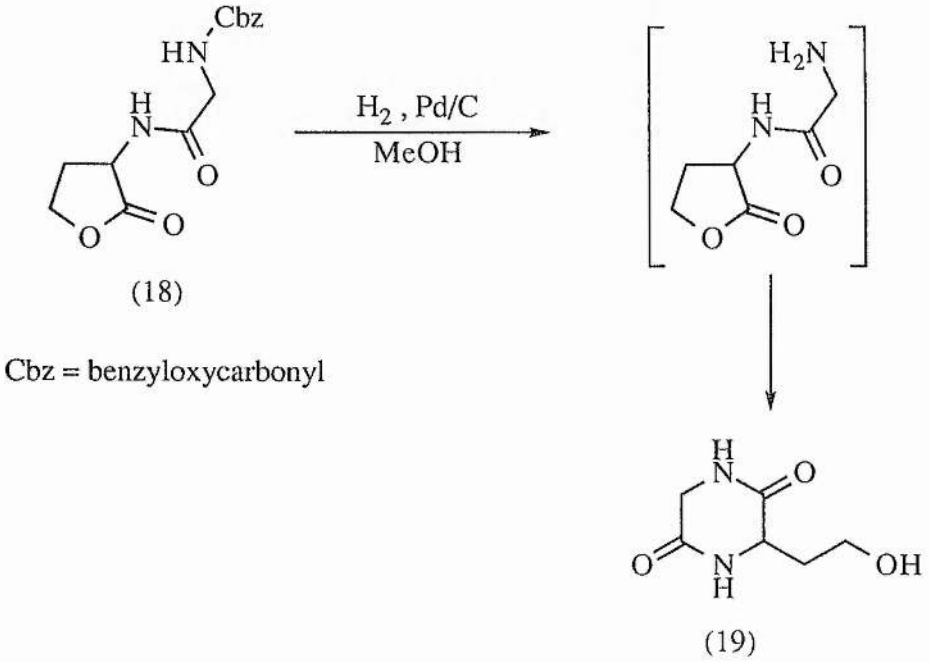
In general a dipeptide will tend to adopt the more thermodynamically favourable *trans*-conformation[20], the barrier for the rotation about this bond being in the order of 83.6 kJ mol^{-1}.

The earliest reported method of cyclisation was by Fischer[21]. The method involved reaction of a dipeptide methyl ester with an excess of ammonia.

Another method for inducing the cyclisation of a dipeptide was reported by Nitecki and co-workers[22]. This method involves the deprotection of an *N*-*t*-butoxycarbonyl dipeptide with formic acid to give the intermediate formate salt. This is then heated in butan-2-ol and toluene whilst azeotropically removing the water produced to form the required dioxopiperazine.

A third method for the cyclisation of dipeptides is *via* acetic acid-catalysed intramolecular aminolysis as reported by Suzuki[23]. This method has been shown to be of great use even when acid-labile groups have been present in the starting dipeptide.

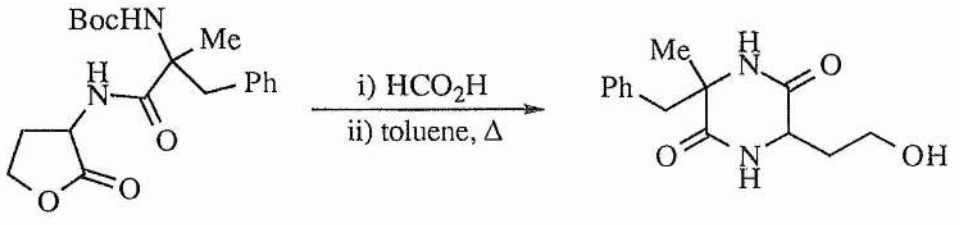
The intramolecular attack of a free amine upon a lactone carbonyl has been shown to be applicable in synthesising some substituted dioxopiperazines[24,25]. For example lactone (**18**) going to the dioxopiperazine (**19**) and lactone (**20**) going to the dioxopiperazine (**21**).



(18)

Cbz = benzyloxycarbonyl

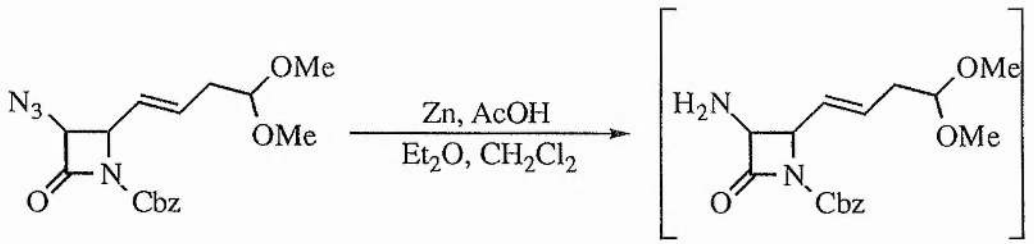
(19)



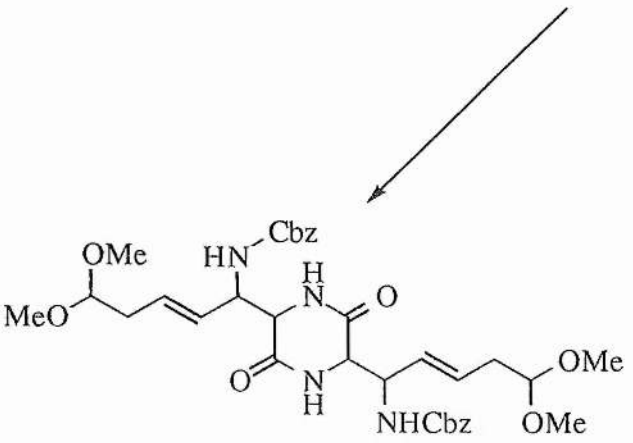
(20) (21)

Boc = *t*-butoxycarbonyl

Activation of the carbonyl towards attack of an amine has also been achieved by the use of a β-lactam ring in the starting materials[26] for example in (**22**).

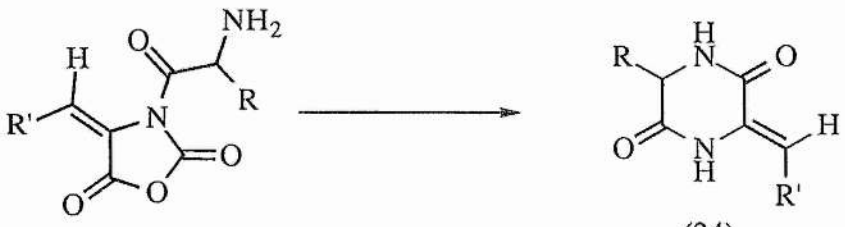


(22)

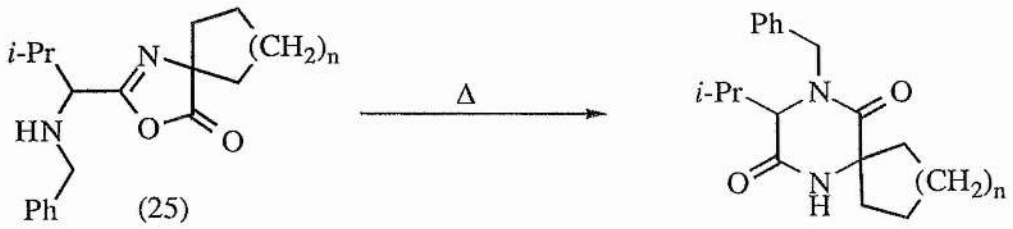


This elegant method of synthesis allows for the inclusion of sensitive functionality, such as the dimethyl acetal group, in the starting material.

Two methods used to activate the carbonyl towards intramolecular attack from an amine leading to ring opening followed by dioxopiperazine formation are shown below[27,28].



(23) (24)



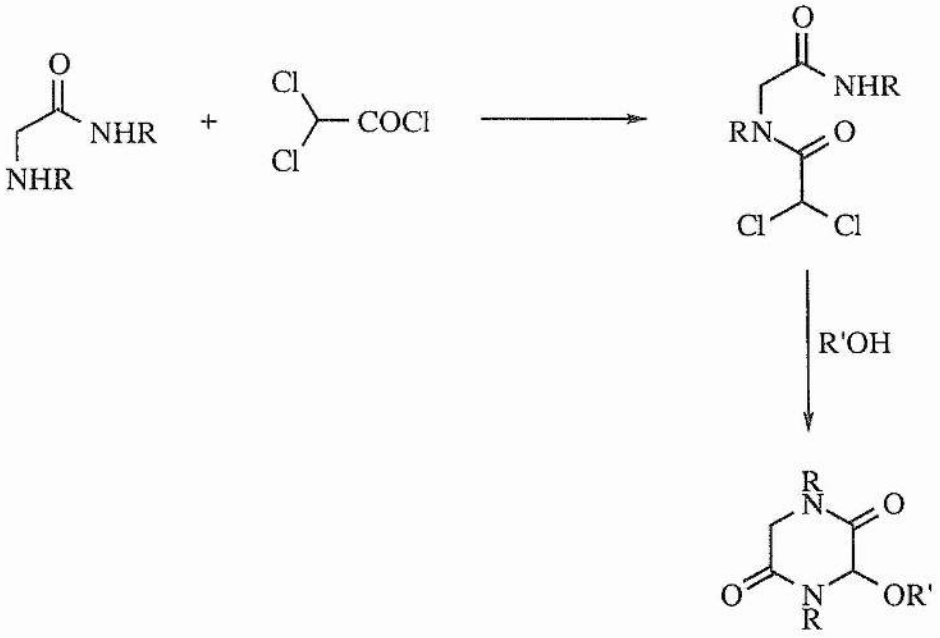
(25) (26)

n = 1 or 2

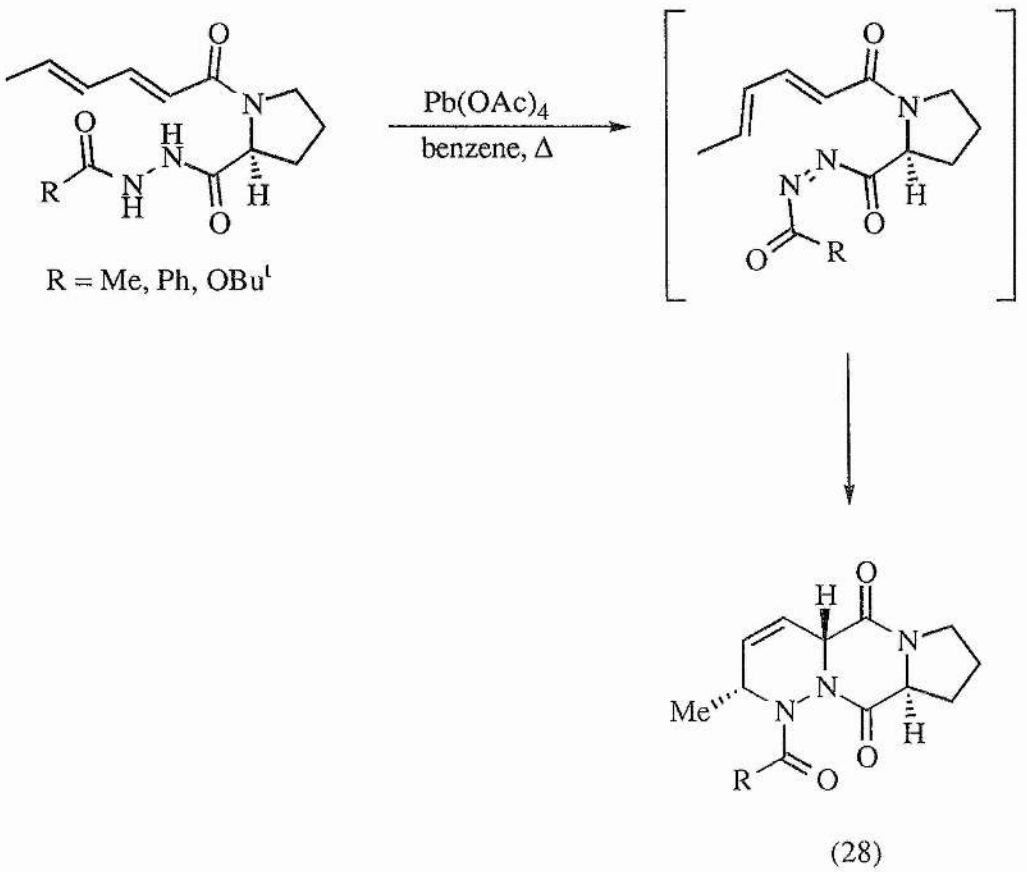
One final interesting method described for the activation of a carbonyl group to amine attack is through the use of an aziridine starting material (**27**)[29].

(27)

Formation of an oxygenated dioxopiperazine is usually achieved after cyclisation and requires a suitably protected dioxopiperazine[30]. In one interesting paper, Kwast and Williams reported they were able to introduce the ether functionality into the dioxopiperazine during cyclisation[31].



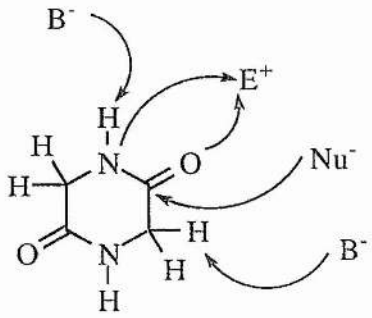
One final and unusual method for the formation of a highly substituted dioxopiperazine (**28**) is *via* an intramolecular hetero Diels-Alder reaction[32].



(28)

Reactivity of Dioxopiperazines

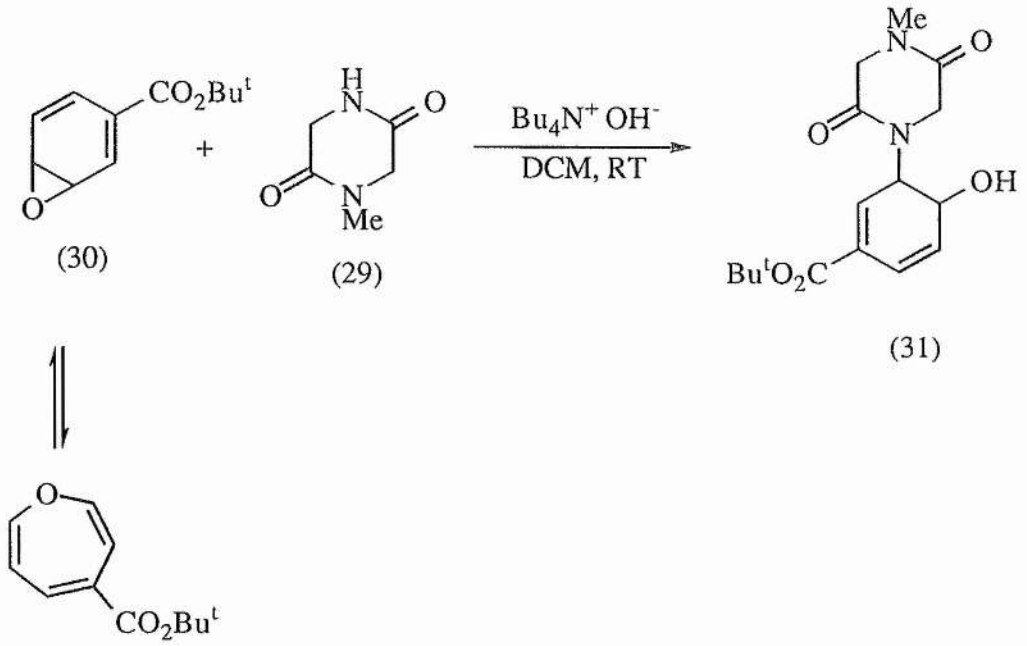
Dioxopiperazine has five possible reaction centres. The full spectrum of reactions has been reviewed relatively recently by Natekar and Rajappa[20] and so will not be covered as comprehensively here although the more salient points will be covered.



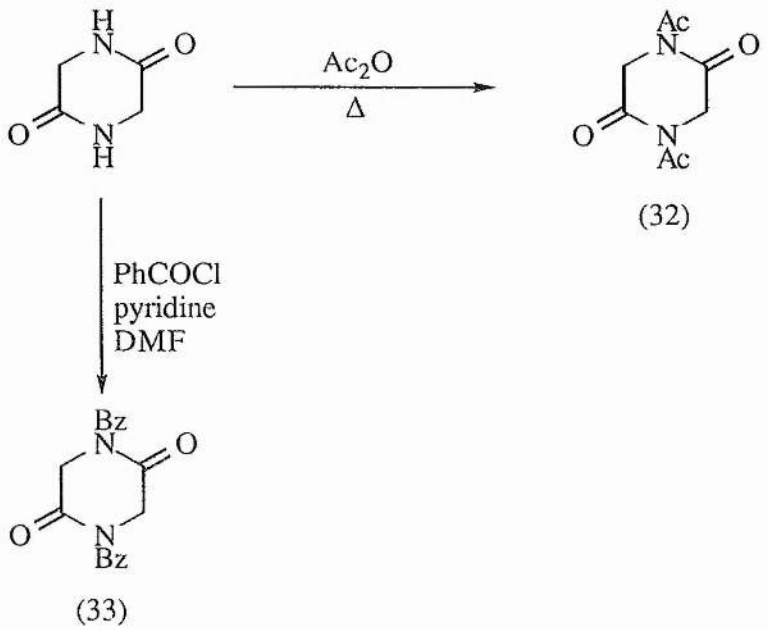
Reaction at Nitrogen

The first reaction sites are the nitrogen atoms at positions 1 and 4. The amide proton is relatively acidic and can be removed by the action of strong base, such as sodium hydride[33,34] or potassium *tert*-butoxide[35] to give the anion. This is an important reaction when protection of the nitrogen is required prior to a further reaction at either the methylene group or carbonyl carbons.

One interesting alkylation reaction uses the weakly nucleophilic character of the amide nitrogen of (**29**). Here the nitrogen is used to attack an epoxide (**30**), causing ring opening of the epoxide and allowing for the incorporation of a dihydrobenzene unit into the product (**31**)[34].

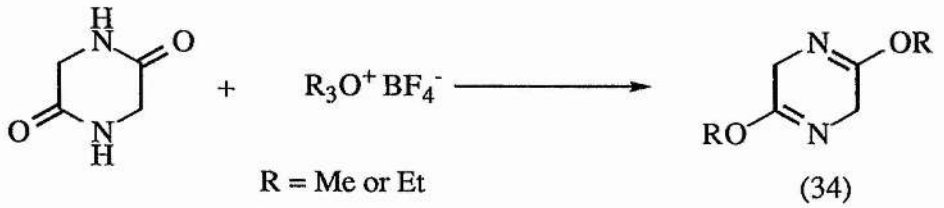


Acylation of the nitrogen can be achieved quite simply by either heating a suspension of the dioxopiperazine in an excess of acetic anhydride for several hours to give the *N,N*-diacetyldioxopiperazine (**32**)[36] or by reaction of an acid chloride with a dioxopiperazine and a base in a suitable solvent, for example, benzoylation using benzoyl chloride and pyridine in *N,N*-dimethylformamide[37] to give *N,N*-dibenzoyldioxopiperazine (**33**).



Reaction at Oxygen

The most commonly cited reaction of dioxopiperazines at the oxygen centre is with Meerwein's reagent (trimethyloxonium tetrafluoroborate) or its triethyl homologue. These reactions result in dihydropyrazines (**34**) (the so called "lactim ethers") being formed[38]. This topic is also part of the review by Natekar and Rajappa[20] and so again only the salient points will be discussed here.

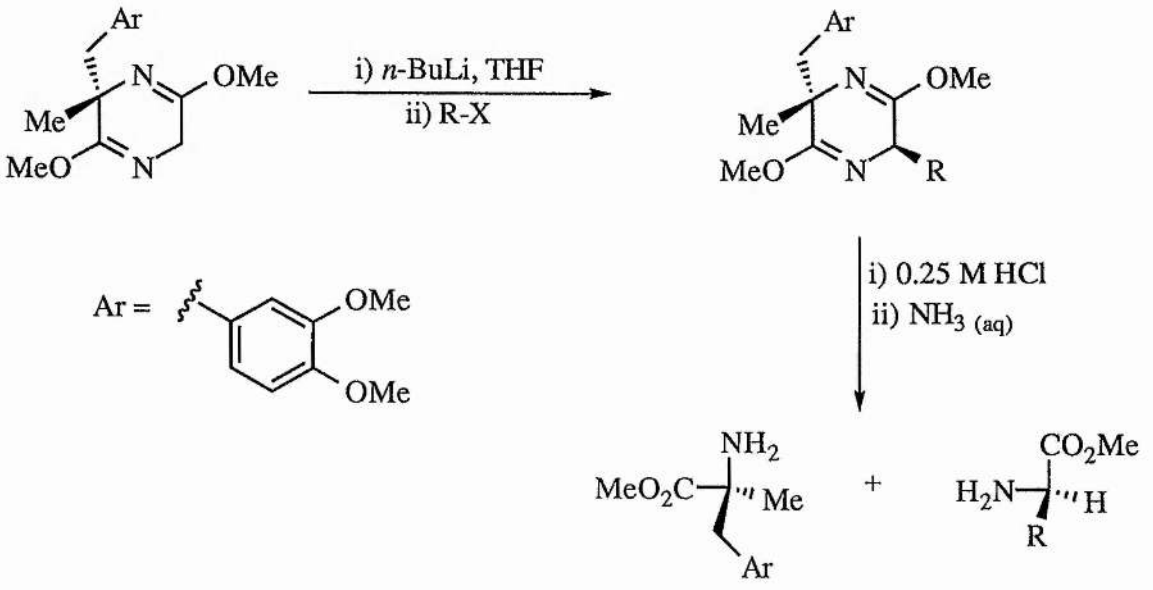


R = Me or Et

(34)

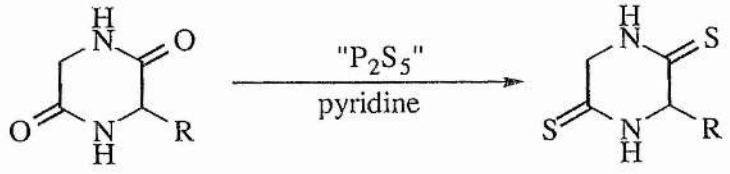
These dihydropyrazines will then undergo alkylation at the C-3 and/or C-6 positions by first deprotonating the methylene centre with strong base followed by reaction with the appropriate alkyl halide.

Schöllkopf and co-workers have shown these dihydropyrazines to be excellent starting materials for the synthesis of a whole range of natural and unnatural amino acids and have also developed excellent methodology to produce these amino acids in good enantiomerically pure forms[39], see below.



Reaction at Carbonyl

The carbonyl groups of a dioxopiperazine will behave as expected from an amide carbonyl. Although they are poor electrophiles they will react with some strong nucleophiles and also with phosphorus pentasulfide to give the corresponding dithioketopiperazine (**35**)[40] and phosphorus oxychloride to yield, after aerial oxidation of the intermediate dihydro compound (**36**), the fully delocalised dichloropyrazine (**37**)[41].



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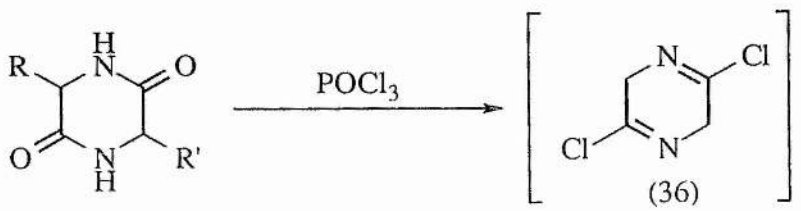

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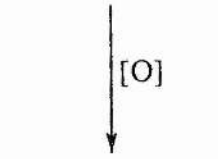
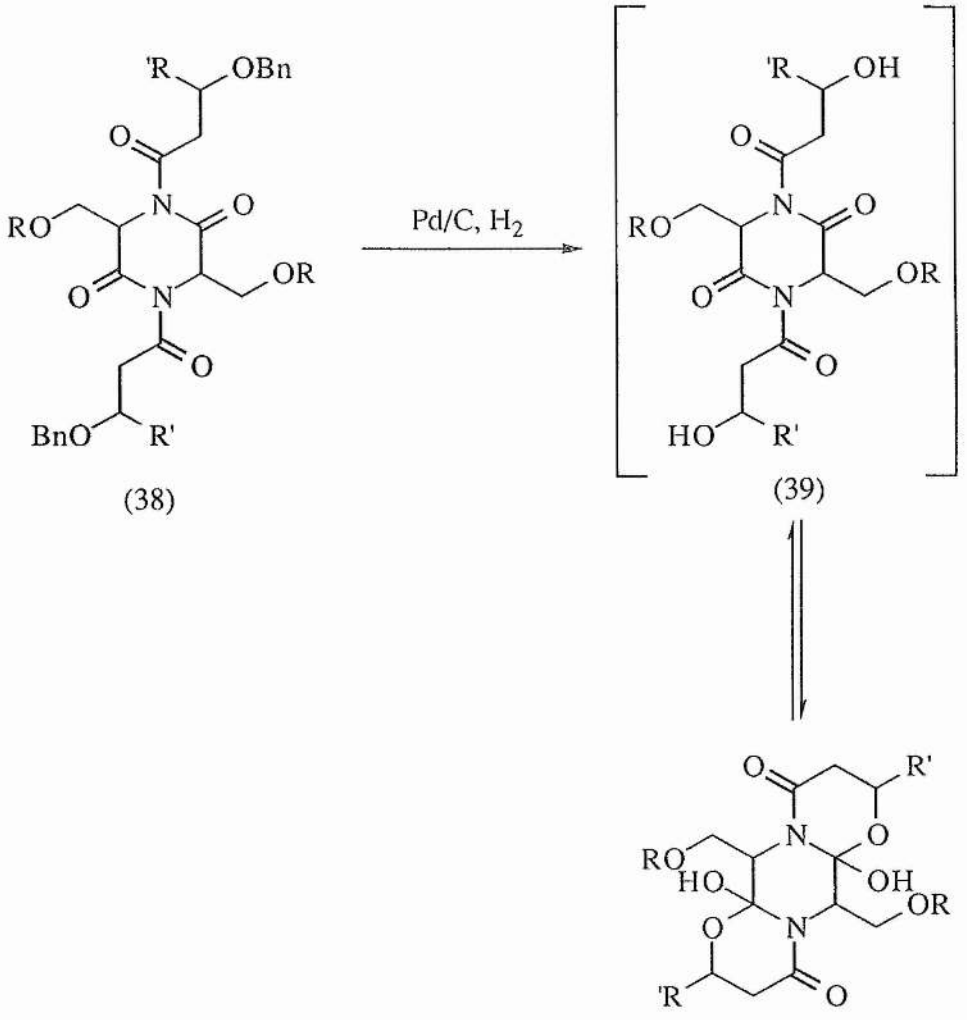


(37)

Nucleophilic attack at the carbonyl group of dioxopiperazines has been used to synthesise some interesting molecules[42,43]. One example is described by Shemyakin and co-workers[44]. Acylation at N-1 (or N-4) gives rise to an imide system (**38**) which helps to activate the ring carbonyl towards nucleophilic attack, in this instance intramolecular attack by a hydroxyl group of (**39**).



(38) (39)

Reaction at C-3 and/or C-6

Reaction at the methylene carbons of a dioxopiperazine is usually achieved by one of the following methods:

A. Protection of the amide nitrogen followed by deprotonation of the methylene group and reaction with a suitable electrophile[30, 45, 46].

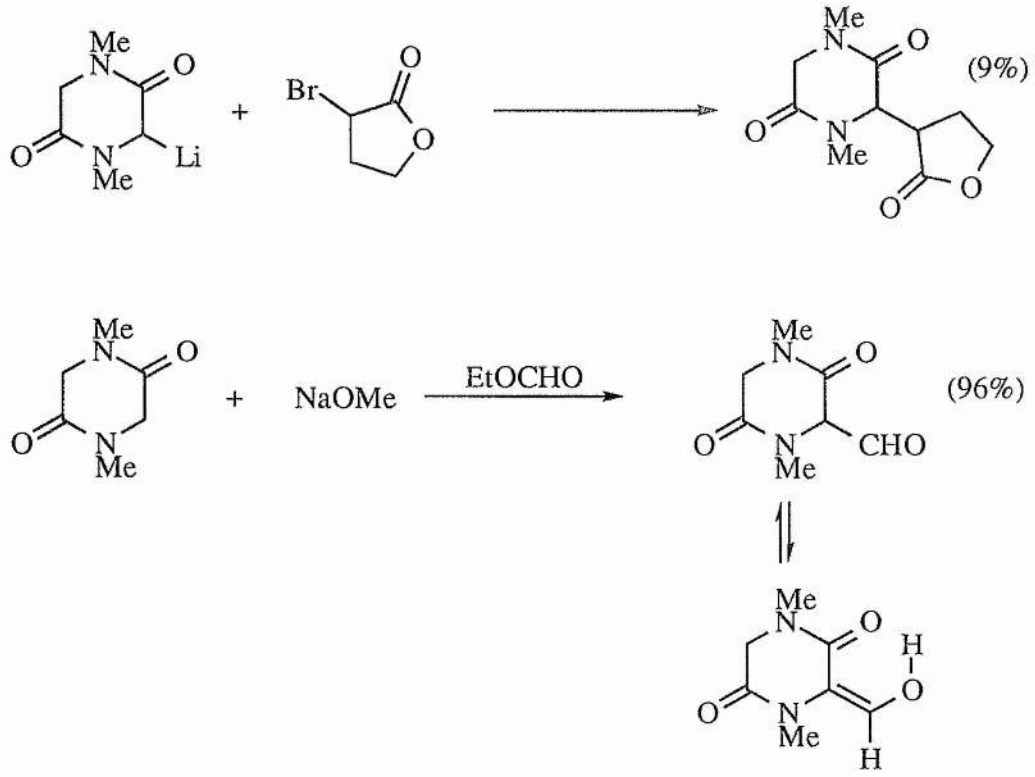
B. Condensation of the methylene with a carbonyl group[47].

C. Bromination using *N*-bromosuccinimide[48].

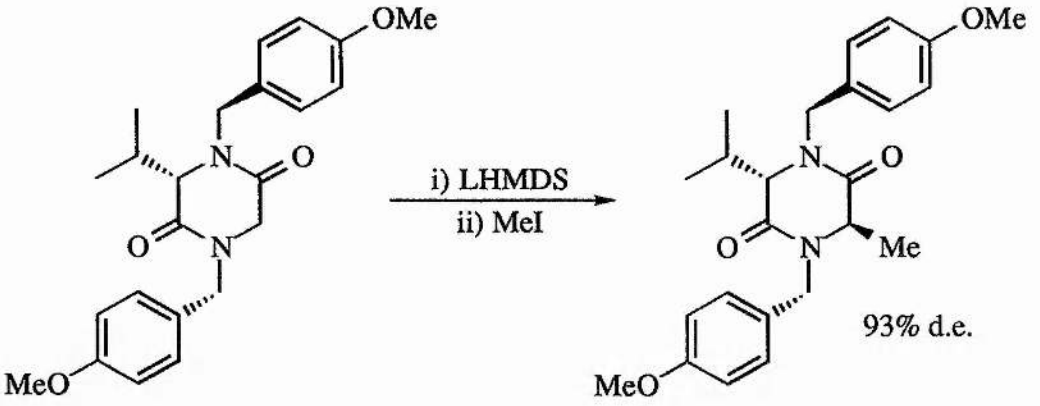
A. Deprotonation

Due to the importance of dioxopiperazines in a range of biologically important molecules the derivatisation of dioxopiperazines by *N*-protection followed by deprotonation with a base and subsequent reaction with an electrophile remains very important.

Use of a strong base will form an enolate in almost quantitative yield which will go on to react with a variety of electrophiles in a range of yields[46,49] .

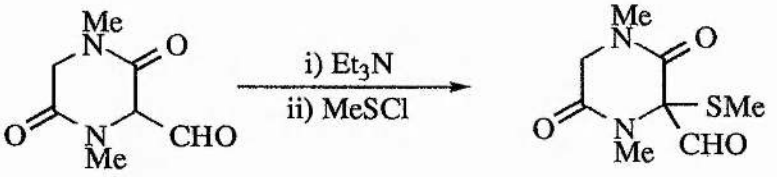


Davies and co-workers[50] have reported excellent diastereocontrol in a dioxopiperazine enolate addition to an electrophile; the resulting diastereomeric excesses are comparable to those obtained when using dihydropyrazine chemistry as explored by Schöllkopf and others[39].



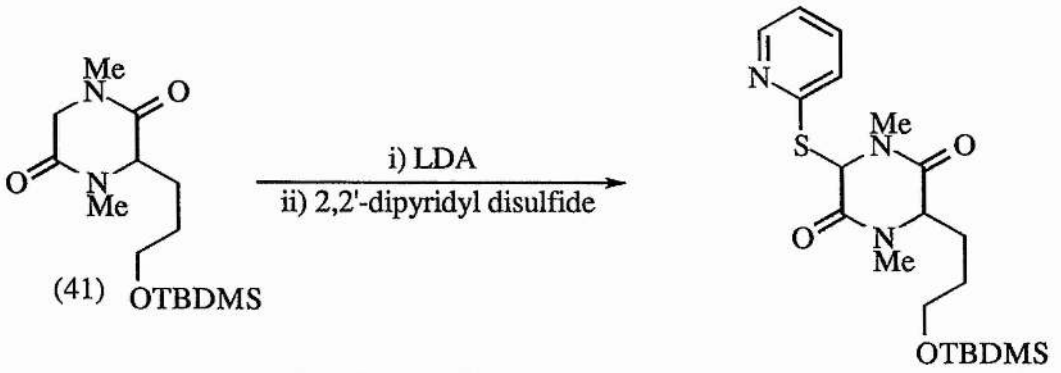
This excellent stereocontrol has been explained by the "knock-on effect" or chiral relay network of the isopropyl group influencing the stereochemistry of the N-1 *p*-methoxybenzyl group. This then affects the stereochemistry of the N-4 *p*-methoxybenzyl group which will have a directing effect on the approaching electrophile.

Introduction of a second substituent on to the dioxopiperazine ring using similar chemistry is possible although the nature of the existing group will determine the position of the second *i.e.* either at C-3 or at C-6. In the example shown below[46] formylation at C-3 leaves a relatively acidic proton bound to C-3 of (**40**). This can then be easily removed and replaced by an electrophile using a simple tertiary amine base.



(40)

If however the group introduced initially is, for example, an alkyl substituent (**41**)[30] then the acidity of the C-3 and C-6 protons will be similar and removal of the less sterically hindered proton, *i.e.* at C-6, will predominate.



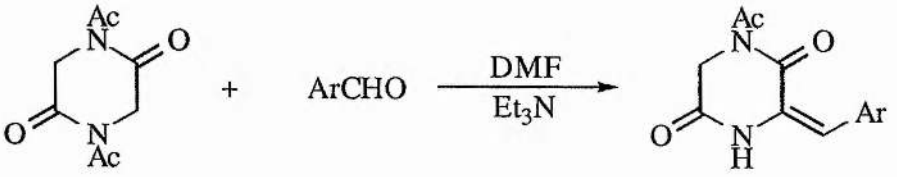
(41)

TBDMS = *tert*-butyldimethylsilyl

B. Condensation

The condensation of aromatic aldehydes with dioxopiperazine which lead to benzylidene derivatives can be achieved quite simply by heating the two together[51,52] The corresponding reactions fail, however, when the aldehyde used is aliphatic. The reaction conditions, involving boiling the reactants with sodium acetate in acetic anhydride are also very harsh and cause unwanted side reactions in some aromatic aldehydes.

An improved synthesis of benzylidene derivatives, which may be extended to incorporate aliphatic aldehydes was introduced by Gallina and Liberatori[53]. This method used much milder conditions for the condensation, namely triethylamine in *N,N*-dimethylformamide although the important difference was the requirement for *N,N*-diacetyldioxopiperazine starting materials, for example (**42**).

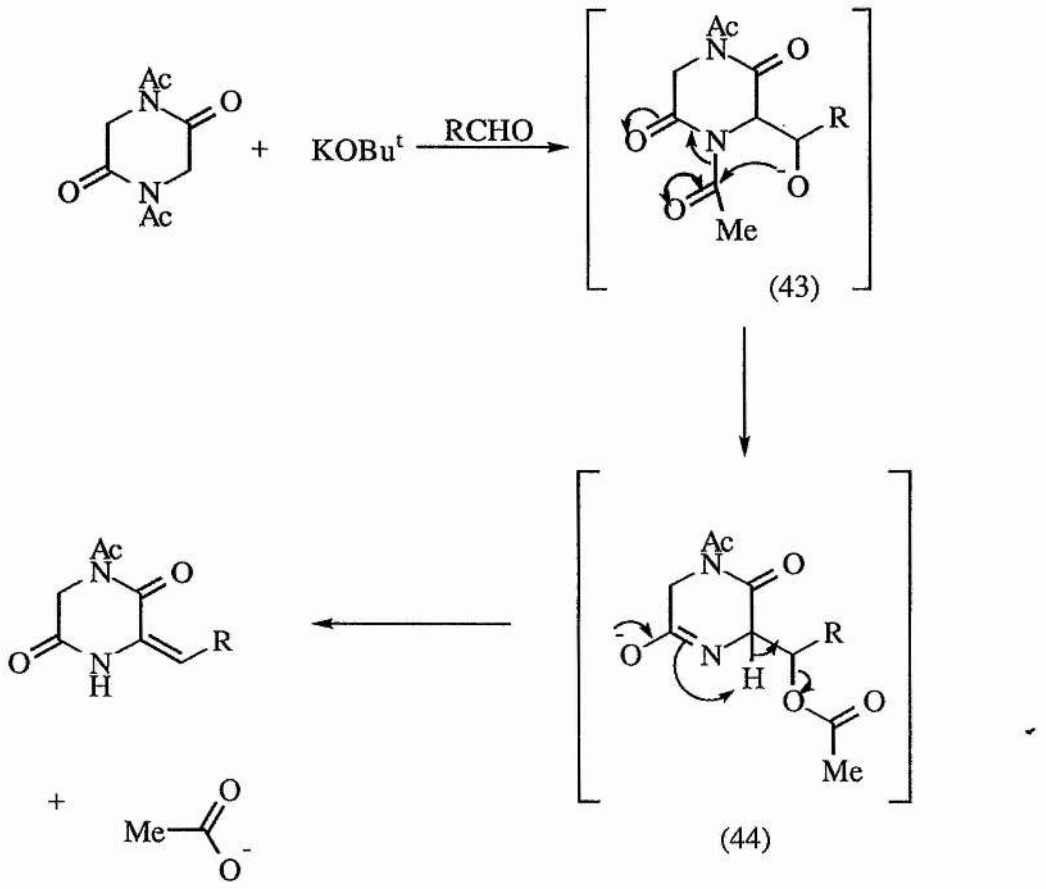


(42)

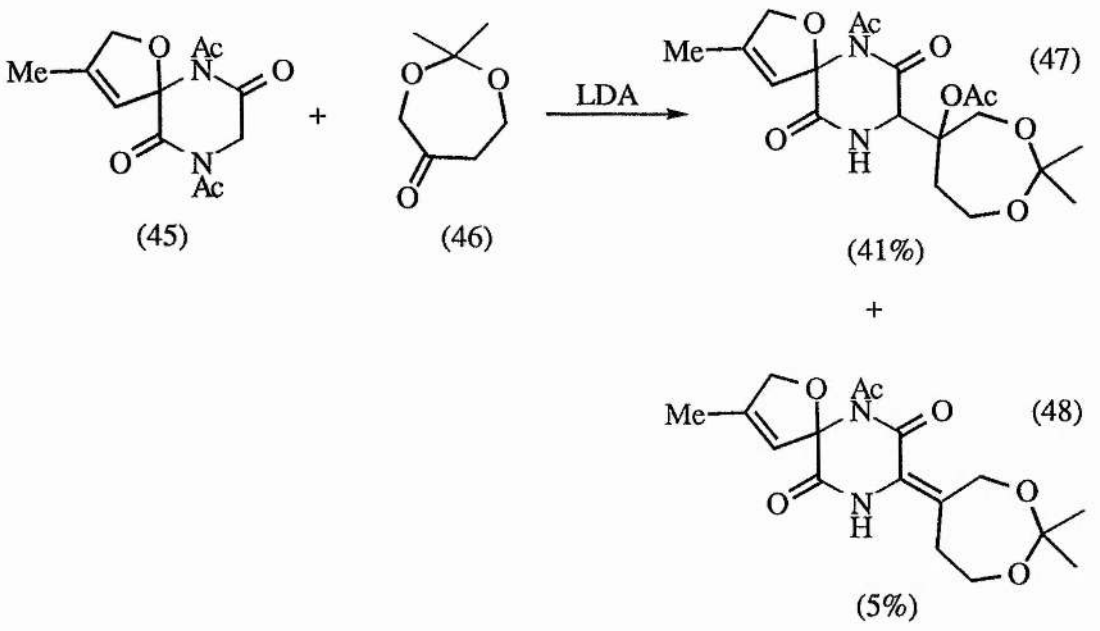
It was discovered that deacylation occurs on the nitrogen α- to the new carbon-carbon double bond and that the reaction of the diacetyldioxopiperazine is quicker than the monoarylidenedioxopiperazine. This means that non-symmetrical bisarylidenedioxo-piperazines can be produced in good yields.

The concomitant condensation/deacylation is thought to arise from an intramolecular transacylation from the dioxopiperazine nitrogen (**43**) to the oxygen of the intermediate aldol product (**44**).

Condensation of aliphatic aldehydes is possible but requires the use of a stronger base, namely potassium *tert*-butoxide.

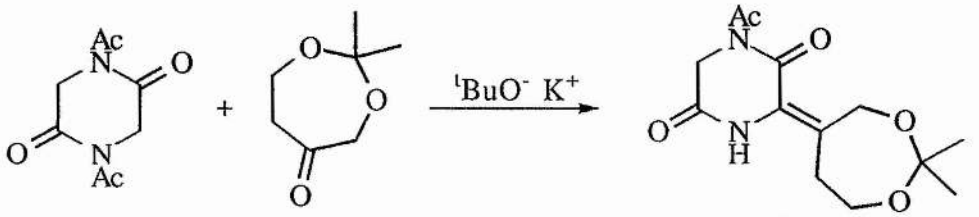


The reaction of a diacetyldioxopiperazine (**45**) with a ketone (**46**) has been described[54] although other examples of this type of reaction are rare. The reaction conditions require the use of a stronger base still, namely lithium diisopropylamide. The reaction is a deprotonation of the methylene group of the dioxopiperazine, followed by nucleophilic attack of the enolate upon the ketone carbonyl. This addition is then followed by the expected nitrogen to oxygen transacylation giving (**47**). Interestingly the bulk of the material isolated from the reaction is the acylated aldol product (**47**), with only a small amount of the expected elimination product (**48**) being formed.



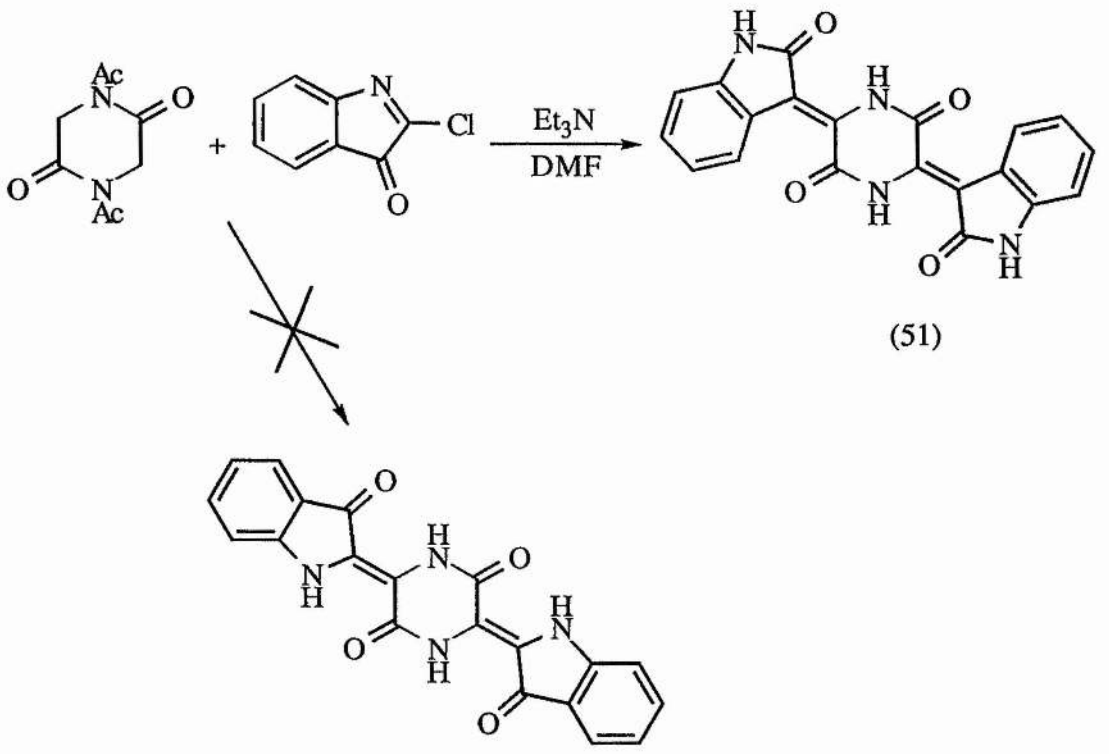
(45) (46)

If, however the starting dioxopiperazine does not contain a spirocentre at C-3 then the reaction with the ketone (**46**) shown above will take place using potassium *tert*-butoxide as the base in a good yield and also, interestingly, with the elimination of the elements of acetic acid of the initial aldol product and introduction of the double bond giving (**49**).



(46) (49)

As previously mentioned Katritzky and co-workers[11, 55] have studied the possibility of condensing *N,N*-diacetyldioxopiperazine with various molecules which contain "activated" carbonyl groups, for example, isatin and ninhydrin, as well as the reaction of diacetyldioxopiperazine with 2-chloroisatin. An interesting result during the course of this work was the product allegedly resulting from the reaction of 2-chloroisatin and diacetyldioxopiperazine.



(51)

(50)

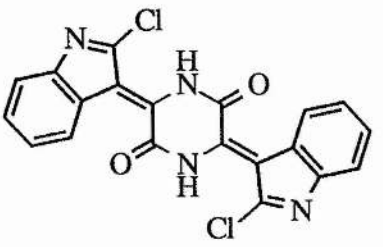
The expected product (**50**), resulting from reaction at C-2 of the "isatin chloride" and the displacement of chloride was not seen, but instead reaction occurred at C-3 of the "isatin chloride" giving rise to the compound with structure (**51**). This is the same compound isolated from the reaction of isatin and diacetyldioxopiperazine and the structure was confirmed *via* X-ray crystallography.

This result was rationalised by one of three explanations:

A. The effective species reacting is isatin, produced by hydrolysis of the (presumably highly reactive) 2-chloroisatin.

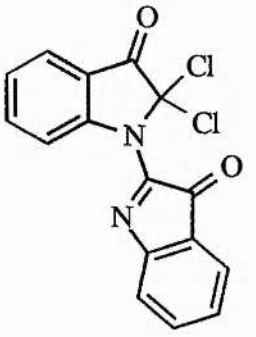
*B. The 2-chloroisatin structure is incorrect, and the observed product (**51**) is derived not from 2-chloroisatin but another intermediate, for example, 3,3-dichloroindol-2-one.*

*C. The greater reactivity of the 3-oxo group in 2-chloroisatin leads to the formation of a compound of type (**52**) and the reaction is accompanied by, or followed by hydrolysis of the imidoyl chloride function in (**52**).*



(52)

The doubts raised about the structure of 2-chloroisatin (point B above), appear to be confirmed by work undertaken by Cornforth and co-workers[56]. Very careful synthesis of the alleged 2-chloroisatin allowed for the isolation of some unstable crystalline material which was shown, by subsequent X-ray structure determination, to be the dimer (**53**).



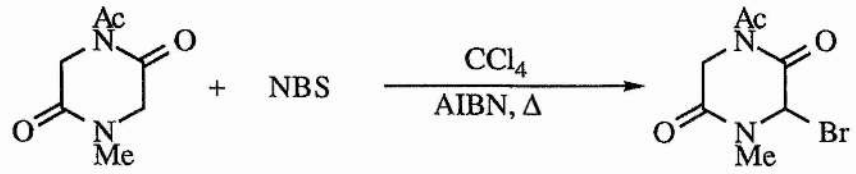
(53)

C. Bromination

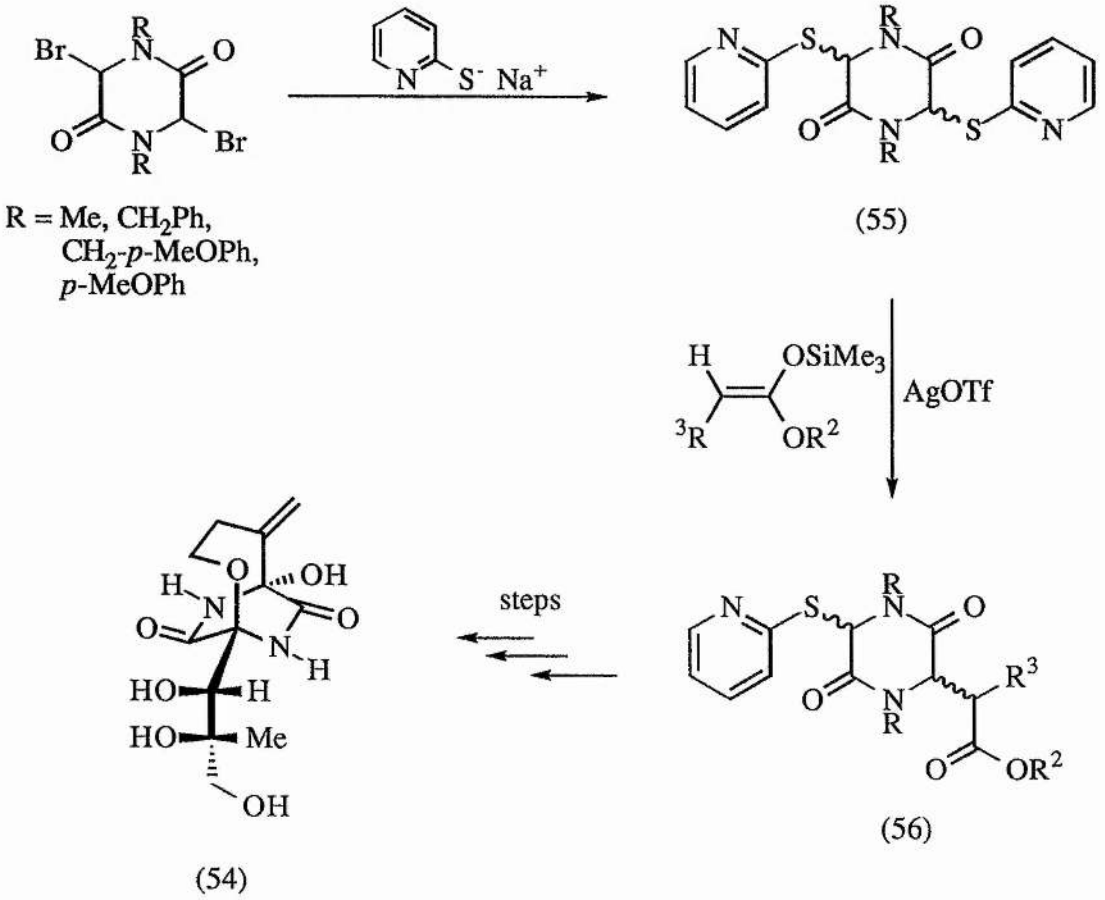
Bromination of dioxopiperazines and subsequent reactions of the bromo-compound have proven useful in the synthesis of some important biological molecules[31, 49]. It has also been shown that the group bound to the nitrogen can have a profound effect upon the degree of bromination and also the stability of the subsequent bromo compound[36, 48, 57].

It has been shown that the reaction of diacetyldioxopiperazine with one equivalent of *N*-bromosuccinimide gave a moderate yield of the unstable monobromodioxopiperazine. In comparison reaction of *N,N*-di(*p*-methoxybenzyl)dioxopiperazine with one equivalent of *N*-bromosuccinimide gave a mixture of unbrominated starting dioxopiperazine and dibrominated dioxopiperazine in a ratio of *ca.*1:1.

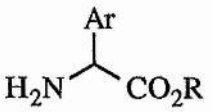
These variations in reactivity have allowed the possibility of directing the bromination in some simple systems by careful selection of the nitrogen protecting group[58].



Bromination of a dioxopiperazine has been used successfully as the starting point in the synthesis of a biologically important molecule, bicyclomycin (**54**)[49]. In this scheme the bromines were displaced by a sulfur-centred nucleophile to give a stable solid (**55**). This was then reacted further by the use of a metal mediated substitution of the sulfur to give an important intermediate (**56**).



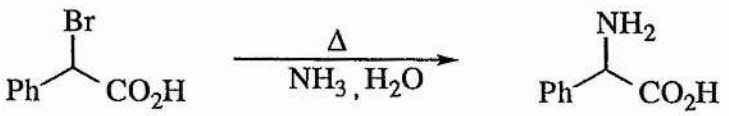
Synthesis of Arylglycines and Their Esters



R = H, Me or Et
Ar = aryl

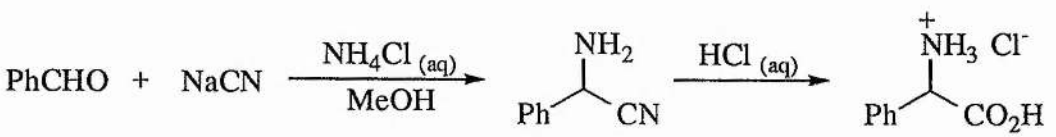
The asymmetric synthesis of arylglycines was reviewed by Williams and Hendrix in 1992, with many of the routes reviewed being derived from the racemic synthesis of arylglycines[58]. This review therefore covers a large area and so only certain examples from here and other references will be examined.

The simplest example of an arylglycine, phenylglycine (**58**), was synthesised by Stockenius in 1878 by the reaction of α-bromophenylacetic acid (**57**) with an excess of aqueous ammonia[59].



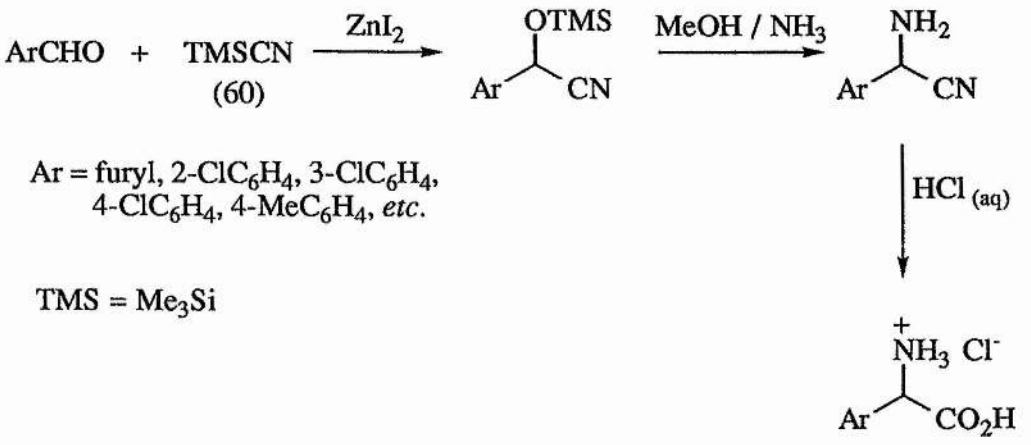
(57) (58)

In later years the advent of the Strecker synthesis[60] using benzaldehyde, followed by acid hydrolysis of the intermediate (**59**), leads to the hydrochloride salt of phenylglycine.



(59)

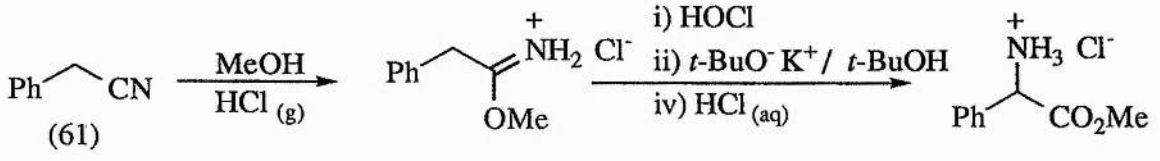
Many years later the introduction of sources of cyanide which were much more soluble in organic solvents, for example trimethylsilyl cyanide (TMSCN) (**60**), led to an expansion of the versatility of the Strecker synthesis[61].



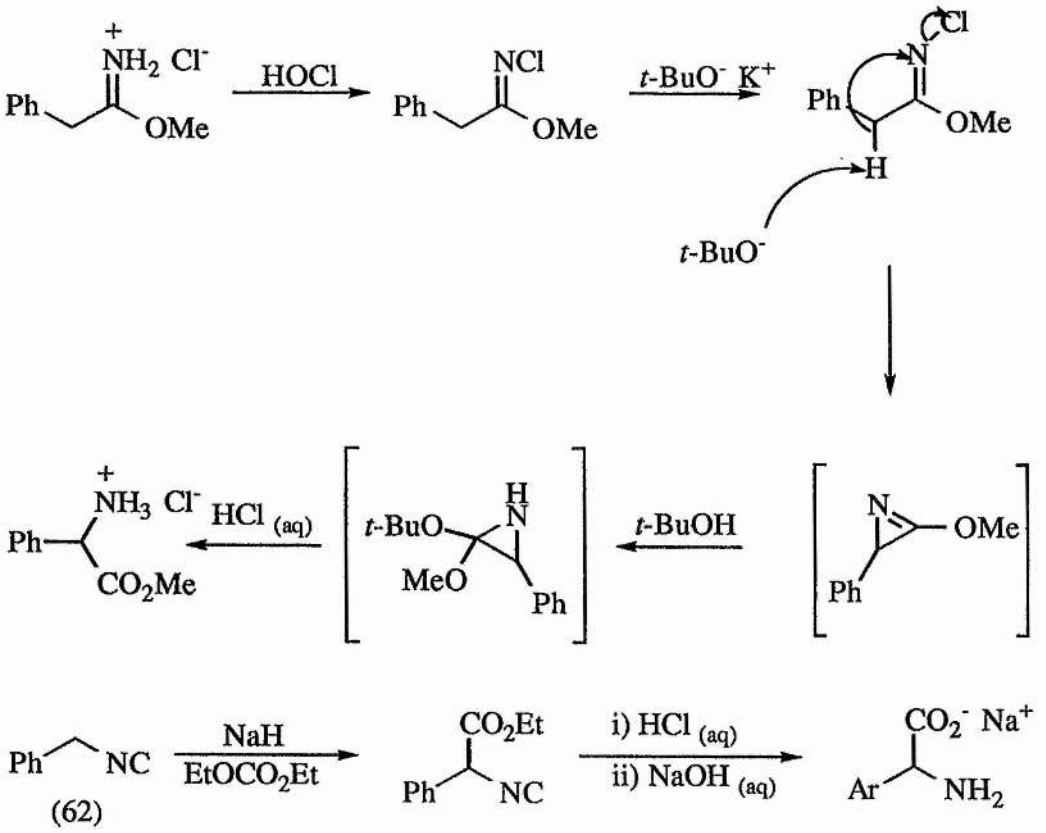
Ar = furyl, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, *etc.*

TMS = Me_3Si

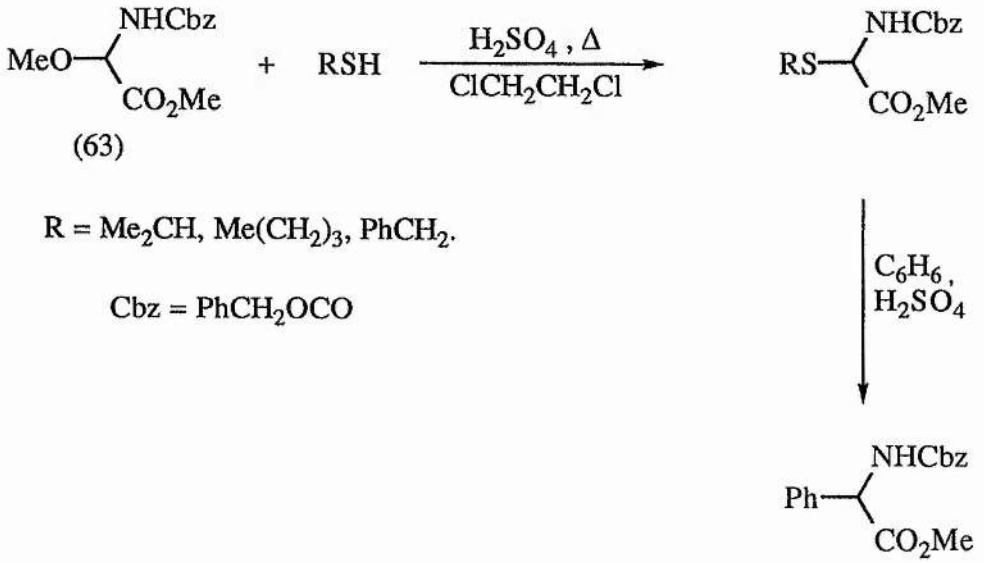
Other starting materials which have been used in the synthesis of arylglycines are nitriles (**61**) and isonitriles (**62**) but their reported use seems to be somewhat limited to ring-substituted phenylglycines[62,63].

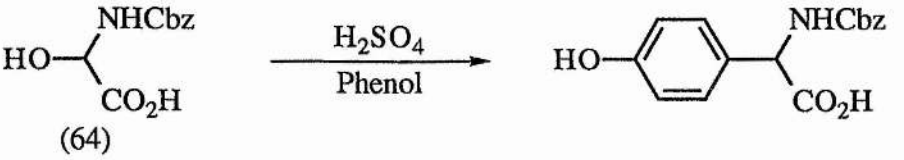


The proposed mechanism for this interesting transformation is shown below but it is believed it follows a similar pathway to the Neber rearrangement.



Reactions of *N*-protected-α-hydroxyglycine equivalents have found use in the synthesis of arylglycines as electrophilic glycine residues[64,65,66], *i.e.* they will react with nucleophiles at C-2 for example (**63**), (**64**) and (**65**).

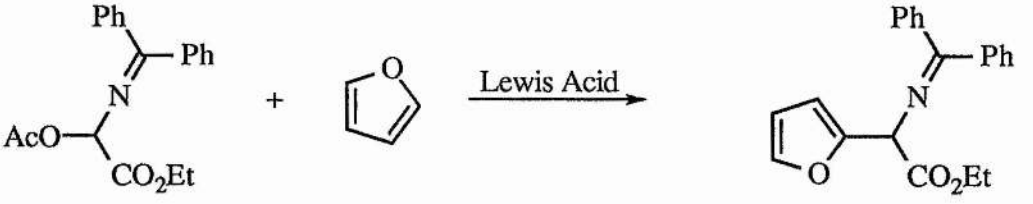




(64)

Cbz = $PhCH_2OCO$

Reactions with acid sensitive aromatic groups require a modification of the above routes, replacing the mineral acid with a Lewis acid[67].

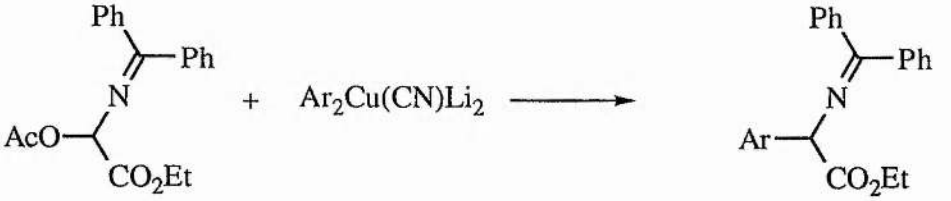


(65) (66)

Lewis Acid = $TiCl_4$, $AlCl_3$, $EtAlCl_2$, TMSOTf

This modification allows the incorporation of the acid-sensitive furan. Acid hydrolysis of the two protecting groups, the benzophenone imine and ester from (**65**), yield the arylglycines although the yields are sometimes, at best, moderate.

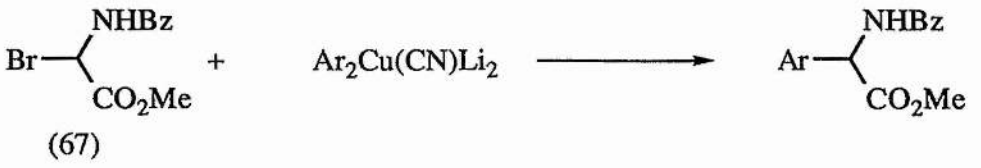
The electrophilic glycine equivalent (**65**) has also been used as a starting material to react with aromatic nucleophiles, generally cuprates[68] or Grignards[69].



(65)

Ar = Ph, 1-naphthyl

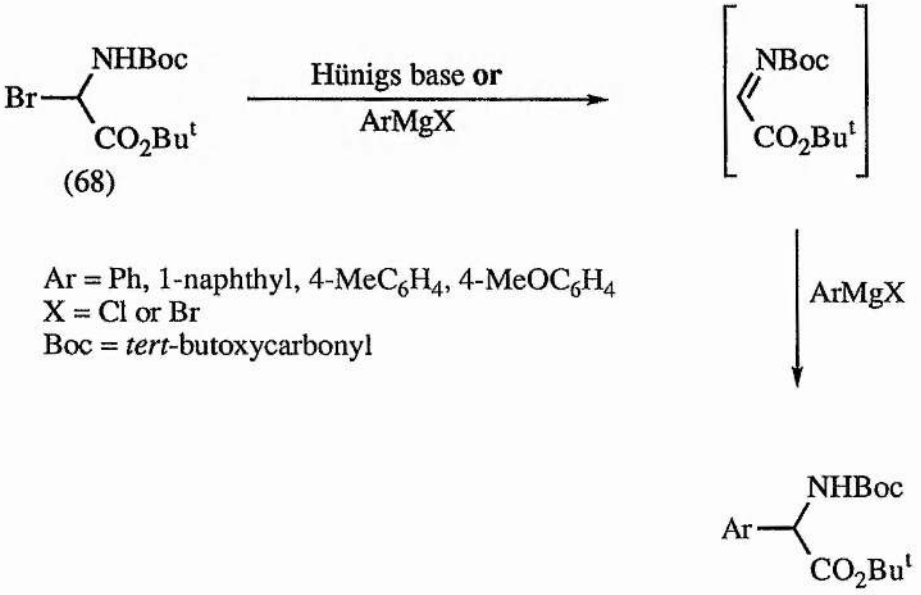
Another example of the use of an electrophilic glycine equivalent reacting with an aromatic nucleophile is the reaction of an arylcuprate[68] with a brominated glycine derivative (**67**) shown below.



(67)

Ar = Ph, 1-naphthyl

The reaction mechanism may well first go *via* elimination of HBr using one equivalent of the cuprate acting as a base. This will give an intermediate imino acetate which will then go on to react with a second equivalent of the arylcuprate. A similar reaction was reported previously by Münster and Steglich[69] who started with a similar electrophilic glycine (**68**) equivalent and reacted it with a Grignard nucleophile.

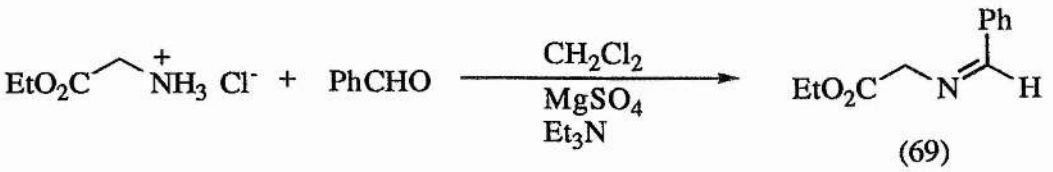


(68)

Ar = Ph, 1-naphthyl, 4-MeC_6H_4, 4-$MeOC_6H_4$
X = Cl or Br
Boc = *tert*-butoxycarbonyl

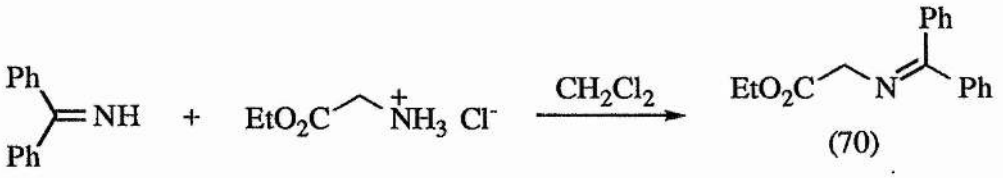
As well as electrophilic glycine equivalents, nucleophilic species have also been used in arylglycine synthesis. Protection of the amine and acid functionality of glycine, followed by deprotonation of the methylene group will lead to a relatively good C-nucleophile. The area of suitable protecting groups has been extensively covered in the literature[70] although commonly carboxyl groups are protected as an ester. The area of amino protecting groups is vast and so only two different examples are described below.

In general, the type of amine protecting group to be used prior to reaction with a strong base requires that both amine protons must be absent. One example of this type of nitrogen protecting group is the formation of Schiff bases, either benzylidenes (**69**) or as a diphenyl methylene (**70**)[71-75]. These are favoured due to their ease of synthesis and their removal, and examples of the various methods of synthesis are given below.



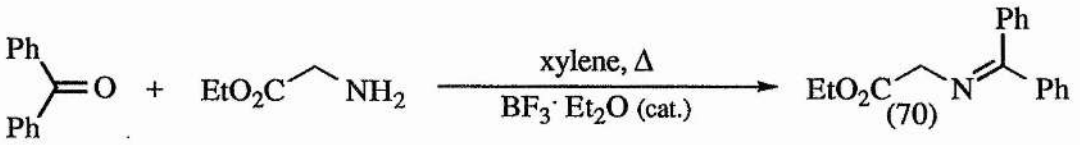
(69)

(95%)



(70)

(97%)

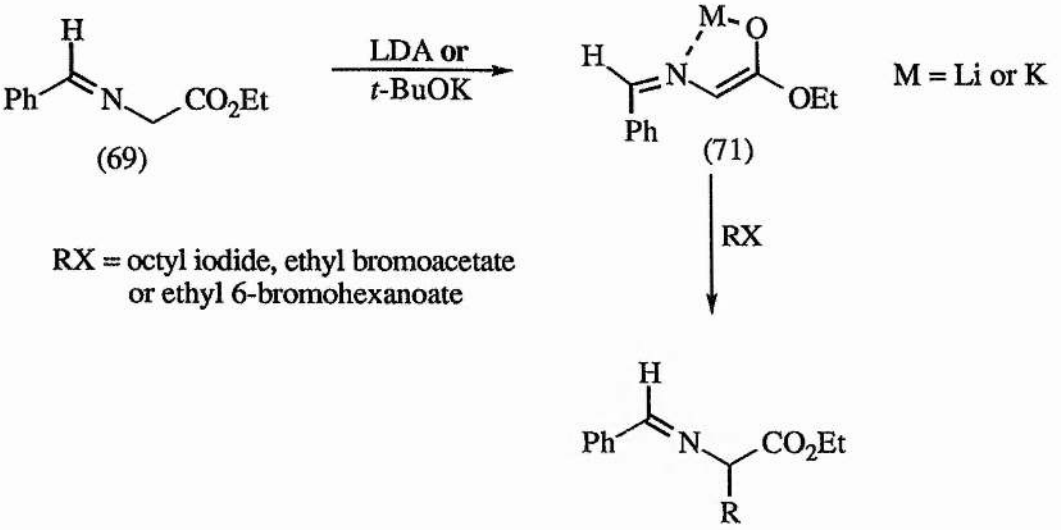


(82%)

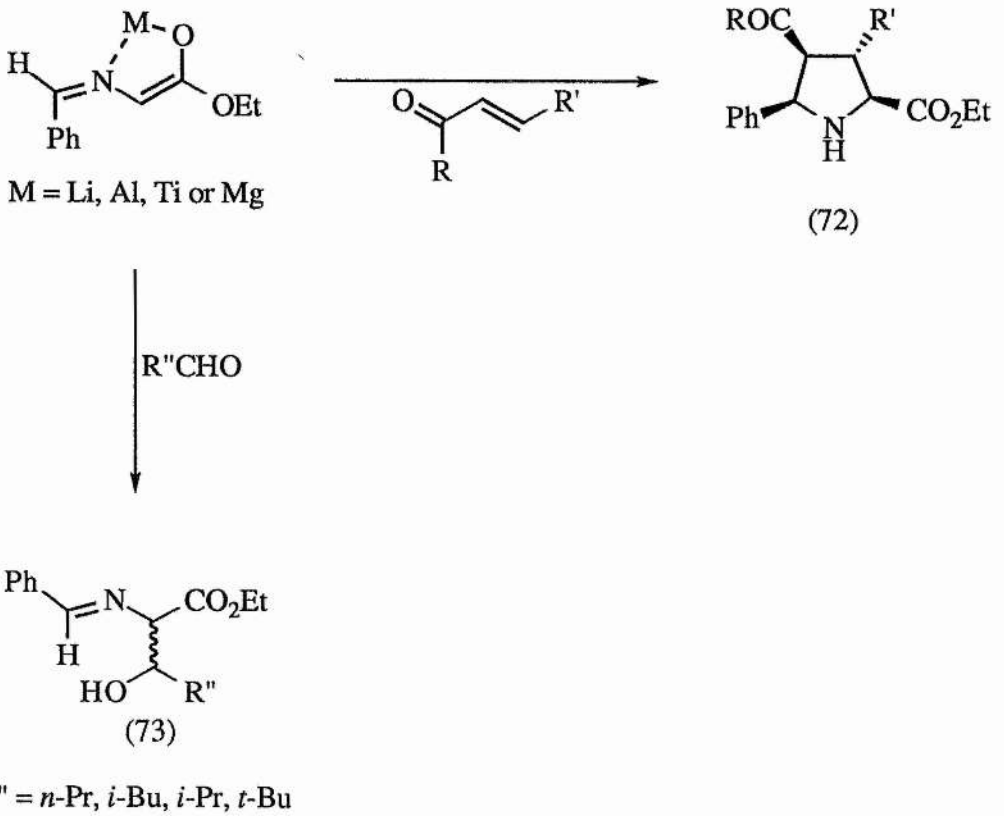
There have, however, been some questions raised over the stability of the benzylidene derivatives[72,76] and so it seems that the more favoured derivative is the benzophenone imine.

Reactions of these protected glycine derivatives can then be achieved by one of two means.

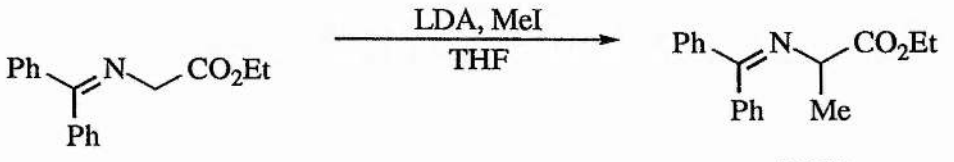
Deprotonation with either LDA or *t*-BuO K forms an enolate (**71**) which will then react with a variety of alkyl halides[72] for example.



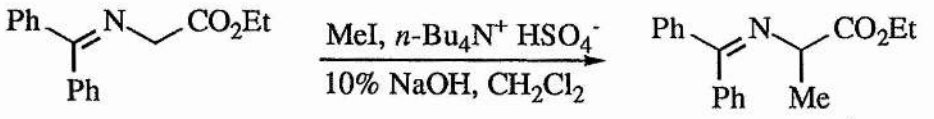
Metallation can also be achieved with a range of other systems[77], for example LiBr / Et_3N, LiBr / DBU, Me_2Al / Et_3N, $TiCl_2(OPr^i)_2$ / Et_3N or Bu^tMgCl giving similar enolates to those shown in the above scheme. These can then be reacted with a range of α,β-unsaturated systems to give imidazoline-4-carboxylates (**72**), or they can be reacted with aliphatic aldehydes to yield β-amino alcohols (**73**).



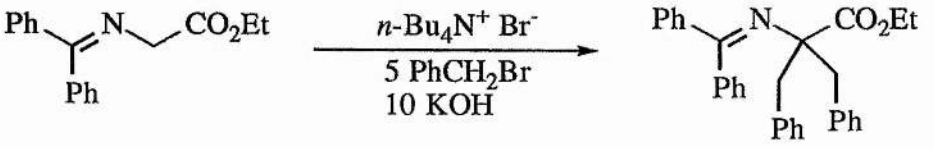
Benzophenone imine protected glycine esters have also been used in phase transfer catalysis reactions[75,76]. The yields of the products from these reactions are in general lower than from the corresponding anhydrous reactions but, like the anhydrous reactions, it is possible to tailor the reaction conditions to produce both mono- and disubstituted amino acid esters, for example the comparison shown below.



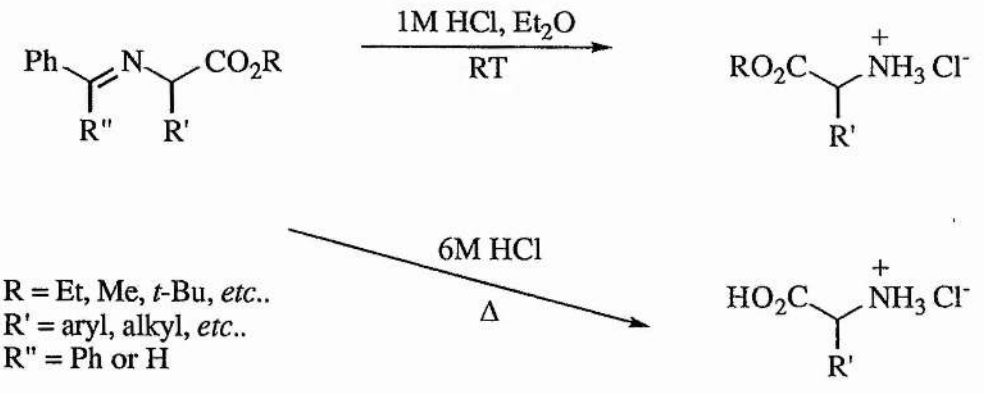
(93%)



(89%)

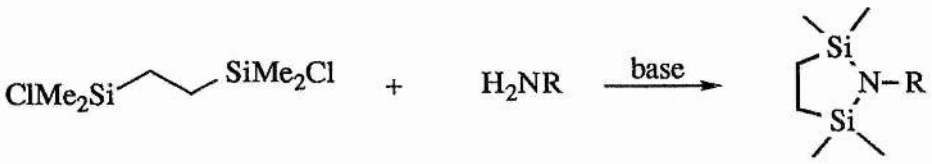


Removal of the Schiff base protecting group is achieved by simple stirring with a mineral acid. Heating with a more concentrated acid will also cleave the ester function giving the salt of the amino acid[75].



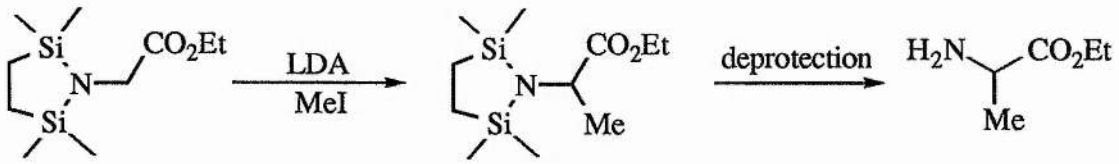
A second protecting group which has been used to protect the primary amine group of glycine ethyl ester is based around silicon. Although in general silicon has a low affinity

for nitrogen causing it to be cleaved easily, the STABASE adduct (tetramethyldisilylazacyclopentane adduct) (**74**) has been shown to more stable[78].



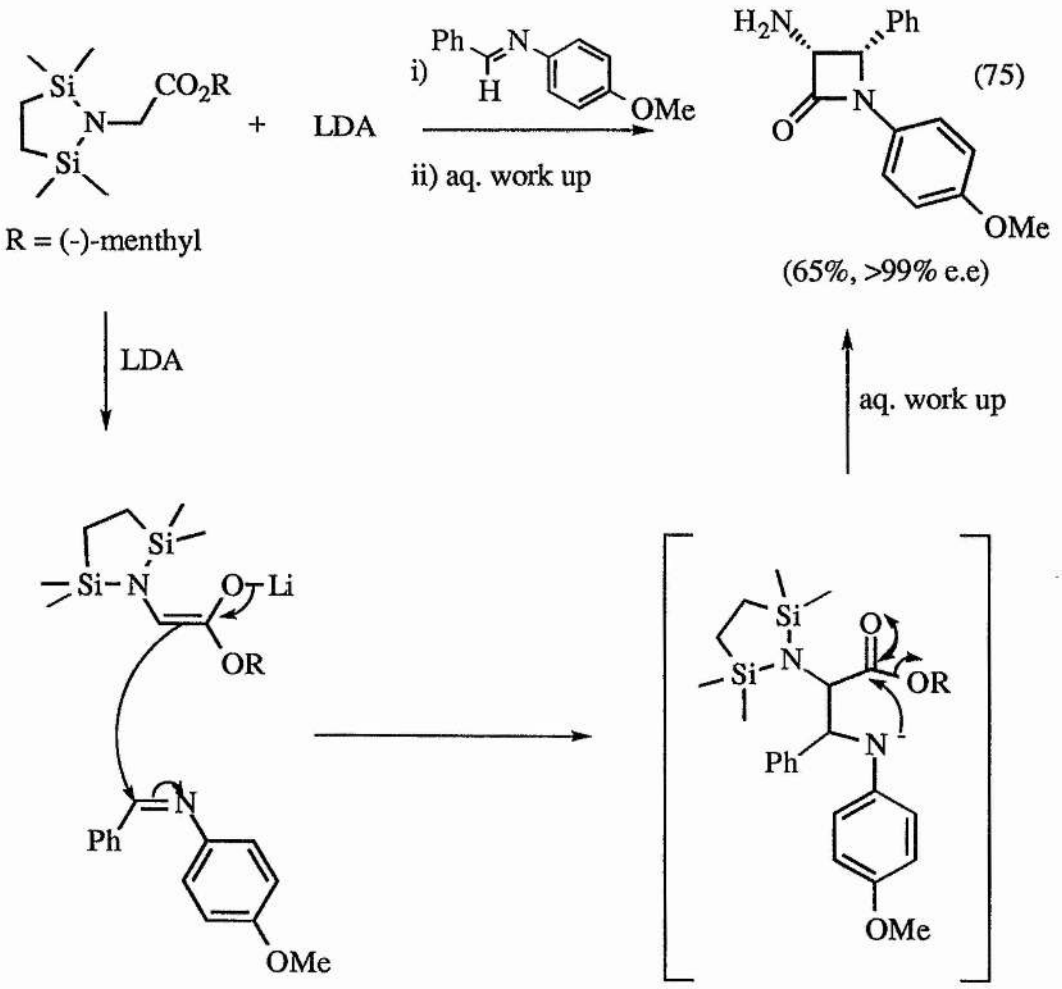
(74)

These systems have so far found only limited use but have been shown to be able to withstand strong base (LDA or *n*-BuLi), and can be cleaved under mild conditions in either an aqueous or anhydrous environment, for example.

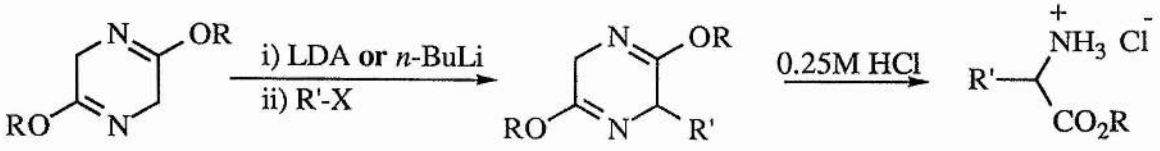


deprotection = pyridinium chlorochromate in CH_2Cl_2,
1M KOH, or
0.1M HCl

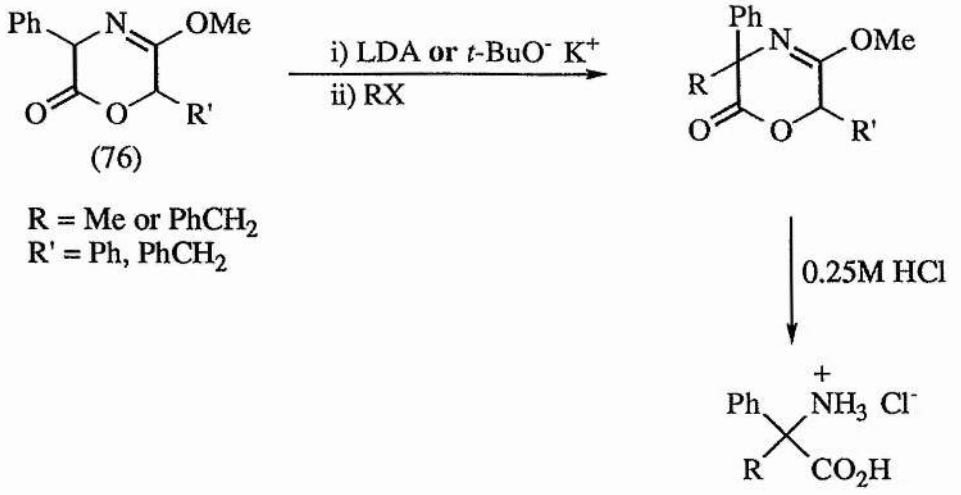
These systems have also found use in the asymmetric synthesis of some β-lactams[79] (**75**), which previously were shown to be useful as starting materials for diketopiperazine synthesis.



Arylglycines have also been synthesised from cyclic precursors. These cyclic starting materials can be dihydropyrazines[80] (**34**) or an oxygen analogue of them (**76**).



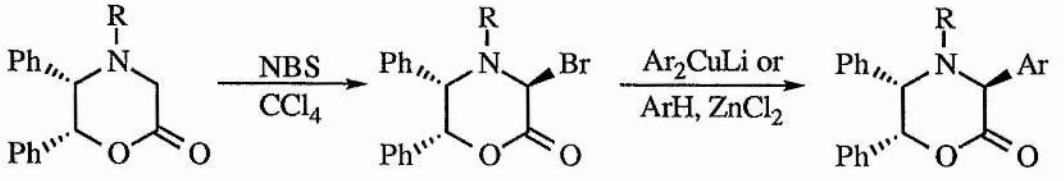
R = Me or Et
R' = alkyl, benzyl, *etc.*.



R = Me or $PhCH_2$
R' = Ph, $PhCH_2$

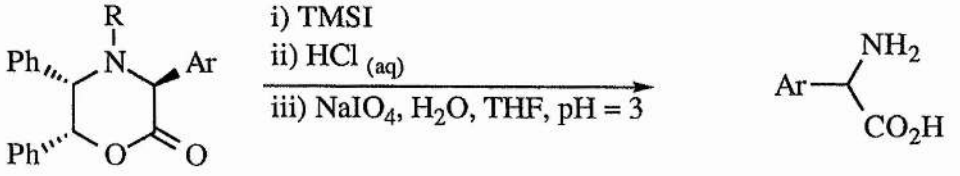
This area of chemistry to produce amino acids was exploited by Schöllkopf and co-workers[80].

Another example of using a cyclic precursor (77) was reported by Hendrix and Williams[81] who use a similar reaction to an acyclic example seen previously, namely the displacement of a bromine using a cuprate or electron rich aromatic under Friedel Crafts conditions.

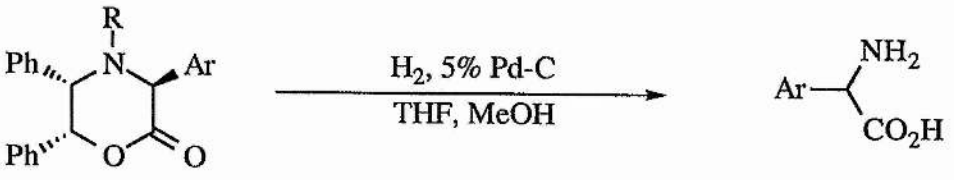


R = Boc or Cbz
Ar = Ph, 1-napthyl, furan

Cleavage of the resultant arylated heterocycle can then be achieved in one of two ways.



R = Boc
Ar = furan, 1-napthyl, Ph

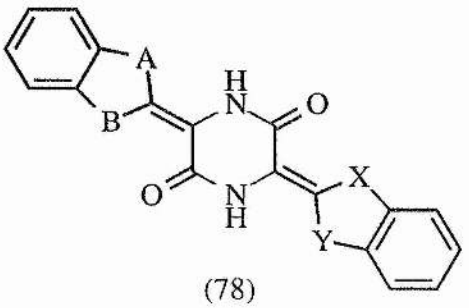


R = Cbz
Ar = furan

Results and Discussion

Results And Discussions

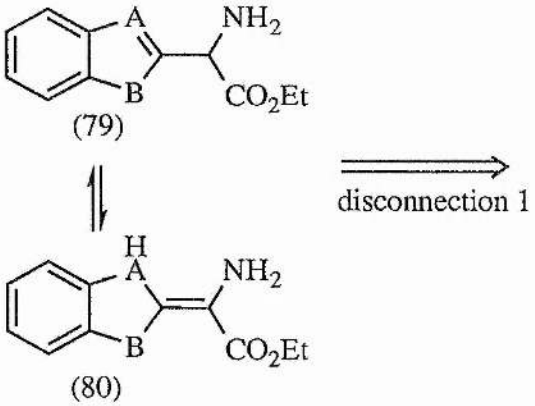
The aim of this project was to synthesise some novel heteroarylated dioxopiperazines of the general type shown below (**78**).



(78)

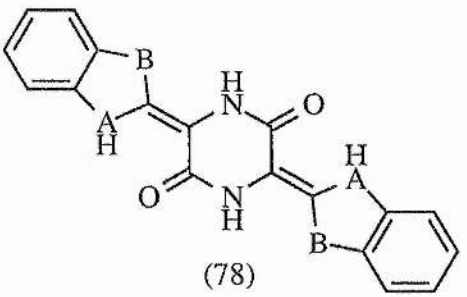
A, B, X, Y = NH, S, O, CO, CH_2

Two routes to these compounds were envisaged: these are based on the following disconnections:



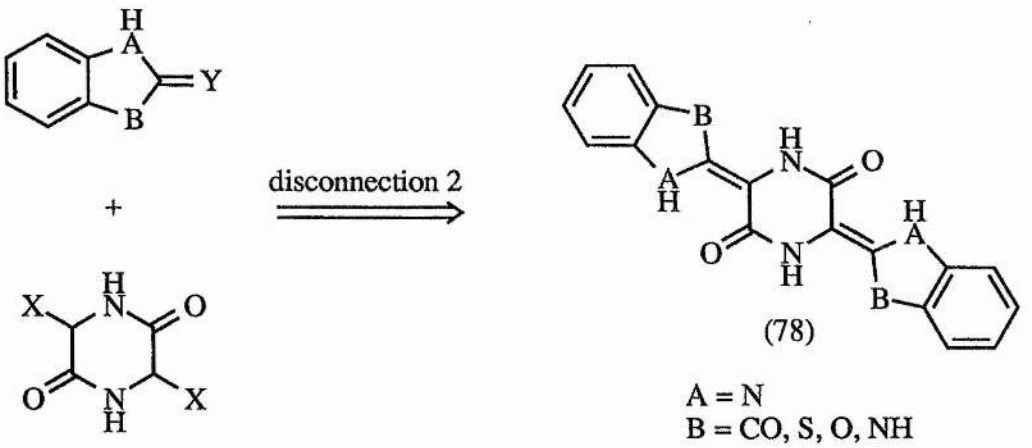
(79) ⇌ (80)

disconnection 1



(78)

A = N
B = CO, S, O, NH



X and Y = "activating" groups

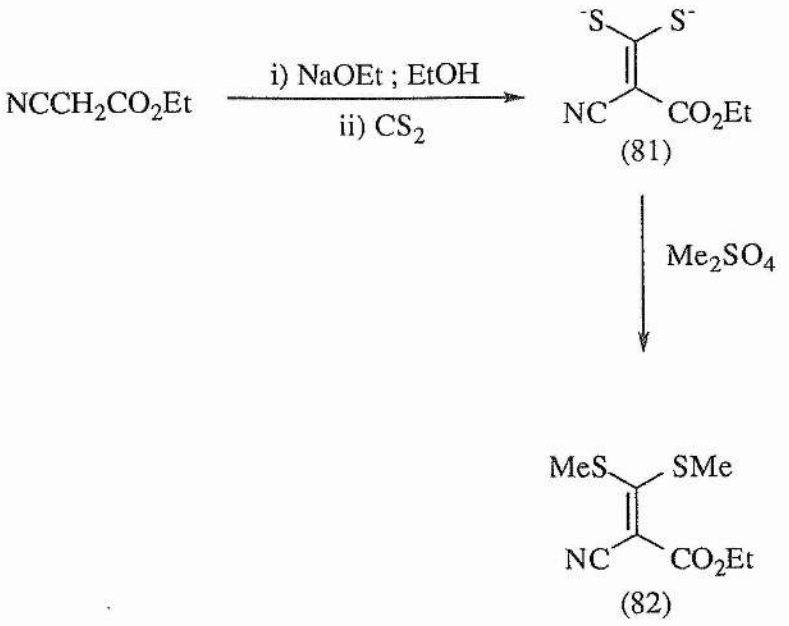
2.1 Disconnection 1

The first disconnection route, Disconnection 1, requires the synthesis of some heteroarylated glycine molecules of general type (**79**). These, if either A or B carry hydrogen, can be rewritten as enamines of general type (**80**). The synthesis of arylated amino acids has been recently reviewed[58] and also briefly covered in the Introduction.

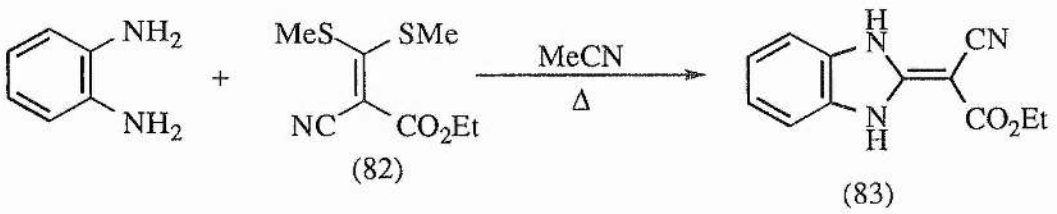
There are no reported synthetic procedures, however, for the formation of the heteroarylated glycine units required for this project, and so some alternative routes were examined.

2.1.1 Synthesis of Some Methylthioacrylate Derivatives

It has been shown that ethyl cyanoacetate will react with carbon disulfide under basic conditions to give the adduct (**81**), which upon methylation gives the bis(methylthio) derivative (**82**)[82].

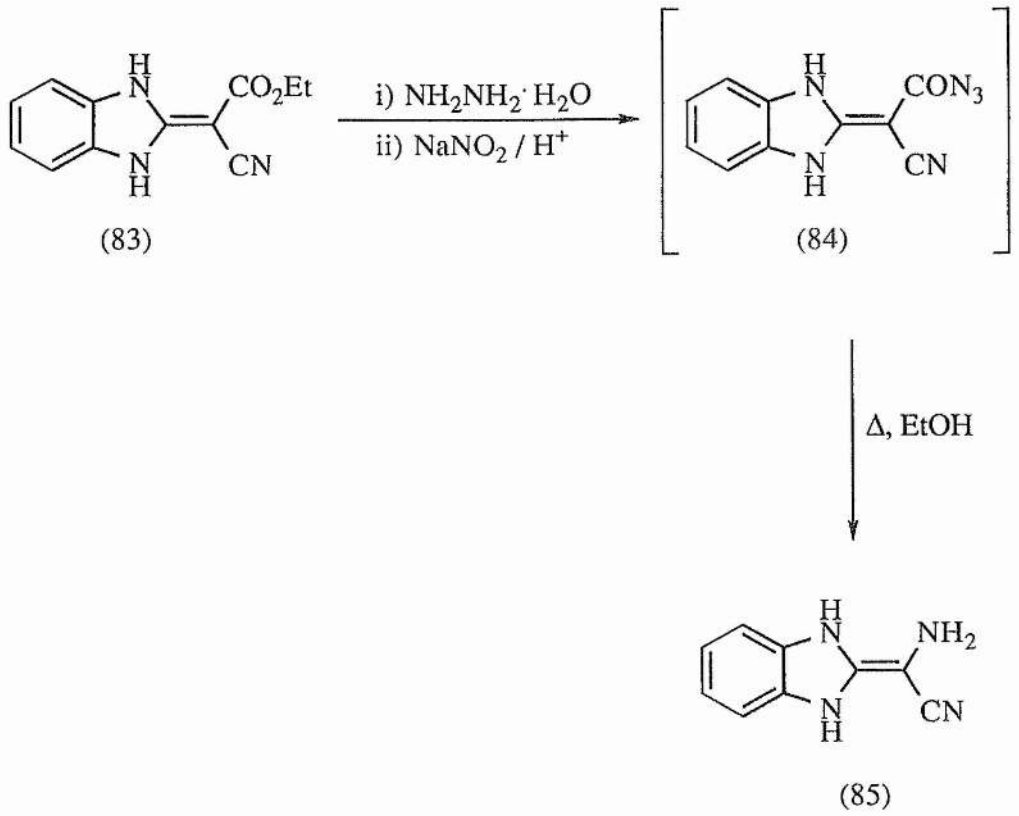


Methylthio groups have been shown to be easily displaced by nitrogen nucleophiles[83] and so it was hoped that the reaction of the bis(methylthio) derivative (**82**) with *o*-phenylenediamine might afford the benzimidazole (**83**).



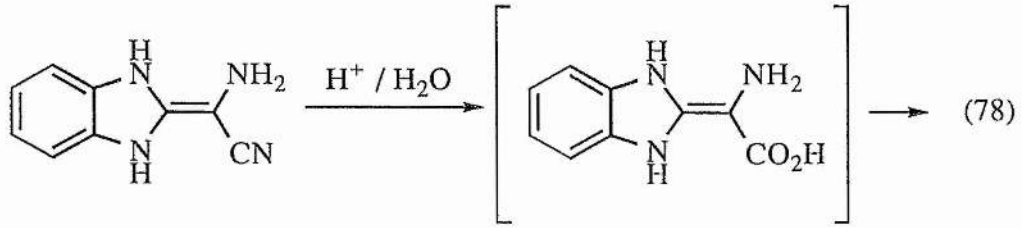
The reaction of ethyl cyanoacetate with ethanolic sodium ethoxide then carbon disulfide and followed by methyl iodide gave the bis(methylthio) derivative (**82**) in good yield. Treatment of (**82**) with *o*-phenylenediamine in refluxing acetonitrile gave an excellent yield of the required benzimidazole (**83**).

It is known that ester functions can be converted into amines through an isocyanate intermediate using a modified Curtius rearrangement[84,85,86]. The proposed route therefore involves the reaction of the benzimidazole (**83**) with hydrazine which when followed by diazotisation of the hydrazide would give the azide (**84**). Rearrangement of compound (**84**) in the normal way would then give the amine (**85**).



(83) (84) (85)

It was hoped that the nitrile could then be converted to the carboxylic acid *via* hydrolysis in aqueous acid to give the required functionalised glycine (**86**) which could then be cyclised to the target molecule (**78**).

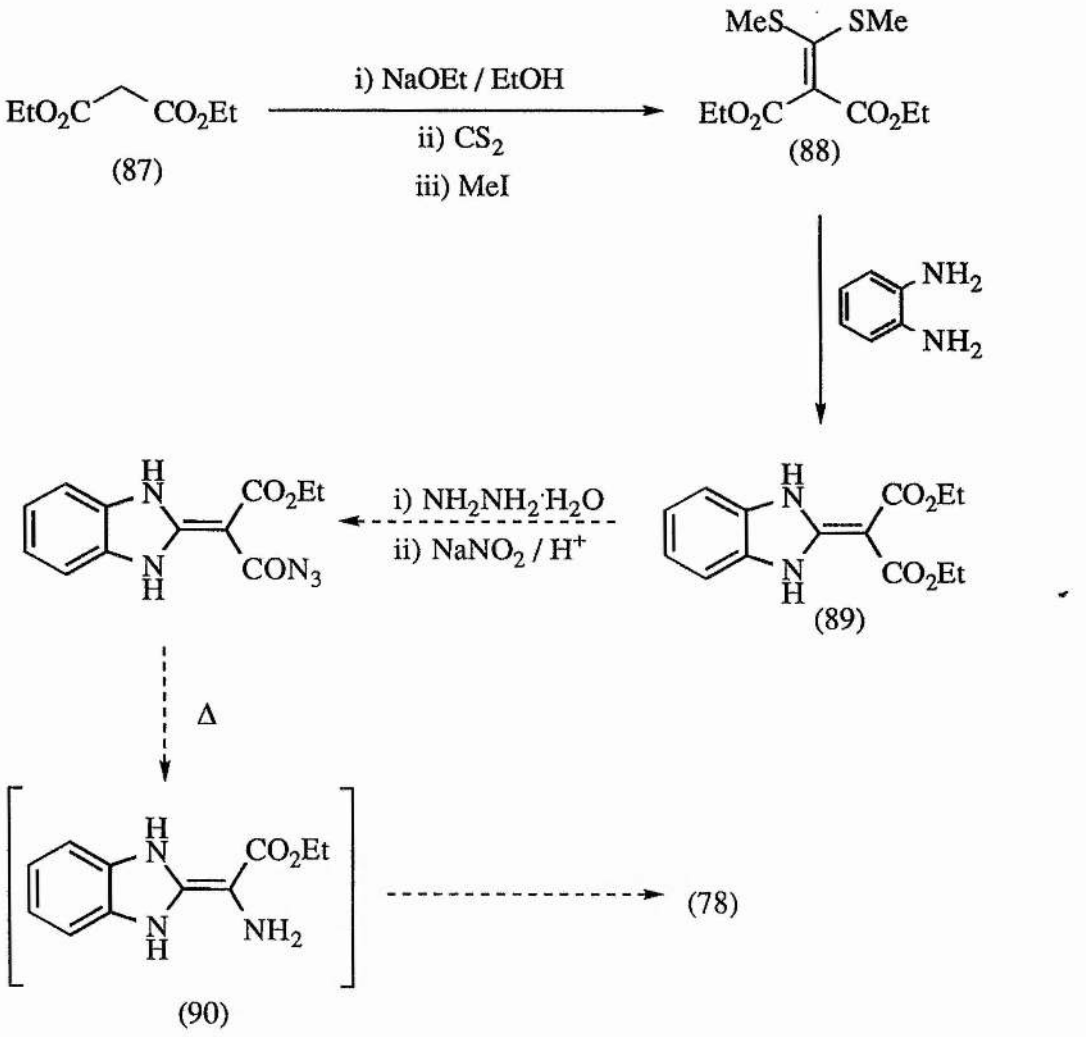


(86)

Heating a suspension of the benzimidazole (**83**) and a large excess of hydrazine monohydrate in ethanol for several hours failed to give any of the desired product, only unchanged starting materials were recovered. A change of solvent from ethanol to

1,4-dioxan increased the reflux temperature but this too failed to give any reaction and again only unchanged starting materials were recovered.

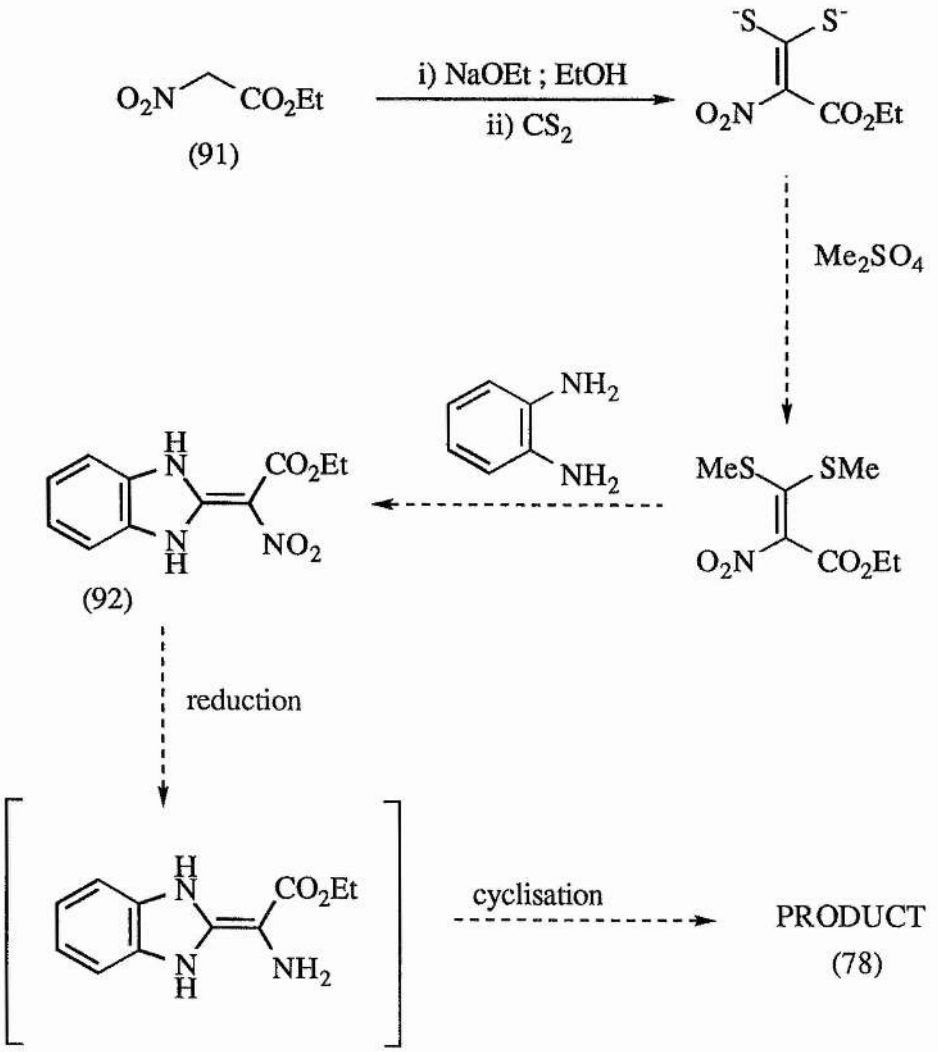
A second possibility, following the same ideas, is to form the bis(methylthio)methylidene derivative (**88**) of diethyl malonate (**87**) which following its reaction with *o*-phenylenediamine could then be treated with hydrazine hydrate. Diazotization of the hydrazone followed by a Curtius rearrangement would give the amine (**90**), which may then spontaneously cyclise to (**78**).



Following the same procedure for the synthesis the compound (**82**) (p. 42) the anion of diethyl malonate (**87**) was treated with carbon disulfide, followed by methyl iodide, to give the bis(methylthio)-compound (**88**) in good yield.

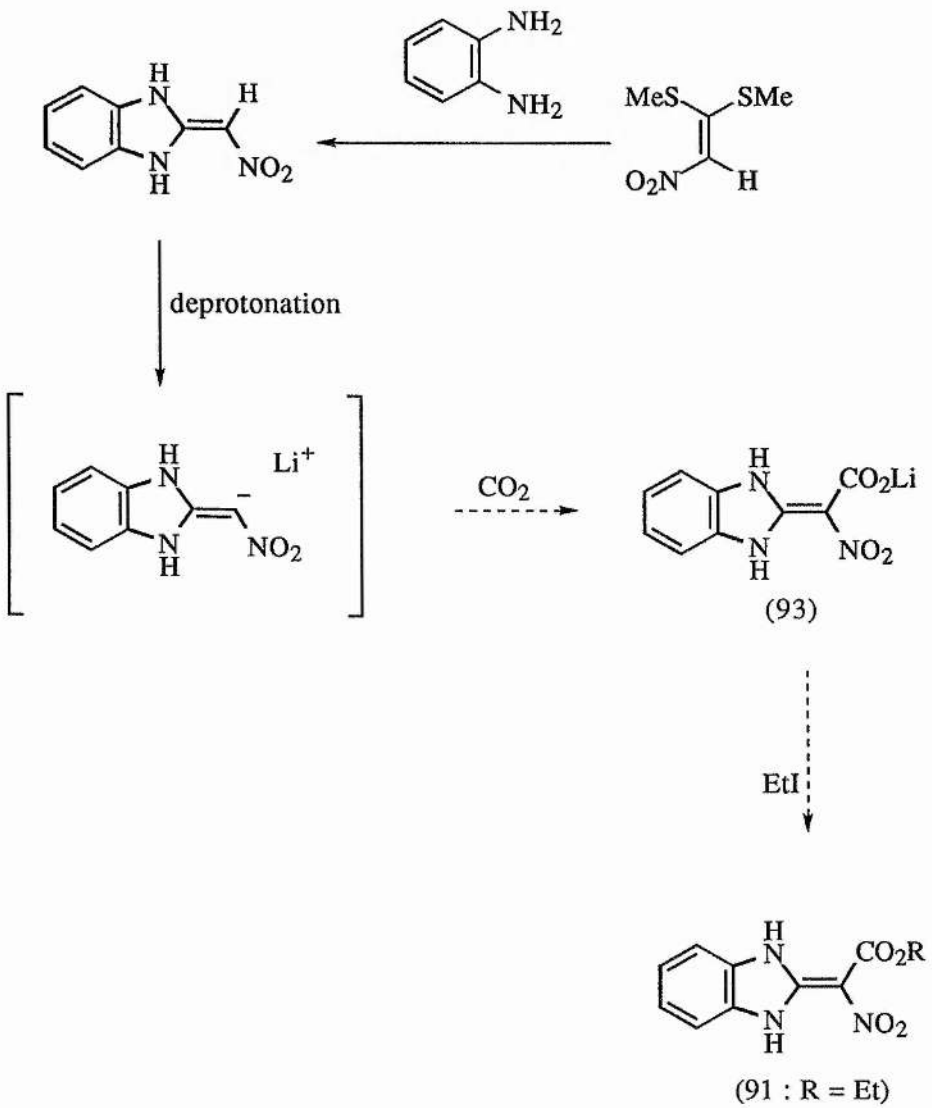
Reaction of this with *o*-phenylenediamine gave, after purification, the required benzimidazole (**89**).This was then treated with hydrazine hydrate in a similar method described above,but this too failed to give any of the hydrazide intermediate. Upon work up of the reaction mixture only unchanged starting materials were recovered.

A third possibility is to follow the above route using ethyl nitroacetate (**91**) instead of the malonic ester to give a benzimidazole of the type (**92**), and this, following reduction of the nitro function to an amino group[87] might give the required intermediate which could then cyclise to give (**78**).



Reaction of ethyl nitroacetate (**91**) with ethanolic sodium ethoxide followed by carbon disulfide failed to give any of the desired bis(methylthio) derivative: only unchanged starting materials were recovered. This lack of reactivity is thought to be due to the extensive delocalisation of the anion throughout the molecule And this will then reduce its nucleophilicity and therefore prevent reaction. Indeed it is known that the methylene protons in ethyl nitroacetate (**91**) are sufficiently acidic, that deprotonation can be achieved using KF[88].

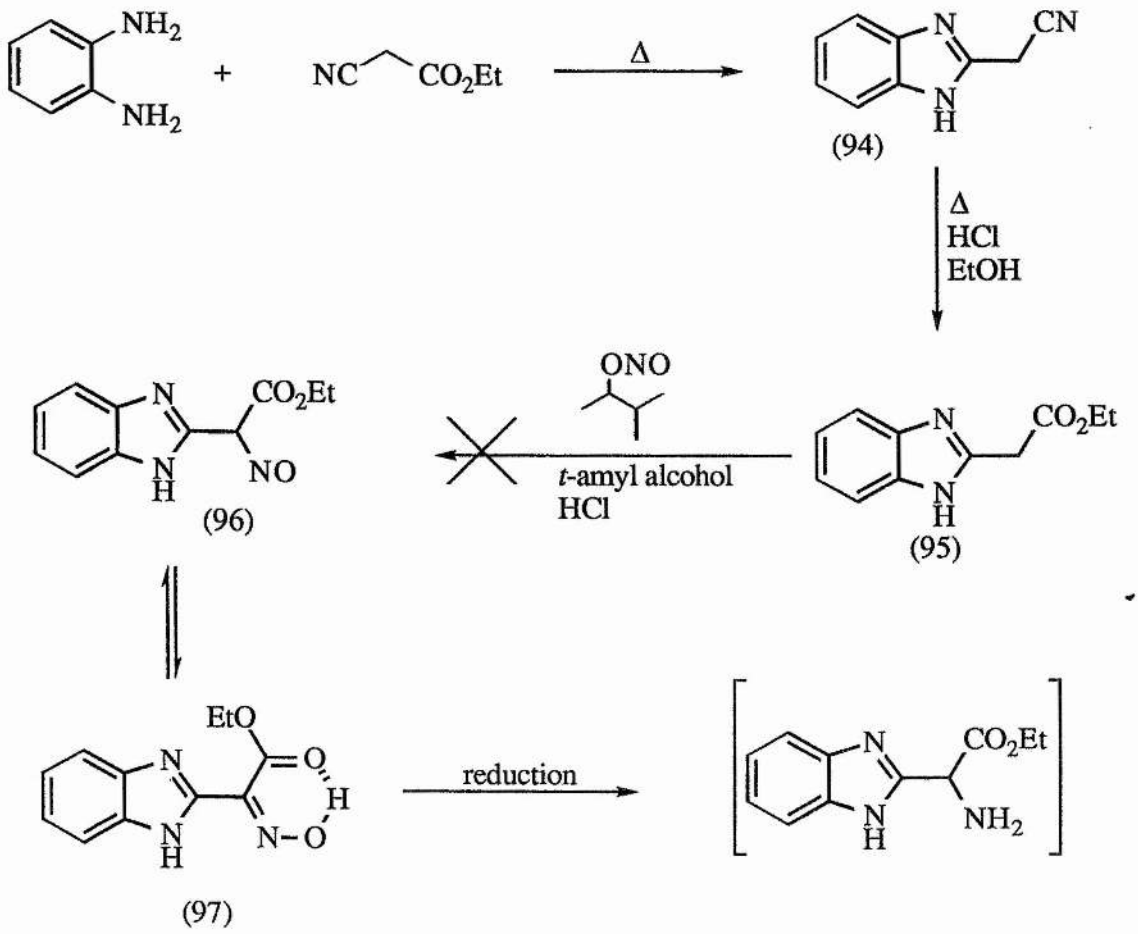
An alternative possible route to the intermediate (**92**: R = Et) entails reaction of *o*-phenylenediamine with 1,1-bis(methylthio)-2-nitroethylene followed by deprotonation α– to the nitro function and quenching with carbon dioxide to lead to the carboxylate salt (**93**).



A solution of 1,1-bis(methylthio)-2-nitroethylene and *o*-phenylenediamine was heated under reflux in acetonitrile for several hours. Upon cooling the mixture only unchanged starting materials were recovered.

2.1.2 Synthesis of Derivatives of 2-(Cyanomethyl)benzimidazole

Another possible route to the desired arylated amino acid ester (**79**) involves the amination of a suitably activated methylene group thus.



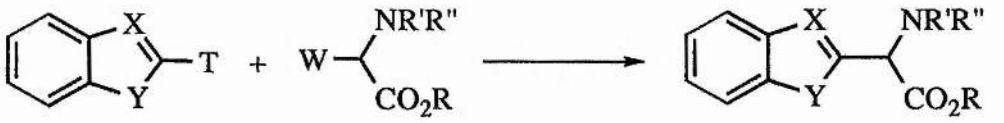
The synthesis of the required 2-(cyanomethyl)benzimidazole (**94**) followed by conversion to the ester (**95**) was reported by Copeland and Day[89]. Accordingly *o*-phenylenediamine and ethyl cyanoacetate were heated together and the desired benzimidazole (**94**) isolated in moderate yield. This was then converted into the ethyl ester (**95**) in good yield by reaction with ethanolic hydrogen chloride.

The nitrosation to give (**96**), or possibly the tautomer (**97**) was then attempted using isoamyl nitrite. The ester (**95**) was stirred with isoamyl nitrite in *t*-amyl alcohol containing hydrochloric acid following the first part of a procedure for the synthesis of butane-2,3-dione dioxime[90].

After several hours the reaction mixture was worked up and the only product isolated from the reaction was unchanged starting ester (**95**).

2.1.3 Investigations into Suitable Amine Protecting Groups

Another route to the required arylated glycine involves the coupling of a suitably protected glycine unit with the desired heterocycle thus:



X = N, Y = CO, CH_2, S, O
X = CH, Y = S, O

(79 : R = Et, R'=R"=H)

T, W = "activating groups"

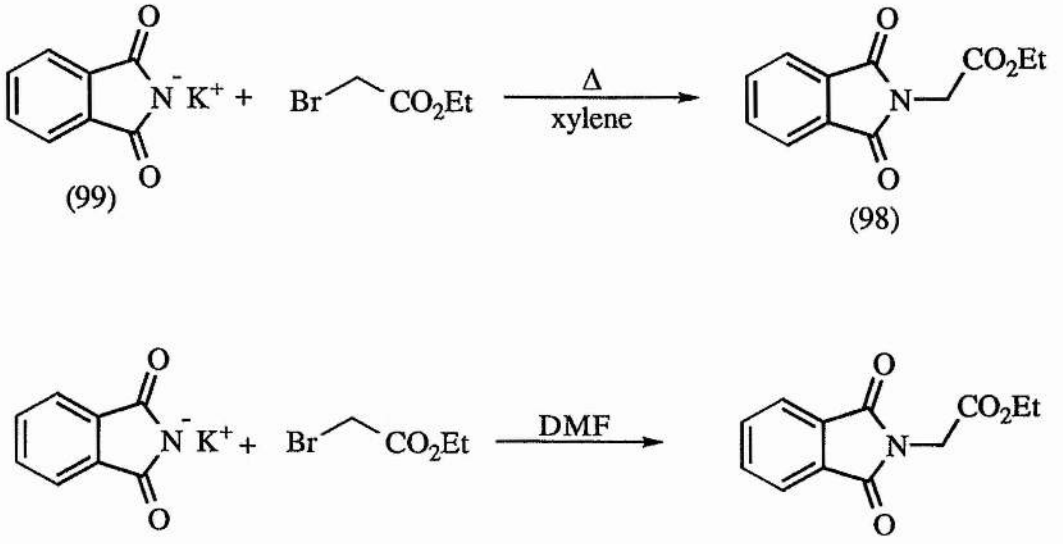
There are many potentially useful amine and carboxyl protecting groups (R, R' and R" above) described in the literature[91], some more suited to these systems than others.

The most prevalent and easily accessible carboxylate protecting group (R above) is an ester, typically methyl, ethyl or benzyl. The range of suitable amino protecting groups is, however, much wider.

2.1.3.1 The Phthalimido Group

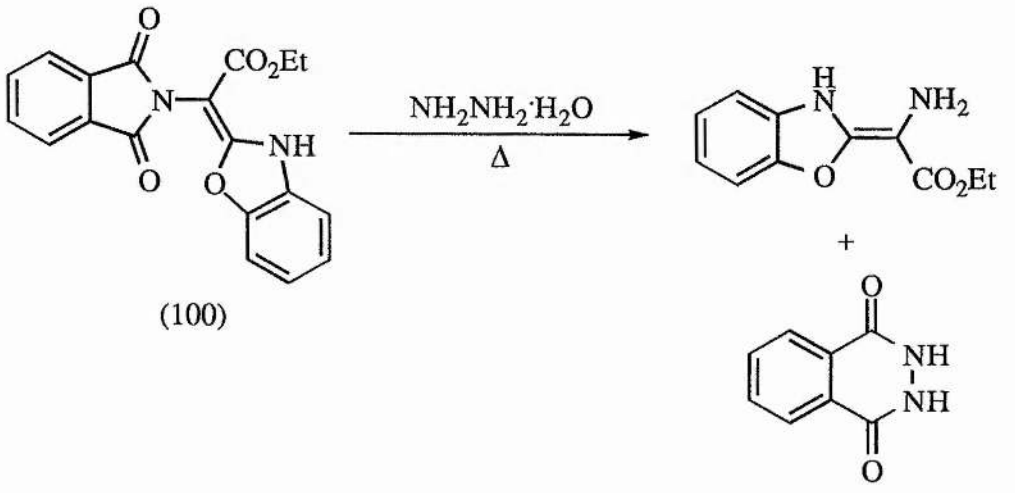
Initially it was believed that a phthalimido-protected glycine ethyl ester would be a useful starting material since it was thought possible that deprotonation of the methylene group using a strong base would form an anion which could then be reacted with an electrophilic aromatic heterocycle.

The synthesis of phthalimidoglycine ethyl ester (**98**) was first reported by Gabriel[92]. This involved potassium phthalimide (**99**) in xylene reacting with ethyl bromoacetate. An improvement in this synthesis was reported[93] which, by changing the solvent from xylene to DMF, shortened the reaction times and improved the yields.

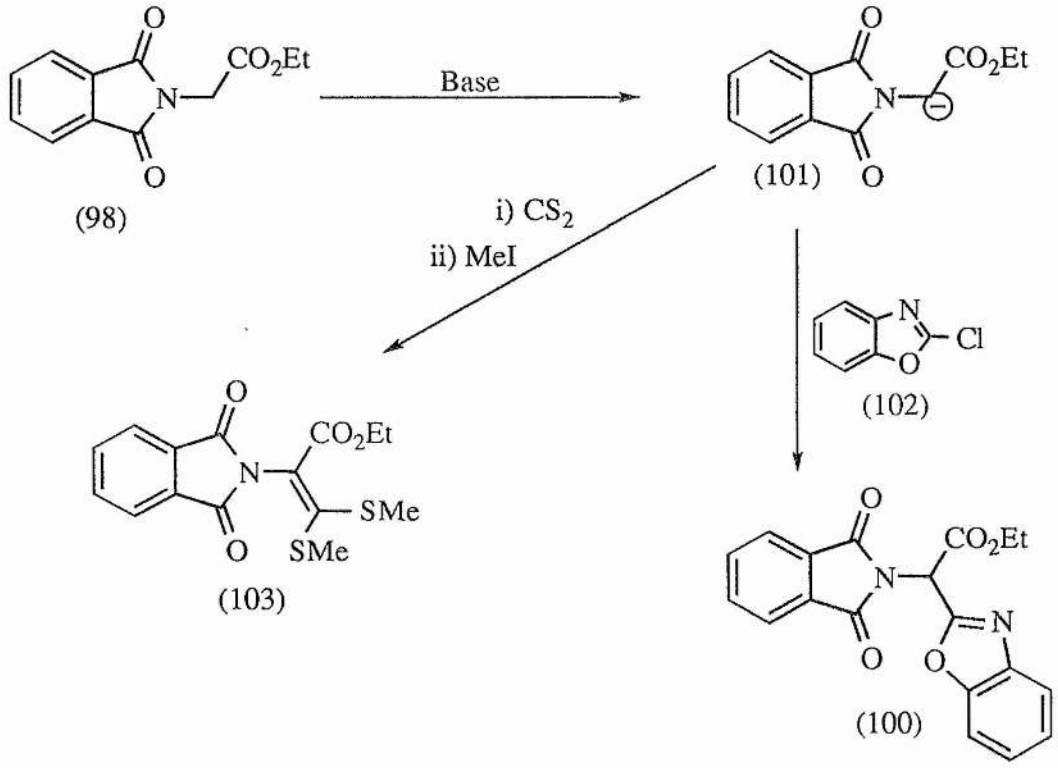


Accordingly potassium phthalimide (**99**) and ethyl bromoacetate were reacted in DMF to give the required product (**98**) in good yield (>75%).

The intention was for protected glycine ester (**98**) to be treated in basic media with 2-chlorobenzoxazole (**102**), and for the protecting group to then be removed by reaction with hydrazine hydrate. [It had already been observed (p. 43) that the ester group was likely to be unaffected under these conditions].



Deprotonation of the phthalimido-protected glycine ester (**98**) was attempted with a range of bases in the hope of forming the anion (**101**) which could then be reacted further with either 2-chlorobenzoxazole (**102**) to give (**100**), or carbon disulfide followed by methyl iodide to give (**103**).



The first base chosen was *n*-butyl lithium. After a low temperature deprotonation followed by addition of 2-chlorobenzoxazole and work-up the resultant oil showed many products by TLC.

The two major spots on the TLC plate were isolated by chromatography and are believed to be the alcohols derived from the nucleophilic attack of the butyl group on the carbonyls of the ester group and the phthalimido- group. Due to the complex mixture of products and the nucleophilicity of the base, use of this particular base was abandoned.

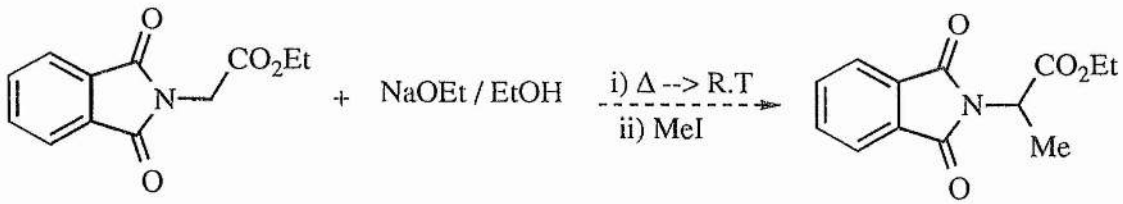
Sodium hydride was the next base chosen due to its distinct lack of nucleophilic character and also its strength as a base. Attempted deprotonation of (**98**) with sodium hydride followed by addition of 2-chlorobenzoxazole and an aqueous work-up gave, surprisingly, a large number of products by TLC: the major two spots (which made up about 95% of the crude mixture) corresponded with the starting materials.

A third base chosen was lithium diisopropylamide (LDA) since it is a strong, hindered, non-nucleophilic base which can be used at low temperatures and therefore minimise any unwanted side reactions taking place.

The reaction was performed at low temperature (-78°C) and the electrophile was again 2-chlorobenzoxazole. This time, after an aqueous work-up, the TLC showed mainly baseline material and so this material was isolated *via* chromatography and found to contain none of the proposed product (**100**), only unidentifiable decomposition products.

The reactions of (**101**) with carbon disulfide were no more successful. Gompper *et al*[82] did report success in this field by reacting activated methylene groups with sodium ethoxide in ethanol followed by carbon disulfide. Attempted reaction with the phthalimido-protected glycine (**98**) followed by addition of carbon disulfide then methyl iodide gave none of the expected product (**103**), only recovered starting materials. The suitability of the alkoxide base for deprotonation of these types of systems was then examined.

Deprotonation to give the anion (**101**) was attempted using sodium ethoxide in ethanol both at room temperature and also at reflux, and both reaction mixtures were quenched with methyl iodide.



(104)

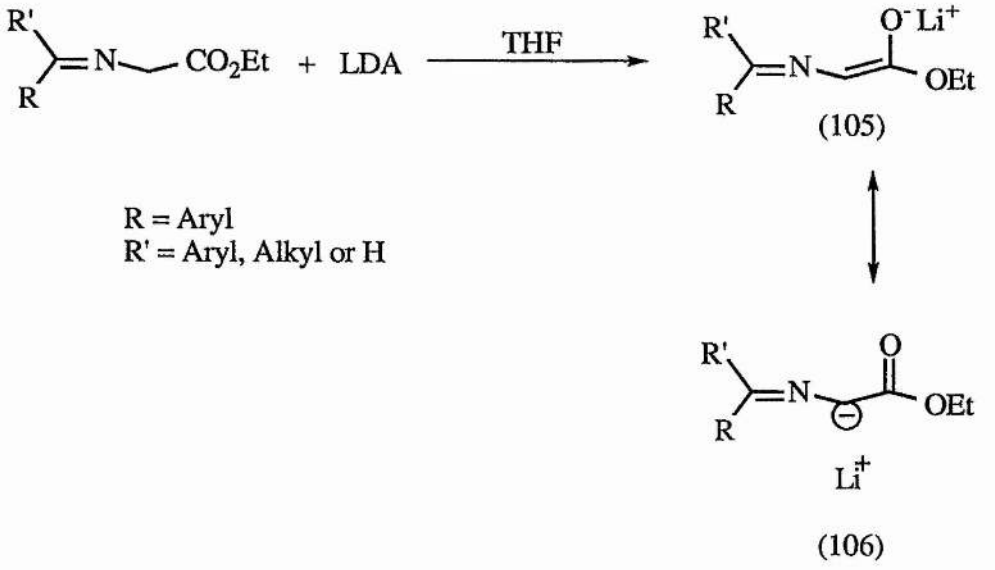
The mixtures were then worked up and the ^1H nmr spectrum of the crude mixture showed no sign of any of the product (**104**), only unreacted starting materials.

Finally sodium hydride was again used as the base, although on this occasion CS_2 was used as the electrophile. After stirring (**98**) for several hours with the base, and quenching with CS_2 followed by reaction of the crude mixture with methyl iodide, only starting materials were recovered from the mixture.

The use of the phthalimido-protected glycine ester (**98**) as a possible masked glycine ester was then abandoned.

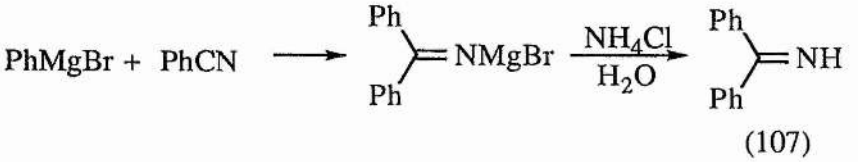
2.1.3.2 The Diphenylmethylidene Group

Aldimine- and ketimine- protected glycine esters have been shown to react with strong, non-nucleophilic bases, for example LDA, thus[77]:



The anion (**105**) has then been shown to react at C-2 (*i.e.* as **106**) with a wide range of electrophiles, giving rise to a large number of *N*-protected amino acid esters.

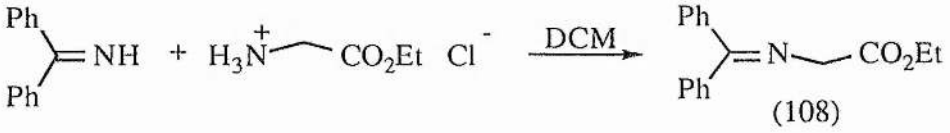
Reports have suggested, however, that the diphenylmethylidene (R = R' = Ph) is the most useful and versatile of the protecting groups[75]. The starting materials for the synthesis of the diphenylmethylidene protected glycine ester are easily obtained in moderate to good yields. Benzophenone imine (**107**) is made simply thus[94]:



(107)

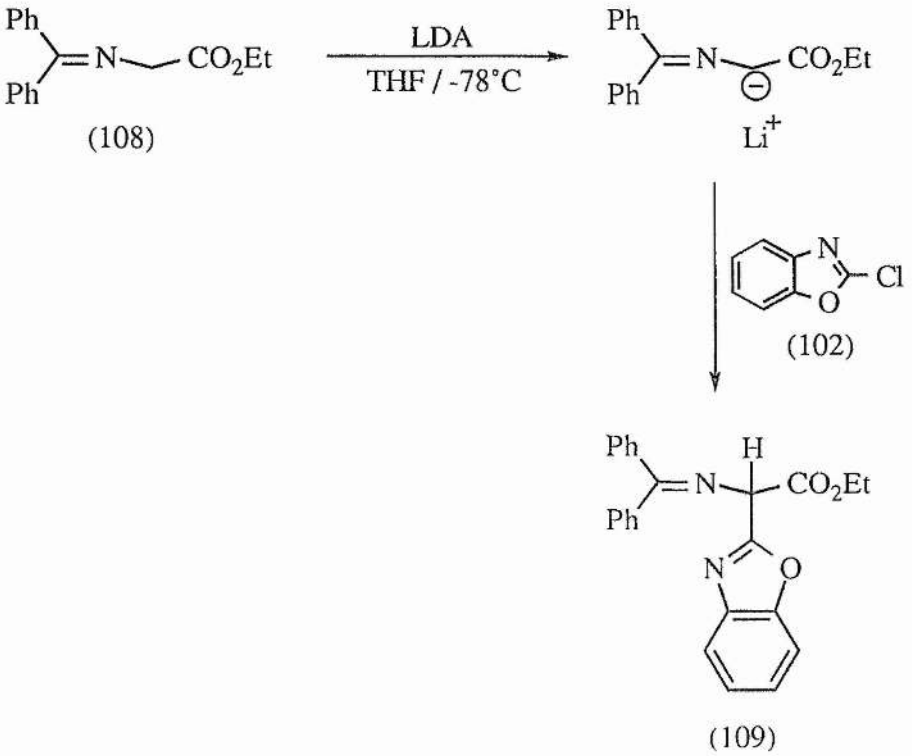
The crude benzophenone imine is then filtered away from any solids and distilled. The imine is quite surprisingly stable towards hydrolysis and can be stored for long periods under nitrogen.

Benzophenone imine was then added to a stirred suspension of glycine ethyl ester in dry dichloromethane and after 24 hours the mixture was filtered to give the diphenylmethylidene protected glycine ester (**108**) in excellent yield[95].



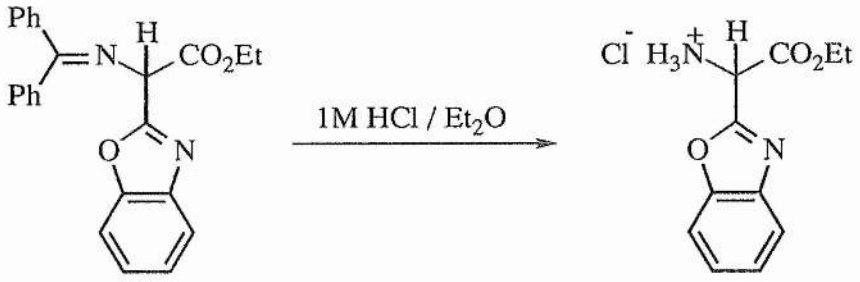
(108)

Reaction at low temperature of the imine (**108**) with LDA followed by addition of 2-chlorobenzoxazole gives after work-up and chromatography a reasonable yield of the product (**109**). Subsequently (p. 57) it was established, however, that the use of such a strong base was not required: potassium carbonate is in fact adequate for this deprotonation.



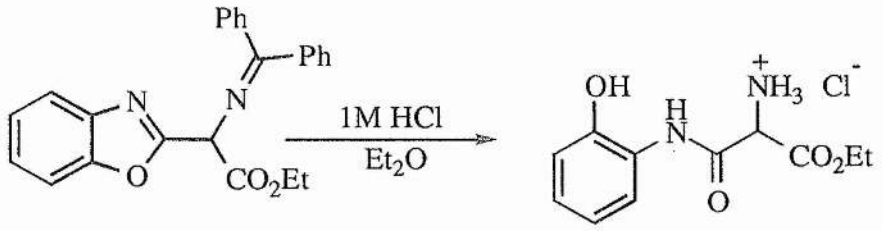
(108) (102) (109)

It was hoped that hydrolysis of the imine group could be achieved quite simply by stirring with aqueous hydrochloric acid to give the hydrochloride salt (**110**) in good yield[95]. This salt could then be cyclised using the same method used for the formation of 2,5-dioxopiperazine[17,18].



(110)

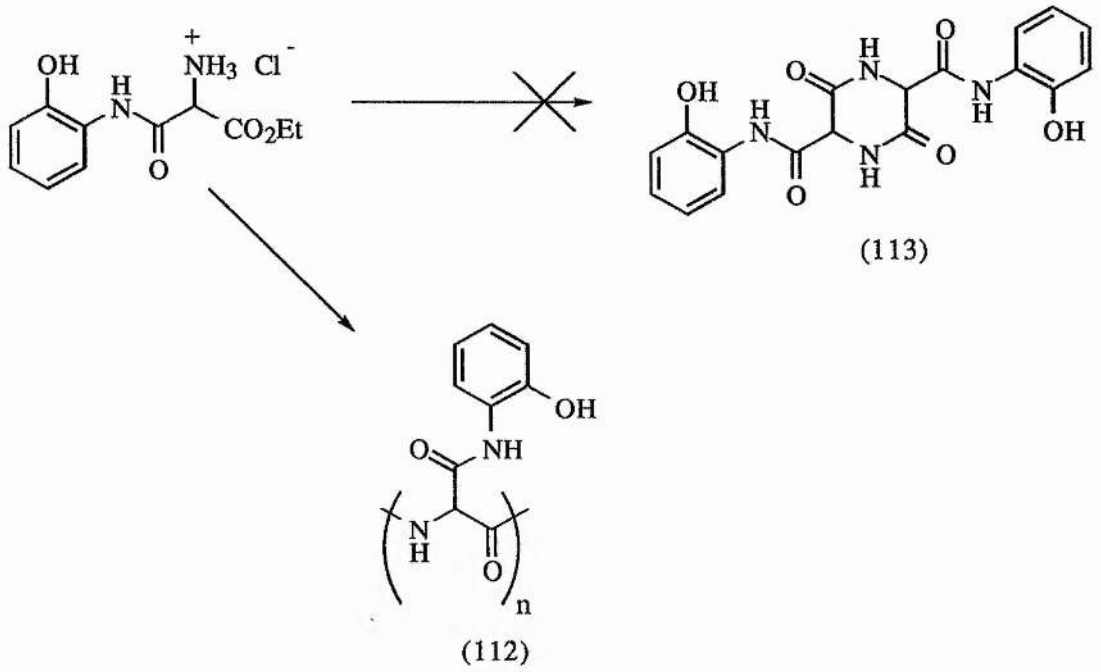
This proposed imine hydrolysis did occur but a second unexpected hydrolysis also occurred, namely hydrolysis of the oxazole ring leading to (**111**).



(111)

The formation of (**111**) was not deemed to be a great problem since *N*-acylated *o*-amino phenols can be cyclised to an oxazole ring with a variety of dehydrating agents[96,97], the best of which is thought to be "polyphosphate esters" (PPE). This reagent has been shown to be mild enough to use with sensitive functionality[98]. "Polyphosphate esters" are simply synthesised by heating together diethyl ether and phosphorus pentoxide in chloroform. Interestingly the ether is consumed as a reagent during the reaction.

The attempted self condensation of (**111**) in a mixture of water and triethylamine gives a dark brown solid which is believed by mass spectral and nmr data to be a polymer of type (**112**). None of the desired product (**113**) was seen using this method for self condensation..

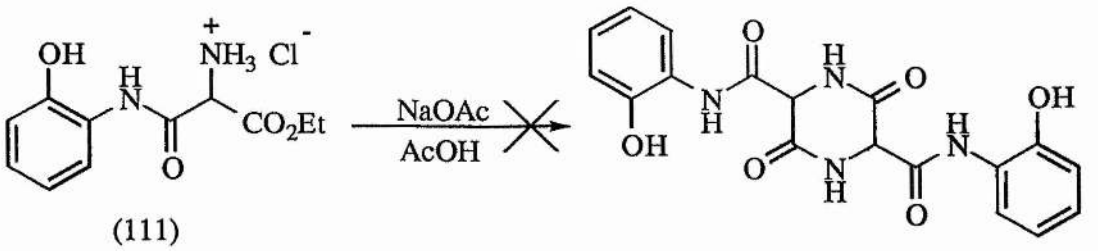


(113)

(112)

One attempt made to hydrolyse the diphenylmethylidene group of (**109**) without hydrolysis of the sensitive oxazole ring was using a catalytic amount of ammonium chloride in 'wet" ethanol. It was hoped that the ammonium chloride was sufficiently acidic to effect the hydrolysis of the imine group, leaving the oxazole ring untouched. The reagents were stirred at room temperature for 3 days but upon work-up of the reaction mixture, no reaction was observed to have taken place and only unchanged starting material was recovered.

An attempt was made using a buffered acetic acid/sodium acetate system to dimerise the hydrochloride (**111**) in an attempt to form (**113**).



(111) (113)

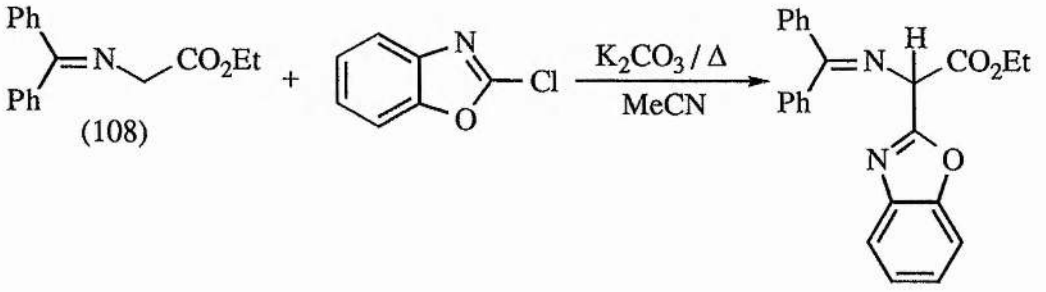
This failed to give any of the required product (**113**) and instead again appears (by mass spectral data) to have given a polymeric mixture of general type (**112**).

All attempts to cyclise the salt (**111**) in water by the addition of triethylamine have also failed to produce the product (**113**) but again gave, by mass spectral data, a polymeric mixture of general type (**112**).

The suitability of PPE to reform the oxazole ring was not examined as attempts to dimerise the hydrochloride (**111**) failed to give anything other than the polymer (**112**).

It has also been shown that heating to reflux a solution of the diphenylmethylidene-protected glycine ester (**108**) with a suitable electrophile in dry acetonitrile with finely powdered potassium carbonate leads to the reaction of the electrophile with the protected glycine ester with the electrophile being bound to the C-2 of the glycine[99].

This method was then applied to the synthesis of (**109**) thus :



(108) (109)

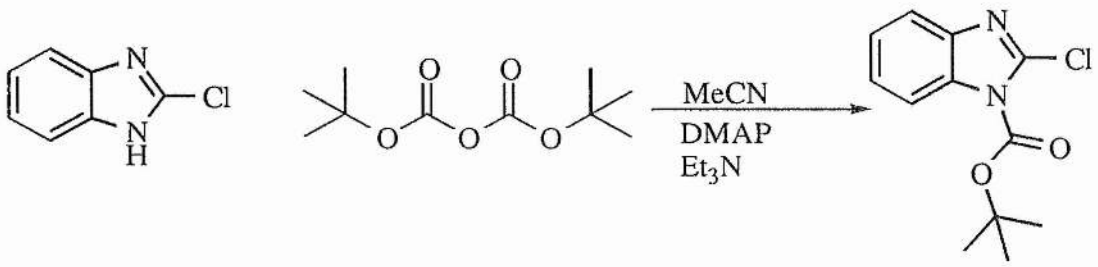
After several hours heating, removal of the solid by filtration, and concentration of the filtrate, a TLC showed the presence of starting materials and also some product. ^1H nmr of the crude product then showed the mixture to contain about 30% of the desired product

(**109**) with the remainder being unchanged starting materials. This crude yield is lower than the yield from the LDA approach, and so this method was ignored.

The 2-chlorobenzoxazole electrophile was then replaced by 2-chlorobenzothiazole and 1-(*t*-butoxycarbonyl)-2-chlorobenzimidazole in the above LDA reaction to obtain three of the desired target molecules in varying yields.

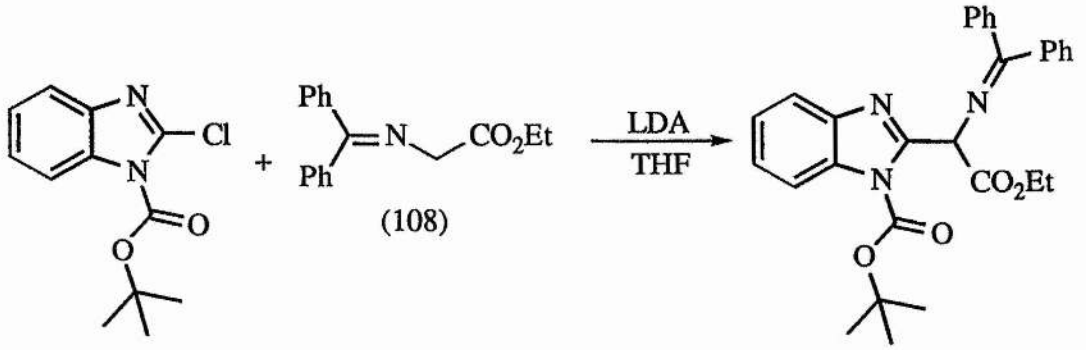
The use of 2-chlorobenzothiazole as the electrophile gave the desired product in good yield [using the LDA approach] but the product was found to be highly unstable upon standing, even when refrigerated, and so the synthesis was not repeated until a satisfactory method for the removal of the diphenylmethylidene protecting group was found.

The use of 1-(*t*-butoxycarbonyl)-2-chlorobenzimidazole as the electrophilic heterocycle first requires the synthesis of 2-chlorobenzimidazole followed by protection of the nitrogen. 2-Chlorobenzimidazole can be made (in variable yields) by the reaction of benzimidazolone (2-hydroxy-benzimidazole), phosphorus oxychloride and hydrogen chloride. The *t*-Boc protected 2-chlorobenzimidazole (**114**) is made quite simply from 2-chlorobenzimidazole and di-*t*-butyl dicarbonate following a standard literature procedure for the protection of the nitrogen in pyrrole[100]. Surprisingly the protected 2-chlorobenzimidazole (**114**) does not appear in the literature as a known compound.



(114)

Reaction of compound (**114**) with the anion of the diphenylmethylidene protected glycine ethyl ester (**108**) gives, after work-up and chromatography, the desired product (**115**), although in relatively poor yield (26%).

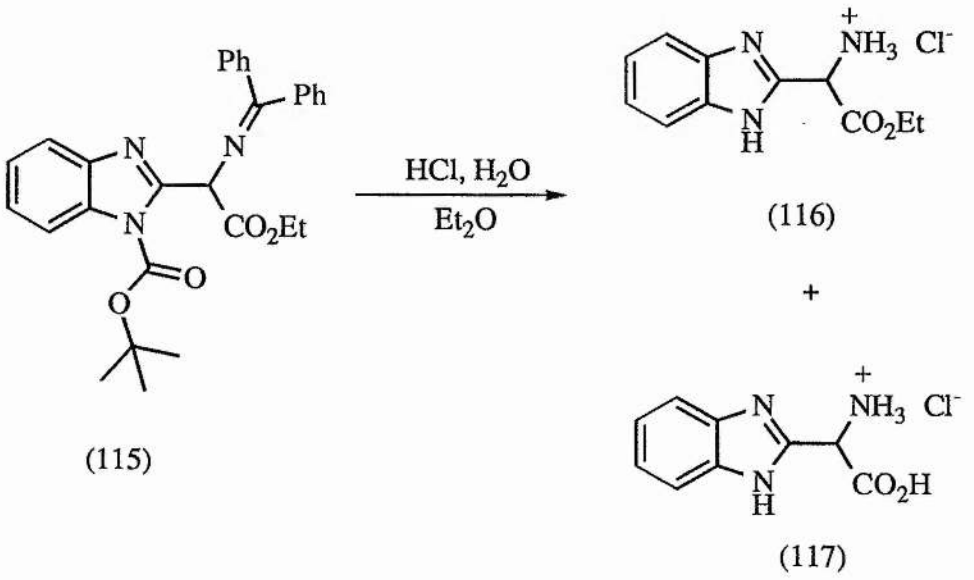


(114) (108) (115)

Attempts to increase the yield of (**115**) by varying the reaction conditions and reaction times have all been unsuccessful and the average yield is still only around 30%.

Deprotection of (**115**) also proved to be less than straightforward. When the literature procedure[77] was followed, by stirring the protected amino acid ester dissolved in ether with dilute mineral acid, a fluorescent green aqueous layer was formed which, upon evaporation, gave a green/yellow solid.

The ^{1}H nmr spectrum of the crude solid showed that not only had the diphenylmethylidene group been removed, (a process which can be confirmed the presence of benzophenone in the ether layer), but also partial de-esterification of the desired product (**116**) (as shown by ^{1}H nmr) appears to have taken place giving, presumably, the acid (**117**).



(115) (116) (117)

This caused many problems in the isolation of either the ester (**116**) or the acid (**117**). Monitoring the reaction closely by TLC, observing the formation of benzophenone and the loss of the starting material (**115**), failed to result in any improvement. The unwanted de-esterification of (**116**) may be due to the long reaction time and so ways to reduce this were examined.

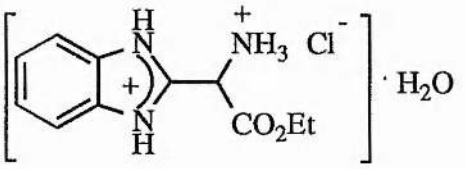
The fully protected starting material (**115**) is only sparingly soluble in ether and so a minimum amount of THF was added with the dual aim of solubilising the starting material (**115**) and also, it was hoped, acting as a phase-transfer catalyst and assist in speeding up the imine hydrolysis reaction.

Since the THF may cause problems during the purification of the product(s) at a later stage, sonication was also employed to solubilise the solid.

Monitoring the reaction closely by TLC, and stopping the reaction before complete loss of the starting material, were shown, upon work-up of the reaction mixture, to have been beneficial.

After sonication and work-up, the aqueous layer, upon evaporation, yielded a bright red solid, and in complete contrast to previous experiments, the ^1H nmr showed the solid to be almost exclusively the desired product (**116**), with no acid (**117**) present.

Purification of (**116**) for elemental analysis, however, proved to be very difficult due to the very hygroscopic nature of the hydrochloride salt. A careful recrystallisation, under nitrogen, using dry acetonitrile did give a clean sample of a red semi-solid which returned a result consistent with the figures calculated for a dihydrochloride monohydrate (**118**).

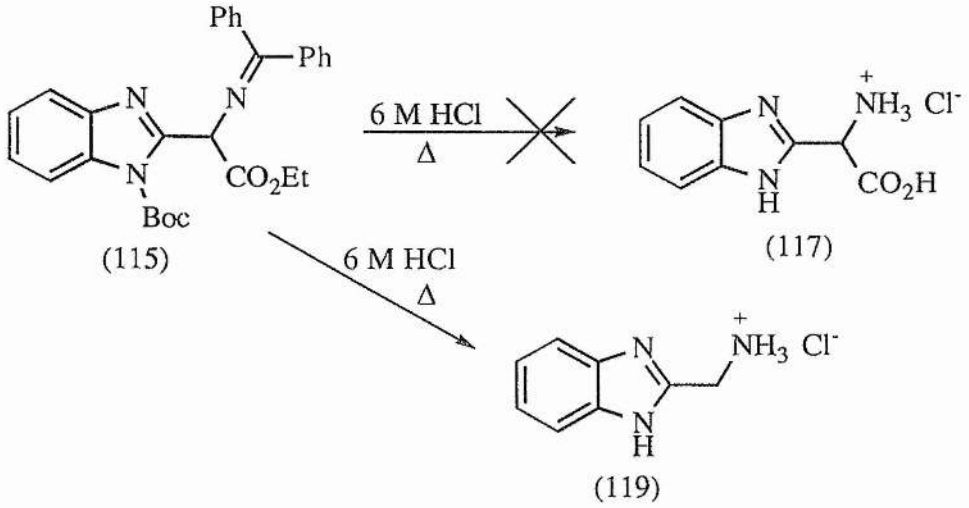


. Cl^- (118)

Since the formation of the amino acid (**117**) using dilute hydrochloric acid failed to give the clean product in good yields an alternative method was sought. It has been shown that the heating of a suspension of diphenylmethylidene protected amino acid ester in strong (6 M) hydrochloric acid causes removal of the nitrogen protecting group as well as de-

esterification[95]. It was therefore decided to repeat this reaction using the starting protected amino acid ester (**115**).

A suspension of (**115**) was heated in the hydrochloric acid before cooling and extracting the mixture to remove the benzophenone. The aqueous layer was then evaporated down to give a solid which was found not to be the desired product (**117**) but instead the decarboxylated product (**119**).



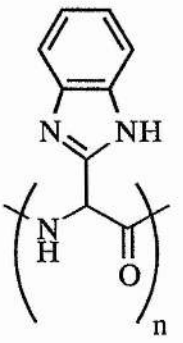
This result meant that attempts to form the amino acid (**117**) directly from (**115**) were abandoned.

All attempts at the dimerisation of the amino acid ester (**116**) gave a polymeric mixture as in the case with the hydrochloride (**111**). It was then decided that the use of a metal centre to act as a Lewis acid might help to increase the chances of some of the required product being formed instead of polymerisation taking place.

The reason for this was that it was thought possible that the under high dilution the Lewis acid may help the intramolecular attack of an amine upon the ester group of the dipeptide leading to the desired product being formed. This cyclisation would be preferred to the competing polymerisation reaction which seemed to be favoured.

One choice of metal salt was to use magnesium chloride. A suspension of magnesium chloride and (**115**) in toluene was heated to reflux for several hours under nitrogen. Upon cooling the reaction mixture the only product isolated was the polymeric material

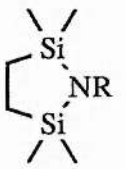
(presumed to be) (**120**). The reaction was repeated with zinc chloride but only polymeric material (**120**) was isolated from the reaction.



(120)

2.1.3.3 The STABASE Group

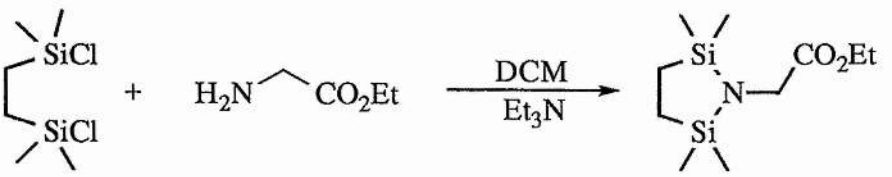
Another potentially useful nitrogen protecting group is the formation, from the free amine, of a 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane ring. These have been abbreviated, somewhat unusually to STABASE adducts[78] (**121**).



STABASE adduct

(121)

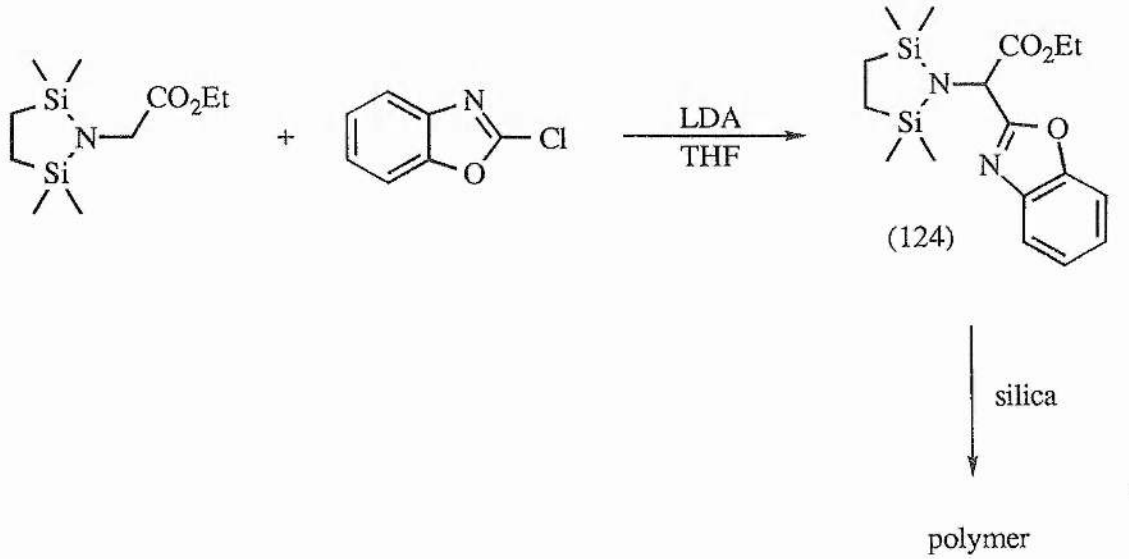
These can be formed in excellent yields by the reaction of a primary amine with 1,1,4,4-tetramethyl-1,4-dichlorodisilethane (**122**) in the presence of a base. In this way STABASE protected glycine ethyl ester (**123**) was formed in excellent yield.



(122) (123)

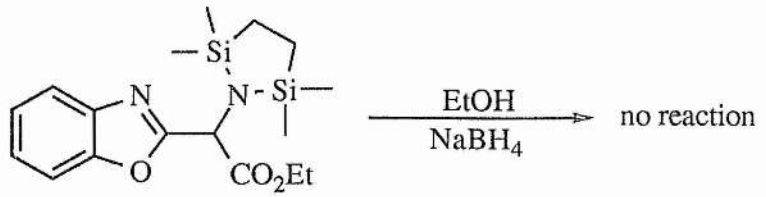
Unlike most other *N*-silyl compounds the cyclic STABASE is quite stable but is removable without the requirement for mineral acids. This means that if a benzoxazole is present as the heterocycle then the silicon protecting group can be removed and leave the acid-sensitive oxazole ring unchanged.

A solution of the STABASE- protected glycine ethyl ester (**123**) was deprotonated with LDA and then allowed to react with 2-chlorobenzoxazole. Initial attempts to purify the product (**124**) from the reaction mixture *via* chromatography resulted in only decomposition products being isolated. This was later believed to be due to the fact that the silyl group was unstable to the chromatographic silica gel used and caused deprotection of the amine, which then resulted in polymerisation.

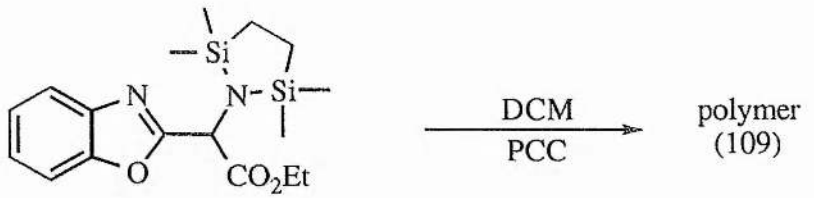


Careful distillation of the reaction mixture did result in some reasonably pure material being isolated in widely variable yields. Removal of the silyl group under controlled conditions was then attempted in several ways.

The first method attempted was using sodium borohydride in ethanol. After 1 h at room temperature there was no sign of any reaction occurring.

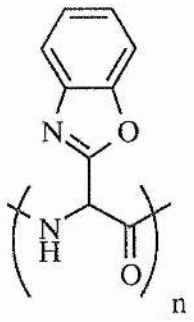


The second method attempted was to use pyridinium chlorochromate (PCC). This method benefits from being totally anhydrous and avoids the use of acid. A solution of the STABASE (**124**) in DCM was stirred with PCC for several hours before adding ether to dilute and filtering the mixture through Celite.



Evaporation of the filtrate showed only the presence of the silicon residue(s) from the deprotection and it was thought that the benzoxazol-2-yl amino acid ester may have been left absorbed onto the Celite.

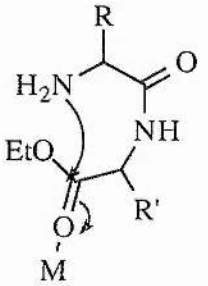
The reaction was therefore repeated but the work-up involved washing the organic layer with dilute potassium hydroxide. This was in an effort to form water-soluble chromium residues and leave the deprotected product in the organic layer. Upon work-up of the reaction only an oily black tar was isolated and this was found to be polymer of general type (**125**).



(125)

Another method which has been reported as being useful for the removal of the silicon groups is tetrabutylammonium fluoride (TBAF)[101]. This was stirred with the STABASE in anhydrous THF for several hours before working the reaction mixture up. The product isolated from the mixture was again found to be the polymer (**125**).

As in the cyclisation of the protected amino acid (**115**) it was suggested that the use of a metal ion may act as a Lewis acid and help cause the cyclisation of the dipeptide in preference to polymerisation.



M = metal

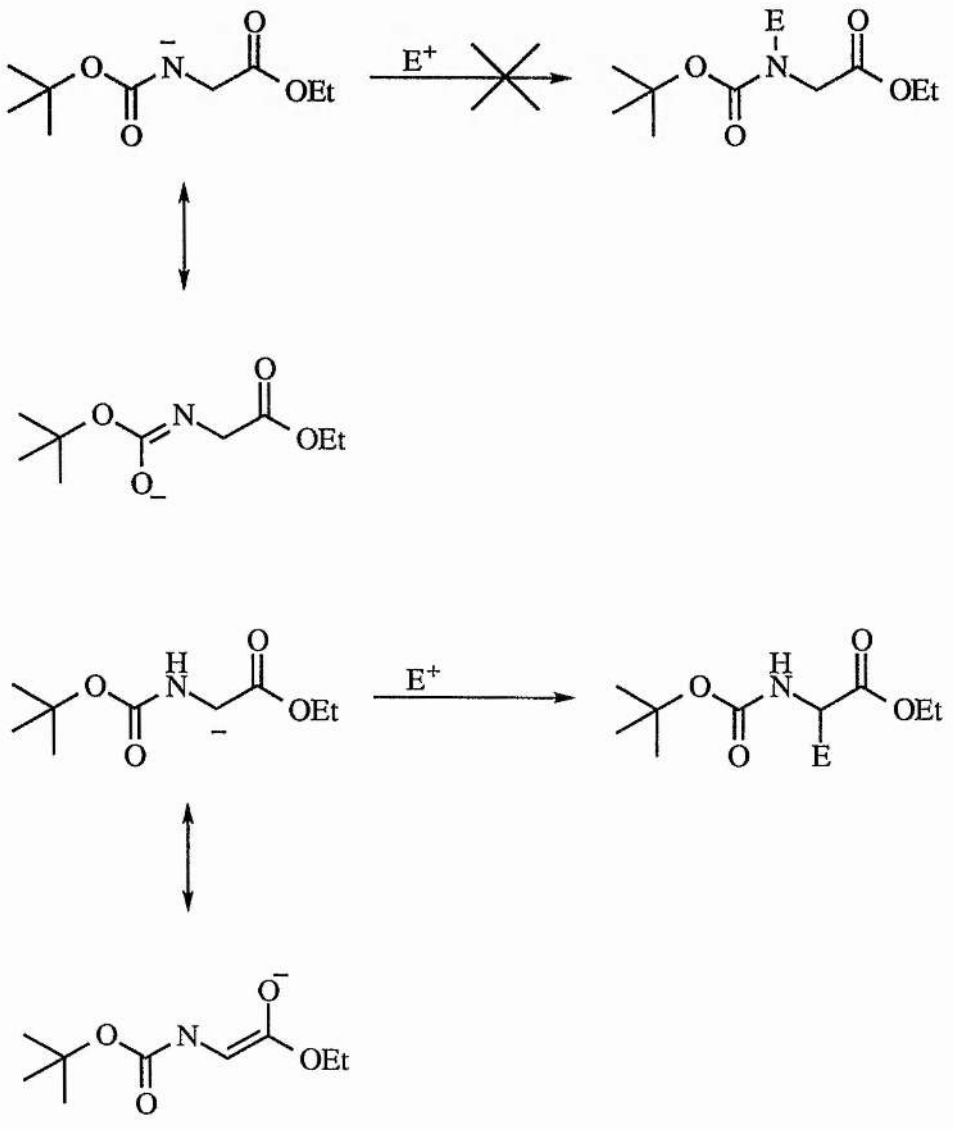
It has been suggested that zinc can be beneficial in the dimerisation of some dipeptides[102] and so a solution of the STABASE (**124**) in toluene was heated under reflux with a catalytic amount of zinc fluoride. It was hoped that the fluoride may remove the silicon group while the zinc could act as a Lewis acid and cause the desired product to form.

After several hours at reflux and 2 days at room temperature there was no sign of any reaction having taken place.

Since PCC has been found to remove the protecting group it was decided to repeat the above reaction using a catalytic amount of zinc fluoride but with the addition of one equivalent of PCC. After several hours at reflux the reaction was worked-up and the only product isolated was the polymer (**125**).

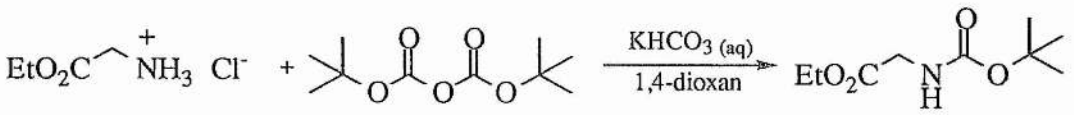
2.1.3.4 The *t*-Butoxycarbonyl Group

A final nitrogen protecting group examined was that of the *t*-butoxycarbonyl (*t*-BOC or Boc) group. This differs greatly from the other groups examined in that it leaves one potentially acidic proton bound to the nitrogen after the protecting group has been introduced. This however was not deemed to be a problem since it was thought that two equivalents of strong base (e.g. LDA) would form a dianion, the more nucleophilic of the two anionic centres being the carbanion.



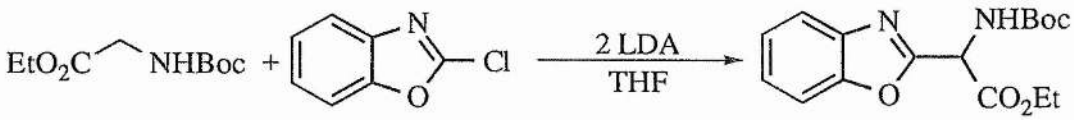
An advantage which the Boc group shares with the STABASE adduct is that it is possible to remove the group selectively by various anhydrous means[103] without the use of aqueous mineral acid, therefore not risking the hydrolysis of the acid sensitive oxazole ring.

The starting *N*-*t*-butoxycarbonylglycine ethyl ester (**126**) is formed following a procedure for the Boc protection of dimethyl aminomalonate hydrochloride[104] to give the desired product in good yield.



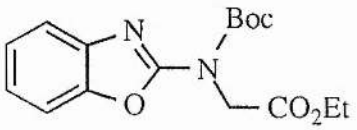
(126)

Deprotonation with 2 equivalents of LDA followed by reaction with 2-chlorobenzoxazole gave, after work-up and chromatography, the protected amino acid ester (**127**) in good yield.



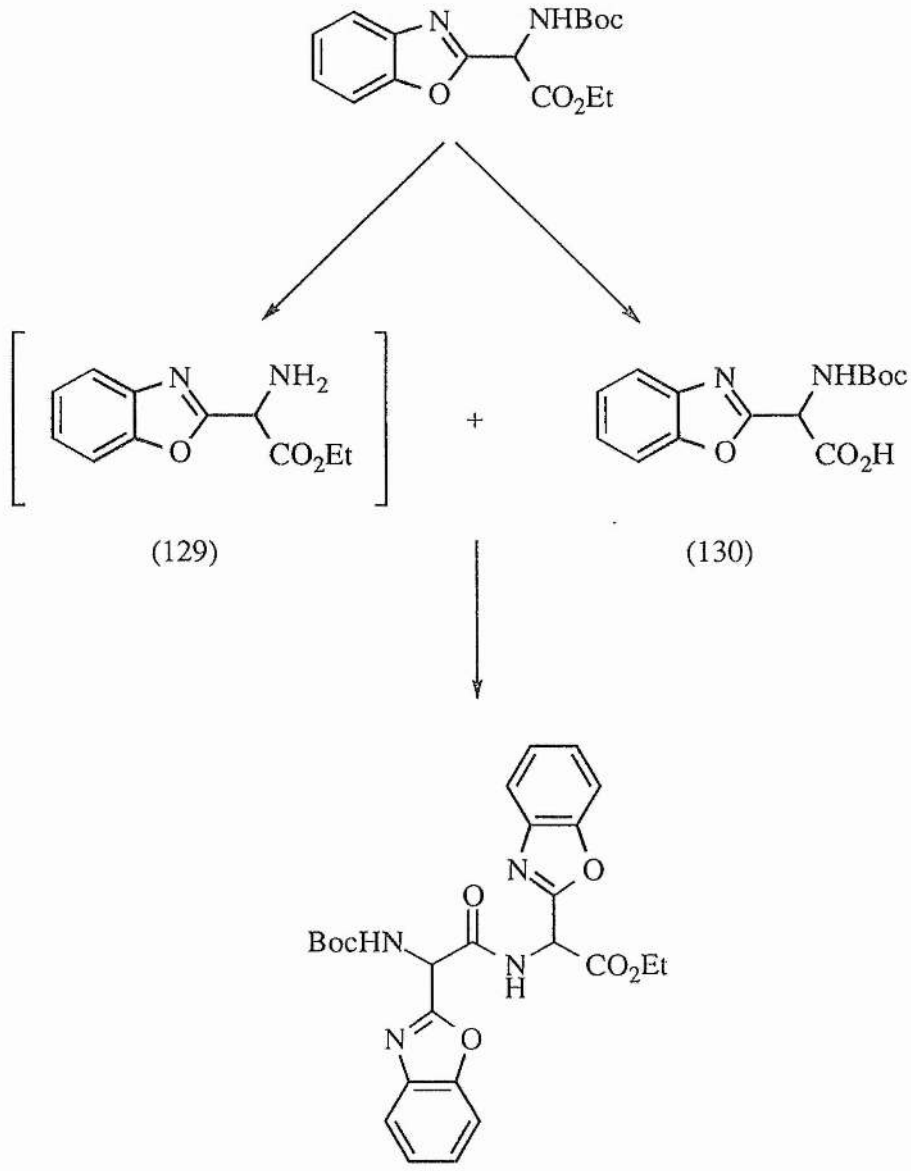
(127)

It is interesting to note that none of the *N*-arylated product (**128**) was seen at all. This therefore confirms the earlier assumption that the carbon would be the more nucleophilic centre than the nitrogen when reacting with these types of electrophiles.



(128)

The *N*-protected arylated amino acid ester was then used as a starting material from which the ester or the Boc groups could be removed selectively, giving two reactive centres *viz* the free amine (**129**) and the free carboxylic acid (**130**), which could be coupled using standard peptide coupling methods to form a dipeptide (**131**).

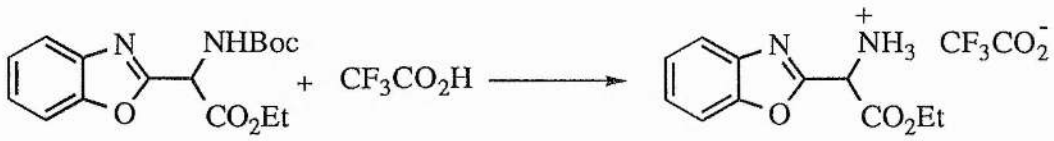


(129) (130)

(131)

The removal of an *N*-Boc group can be achieved in a large number of ways[105,106] although in the example above the methods are limited to the avoidance of aqueous acid.

Trifluoroacetic acid (TFA) has been shown to remove *N*-Boc groups giving the corresponding trifluoroacetate salts in almost quantitative yields[107]. To this end a solution of the aryl amino acid ester (**127**) in freshly distilled TFA was stirred at room temperature before evaporating under reduced pressure to remove any excess TFA giving the product (**132**) as a green oil.

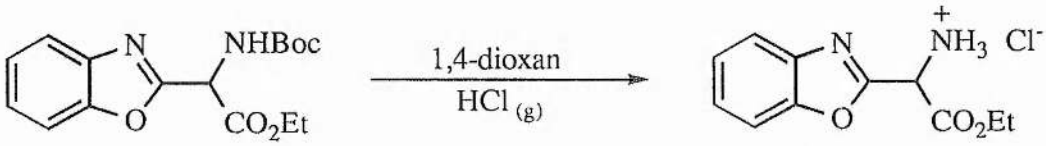


(127) (132)

The oil was found to be hygroscopic and highly unstable even when stored under nitrogen and refrigerated. It is believed that moisture is absorbed by the solid and in conjunction with any traces of TFA causes hydrolysis of the oxazole ring.

Another useful method for the removal of *N*-Boc groups is the use of anhydrous hydrogen chloride[108,109] bubbled through a solution of the protected compound in various solvents.

A solution of the aryl amino acid ester in dry 1,4-dioxan was stirred and anhydrous hydrogen chloride was bubbled through the mixture. The reaction was monitored by TLC and after a few minutes the gassing was stopped and the mixture evaporated down giving a pink foam.



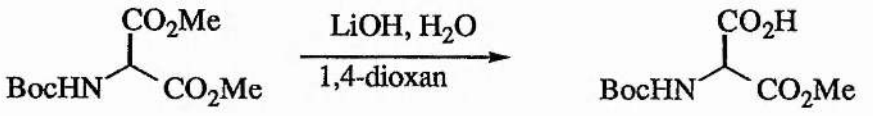
(127) (133)

The solid hydrochloride salt (**133**) produced was also found to be hygroscopic and so stored under nitrogen although it was much more stable than the corresponding TFA salt and showed, by ^{1}H nmr, no decomposition after 1 week at room temperature.

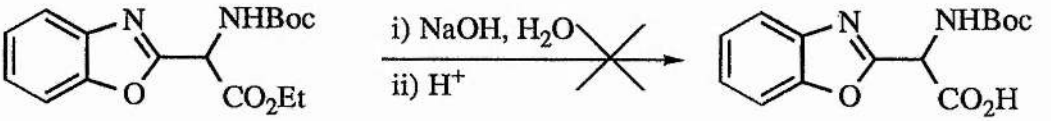
The formation of the two aryl amino acid hydrochlorides, the benzimidazole (**116**) and the benzoxazole derivatives (**133**), was now complete and the synthesis of both reproducible

in good yields. The focus of the project now turned upon the synthesis of a corresponding *N*-protected aryl amino acid (**130**).

Early work had shown that heating a suspension of an *N*-protected benzimidazol-2-yl amino acid ester (**115**) in hydrochloric acid causes decarboxylation to take place. Stirring the mixture at room temperature with a more dilute acid will cause de-esterification to take place but the reaction is slow and incomplete leading to a mixture of products which prove difficult to separate. Saponification of *N*-Boc amino acid esters has been reported to proceed in good yield using lithium hydroxide as the base and using phase transfer conditions[110].



A solution of the *N*-Boc protected aryl amino acid ester (**127**) was dissolved in 1,4-dioxan and stirred with a solution of sodium hydroxide.



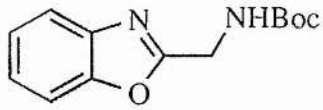
(127)

Upon quenching the reaction with citric acid and extracting the product a solid was isolated, the spectra (^{1}H nmr, ^{13}C nmr and mass spectra) of which did not appear to correspond with the expected acid.

The ^{1}H nmr failed to shown any signal which would correspond to the carboxylic acid proton which in itself was most unusual but, the ^{13}C nmr did not shown any signal which would correspond to the carboxylate carbonyl and the low resolution mass spectra showed a molecular ion peak 44 less than that expected for the product.

The mass spectra could possibly be explained by the instability of the acid in the mass spectrometer and the loss of carbon dioxide from the molecular ion giving an apparently low molecular weight, although the results from the other spectra could not be as easily explained.

Further examination of the results from the elemental analysis of the solid from the reaction suggested that the sample had indeed decarboxylated and given rise to the compound shown below (**134**).

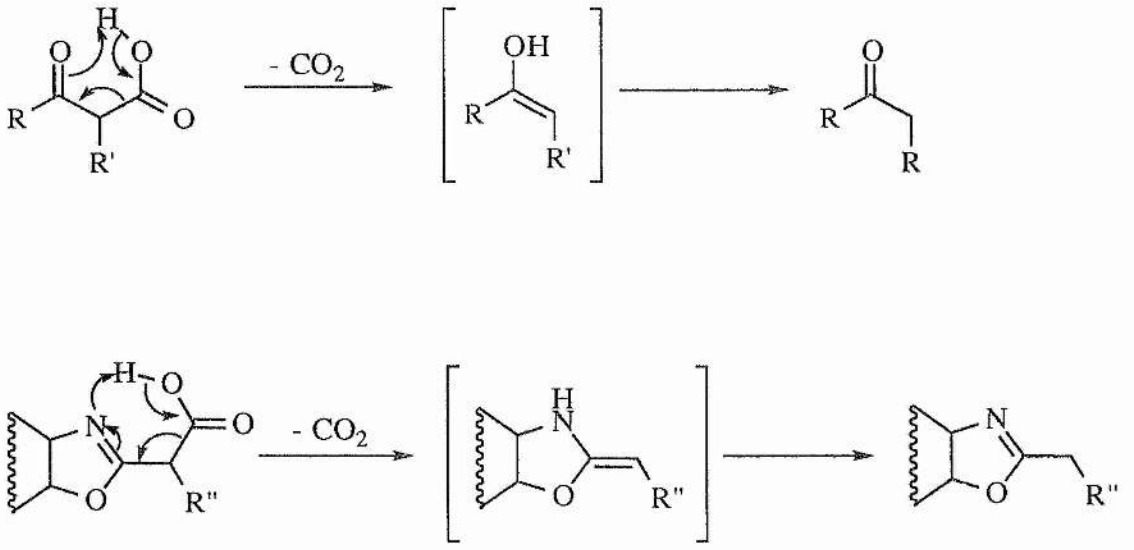


(134)

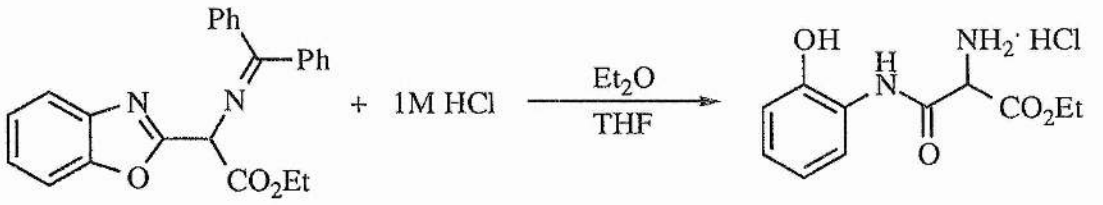
The expected spectra for the above compound do correspond with those obtained from the solid and it is thought this decarboxylation occurs upon quenching of the crude reaction mixture with citric acid.

The decarboxylation of this arylated amino acid under such relatively mild conditions was a surprise although it should not have been totally unexpected in the light of previous experiments which have suggested that the oxazole ring does not behave as a fully delocalised system. Instead the electrons are more localised between the nitrogen and C-2 of the ring.

This means that the expected *N*-Boc arylated amino acid is behaving as a β-imino acid and will decarboxylate in a similar way to a β-keto acid.



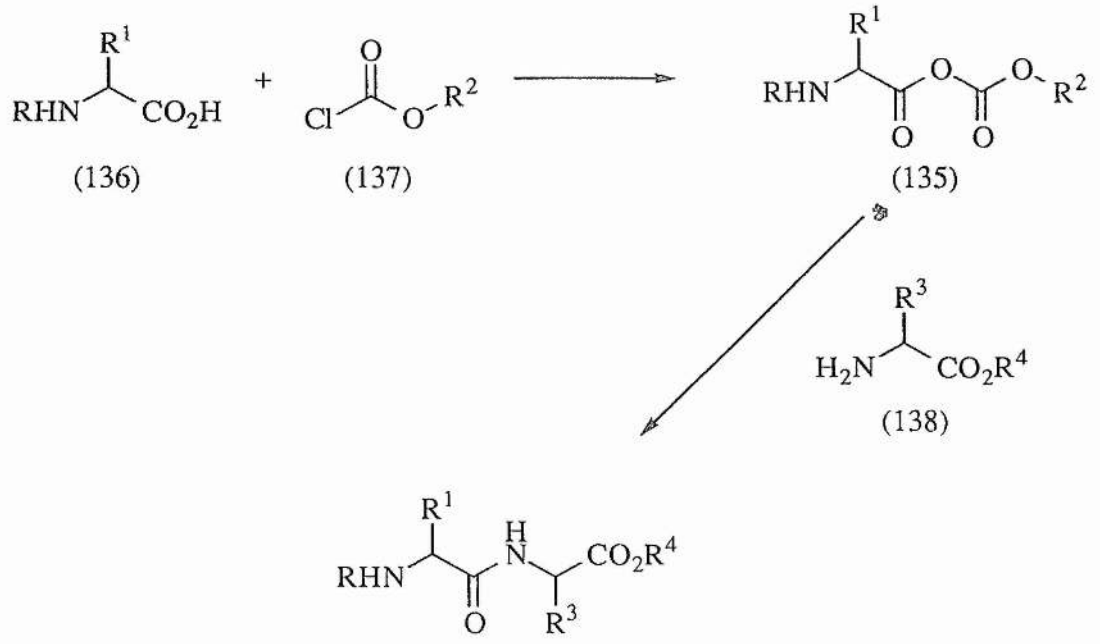
The lack of delocalisation in the oxazole ring is implied by the ease by which the ring will hydrolyse under relatively mild aqueous acidic conditions.



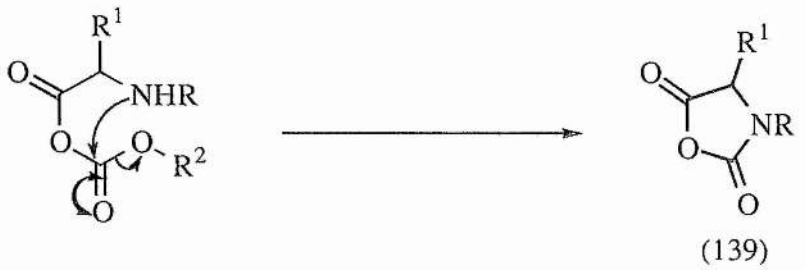
It was predicted that the problem of isolating the amino acid may be alleviated by using a peptide coupling method which will allow the coupling of a carboxylate salt as opposed to one which requires a protonated carboxylic acid, for example carbodiimide couplings.

One possible peptide coupling method is to use a mixed anhydride coupling procedure. The mixed anhydride (**135**) being formed from an *N*-protected amino acid (**136**) and an alkyl chloroformate (**137**). The resultant anhydride means that the amino acid carbonyl is

now activated towards the subsequent nucleophilic attack from a second amino acid ester (**138**).



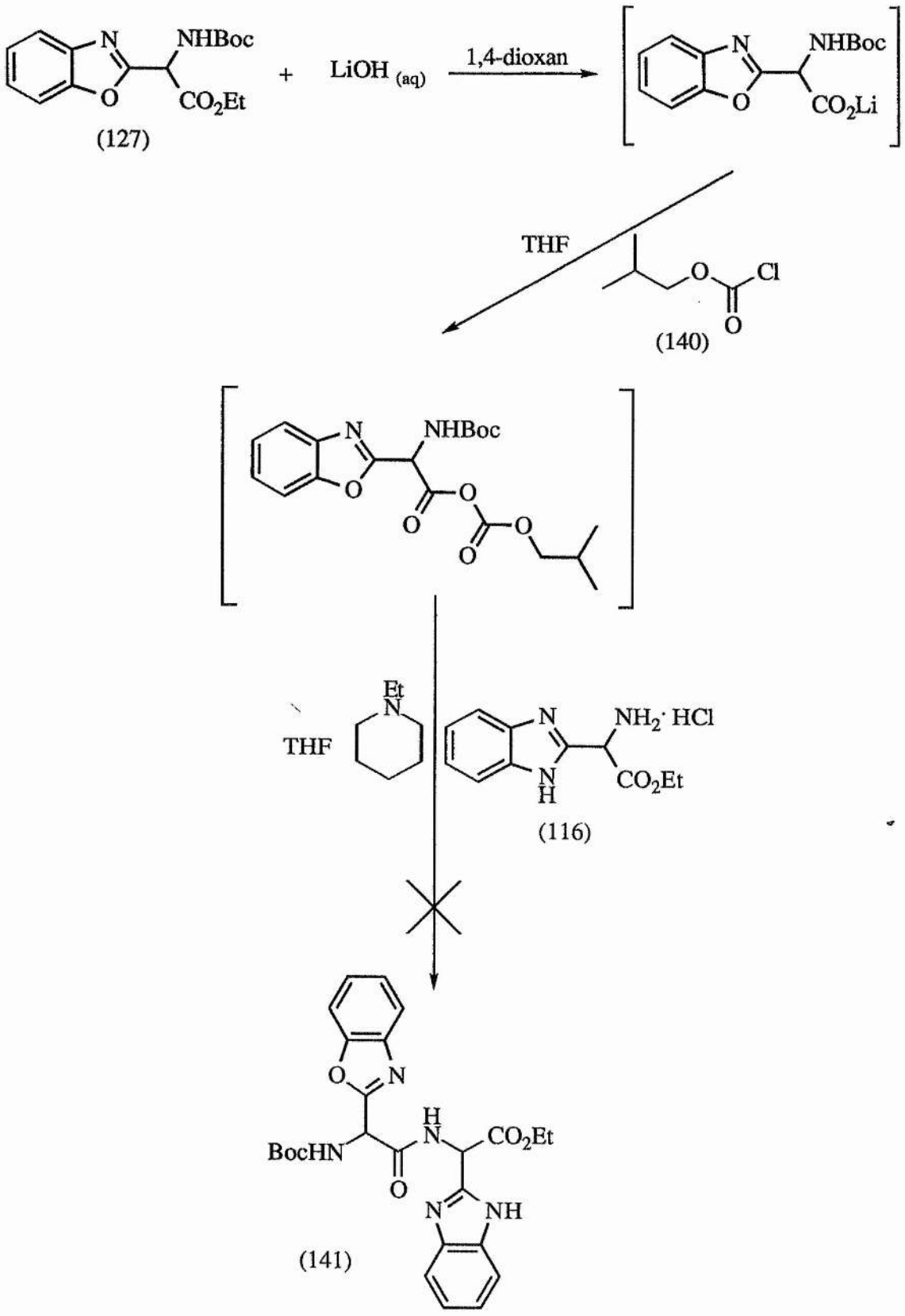
The use of an alkyl chloroformate as opposed to a simple acid chloride means that the reaction of the amine upon the anhydride causes carbon dioxide to be produced, providing a strong driving force for the reaction. There is, however, a possibility of some urethane (**139**) formation.



This side reaction can, however, be minimised by careful choice of the base used, for example an *N*-alkylpiperidine[111].

An advantage that this method holds over others is that it may be possible for the salt of the *N*-protected amino acid to be used to form the mixed anhydride. This would mean that the compound (**127**) could be saponified, giving the lithium salt, but instead of attempting to isolate the acid, the salt could be used directly to form the mixed anhydride.

A solution of the benzoxazole *N*-Boc amino acid ester (**127**) was saponified with one equivalent of lithium hydroxide. The mixture was then evaporated down, dissolved in THF and added to a solution of *iso*-butyl chloroformate (**140**). After several minutes a solution of 2-(benzimidazol-2-yl)glycine ethyl ester hydrochloride (**116**) and *N*-ethyl-piperidine was added. After several hours the reaction was worked-up and the two products isolated were the decarboxylated benzoxazolyl amino acid (**134**) and a polymeric material arising from the polymerisation of the benzimidazolyl amino acid ester (**116**); none of the desired product (**141**) was seen.


NHBoc
CO2Et
(127)
+
LiOH (aq)
1,4-dioxan
NHBoc
CO2Li
THF
Cl
O
O
(140)
NHBoc
THF
Et
N
NH2· HCl
CO2Et
(116)
BocHN
CO2Et
NH
(141)

2.2 Disconnection 2

The second disconnection, disconnection 2, implies a synthetic route involving the coupling of a suitable heterocycle to a preformed dioxopiperazine ring. As described in the introduction there are various possible ways of achieving this:

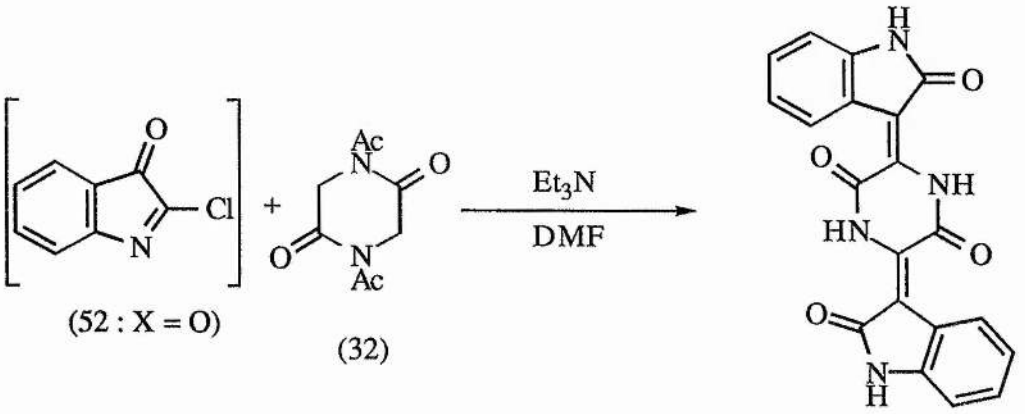
1. Condensation of a heterocycle with the methylene group of a dioxopiperazine.

2. Coupling of a nucleophilic heterocycle and an electrophilic dioxopiperazine.

3. Coupling of an electrophilic heterocycle and a nucleophilic dioxopiperazine.

2.2.1. Direct Condensation

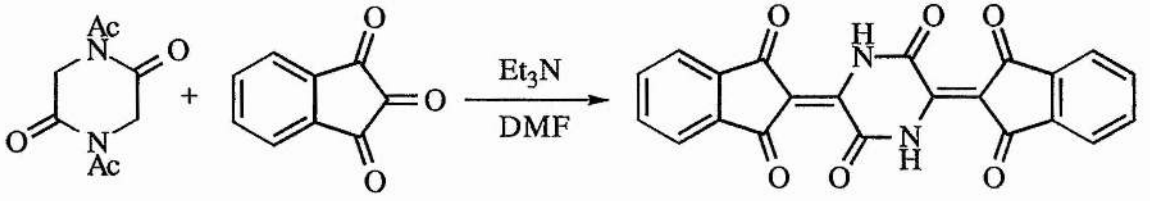
One piece of work already published in this area was by Katritzky *et al.* in 1989[55]. A compound arising from the reaction of indole and phosphorus pentachloride was, at the time of publication, thought to be 2-chloro-3*H*-indol-3-one (**52** : X = O). This compound was later found to be the dimer (**53**)[56]. The dimer was then reacted in dry DMF with 1,4-diacetyl-2,5-dioxopiperazine (**32**) in the presence of triethylamine, with the concomitant loss of the acetyl groups and gave rise to 3,6-bis(2-oxo-3-indolylidene)-2,5-dioxopiperazine (**11**).



(52 : X = O) (32) (11)

The product isolated from the reaction mixture was a purple solid (**11**). This was tested by chemists at Ciba-Geigy for use a pigment but was found to perform poorly in their tests.

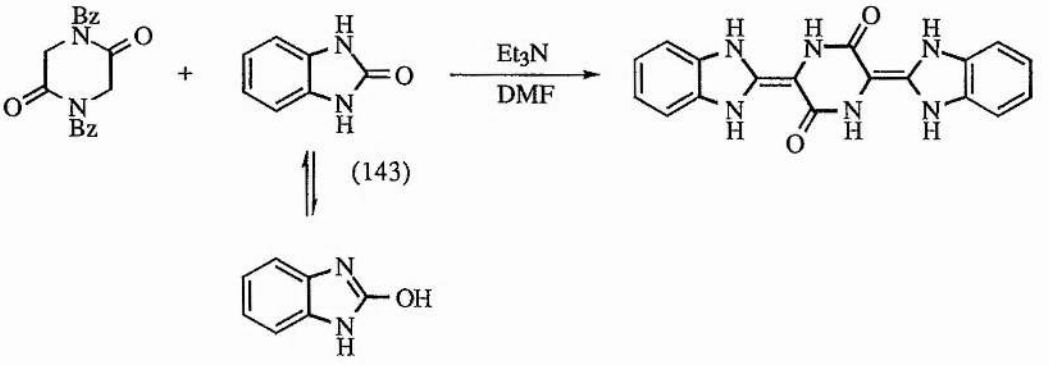
Another potentially interesting molecule, (**10**), which was formed using the same conditions arises from the reaction of 1,4-diacetyl-2,5-dioxopiperazine (**32**) and ninhydrin (**142**).



(32) (142) (10)

This was also tested for potential pigment applications but again found to perform poorly under the test conditions.

By following the procedure laid out by Katritzky *et al.* it was considered possible that a similar reaction may occur between benzimidazolone (**143**) and 1,4-dibenzoyl-2,5-dioxopiperazine thus:

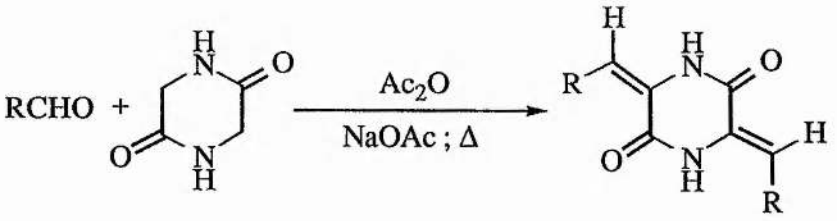


A mixture of benzimidazolone and 1,4-dibenzoyl-2,5-dioxopiperazine was stirred at room temperature for several days and then for several hours at 100°C but none of the desired product was seen to form (by TLC), and upon work-up of the reaction mixture only unchanged starting materials were recovered (by ^{1}H nmr).

The only deviation from the route used by Katritzky and co-workers was the *N*-protecting group of the dioxopiperazine; Katritzky used acetyl whereas in this set of experiments it was benzoyl. This difference was not believed to be responsible for the lack of reactivity; nevertheless, it was decided to confirm this.

A solution of isatin and 1,4-dibenzoyl-2,5-dioxopiperazine in DMF with triethylamine was stirred for several hours before producing a purple/red solid (as described by Katritzky) . The solid was identified but its colour, infra red spectrum and insolubility in organic solvents seem to indicate that the change of nitrogen protecting group from acetyl to benzoyl had no effect upon the reactivity of the 2,5-dioxopiperazine moiety.

2,5-Dioxopiperazine has been shown to react with aldehydes thus:



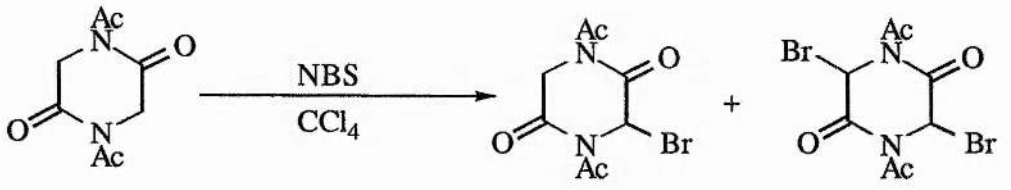
It was predicted therefore, that by heating under reflux a solution of dioxopiperazine, benzimidazolone and sodium acetate in acetic anhydride then the desired product (**78**) might be formed.

Dioxopiperazine was heated to reflux in the above system with benzimidazolone, but even after several hours only unchanged starting materials were recovered. This lack of reactivity was not a complete surprise however, since the carbonyl of the benzimidazolone is more amide in character and therefore less electrophilic than an aldehyde or ketone carbonyl.

2.2.2. Reaction Between an Electrophilic Dioxopiperazine and a Nucleophilic Heterocycle

One method to activate the dioxopiperazine molecule is *via* halogenation. The literature shows that it is possible to mono- and di-brominate the methylene group(s) of a dioxopiperazine using *N*-bromosuccinimide. The degree of bromination and the stability of the bromide produced are dependent upon the nitrogen protecting group.

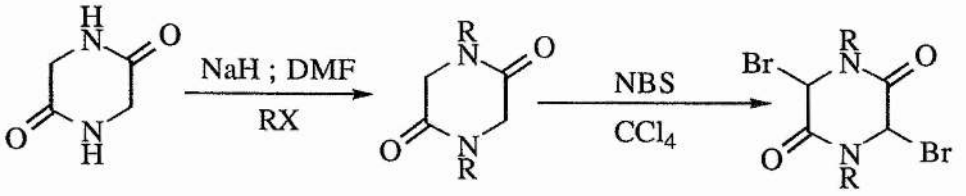
It has been recorded that protection of dioxopiperazine with an acyl group leads to deactivation of the methylene group towards bromination with *N*-bromosuccinimide when compared to the effect of an alkyl group. Indeed bromination of 1,4-diacetyl-2,5-dioxo-piperazine with one equivalent of *N*-bromosuccinimide leads to the unstable 1,4-diacetyl-3-bromo-2,5-dioxopiperazine (**144**)[48] as well as some (~15% crude yield by ^{1}H nmr) 1,4-diacetyl-3,6-dibromo-2,5-dioxopiperazine (**145**) being formed.



(144) (145)

The advantage of mono-bromination is that it may allow for the sequential addition of two different heterocycles and also the use of an acetyl protecting group means that removal of the *N*-acyl group from the final product should prove relatively simple.

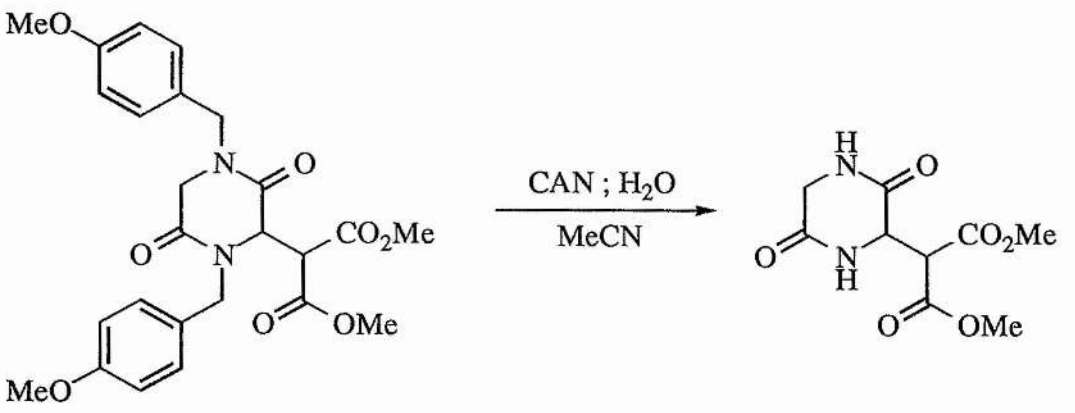
Following the same method as above but instead using an alkyl protecting group allows di-bromination to occur[49], almost exclusively, giving products of general type (**146**).



(146)

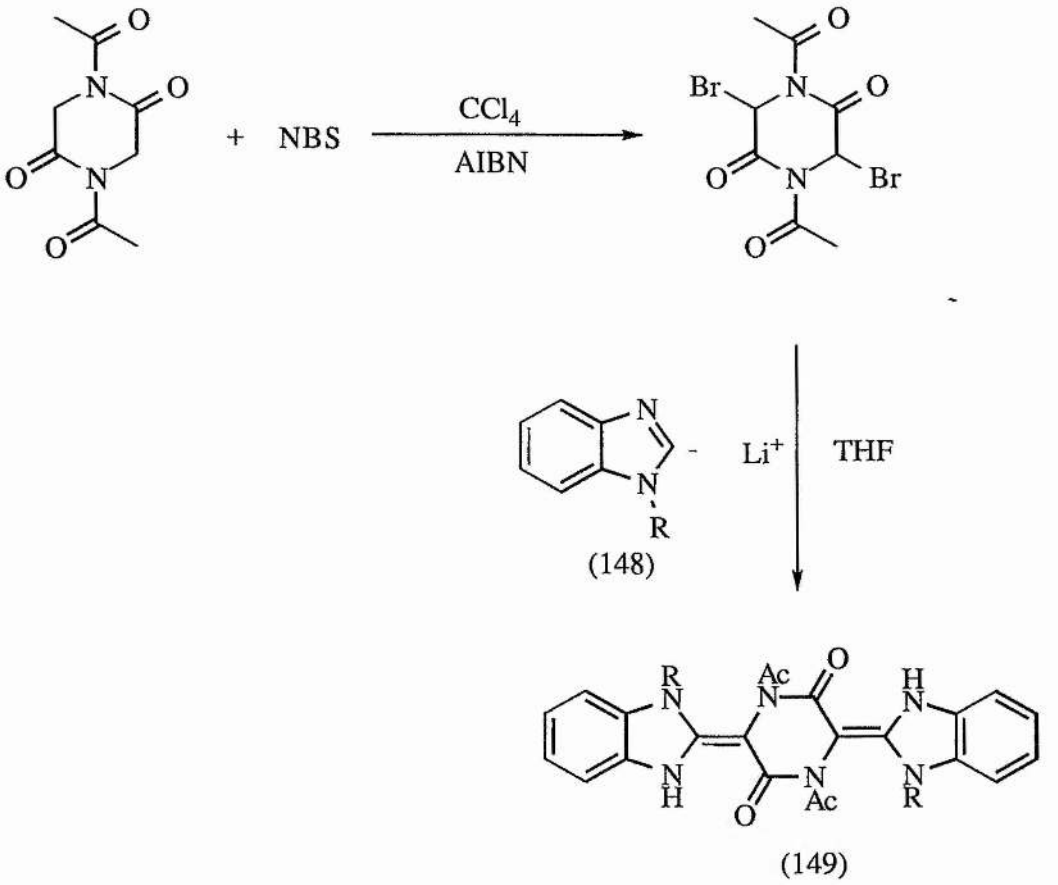
A major problem in following this route could arise from the eventual removal of the *N*-alkyl functions, since by their nature the final target molecules are insoluble and therefore normal methods of removing the alkyl protecting group on the nitrogen may prove impracticable.

An exception to this trend is provided by methoxybenzyl as it has been shown that the removal of this group from a 3-substituted-1,4-bis(*p*-methoxybenzyl)-2,5-dioxopiperazine (**147**) can be effected using ceric ammonium nitrate (CAN) in aqueous acetonitrile[49].



(147)

As stated above the requirement is now for a nucleophilic heterocycle to displace the bromine atoms. The first choice of heterocycle was that of an anion of an *N*- protected benzimidazole (**148**) which would, upon reaction, lead to a product of general type (**149**).



(149)

The basicity of a lithiated benzimidazole when compared to its nucleophilic character is unknown. It was thought, therefore, that there may be a possibility that the methyl of the acetyl protecting group could be deprotonated which may lead to decomposition of the dioxopiperazine, or indeed some other unexpected side reaction may occur.

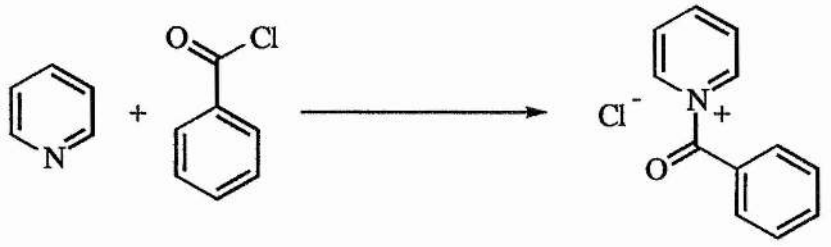
To overcome this potential problem an alternative dioxopiperazine nitrogen protecting group was investigated. One possibility is a benzoyl group, since it contains no potentially acidic protons and could simply be removed in principle by treatment of the product with strong aqueous base.

Initially benzoylation of 2,5-dioxopiperazine was attempted using a suspension of dioxopiperazine and benzoyl chloride in dichloromethane with triethylamine as the base. This method did not however produce any of the required product and this is probably due to the insolubility of the dioxopiperazine in the solvent.

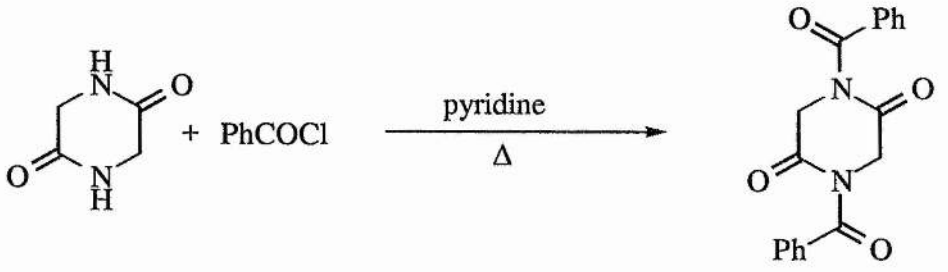
A second attempt was therefore made using *N,N*-dimethylformamide (DMF) as the solvent and sodium hydride as the base. This method did produce some product (by

^{1}H nmr) but all attempts at purification led to decomposition of the product into a black tar. No pure product could be isolated *via* this method and so this route was abandoned.

A literature method was finally identified[51] which involved heating benzoyl chloride and dioxopiperazine in a large excess of pyridine. It is proposed that the pyridine acts not only as a base and solvent but also as the benzoylating catalyst much in the same way as *N,N*-dimethylaminopyridine (DMAP) is an excellent acylating catalyst.



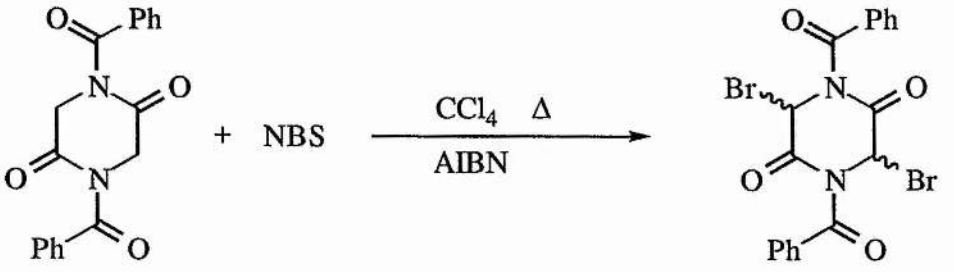
This method then provided a good (75%) yield of pure 1,4-dibenzoyl-2,5-dioxopiperazine (**33**)[51].



(33)

Bromination of the dibenzoyldioxopiperazine (**33**) followed the literature method for bromination of diacetyldioxopiperazine[57] but using an excess of *N*-bromosuccinimide. The reagents were heated to reflux in carbon tetrachloride before cooling, filtering and evaporating the mother liquors to give an orange solid which showed the presence of dibromodioxopiperazine (**150**) (by ^{1}H nmr). As expected the crude dibromide was contaminated with unreacted starting material and some monobromo derivative. Due to reported instability of the bromo and dibromo derivatives[48,57] the mixture was used

immediately. All attempts at isolation and purification of dibenzoyldibromodioxopiperazine (**150**) led to decomposition and so the mixture of products was used crude.

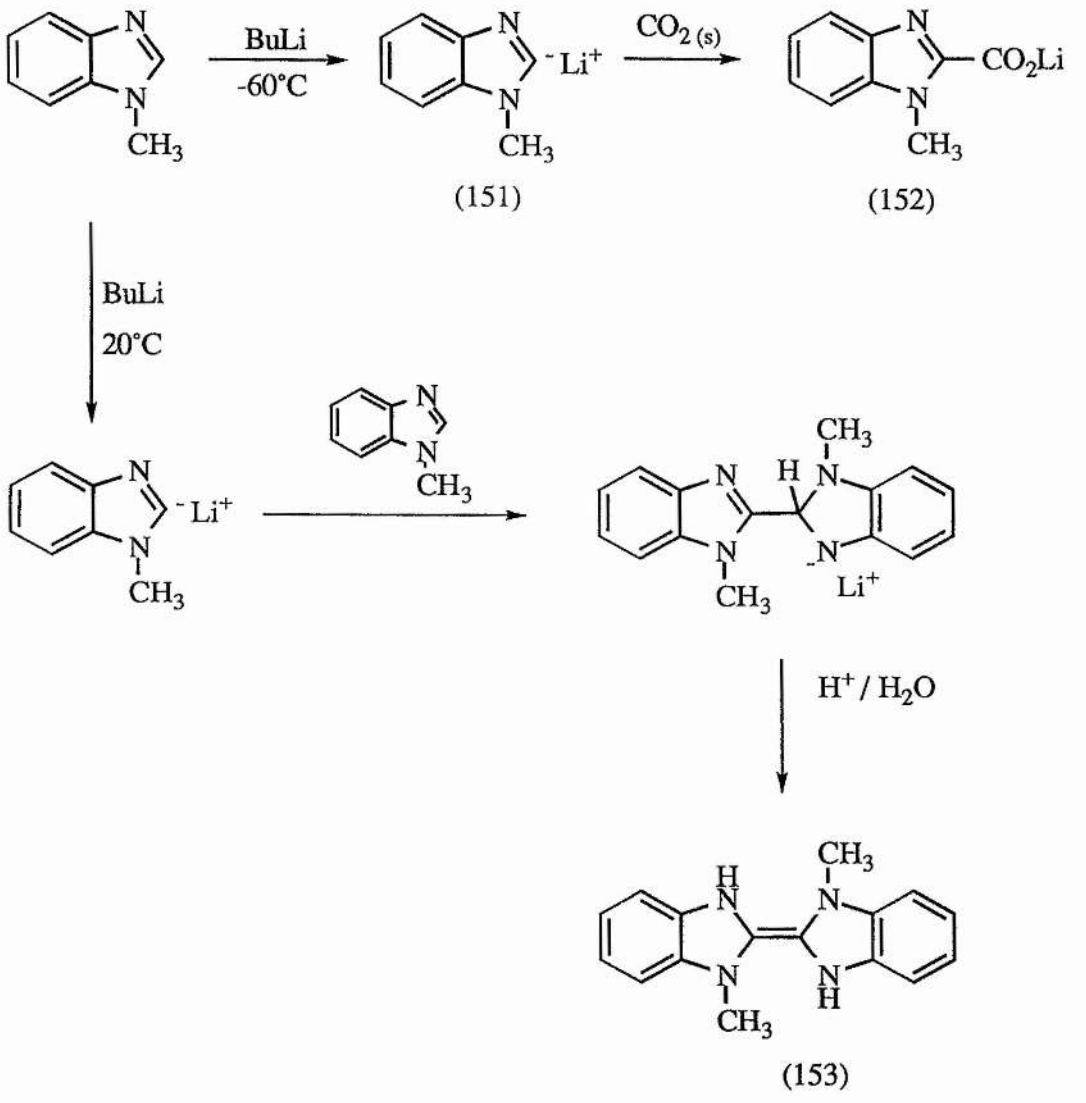


(33) (150)

The first choice of nucleophile to attack the dibrominated and *N*-protected dioxopiperazine (**150**) was an *N*-protected benzimidazole anion.

It has been shown that lithiation of 1-methylbenzimidazole gives the 2-lithio compound (**151**)[112]. If metallation takes place at -60°C followed by carboxylation (with solid CO_2) then the lithium salt of the 1-methylbenzimidazole-2-carboxylic acid (**152**) is produced in reasonable yield[112]. This then provides proof that the lithiated benzimidazole is a good nucleophile since carbon dioxide is a relatively poor electrophile.

When deprotonation with *n*-butyl lithium is performed at room temperature followed by quenching with solid CO_2 then very little of the lithium carboxylate salt is observed. In this case it is the dimer of benzimidazole (**153**) which is the major product.

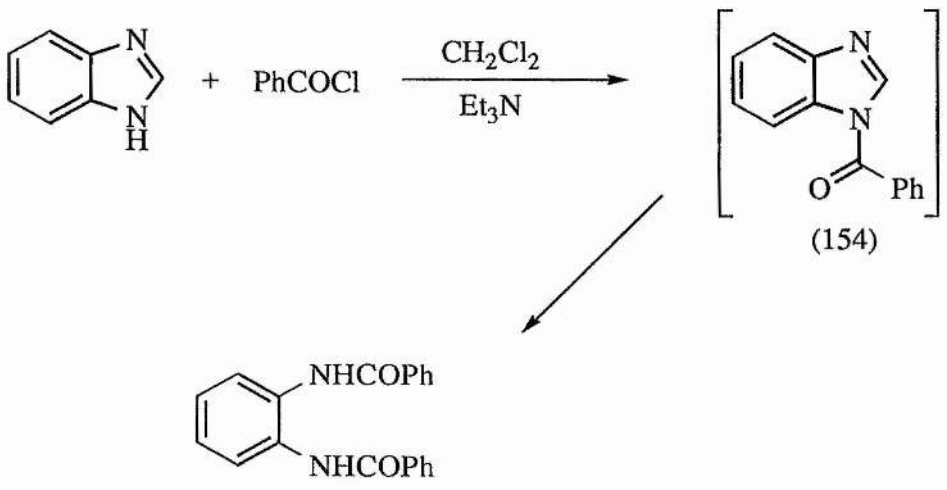


The production of the dimer (**153**) shows that the lithiation of the benzimidazole occurs quite slowly, even at room temperature, when compared to the rate of nucleophilic attack.

Due to the perceived difficulty in the removal of an *N*-methyl group from a benzimidazole a different protecting group was investigated. The first choice of protecting group was the benzoyl group since it was also to be used to protect the dioxopiperazine and so deprotection of both types of nitrogen in the product could conceivably be achieved in one step.

Attempted protection of benzimidazole with a benzoyl group by stirring the benzimidazole with triethylamine and benzoyl chloride in dichloromethane gave not the product (**154**), but instead a high melting material corresponding to *N,N'*-dibenzoyl-*o*-phenylenediamine, which results from dibenzoylation followed by ring opening. Rather than attempt to

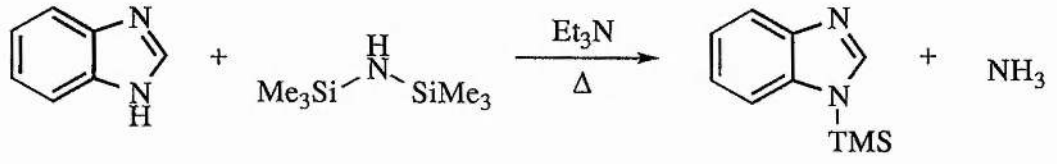
modify the conditions in order to obtain (**154**), an alternative protecting group was sought.



(154)

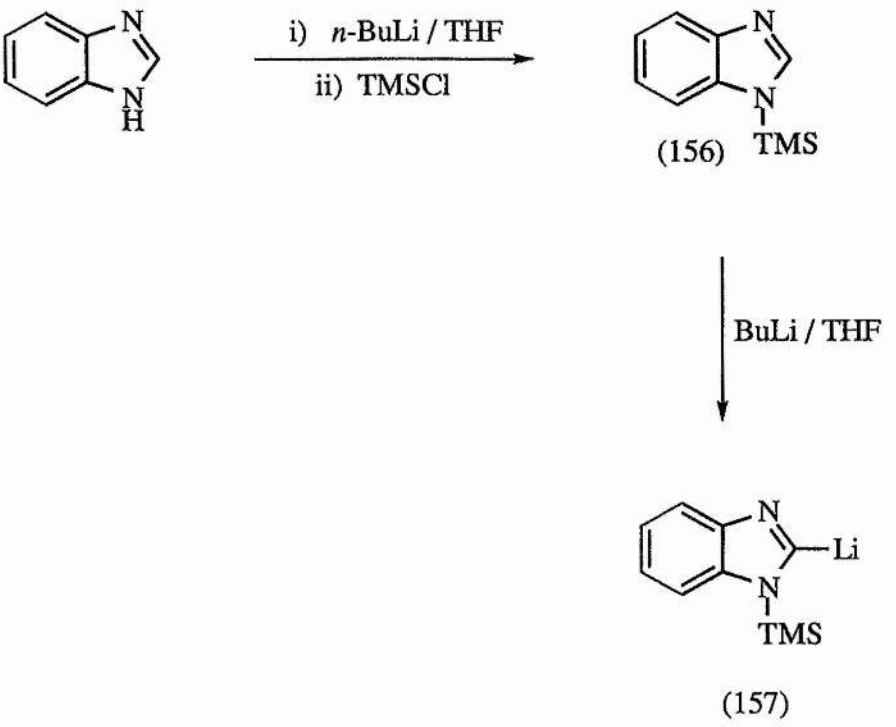
Silyl groups have been known for some time to be resistant to strong bases (e.g. *n*-BuLi and LDA) and also easily removed (*e.g.* by KF, CsF, H^+(aq)) and so this was the next choice of protecting group.

Protection of benzimidazole with a trimethylsilyl (TMS) group, to give *N*-trimethylsilyl-benzimidazole (**156**), is known using hexamethyldisilazane (**155**)[113].



(155) (156)

It was predicted, however, that a solution of benzimidazole in THF could be deprotonated with one equivalent of *n*-butyl lithium followed by quenching with chlorotrimethylsilane (TMSCl) to give the TMS-protected benzimidazole (**156**) in solution. This would then negate the need for a purification step as the protected benzimidazole could be cooled to -78°C and treated *in situ* with a second equivalent of base to give the required 2-lithio species (**157**).



(157)

The reaction appeared to proceed smoothly and after several hours at -78°C the metallated benzimidazole was reacted with a solution of the crude dibromide (**150**). Upon work-up TLC showed no sign of the desired product, only starting materials, and so it was questioned as to whether any effective lithiation took place at all.

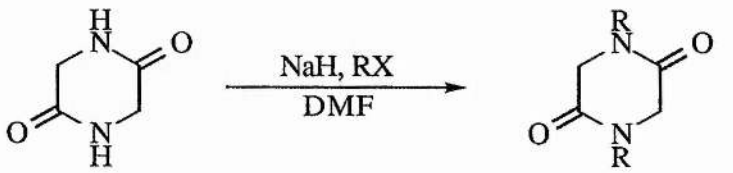
To investigate this metallation, the lithiation step of the reaction was repeated and then the mixture quenched with a solution of D_2O in THF. After warming to room temperature and working the reaction up nmr spectra (both ^1H and ^{13}C) showed that no deuterium incorporation had taken place.

It was now decided that the use of an acyl protecting group, either a benzoyl or an acetyl, for the dioxopiperazine was proving to be unsuccessful. The inconsistent degree of bromination and the instability of the resultant bromides made these groups impracticable. The change was now made to *N*-alkyl protecting groups since these allow for almost exclusive dibromination and the dibromides formed have been shown to be much more stable[49].

1,4-Dialkyl-2,5-dioxopiperazines have been found to dibrominate readily with *N*-bromosuccinimide (NBS) in carbon tetrachloride[49]. The activation by an alkyl group, when compared to the seemingly deactivating effect of an acetyl group, is such that

bromination of 1,4-bis(*p*-methoxybenzyl)-2,5-dioxopiperazine with one equivalent of NBS will lead to *ca.* 50% 3,6-dibromo and *ca.* 50% unreacted starting material[49].

Alkylation of dioxopiperazine has been shown to proceed in good yields using sodium hydride and the required alkyl halide in DMF[33].

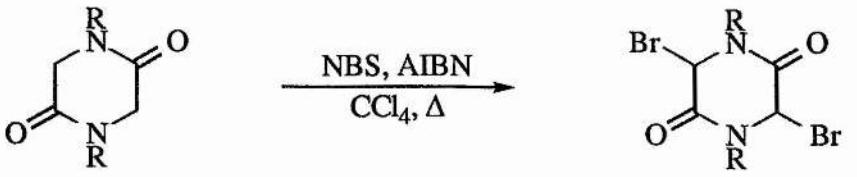


RX = EtI, *n*-PrI, $PhCH_2Cl$,
p-MeO-$C_6H_4CH_2Cl$

Initially, to ascertain the ease of alkylation the two alkyl halides chosen were iodoethane and 1-iodopropane and the literature procedure followed. The reaction proceeded smoothly although giving poor yields (26% and 27% respectively) of the clean 1,4-dialkyl-2,5-dioxopiperazine.

The first choice of alkyl protecting group was *p*-methoxybenzyl, since it has been shown to be removed using aqueous ceric ammonium nitrate[33]. Due to the greater cost of *p*-methoxybenzyl chloride compared to benzyl chloride it was decided to use the benzyl group as a model for the trial reactions. Dialkylation of 2,5-dioxopiperazine proceeded smoothly for both benzyl chloride and *p*-methoxybenzyl chloride using the sodium hydride/DMF system. This resulted in isolated yields of 71% for 1,4-dibenzyl-2,5-dioxopiperazine (**158** : R = benzyl) and 81% for 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159** : R = *p*-methoxybenzyl).

Bromination of 1,4-dibenzyl-2,5-dioxopiperazine (**158**) and 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159**) proceeds smoothly in the now standard manner, with NBS in carbon tetrachloride, to give a very good yield of the 3,6-dibromo products.

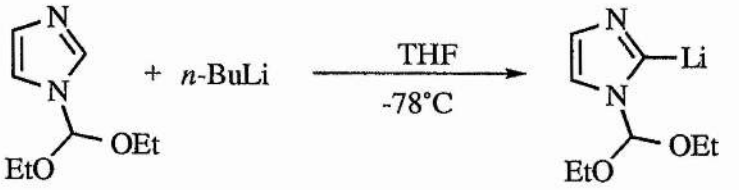


(158), R = $PhCH_2$-
(159), R = *p*-MeO-$C_6H_4CH_2$-

(160), R = $PhCH_2$-
(161), R = *p*-MeO-$C_6H_4CH_2$-

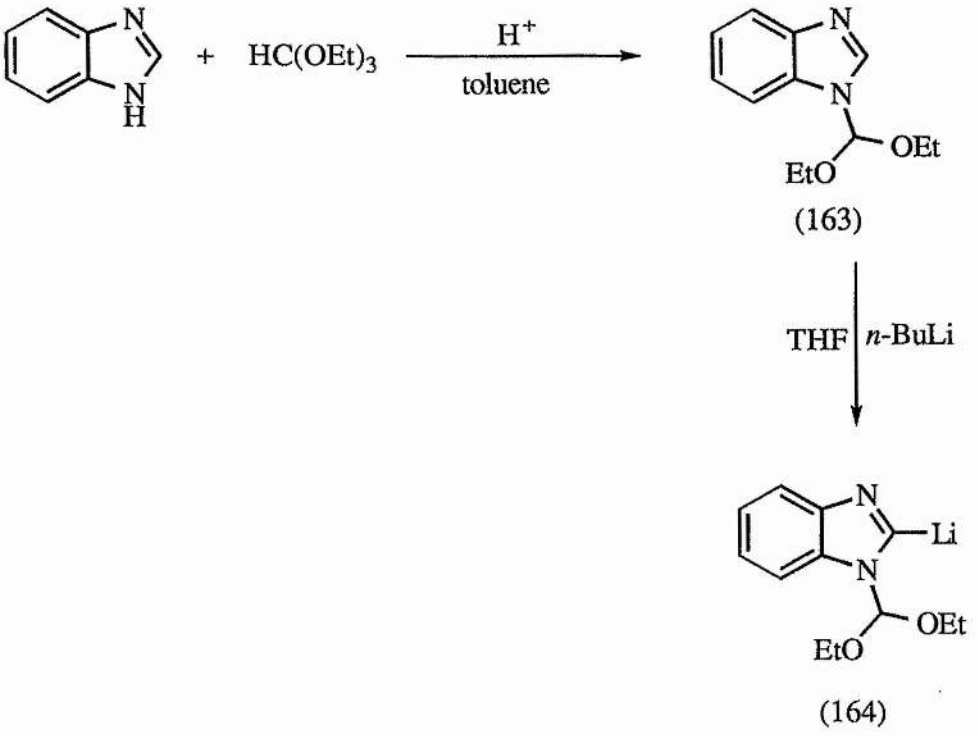
No purification method has been quoted for the dioxopiperazine (**160**) and the structure has previously been confirmed using accurate mass spectra and also from nmr data of the oil isolated from the reaction mixture. The stability of this crude oil (**160**) in air has also been questionable since it appears to decompose upon standing. We have since found that a careful crystallisation from toluene/petrol yields rosettes of white crystals, storage of which is possible over many weeks.

It has been shown[114] that protection of imidazole with a diethoxymethyl group is simply achieved using triethyl orthoformate and acid catalysis, this group also benefits from the fact that it is be removed during an aqueous work-up. This product can then be taken crude and metallated at -78°C to give the 2-lithio species (**162**) in good yield.



(162)

It was therefore predicted that protection of benzimidazole should give the *N*-protected benzimidazole (**163**) and thence the lithiated benzimidazole (**164**).



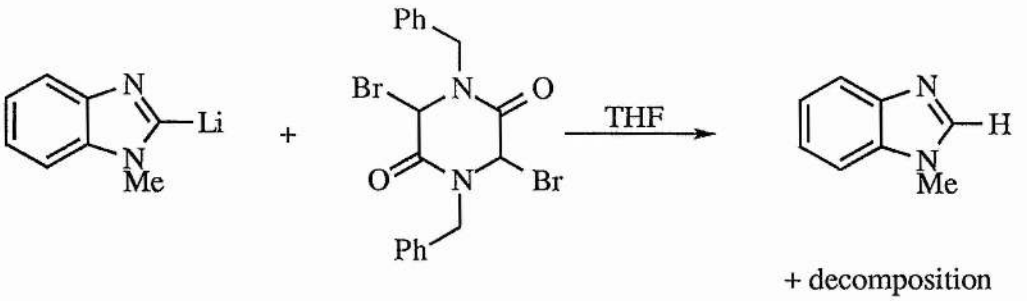
A suspension of benzimidazole, triethyl orthoformate and a catalytic amount of *p*-toluenesulphonic acid in toluene was heated to reflux. The mixture was then evaporated to dryness and more triethyl orthoformate and toluene added. The mixture was again heated to reflux and some of the solvent distilled off to remove any ethanol which had formed. The mixture was again evaporated and due to the perceived instability of the product (**163**) towards purification, was used crude.

A solution of the protected benzimidazole (**163**) was lithiated at low temperature using *n*-butyl lithium. The lithiated material (**164**) was then stirred with a solution of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**160**). After several minutes the reaction was quenched and worked-up. The product from the reaction was a black tar and the only identifiable component of the tar was found to be benzimidazole. It was thought that lithiation had not taken place and the butyl lithium had caused decomposition of the dioxopiperazine ring. The extent of lithiation was then examined.

The above reaction was repeated but the electrophile added to the reaction was this time not the dioxopiperazine (**160**) above but instead deuterium oxide. It was hoped that by observing the level of deuterium incorporation then the degree of lithiation could be deduced. After working the reaction up it was found that no lithiation had taken place and the starting benzimidazole was recovered unchanged.

A second choice of heterocyclic nucleophile chosen to react with a dibromo-dioxopiperazine was 2-lithio-1-methylbenzimidazole. As shown above this can be formed in good yield and is a strong nucleophile[112].

A solution of 1-methylbenzimidazole in THF was lithiated at -78°C with *n*-butyl lithium. This solution, when added to a solution of the dibromodioxopiperazine at low temperature, gave a very dramatic colour change, but upon work-up the mixture gave rise only to recovered 1-methylbenzimidazole and unidentifiable decomposition products.

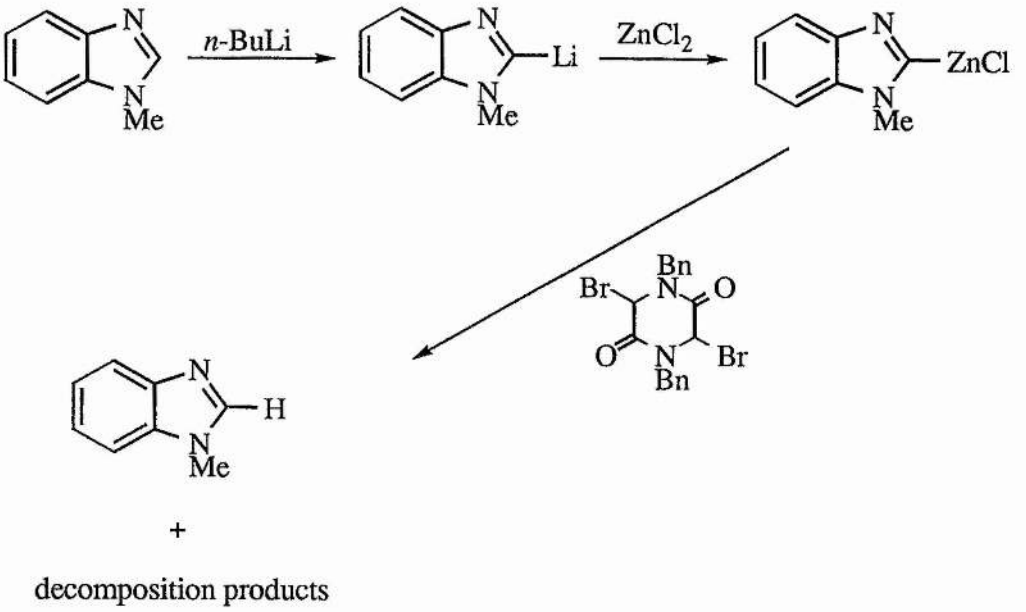


+ decomposition

It was then thought that the lithiobenzimidazole may be too nucleophilic[112] and hence attack a carbonyl of the dioxopiperazine, causing decomposition, or else may be too basic and again cause decomposition.

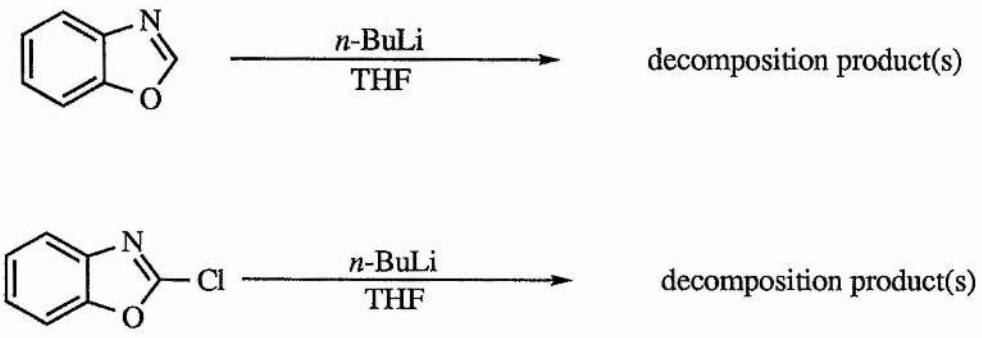
To overcome these possible problems a "softer" nucleophile was envisaged. Organozinc reagents have been shown to have a reduced reactivity when compared to organolithium or organomagnesium halides[115] and so it was hoped that the reaction of a suitable organozinc reagent may allow for the desired displacement reaction to occur.

Following a procedure laid down for the formation of 2-(1-methylindolyl)zinc chloride[115], 1-methylbenzimidazole was lithiated in the 2-position and then a transmetallation to give the zinc derivative was attempted. The crude product from this reaction was then reacted with the dibenzyldibromodioxopiperazine (**160**) thus :



This reaction when attempted at low temperature again only led to starting 1-methylbenzimidazole and decomposition products being isolated.

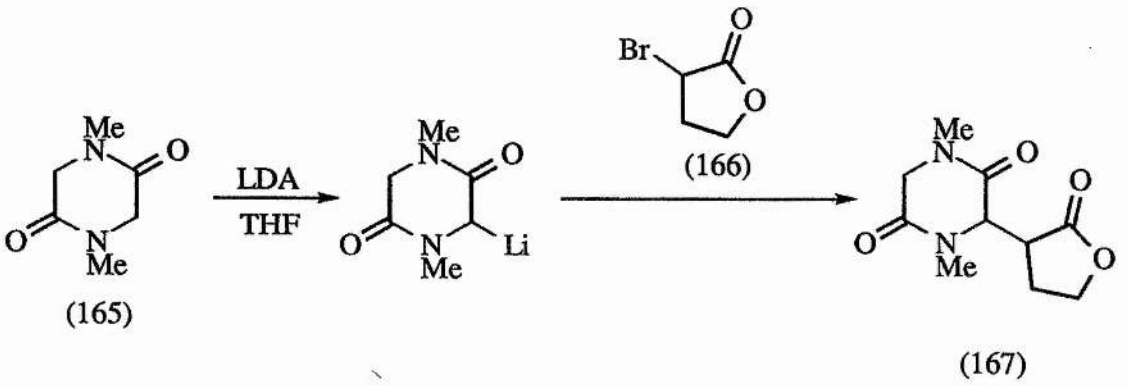
A change of the heterocycle was then made from a benzimidazole to a benzoxazole. Attempted lithiation of 2-chlorobenzoxazole to give the 2-lithiobenzoxazole gave only unidentifiable decomposition product(s) and an attempt to lithiate benzoxazole directly again failed to give any 2-lithiobenzoxazole. These failures in the formation of a suitably nucleophilic heterocycle which could displace the bromines in the dibenzyldibromo-dioxopiperazine (**160**) without causing decomposition meant that this route was abandoned.



2.2.3. Reaction Between an Electrophilic Heterocycle and a Nucleophilic Dioxopiperazine

The second proposed synthetic route corresponding to disconnection along route 2 (page 41) can also rely upon the reaction of a preformed nucleophilic dioxopiperazine and an electrophilic heterocycle.

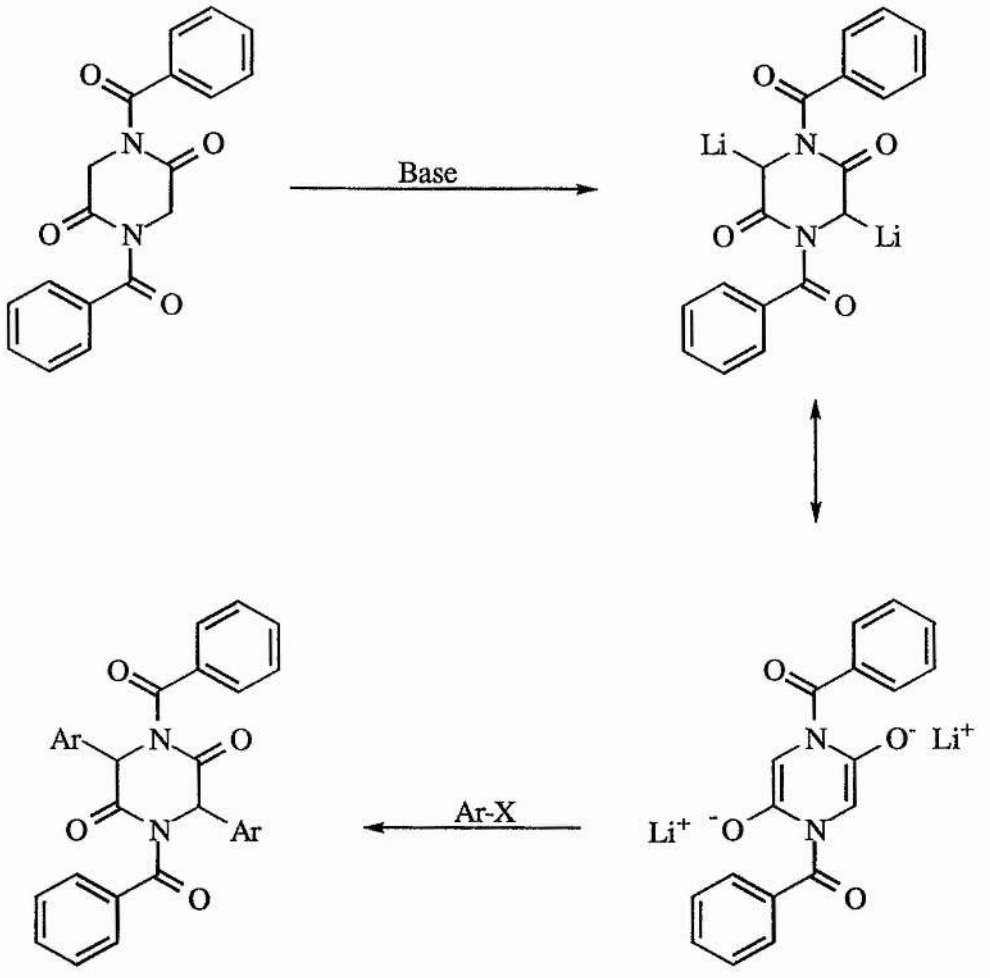
1,4-Dimethyl-2,5-dioxopiperazine (sarcosine anhydride) (**165**) has been shown to be deprotonated when treated with a suitable base[33]. The anion can then perform a nucleophilic displacement of, for example, a halogen from a suitable electrophile such as (**166**)[33].



The reported yield of the product (**167**), is however, low (9%) with a considerable amount of unidentifiable side-products which probably arise from decomposition of the lactone.

A second paper[30], however, suggests that mono-deprotonation of sarcosine anhydride (1,4-dimethyl-2,5-dioxopiperazine) (**165**) can be achieved followed by quenching with a suitable electrophile (in this case 1-iodo-3-(trimethylsilyloxy)propane) giving the desired product in a moderate yield (55%). This, therefore, shows possible scope for the coupling of a nucleophilic dioxopiperazine and an electrophilic heterocycle.

The first series of reactions used the *N,N*-dibenzoyldioxopiperazine. It was thought that by using two equivalents of base a dianion may be formed which, when reacted with the electrophilic aromatic heterocycle, might give the desired *N*-protected product in one step.



To a solution of dibenzoyldioxopiperazine in THF (at -78°C) were added 2 equivalents of *n*-butyl lithium. This immediately produced an exothermic reaction and the solution went a very dark brown colour. Upon complete addition of the base the black solution was only stirred for a few minutes due to a fear of decomposition, before addition of a solution of 2-chloro-1-trimethylsilylbenzimidazole in THF.

Upon addition of the benzimidazole the colour changed to orange and a precipitate appeared. Upon warming to room temperature the precipitate went into solution and the mixture turned red. The reaction was then quenched with saturated aqueous ammonium chloride and worked-up. The two major components of the mixture were isolated *via* chromatography. They were found to correspond to starting dibenzoyldioxopiperazine and 2-chlorobenzimidazole. One other very minor component was also isolated and this was

believed to arise, by studying the ^1H nmr spectrum, from butyl group incorporation into the dioxopiperazine.

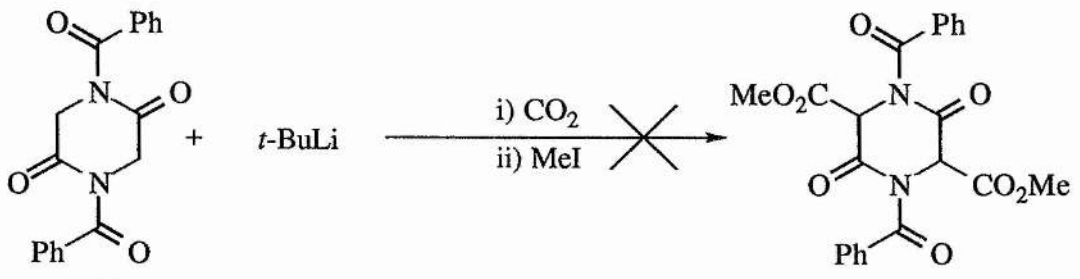
The problem of the butyl group being so nucleophilic as to attack the carbonyl groups of the protected dioxopiperazine was overcome by the use of *t*-butyl lithium. This base is not only very strong but due to the steric bulk of the butyl group is also a poor nucleophile.

The use of a benzoyl protecting group also benefits from the fact that there are no potentially abstractable protons when used with such a strong base as *t*-butyl lithium. It was hoped that by using this very strong base the dianion of the dioxopiperazine might be formed which could then go on to react with a range of electrophiles.

The first step was the deprotonation of a solution of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) in ether using *t*-butyl lithium. The solvent chosen for the reaction was diethyl ether since reaction of *t*-butyl lithium with the ethereal solvent THF can take place. This caused a problem since the dibenzoyldioxopiperazine is only very sparingly soluble in ether at room temperature and even less so at -78°C.

The first choice of electrophile was carbon dioxide followed by methyl iodide since it was hoped that the dianion of the dioxopiperazine would react with the carbon dioxide to give a dicarboxylate salt. This would then be methylated giving the diester.

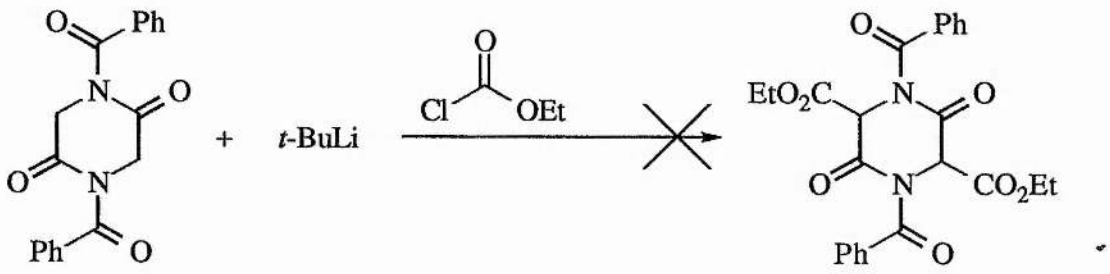
Addition of the base to a suspension of dibenzoyldioxopiperazine (**33**) in ether did result in a colour change being observed. This suggested that some lithiation was taking place. The mixture was then stirred for some time before being added to a suspension of solid carbon dioxide in ether. The reaction was finally quenched with methyl iodide and worked-up. Isolation of all the components from the reaction only resulted in the starting dioxopiperazine being recovered in good yield and none of the expected product (**168**) being found.



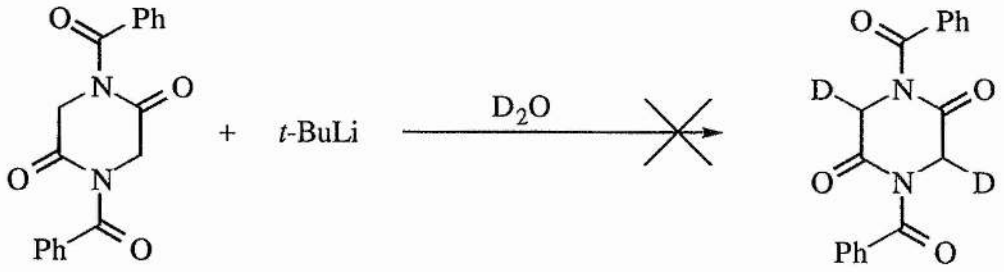
It was thought that the reason for the lack of reaction was due to a number of possible factors. The first problem was the lack of solubility of the dioxopiperazine in ether and so a change was made to THF. It was believed that any reaction of the base with the THF would be slow compared to the deprotonation of the dioxopiperazine. A second perceived problem was that the carbon dioxide is a relatively poor nucleophile and so it may be that the dianion is forming but not reacting to form the carboxylate salt. This meant a change of electrophile was required.

One possibility is ethyl chloroformate since this could react with the dianion, which could displace the chloride and give the ester in one step.

The above reaction was repeated using THF instead of ether. This did seem to result in less precipitate being seen but still did not give a clear solution. The base was added at low temperature and again a colour change was seen. This time the reaction was quenched with a solution of ethyl chloroformate in THF. Upon work-up of the reaction and isolation of the products it was again found that only unchanged starting materials were found.



To confirm that lithiation was taking place the above reaction was again repeated and D_2O was used to quench the reaction. This failed to result in any deuterium incorporation into the dioxopiperazine system, as shown by ^1H and ^{13}C nmr. The use of *t*-butyl lithium to obtain a dianion was therefore abandoned.



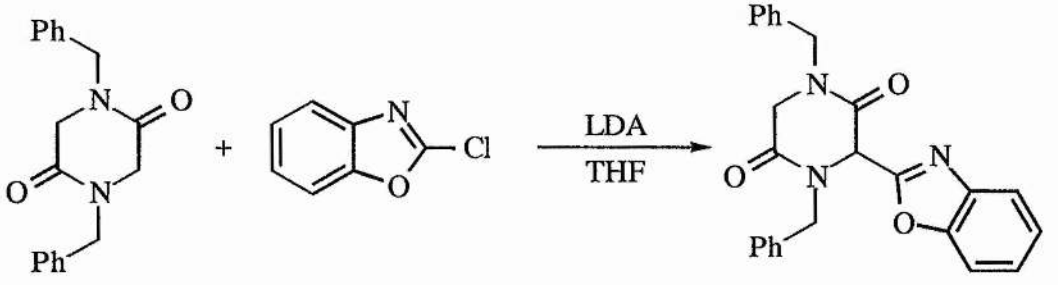
The next choice of protecting group was benzyl. This was used in the first instance as a model system. When a suitable route to the desired product has been devised then a change would be made to the *p*-methoxybenzyl group since this can be removed more easily than the benzyl group[30].

A suspension of 1,4-dibenzyl-2,5-dioxopiperazine (**158**) in THF was treated with one equivalent of LDA. The lithiated dioxopiperazine was then added to a solution of 2-chlorobenzoxazole (**102**) , before warming to room temperature and working the reaction up.

The lithiated dioxopiperazine was added to the 2-chlorobenzoxazole because it was thought that the methine proton bonded to C-3 of the product from the reaction would be more acidic than the protons bound to the methylene group of the starting material. This would mean it might be possible for the lithiated dioxopiperazine to deprotonate the methine group of the product, and this would then mean the reaction would only go to 50% completion.

The isolated yield of the product 3-(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**169**), after chromatography, was a disappointing 20%. This is possibly due to the fact that the starting 1,4-dibenzyl-2,5-dioxopiperazine is very sparingly soluble in the solvent (THF). In the literature it has been claimed[30] that clear solutions can be obtained with minimal solvent (1.47 g of the dibenzyldioxopiperazine in 50 ml of THF at -78°C) although in practice it has been found that 1 g of dibenzyldioxopiperazine will not dissolve in 200 ml THF at -78°C.

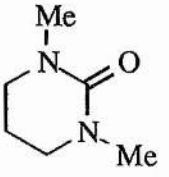
The yield of the product (**169**) is poor although the reaction is clean with no observed decomposition of either the dioxopiperazine ring or of the 2-chlorobenzoxazole.



(169)

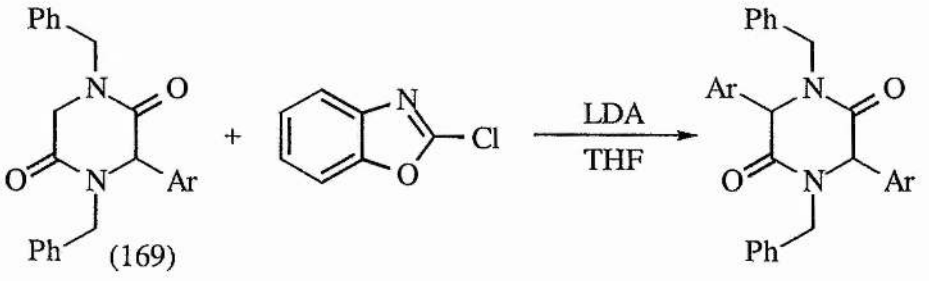
The use of a co-solvent was then examined to increase the solubility of the starting dibenzyldioxopiperazine in THF. Hexamethylphosphoramide (HMPA) is a common choice although it has been quoted that "HMPA ranks in the super league of experimental carcinogens and must be considered as potentially posing a serious risk to man"[116]. Therefore an alternative was found.

DMPU (*N,N'*-dimethyl-*N,N'*-propyleneurea or 1,3-dimethyl-2-oxohexahydropyrimidine) (**170**) has been shown to be one possible alternative. This was used as a co-solvent in the above reaction but failed to give any increase in the crude yield of the desired product (by ^{1}H nmr) and the DMPU was also found to be difficult to remove from the reaction mixture.



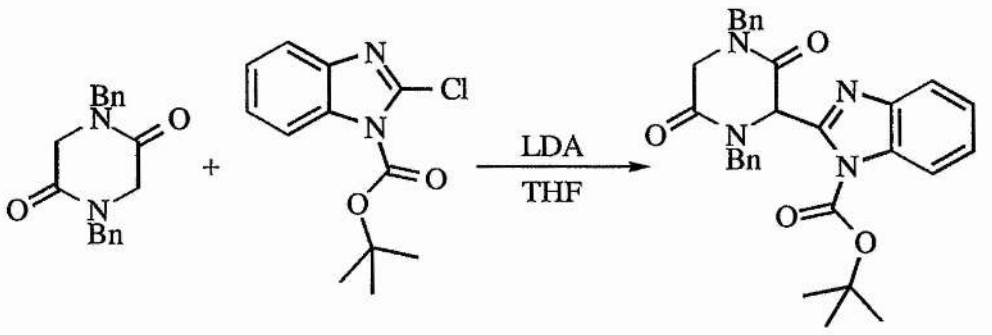
(170)

Reaction of the compound (**169**) with a second equivalent of LDA followed by 2-chlorobenzoxazole under similar conditions to above gave a good yield (73%), after chromatography, of the product 3,6-bis(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**171**). This increase in yield is thought to be due to the much higher solubility of the monobenzoxazolyldioxopiperazine (**169**) in THF at -78°C when compared to the starting material, dibenzyldioxopiperazine (**158**).



(Ar = benzoxazol-2-yl)

Reaction of 1-*t*-butoxycarbonyl-2-chlorobenzimidazole with a solution of lithiated dibenzyldioxopiperazine in a manner similar to the one above results in a three component mixture. Two of the components were found to be starting materials and the third believed to be the monobenzimidazolyldioxopiperazine (**172**). Identification of the structure of the product from this reaction proved to be difficult.



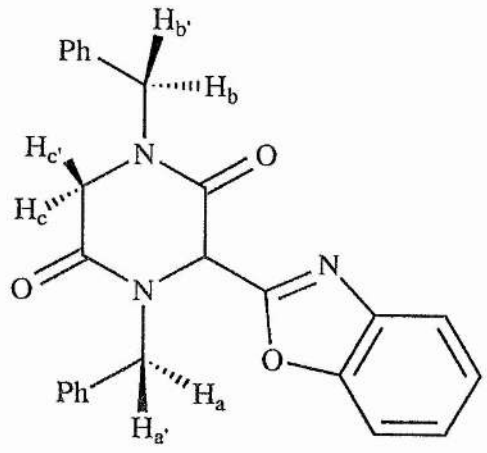
(172)

The ^{1}H nmr spectrum of the compound (**169**) showed the expected splitting pattern normally associated with 1,4-dibenzyl-3-substituted-2,5-dioxopiperazines (see figure 1, page 106). The ^{1}H and ^{13}C spectra for the product (**172**) isolated from the reaction with the protected 2-chlorobenzimidazole was not as simple (see figure 2). It was also found that both the ^{1}H and ^{13}C nmr spectra varied with temperature (see figure 3 and figure 4) and so these anomalies were then studied further.

Since it had proven difficult to obtain an elemental analysis of the sample, a high resolution mass spectrum showed that the sample contained the correct product although it was proven to be contaminated with starting dibenzyldioxopiperazine. This meant that the signals obtained in the ^{1}H nmr were due to the desired product (**172**) and some starting material (**158**).

Figure 1

Expansion of ^{1}H nmr spectrum of compound (**169**)



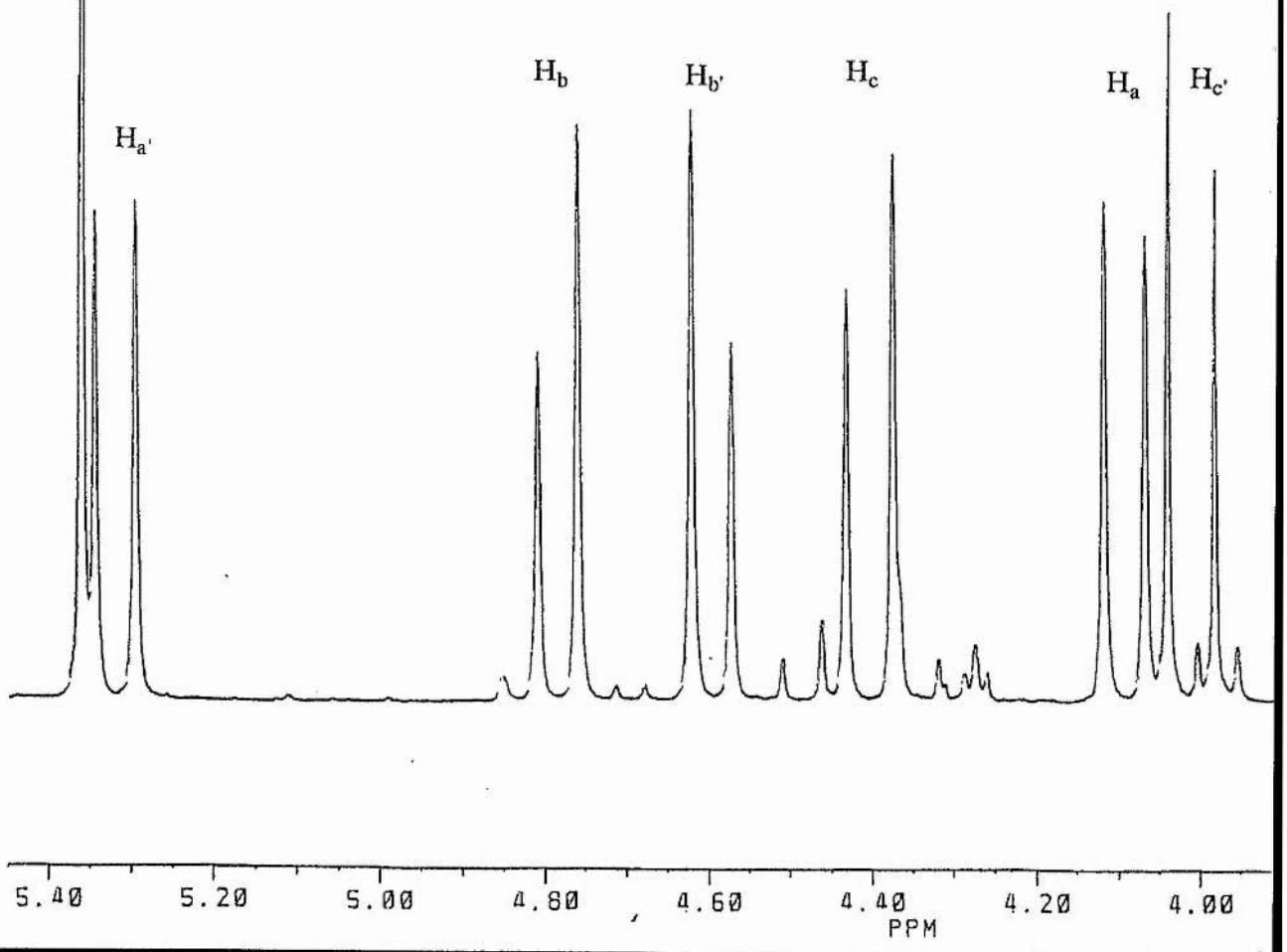
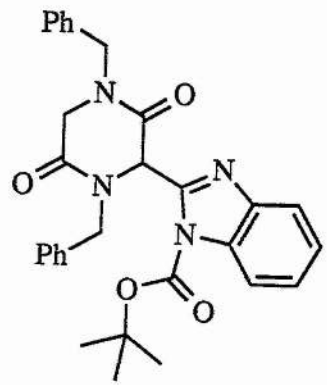


Figure 2

^{1}H spectrum of compound (**172**)



Containing some unchanged starting material (**158**) *

Figure 3

^{1}H nmr spectra of (**172**) at 325K and 303K

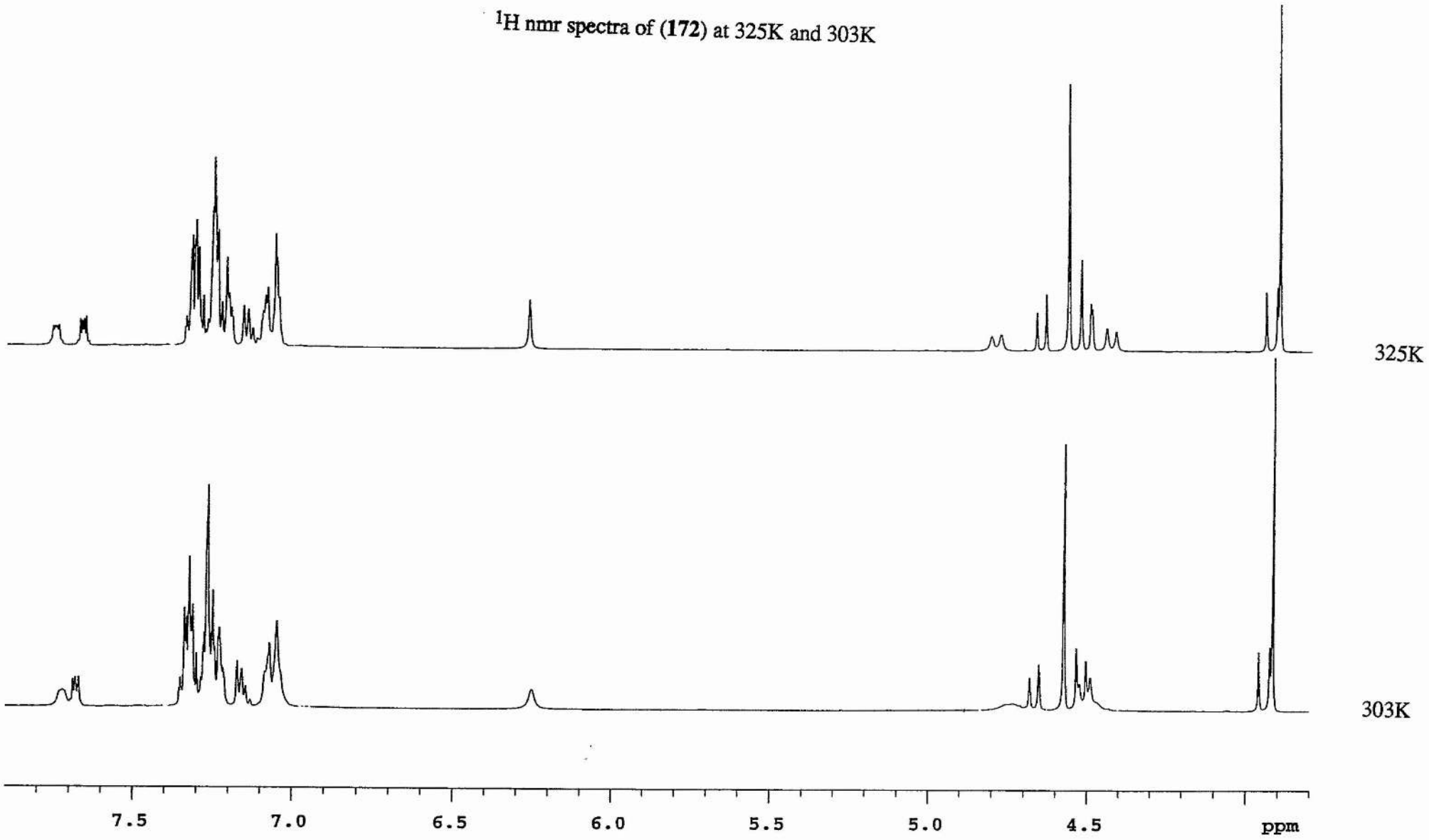
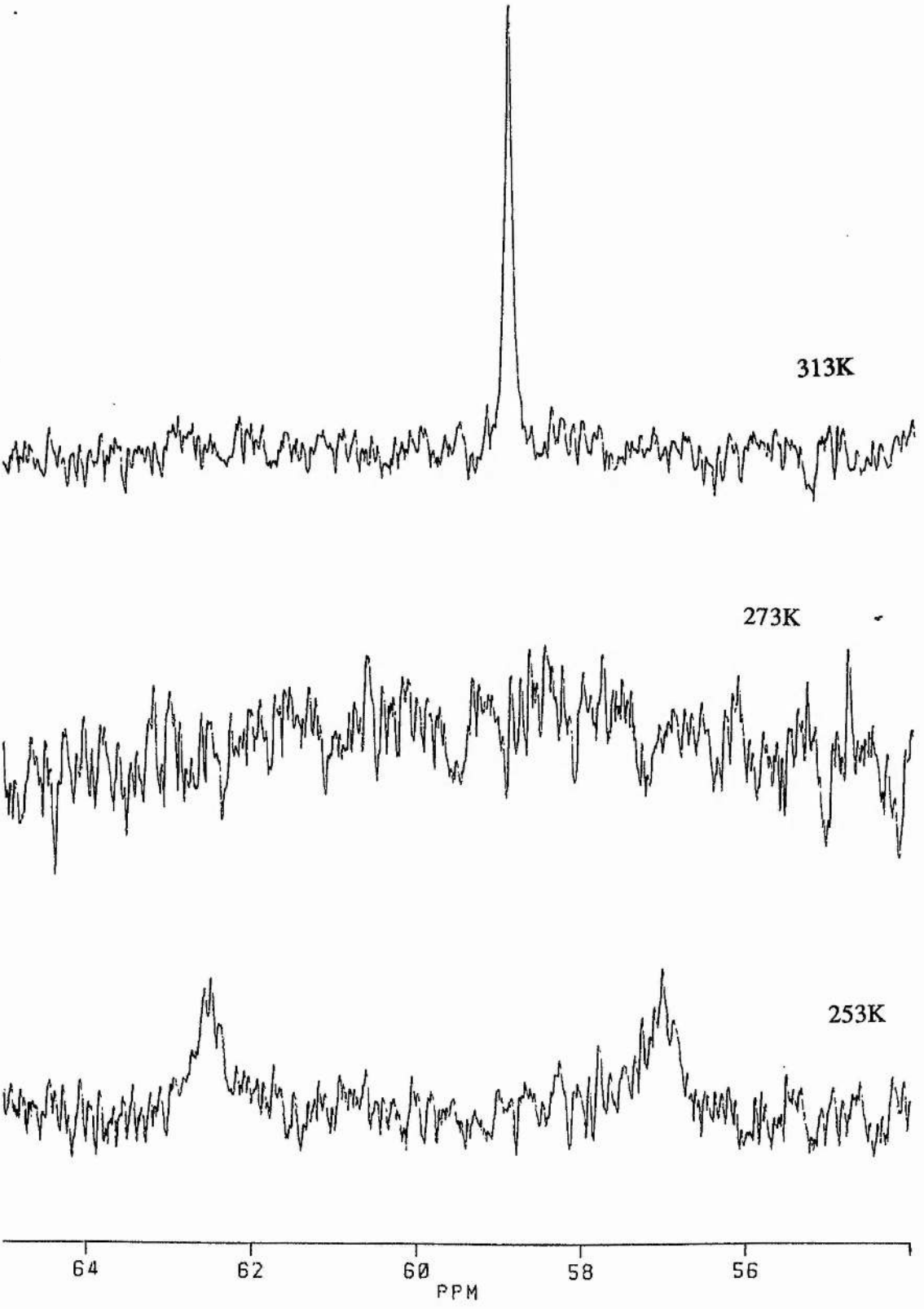
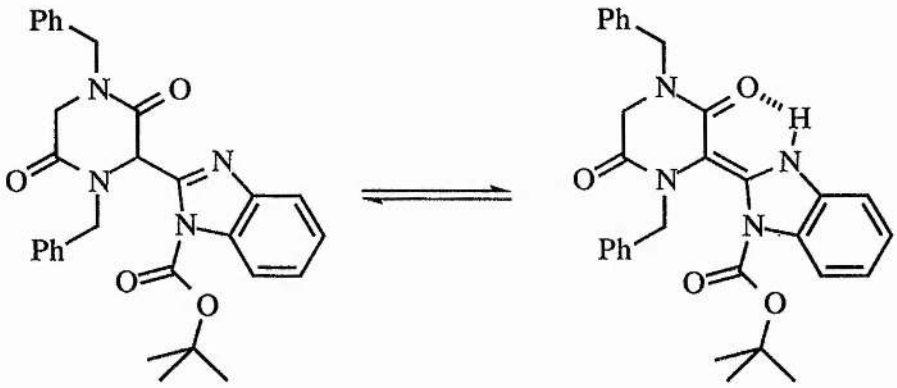


Figure 4

^{13}C nmr spectra of (**172**) at 313K, 273K, and 253K



The first possible explanation for these results was that the ^1H spectra obtained were due to a tautomerisation of the type shown below.

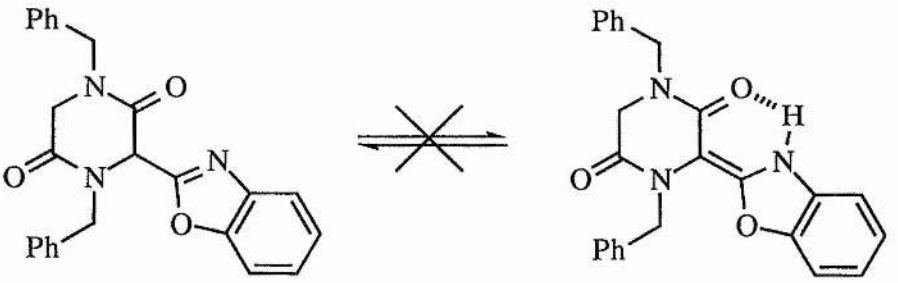


This explanation was soon discounted however. For the tautomerisation to occur the delocalised system of electrons in the imidazole ring would be disturbed and a proton shift would occur causing the imidazole nitrogen to become protonated and a double bond to form between the dioxopiperazine ring and the imidazole ring.

For this to occur then the energy gained by the molecule by disturbing the delocalised benzimidazole ring system would have to be offset by the energy loss occurring by the formation of an intramolecular hydrogen bond and the formation of a double bond *exo*- to the imidazole ring.

From previous experiments it can bee seen that the oxazole ring of a C-2 substituted benzoxazole will hydrolyse very quickly and easily in aqueous acid. It has also been found that (benzoxazol-2-yl)*N*-Boc-glycine will behave as a β-imino acid and decarboxylate very readily. This suggests that the benzoxazole ring does not have a fully delocalised system of π-electrons but that they are more unsymmetrically distributed, and therefore behave more like a C=N.

These results then suggest that the 3-(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**169**) should also exist in a tautomeric mixture, with even more of the NH tautomer being seen than in the corresponding benzimidazole example.



This can clearly be seen not to occur by examination of the ^{1}H, ^{13}C, DEPT and 2D C-H correlation spectra run on a sample of 3-(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxo-piperazine, since all the signals can be assigned on the basis of a single isomer without any evidence of any signal corresponding to an NH group.

This is therefore strong evidence that the complexity of the spectra of (**172**) is not due to a tautomerisation but instead some other kind of event.

The assumption that the complexity of the spectra was not due to a tautomerisation was confirmed by the attempted reaction between the 3-benzimidazolyldioxopiperazine, sodium hydride and di-*t*-butyl dicarbonate. This was attempted in the hope that if any of the 1*H*-benzimidazole tautomer were present then it would be trapped out as the di-Boc derivative.

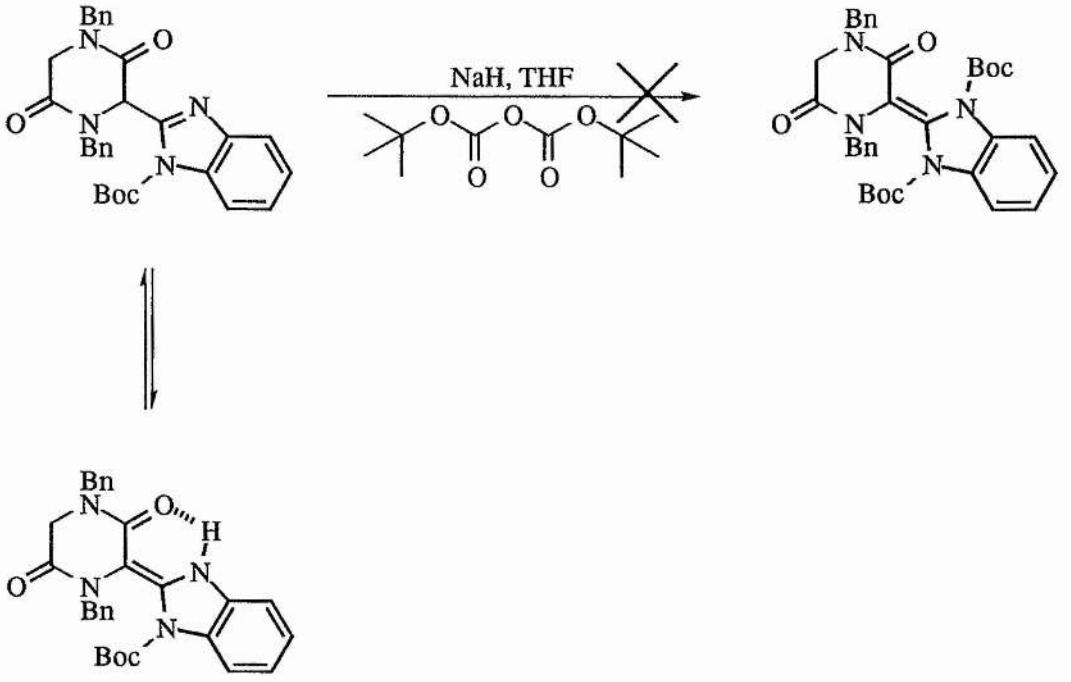
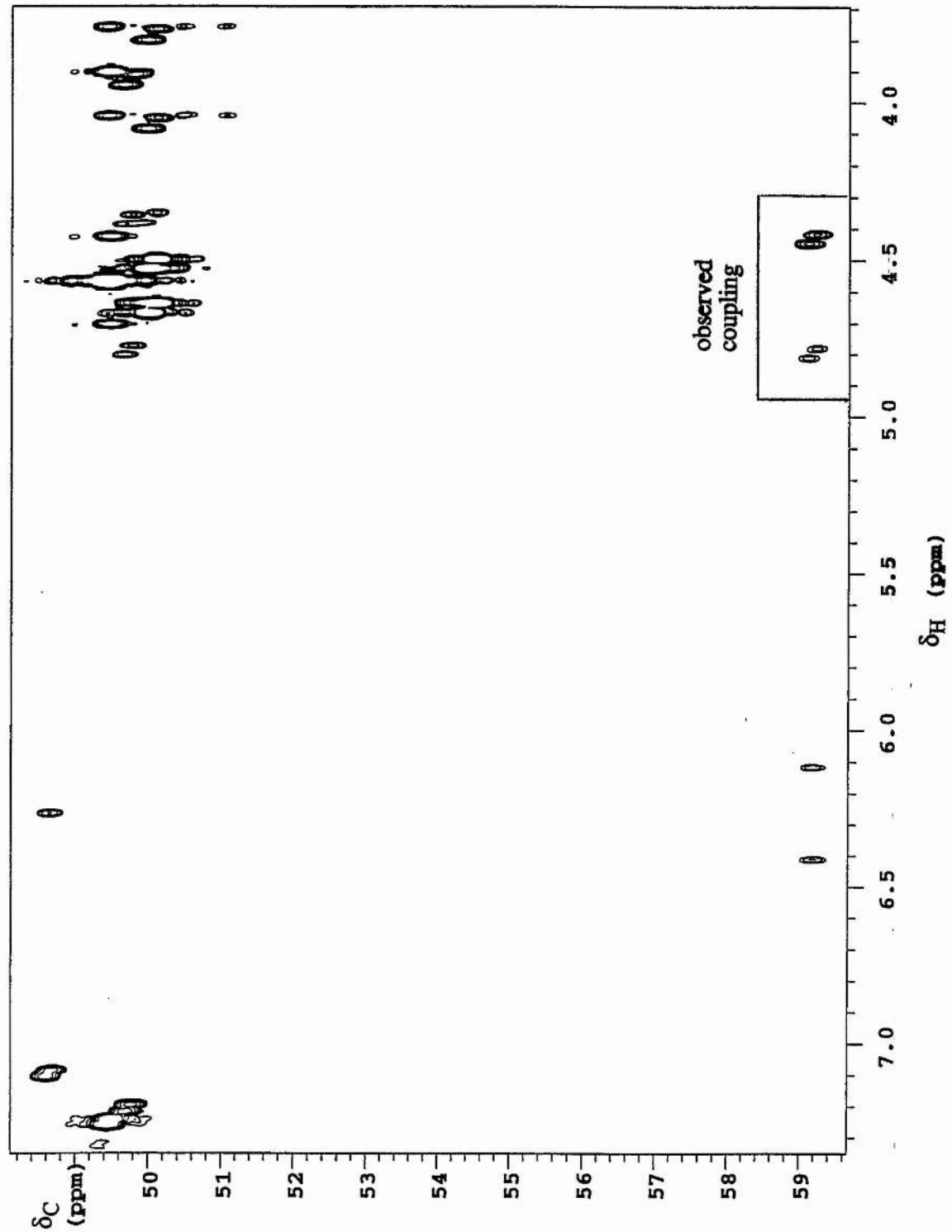
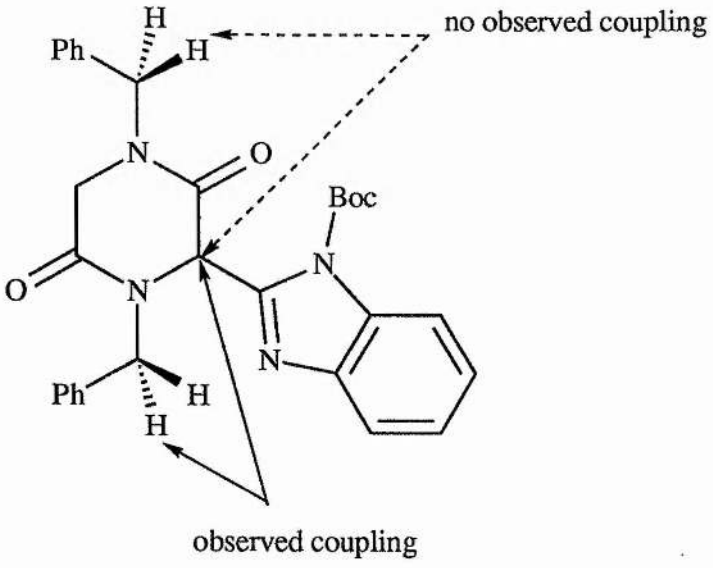


Figure 5


observed coupling
δC (ppm)
δH (ppm)
50
51
52
53
54
55
56
57
58
59
4.0
4.5
5.0
5.5
6.0
6.5
7.0

From a long range C-H correlation spectrum run on a sample of the dioxopiperazine (**172**) the signals corresponding to the various methylene groups could be identified. Specifically it could be seen that the benzylic protons nearest in space to the benzimidazole were responsible for the complicated ^1H spectrum obtained. See figure 5.

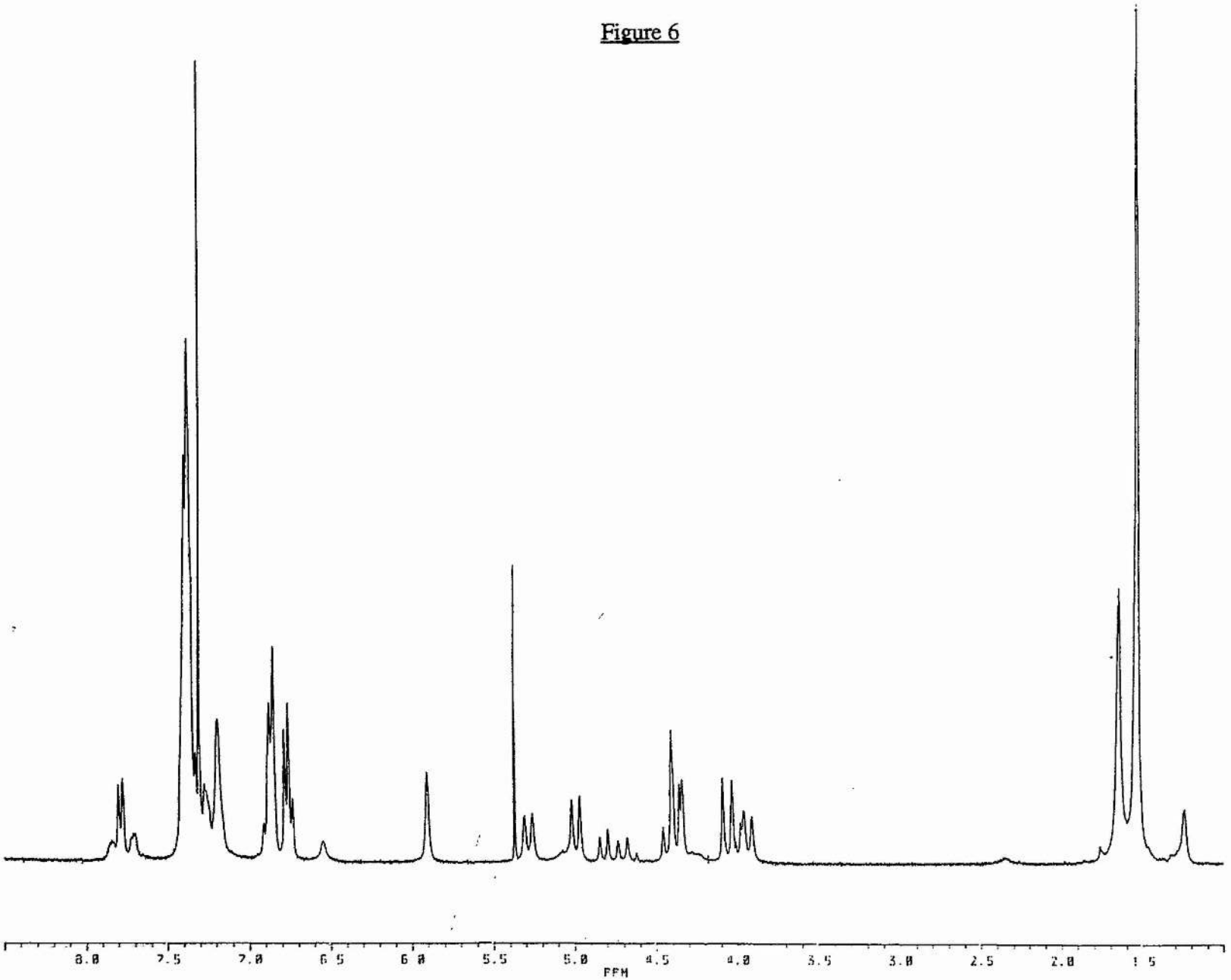
It could be seen that a coupling was observed between the dioxopiperazine ring methine carbon and two methylene protons. The couplings that were observed were between the carbon and the methylene protons nearest to the benzimidazole as this coupling was through three bonds. Couplings through four bonds were not observed and both the dioxopiperazine ring methylene and also the other benzyl methylene protons are both four bonds removed from the ring methine carbon.



Confirmation that the broad signals in the ^1H nmr spectrum were due to the benzylic protons nearest in space to the bulky benzimidazole and also the fact that the methine proton is broad suggested that a rotational process is occurring on or about the benzimidazole moiety.

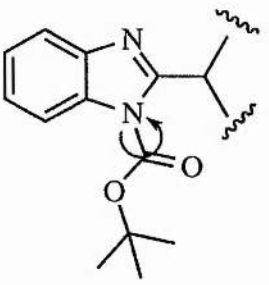
Furthermore the time taken for the event(s) to occur must be comparable with that of the nmr timescale when the experiments were run at room temperature. This meant that the spectra obtained at room temperature were over complicated by the fact that some of the peaks were not fully developed.

Figure 6

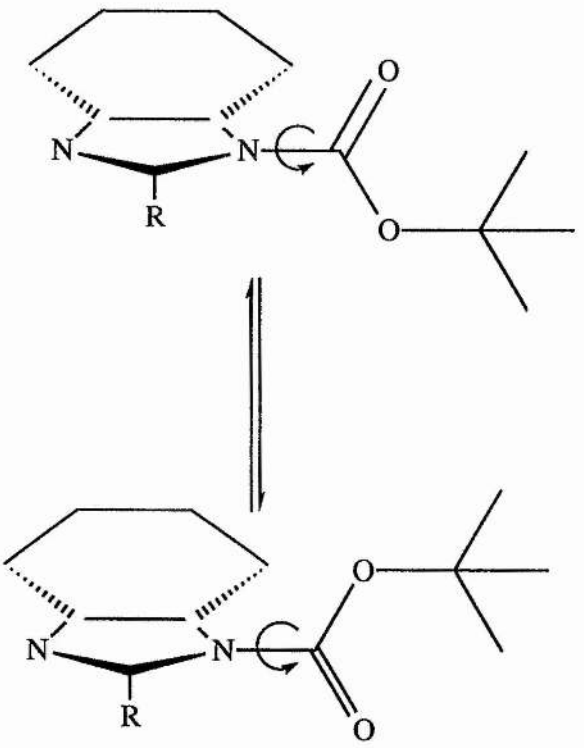


213K

When these results are combined with some simple modelling studies it was decided that the event causing the effects seen in the ^{1}H and ^{13}C spectra was due to the rotation about the bond between the *t*-Boc carbonyl and the N-1 of the benzimidazole.



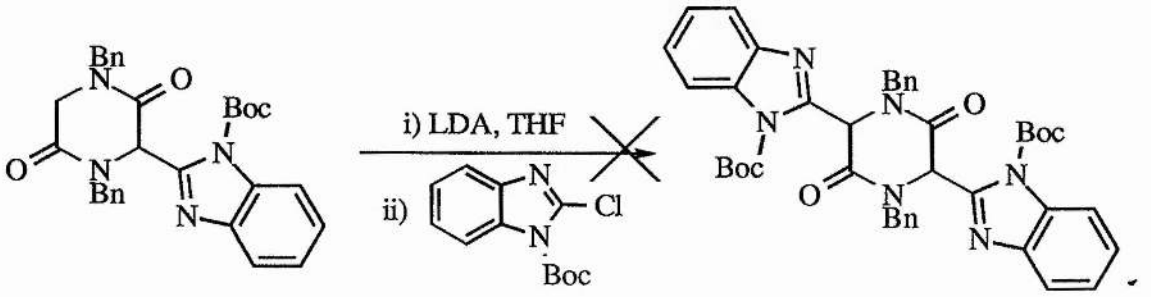
This was then confirmed by cooling a $CDCl_3$ solution of the sample down to 213K. It was then seen that the *t*-butyl signal had split into two. This then showed the butyl group being in two environments and by a crude comparison of the area of the peaks it was deduced that the ratio of the population of these environments was in the order of 3:1. See figure 6.



The ^{13}C nmr spectra of the sample over a range of temperatures also showed some, at first, unexpected line broadening. The most obvious example seen was that of the dioxopiperazine methine carbon at *ca.* 60 ppm. At room temperature this signal can be seen as a broad singlet. Upon cooling the signal flattens and further cooling results in the appearance of two signals. This is again indicative of the *t*-Boc group being seen in two environments when the sample is cooled and the rotation slowed enough for the two carbon environments to be seen in the nmr timescale. See figure 4 (see p.101).

These results therefore confirm that the desired product was obtained and the unusual nmr spectra could also be explained. The reason for the complication of the spectra should not have come as a complete surprise.

It was then thought possible that a second benzimidazole group could be introduced at the C-6 position of the compound (**172**), to give the bis(benzimidazolyl)dioxopiperazine (**173**).



(172) (173)

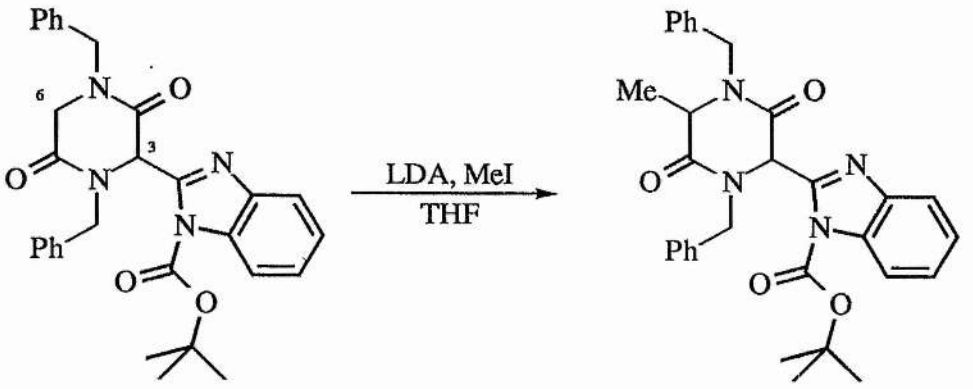
The, by now standard, reaction was repeated using the dioxopiperazine (**172**) and two equivalents of LDA. Upon addition of the base the usual red solution was obtained which generally suggested anion formation. Upon addition of the 1-*t*-butoxycarbonyl-2-chlorobenzimidazole followed by quenching the reaction and working the mixture up it was found that no reaction had taken place. The reaction was repeated using three equivalents of LDA and again the red colour was seen and again no reaction was found to have taken place.

It was thought that this problem may be arising from steric factors. It has already been seen that the *N*-protected benzimidazole is sterically demanding and causing problems in

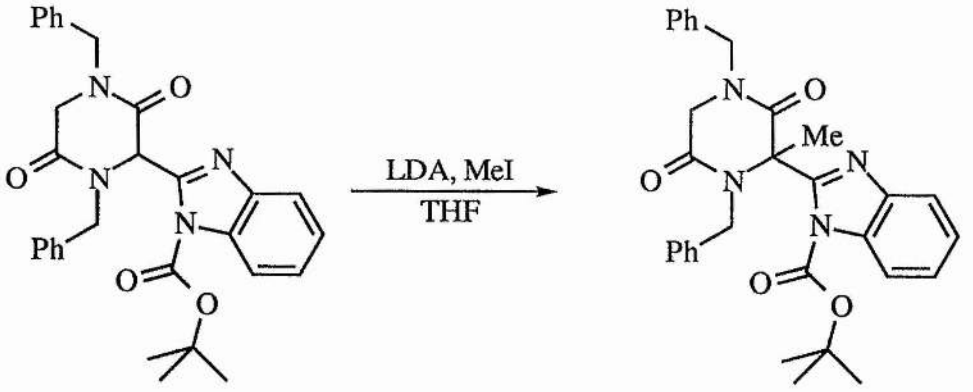
the free rotation of the groups around the dioxopiperazine. It was therefore possible that the addition of a second *N*-protected benzimidazole may be impossible.

To investigate this possibility the dioxopiperazine was deprotonated in the standard manner with LDA and then quenched with methyl iodide. It was thought that any reaction which does occur would result in a noticeable change in the ^{1}H nmr spectra of the crude product.

If methylation takes place at C-6 then in principle a pair of diastereomers may result (*cis*- and *trans*). Each of these would then be expected to give rise to a singlet for the newly introduced methyl group.



(172)



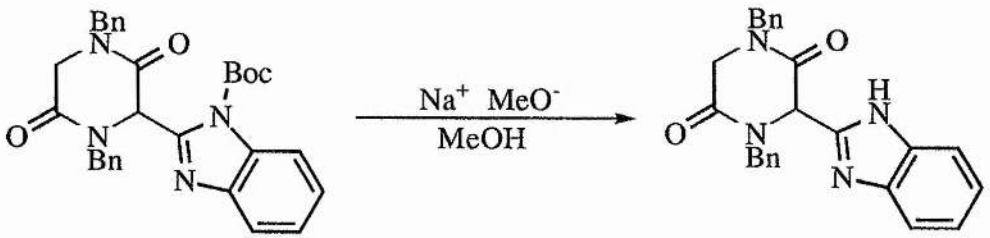
If, however, methylation takes place at C-3 then the ^{1}H nmr would show the loss of the singlet at *ca.* 6.30 ppm, as well as the appearance of a singlet corresponding to the newly

introduced methyl group. It is also possible that a mixture of the two products, both 3- and 6- methylated, may appear.

In the event the deprotonation using LDA followed by quenching with methyl iodide gave neither of the expected products only unchanged starting materials. The reaction was repeated using various equivalents of LDA but all gave unchanged starting materials.

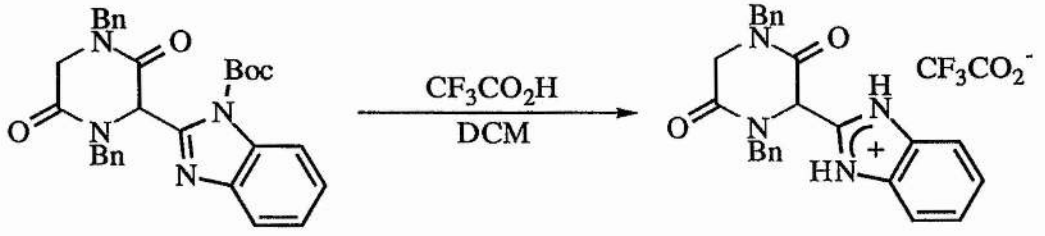
The reaction was then repeated using a hindered base, lithium hexamethyldisilazide. It was thought that the use of a strong hindered base would allow for the selective deprotonation of the methylene group of the dioxopiperazine as opposed to the more acidic proton at C-3. This also failed to give any of the desired methylated product, only unchanged starting material.

The next reaction attempted was the used of sodium methoxide to effect the deprotonation, again followed by methyl iodide. This reaction was done at room temperature in methanol and after quenching the reaction mixture with methyl iodide and working the reaction up it was found that the product isolated results from the removal of the Boc group from the benzimidazole giving (**174**). This result is not totally unexpected since it has been shown that the removal of a Boc group using methoxide has been used before[100].



(172) (174)

This deprotection can be also seen by the use of trifluoroacetic acid (TFA). TFA has been shown to cleave Boc groups very readily giving the amine as a TFA salt. Stirring a solution of the dioxopiperazine (**172**) in dichloromethane and adding freshly distilled TFA gave, after evaporation, the salt (**175**) in good yield.

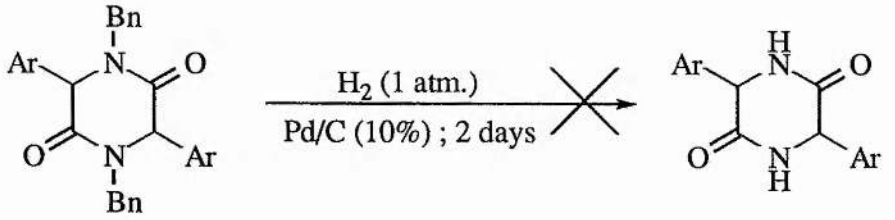


(172) (175)

Since it had proven impossible to add a second benzimidazole function to the dioxopiperazine using the standard deprotonation followed by addition of the heterocycle, the remaining studies were directed towards deprotection of the dioxopiperazine (**171**).

The problem which now arose was the removal of the benzyl groups from the dioxopiperazine ring. Debenzylation of *N*-benzylamides has been shown to be problematic[117]. Hydrogenation is one possibility although it requires large amounts of "catalyst", acidic conditions and moderately high pressures of hydrogen (approx. 3 atm). Even under these conditions success cannot be guaranteed.

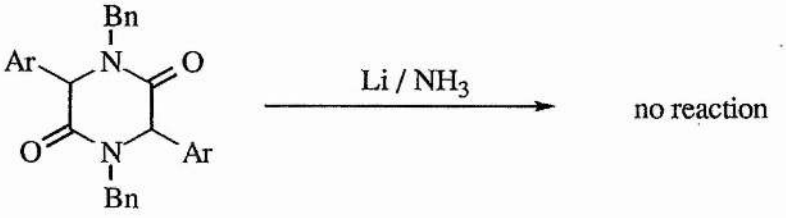
Catalytic hydrogenation has another major disadvantage, namely, that upon removal of the benzyl groups from the dioxopiperazine it is expected that the product (**78**; A, X = NH; B, Y = O) is predicted to be highly insoluble and therefore removal of the catalyst from the product may prove difficult. One attempt was however made using 10% palladium on carbon and one atmosphere of hydrogen at room temperature, but this failed to result in any product being formed, only starting materials being recovered.



(171; Ar = benzoxazol-2-yl)

One method which is reported to be the most successful and which also gives good yields for the removal of the amide *N*-benzyl groups is dissolving metal reduction using sodium or lithium in liquid ammonia. This method has the distinct advantages that it is a homogeneous system and it has been shown to leave sensitive functionality untouched.

One method which is reported to be the most successful and which also gives good yields for the removal of the amide *N*-benzyl groups is dissolving metal reduction using sodium or lithium in liquid ammonia. This method has the distinct advantages that it is a homogeneous system and it has been shown to leave sensitive functionality untouched. Several systems are reported in the literature as being of potential use[118] but the first attempt was made using lithium metal[119].



(Ar = benzoxazol-2-yl)

In this first reaction the protected dibenzyldioxopiperazine (**171**) was dissolved in THF and added to the liquid ammonia at -78°C. Small pieces of lithium were then added and the mixture stirred at -78°C for 15 minutes. After quenching the reaction and working up the mixture only recovered starting material (**171**) was recovered and so model studies were undertaken to identify the best system.

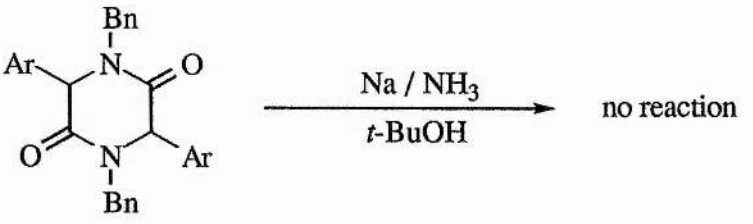
The model compound used was 1,4-dibenzyl-2,5-dioxopiperazine. The next attempt at debenzylation was using sodium. Small pieces of the metal were added to a suspension of dibenzyldioxopiperazine in liquid ammonia at -32°C. The reaction mixture was then stirred for 1 h before evaporating off the ammonia and adding solid ammonium chloride to quench the reaction. The solid recovered from the reaction was found to be unchanged starting material.

In some instances it has been shown that the addition of a proton source can aid the reaction so therefore *t*-butanol was added as the proton source. The above reaction was then repeated. Again the solid recovered from the reaction mixture upon work-up was found to be unchanged starting material.

The final system used was again sodium added to a suspension of dibenzyl-dioxopiperazine in liquid ammonia at -32°C. Again *t*-butanol was added as a proton source but this time the reaction was stirred at -32°C for 1 h. No product isolated and only recovered starting material were found.

The reason for the failure of all the above reactions to give any of the required product is thought to be due to the low solubility of dibenzyldioxopiperazine in liquid ammonia. Dibenzyldioxopiperazine is only very sparingly soluble in ethereal solvents and most of the literature methods for debenzylation require a solution of the protected compound prior to the attempted reaction. This insolubility was not thought to be a problem for the protected arylated dioxopiperazines since they are soluble in THF.

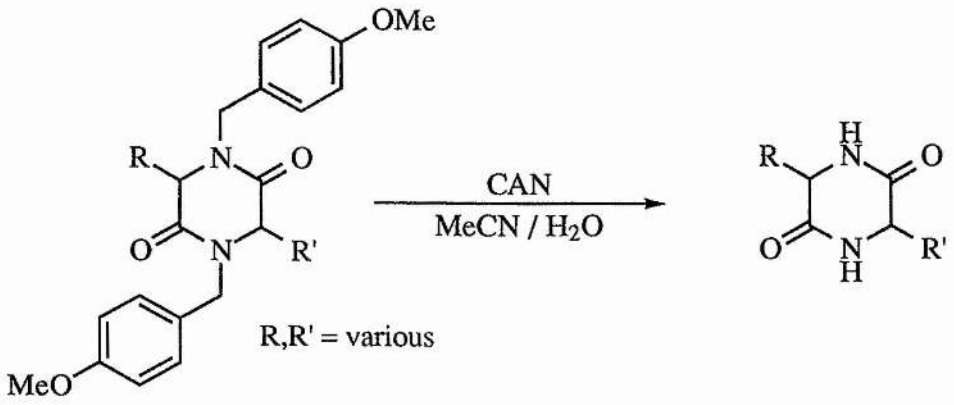
The above reactions were repeated using a solution of the bisbenzoxazolyldioxopiperazine (**171**) in THF. None of the above reactions resulted in anything but the recovery of unchanged starting materials. It seems that the removal of the benzyl group from the dioxopiperazine is very problematic.



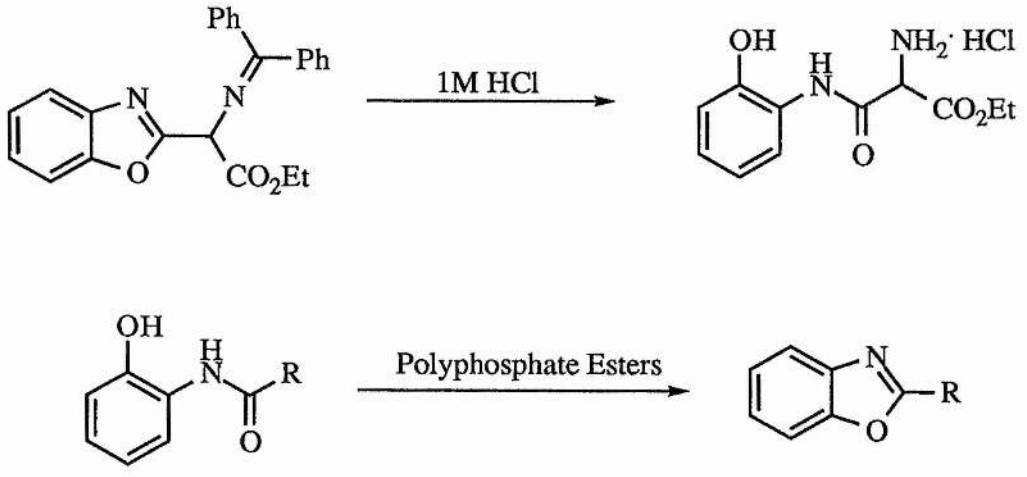
(Ar = benzoxazol-2-yl)

(171)

This difficulty in the removal of the benzyl groups was not deemed to be a huge problem since most literature work on dioxopiperazines initially uses the benzyl group for *N*-protection for use in model studies but when the best route has been identified then a change is made from benzyl to *p*-methoxybenzyl and therefore allowing easier deprotection. This is due to the fact that this group can be removed oxidatively using ceric ammonium nitrate (CAN) thus:

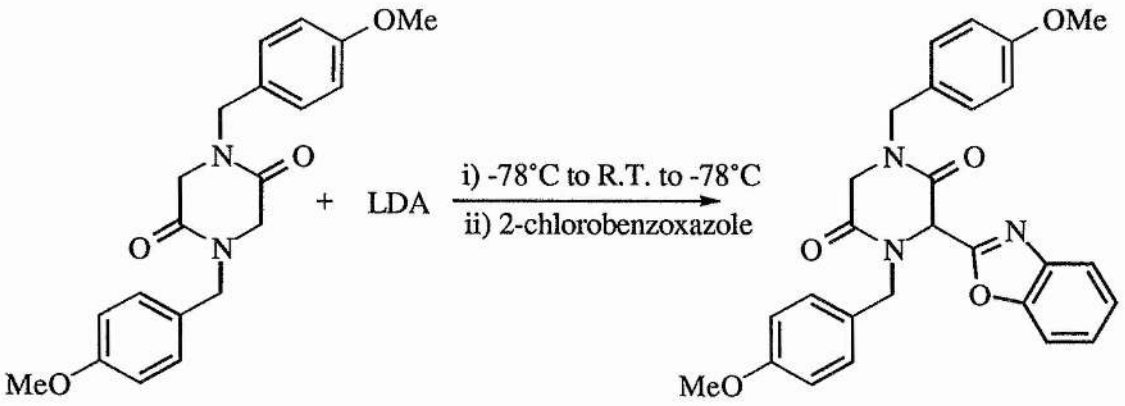


This method is quick, mild and homogeneous but may suffer from one drawback, namely it involves acidic conditions. As shown earlier the benzoxazole ring is easily cleaved under dilute acidic conditions and this may be a problem, although reforming the oxazole ring is possible at a later stage.



The synthesis of the bis(benzoxazolyl)dioxopiperazine with the *p*-methoxybenzyl protecting group (**176**) follows the procedure for the synthesis of the benzyl protected dioxopiperazine exactly but it was beset by one major problem. It seems that the solubility of the starting 1,4-di-*p*-methoxybenzyl-2,5-dioxopiperazine (**159**) is even LESS than that of the dibenzyldioxopiperazine used previously. This means that the yields of the monobenzoxazolyldioxopiperazine (**177**) are very low, in the order of 4%.

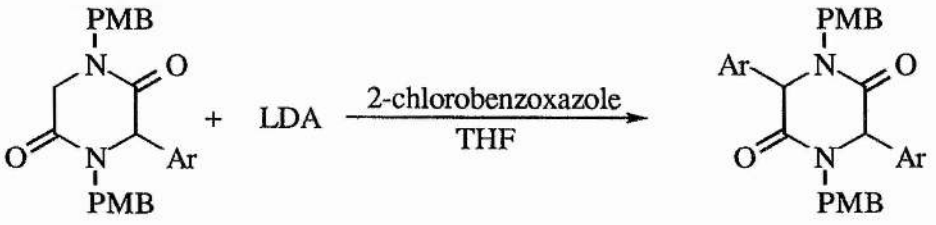
The solubility of the dioxopiperazine (**159**) does increase with temperature and so the suspension of dioxopiperazine (**159**) and LDA was allowed to warm up to room temperature before cooling back to -78°C and transferring to a solution of 2-chlorobenzoxazole.



(159) (177)

This modification then resulted in a small increase in yield (to 17%) but overall the yields are still very poor. The reaction is however clean, if low yielding, and so the two starting materials can be recovered.

The monobenzoxazolyldioxopiperazine (**177**) is then reacted with 2 equivalents of base and a second equivalent of 2-chlorobenzoxazole to give the desired product (**176**) in good yield thus:



(177) (176)

(PMB = *p*-methoxybenzyl)

(Ar = benzoxazol-2-yl)

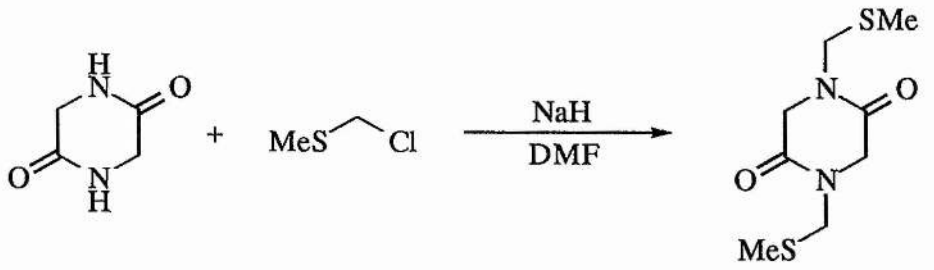
To confirm that the removal of the *p*-methoxybenzyl group is possible a solution of 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159**) in aqueous acetonitrile was stirred with ceric ammonium nitrate. After several hours the reaction mixture was evaporated down and water added. The solid was then filtered off and found to be 2,5-dioxopiperazine. The reaction was therefore attempted on the bisbenzoxazolyl-dioxopiperazine (**176**).

The bisbenzoxazolyldioxopiperazine (**176**) was then stirred in a solution of ceric ammonium nitrate in an acetonitrile / water mixture. After several minutes the orange solution becomes dark brown. Upon complete reaction the solution was evaporated down and water added. The sticky brown solid was then filtered off.

The solid was found to be insoluble in most solvents but a ^{1}H nmr of the sample in deuterated acetone did show a complex mess of signals. The infra red stretch of the sample as a Nujol mull showed what is believed to be an OH and an NH signal. This would then suggest that the oxazole ring has indeed been hydrolysed but due to the very small scale of the reaction it was not possible to obtain more information.

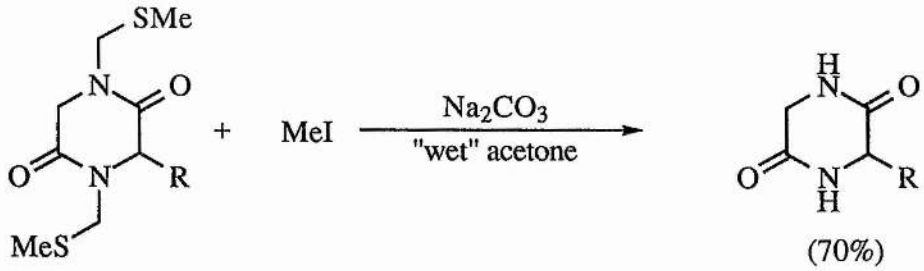
It has been found in the literature that a sulfur analogue to the MOM group (methoxymethyl) can be used to protect amide nitrogens, and more specifically dioxopiperazine derivatives[34]. This group has many advantages for the protection of the dioxopiperazine ring used in the above reactions.

The methylthiomethyl group is reported to be introduced *via* the now standard method of *N*-alkylation of dioxopiperazines, namely alkyl halide, sodium hydride and DMF as the solvent giving the product (**178**).



(178)

The group is also reported to be stable to strong base and dilute aqueous acid and so should not be affected by the reaction conditions to be used. It is thought that the methylthiomethyl group will exert less steric constraint upon the lithiated dioxopiperazine therefore making arylation easier. The final advantage that this group has is in its cleavage. It has been shown that stirring a mixture of the protected dioxopiperazine in wet acetone with a suspension of sodium carbonate and methyl iodide effects deprotection in reasonable yields.



(70%)

(R = alkyl, aryl)

In an attempt to synthesise the methylthiomethyl protected dioxopiperazine a suspension of 2,5-dioxopiperazine in dry DMF was stirred at room temperature and sodium hydride added. The mixture was stirred for several minutes before adding methylthiomethyl chloride. After quenching the reaction the major product isolated was unchanged dioxopiperazine as well as a small quantity of a foul smelling oil which resisted attempts at characterisation.

Conclusion

In conclusion both routes to the desired target compound (**78**), corresponding to Disconnections 1 and 2, have had some degree of success.

Synthesis of a heteroarylated glycine ester proved to be the least promising route towards the target compound (**78**) since the amino acid esters seemed to be very prone to polymerisation. Attempted synthesis of the heteroarylated amino acid also proved to be problematic since these systems seemed to be very prone towards decarboxylation. Further work in this area should therefore be focused upon identifying a suitable method for coupling an *N*-protected amino acid salt and an amino acid ester.

The synthesis of heteroarylated dioxopiperazines results in some interesting observations. The identification of an amide protecting group which could be cleaved under mild acidic conditions proved to be problematic. The synthesis of a sterically crowded dioxopiperazine resulted in some very interesting nmr spectra being obtained which could be attributed to a conformational variations rather than to tautomerisation. This route towards the target compound (**78**) did prove to be more successful and any further work towards these types of compounds should probably proceed along this route.

Experimental

EXPERIMENTAL

Materials and Apparatus

Melting points were determined on an Electrothermal model 9100 apparatus and are uncorrected.

All infra-red spectra of solids were recorded as Nujol mulls. All liquids were recorded as thin films.

Unless otherwise indicated routine nmr spectra were recorded at 200 MHz for ^{1}H nmr and at 50.3 MHz for ^{13}C nmr spectra, on a Varian Gemini spectrometer. High resolution and 2D spectra were obtained on a Bruker AM-300 spectrometer at 300 MHz for ^{1}H nmr and 75.4 MHz for ^{13}C nmr. All ^{1}H and ^{13}C spectra were obtained from solutions in $CDCl_3$ except where indicated otherwise. Chemical shifts are expressed in parts per million and tetramethylsilane used as an internal standard except for compounds which contain $SiCH_3$ groups where $CHCl_3$ at δ 7.27 was used. Coupling constants (J) are expressed in Hertz.

Mass spectra and accurate mass measurements were obtained on an A.E.I./Kratos M.S.-50 spectrometer. Unless otherwise indicated, the spectra were obtained using EI (electron impact ionisation) (70 eV). CI spectra were obtained on a VG Autospec using isobutane as the ionising gas.

Elemental analyses for carbon, hydrogen and nitrogen were carried out using a Carlo-Erba 1106 elemental analyser.

Thin layer chromatography was carried out using 0.2 mm layers of silica (Merck, Kieselgel $60F_{254}$) on polyester sheets. The components were observed under ultraviolet light or using iodine development.

Preparative thin layer chromatography was carried out using 1.0 mm layers of silica (Merck, Kieselgel 60-80 mesh), containing 0.5% Wolem fluorescent green indicator on glass plates.

Dry flash chromatography was carried out using Fluka Kieselgel H (5-40 μm particle size).

Organic solutions were dried by standing over anhydrous magnesium sulfate and were evaporated under reduced pressure using a rotary evaporator.

Commercially available solvents were used without further purification unless otherwise stated. The term 'petrol' refers to the fraction of petroleum ether which boils between 40 and 60°C. Dry acetonitrile and ethyl acetate were prepared by storing over activated 4Å molecular sieves. Dry ethanol was prepared by heating a suspension of magnesium ethoxide and ethanol for 1 h followed by distillation on to activated 4Å molecular sieves. Dry ether and THF were prepared by the addition of sodium wire followed by distillation. Dry dichloromethane was distilled from phosphorus pentoxide and stored over 4Å molecular sieves. Triethylamine was dried and purified by heating under reflux with potassium hydroxide for 2 h then fractionally distilling on to 4Å molecular sieves. Dry DMF was prepared by heating a suspension of DMF and calcium hydride to 130°C for 1 h before distilling, under reduced pressure, on to 4Å molecular sieves.

Symbols and Abbreviations

nmr	Nuclear magnetic resonance
δ	Chemical shift (ppm)
s	Singlet
br s	Broad singlet
d	Doublet
dd	Double doublet
m	Multiplet
i.r.	Infra-red
m.p.	Melting point
m/z	Mass-to-charge ratio
AIBN	2,2'-Azobisisobutyronitrile
ether	Diethyl ether
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
LDA	Lithium diisopropylamide
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Ethyl 3,3-bis(methylthio)-2-cyanoacrylate (**82**)

To a solution of sodium (4.27 g; 185.6 mmol) in ethanol (75 ml) was added a solution of ethyl cyanoacetate (10.00 g; 88.4 mmol) in ethanol (25 ml) under nitrogen with the temperature kept below 20°C. The white suspension was then stirred at room temperature for 15 min before a solution of carbon disulfide (7.40 g; 97.2 mmol) in ethanol (15 ml) was added and stirring continued for 12 h at room temperature. A solution of methyl iodide (27.61 g; 194.5 mmol) in ethanol (15 ml) was then added and the mixture stirred for 24 h before evaporating to half volume and adding water (250 ml). The solution was allowed to stand for 48 h before filtering off the yellow precipitated solid which was then recrystallised from propan-2-ol.

Yield, 3.52g (18%), m.p. 53-54°C; (Found: C, 44.3; H, 5.15; N, 6.5. $C_8H_{11}NO_2S_2$ requires C, 44.2; H, 5.1; N, 6.45%); δ_H 1.35 (3H, t, CH_2CH_3), 2.63 (3H, s, CH_3S), 2.78 (3H, s CH_3S), 4.31 (2H, q, CH_2); δ_C 14.3 (CH_2CH_3), 19.2 (CH_3S), 21.1 (CH_3S), 61.9 (CH_2CH_3), 98.7 (CN), 116.2 ($C(SCH_3)_2$), 162.3 ((CN)(CO_2Et)C), 181.2 (CO_2Et).

Reaction between *o*-phenylenediamine and ethyl 3,3-bis(methylthio)-2-cyanoacrylate to give (**83**)

A solution of *o*-phenylenediamine (0.50 g; 4.60 mmol), 3,3-bis(methylthio)-2-cyano-acrylate (**82**) (1.00 g; 4.6 mmol) and triethylamine (0.19 g; 1.8 mmol) in ethanol (10 ml) was heated under reflux for 1 h with any methanethiol produced being absorbed into a bleach scrubber. The solution was then cooled and stood for 14 h before the precipitated solid was filtered off and recrystallised from a mixture of 1,4-dioxan and propan-2-ol (1:1).

Yield, 0.77g (73%); m.p. 280°C. (Found: C, 62.8; H, 4.7; N, 18.6. $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.3%); δ_H 1.15 (3H, t, CH_3), 4.21 (2H, q, CH_2), 7.20-7.60 (4H, m, Ar), 12.40 (2H, br s, NH).

Attempted synthesis of benzimidazole (**85**)

A stirred suspension of the benzimidazole (**83**) (0.50 g; 2.18 mmol) in hydrazine hydrate (98%; 0.28 ml; 5.73 mmol) and ethanol (5 ml) was heated to reflux for 2 h. No reaction was visible (TLC): only unchanged starting materials recovered (by ^1H nmr).

The reaction was then repeated using the same scale but 1,4-dioxan as the solvent. The reaction was heated to reflux for 2 h and again only unchanged starting materials were recovered (by ^{1}H nmr).

Synthesis of diethyl 3,3-bis(methylthio)malonate (**88**)

To a solution of sodium (3.16 g; 137.35 mmol) in ethanol (60 ml) was added a solution of diethyl malonate (**87**) (10.00 g; 62.43 mmol) in ethanol (20 ml) under nitrogen with the temperature kept below 20°C. The white suspension was then stirred at room temperature for 15 min before a solution of carbon disulfide (5.23 g; 68.68 mmol) in ethanol (15 ml) was added and stirring continued for 12 h at room temperature. A solution of methyl iodide (19.50 g; 137.35 mmol) in ethanol (15 ml) was then added and the mixture stirred for 24 h before evaporating to half volume and adding water (250 ml). The solution was then extracted with dichloromethane (3 x 50 ml), the organic layers combined, washed with water, dried ($MgSO_4$) and evaporated to give a red oil which was used crude.

Yield, 8.50 g (51%); δ_H 1.40 (6H, t, CH_2-CH_3), 2.55 (6H, s, SMe), 4.35 (4H, q, OCH_2).

Attempted reaction between *o*-phenylenediamine and diethyl 3,3-bis(methylthio)malonate to give (**89**)

A solution of *o*-phenylenediamine (3.48 g; 32.15 mmol), diethyl 3,3-bis(methylthio)-malonate ((**88**) 8.50 g; 32.15 mmol) and triethylamine (1.30 g; 12.86 mmol) in ethanol (70 ml) was heated under reflux for 4 h with any methanethiol produced being absorbed into a bleach scrubber. The solution was then cooled with no reaction being visible (TLC): only unchanged starting materials were recovered.

Attempted synthesis of ethyl 3,3-bis(methylthio)-2-nitropropenoate

To a stirred solution of sodium (0.35 g; 15.0 mmol) in methanol (5 ml) under nitrogen was added a solution of ethyl nitroacetate (**91**) (1.00 g; 7.5 mmol) in methanol (5 ml). The solution was then stirred for 10 min at room temperature before addition of a solution of carbon disulfide (0.63 g; 8.2 mmol) in methanol (10 ml). The mixture was then stirred at room temperature for 7 days, before a solution of methyl iodide (1.18 g; 8.2 mmol) in methanol (10 ml) was added dropwise at room temperature. The solution was then stirred

for a further 24 h. Water (20 ml) was added and the mixture extracted with dichloromethane (4 x 30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of ethyl nitroacetate and a trace of carbon disulfide with no product present (by ^1H nmr).

Attempted synthesis of 2-(nitromethyl)benzimidazole

A suspension of *o*-phenylenediamine (0.65 g; 6.1 mmol) and 1,1-bis(methylthio)-2-nitroethylene (1.00 g; 6.1 mmol) in dry acetonitrile (20 ml) was heated to reflux for 3 h with any methanethiol produced trapped by a bleach scrubber. The suspension was then filtered but both the solid and mother liquor were found to contain only unchanged starting material (by ^1H nmr and TLC).

2-(Cyanomethyl)benzimidazole (**94**)

A stirred mixture of *o*-phenylenediamine (5.40 g; 50.00 mmol) and ethyl cyanoacetate (8.48 g; 75.00 mmol) was heated to 180°C for 20 min then cooled to room temperature. Ether (50 ml) was added and the solid was then broken up into a fine powder in the ether, filtered off, washed exhaustively with ether (approx. 300 ml) and recrystallised from water (with charcoal), giving pale yellow crystals which were dried *in vacuo* over P_2O_5.

Yield, 2.68 g (34%); m.p. 205-209°C (dec.) [lit.[65]., 209.7-210.7°C]; δ_H (d_6-DMSO) 4.45 (2H, s, CH_2), 7.22 (2H, dd, *J* 4.5, Ar), 7.60 (2H, dd, *J* 4.5, Ar).

Ethyl 1*H*-benzimidazole-2-acetate (**95**)

To a stirred solution of dry hydrogen chloride (1.35 g; 9% by weight), in dry ethanol (15 ml) was added 2-(cyanomethyl)benzimidazole (**94**) (1.00 g; 6.36 mmol). The mixture was then heated to reflux for 90 min, cooled to room temperature, filtered, and the filtrate concentrated. The residue was then stirred with aqueous sodium hydrogen carbonate (2.5 M; 50 ml) and dichloromethane (30 ml) added. The aqueous layer was removed and extracted with dichloromethane (2 x 50 ml); The organic layers were combined, washed with water (50 ml), dried ($MgSO_4$) and evaporated. The yellow solid was then recrystallised from aqueous ethanol.

Yield, 0.47 g (36%); m.p. 124-126°C [lit.[65]., 125.5-126.5°C]; δ_H 1.20 (3H, t, CH_3), 4.05 (2H, s, benzimidazole-CH_2), 4.12 (2H, q, OCH_2), 7.20 (2H, dd, *J* 4, Ar), 7.56 (2H, dd, *J* 4, Ar), 11.25 (1H, br s, NH); δ_C 13.9 (CH_3), 34.8 (benzimidazole-CH_2), 61.6 (OCH_2), 114.9 (C-4 + C-7), 122.4 (C-5 + C-6), 138.3 (C-3a + C-7a), 147.4 (C-2), 169.3 (C=O).

Attempted nitrosation of (**95**)

To a stirred solution of benzimidazole (**95**) (0.47 g; 2.30 mmol) and concentrated hydrochloric acid (1 ml) in *t*-amyl alcohol (5 ml) was added isoamyl nitrite (0.30 g; 2.30 mmol). The reaction mixture was then stirred at 45°C for 6 h before cooling to room to room temperature; water (10 ml) was then added, and the mixture extracted with DCM (3 x 10 ml). The organic layers were then combined, washed with water (20 ml), dried ($MgSO_4$) and the solvent evaporated off. Only unchanged starting materials were recovered (by ^1H nmr).

N-Phthalimidoglycine ethyl ester (**98**)

To a stirred solution of ethyl bromoacetate (2.46 g; 14.72 mmol) in dry DMF (15 ml) was added, in one portion, solid potassium phthalimide (**99**) (3.00 g; 16.20 mmol). The reaction was mildly exothermic and the white suspension was then stirred for 10 h; water (60 ml) was then added, and the mixture extracted with DCM (4 x 50 ml). The organic layers were then combined, washed with water (2 x 40 ml), dried ($MgSO_4$) and the solvent evaporated off. The remaining DMF was removed at the oil pump (1mm Hg ; 60°C) and the resultant white solid recrystallised from toluene.

Yield, 2.72 g (79%); m.p. 110-112°C [lit.[91] 112-113°C]; δ_H 1.15 (3H, t, CH_3), 4.10 (2H, q, OCH_2), 4.32 (2H, s, NCH_2), 7.60-7.76 (4H, m, Ar); δ_C 13.8 (CH_3), 38.6 (NCH_2), 61.5 (OCH_2), 123.2 + 133.9 (C-2 + C-3), 131.6 (*quat*-C), 166.9 and 167.0 (2 x C=O).

Attempted synthesis of (**100**)

Using *n*-butyl lithium as the base.

To a stirred solution of the phthalimido protected glycine ester (**98**) (0.50 g; 2.14 mmol) in dry THF (15 ml) at -78°C under nitrogen was added *n*-butyl lithium (1.6M in hexanes; 1.50 ml; 2.36 mmol) with the temperature kept below -65°C. The orange / brown solution was then stirred at -78°C for 30 min before a solution of 2-chlorobenzoxazole (**102**) (0.37 g; 2.36 mmol) in dry THF (5 ml) was added with the temperature maintained below -70°C. The mixture was then stirred at -78°C for 1 h before being allowed to warm slowly to room temperature and then stirred for another 90 min at room temperature. The orange solution was then quenched with water (10 ml), extracted with ether (4 x 30 ml), the organic layers combined and dried ($MgSO_4$), and the solvent evaporated off. The product was shown to consist of a complex mixture (by TLC). Isolation of the major components by chromatography showed the presence of some 2-chlorobenzoxazole and some starting phthalimido-protected glycine ester in the mixture as well as some products, the complicated and messy ^1H nmr of which, suggested butyl incorporation into the phthalimido-protected glycine ester.

Using sodium hydride as the base.

To a stirred suspension of sodium hydride (60 wt. % in oil; 0.13 g; 3.26 mmol) (pre-washed with petrol) under nitrogen in dry THF (10 ml) was added a solution of the phthalimido-protected glycine ester (**98**) (0.76 g; 3.26 mmol) in dry THF (20 ml). The suspension was then stirred at room temperature for 10 min before addition of a solution of 2-chlorobenzoxazole (**102**) (0.50 g; 3.26 mmol) in dry THF (10 ml). The mixture was then stirred at room temperature for 19.5 h, water (10 ml) was added and the mixture extracted into ether (2 x 20 ml) and DCM (2 x 20 ml). The combined extracts were then dried and evaporated to yield a yellow solid which was seen to consist of a large number of components (TLC), the majority of the mixture (95%) was found to be starting materials (by ^1H nmr).

Using LDA as the Base.

A solution of freshly prepared LDA [made from stirring a solution of diisopropylamine (0.73 g; 7.16 mmol) and *n*-butyl lithium (1.6M in hexanes; 4.5 ml; 7.16 mmol) in THF (7 ml)] was cooled to -78°C and stirred under nitrogen. To this was added a stirred solution of the phthalimido protected glycine ester (**98**) (0.84 g; 3.58 mmol) and 2-chlorobenzoxazole (**102**) (0.50 g; 3.26 mmol) in THF (10 ml) at -78°C under nitrogen, maintaining the temperature below -65°C. After 1 h at -78°C the red mixture was allowed to warm up to room temperature where it was stirred for 20 h. The mixture was then quenched with water (20 ml) and extracted with ether (4 x 30 ml) and then DCM (40 ml).

The combined organic extracts were then dried ($MgSO_4$) and evaporated to give an orange solid which was shown to consist of a number of products (by TLC), the major being a baseline spot. This product was then isolated by chromatography and found, by ^1H nmr, to be unidentifiable decomposition product(s).

Attempted Synthesis of (**103**).

Using Sodium Ethoxide as the Base.

To a stirred solution of the phthalimido-protected glycine ester (**98**) (1.00 g; 4.29 mmol) in dry ethanol (20 ml) was added a solution of freshly prepared sodium ethoxide [made by dissolving sodium (0.21 g; 9.00 mmol) in ethanol (15 ml)]. The reaction mixture was then stirred at room temperature for 30 min before the mixture formed a gel. Ethanol (20 ml) was then added to break-up the gel followed by carbon disulfide (0.80 g; 9.44 mmol). The mixture was then stirred for a further 30 min before methyl iodide (1.29 g; 9.00 mmol) was added and the reaction again stirred for 1 h. Water (200 ml) was then added and the solid precipitate, when filtered off, was found to be the unchanged starting ester (**98**) (by ^1H nmr).

Using Sodium Hydride as the Base.

To a stirred suspension of sodium hydride (60 wt. % in oil; 0.36 g; 9.01 mmol) [pre-washed with petrol] under nitrogen in dry 1,4-dioxan (10 ml) was added a solution of the phthalimido-protected glycine ester (**98**) (1.00 g; 4.29 mmol) in dry 1,4-dioxan (20 ml). The suspension was then stirred for 1 h, carbon disulfide (0.40 g; 4.72 mmol) was added, stirring continued for 4.5 h, and methyl iodide (1.34 g; 9.44 mmol) then added. After stirring for a further 16 h , water (10 ml) was added and the mixture extracted with ether (3 x 50 ml) and DCM (2 x 30 ml); the organic layers were combined, dried ($MgSO_4$) and evaporated to give a white solid which was found to be the recovered ester (**98**) (by ^1H nmr).

Attempted synthesis of (**104**)

Method A:

To a stirred solution of sodium (0.011 g; 0.47 mmol) in dry ethanol (10 ml) under nitrogen was added a solution of phthalimido-protected glycine ester (**98**) (0.10 g; 0.43 mmol) in dry ethanol (5 ml). The reaction mixture was then stirred at room temperature for 15 min before methyl iodide (0.07 g; 0.47 mmol) was added. The reaction was then allowed to stir at room temperature for a further 1.5 h before adding water

(20 ml). The mixture was then extracted with DCM (3 x 15 ml), the extracts combined, washed with water (20 ml) then brine (20 ml), and dried ($MgSO_4$) before evaporating off the solvent. The solid was then found to be unchanged starting material (by ^1H nmr)

Method B:

The above reaction was repeated but the reagents were heated to reflux for 1.5 h before cooling and the reaction mixture worked up. Again only unchanged starting material was recovered (by ^1H nmr).

Benzophenone imine (**107**)

To a stirred suspension of magnesium turnings (2.43 g; 100 mmol) in dry ether (30 ml) was added a few drops of a solution of bromobenzene (15.7 g; 100 mmol) in ether (20 ml). After the reaction had been initiated the addition of the remaining bromobenzene was controlled so that a steady reflux was maintained. Upon complete addition and cooling of the black solution to room temperature a solution of benzonitrile (10.31 g; 100 mmol) in ether (10 ml) was added, again maintaining a steady reflux by controlled addition. After complete addition the mixture was heated to reflux for a further 10 min and then cooled and quenched with aqueous ammonium chloride. The resultant "sludge" was then filtered through Celite and the filtrate extracted with DCM (3 x 60 ml), dried and evaporated to give a viscous oil which was then distilled.

Yield, 7.16 g (40%); b.p 112°C / 0.5 mm Hg [lit.[92] 151-153°C / 10 mm Hg]; δ_H 7.20-7.60 (10H, m, Ar), 9.6-9.8 (1H, br s, NH); δ_C 127.7+127.8 (*o*- and *m*-C), 129.7 (*p*-C), 138.7 (*quat*-C), 177.4 (C=N).

Ethyl *N*-(diphenylmethylene)glycinate (**108**)

To a stirred suspension of glycine ethyl ester hydrochloride (3.46 g, 27.59 mmol) in dry DCM (90 ml) was added a solution of benzophenone imine (**107**) (5.00 g; 27.59 mmol) in dry DCM (10 ml). The suspension was then stirred at room temperature for 24 h, with the exclusion of moisture ($CaCl_2$), and then the solid was filtered off and the filtrate concentrated. The resultant oil was then warmed to *ca.* 60°C in petrol (40 ml), chilled in ice and the white crystalline solid filtered off.

Yield, 5.87 g (80%); m.p. 51-52°C [lit.[93] 51-52°C]; δ_H 1.34 (3H, t, CH_3), 4.27 (2H, q, OCH_2), 4.32 (2H, s, NCH_2), 7.20-7.80 (10H, m, Ar); δ_C 13.7 (CH_3), 55.2 (NCH_2),

60.2 (OCH_2), 127.1 (*o*-C), 127.6 (*o*'-C), 128.2 (*m*-C), 128.3 (*m*'-C), 130.0 (2 x *p*-C), 135.4 (*quat*-C), 138.7 (*quat*'-C), 170.0 and 171.2 (C=O) and (C=N).

Ethyl 2-(benzoxazol-2-yl)-*N*-(diphenylmethylene)glycinate (**109**)

Method A:

To a stirred solution of ethyl *N*-(diphenylmethylene)glycinate (**108**) (2.61 g; 9.77 mmol) in dry THF (50 ml) at -78°C under nitrogen was added LDA (1.5M in THF; 7.2 ml; 10.75 mmol) with the temperature maintained below -60°C. The mixture was then stirred at -78°C for 1 h before the addition of a solution of 2-chlorobenzoxazole (1.50 g; 9.77 mmol) in THF (10 ml) with the temperature maintained below -65°C. The red solution was then stirred at -78°C for 1 h before being slowly warmed to room temperature and stirred at room temperature for 8 h. The reaction was then quenched with saturated aqueous ammonium chloride (50 ml), extracted with ether (3 x 50 ml), dried and evaporated to give a red oil. This was then purified *via* flash chromatography (eluent = 4:1 petrol : ethyl acetate), to give a viscous red oil.

Yield, 1.91 g (51%); does not boil below 200°C / 0.10mm Hg; (Found: C, 74.9; H, 5.45; N, 7.6. $C_{24}H_{20}N_2O_3$ requires C, 75.0; H, 5.2; N, 7.3%); *m/z* 384 ($M^{+\cdot}$, 2%), 311 (100), 266 (10), 194 (30), 182 (33), 165 (28), 105 (57), 91 (40), 77 (37), *etc.*; (Found: *m/z* 384.1486. $C_{24}H_{20}N_2O_3$ requires *m/z* 384.1474); δ_H 1.22 (3H, t, CH_3), 4.22 (2H, q, CH_2), 5.67 (1H, s, CH), 7.15-7.85 (14H, m, Ar); δ_C 13.9 (CH_3), 62.1 (CH_2), 64.6 (CH), 110.8 (C-7), 120.2 (C-4), 124.2 (C-6), 125.2 (C-5), 127.6 (*m*-C), 127.9 (*m*'-C), 128.7 (*o*-C), 129.2 (*o*'-C), 130.9 (*p*-C), 135.1 (*quat*-C), 138.7 (*quat*'-C), 140.7 (C-3a), 150.9 (C-7a), 161.6 (C-2), 167.1 and 174.0 (C=N) and (C=O).

Method B:

To a stirred solution of 2-chlorobenzoxazole (1.00 g; 6.51 mmol) and ethyl *N*-(diphenylmethylene)glycinate (**108**) (1.74 g; 6.51 mmol) in dry acetonitrile (50 ml) was added finely powdered potassium carbonate (1.80 g; 13.02 mmol). The mixture was then heated to reflux for 7 h, cooled, the solid filtered off and the filtrate evaporated. The resultant red oil was then found to be a mixture of the desired product (30%) and starting glycinate (70%) (by ^1H nmr).

Hydrolysis of (**109**)

To a stirred solution of ethyl 2-(benzoxazol-2-yl)-*N*-(diphenylmethylene)glycinate (**109**) (2.38 g; 6.19 mmol) in ether (15 ml) was added dilute hydrochloric acid (1 M; 7.4 ml; 7.43 mmol). The mixture was then stirred at room temperature for 36 h before the aqueous layer was separated and evaporated down. The brown solid was then recrystallised from ethanol and identified as the ring opened hydrochloride (**111**).

Yield, 1.36 g (86%), m.p. 185-186°C (dec. with the evolution of gas); υ_{max} 1760 (C=O, ester), 1700cm^{-1} (C=O, amide); (Found: C, 48.3; H, 5.5; N, 10.15. $C_{11}H_{15}ClN_2O_4$ requires C, 48.1; H, 5.5; N, 10.2%); δ_H (d_6-DMSO) 1.20 (3H, t, CH_3), 3.76 (1H, s, CH), 4.25 (2H, m, CH_2), 6.75-7.50 (4H, m, Ar); δ_C 15.9 (CH_3), 42.9 (CH) 67.6 (CH_2), 115.5 (C-6), 118.8 (C-4), 121.5 (C-3), 125.0 + 125.4 (C-5 + C-2), 148.0 (C-1), 161.0 +165.0 (2 x C=O); *m/z* 238 (M^+·of free base, 13%), 165 (16), 148 (14), 136 (22), 109 (76), 103 (100), *etc.*

Synthesis of polyphosphate esters

A suspension of phosphorus pentoxide (22.50 g; 140.9 mmol) in a mixture of ether (45 ml) and chloroform (22.5 ml) under nitrogen was heated to reflux for 22 h before cooling to room temperature and filtering off any solid, again under nitrogen. The filtrate was then evaporated down with a water bath temperature of 40°C to yield a viscous colourless oil. According to the literature this is of sufficient purity to be used without further purification. The oil was then stored under nitrogen in a refidgerator.

Attempted selective hydrolysis of *N*-(diphenylmethylene) group from ethyl 2-(benzoxazol-2-yl)-*N*-(diphenylmethylene)glycinate (**109**)

To a solution of the benzophenone imine protected amino acid (**109**) (0.95 g; 2.47 mmol) in ethanol (10 ml) and water (2 drops) was added ammonium chloride (20 mg). The mixture was then stirred at room temperature for 3 days. Water (10 ml) was then added and the mixture extracted with dichloromethane (3 x 15 ml). The organic layers were then combined, washed with water (20 ml), dried ($MgSO_4$) and evaporated to give a thick brown/black oil. The complexity of the ^{1}H nmr spectrum and the observation of high molecular mass fragments in the mass spectrum suggested that the material was probably polymeric.

Attempted dimerisation of amino acid ester (**111**)

To a rapidly stirred solution of the amino acid ester hydrochloride (**111**) (0.16 g; 0.58 mmol) in water (2 ml) was added triethylamine (0.063 g; 0.62 mmol). The suspension was then stirred at room temperature for 5 days before filtering off the solid and washing exhaustively with water (approx. 20 ml). The sticky brown/black solid was shown to be polymeric by its mass spectrum.
Yield, 0.003 g; Highest molecular ion seen at 560 (2%), regular fragmentation pattern from then on.

Ethyl 2-(benzothiazol-2-yl)-*N*-(diphenylmethylene)glycinate

To a stirred solution of ethyl *N*-(diphenylmethylene)glycinate (**108**) (2.37 g; 8.84 mmol) in dry THF (70 ml) at -78°C under nitrogen was added LDA (1.5 M in THF; 6.5 ml; 9.73 mmol) with the temperature maintained below -60°C. The mixture was then stirred at -78°C for 1 h before adding a solution of 2-chlorobenzothiazole (1.50 g; 8.84 mmol) in THF (3 ml) with the temperature maintained below -65°C. The red solution was then stirred at -78°C for 1 h before being slowly warmed to room temperature and stirred at room temperature for 8 h. The reaction was then quenched with aqueous ammonium chloride, extracted with ether (3 x 50 ml), dried and evaporated to give a red oil. This was then purified *via* flash chromatography (silica gel, eluent, 4:1 petrol : ethyl acetate), to give a viscous red oil. The product was found to be unstable and decomposes very quickly even in a refrigerator.

Yield, 1.62 g (46%); does not boil below 200°C / 0.10mm Hg; *m/z* ($M^{+\cdot}$ not seen), 327 (17), 266 (15), 235 (15), 194 (61), 182 (81), 162 (49), 134 (47), 105 (100), 91 (57), 77 (72) *etc.*; δ_H 1.22 (3H, t, CH_3), 4.20 (2H, q, CH_2), 5.72 (1H, s, CH), 7.15-7.85 (14H, m, Ar); δ_C 13.9 (CH_3), 62.0 (CH_2), 68.3 (CH), 121.6 (C-4), 123.1 (C-7), 124.9 (C-5), 125.8 (C-6), 127.6 (*m*-C), 128.1 (*m*'-C), 128.7 (*o*-C), 129.2 (*o*'-C), 131.0 (*p*-C), 135.2 (*quat*-C), 138.6 (*quat*'-C), 139.1 (C-7a), 152.8 (C-3a), 168.0 (C-2), 169.9 and 173.0 (C=N) and (C=O).

2-Chlorobenzimidazole

A suspension of benzimidazolone (10.00 g; 74.6 mmol) in phosphorus oxychloride (100 ml; 1.1 mol) was heated to reflux for 30 min before HCl gas was bubbled through the mixture. The reaction mixture was then maintained at reflux with continued passage of

HCl for a further 3 h then the excess phosphorus oxychloride was distilled off. The residue was then shaken with ice-water (30 ml) until a white solid had formed; this was filtered off and washed with dilute hydrochloric acid (40 ml water / 10 ml conc. HCl) and water (30 ml). The filtrate was then adjusted to pH 8 with ammonia solution (2 M), and the resulting precipitate was then filtered off and dried *in vacuo* at 45°C over phosphorus pentoxide.

Yield, 6.57g (58%); m.p. 186-188°C [lit.[120] 180°C].

1-*t*-Butoxycarbonyl-2-chlorobenzimidazole (**114**)

To a stirred suspension of 2-chlorobenzimidazole (0.50 g; 3.27 mmol) and DMAP (10 mg) in dry acetonitrile (20 ml) excluding moisture ($CaCl_2$) was added a solution of di-*t*-butyl dicarbonate (0.72 g; 3.27 mmol) in dry acetonitrile (10 ml). The reaction was then stirred at room temperature for 24 h before the addition of ether (30 ml). The mixture was washed with potassium hydrogen sulfate (1 M; 6 x 50 ml); the organic layer was then washed with water (50 ml), brine (50 ml), dried ($MgSO_4$) and the solvent evaporated. The resulting solid was then deemed pure enough to be used immediately (99% pure by ^1H nmr) although it was stored refrigerated under nitrogen. An analytically pure sample was obtained by reprecipitating the benzimidazole from a dichloromethane solution into hexane.

Yield, 0.69 g (84%); m.p. 62-63°C; (Found: C, 56.7; H, 5.3; N, 10.9. $C_{12}H_{13}ClN_2O_2$ requires C, 57.0; H, 5.2; N, 11.1%); δ_H 1.69 (9H, s, $(CH_3)_3$), 7.27-7.35 (2H, m, Ar), 7.60-7.67 (1H, m, Ar), 7.85-7.92 (1H, m, Ar); δ_C 27.9 (CH_3), 86.6 ($C(CH_3)_3$), 114.6 (C-7), 119.4 (C-4), 124.5 (C-5 or C-6), 125.0 (C-6 or C-5), 133.2 (C-3a), 140.9 (C-7a), 147.0 (C-2), 148.1 (C=O).

Ethyl 2-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-*N*-(diphenylmethylene)glycinate (**115**)

To a stirred solution of diisopropylamine (3.18 g; 31.42 mmol) in THF (60 ml) under nitrogen at room temperature was added *n*-butyl lithium (1.6 M in hexanes; 11.5 ml; 28.80 mmol) with the temperature maintained at 30°C. The mixture was then stirred at room temperature for 10 min, cooled to -78°C and a solution of the protected glycine (**108**) (7.00 g; 31.42 mmol) was added with the temperature kept below -65°C. The reaction mixture was then stirred at -78°C for 1 h before addition of a solution of 1-*t*-butoxycarbonyl-2-chlorobenzimidazole (**114**) (6.62 g; 26.18 mmol) in THF (40 ml)

with the temperature kept below -70°C. The reaction was then stirred at -78°C for 1 h, allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was then quenched (saturated aqueous ammonium chloride) and extracted with ether (3 x 100 ml), the extracts combined, dried ($MgSO_4$) and evaporated. The solid was then chromatographed using 4 : 1 petrol : ether eluent to give a white solid.

Yield, 3.24 g (26%); m.p. 123-126.5°C (with evolution of gas). (Found: C, 71.8; H, 6.3; N, 8.65. $C_{29}H_{29}N_3O_4$ requires C, 72.0; H, 6.0; N, 8.7%); δ_H 1.22 (3H, t, CH_2CH_3), 1.60 (9H, s, *t*-Bu), 4.20 (2H, q, CH_2), 6.00 (1H, s, CH), 7.25-7.45 (10H, m, Ar), 7.75-7.85 (3H, m, Ar), 7.93-8.00 (1H, m, Ar); δ_C 13.8 (CH_2CH_3), 27.6 ($C(CH_3)_3$), 61.4 (CH_2), 66.0 (CH), 85.5 ($C(CH_3)_3$), 114.5 (C-7), 120.2 (C-4), 123.8 (C-5 or C-6), 124.6 (C-6 or C-5), 127.5 + 127.6 (*m*-C + *m'*-C), 128.3 + 129.0 (*o*-C + *o'*-C), 128.6 + 130.4 (*p*-C + *p'*-C), 132.7 (C-3a), 135.8 + 138.9 (*quat*-C + *quat'*-C), 141.9 (C-7a), 148.2 (*t*-BuO-C=O)*, 151.5 (C-2)*, 168.1 (C=N), 173.1 (EtO-C=O); HRMS: Found, *m/z* 483.2144. $C_{29}H_{29}N_3O_4$ requires 483.2158; *m/z* 463 ($M^{+\cdot}$ 6%), 410 (15), 383 (42), 310 (87), 266 (30), 194 (83), 165 (52),105 (56), 91 (100), *etc.*

* provisional assignment

Synthesis of the dihydrochloride salt (**118**)

Method A:

A suspension of ethyl 2-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-*N*-(diphenylmethylene)-glycinate (**115**) (0.21g; 0.43 mmol) in ether (5 ml) was stirred with dilute hydrochloric acid (1 M; 0.5 ml; 0.50 mmol) for 20 h monitoring the reaction by TLC. Upon loss of the starting material (by TLC) the ether layer was removed and the aqueous layer washed with ether (10 ml) then evaporated.

Yield, 0.11 g; ^1H nmr shows a mixture of desired amino acid ester hydrochloride (**118**) and the amino acid hydrochloride (**117**): δ_H (d_6-DMSO) for (**118**) 5.40 (1H, s, CH), 7.40-7.50 (2H, m, Ar), 7.80-7.90 (2H, m, Ar); δ_H for (**117**) 1.20 (3H, t, OCH_2CH_3), 4.10-4.40 (2H, m, CH_2), 5.75 (1H, s, CH), 7.20-7.30 (2H, m, Ar), 7.60-7.70 (2H, m, Ar), 8.90-9.60 (4H, br s, NH and $(NH_3)^+$).

Method B:

A solution of ethyl 2-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-*N*-(diphenylmethylene) glycinate (**115**) (1.00 g; 2.07 mmol) in THF (4 ml) and ether (20 ml) was mixed with dilute hydrochloric acid (1 M; 2.1 ml; 2.10 mmol) and the mixture sonicated for 1.5 h.

The ether layer was then removed and extracted with water (5 ml) and the combined aqueous layers were washed with ether (3 x 10 ml) then evaporated to give a red solid.

Yield, 0.41 g (77%); (Found: C, 42.65; H, 5.2; N, 13.1. $C_{11}H_{17}Cl_2N_3O_3$ requires C, 42.6; H, 5.5; N, 13.55); δ_H (d_6-DMSO) 1.20 (3H, t, CH_3), 4.10-4.40 (2H, m, CH_2), 5.80 (1H, s, CH), 7.35 (2H, dd, *J* 4, Ar), 7.70 (2H, dd, *J* 4, Ar), 8.10-9.80 (5H, br s, $(NH_2)^+$ and $(NH_3)^+$); δ_C 13.9 (CH_3), 49.8 (CH), 63.3 (CH_2), 115.4 (C-4, C-7), 124.4 (C-5, C-6), 135.5 (C-3a, C-7a), 144.8 (C-2), 164.8 (C=O); *m/z* 219 ($M^{+\cdot}$ of free base, 19%), 146 (100), 119 (51), 90 (13), 69 (28), *etc.*

2-(Aminomethyl)benzimidazole dihydrochloride (**119**)

A suspension of the benzimidazole (**115**) (1.00 g; 2.07 mmol) in hydrochloric acid (6 M; 4.1 ml; 24.6 mmol) was heated to reflux for 6 h, cooled to room temperature, and water (10 ml) was then added. The aqueous layer was washed with ether (2 x 20 ml) then evaporated to dryness, and the resultant white solid (possibly a partial hydrate) was recrystallised from ethanol.

Yield, 0.34 g (89%); m.p. 257-259°C; (Found: C, 43.1; H, 5.4; N, 18.7. $C_8H_{11}Cl_2N_3$ requires C, 43.7; H, 5.0; N, 19.1%); δ_H (d_6-DMSO) 4.60 (2H, s, CH_2), 7.50-7.45 (2H, m, Ar), 7.82-7.92 (2H, m, Ar), 9.00 (3H, br s, NH_3); δ_C 34.6 (CH_2), 114.6 (C-4), 125.5 (C-5), 131.9 (C-3a), 146.9 (C-2); *m/z* 147 ($M^{+\cdot}$ of free base, 100%), 131 (11), 119 (88), 118 (77), 91 (30), *etc.*

Attempted dimerisation of (**118**)

To a stirred solution of the salt (**118**) (0.24 g; 0.94 mmol) in water (10 ml) was added triethylamine (0.10 g; 1.03 mmol). The reaction was stirred at room temperature for 48 h before the sticky solid was filtered off and washed with water (approx. 30 ml). The ^1H nmr (d_6-DMSO) showed no signals corresponding to an ethoxy group. From the mass spectrum the material was evidently polymeric.

Yield, 0.04 g; $\nu_{max.}$ 3400 cm^{-1} (NH), 1600 (NH);*m/z* 562 (2%), 551 (1.5), 550 (1), 549 (1), 534 (3), 337 (100) *etc.*

Reaction between ethyl 2-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-*N*-(diphenylmethylene)-glycinate (**115**) and magnesium chloride

A suspension of the protected amino acid (**115**) (0.50 g; 1.03 mmol) and magnesium chloride hexahydrate (0.021 g; 0.103 mmol) in toluene (30 ml) was heated to reflux, under nitrogen, for 12 h before cooling to room temperature. The magnesium chloride was then filtered off and the filtrate evaporated down to give a black/brown tar which was presumed to be polymeric material (by mass spectrum).

Reaction between ethyl 2-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-*N*-(diphenylmethylene)-glycinate (**115**) and zinc chloride

The above reaction was then repeated using zinc chloride (0.014 g; 0.103 mmol) and the same polymeric material was isolated after 10 h.

STABASE of glycine (**123**)

To a stirred suspension of glycine ethyl ester hydrochloride (0.71 g; 5.11 mmol) in dry dichloromethane (20 ml) under nitrogen was added triethylamine (1.55 g; 15.33 mmol). The white suspension was then stirred at room temperature for 10 min before the addition of a solution of 1,2-bis(chlorodimethylsilyl)ethane (**122**) (1.00 g; 4.65 mmol) in dry dichloromethane (5 ml) with the temperature maintained below 30°C. The reaction was stirred at room temperature for 2.5 h, filtered through Celite and the filtrate concentrated. The residue was then dissolved in petrol and filtered through Celite before evaporation of the solvent. The residue was then distilled.

Yield, 0.84 g (74%); b.p. 130°C / 2 mmHg [lit.[78] , 80-82°C / 0.25 mmHg]; δ_H 0.02 (12H, s, Si-CH_3), 0.51 (4H, s, Si-CH_2), 1.23 (3H, t, CH_3-CH_2), 3.49 (2H, s, NCH_2), 4.11 (2H, q, OCH_2); δ_C -0.9 (Si-CH_3), 7.8 (Si-CH_2), 14.0 (CH_3-CH_2), 44.1 (NCH_2), 60.1 (OCH_2), 173.4 (C=O).

Reaction of the STABASE- protected glycine (**123**) with 2-chlorobenzoxazole

To a stirred solution of freshly prepared LDA [from diisopropylamine (0.80 g; 7.81 mmol) and *n*-butyl lithium (2.5 M in hexanes; 2.9 ml; 7.16 mmol) in dry THF (20 ml)] at -78°C under nitrogen was added a solution of the STABASE compound (**123**)

(1.60 g; 6.51 mmol) in THF (5 ml) with the temperature kept below -65°C. The reaction was then stirred at -78°C for 1 h, before addition of a solution of 2-chlorobenzoxazole (1.00 g; 6.51 mmol) in THF (3 ml). The reaction was then stirred at -78°C for 30 min, warmed to room temperature and stirred for a further 2 h before the reaction was quenched with saturated aqueous ammonium chloride. The mixture was then extracted with ether (3 x 50 ml), the combined extracts, washed with water (50 ml) then brine (50 ml), and dried ($MgSO_4$) and the solvent evaporated. The product (**124**) was then distilled.

Yield, 1.34 g (57%); b.p. 150°C / 2 mmHg; δ_H -0.05 (6H, s, Si-CH_3), 0.15 (6H, s, Si-CH_3'), 0.72 (4H, s, Si-CH_2), 1.22 (3H, t, CH_3-CH_2), 4.20 (2H, q, OCH_2), 5.08 (1H, s, CH), 7.25-7.35 (2H, m, Ar), 7.48-7.52 (1H, m, Ar), 7.65-7.75 (1H, m, Ar); δ_C -0.5 (Si-CH_3), 0.0 (Si-CH_3'), 8.1 (Si-CH_2), 14.0 (CH_3-CH_2), 55.3 (CH), 61.6 (OCH_2), 110.5 (C-7), 120.4 (C-4), 124.3 (C-6), 125.2 (C-5), 140.9 (C-3a), 150.6 (C-7a), 163.7 (C-2), 170.2 (C=O).

Attempted removal of the protecting group from (**124**) using sodium borohydride

To a stirred suspension of sodium borohydride (0.02 g; 0.50 mmol) in ethanol (3 ml) was added a solution of the STABASE compound (**124**) (0.60 g; 1.65 mmol) in ethanol (6 ml). The mixture was stirred at room temperature for 1 h then saturated aqueous ammonium chloride (10 ml) was added and the mixture extracted with dichloromethane (3 x 30 ml). The organic layers were then combined, washed with water (20 ml) then brine (20 ml), dried ($MgSO_4$) and then evaporated down. The viscous oil was found to be unchanged starting material (by ^1H nmr).

Attempted removal of the protecting group from (**124**) using pyridinium chlorochromate

To a stirred solution of the STABASE compound (**124**) (0.50 g; 1.38 mmol) in dichloromethane (10 ml) was added a solution of pyridinium chlorochromate (0.45 g; 2.07 mmol) in dichloromethane (5 ml). The reaction was then stirred at room temperature for 24 h, diluted with ether (50 ml) and filtered through Celite. The filtrate was then evaporated giving a yellow oil. This was found to comprise silicon containing residues resulting from the deprotection (by ^1H and ^{13}C nmr) and the product was thought to have been left adsorbed on the Celite, therefore an alternative work-up was examined.

The above reaction was repeated and after 24 h at room temperature dichloromethane (50 ml) and potassium hydroxide (2 M; 20 ml) were added. The organic layer was then

removed, washed with water (30 ml), dried ($MgSO_4$) and evaporated, giving an intractable black tar.

Attempted removal of the protecting group from (**124**) using tetrabutylammonium fluoride

To a solution of tetrabutylammonium fluoride (1 M; 14.0 ml; 14.00 mmol) in THF was added a solution of the STABASE compound (**124**) (0.50 g; 1.38 mmol) in THF (1 ml). The mixture was stirred at room temperature for 2 h before water (20 ml) was added and the mixture extracted with dichloromethane (2 x 30 ml). The extracts were then combined, washed with water (20 ml), dried ($MgSO_4$) and evaporated giving a black oil. The mass spectrum of this oil suggested a polymeric (oligomeric) structure; the ^1H nmr spectrum of the oil showed the absence of any ester peaks.

Attempted removal of the silicon group from (**124**)

Method A:

To a stirred suspension of the STABASE compound (**124**) (2.36 g; 6.51 mmol) and zinc fluoride tetrahydrate (1.14 g; 6.51 mmol) in toluene (30 ml) under nitrogen was heated to reflux for 8 h, before being cooled to room temperature and stirred at room temperature for 2 days. The suspension was then filtered to remove the zinc fluoride and the filtrate evaporated down to give unchanged STABASE compound (by ^1H and ^{13}C nmr).

Method B:

A stirred suspension of the STABASE compound (**124**) (1.30 g; 3.59 mmol), pyridinium chlorochromate (1.55 g; 7.17 mmol) and a catalytic amount of zinc chloride (20 mg) in toluene (40 ml) under nitrogen was heated to reflux for 6 h. The mixture was then filtered through Celite, and the solid was washed off the Celite using acetone. The acetone was then evaporated down and gave an intractable black tar.

N-*t*-Butoxycarbonylglycine Ethyl Ester (**126**)

To a stirred suspension of glycine ethyl ester hydrochloride (5.00 g; 35.82 mmol) and aqueous potassium hydrogen carbonate (2 M; 46 ml; 92.02 mmol) in 1,4-dioxan (46 ml) was added a solution of di-*t*-butyl dicarbonate (9.38 g; 42.99 mmol) in 1,4-dioxan (11 ml). The reaction mixture was then stirred at room temperature for 17 h, the solid

precipitate was filtered off and the filtrate extracted with ethyl acetate (3 x 75 ml). The organic layers were combined and washed with water (100 ml) then brine (100 ml) and dried ($MgSO_4$); The solvent was evaporated off and the resultant oil was then distilled.

Yield, 6.55 g (90%); b.p. 95°C / 0.5 mmHg [lit.[121]., 83°C / 0.34 mmHg]; δ_H 1.25 (3H, t, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 3.90 (2H, br s, CH_2N), 4.20 (2H, q, CH_2O), 5.12 (1H, br s, NH); δ_C 13.7 (CH_3CH_2), 27.8 ($C(CH_3)_3$), 42.0 (CH_2N), 60.7 (CH_2O), 79.2 ($C(CH_3)_3$), 155.5 (*t*-BuO-*C*=O), 170.0 (EtO-*C*=O).

Ethyl 2-(benzoxazol-2-yl)-*N*-(*t*-butoxycarbonyl)glycinate (**127**)

To a stirred solution of freshly prepared LDA [diisopropylamine (1.88 g; 18.62 mmol) and *n*-butyl lithium (2.5 M in hexanes; 7.1 ml; 17.78 mmol)] in THF (70 ml) under nitrogen at -78°C was added a solution of the protected glycine ester (**126**) (1.88 g; 9.31 mmol) in THF (20 ml) with the temperature kept below -65°C. The suspension was then stirred at -78°C for 30 min before adding a solution of 2-chlorobenzoxazole (1.30 g; 8.47 mmol) in THF (10 ml). The reaction was then stirred at -78°C for 15 min, allowed to warm to room temperature and stirring continued for a further 20 min. The reaction was then quenched with saturated ammonium chloride (100 ml), and extracted with ether (3 x 100 ml). The organic layers were then combined, washed with water (100 ml) then brine (100 ml), dried ($MgSO_4$) and the solvent evaporated. The resultant solid was then dry flash chromatographed [silica gel; eluent, 4:1 petrol : ether].

Yield, 1.37 g (51%); m.p. 98.5-99.5°C (from ether); (Found: C, 60.3; H, 6.3; N, 8.7. $C_{16}H_{20}N_2O_5$ requires C, 60.0; H, 6.3; N, 8.7%); δ_H 1.25 (3H, t, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 4.12-4.37 (2H, m, CH_2O), 5.82 (1H, d, *J* 8.5 , CH), 6.31 (1H, d, *J* 8, NH), 7.32 (2H, t, Ar), 7.50 (1H, t, Ar), 7.72 (1H, t, Ar); δ_C 13.5 (CH_3CH_2), 27.8 ($C(CH_3)_3$), 52.3 (CH), 62.3 (CH_2O), 80.3 ($C(CH_3)_3$), 110.5 (C-7), 120.0 (C-4), 124.3 (C-6), 125.2 (C-5), 140.3 (C-3a), 150.5 (C-7a), 154.5 (*t*-BuO-*C*=O), 160.2 (C-2), 166.7 (EtO-*C*=O).

Reaction between ethyl 2-(benzoxazol-2-yl)-N-(t-butoxycarbonyl)glycinate (**127**) and trifluoroacetic acid

To a stirred solution of the amino acid (**127**) (0.10 g; 0.31 mmol) in dry dichloromethane (4 ml) was added freshly distilled trifluoroacetic acid (0.5 ml). The reaction was then stirred at room temperature for 24 h before being evaporated to dryness. The green oil

isolated, presumed to be (**132**), was then found to be unstable to storage, even under nitrogen, and in deuteriochloroform.

2-(Benzoxazol-2-yl)glycine ethyl ester hydrochloride (**133**)

To a stirred solution of the amino acid (**127**) (0.60 g; 1.87 mmol) in dry 1,4-dioxan (10 ml) at room temperature was saturated with dry hydrogen chloride gas. The reaction mixture was maintained at room temperature through cooling. The passage of gas was continued for 10 min before the solution was evaporated, giving a very hygroscopic pink solid/foam. The product was then stored in a refrigerator at 3°C under nitrogen.

Yield, 0.46 g (96%); m.p. not measurable; δ_H 1.21 (3H, t, CH_3), 4.25 (2H, q, CH_2), 5.98 (1H, s, CH), 7.23-7.41 (2H, m, Ar), 7.45-7.56 (1H, m, Ar), 7.72-7.81 (1H, m, Ar), 9.78 (3H, br s, NH_3).

Attempted synthesis of amino acid (**130**)

To a stirred solution of the amino ester (**127**) (0.93 g; 2.90 mmol) in 1,4-dioxan (4 ml) was added aqueous sodium hydroxide (1 M; 2.9 ml; 2.90 mmol) dropwise over 5 min. The reaction mixture was then stirred at room temperature for 24 h before evaporating off the dioxan *in vacuo* with the bath temperature maintained below 35°C. Water (10 ml) was then added and the aqueous layer was washed with ether (2 x 20 ml) before the addition of a solution of citric acid (1 M; 25 ml; 25 mmol). The aqueous layer was then extracted with ethyl acetate (2 x 20 ml), and the organic layers were combined, washed with water (20 ml), then brine (20 ml), dried ($MgSO_4$) and the solvent evaporated giving an oil which solidified on standing. This was identified as the decarboxylated compound (**134**).

Yield, 0.56 g (78%); m.p. 124-126°C; (Found: C, 62.6; H, 6.6; N, 11.1. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.5; N, 11.3%); δ_H (d_6-DMSO) 1.40 (9H, s, $C(CH_3)_3$), 4.51 (2H, d, *J* 5.3, CH_2), 7.33-7.42 (2H, m, Ar), 7.65-7.75 (2H, m, Ar), NH signal not seen; δ_C 28.2 ($C(CH_3)_3$), 37.9 (CH_2), 78.5 ($C(CH_3)_3$), 110.7 (C-7), 119.5 (C-4), 124.4 (C-6), 125.0 (C-5), 140.9 (C-3a), 150.2 (C-7a), 155.7 (C=O), 164.3 (C-2).

Attempted synthesis of dipeptide (**141**)

To a stirred solution of the protected amino acid ester (**127**) (0.66 g; 2.06 mmol) in 1,4-dioxan (15 ml) was added a solution of lithium hydroxide (0.087 g; 2.06 mmol) in waster (2.1 ml). The reaction was then stirred at room temperature for 3 h before evaporating the mixture to dryness. THF (15 ml) was then added and the solution stirred at room temperature as a solution of isobutyl chloroformate (0.28 g; 2.06 mmol) in THF (3 ml) was added. The reaction mixture was then stirred at room temperature for 15 min before a suspension of the amino acid salt (**118**) in THF (5 ml) was added and the mixture stirred for a further 2 min. *N*-ethylpiperidine (0.47g ; 4.12 mmol) was then added and the mixture stirred at room temperature for 48 h before the reaction was quenched with citric acid (0.05 M; 20 ml). The reaction was then extracted with ether (2 x 30 ml) and DCM (30 ml). The extracts were combined, washed with water (40 ml) then brine (40 ml), dried ($MgSO_4$) and the solvents evaporated off. The crude product showed 2 spots on TLC which were isolated by chromatography and found to be the polymer (**120**) and the compound (**134**) (by ^1H nmr).

2,5-Dioxopiperazine (**9**)

To a stirred suspension of glycine ethyl ester hydrochloride (150.00 g; 1.10 mol) in water (130 ml) was added triethylamine over 40 min with the temperature maintained below 5°C throughout the addition. The colourless solution was then stirred at room temperature for 5 days; the fine white solid was then filtered off and recrystallised from water.

Yield, 19.80g (16%); m.p. >300°C

1,4-Diacetyl-2,5-dioxopiperazine (**32**)

A suspension of 1,4-dioxopiperazine (5.00 g; 43.8 mmol) in acetic anhydride (44.7 g; 438.2 mmol) was heated to reflux for 6 h, then some of the acetic anhydride (*ca.* 35 g) was distilled off. The mixture was then allowed to cool to room temperature and the brown solid was filtered off and recrystallised from water.

Yield, 3.07g (35%); m.p. 98-99°C [lit.[122] 102°C]; $\nu_{max.}$ 3350 (CH), 1800 and 1650cm^{-1} (C=O); δ_H 2.57 (6H, s, CH_3), 4.61 (4H, s, CH_2); δ_C 26.3 (CH_3), 46.8 (CH_2), 165.9 and 170.5 (2 x C=O).

1,4-Dibenzoyl-2,5-dioxopiperazine (**33**)

Method A:

To a stirred suspension of 2,5-dioxopiperazine (1.00 g; 8.8 mmol) and benzoyl chloride (2.71 g; 19.3 mmol) in dichloromethane (30 ml) at room temperature was added a solution of triethylamine (1.95 g; 19.3 mmol) in dichloromethane (5 ml). The suspension was then stirred at room temperature for five days before the solid was filtered off, the organic layer washed with water (2 x 30 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give only a mixture of unchanged dioxopiperazine and benzoic acid (by ^1H nmr and TLC).

Method B:

To a stirred suspension of 2,5-dioxopiperazine (10.00 g; 87.65 mmol) and sodium hydride (60% dispersion in oil; 7.35 g; 184.1 mmol) in *N,N*-dimethylformamide (DMF) (120 ml) at room temperature under nitrogen was added a solution of benzoyl chloride (25.85 g; 184.1 mmol) in DMF (20 ml) with the temperature less than 20°C. The mixture was stirred for seven days before water (100 ml) was added and the mixture extracted with dichloromethane (4 x 50 ml). The organic layers were then combined, washed with water (3 x 50 ml) and dried ($MgSO_4$) before the solvent was evaporated off under reduced pressure to give a black intractable tar which resisted all attempts at purification.

Method C:

A suspension of 2,5-dioxopiperazine (15.0 g; 0.13 mol) in benzoyl chloride (46.2 g; 0.33 mol) and pyridine (93.6 g; 1.18 mol) was heated to 100°C until all the solid was in solution and then for a further 3 h at 100°C. The dark red mixture was then left to cool and stand for 8 h before the solid was filtered off, sucked dry and washed with ether : ethanol (75 : 25; 50 ml). The solid was then stirred with boiling ethanol (50 ml), cooled, filtered off and washed again with ether : ethanol (3: 1; 50 ml) to give a tan solid which was then recrystallised from aqueous ethanol.

Yield, 29.00g (74%) ; m.p. 240-241°C [lit.[37] 239-240°C (from aqueous ethanol)]; δ_H 4.60 (4H, s, CH_2), 7.44 (4H, t, *m*-H), 7.57 (2H, d, *p*-H), 7.81 (4H, d, *o*-H); δ_C 48.8 (CH_2), 128.3 and 129.3 (C-2 and C-3), 132.4 (C-4), 134.9 (C-1), 167.7 and 171.2 (2 x C=O).

Attempted reaction between benzimidazolone and 1,4-dibenzoyl-2,5-dioxopiperazine (**33**)

To a stirred solution of dibenzoyldioxopiperazine (**33**) (1.00 g, 3.36 mmol) and triethylamine (0.68 g, 6.71 mmol) in dry DMF (15 ml) was added benzimidazolone (0.90 g, 6.71 mmol). The reaction was then stirred at room temperature for 24 h before water (30 ml) was added and the reaction mixture extracted with DCM (3 x 30 ml). The combined organic layers were then washed with water (2 x 40 ml), dried ($MgSO_4$) and the solvent evaporated. Only unchanged starting materials were recovered (by ^1H nmr).

The above reaction was then repeated but the reaction mixture was heated to 100°C for 4 h before cooling to room temperature and working up as above. Only unchanged starting materials were isolated (by ^1H nmr).

Reaction between isatin and 1,4-dibenzoyl-2,5-dioxopiperazine (**33**)

A suspension of isatin (1.47 g; 10.0 mmol), 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (1.49 g; 5.0 mmol) and triethylamine (1.10 g; 11.0 mmol) in DMF (20 ml) was stirred for 20 h at room temperature with a colour change from colourless to a red precipitate. The precipitate was filtered off to give a red/purple solid.

Yield, 0.33 g (18%), ν_{max}. 3200 cm^{-1} (NH), 1685 (C=O), 1660 (C=O).

Attempted reaction of benzimidazolone and 2,5-dioxopiperazine (**9**)

A suspension of benzimidazolone (2.94 g; 21.9 mmol), 2,5-dioxopiperazine (1.00 g; 8.8 mmol) and sodium acetate (3.00 g; 21.9 mmol) in acetic anhydride (4.50 g; 43.8 mmol) was heated at 100°C for 6 h. The mixture was then allowed to cool to 50°C before water (50 ml) was added and the solid filtered off. The aqueous mother liquor was then extracted with dichloromethane (3 x 50 ml), and the extracts combined, dried ($MgSO_4$) and evaporated to give unchanged benzimidazolone (by ^1H nmr). The solid was then found to be unchanged 2,5-dioxopiperazine.

1,4-Dibenzoyl-3,6-dibromo-2,5-dioxopiperazine (**150**)

A suspension of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (3.00 g; 10.1 mmol), AIBN (5 mg) and *N*-bromosuccinimide (7.17 g; 40.3 mmol) in carbon tetrachloride (100 ml)

was heated to reflux for 5 h then cooled to room temperature. The red solution was then filtered through Celite and the filtrate evaporated under reduced pressure to give a red gum. The singlet at δ 6.93 in ^{1}H spectrum of the crude product shows presence of some (*ca.* 15% by ^{1}H nmr) of the required brominated product; this was then used crude without further purification.

Attempted *N*-benzoylation of benzimidazole

To a stirred solution of benzimidazole (5.00 g; 42.3 mmol) and triethylamine (6.54 g; 46.6 mmol) in dichloromethane (40 ml) was added a solution of benzoyl chloride (6.54 g; 46.6 mmol) in dichloromethane (30 ml) with the temperature kept below 20°C. After stirring for 2 h water (20 ml) was added, the mixture extracted with dichloromethane (3 x 50 ml), the organic layers combined, washed with water (2 x 20 ml) and dried ($MgSO_4$) Evaporation under reduced pressure gave a cream solid which was then suspended in ethanol (80 ml), brought to reflux, cooled and the solid filtered off.

Yield, 1.26g; m.p. 310-311°C [lit.[123]. for *N,N'*-dibenzoyl-*o*-phenylenediamine 301°C].

2-Lithio-1-trimethylsilylbenzimidazole (**157**)

A solution of benzimidazole (0.32 g; 2.7 mmol) in THF (20 ml) was cooled to 10°C and *n*-butyl lithium (1.6 M in hexanes; 1.7 ml; 2.7 mmol) was added with the temperature kept below 10°C. The suspension was then stirred for 5 min and chlorotrimethylsilane (0.34 ml; 2.7 mmol) was added with the temperature kept below 20°C. The suspension was then cooled to -78°C and *n*-butyl lithium (1.6 M in hexanes; 1.7 ml; 2.7 mmol) was added with the temperature kept below -75°C. The reaction mixture was then stirred at -78°C for 3 h before being used crude.

Attempted reaction between lithiated 1-trimethylsilylbenzimidazole and 3,6-dibromo-1,4-di-(*p*-methoxybenzyl)-2,5-dioxopiperazine

To a suspension of the crude lithiated 1-trimethylsilylbenzimidazole (2.7 mmol) in THF (20 ml) at -78°C was added a solution of 3,6-dibromo-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (*ca.* 1.7 mmol) in THF (5 ml) with the temperature kept below -75°C. A pale yellow solution formed upon addition. The mixture was stirred at -78°C for 10 min before being slowly warmed to room temperature and stirred continued for 72 h. Water

(10 ml) was then added and the mixture extracted with ether (2 x 20 ml), dried ($MgSO_4$) and the solvent evaporated to give only unchanged dibromodioxopiperazine and benzimidazole (by ^1H nmr).

Attempted synthesis of 2-deuteriobenzimidazole

To a solution of benzimidazole (1.00 g; 8.5 mmol) in THF (20 ml) under N_2 was added *n*-butyl lithium (1.6 M in hexanes; 5.3 ml; 8.5 mmol) with the temperature kept below 20°C. The suspension was then stirred for 10 mins before chlorotrimethylsilane (0.92 g; 8.46 mmol) was added with the temperature kept below 20°C and the suspension stirred for 30 mins at room temperature before being cooled to -78°C. The suspension was then kept below -75°C, *n*-butyl lithium (1.6 M in hexanes; 5.3 ml; 8.5 mmol) was added and the mixture was then stirred for a further 3 h at -78°C before being quenched with D_2O (1.60 g; 8.0 mmol) in THF (10ml). The mixture was allowed to warm to room temperature, then stirred for 2 days before the solvent was evaporated off, the residual oil dissolved in dichloromethane (20 ml) and washed with HCl (2 M; 10 ml). Evaporation of the solvent then gave a cream oil which contained benzimidazole (by TLC) however no deuterium incorporation was found to have taken place (by ^1H and ^{13}C nmr).

Typical *N*-alkylation of 2,5-dioxopiperazine

To a suspension of 2,5-dioxopiperazine (0.36 g; 3.2 mmol) and alkyl halide (6.4 mmol) in DMF (10 ml) under N_2 was added, in one portion, sodium hydride (60% dispersion in oil; 0.25 g; 6.4 mmol). The mixture was stirred at room temperature for 24 h before water (15 ml) was added and the mixture was then extracted with dichloromethane (4 x 30 ml), dried ($MgSO_4$) and the solvent evaporated to give a solid suspended in a viscous liquid. The precipitate was then filtered off and recrystallised from ethanol.

1,4-Diethyl-2,5-dioxopiperazine

This was prepared following the above general method using 2,5-dioxopiperazine (1.00 g; 8.8 mmol), iodoethane (3.01 g; 19.3 mmol) and sodium hydride (0.79 g; 19.3 mmol).

Yield, 0.40 g (26%); m.p. 128-129°C [lit.[124], 129°C]; δ_H 1.20 (6H, t, CH_3), 3.50 (4H, q, N-CH_2-CH_3), 4.02 (4H, s, N-CH_2-CO).

1,4-Di(*n*-propyl)-2,5-dioxopiperazine

This was prepared following the above general method using 2,5-dioxopiperazine (5.00 g; 43.8 mmol), 1-iodopropane (15.61 g; 92.0 mmol) and sodium hydride (3.68 g; 43.8 mmol).

Yield, 2.37 g (27%); m.p. darkens above 200°C and decomposes above 280°C. Does not melt below 320°C; δ_H 0.69 (6H, t, CH_3), 1.40-1.50 (4H, m, CH_2-CH_2-CH_3), 2.22 (N-CH_2-CH_2), 3.98 (4H, s, N-CH_2-CO).

1,4-Dibenzyl-2,5-dioxopiperazine (**158**)

This was prepared following the above general method using 2,5-dioxopiperazine (2.00 g; 17.53 mmol), benzyl chloride (4.54 g; 35.06 mmol) and sodium hydride (1.40 g; 35.06-mmol).

Yield, 3.56 g (69%); m.p. 175-177°C [lit.[125], 176°C]; δ_H 3.91 (4H, s, CH_2-ring), 4.55 (4H, s, CH_2-benzyl), 7.20-7.40 (10H, m, Ph); δ_C 49.1 (CH_2-benzyl + CH_2-ring), 128.1 (C-4), 128.4 (C-2 or 3), 128.8 (C-3 or 2), 134.8 (*quat*-C), 163.1 (C=O).

1,4-Di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159**)

This was prepared following the above general method using 2,5-dioxopiperazine (0.36 g; 3.19 mmol), *p*-methoxybenzyl chloride (1.00 g; 6.39 mmol) and sodium hydride (0.25 g; 6.39-mmol).

Yield, 0.91 g (81%); m.p. 202-204°C, [lit.[124], 206°C]; δ_H 3.80 (6H, s, OCH_3), 3.91 (4H, s, N-CH_2-CO), 4.52 (4H, s, -CH_2-Ar), 6.87-7.22 (8H, m, Ar); δ_C 48.0 and 48.5 (CH_2-ring) and (CH_2-benzyl), 54.8 (OCH_3), 113.8 (C-2), 126.7 (C-4), 129.4 (C-3), 159.1 (C-1), 162.8 (C=O).

1,4-Dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**157**)

To a solution of 1,4-dibenzyl-2,5-dioxopiperazine (**155**) (2.00 g; 6.79 mmol) and AIBN (10 mg) in carbon tetrachloride (68 ml; 0.1M w.r.t. 1,4-dibenzyl-2,5-dioxopiperazine) was added *N*-bromosuccinimide (2,54 g; 14.27 mmol) and the mixture heated to reflux

for 75 min, filtering of the cooled the suspension through Celite and evaporation of the solvent from the filtrate gave a yellow oil which was then warmed, to *ca.* 60°C, in a petrol (60 : 80) / toluene mixture (1:1) and then left to cool slowly. The white solid was then filtered off and dried *in vacuuo*.

Yield, 2.32 g (76%); m.p. 133-135°C [lit.[49], no m.p. recorded]; (Found: C, 48.05; H, 3.3; N, 6.2. $C_{18}H_{16}Br_2N_2O_2$ requires C, 47.8; H, 3.6; N, 6.2%); δ_H 4.05 (2H, d, *j* 14.75, CH_2-Ph), 5.40 (2H, d, CH_2-Ph), 5.95 (2H, s, C*H*Br), 7.20-7.50 (10H, m, Ph); δ_C 48.7 (*C*H_2Ph), 57.9 (*C*HBr), 129.6 (*p*-C), 129.7+129.9 (*m*- and *o*-C), 133.3 (*ipso*-C), 162.1 (C=O); *m/z* 452 ($M^{+\cdot}$, 0.5%), 373 (28), 371 (29), 306 (22), 291 (12), 264 (22), 201 (26), 91 (100), *etc.*

3,6-Dibromo-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**158**)

A suspension of 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (0.45 g; 1.3 mmol), *N*-bromosuccinimide (0.57 g; 3.2 mmol) and AIBN (5 mg) in carbon tetrachloride (13 ml) was heated to reflux for 2.5 h, cooled, filtered through Celite and evaporated to give an orange oil which was then used crude.

δ_H 3.78 (6H, s, OCH_3), 3.95 (2H, d, *J* 14.1, CH-benzyl), 5.21 (2H, d, *J* 14.1, CH-benzyl), 5.90 (2H, s, CHBr), 6.85 (4H, d, *J* 9.0, H-2), 7.21 (4H, d, *J* 9.0, H-3).

Attempted synthesis of 1-(diethoxymethyl)benzimidazole (**163**)

A suspension of benzimidazole (0.40 g; 3.4 mmol), triethyl orthoformate (3.40 ml; 20.4 mmol) and *p*-toluenesulphonic acid (10 mg) in toluene (10 ml) was heated to reflux for 30 min then cooled and the solvent evaporated off. The residue was then taken up in triethyl orthoformate (3.40 ml; 20.4 mmol) and toluene (10 ml) and again heated to reflux with the slow removal of 4 ml of solvent. The solution was then cooled and evaporated under reduced pressure to give an oil which was stored for use in the next stage.

Attempted reaction between lithiated 1-(diethoxymethyl)benzimidazole (**164**) and 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**160**)

To a stirred solution of crude 1-(diethoxymethyl)benzimidazole (**163**) (3.40 mmol) in THF (8 ml) under nitrogen at -78°C was added *n*-butyl lithium (1.6 M in hexanes;

2.30 ml; 3.56 mmol) with the temperature kept below -65°C. The solution was then stirred at -78°C for 30 min before the addition of a solution of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**160**) (0.77 g; 1.70 mmol) in THF (8 ml) with the temperature kept below -65°C. The dark brown reaction mixture was then stirred at -78°C for 30 min, allowed to warm to room temperature, and a saturated solution of aqueous ammonium chloride (30 ml) was then added. The mixture was extracted with ether (3 x 50 ml), the extracts combined, washed with water (50 ml) then with brine (50 ml), dried ($MgSO_4$) and evaporated to give a brown tar. The tar was chromatographed with a gradient of ether to dichloromethane eluent to give only one identifiable product which was benzimidazole (by ^1H nmr).

Attempted synthesis of 2-deuteriobenzimidazole using 1-(diethoxymethyl)benzimidazole (**163**)

To a stirred solution of crude 1-(diethoxymethyl)benzimidazole (**163**) (0.90 g; 4.09 mmol) in THF (20 ml) under nitrogen at -78°C was added *n*-butyl lithium (1.6 M in hexanes; 2.8 ml; 4.49 mmol) with the temperature kept below -65°C. The mixture containing the lithiated product (**164**) was then stirred at -78°C for 3 h before addition of a solution of D_2O (2 ml) in THF (5ml) with the temperature kept at -50°C. The mixture was allowed to warm up to room temperature and saturated aqueous ammonium chloride (20 ml) added. The mixture was then extracted with ethyl acetate (3 x 40 ml), and the extracts were combined, washed with water (20 ml) then with brine (30 ml), dried ($MgSO_4$) and evaporated. The nmr (^1H and ^{13}C) of the resultant solid showed no sign of deuterium incorporation.

Reaction of 2-lithio-1-methylbenzimidazole and 1,4-dibenzyl-3,6-dibromo-2,5-dioxo-piperazine

To a stirred solution of 1-methylbenzimidazole (1.00 g; 7.57 mmol) in dry THF (10 ml) at -78°C under nitrogen was added *n*-butyl lithium (1.6M in hexanes; 5.2 ml; 8.32 mmol) with the temperature kept below -70°C. The solution was then stirred at -78°C for 2 h before a solution of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (1.30 g; 2.87 mmol) in dry THF (10 ml) was added, with the temperature kept below -65°C. The dark red mixture was then stirred at -78°C for 1 h, slowly warmed to room temperature and then stirred at room temperature for 8 h before the reaction was quenched with saturated aqueous ammonium chloride (30 ml). The mixture was then extracted with ether (4 x 30 ml) and DCM (30 ml), the organic layers combined, dried ($MgSO_4$) and evaporated to

give a red / black oil which was found to contain 1-methylbenzimidazole and unidentifiable decomposition products (^{1}H nmr).

Reaction of (1-methylbenzimidazol-2-yl)zinc chloride with 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**160**)

To a stirred solution of 1-methylbenzimidazole (0.88 g; 6.60 mmol) in dry THF (10 ml) at -78°C under nitrogen was added *n*-butyl lithium (2.5M in hexanes; 3.2 ml; 7.92 mmol) with the temperature kept below -65°C. The solution was then stirred at -78°C for 3 h before a solution of anhydrous zinc chloride (0.99 g; 7.26 mmol) in THF (15 ml) was added with the temperature maintained below -65°C. The mixture was then slowly warmed to room temperature, stirred at room temperature for 15 min and then cooled back down to -78°C and a solution of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (**160**) (1.50 g; 3.30 mmol) in THF (5 ml) was added with the temperature maintained below -65°C. The red reaction mixture was then stirred at -78°C for 15 min, then allowed to warm to room temperature and stirred at room temperature for 8 h. The mixture was then quenched with dilute HCl (0.5M; 10 ml) and the resultant white solid filtered off. The filtrate was then extracted with DCM (3 x 50 ml), dried ($MgSO_4$) and evaporated. The white solid filtered off was found to be unchanged 1,4-dibenzyl-2,5-dioxopiperazine (**160**) (by ^{1}H nmr) and the extracts proved to be intractable tars.

Attempted reaction of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine and lithiated 2-chlorobenzoxazole

To a stirred solution of 2-chlorobenzoxazole (0.44 g, 2.86 mmol) in THF (10 ml) under nitrogen at -78°C was added *n*-butyl lithium (1.6 M in hexanes; 1.8 ml; 2.86 mmol) with the temperature kept below -65°C. The solution was then stirred at -78°C for 2 h before adding a solution of 1,4-dibenzyl-3,6-dibromo-2,5-dioxopiperazine (0.61 g; 1.36 mmol) in THF (10 ml) with the temperature kept below -70°C. The reaction was then stirred at -78°C for 30 min before warming to room temperature and stirring for a further 2 h. Water (10 ml) was then added and the mixture extracted with ethyl acetate (2 x 50 ml). The extracts were then combined, washed with water (30 ml), brine (30 ml) and dried ($MgSO_4$) before evaporating off the solvent giving a red/black intractable tar.

Attempted lithiation of 2-chlorobenzoxazole

To a stirred solution of 2-chlorobenzoxazole (0.44 g; 2.86 mmol) in THF (10 ml) at -78°C under nitrogen was added *n*-butyl lithium (1.6M in hexanes; 1.8 ml; 2.86 mmol) with the temperature maintained below -70°C. The mixture was stirred at -78°C for 2 h before adding a solution of D_2O (2 ml) in THF (5 ml) and allowing the solution to warm to room temperature. Evaporation of the solvent led to a semi-solid which showed no sign of deuterium incorporation (by ^1H and ^{13}C nmr).

Attempted synthesis of 2-methylbenzoxazole

To a stirred solution of benzoxazole (1.00 g; 8.39 mmol) in THF (10 ml) at -78°C under nitrogen was added *n*-butyl lithium (1.6M in hexanes; 5.8 ml; 9.23 mmol) with the temperature maintained below -55°C. The black suspension was then stirred at -78°C for 10 min before a solution of methyl iodide (1.31 g; 9.23 mmol) in THF (3 ml) was added and the mixture allowed to warm to room temperature. The reaction was then stirred at room temperature for a further 8 h before being quenched with aqueous ammonium chloride and extracted into ether (4 x 30 ml), dried ($MgSO_4$) and evaporated. The resultant oil showed no sign of any 2-methylbenzoxazole or benzoxazole, only what appeared to be decomposition products (by ^1H nmr).

Reaction of lithiated 1,4-dibenzoyl-2,5-dioxopiperazine with 2-chloro-1-trimethylsilylbenzimidazole

To a stirred solution of 1,4-dibenzoyl-2,5-dioxopiperazine (**146**) (1.00 g; 3.4 mmol) in dry THF (20 ml) at -78°C under nitrogen was added *n*-butyl lithium (1.6 M in hexanes; 4.2 ml; 6.7 mmol) with the temperature kept below -75°C during the addition. Upon addition of the *n*-butyl lithium the suspension went from cream to dark red and finally to black. The mixture was then stirred at -78°C for 15 min before a solution of the crude 2-chloro-1-trimethylsilylbenzimidazole (8.4 mmol) in THF (40 ml) was added with the temperature kept below -75°C during the addition. Upon addition the suspension turned brown and it was then allowed to warm slowly to room temperature with stirring over 8 h. Water (10 ml) and then dilute HCl (3 M; 5 ml) was added, the mixture extracted with diethyl ether (3 x 50 ml), dried ($MgSO_4$), the solid filtered off and the solvent evaporated. Only unchanged starting 1,4-dibenzoyl-2,5-dioxopiperazine and 2-chlorobenzimidazole were isolated.

Attempted methoxycarbonylation of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**)

Method A:

To a stirred suspension of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (1.30 g; 4.05 mmol) in dry ether (70 ml) under nitrogen at -78°C was added *t*-butyl lithium (1.7 M in pentane; 5.0 ml; 8.50 mmol) with the temperature kept below -65°C. The reaction mixture was then stirred at -78°C for 30 min before being added to a suspension of solid carbon dioxide (20 g) in ether (80 ml) at -78°C. The mixture was then stirred at -78°C for 30 min, warmed to -50°C (allowing approximately half of the carbon dioxide to evaporate off), before being cooled again to -78°C. A solution of methyl iodide (1.21 g; 8.50 mmol) in ether (10 ml) was then added and the reaction stirred at -78°C for 1.5 h, before being allowed to warm to room temperature and stirred for a further 30 min. The reaction was then quenched by careful addition of a saturated solution of ammonium chloride (50 ml). Dichloromethane (50 ml) was then added and the organic layer washed with water (3 x 50 ml), brine (100 ml), dried ($MgSO_4$) and evaporated. Unchanged 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (by ^1H nmr) was recovered in quantitative yield.

Method B:

To a stirred solution of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (1.00 g; 3.01 mmol) in THF (60 ml) at -78°C under nitrogen was added *t*-butyl lithium (1.7 M in pentane; 3.7 ml; 6.32 mmol) with the temperature maintained below -70°C. The black solution was then stirred at -78°C for 1 h before being added to a solution of ethyl chloroformate (3.27 g; 30.10 mmol) in THF (10 ml) with the temperature kept below -70°C. The mixture was stirred at -78°C for 40 min, allowed to warm to room temperature and stirred for a further 30 min. The reaction was then quenched with saturated ammonium chloride (30 ml) and ethyl acetate (50 ml) added. The organic layer was then washed with water (2 x 50 ml), brine (100 ml), dried ($MgSO_4$) and the solvent evaporated. The product was shown to contain mainly starting 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (90%) with one other fraction. This was isolated and found to be a black tar, the ^1H nmr spectrum of which shows a resonance attributable to a *t*-butyl group.

Attempted deuteration of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**)

To a stirred solution of 1,4-dibenzoyl-2,5-dioxopiperazine (**33**) (0.20 g; 0.60 mmol) in THF (20 ml) at -78°C under nitrogen was added *t*-butyl lithium (1.7 M in pentane; 0.8 ml; 1.20 mmol) with the temperature maintained below -70°C. The black solution was then stirred at -78°C for 1 h before being added to a solution of D_2O (1 ml) in THF (5 ml) with

the temperature kept below -70°C. The reaction was then warmed to room temperature and saturated ammonium chloride (30 ml) and ethyl acetate (50 ml) were added. The organic layer was then washed with water (2 x 50 ml), brine (100 ml), dried ($MgSO_4$) and the solvent evaporated. The product was found to contain no deuterium (by ^1H nmr) but there did appear to be some (ca. 5%) decomposition product(s) again thought to be attributable to a *t*-butyl group being incorporated into the dioxopiperazine.

Attempted synthesis of 3-(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**169**)

To a stirred suspension of 1,4-dibenzyl-2,5-dioxopiperazine (**158**) (0.30 g; 1.02 mmol) in THF (20 ml) under nitrogen at -78°C was added *n*-butyl lithium (0.6 M in hexanes; 1.34 ml; 2.14 mmol) with the temperature kept below -60°C. The orange suspension was then stirred at -78°C for 30 min before addition of a solution of 2-chlorobenzoxazole (0.33 g; 2.14 mmol) in THF (5 ml) with the temperature kept below -60°C. The red reaction mixture was then stirred at -78°C for 1 h, before being allowed to warm to room temperature. Water (10 ml) was added and the mixture was extracted with ether (3 x 50 ml); the extracts were combined, washed with water (50 ml) and then brine (50 ml) and dried ($MgSO_4$). The ether was then evaporated off and TLC showed eight spots, the major two corresponding to starting materials. One other major spot was isolated *via* chromatography the ^1H nmr spectrum of which shows resonances attributable to a *t*-butyl group.

3-(Benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**169**)

To a stirred suspension of 1,4-dibenzyl-2,5-dioxopiperazine (**158**) (3.83 g; 13.02 mmol) in dry THF (300 ml) at -78°C was added a solution of freshly prepared LDA [diisopropylamine (1.58 g; 15.63 mmol) and *n*-butyl lithium (2.5 M in hexanes; 5.7 ml; 14.33 mmol) in THF (20 ml)] with the temperature kept below -65°C. The suspension was then stirred at -78°C for 1 h before being added to a solution of 2-chlorobenzoxazole (2.00 g; 13.02 mmol) in THF (30 ml), with the temperature kept below -65°C. The reaction was then stirred at -78°C for 30 min before being allowed to warm to room temperature. Stirring was continued at room temperature for a further 30 min, and the reaction was then quenched with saturated ammonium chloride (100 ml), and the mixture extracted with ether (3 x 100 ml). The organic layers were then combined, washed with water (100 ml) then brine (100 ml), dried ($MgSO_4$), and the solvent evaporated. The resultant solid was then dry flash chromatographed (silica gel; eluent, ether).

Yield, 1.08 g (20%); m.p. 111-113.5°C (from toluene); (Found: C, 73.3; H, 4.8; N, 10.1. $C_{25}H_{21}N_3O_3$ requires C, 73.0; H, 5.1; N, 10.2%); *m/z* 411 ($M^{+\cdot}$ 79%), 380 (18), 320 (19), 306 (25), 292 (7), 242 (14), 187 (41),155 (32), 120 (14), 91 (100), *etc.* δ_H 3.95 (1H, d, *J* 14.65, CH-ring), 4.03 (1H, d, *J* 14.75, CH-benzyl'), 4.35 (1H, d, *J* 14.65, CH-ring), 4.55 (1H, d, *J* 17.5, CH-benzyl), 4.75 (1H, d, *J* 17.5, CH-benzyl), 5.27 (1H, d, *J* 14.75, CH-benzyl'), 5.30 (1H, s, CH), 7.15-7.55 (13H, m, Ar), 7.69-7.78 (1H, m, Ar); δ_C 47.8 (CH_2-benzyl), 49.2 (CH_2-benzyl'), 49.6 (CH_2-ring), 57.8 (CH), 110.8 (C-7), 120.5 (C-4), 124.8 (C-6), 125.8 (C-5), 128.1 (*m*-C), 128.5(*o*-C), 128.7 (*p*-C), 128.8 (*o*-C'), 134.2 (*quat*-C), 134.4 (*quat*-C'), 140.4 (C-3a), 150.7 (C-7a), 159.6 (C-2), 161.0 (C=O), 164.4 (C=O').

The assignments of the various ^1H resonances are displayed in Figure 1 (p. 98)

The above reaction was repeated with the addition of dry DMPU (60 ml) to help solubalise the starting dioxopiperazine (**169**). Upon work up of the reaction the crude product was found to contain some DMPU. The crude product was therefore re-dissolved in ether (150 ml) and washed again with water (3 x 75 ml). The organic layer was then dried ($MgSO_4$) and the solvent evaporated off. Some DMPU was still seen to remain.

3,6-bis(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**171**)

To a stirred solution of 3-(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**169**) (0.20 g; 0.49 mmol) in dry THF (20 ml) at -78°C was added a solution of freshly prepared LDA [diisopropylamine (0.11 g; 1.07 mmol) and *n*-butyl lithium (2.5 M in hexanes; 0.4 ml; 1.02 mmol)] in THF (20 ml) with the temperature kept below -65°C. The reaction was then stirred at -78°C for 30 min before addition of a solution of 2-chlorobenzoxazole (0.075 g; 0.49 mmol) in THF (3 ml) with the temperature kept below -70°C. The mixture was then stirred at -78°C for 15 min before being allowed to warm to room temperature. Stirring was continued for a further 10 min, the reaction was then quenched with saturated ammonium chloride (10 ml) and the mixture extracted with ether (3 x 30 ml). The organic layers were combined, washed with water (50 ml) then brine (50 ml), dried ($MgSO_4$), and the solvent evaporated. The resultant solid was then dry flash chromatographed (silica gel; eluent, ether).

Yield, 0.19 g (73%); m.p. 212-215°C; (Found: C, 73.0; H, 4.4; N, 10.5. $C_{32}H_{24}N_4O_4$ requires C, 72.7; H, 4.6; N, 10.6%); *m/z* 528 ($M^{+\cdot}$ 0.5%), 500 (4), 381 (52), 323 (34), 283 (49), 253 (22), 225 (74),163 (52), 120 (100), 102 (12), 91 (10), *etc.*; δ_H 4.19 (2H, d, *J* 15.00, CH-benzyl), 5.42 (2H, s, CH-ring), 5.61 (2H, d, *J* 15.00, CH-benzyl),

7.10-7.45 (18H, m, aromatics).δ_C 48.9 (CH_2), 57.6 (CH), 110.5 (C-7), 120.0 (C-4), 124.5 (C-6), 125.5 (C-5), 128.6 (*o*-C + *p*-C), 129.0 (*m*-C), 134.0 (*quat*-C), 140.2 (C-3a), 150.8 (C-7a), 158.6 (C-2), 161.7 (C=O).

1,4-Dibenzyl-3-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-2,5-dioxopiperazine (**172**)

To a stirred solution of diisopropylamine (1.44 g; 14.25 mmol) in dry THF (20 ml) under nitrogen at room temperature was added *n*-butyl lithium (2.5 M; 5.2 ml; 13.06 mmol) with the temperature kept below 30°C. The mixture was then stirred at room temperature for 10 min, then cooled to -78°C, and added to a suspension of 1,4-dibenzyl-2,5-dioxopiperazine (**158**) (3.49 g; 11.87 mmol) in dry THF (300 ml) with the temperature kept below -65°C. The reaction mixture was then stirred at -78°C for 1 h before being added to a solution of 1-*t*-butoxycarbonyl-2-chlorobenzimidazole (3.00 g; 11.97 mmol) in THF (30 ml) with the temperature kept below -65°C. The reaction was then stirred at -78°C for 1 h before being allowed to warm to room temperature, and stirring was then continued for a further 30 min. The reaction was then quenched with saturated ammonium chloride (50 ml), and extracted with ether (3 x 100 ml). The organic layers were then combined, washed with water (100 ml) then brine (100 ml), dried ($MgSO_4$) and the solvent evaporated. The resultant solid was then dry flash chromatographed (silica gel; eluent, gradient from 3:1 petrol : ethyl acetate to neat ethyl acetate).

Yield, 3.41 g (56%); m.p. 173-175°C (with evolution of gas); δ_H (500 MHz @ 318K) 1.59 (9H, s, $C(CH_3)_3$), 3.94 (1H, d, *J* 17.2, CH-ring), 4.38 (1H, d, *J* 14.3, CH-benzyl'), 4.52 (1H, d, *J* 14.3, CH-benzyl), 4.52 (1H, d, *J* 17.2, CH-ring), 4.66 (1H, d, *J* 14.3, CH-benzyl), 4.79 (1H, d, *J* 14.3, CH-benzyl'), 7.04-7.10 (5H, m, Ar), 7.20-7.41 (7H, m, Ar), 7.65-7.69 (1H, m, Ar), 7.72-7.77 (1H, m, Ar); δ_C (500 MHz @ 318K) 27.9 ($C(CH_3)_3$), 48.5 (CH_2-benzyl'), 49.6 (CH_2-benzyl), 49.9 (CH_2-ring), 86.5 ($C(CH_3)_3$), 115.0 (C-7), 120.4 (C-4), 124.5 (C-5 or C-6), 125.5 (C-6 or C-5), 128.2 (*m*-C), 128.4 (*m*-C'), 128.6 (*o*-C), 129.0 (*o*-C'), 129.0 (*p*-C + *p*-C'), 135.0 (*ipso*-C), 135.4 (*ipso*-C'), 133.0 (C-3a), 141.6 (C-7a) 148.3 (*t*-BuO-*C*=O), 150.3 (C-2), 162.6 (C=O'), 165.5 (C=O); (Found (CI): *m/z* 511.2337. $C_{30}H_{31}N_4O_4$ requires *m/z* 511.2345); *m/z* 511 (MH^+· 4%), 411 (5), 395 (14), 339 (10), 253 (44), 197 (17), 153 (100), 119 (28), 107 (21), *etc.*

The above reaction was also repeated using different temperatures for the lithiation of the dioxopiperazine ring.

Metalation at -40°C for 1 h gave a yield, after chromatography, of 35%.
Metalation at 0°C for 1 h gave a yield, after chromatography, of 10%.

Sodium hydride as base gave no reaction at reflux in THF.

Attempted synthesis of 3,6-bis(1-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**173**)

To a stirred solution of freshly prepared LDA [diisopropylamine (0.46 g; 4.55 mmol) and *n*-butyl lithium (2.5 M in hexanes; 1.8 ml; 4.35 mmol)] in THF (20 ml) under nitrogen at -78°C was added a solution of 3-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**172**) (1.01 g; 1.98 mmol) in THF (15 ml) with the temperature kept below -65°C. The red solution was then stirred at -78°C for 1 h before addition of a solution of 1-*t*-butyl-2-chlorobenzimidazole (**114**) (0.50 g; 1.98 mmol) in THF (5 ml) with the temperature kept below -65°C. The reaction mixture was stirred at -78°C for 40 min before being allowed to warm to room temperature, and stirring was then continued for a further 30 min. The reaction was then quenched with saturated ammonium chloride (30ml), and the products extracted with ether (3 x 30 ml). The organic layers were then combined, washed with water (50 ml) then brine (50 ml), dried ($MgSO_4$) and the solvents evaporated. The resultant solid was then dry flash chromatographed (silica gel; eluent, 3:1 petrol : ethyl acetate). Only unchanged starting materials were isolated (by ^1H nmr).

The above procedure was repeated using 3 equivalents of LDA, and also using a longer reaction time; these modifications again gave no apparent reaction.

Attempted synthesis of 3-(1,3-di-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine

To a stirred solution of 3-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**172**) (0.15 g; 0.29 mmol) and di-*t*-butyl dicarbonate (0.13 g; 0.59 mmol) in dry THF (10 ml) was added sodium hydride (60 wt. % in oil; 0.018 g; 0.44 mmol) (pre-washed in petrol). The reaction was stirred excluding moisture ($CaCl_2$) for 3 days before adding water (10 ml) and extracting with ether (3 x 15 ml). The extracts were combined, washed with brine (20 ml), dried ($MgSO_4$), and evaporated to give only unchanged starting materials (by ^1H nmr).

Attempted methylation of 3-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**172**)

To a stirred solution of freshly prepared LDA [diisopropylamine (0.052 g; 0.52 mmol) and *n*-butyl lithium (2.5 M in hexanes; 0.2 ml; 0.5 mmol)] in THF (10 ml) under nitrogen at -78°C was added a solution of 3-(1-*t*-butoxycarbonylbenzimidazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**172**) (0.12 g; 0.24 mmol) in THF (5 ml) with the temperature kept below -65°C. The red solution was then stirred at -78°C for 15 min before addition of methyl iodide (0.15 g; 1.06 mmol). The reaction mixture was stirred at -78°C for 10 min before being allowed to warm to room temperature, and stirring was then continued for a further 15 min. The reaction was then quenched with saturated ammonium chloride (10ml), and the products extracted with ether (3 x 15 ml). The organic layers were then combined, washed with water (20 ml) then brine (20 ml), dried ($MgSO_4$) and the solvents evaporated. The ^1H nmr spectrum of the crude solid contained a large number of signals and interpretation of the signals proved to be inconclusive.

The above reaction was repeated using lithium hexamethyldisilazide but this too gave a very complicated ^1H nmr spectrum of the crude product.

Removal of *t*-butoxycarbonyl group from (**172**) using sodium methoxide

To a stirred solution of dioxopiperazine (**172**) (0.25 g; 0.49 mmol) in dry methanol (10 ml) under nitrogen was added solid sodium methoxide (0.055 g; 0.99 mmol). The reaction was then stirred at room temperature for 1 h before adding methyl iodide (0.14 g; 0.99 mmol) and stirring continued for a further 15 min. Water (10 ml) was added and the mixture extracted with dichloromethane (3 x 15 ml). The extracts were combined, washed with water (20 ml), dried ($MgSO_4$), and evaporated to give a mixture of unchanged starting material and the desired product (**174**) (by ^1H nmr).

Removal of *t*-butoxycarbonyl group from (**172**) using trifluoroacetic acid

To a solution of dioxopiperazine (**172**) (0.30 g; 0.59 mmol) in toluene (5 ml) was added freshly distilled TFA (0.335 g; 2.94 mmol). The solution was heated to reflux for 20 min then cooled to room temperature and evaporated to dryness. The resultant yellow / green oil solidified on standing and was then recrystallised from 1,4-dioxan to give a white solid.

Yield, 0.18 g (74%); m.p. 177-180°C; δ_H (d_6-DMSO) 3.95 (1H, d, *J* 14.5, CH-benzyl'), 4.01 (1H, d, *J* 18.4, CH-ring), 4.40 (1H, d, *J* 18.4, CH-ring), 4.50 (1H, d, *J* 13.2, CH-benzyl), 4.64 (1H, d, *J* 13.2, CH-benzyl), 5.07 (1H, d, *J* 14.5, CH-benzyl'), 5.32 (1H, s, CH), 7.15-7.40 (12H, m, Ar), 7.55-7.65 (2H, m, Ar); (Found: *m/z* 410.1734. $C_{25}H_{22}N_4O_2$ requires *m/z* 410.1742); *m/z* 410 ($M^{+\cdot}$ 25%), 319 (10), 305 (7), 294 (27), 241 (7), 179 (9), 159 (22), 111 (13), 91 (100), *etc.*

Attempted debenzylation of *N*-benzyl groups from (**171**)

To a stirred solution of dioxopiperazine (**171**) (0.50 g; 0.95 mmol) in methanol (10 ml) under a hydrogen atmosphere was added 10% palladium on carbon (0.50 g; 10% by weight). The suspension was then stirred at room temperature for 16 h before filtering off the catalyst and evaporating off the solvent. Only unchanged starting material was recovered unchanged (by ^{1}H nmr).

Typical Method Used to Attempted the Removal of *N*-benzyl Group from 3,6-bis(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**171**)

A suspension of 3,6-bis(benzoxazol-2-yl)-1,4-dibenzyl-2,5-dioxopiperazine (**171**) in liquid ammonia was stirred at -32°C while portions of the metal were added. The blue solution was then stirred at -32°C for a set time before adding solid ammonium chloride to quench the reaction. The ammonia was then allowed to evaporate off and dichloromethane added. The organic layer was then washed with water (2 x 50 ml), dried and evaporated. In no instances was any solid found to have precipitated during the work up.

Method A:

Following the above general method the dioxopiperazine (**171**) (0.15 g; 0.28 mmol) was suspended in liquid ammonia (25 ml) while lithium (0.055 g; 7.84 mmol) was added. The reaction was stirred at -32°C for 30 min before being quenched and worked up. Only unchanged starting material recovered (by ^{1}H nmr).

Method B:

Following the above general method the dioxopiperazine (**171**) (0.50 g; 1.70 mmol) was suspended in liquid ammonia (50 ml) while sodium (0.18 g; 7.64 mmol) was added in six portions. The reaction was stirred at -32°C for 30 min before being quenched and worked up. Only unchanged starting material recovered (by ^{1}H nmr).

Method C:

Following the above general method the dioxopiperazine (**171**) (0.50 g; 1.70 mmol) was suspended in liquid ammonia (50 ml) and *t*-butanol (0.21 g; 2.89 mmol) while sodium (0.18 g; 7.64 mmol) was added. The reaction was stirred at -32°C for 1 h before being quenched and worked up. Only unchanged starting materials recovered (by ^{1}H nmr).

Method D:

Following the above general method a solution of the dioxopiperazine (**171**) (0.056 g; 0.11 mmol) in dry THF (1 ml) was stirred in liquid ammonia (20 ml) and *t*-butanol (0.10 g), while sodium (0.03 g; 1.30 mmol) was added. The reaction was stirred at -32°C for 30 min before being quenched and worked up. Only unchanged starting materials recovered (by ^{1}H nmr).

Synthesis of 3-(benzoxazol-2-yl)-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**177**)

To a stirred suspension of 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159**) (1.00 g; 2.82 mmol) in dry THF (300 ml) at -78°C was added a solution of freshly prepared LDA [diisopropylamine (0.35 g; 3.38 mmol) and *n*-butyl lithium (2.5 M in hexanes; 1.25 ml; 3.10 mmol) in THF (20 ml)] with the temperature kept below -65°C. The suspension was then stirred at -78°C for 10 min before warming to room temperature for 15 min and then cooling again back to -78°C for a further 1 h before being added to a solution of 2-chlorobenzoxazole (0.44 g; 2.82 mmol) in THF (20 ml), with the temperature kept below -65°C. The reaction was then stirred at -78°C for 30 min before warming to room temperature and stirring at room temperature for a further 30 min. The reaction was then quenched with saturated ammonium chloride (50 ml) and the mixture extracted with ether (3 x 50 ml). The organic layers were then combined, washed with water (50 ml), brine (50 ml), dried ($MgSO_4$), and evaporated. The resultant solid was then dry flash chromatographed (silica gel; eluent, ether).

Yield, 0.22 g (16.5%); m.p. 78-85°C; δ_H 3.73 (3H, s, OCH_3), 3.80 (3H, s, OCH_3'), 3.92 (1H, d, *J* 17.55, CH-ring), 4.02 (1H, d, *J* 15.0, CH-benzyl'), 4.30 (1H, d, *J* 17.55, CH-ring), 4.49 (1H, d, *J* 14.50, CH-benzyl), 4.66 (1H, d, *J* 14.50, CH-benzyl), 5.15 (1H, d, *J* 15.0, CH-benzyl'), 5.28 (1H, s, CH), 6.79 (2H, d, *J* 8.7, H-2), 6.85 (2H, d, *J* 8.6, H-2*), 7.18 (4H, d, *J* 7.7, H-3 + H-3*), 7.33-7.41 (2H, m, benzoxazole), 7.45-7.55 (1H, m, benzoxazole), 7.70-7.77 (1H, m, benzoxazole); δ_C 47.3 (CH_2-ring), 49.0 (CH_2-benzyl + benzyl'), 55.1 (CH), 57.7 (OCH_3), 110.8 (C-7), 114.1 (*m*-C), 120.5 (C-4), 124.8 (C-6), 125.8 (C-5), 126.2 (*quat*-C), 126.5 (*quat*-C'), 129.6 (*o*-C), 130.1 (*o*-C'), 140.5 (C-3a), 150.8 (C-7a), 159.4 (*C*-OCH_3), 161.0 (C=O), 164.5

(C=O'); *m/z* 471 ($M^{+\cdot}$ 25%), 350 (5), 336 (100), 239 (10), 160 (34), 150 (18), 136 (23),121 (87), 91 (17), *etc.*

* signifies *p*-methoxybenzyl aromatic protons are different in the two rings.

3,6-bis(benzoxazol-2-yl)-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**176**)

The above procedure was repeated using 3-(benzoxazol-2-yl)-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**177**) (0.22 g; 0.47 mmol) in THF (20 ml), diisopropylamine (0.104 g; 1.03 mmol), *n*-butyl lithium (2.5 M in hexanes; 0.4 ml; 0.98 mmol) in THF (10 ml), and 2-chlorobenzoxazole (0.072 g; 0.47 mmol).

Yield, 0.18 g (65%); m.p. 176-177.5°C (toluene); υ_{max}/cm^{-1} 1680 (C=O); δ_H 3.78 (6H, s, OCH_3), 4.12 (2H, d, *J* 14.65, CH-benzyl), 5.38 (2H, s, CH-ring), 5.50 (2H, d, *J* 14.65, CH-benzyl), 6.84 (4H, d, *J* 8.14, H-3), 7.11-7.30 (12H, m, H-2 + benzoxazole); *m/z* 588 ($M^{+\cdot}$ 19%), 453 (9), 426 (10), 322 (9), 294 (6), 160 (10), 136 (13), 121 (100), *etc.*

Deprotection of 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**159**) using ceric ammonium nitrate

To a stirred solution of ceric ammonium nitrate (0.77 g; 1.41 mmol) in water (1.3 ml) and acetonitrile (2.7 ml) was added solid 1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (0.10 g; 0.28 mmol) in one portion. The mixture was then stirred at room temperature for 4 h before evaporating the mixture to dryness. The residue was then taken up in boiling water and then allowed to cool giving 2,5-dioxopiperazine.

Yield, 0.03g (94%); m.p. does not melt below 300°C.

Deprotection of 3,6-bis(benzoxazol-2-yl)-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**176**) Using Ceric Ammonium Nitrate

To a stirred solution of ceric ammonium nitrate (0.70 g; 1.27 mmol) in water (1.2 ml) and acetonitrile (2.3 ml) was added 3,6-bis(benzoxazol-2-yl)-1,4-di(*p*-methoxybenzyl)-2,5-dioxopiperazine (**177**) (0.15 g; 0.25 mmol). The reaction was then stirred at room

temperature for 16 h. The reaction mixture was then evaporated down and water (10 ml) added, before sonicating for 5 min. The brown solid was then filtered off. The ^1H nmr of the product in both deuterated acetone or DMSO showed a very complicated spectra which was not believed to be the desired product. The i.r did show a strong absorption at 3600-3200 cm^{-1} which may be due to a phenolic OH.

Attempted synthesis of 1,4-(methylthiomethyl)-2,5-dioxopiperazine (**178**)

To a stirred suspension of 2,5-dioxopiperazine (1.10 g; 9.66 mmol) and sodium hydride (60 wt. % in oil; 0.51 g; 21.25 mmol) (pre-washed in petrol) in dry DMF (100 ml) was added chloromethyl methyl sulfide (2.00 g; 20.29 mmol). The mixture was then stirred at room temperature, excluding moisture, for 24 h before adding water (20 ml) and filtering off the solid. The filtrate was then extracted with dichloromethane (3 x 75 ml), the extracts combined, washed with water (2 x 75 ml), dried ($MgSO_4$), and evaporated to give unchanged chloromethyl methyl sulfide. The solid filtered off was found to be unchanged 2,5-dioxopiperazine.

Bibliography

References

1. R.L. Feller, *'Artists' Pigments : A Handbook of their History and Characteristics'*, Cambridge University Press, Cambridge, 1985, p. 255.

2. R.L. Feller, *'Artists' Pigments : A Handbook of their History and Characteristics'*, Cambridge University Press, Cambridge, 1985, p. 17.

3. H. Zollinger, in *'Colour Chemistry: Synthesis, Properties and Applications of Organic Dyes and Pigments'*, 2nd ed. VCH, Weinheim, 1991, pp. 14-15.

4. A. Braun and J. Tcherniac, *Ber.*, 1907, **40**, 2709.

5. V.D. Poole, in *'Rodd's Chemistry of Carbon Compounds' ed.* S. Coffey, Elsevier, Amsterdam, 1977, vol. 4, pp. 334-340.

6. H. Zollinger, in *'Colour Chemistry: Synthesis, Properties and Applications of Organic Dyes and Pigments'* 2nd ed. VCH, Weinheim, 1991, pp. 101-104 and refs cited therein.

7. M. Sainsbury, in *'Rodd's Chemistry of Carbon Compounds' ed.* S. Coffey, Elsevier, Amsterdam City, 1977, vol. 4 (part B), pp. 341-367.

8. D.G. Farnum, G. Mehata, G.G.I. Moore and F.P. Siegal, *Tetrahedron Lett.*, 1974, 2549.

9. A. Iqbal, M. Jost, R. Kirchmayer, J. Pfenninger, A. Rochat and O. Wallquist, *Bull. Soc. Chim. Belg.*, 1988, **97**, 615.

10. A. Iqbal, J. Pfenninger, A. Rochat, Eur. Pat. Appl. EP 232222, *Chem. Abs.*, 1986, **108**, 23336.

11. K.C. Caster, W-Q. Fan, A.R. Katritzky, Q-L. Li and M. Szajda, *J. Heterocycl. Chem.*, 1988, **25**, 591.

12. G. Wooden (Ciba Speciality Chemicals), unpublished results.

13. J. Griffiths and J. Sekihachi, *Dyes and Pigments*, 1996, **32**, 43.

14. N. Yasuda, *J. Heterocycl. Chem.*, 1985, **22**, 413.

15. S.N. Danthi and R.A. Hill, *J. Heterocycl. Chem.*, 1997, **34**, 835.

16. R.O. Cain and A.A.E Porter, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3111.

17. J.P. Greenstein and M. Winitz, *'Chemistry of the Amino-acids'*, Krieger, 1961, Vol. 2, p. 803.

18. U. Groth, T. Huhn, B. Porsch, C. Schmeck and U. Schöllkopf, *Liebigs Ann., Chem.,* 1993, 715.

19. K. Harada and H. Naraoka, *J. Chem. Soc., Perkin Trans 1*, 1986, 1557.

20. M.V. Natekar and S. Rajappa, *Adv. Heterocycl. Chem.*, 1993, **57**, 187.

21. E. Fischer, *Ber.,* 1906, **39**, 2893.

22. D.E.Nitecki, B. Halpern and J.W. Westley, *J. Org. Chem.,* 1968, **33**, 864.

23. N. Endo, Y. Mihara, Y. Sasaki and K. Suzuki, *Chem. Pharm. Bull.,* 1981, **29**, 233.

24. D.S. Kemp and P.E. McNamara, *J. Org. Chem.,* 1984, **49**, 2286.

25. D.M. Kalvin, K. Ramalingham, P.K. Subramanian and R.W. Woodard, *J. Org. Chem.,* 1989, **54**, 270.

26. R.K. Frank, T. Fukuyama and C.F. Jewell Jr., *J. Am. Chem. Soc.,* 1980, **102**, 2122.

27. K. Ogawa, C. Shin and Y. Yonezawa, *Heterocycles,* 1987, **26**, 2087.

28. D. Marquarding, *Angew. Chem. Int. Ed. Engl.,* 1973, **12**, 79.

29. K. Kaiser and P. Rosenmund, *Angew. Chem. Int. Ed. Engl.,* 1970, **9**, 162.

30. For an example see O.P. Anderson, R.W. Armstrong, C. Eriksson, J. Josey, H. Meyers and R.M. Williams, *J. Am. Chem. Soc.,* 1982, **104**, 6092.

31. A. Kwast and R.M. Williams, *J. Org. Chem.,* 1988, **53**, 5785.

32. I.E. Pollak, J. Milvitskaya and T. Sheradsky, *Tetrahedron Lett.,* 1991, **32**, 133.

33. O.P. Anderson, R.W. Armstrong, J-S. Dung, L.K. Maruyama and R.M. Williams, *J. Am. Chem. Soc.,* 1985, **107**, 3246.

34. T. Goto, H. Miyazaki and S. Nakatsuka, *Tetrahedron Lett.,* 1980, 2817.

35. T. Fukuyama, Y. Kishi and S.I. Nakatsuka, *Tetrahedron*, 1991, **47**, 2045

36. C.L.L. Chai, D.B. Hay and A.R. King, *Aust. J. Chem.,* 1996, **49**, 605.

37. T. Hashimoto and T. Sasaki, *Ber.*, 1921, **54**, 2688.

38. J.L. Markham and P.G. Sammes, *J. Chem. Soc. Perkin Trans. 1*, 1979, 1889.

39. U. Groth, W. Hartwig, U. Schöllkopf, K.O. Westphalen, *Liebigs Ann. Chem.*, 1981, 696; also see W. Hartwig, H. Kehne, K-H. Pospichil and U. Schöllkopf, *Synthesis*, 1981, 966 and C. Deng, U. Groth, K-O. Westphalen and U. Schöllkopf, *Synthesis*, 1981, 969.

40. W. Breitschaft and R. Gompper, *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 717.

41. A.K. Göktürk, A.E.A. Porter and P.G. Sammes, *J. Chem. Soc., Perkin Trans 1*, 1982, 953.

42. T. Fukuyama and R.A. Sachleben, *J. Am. Chem. Soc.*, 1982, **102**, 4957.

43. S. Cerrini, W. Fedeli, E. Gavuzzo, G. Lucente, F. Pinnen and G. Zanotti, *Tetrahedron Lett.*, 1981, 3671.

44. V.K. Antonov, V.T. Ivanov, A.A. Kiryushkin, Yu.A. Ovchinnikov, V.I. Shchelokov, M.M. Shemyakin and A.M. Schkrob, *Tetrahedron Lett.*, 1964, 47.

45. T. Glinka and R.M. Williams, *Tetrahedron Lett.*, 1986, **27**, 3581; and H. Coffman, T. Glinka, E. Kwast, R.M. Williams and J.K. Stille, *J. Am. Chem. Soc.*, 1990, **112**, 808.

46. W.H. Rastetter and R.M. Williams, *J. Org. Chem.*, 1980, **45**, 2625.

47. M. Masaki, M. Ohta and C-G, Shin, *J. Org. Chem.*, 1967, **32**, 1860.

48. C.L.L. Chai and D.M. Page, *Tetrahedron Lett.*, 1993, **34**, 4373.

49. O.P. Anderson, R.W. Armstrong, J-S. Dung, L.K. Maruyama and R.M. Williams, *J. Am. Chem. Soc.*, 1985, **107**, 3246.

50. S.D. Bull, S.G. Davies, S.W. Epstein and J.V.A. Ouzman, *Chem. Comm.*, 1998, 659.

51. T. Sasaki, *Ber.*, 1921, **54**, 163.

52. S. Calvert, L.R. Richardson and C.E. Welch, *J. Am. Chem. Soc.*, 1929, **51**, 3074.

53. C. Gallina and A. Liberatori, *Tetrahedron*, 1974, **30**, 667.

54. J.F. Blount, D.L. Coffen, H. Maag, T.V. Steppe and F. Wong, *J. Am. Chem. Soc.*, 1978, **100**, 6786.

55. W.Q. Fan, A.R. Katritzky, A.E. Koziol and G.J. Palenik, *J. Heterocycl. Chem.*, 1989, **26**, 821.

56. J. Cornforth, P.B. Hitchcock and P. Rozos, *J. Chem. Soc. Perkin Trans. 1*, 1996, 2787.

57. T.W. Badran, C.L.L. Chai, C.J. Easton, J.B. Harper and D.M. Page, *Aust. J. Chem.*, 1995, **48**, 1379.

58. J.A. Hendrix and R.M. Williams, *Chem. Rev.*, 1992, **92**, 889.

59. O. Stöckenius, *Ber.*, 1878, **11**, 2002.

60. A. Strecker, *Liebigs Ann. Chem.*, 1850, **75**, 27.

61. K. Mai and G. Patil, *Tetrahedron Lett.*, 1984, **25**, 4583.

62. H.E. Baumgarten, J.E. Dirks, J.M. Petersen and R.L. Zey, *J. Org. Chem.*, 1966, **31**, 3708.

63. K. Matsumoto, M. Miyoshi and M. Suzuki, *J. Org. Chem.*, 1973, **38**, 2094.

64. J-C. Fiaud and H.B. Kagan, *Tetrahedron Lett.*, 1970, 1813.

65. D. Ben-Ishai and U. Zoller, *Tetrahedron*, 1975, **31**, 863.

66. D. Ben-Ishai, Z. Bernstein and I. Sataty, *Tetrahedron*, 1976, **32**, 1571.

67. W.D. Bennett and M.J. O'Donnell, *Tetrahedron*, 1988, **44**, 863.

68. T. Bretschneider, W. Miltz, P. Munster and W. Steglich, *Tetrahedron*, 1988, **44**, 5403.

69. P. Munster and W. Steglich, *Synthesis*, 1987, 223.

70. P.J. Kocienski, *'Protecting Groups'*, Thieme, New York, 1994, p. 118 - 151 and p. 185 - 237 and references cited therein.

71. D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, 1975, **14**, 426.

72. A.Y.W. Leong, G. Stork and A.M. Touzin, *J. Org. Chem.*, 1976, **41**, 3491.

73. P. Bey and J.P. Vevert, *Tetrahedron Lett.*, 1977, 1455.

74. J.J. Fitt and H.W. Gschwend, *J. Org. Chem.*, 1977, **42**, 2639.

75. J.M. Boniece, S.E. Earp and M.J. O'Donnell, *Tetrahedron Lett.*, 1978, 2641.

76. J. Ezquerra, M. Moreno-Mañas, C. Pedregal, R. Pleixats and A. Roglans, *Tetrahedron Lett.*, 1993, **34**, 8535.

77. S. Kanemasa, T. Mori, A. Tatsukawa and E. Wada, *Tetrahedron Lett.*, 1993, **34**, 677.

78. S. Djuric, P. Magnus and J. Venit, *Tetrahedron Lett.*, 1981, 1787.

79. I. Habus and I. Ojima, *Tetrahedron Lett.*, 1990, **31**, 4289.

80. W. Harwig and U. Schöllkopf, *Liebigs Ann. Chem.*, 1882, 1952.

81. J.A. Hendrix and R.M. Williams, *J. Org. Chem.*, 1990, **55**, 3723.

82. R. Gompper and W. Topfl, *Chem. Ber.*, 1962, **95**, 2861.

83. D.M. Smith, in *'The Chemistry of Heterocyclic Compounds'*, ed. P.N. Preston, Wiley-Interscience, New York, 1981, vol. 40, Chapter 3, p. 331-389.

84. T. Curtius, *J. Prakt. Chem.*, 1904, **70**, 57.

85. Y.S. Klausner and M. Bodanszky, *Synthesis*, 1974, 549.

86. B. Chantegrel and S. Grelin, *Synthesis*, 1981, 315.

87. R.E. Ehrenkaufer and S. Ram, *Synthesis,* 1986, 133 and references cited therein.

88. M.T. Shipchandler, *Synthesis*, 1979, 666.

89. R.A.B. Copeland and A.R. Day, *J. Am. Chem. Soc.*, 1943, **65**, 1072

90. E. Vogel, *T'extbook of Practical Organic Chemistry'*, 5th ed., Longman, Harlow, 1989, p. 630.

91. P.J. Kocienski, *'Protecting Groups'*, Thieme, New York, 1994, p. 118-143 and p. 233-234 and references cited therein.

92. S. Gabriel, *Ber.*, 1908, **41**, 1132.

93. W.A. Bolhofer and J.C. Sheenhan, *J. Am. Chem. Soc.*, 1950, **72**, 2786.

94. P.L. Pickard and T.L. Tolbert, *Org. Synth.*, 1964, **44**, 51.

95. M.J. O'Donnell and R.L. Polt, *J. Org. Chem.*, 1982, **47**, 2663.

96. Y. Kanacka, M. Machida, O. Yonemitsu and Y. Ban, *Chem. Pharm. Bull.*, 1965, **13**, 1065.

97. Y. Kanacka, E. Sato, O. Yonemitsu and Y. Ban, *Tetrahedron Lett.*, 1964, 2419.

98. N. R. Kotecha, S. V. Ley and S. Mantegan, *Synlett.*, **1992**, 395.

99. J. Ezquerra, C. Pedregal, M. Moreno-Manas, R. Pleixats and A. Roglans, *Tetrahedron Lett.*, 1993, **34**, 8535,

100. L. Grehn and U. Ragnarsson, *Angew. Chem. Int. Ed. Eng.*, 1984, **23**, 296.

101. J.I. Haruta, K. Kikuchi, Y. Kita, S. Marsuda, K. Nishi and Y. Tamura, *Chem. Pharm. Bull.*, 1989, **37**, 2338.

102. G. Wooden (Ciba Speciality Chemicals), unpublished results.

103. P.J. Kocienski, *'Protecting Groups'*, Thieme, New York, 1994, p. 192-194 and references cited therein.

104. T. Gräther, H. Griesser, A. Lieberknecht, J. Schmidt and U. Schmidt, *Synthesis*, 1993, 765.

105. E.F. Evans, I. Kapfer, N.J. Lewis, G. Macdonald and R.J.K. Taylor, *Synth. Commun.*, 1997, **27**, 1819.

106. F.W. Fowler, I. Hasan, A.B. Levy, L-C.C. Lin and E.R. Marinelli, *J. Org. Chem.*, 1981, **46**, 157.

107. Y. Ohfune and N. Sakai, *J. Am. Chem. Soc.*, 1992, **114**, 5872.

108. N.F. Albertson and F.C. McKay, *J. Am. Chem. Soc.*, 1957, **79**, 4686.

109. G.W. Anderson and A.C. McGregor, *J. Am. Chem. Soc.*, 1957, **79**, 6180.

110. H. Griesser, V. Lietenberger, R. Meyer, J. Schmidt and U. Schmidt, *Synthesis*, 1992, 1248.

111. N.L. Benoiton, F.M.F. Chen and R. Steinaur, *J. Org. Chem.*, 1983, **48**, 2939.

112. P.W. Alley and D.A. Shirley, *J. Org. Chem.*, 1958, **23**, 1791.

113. L. Birkofer, P. Richter and A. Ritter, *Chem. Ber.*, 1960, **93**, 2804.

114. M. Matsukawa, K. Nagayama, N. Ohashi and S. Ohta, *Synthesis*, 1990, 78.

115. Y. Kondo, T. Sakamoto, N. Takazawa and H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1*, 1996, **23**, 1927.

116. T. Mukhpadhyay and D. Seebach, *Helv. Chim. Acta.*, 1982, **65**, 385.

117. T. W. Greene and P.G.M. Wuts, in *'Protective Groups in Organic Synthesis'*, 2nd ed.,Wiley-Interscience, New York, 1991, p. 401 and refs cited therein.

118. O.P. Anderson, B.H. Lee, M.M. Millar and R.M. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 1073; and M. Shibasaki, *J. Org. Chem.*, 1987, **52**, 3489.

119. M.Y. Kim, J.E. Starrett and S.M. Weinreb, *J. Org. Chem.*, 1981, **46**, 5383.

120. D. Harrison, J.T. Ralph and A.C.B. Smith, *J. Chem. Soc.*, 1963, 2930.

121. K. Ninomiya, T. Shioiri and S-I. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 1795.

122. A.P.N. Franchimont and H. Friedmann, *Rec. trav. Chim.*, 1908, **27**, 192.

123. E. Bamberger and B. Berle, *Ann.*, 1893, **273**, 342.

124. L. Bilek, J. Derkosh, H. Michl and F. Wessely, *Monatsh. Chem.*, 1953, **84**, 717.

125. C. Gränacher, A. Weidengor and G. Wolf, *Helv. Chim. Acta.*, 1928, **11**, 1228.